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Efforts towards the Total Synthesis of Vinigrol, Stereoselective Synthesis of Carbocycles and Gold-catalyzed Benzannulation

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Efforts Towards the Total Synthesis of Vinigrol, Stereoselective Synthesis of Carbocycles and Gold-Catalyzed Benzannulation

by

Christiane Grisé-Bard

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the
Philosophiae Doctor (Ph.D.) degree in chemistry

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À mes parents, Diane et Antoine

Abstract

The Diels-Alder reaction is a very useful tool for the art and science of total synthesis. This thesis describes the exploitation of this reaction in the context of the synthesis of two different natural products, a diterpene and a steroid.

A new approach to the total synthesis of vinigrol relied on an intramolecular Diels-Alder reaction to generate two of three rings of the carbocyclic skeleton in one step. Initially, it was possible to prove that the intramolecular cycloaddition could effectively form the desired six and eight-membered ring with the right regiochemistry. Then, the starting materials were modified in order to accommodate the necessary functionality needed for the total synthesis. As a result, a functionalized tricyclic core of vinigrol was synthesized. A second-generation synthesis of a functionalized core was established taking advantage of a diastereoselective ketal Claisen rearrangement. The functionalization of the C8-C8a was studied as well as the synthesis of the allylic diol of the B ring.

The Diels-Alder reaction was also examined in the context of domino reactions. Optimization of the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction was achieved. It was also possible to study this reaction in order to accommodate *cis* precursors and apply it to the synthesis of digitoxigenin, a 14β-hydroxy steroid. Many approaches were investigated to synthesize a functionalized *cis* precursor designed for the total synthesis. The rearrangement of a functionalized *cis*-precursor is also discussed.

During the studies aimed at the application of the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction, a novel gold-catalyzed benzannulation reaction was discovered. Treating 3-hydroxy-1,5-enynes with a cationic gold catalyst led to tetrahydronaphthalenes in good yield. The scope and limitations of this methodology was examined. During this research, a new Au(PPh$_3$)Cl and acid catalyst system was detected.

Acknowledgements

Lors de ma deuxième année d'université, un professeur m'a fait comprendre que la chimie organique était une science qui était logique et utile. Ceci a influencé la direction de mes études et mon choix de carrière. Ce professeur, Louis Barriault, est devenu mon superviseur de thèse de doctorat. Je tiens à te remercier sincèrement de m'avoir partagé ton enthousiasme pour la synthèse organique. J'ai tellement appris dans les dernières années et c'est grâce à toi. Merci pour toutes les discussions de chimie et pour tous tes conseils durant les dernières neuf années. Je suis très reconnaissante de toutes les connaissances que tu m'as transmises.

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Chapter 1

Introduction

'Chemical synthesis is uniquely positioned at the heart of chemistry, the central science, and its impact on our lives and society is all pervasive. For instance, many of today's medicines are synthetic and many of tomorrow's will be conceived and produced by synthetic chemists.'

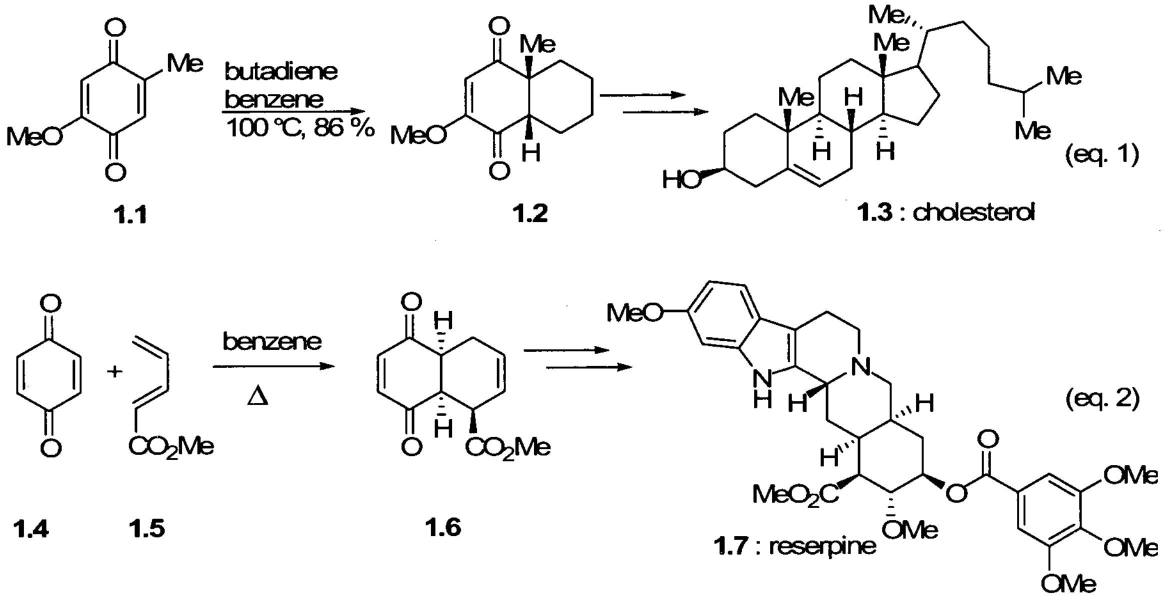
E.J.Corey[1]

Natural product synthesis

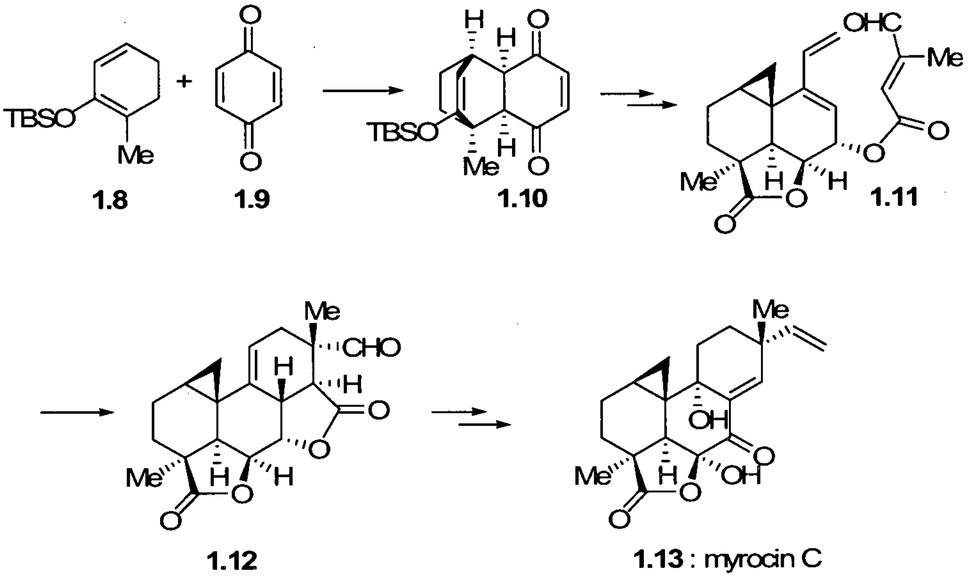
Organic synthesis can be described as the transformation of organic molecules into the desired product using one or more reactions. The application of this science towards the synthesis of complex molecules has begun in the 1930's. Woodward and Doering's synthesis of quinine in 1944 represented a seminal achievement.[2] Since then, the field of total synthesis of natural products has prospered. The development of new methods allowed the chemical synthesis of new synthetic targets that were not imaginable before. At the end of the twentieth century, the advancement of catalytic reactions and stereoselective processes has enabled the synthesis of very complex natural products such as palytoxin, taxol and brevetoxin B.[3] In the twenty-first century, researchers have focused their attention on the development of efficient methods in order to do the desired transformations economically and with minimization of waste. In that context, efforts to develop catalytic asymmetric reactions and domino reactions are essential. As the syntheses of new targets are investigated, one must carefully select routes that will provide the natural products in an efficient way. In order to undertake this challenge, creative syntheses and new methodologies are necessary. For that reason, natural product synthesis and method development are fields that are interconnected. Together, they allow chemists to push the limits of organic synthesis and advance the science.

One reaction that is used often in the synthesis of natural products is the Diels-Alder reaction. Since its discovery, the [4+2] cycloaddition has been considered as one of the most versatile reaction due to its ability to generate efficiently and predictably six-membered rings. There are many examples of the application of Diels-Alder reaction to the synthesis of complex natural products in the last fifty years.[4] To highlight the utility of this reaction, a few cases are presented. Woodward recognized the synthetic usefulness of the Diels-Alder reaction and applied it to the synthesis of cholesterol[5] and reserpine (Scheme 1.1).[6] Later, the research group of Danishefsky used two Diels-Alder reactions in their synthesis of myrocin C.[7] The intermolecular reaction generates the decalin system while the subsequent intramolecular Diels-Alder reaction completes the carbon skeleton of the natural product (Scheme 1.2). A domino conrotatory ring opening/Diels-Alder reaction of benzocyclobutene **1.14** was developed by Oppolzer in the context of the total synthesis of chelidonine (Scheme 1.3).[8] Another impressive use of the Diels-Alder reaction in total synthesis is shown in Scheme 1.4. Stork and Nakamura demonstrated that the pericyclic reaction could effectively close the macrocycle (**1.18**) in route to cytochalasin B (Figure 1.1). Corey and co-workers have used the Diels-Alder reaction in their synthesis of prostaglandin $F_{2\alpha}$ ($PF_{2\alpha}$) (Figure 1.1).[9] A racemic synthesis was initially developed but they eventually developed an asymmetric synthesis using a chiral auxiliary.[10] Further research in the area gave access to chiral Lewis acids that catalyze the Diels-Alder reaction.[11] This example demonstrates the inter-correlation of total synthesis and methodology development. The Diels-Alder reaction has also been used in the synthesis of the necessary synthons for the total synthesis of taxol (Figure 1.1).[12] These examples only represent a few of the impressive total syntheses of natural products using Diels-Alder reactions reported in the literature.

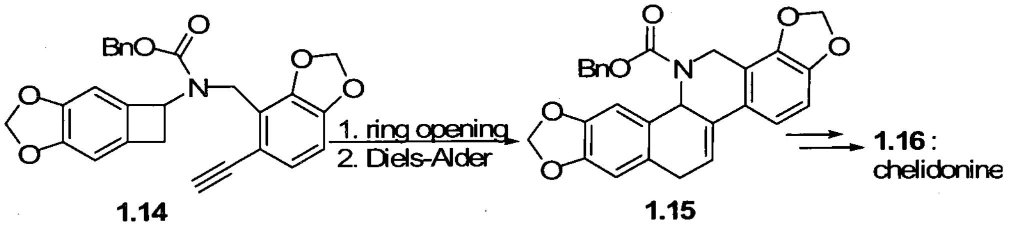
Scheme 1.1-Woodward's synthesis of cholesterol and reserpine



Scheme 1.2-Danishefsky's synthesis of myrocin C



Scheme 1.3-Synthesis of chelidonine (Oppolzer)



Scheme 1.4-Macrocyclization via a Diels-Alder reaction (Stork)

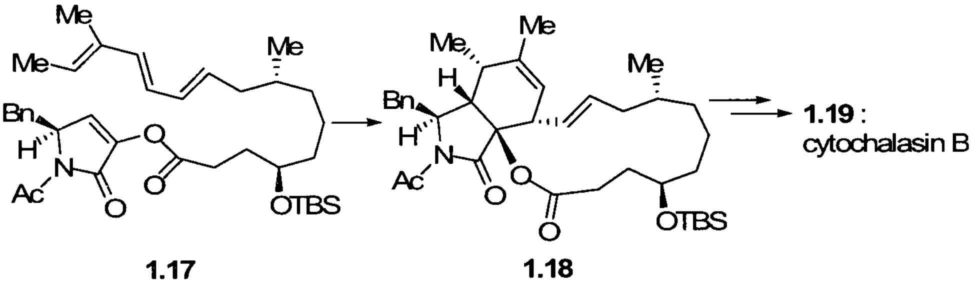
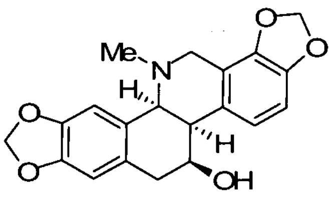
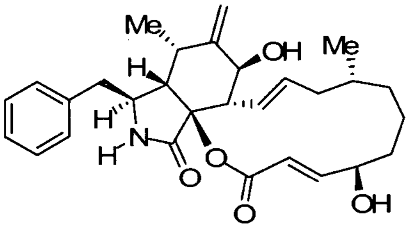


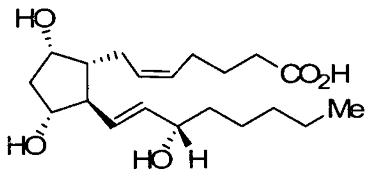
Figure 1.1-Natural products synthesized using a Diels-Alder reaction



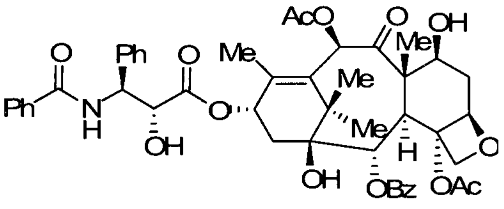
1.16 : chelidonine



1.19 : cytochalasin B



1.20 : PGF$_{2\alpha}$

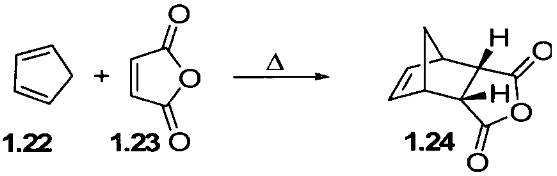


1.21 : taxol

Introduction to the Diels-Alder reaction

In 1928, Otto Diels and Kurt Alder reported the [4+2]-cycloaddition of cyclopentadiene with quinone.[13] The concerted pericyclic reaction has been named after its inventors who received the Nobel Prize in 1950 for the discovery and development of the diene synthesis. The reaction of a diene with a dienophile in a $[\pi_{4s}+\pi_{2s}]$ fashion is allowed according to the Woodward-Hoffmann rules. In a 'normal' Diels-Alder reaction, the HOMO of the diene (**1.22**) reacts with the LUMO of the dienophile (**1.23**) (Scheme 1.5). For that reason, electron-donating groups on the diene and electron-withdrawing groups on the dienophile increase the rate of the reaction. In an inverse-demand Diels-Alder reaction, the HOMO of the dienophile reacts with the LUMO of the diene.

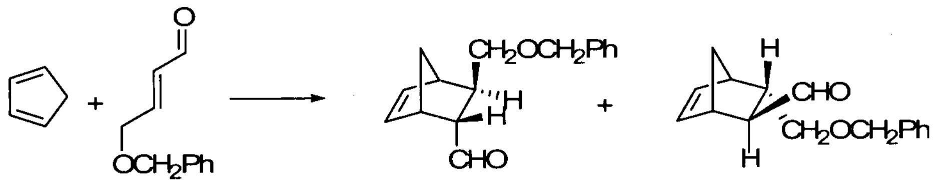
Scheme 1.5-Normal Diels-Alder reaction



As illustrated in the last section, the Diels-Alder reaction has been used extensively for the synthesis of natural products. The reaction has also shown application in the synthesis of biologically active, structurally interesting and other molecules. The reaction generates molecular complexity with stereocontrol in a predictive way. The stereospecificity of the Diels-Alder reaction is due to the supra-suprafacial attack during the 'concerted'[14] pericyclic process. In addition, the regiochemistry of the reaction depends on the substituent on both reaction partners. It is possible to predict the regiochemical outcome of the reaction by considering the atomic coefficients of the frontier orbitals.[15] Another feature of the Diels-Alder reaction is the '*endo* rule'.[16] It is possible to predict the stereochemistry of the 'normal' reaction when a dienophile containing an unsaturated substituent(s) is used: The lowest energy transition state has the unsaturated substituent of the dienophile overlapping with the π-system of the diene. In the example in Scheme 1.5, the endo product **1.24** was the favored product. The *endo* versus *exo* selectivity can be well predicted in the intermolecular cases. However, the stereoselectivity of the intramolecular reaction can be '*exo*' or '*endo*' since the lowest energy transition state is greatly affected by the strain created during reaction.

It has been demonstrated that Lewis acids catalyze the Diels-Alder reaction.[17] Furthermore, the Lewis acids can lead to increase selectivity of the reaction. Typically, the affected reactions have a carbonyl substituent on the dienophile. The Lewis acid binds to the carbonyl, thus lowering the energy of the LUMO and accentuating the coefficient of the frontier orbital. Many Lewis acids can be used including $SnCl_4$, $ZnCl_2$ and $AlCl_3$. The influence of $BF_3{\cdot}OEt_2$ was demonstrated in the case of the reaction of cyclopentadiene with dienophile **1.25** (Scheme 1.6).[18] The selectivity for the *endo* product was much greater in the case of the added Lewis acid.

Scheme 1.6-Effect of a Lewis acid on the selectivity of the Diels-Alder reaction



1.22 **1.25** **1.26** (*endo*) **1.27** (*exo*)

	1.26 (*endo*)	**1.27** (*exo*)
No BF_3-OEt_2 (0 °C, benzene)	66	34
10 mol% BF_3-OEt_2 (-20 °C, benzene/toluene)	90	10

The regio- and stereoselectivy of the Diels-Alder reaction has been discussed. To further increase the synthetic utility of the reaction, the facial selectivity can also be addressed. Considering the example shown in Figure 1.2 where the group of substituents A is different from B, the '*endo*' attack can give two possible cycloadducts. By controlling the face of attack, it is possible to control the diastereoselectivity of the reaction. It has been proposed that orbital interactions and steric, torsional and electronic effects can explain the facial selectivity of the Diels-Alder reaction.[19] Although these factors can contribute to good selectivity in some examples, it is not always the case. For this reason, the use of temporary tethers to control the facial selectivity of the Diels-Alder reaction has been developed,[20] with the concept being that the disposable tether renders the intermolecular Diels-Alder reaction into an intramolecular process leading to an increase in the rate and higher selectivity (Figure 1.3). Numerous metal-based temporary tethers have been utilized in the past including Si, Mg, Zn, B, Ti and Al tethers.[21] In 2000, Ward and Abaee reported the Lewis acid-catalyzed Diels-Alder reaction of a 'self-assembled' complex using a magnesium tether (Scheme 1.7).[22] The Lewis acid made it possible to do the Diels-Alder reaction with high regio- and stereoselectivity to produce compound **1.36** in high yield. In 2003, Barriault and co-workers developed a hydroxy-directed Diels-Alder reaction to address the facial selectivity problem of semicyclic dienes (Scheme 1.8).[23] They showed that it was possible to produce Diels-Alder product **1.40** in a stereoselective fashion. A magnesium alkoxide is generated when alcohol **1.37** is treated with magnesium bromide dietherate and a base (triethylamine or 2,6-lutidine). Subsequently, the dienophile forms a complex with the magnesium. The Diels-Alder reaction then proceeds through transition state **1.39** generating cycloadduct **1.40** (12:1 to > 25:1 diastereoselectivity). A variety of substrates and dienophiles were used in the hydroxy-directed Diels-Alder (HDDA) reaction. Thus, a highly stereoselective method to construct bicyclic compounds has been described that addresses the π-facial selectivity of the Diels-Alder reaction. Research in the development of asymmetric Diels-Alder reactions has also focused on the facial selectivity of the reaction.[24] In order to achieve enantioselective Diels-Alder reactions, it is important to control the face attack of either the dienophile or the diene. Chiral cationic Lewis acids that activate dienophiles have been developed and they allow the formation of the cycloadducts with high enantioselectivity. In summary, methods that control the facial selectivity of the Diels-Alder reaction have been established.

Figure 1.2-Facial selectivity of the Diels-Alder reaction

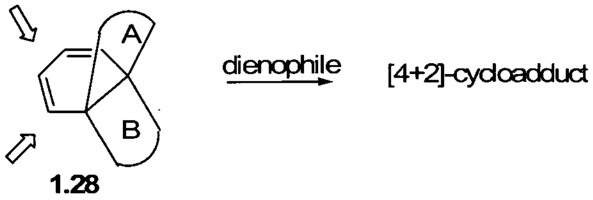
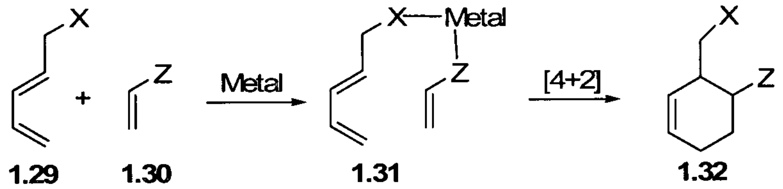
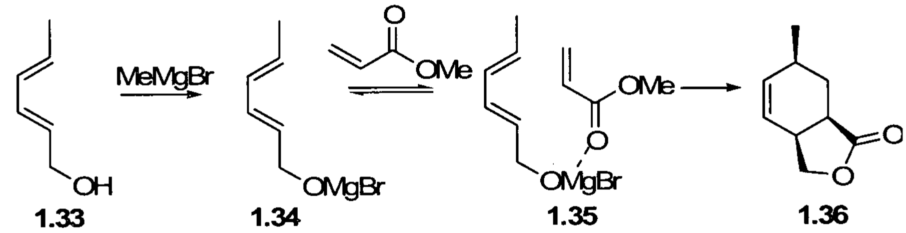


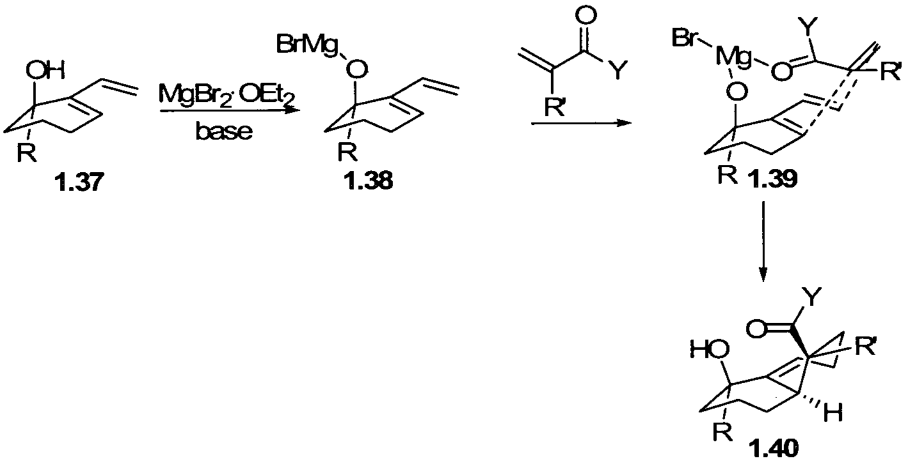
Figure 1.3-Mechanism of the tethered Diels-Alder reaction



Scheme 1.7-Lewis acid-catalyzed Diels-Alder reaction of a 'self-assembled' complex (Ward)



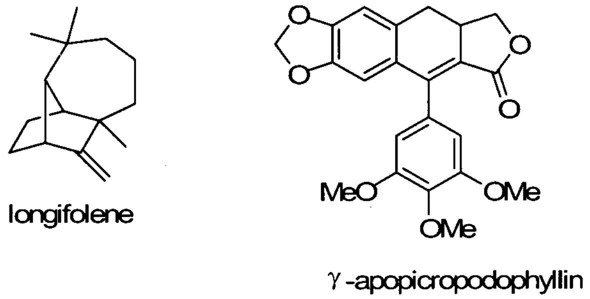
Scheme 1.8-Hydroxy-directed Diels-Alder (Barriault et al.)



Intramolecular Diels-Alder reaction

The intramolecular Diels-Alder reaction is a very useful process that exhibits regiochemical and stereochemical control not seen in the intermolecular variant.[25] The reaction creates molecular complexity in a single step. This is especially noteworthy in the cases where more than one ring is created during the cycloaddition. Consequently, the intramolecular Diels-Alder reaction has been utilized in the synthesis of many natural products.[26] Historically, the first examples of the application of the intramolecular Diels-Alder reaction in synthesis have been reported in 1963 (Figure 1.4). Brieger reported the use of an 'internal Diels-Alder reaction' for the synthesis of longifolene.[27] The same year, Klemm and Gopinath described an intramolecular Diels-Alder reaction for the synthesis of a podophyllotoxin degradation product, γ-apopicropdophyllin.[28]

Figure 1.4-First examples of synthesis using intramolecular Diels-Alder reactions

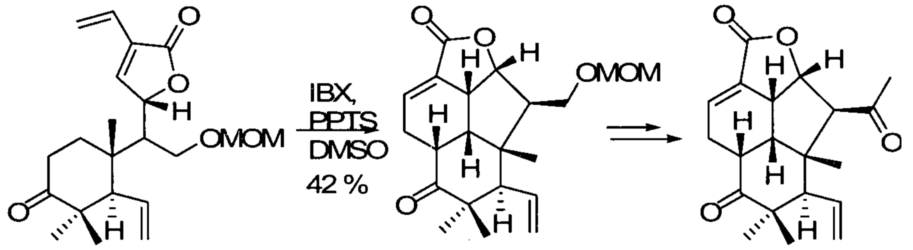


longifolene

γ-apopicropodophyllin

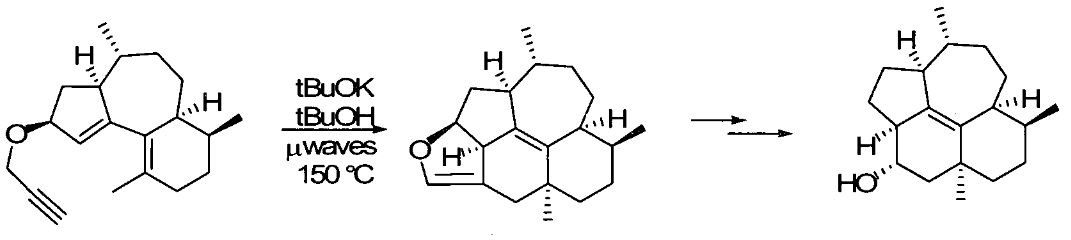
Since the initial reports, numerous syntheses have relied on the intramolecular Diels-Alder reaction. A few recent selected examples are described. Wong and Dong have used the technology in their synthesis of pallavicinolide A (Scheme 1.9).[29] They performed a domino oxidation/Diels-Alder reaction of substrate **1.41** to afford exclusively the tetracyclic molecule **1.42** in 42% yield. The enantioselective synthesis of the diterpene 4-desmethyl-3α-hydroxy-15-rippertene (**1.46**) also utilized an intramolecular Diels-Alder reaction as a key step.[30] Henning and Metz generated the allene by treating substrate **1.44** with potassium *tert*-butoxide. By heating the reaction mixture in the microwave, the desired [4+2] cycloaddition occurred to provide **1.45** with complete diastereoselectivity. Another impressive example of the diastereoselectivity exhibited in the intramolecular Diels-Alder reaction is in the context of the synthesis of yohimbine by Jacobsen and co-workers (Scheme 1.11).[31] They used their enantioselective Pictet-Spengler reaction to synthesize a substrate that was converted to chiral triene **1.47**. Then, the intramolecular Diels-Alder reaction was catalyzed by a scandium Lewis acid to provide the desired product (**1.48**) in 87% yield with a 20:1 diastereoselectivity. It was then possible to convert this product into the natural alkaloid in two steps. The intramolecular Diels-Alder reaction can also be useful for the synthesis of bridged compounds. One example is the synthesis of colombiasin reported by Nicolaou and co-workers (Scheme 1.12).[32] The cheletropic elimination of sulfur dioxide revealed the diene that underwent the [4+2]-cycloaddition to give the bridged core of colombiasin (**1.51**) in 89% yield. These examples illustrate the use of the intramolecular Diels-Alder reaction in the synthesis of complex natural products.

Scheme 1.9-Synthesis of pallavicinolide A (Dong and Wong)



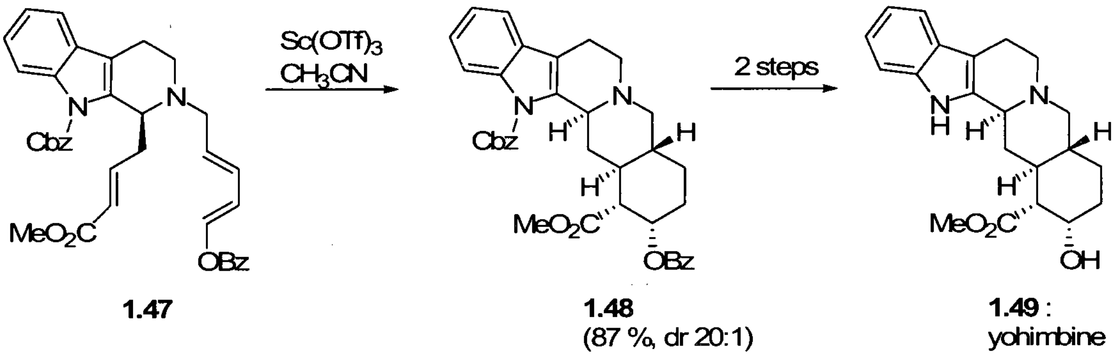
1.41 **1.42** **1.43**: pallavicinolide A

Scheme 1.10-Synthesis of 4-desmethyl-3α-hydroxy-15-rippertene

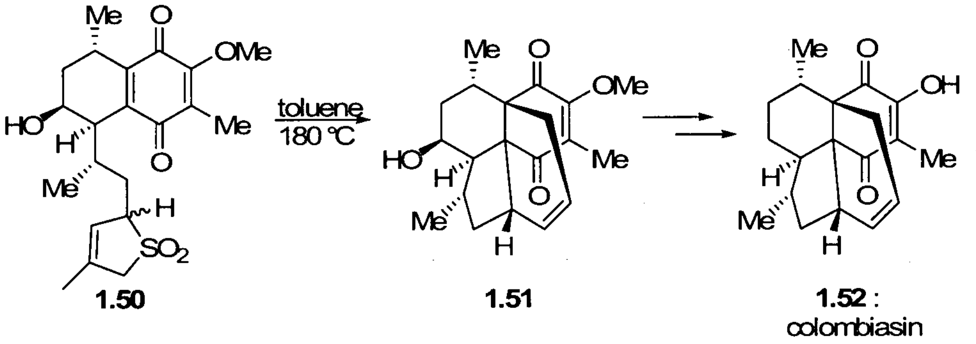


1.44 **1.45** (83 %) **1.46**

Scheme 1.11-Jacobsen's synthesis of yohimbine



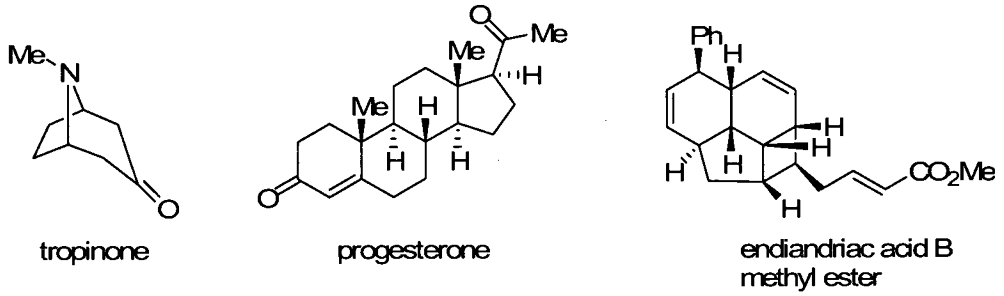
Scheme 1.12-Nicolaou's synthesis of colombiasin



Domino reactions

From the beginning, Nature has been synthesizing complex molecules. Amazingly, natural products containing numerous stereocenters are often isolated as a sole diastereoisomer. This can be attributed to the chirality embedded in the enzymes that synthesize these products. Studies into the biosynthesis of certain natural molecules described efficient processes by which Nature can transform simple substrates into complex molecules, often in one-step. Chemists have recognized the utility and efficiency of these cascading reactions. As a result, biomimetic syntheses have been reported such as tropinone, progesterone and endiandric acid.[33] In addition, various domino reactions have been developed for the synthesis of natural products, biologically active molecules and others.[34] The advantage of domino reactions is the economy and efficiency of the overall process. Indeed, the ability of promoting more than one reaction in a single chemical step diminishes the amount of labor, reagents and waste.

Figure 1.5-Natural products synthesized via biomimetic cascades



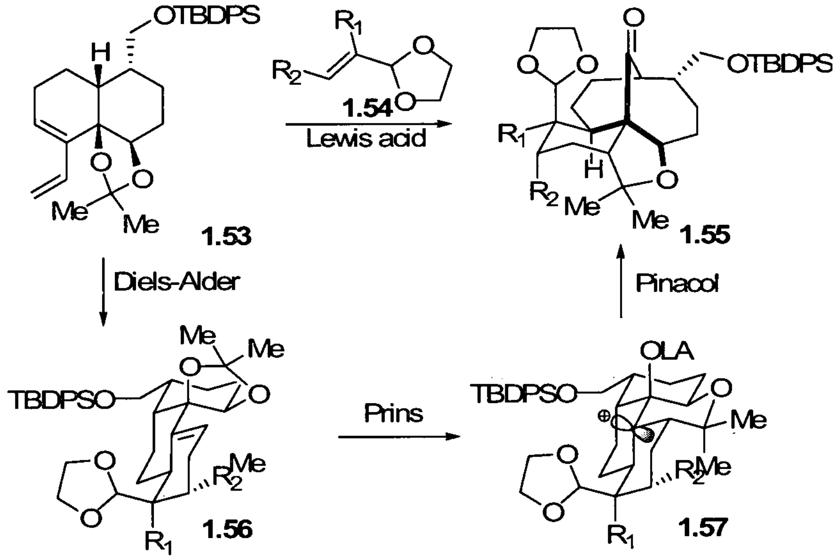
Domino reactions (sometimes called tandem reactions in the literature) are time-resolved transformations where one reaction occurs after the other in a same reaction flask. These cascading processes can include two or more reactions in a single flask. In the strict sense, domino reactions should proceed without the addition of other reagents or modification of the reaction conditions. However, many examples in the literature of cascading reaction have the reaction conditions altered during the process (termed 'one-pot'). As domino reactions, these processes allow the rapid generation of complexity in a single flask.

Chemical transformations can be combined in various ways to provide domino reactions. Examples incorporating cationic, anionic, radical, pericyclic, photochemical and metal-catalyzed reactions have all been reported.[34] Domino reactions comprising of pericyclic reactions are particularly useful in synthesis due to the predictive stereoselectivity. Numerous pericyclic transformations have been combined in order to generate complex molecules: cycloadditions, sigmatropic rearrangements, electrocyclic reactions and ene reactions. In addition, cascading reactions consisting of pericyclic reactions and non-pericyclic processes are numerous and provide unique frameworks.

Selected examples highlighting domino reactions that include a Diels-Alder reaction in the cascade are portrayed here. Barriault and co-workers developed a cationic reaction cascade that transforms bicyclic ketals into bicyclo[m.n.1]alkanones.[35] The rearrangement of the ketal into the bridged compound was believed to proceed via a Prins/pinacol reaction.

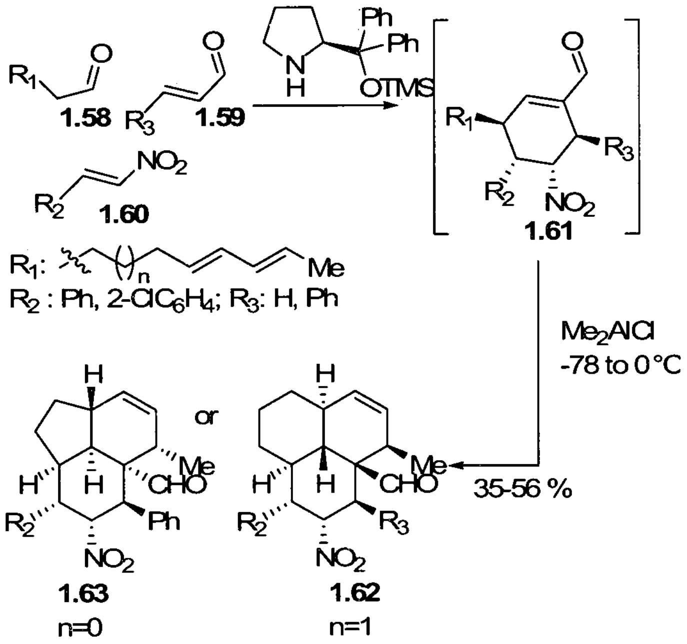
To increase the molecular complexity of the reaction, they expanded their methodology to include a Diels-Alder/Prins/pinacol domino reaction (Scheme 1.13). To this end, they reacted diene **1.53** with Gassman type dienophile **1.54** in the presence of a Lewis acid. The endo cycloadduct **1.56** was formed in-situ and the Prins/pinacol reaction proceeded to give exclusively bicyclo[3.4.1]decanone **1.55** in 44 to 96% yield.

Scheme 1.13-Domino Diels-Alder/Prins-Pinacol reaction (Barriault et al.)



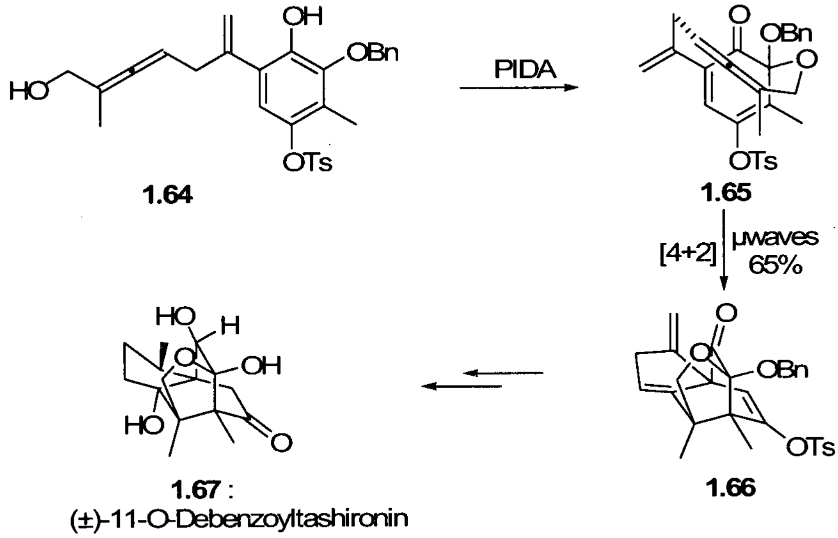
Enders and co-workers combined their useful organocatalyzed enantioselective multicomponent three-step domino reaction with an intramolecular Diels-Alder reaction to access tricyclic carbon frameworks (Scheme 1.14).[36] The organocatalyzed domino Michael/Michael/aldol condensation of aldehyde **1.58**, α,β-unsaturated aldehyde **1.59** and nitroalkene **1.60** gave carbocycle **1.61** as the sole product (de, ee ≥ 99%). The proposed cascade cycle involves enamine catalysis, iminium catalysis and finally, another enamine catalysis.[36a] The intramolecular Diels-Alder reaction proceeds after the addition of a Lewis acid (Me_2AlCl) to afford tricyclic molecules **1.63** (n=0) or **1.62** (n=1) in moderate to high diastereoselectivity.

Scheme 1.14-Enders' domino reaction



In 2006, Danishefsky and co-workers reported the total synthesis of (±)-11-O-debenzoyltashironin using an oxidative dearomatization/transannular Diels-Alder cascade of allenic phenol **1.64**.[37] This transformation constructed the tetracyclic core of (±)-11-O-debenzoyltashironin containing appropriate synthetic handles to enable the group to finish the synthesis.

Scheme 1.15-Synthesis of 11-O-debenzoyltashironin (Danishefsky et al.)



There are numerous other examples of domino reactions incorporating the Diels-Alder reaction in the literature.[25] These reactions are very useful for the total synthesis of natural products. Recent examples include the total synthesis of stenine using a Diels-Alder/Schimdt cascade,[38] vindorosine using a domino [4+2]/[3+2] cycloadditions[39] and the *Strychnos* alkaloids via a Diels-Alder/rearrangement sequence.[40] All the cases mentioned demonstrate the effectiveness of domino reactions for the synthesis of complex molecules. Furthermore, the Diels-Alder reaction has proven to be a very important tool for total synthesis.

Research goals

This thesis describes a journey towards the total synthesis of natural products where the Diels-Alder reaction played a pivotal role. In Chapter 2, the use of the intramolecular Diels-Alder reaction towards the total synthesis of vinigrol is illustrated. Since methodology development and total synthesis are intertwined aspects of organic synthesis, the next chapter focuses on both. A sequential oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction was improved and adapted for the total synthesis of digitoxigenin. These studies led to the discovery of a gold-catalyzed benzannulation, described in Chapter 4. A thesis summary is depicted in Chapter 5 and the experimental procedure and characterization are detailed in Chapter 6.

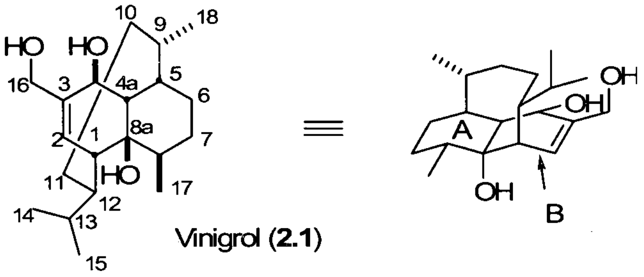
Chapter 2

Towards the Total Synthesis of Vinigrol

Introduction

Ando and coworkers collected a soil sample from the bottom of Mount Aso in Japan that contained the fungal strain Virgaria nigra F-5408. From this species, they were able to isolate a novel diterpenoid named vinigrol (**2.1**).[41] The structure elucidation revealed a unique tricyclic molecule.[42] The compact structure consists of a tricyclo[4.4.4.0^{4a,8b}]tetradecane skeleton with eight continuous stereocenters. In addition to its interesting structure, vinigrol has demonstrated significant biological activity. Ando and co-workers found that vinigrol had antihypertensive and platelet aggregation-inhibiting properties.[41] A few years later, a patent filed by Norris and coworkers indicated that vinigrol was also identified as a tumor necrosis factor (TNF) antagonist.[43] They suggested that vinigrol could be used in the treatment of endotoxic shock, inflammation, cachexia and stop the conversion of AIDS-related complex into AIDS.[43] In 1995, Fujisawa Pharmaceutical Company Limited released a patent suggesting that HIV infectious diseases could be treated by vinigrol.[44] Furthermore, studies have disclosed that vinigrol could also be useful in the treatment of inflammation[45,46] and neurological diseases.[47]

Figure 2.1-Structure of vinigrol

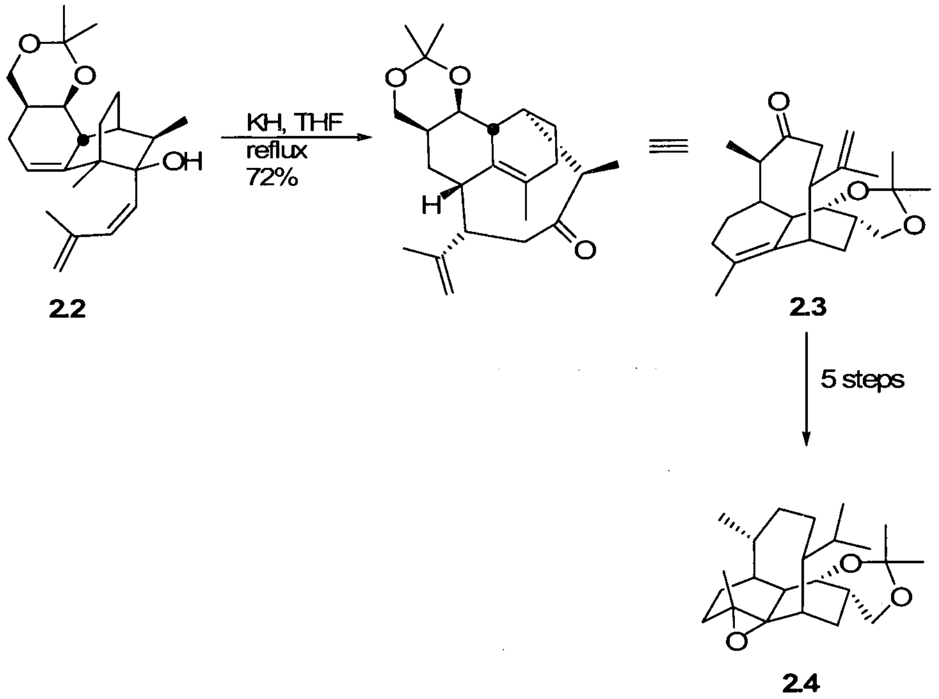


Vinigrol (2.1)

Vinigrol (**2.1**) has presented chemists with a significant synthetic challenge. A cursory inspection of the structure reveals a tricyclic core containing a *cis*-fused [4.4.0] system (namely, rings A and B) bridged by an eight-membered ring and eight contiguous stereocenters. These features in addition to the poly-oxygenated nature of the molecule contribute to the complexity of the natural product. Thus, efforts towards the total synthesis have been numerous in the past fifteen years.[48] Yet, no total synthesis has been reported to date.

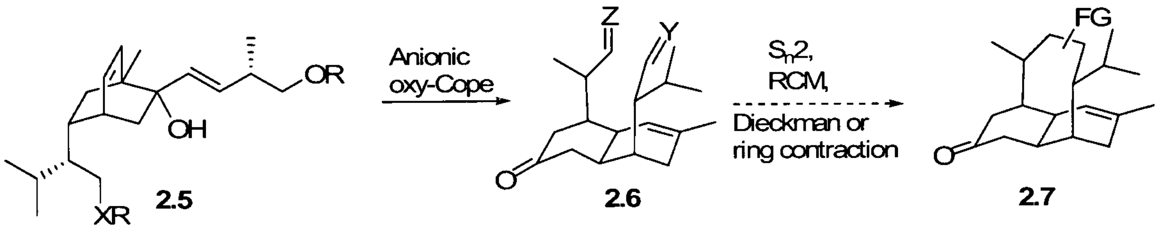
Many strategies have been developed to synthesize the tricyclic core of vinigrol.[49] Hanna and co-workers were the first to synthesize to the complete skeleton of vinigrol.[49a-e] The key step involved an anionic oxy-Cope of a tricyclic vinyl carbinol (**2.2**) (Scheme 2.1). It was possible to functionalize the anionic oxy-Cope product **2.3** into advanced intermediate **2.4**. Although compound **2.4** had all the carbons and the oxygen in the necessary positions for vinigrol, they have not yet reported the total synthesis of the natural product.

Scheme 2.1-Hanna's synthesis of the functionalized tricyclic core



Paquette and co-workers have also used an anionic oxy-Cope in their quest towards the total synthesis of vinigrol (Scheme 2.2).[49h-k] The sigmatropic rearrangement of **2.5** provided *cis*-decalin **2.6** in good yield. Their strategy was to connect the two side chains and form the 8-membered ring. Numerous reactions (S_n2, ring closing metathesis (RCM), Dieckman and ring contractions) were attempted but it was not possible to generate the tricyclic core of vinigrol. They also conducted calculations and found that the major conformer of the *cis*-decalin had the two substituent groups in remote position one from another explaining the difficult ring closing reaction.

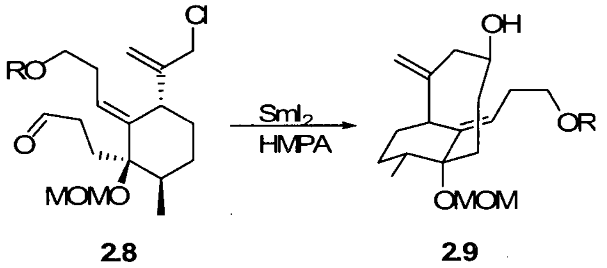
Scheme 2.2-Paquette's attempt at the tricyclic core of vinigrol



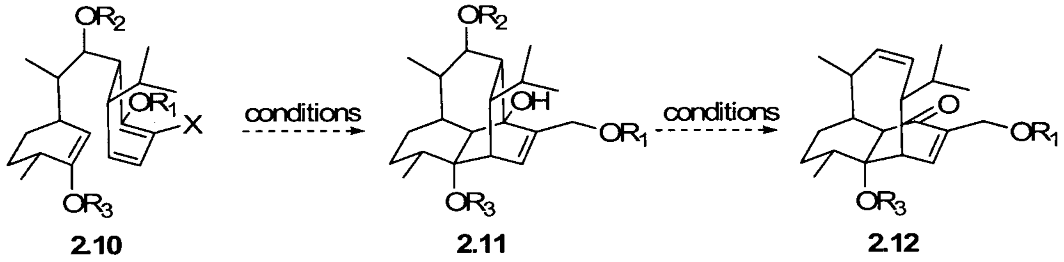
In 1996, Matsuda and co-workers published their approaches towards vinigrol.[49m-n] Using a Barbier SmI_2-mediated cyclization, they generated the *cis*-decalin of vinigrol. Subsequently, they reported the synthesis of bicyclo[5.3.1]undecene **2.9** from precursor **2.8** using the same type of cyclization (Scheme 2.3). Although they had successfully generated two of the rings, they have not disclosed a synthesis of the full tricyclic core of vinigrol.

Goodman and Corey studied a different approach towards the total synthesis of vinigrol (Scheme 2.4).[50] They imagined the intramolecular Diels-Alder reaction of substrate **2.10** to form the tetracyclic molecule **2.11**. Then, a Grob fragmentation would generate the tricyclic core (**2.12**). Unfortunately, all attempts at the intramolecular Diels-Alder reaction were unsuccessful.

Scheme 2.3-Matsuda's approach towards the synthesis of vinigrol



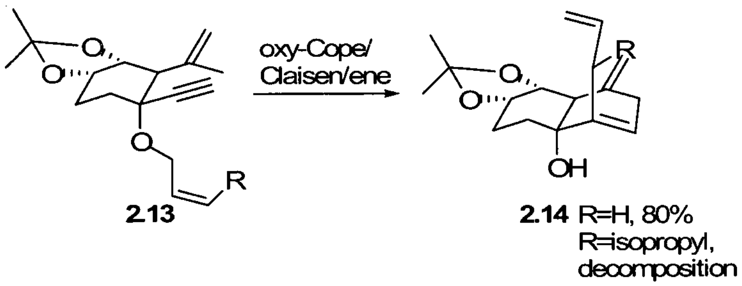
Scheme 2.4-Corey's approach towards the synthesis of vinigrol



In 2002, synthetic efforts towards the total synthesis of vinigrol were initiated in our group. Dr. Louis Morency developed four synthetic routes towards the synthesis of the tricyclic core of vinigrol.[51] In a first approach, a domino microwave reaction of an allyl ether was envisaged to synthesize the *cis*-decalin.[49g] As shown in Scheme 2.5, an oxy-

Cope/Claisen/ene rearrangement of allyl ether **2.13** provided *cis*-decalin **2.14**. If R=H, an excellent yield of 80% was obtained. However, the reaction did not work when R was the necessary isopropyl group. For this reason, a second approach was devised (Scheme 2.6).[49f] A hydroxy-directed Diels-Alder[23] reaction between diene **2.15** and methyl acrylate gave selectively one diastereoisomer that was then functionalized to *cis*-decalin **2.16**. The precursor for the sigmatropic rearrangement (**2.17**) was then obtained after four more steps. With enol ether **2.17** in hand, the Claisen rearrangement was attempted. Thermal conditions as well as hard and soft Lewis acids were screened but the desired product (**2.18**) was not observed.

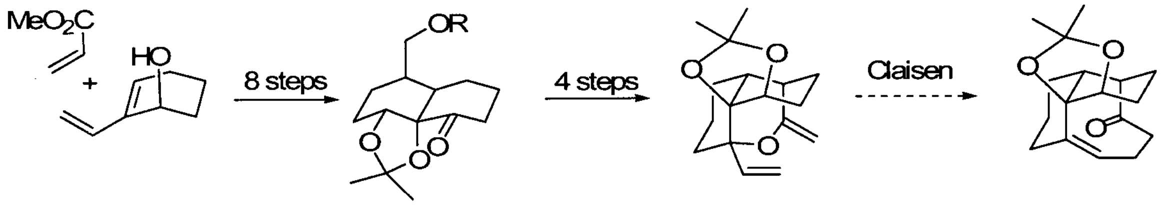
Scheme 2.5-Morency and Barriault's first approach to vinigrol



2.13

2.14 R=H, 80%
R=isopropyl, decomposition

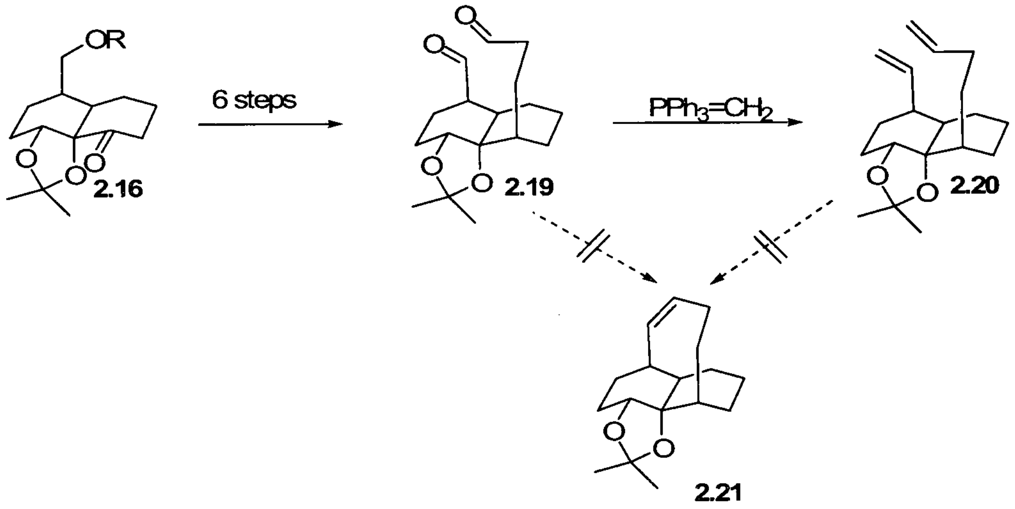
Scheme 2.6-Morency and Barriault's ring expansion strategy



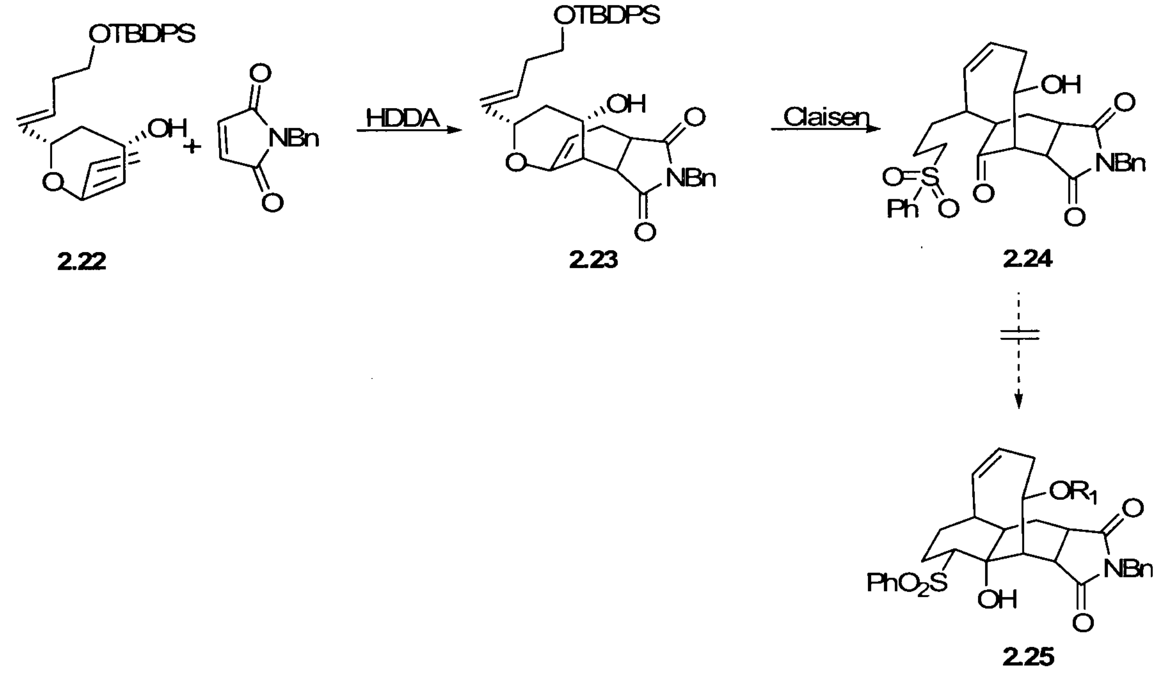
2.15 **2.16** **2.17** **2.18**

At the same time as Paquette and co-workers, Dr. Louis Morency transformed decalin **2.16** into **2.19** and **2.20** to study the construction of the octalin belt by various ring closing reactions (Scheme 2.7). [49f] Since all attempts to close the ring to generate the tricyclic core were unproductive, a fourth strategy was investigated. In 2004, Barriault and co-workers reported an efficient synthesis of bicyclo[5.3.1]undecanone subunits using a sequential hydroxy-directed Diels-Alder/Claisen reaction.[52] This methodology was expanded to synthesize the octalin belt of vinigrol (Scheme 2.8). Accordingly, substituted tetrahydropyran **2.22** was reacted with *N*-phenylmaleimide in the presence of magnesium bromide to afford **2.23** selectively. Then, the Claisen rearrangement occurred upon heating the substrate in the microwave. In order to finish the tricyclic core of vinigrol (**2.25**), an intramolecular alkylation reaction was imagined. Various conditions were tested to close the six-membered ring but none could promote the desired cyclization.

Scheme 2.7-Morency and Barriault's third approach



Scheme 2.8-Morency and Barriault's sequential HDDA/Claisen reaction

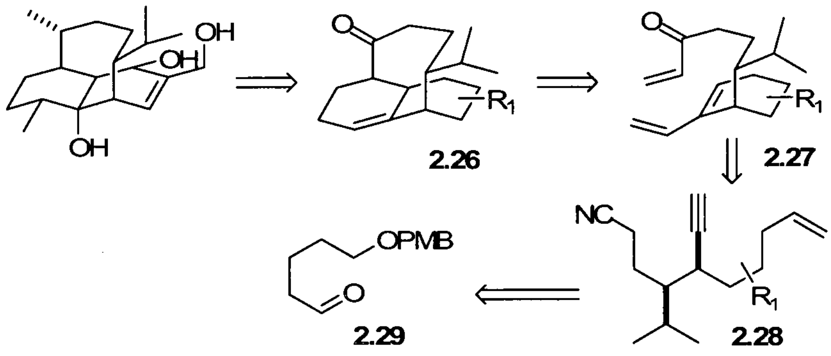


A new approach to vinigrol using the intramolecular Diels-Alder reaction

It was clear that our initial approaches were plagued by the incapacity to form the final eight-membered or six-membered rings via various ring-closing reactions. From our approaches and those reported by the others groups, we learned that the formation of two of the three rings of vinigrol can be achieved without posing serious problems. However, the formation of the third ring, especially the eight-membered ring, via alkylation type reactions or ring closing metathesis remained problematic.[49a,e,h] It was suggested that the preferential conformation and the compact nature of the substrate are the responsible factors that inhibit the desired cyclization.

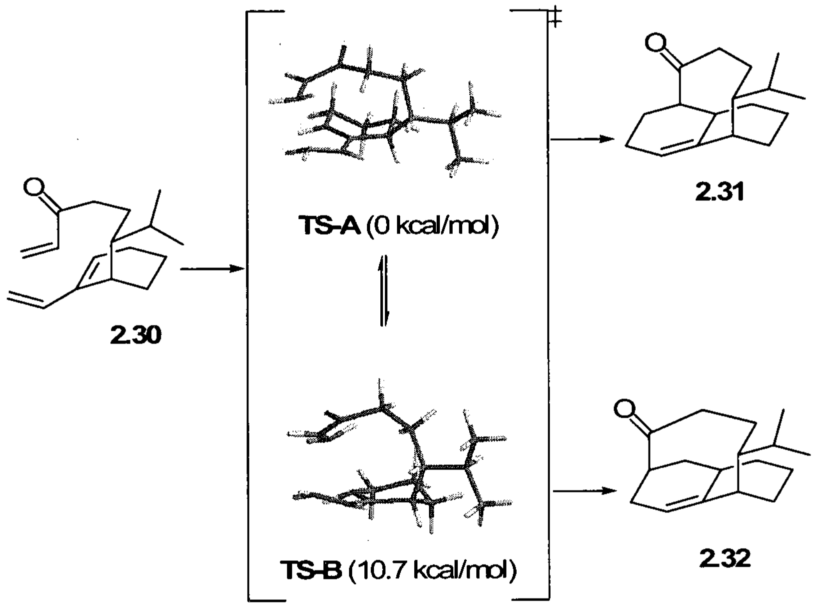
Based on these results, we contemplated the generation of two rings in one step. Thus, we envisaged the synthesis of tricycle **2.26** via an intramolecular Diels-Alder reaction of triene **2.27** (Figure 2.2). The latter could be formed from an enyne metathesis reaction of alkyne **2.28** that could be derived from readily available aldehyde **2.29**.[53]

Figure 2.2-Retrosynthetic analysis



A close inspection of the intramolecular Diels-Alder reaction of semicyclic diene **2.30** revealed that two *endo* cycloadducts **2.31** and **2.32** could be formed (Figure 2.3). At first glance, one might propose that electronic and steric factors should favor the formation of **2.31** over **2.32**. In accordance, DFT calculations of the Diels-Alder reaction of triene **2.30** predicted the exclusive formation of the cycloadduct **2.31** over **2.32** (Figure 2.3). DFT calculations[54] for the gas-phase relative free energies at 298 K were obtained on the Jaguar 6.0 program[55] using Khon-Sham DFT[56] at the B3LYP[57] level of theory with a 6-31G** basis set.[58] It was found that **TS-B** was 10.7 kcal/mol higher in energy than **TS-A**. In order to validate this new approach, we investigated the synthesis of a Diels-Alder precursor of triene **2.30**.

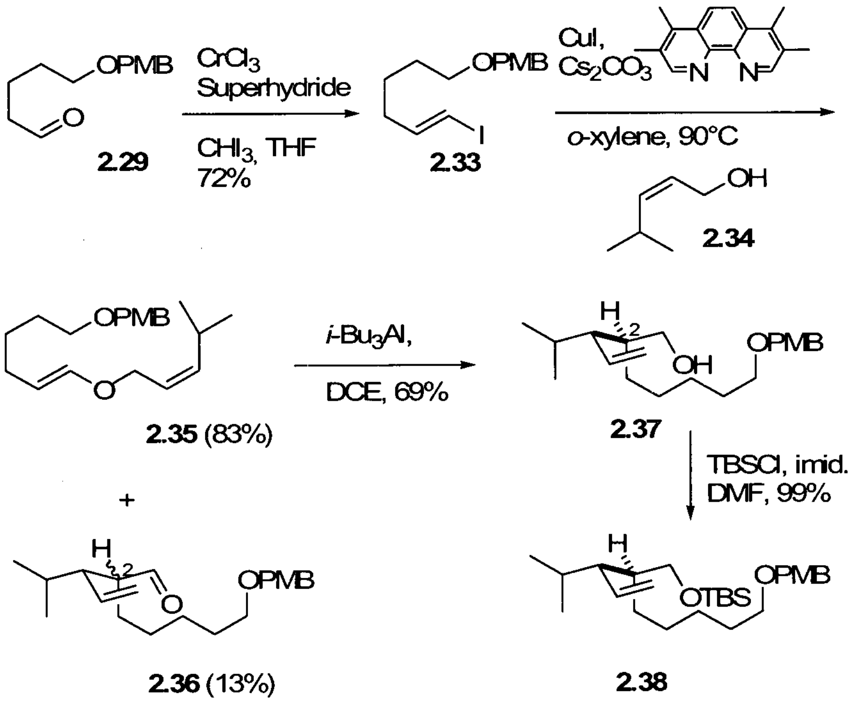
Figure 2.3-Calculations of the transition state energy for both possible mode of attack in the intramolecular Diels-Alder reaction



Proof of principle: Synthesis of the tricyclic core of vinigrol

The synthesis began by a Takai olefination of aldehyde **2.29** to give vinyl iodide **2.33** in 72% yield (Scheme 2.9).[59] Buchwald's copper-(I) mediated coupling[60] between iodide **2.33** and alcohol **2.34**[61] in the presence tetramethylphenantroline and cesium carbonate at 90 °C led to the desired enol ether **2.35** in 83% yield along with aldehyde **2.36** in 13% yield as a mixture of epimers at C2. This reaction was particularly sensitive to the thermal conditions as a slight increase of the temperature above 90 °C led to a significant increase in the amount of the Claisen rearrangement product **2.36**. Owing to the facile epimerization of the resulting aldehyde **2.36**, we turned our attention toward the use of a Lewis acid that will catalyze the sigmatropic rearrangement and at the same time reduce the aldehyde moiety. To this end, enol ether **2.35** was subjected to triisobutylaluminum in dichloroethane to give alcohol **2.37** in 69% yield as the sole detectable diastereomer.[62] Protection of the primary alcohol as a siloxyether using TBSCl and imidazole in THF provided **2.38** in 99% yield.

Scheme 2.9-Installation of the correct stereochemistry via a Claisen rearrangement



At this point, we envisaged the conversion of olefin **2.38** to an unsaturated nitrile through a cross metathesis reaction, after which hydrogenation should give nitrile **2.40** (Scheme 2.10). We scanned several ruthenium carbene catalysts in various solvents.[63] In all cases, the formation of the desired cross-metathesis product was not observed, only starting material was recovered. Other coupling partners such as methyl acrylate and *N,O*-dimethyl acrylamide were tried without success. To circumvent this problem, olefin **2.38** was treated with a borane reagent followed by an oxidative work-up to give the corresponding primary alcohol. Initially, the reaction was performed with borane-dimethyl sulfide complex with a 42% isolated yield. To optimize the reaction conditions, different reagents were tried with various oxidative work-ups (Table 2.1). Catecholborane did not give any desired product (entry 2). In contrast, the product was obtained in 66% yield when 9-BBN dimer was used (entry 3). The optimal conditions were found by varying the number of equivalents of each reagent (entries 4-6) and the temperature of the oxidative work-up. Thus, hydroboration gave the desired alcohol in 73% yield (entry 6) or it could be used crude in the next step.

Tosylation afforded compound **2.39** in 66% yield over two steps. Treatment of **2.39** with sodium cyanide and 18-crown-6 ether in acetonitrile led to nitrile **2.40** in 97% yield.

Scheme 2.10-Functionalization of the alkene

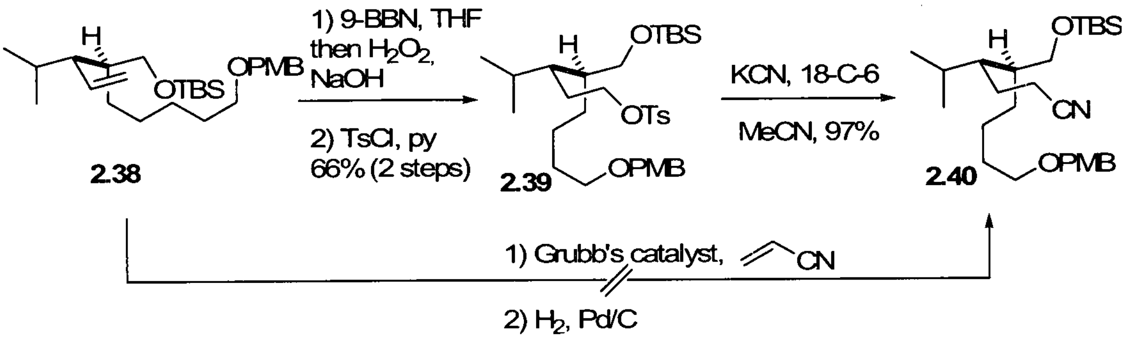
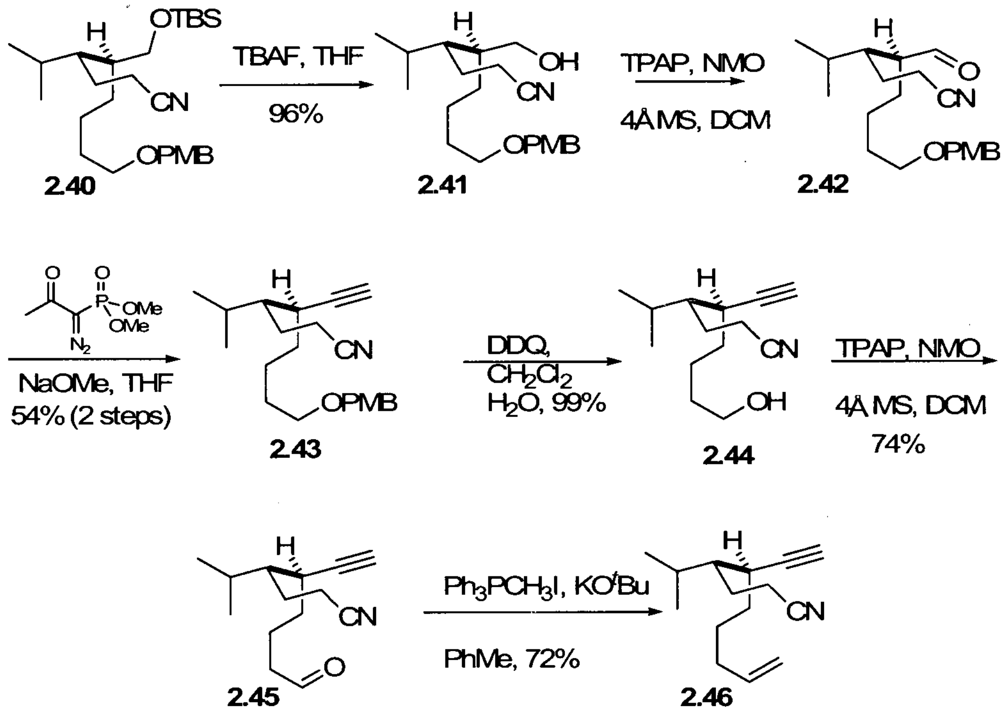


Table 2.1-Hydroboration conditions

Entry	Borane reagent (equiv)	Oxidative work-up	Yield (%)
1	BH_3-DMS (1.5)	NaOH (2.0 equiv) H_2O_2 (2.0 equiv) Reflux	42
2	Catecholborane (1.5)	N/A	SM
3	9-BBN dimer (1.5)	NaOH (4.0 equiv) H_2O_2 (4.0 equiv) Reflux	66
4	9-BBN dimer (1.2)	NaOH (16 equiv) H_2O_2 (48 equiv) 23 °C	70
5	9-BBN dimer (0.55)	NaOH (16 equiv) H_2O_2 (48 equiv) 23 °C	25 + recovered SM (47)
6	9-BBN dimer (1.05)	NaOH (2 equiv) H_2O_2 (4 equiv) 23 °C	73

Removal of the TBS group in the presence of fluoride anion gave alcohol **2.41** in 96% yield (Scheme 2.11). TPAP/NMO oxidation of **2.41** generated the corresponding aldehyde, which was immediately subjected to a solution of dimethyl (1-diazo-2-oxo-propyl)-phosphonate and K_2CO_3 in MeOH (Ohira's protocol).[64] The desired alkyne **2.43** was obtained, although, as a mixture of epimers at C2. In fact, treating aldehyde **2.42** with potassium carbonate in methanol led to epimerization of the aldehyde. This problem was solved using a modified version of the Ohira's protocol.[65] The sensitive aldehyde was treated with dimethyl (1-diazo-2-oxo-propyl)-phosphonate in the presence of sodium methoxide in THF to provide the desired alkyne **2.43** as the sole diastereomer in 54% yield over two steps (64% brsm). Removal of the PMB group with DDQ followed by TPAP oxidation alcohol provided aldehyde **2.45** in 74% yield for two steps. Wittig olefination using the typical conditions of KHMDS and Ph_3PCH_3I gave the desired product but the yield was not reproducible (18-63%). Gratifyingly, conditions developed by Conia proceeded smoothly to afford **2.46** in 72% yield.[66]

*Scheme 2.11-Functionalization into enyne **2.46***



Transformation of enyne **2.46** to diene **2.47** using 10 mol% of Grubbs' second generation catalyst was achieved in 89% yield (Scheme 2.12).[67] Attempts to convert directly nitrile **2.47** to the corresponding enone **2.30** employing alkylating agents (vinyl magnesium bromide, vinyl lithium) in the presence of various additives (copper salts, $BF_3{\cdot}OEt_2$, TMSCl) were fruitless. Nevertheless, the formation enone **2.30** was realized over a three steps sequence. Dibal-H reduction of the nitrile group gave aldehyde **2.48** in 73% yield. Subjection of the latter to vinyl magnesium bromide afforded the corresponding allylic alcohol, which upon exposure to TPAP and NMO led to enone **2.30** in 30% yield over two steps. Treatment of enone **2.30** with $BF_3{\cdot}OEt_2$ in dichloromethane at –78 °C gave the cycloadduct **2.31** in nearly quantitative yield. 2-D NMR experiments such as NOESY, COSY, HMQC and HMBC confirmed the correct carbon-carbon connectivity of structure **2.31** (Figure 2.4).

Scheme 2.12-Synthesis of the tricyclic core of vinigrol

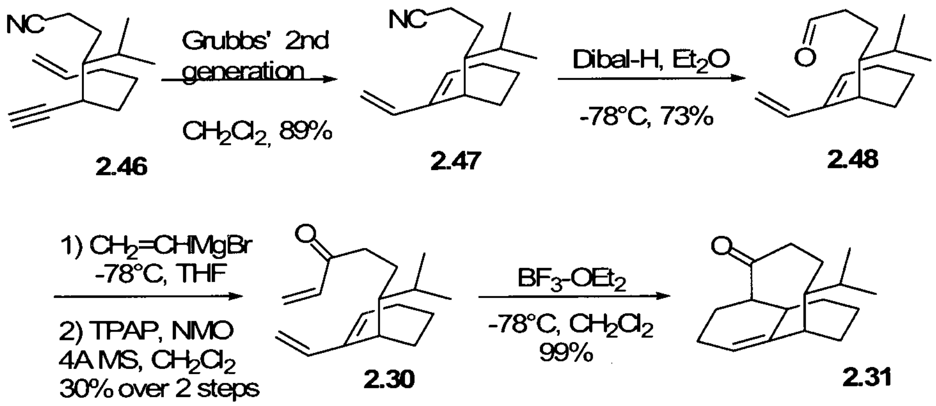
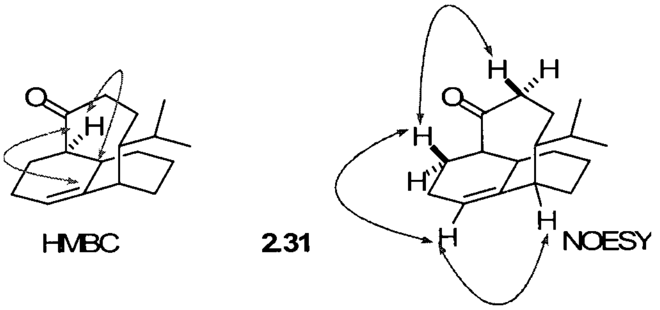
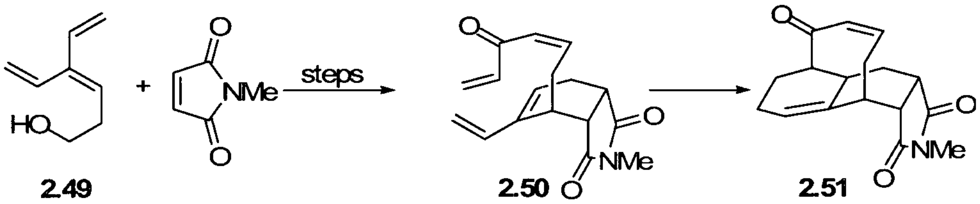


Figure 2.4- Sample correlations for ***2.31***

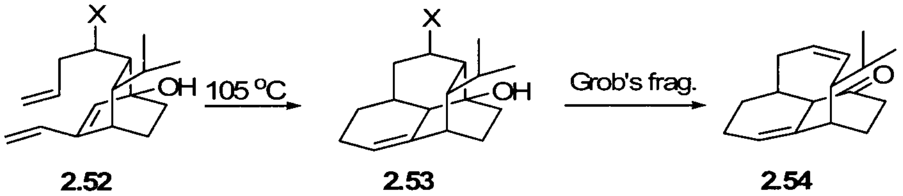


Since our publication in 2007, two other groups have demonstrated the use of the intramolecular Diels-Alder reaction as a powerful key step en route to the tricyclic core of vinigrol. Fallis and co-workers applied their Lewis acid catalyzed and self-assembled Diels-Alder reaction to generate cyclic diene **2.50** (Scheme 2.13).[68] Functionalization of this diene followed by an intramolecular Diels-Alder reaction gave the tricyclic core of vinigrol (**2.51**). Subsequently, Baran and co-workers reported a strategy reminiscent of Corey and Goodman using an intramolecular Diels-Alder cycloaddition followed by a Grob fragmentation to generate the carbon skeleton of the natural product (Scheme 2.14).[69]

Scheme 2.13-Synthesis of the tricyclic core (Fallis, 2007)



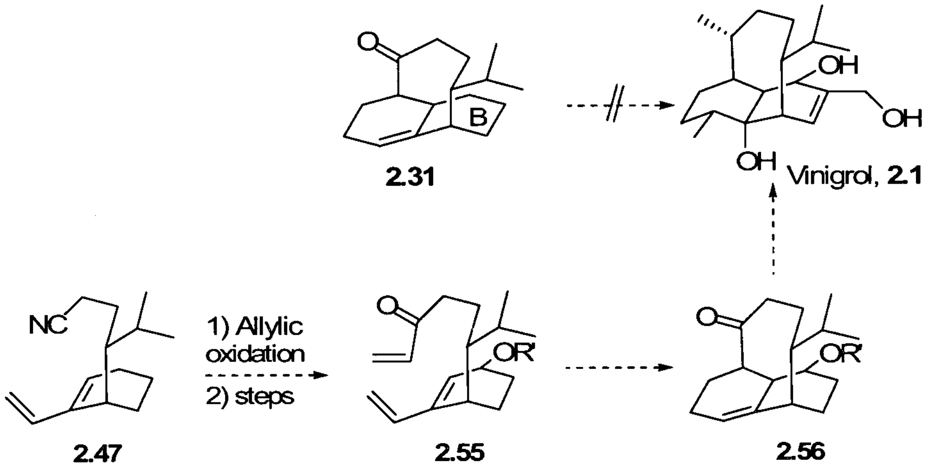
Scheme 2.14-Synthesis of the tricyclic core (Baran, 2008)



In summary, a successful synthesis of the tricyclic core of vinigrol has been described. Our approach took advantage of a highly regioselective intramolecular Diels-Alder of the semicyclic diene **2.30** to construct simultaneously two rings of the tricyclic vinigrol skeleton.

This study demonstrated that an intramolecular Diels-Alder reaction was a viable approach towards vinigrol. However, the natural product could not be derived from **2.31** since there was no functionality on the B ring (Scheme 2.15). One could imagine performing an allylic oxidation on substrate **2.47**. After transformation of the nitrile to an enone, Diels-Alder precursor **2.55** should be achieved. Intramolecular Diels-Alder reaction of substrate **2.55** should give access to **2.56**, which has all the necessary functionalities for the synthesis of vinigrol. Although this was a feasible approach to installing the functionality, we were concerned with the allylic oxidation reaction and the low yield obtained for the conversion of the nitrile into the dienophile. Thus, we believed that a route where the oxygen was introduced earlier in the sequence should be better.

Scheme 2.15-Applying the intramolecular Diels-Alder reaction to the total synthesis

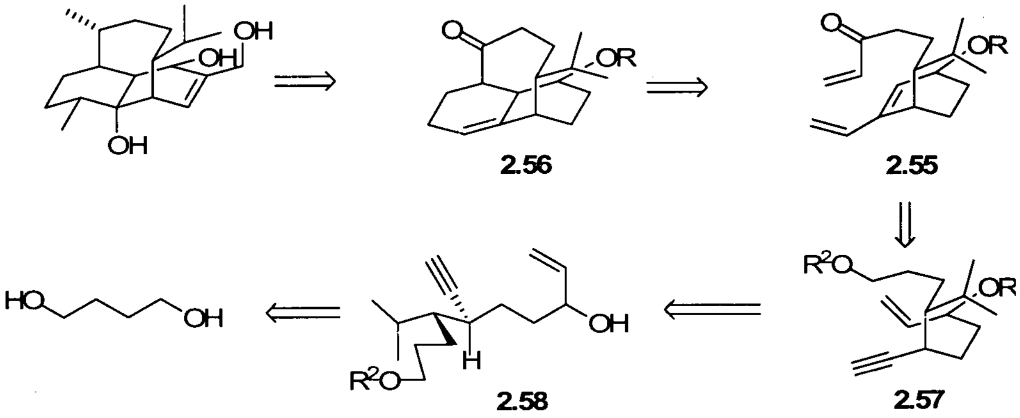


Synthesis of the functionalized tricyclic core of vinigrol

Route 1: Pivaloate as a protecting group

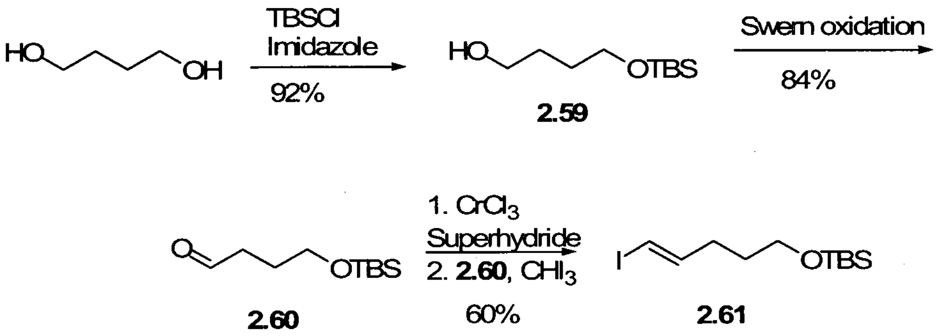
In order to synthesize the functionalized core of vinigrol, a general approach similar to the one used to generate the unsubstituted core was formulated. The retrosynthesis is presented in Figure 2.5. Accordingly, an intramolecular Diels-Alder reaction of **2.55** should provide the functionalized tricyclic carbon skeleton of vinigrol. The six-membered ring diene could be obtained via an enyne metathesis of substrate **2.57** that already contains the extra functionality needed. Finally, enyne **2.58** could come from 1,4-butanediol using the Claisen rearrangement to install the correct relative stereochemistry.

Figure 2.5-Adapted retrosynthetic analysis

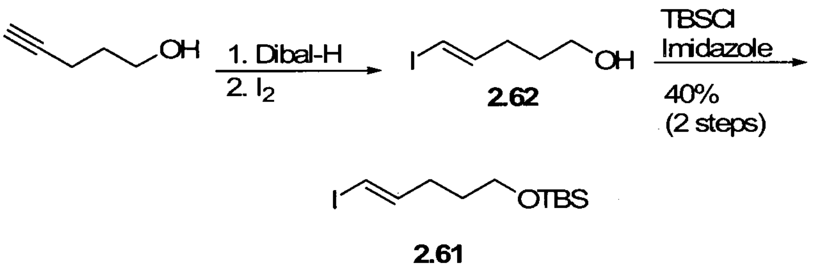


To start the synthesis, vinyl iodide **2.61** and alcohol **2.66** needed to be synthesized. Both molecules could be obtained from 1,4-butanediol. Firstly, monoprotection of the diol with TBSCl and imidazole in DMF gave alcohol **2.59** in 92% yield (Scheme 2.16). This alcohol was oxidized using the Swern protocol to afford aldehyde **2.60** in 84% yield. Vinyl iodide **2.61** was obtained in 60% yield by a Takai reaction in THF with the aldehyde. The vinyl iodide was impure with 14% of the *Z*-isomer. The Takai reaction was attempted in a solvent mixture of 3:1 dioxanes:THF to improve the ratio but the vinyl iodide was obtained in only 16% yield with 30% of the *Z*-isomer. To improve the synthesis of vinyl iodide **2.61**, known procedures were followed (Scheme 2.17).[70,71] Commercially available 4-pentyn-1-ol was treated with Dibal-H followed by iodine to provide vinyl iodide **2.62** as sole isomer. Protection using TBSCl and imidazole gave the desired product, **2.61**, in 40% yield over two steps.

Scheme 2.16-Synthesis of vinyl iodide ***2.61***

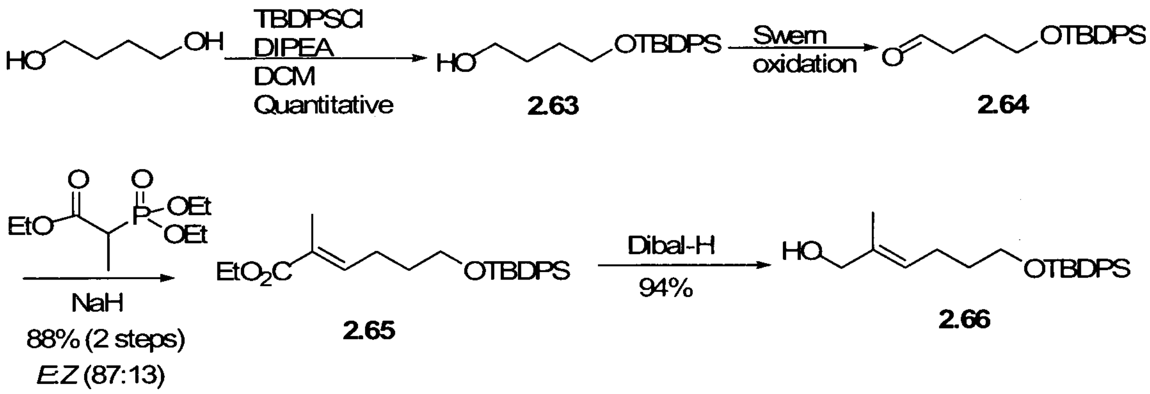


Scheme 2.17-Synthesis of vinyl iodide ***2.61****-Second approach*



The synthesis of alcohol **2.66** started with monoprotection of 1,4-butanediol with TBDPSCl and DIPEA in dichloromethane in quantitative yield. Oxidation followed by a Horner-Wadsworth-Emmons olefination gave the desired known ester[72] in 88% yield over two steps. The mixture of *E* and *Z* isomers was used in the next step. Reduction of ester **2.65** with Dibal-H gave the alcohol **2.66** in 94% yield and the desired isomer could be separated from the minor *Z* isomer. It became common practice to perform the reduction on crude ester **2.65** to afford the desired alcohol in 70% yield over 3 steps.

Scheme 2.18-Synthesis of allylic alcohol ***2.66***



Having the vinyl iodide and the alcohol in hand, the copper-catalyzed C-O coupling was attempted (Scheme 2.19). The first trial was done using the optimized conditions found for vinyl iodide **2.33** and alcohol **2.34**. The coupling product, enol ether **2.67**, was obtained as well as aldehyde **2.68**. It appeared that the Claisen rearrangement of **2.67** was much more facile at 90 °C in *o*-xylenes than in the case of enol ether **2.35**. Thus, a 1:1 ratio was obtained of the desired enol ether and aldehyde **2.68**. Yet again, a mixture of epimers of **2.68** was observed since the coupling is done under basic conditions. Thus, various reaction temperatures and solvents were explored to minimize aldehyde formation while achieving the coupling reaction (Table 2.2). Lowering the temperature to 80 °C with 3.6 equivalents of alcohol **2.66** in *o*-xylenes gave exclusively enol ether **2.67** (entry 2). However, the reaction only proceeded to 60% conversion after 2 days. By lowering the temperature even more to 70 °C and leaving the reaction for 3 days, the reaction did go to completion and there was no aldehyde **2.68** present (entry 3). However, it was found that alcohol **2.66** was oxidized to aldehyde **2.69** (Figure 2.6) under the reaction conditions. Since it was advantageous to recover the excess alcohol at the end of the reaction, we looked at changing the solvent and increasing the temperature to minimize the reaction time (entry 4). Thus, the best reaction conditions found (80 °C for 18 hours in toluene) gave the enol ether in 65% yield.

Scheme 2.19-Copper-catalyzed C-O coupling

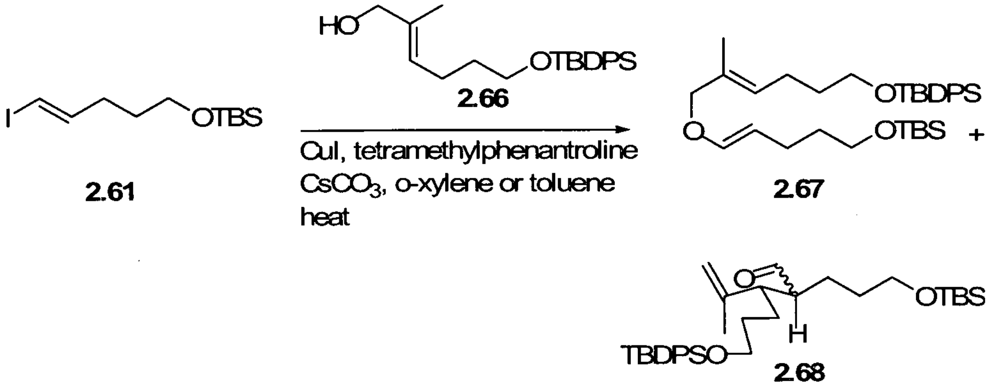
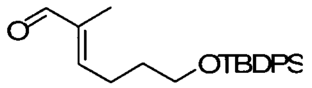


Table 2.2-Copper-catalyzed C-O coupling

Entry	Conditions[a] (equiv)	Solvent	Temperature (°C)	Time	Ratio **2.61**:**2.67**:**2.68**	Yield (%)
1	**2.66** (2.8) $CsCO_3$ (3.0)	*o*-xylenes	90	3 days	0: 1: 1	38
2	**2.66** (3.6) $CsCO_3$ (3.0)	*o*-xylenes	80	2 days	0.7: 1: 0	46
3	**2.66** (3.0) $CsCO_3$ (3.0)	*o*-xylenes	70	3 days	0: 1: 0	55
4	**2.66** (3.0) $CsCO_3$ (3.0)	Toluene	80	1 day	0: 1: 0	65

[a] All reactions were done with CuI (10 mol%) and tetramethylphenantroline (20 mol%) in 1 M solution of the solvent

Figure 2.6-Side product observed in the coupling reaction



2.69

The necessary relative stereochemistry was installed using a stereoselective Claisen rearrangement. Since the sigmatropic rearrangement proceeds through a chair-like transition state, a single isomer of the product should be observed. The Claisen rearrangement of **2.67** was performed in the presence of triisobutylaluminum to give **2.70** in 61% yield (Scheme 2.20). Next, hydrogenation of the double bond was necessary in order to generate the isopropyl group. Although hydrogenation of isopropenyl groups was well documented,[73] the reaction was problematic (Table 2.3). Hydrogenation with Pd/C with a balloon of hydrogen gave a maximum of 50% conversion (entries 1-2). Generating hydrogen in situ from ammonium formate did not give any desired product even upon heating (entry 4). Raney nickel gave a conversion of 85% but a large amount of catalyst was needed (entry 3). Promising results were obtained with palladium hydroxide. The reaction proceeded to 75% conversion with 10 mol% of catalyst (entry 5). However, when the reaction was done in ethanol, the TBS group was removed and diol **2.72** was obtained (Scheme 2.21). A paper published by Hirota and coworkers reported the loss of the TBS protecting group when hydrogenation was performed in ethanol.[74] Although they do not provide a mechanistic rationale for their observation, they mentioned that running the reaction in ethyl acetate or acetonitrile prevented this side reaction from occurring. In ethyl acetate, the reaction went to 50% conversion but the TBS group was still intact (entry 6). In acetonitrile, the reaction went to completion (entry 7). However, analysis of the carbon NMR showed the presence of two isomers. Looking carefully to the carbon NMR of diol **2.72**, it was also noticed that two isomers were also present. To eliminate the possibility that the protecting group had migrated, diol **2.72** was treated with TBAF. Again, analysis of triol **2.73** showed the presence of two isomers. To explain this isomerization, it was believed that the Pd-H inserts into the alkene but β-hydride elimination occurs to generate the tetrasubstituted olefin. Again, Pd-H inserts into the bond and β-hydride elimination occurs again to give back the original alkene but the chiral center was epimerized in the process. To solve this problem, the more reactive platinum oxide catalyst was tested and fortunately, the desired product (**2.71**) was obtained as a sole isomer (entry 8). Gratifyingly, hydrogenation of alkene **2.70** could be done reproducibly using 10 mol% of PtO_2 in freshly distilled ethyl acetate in 94% yield.

Scheme 2.20-Installation of the desired stereochemistry

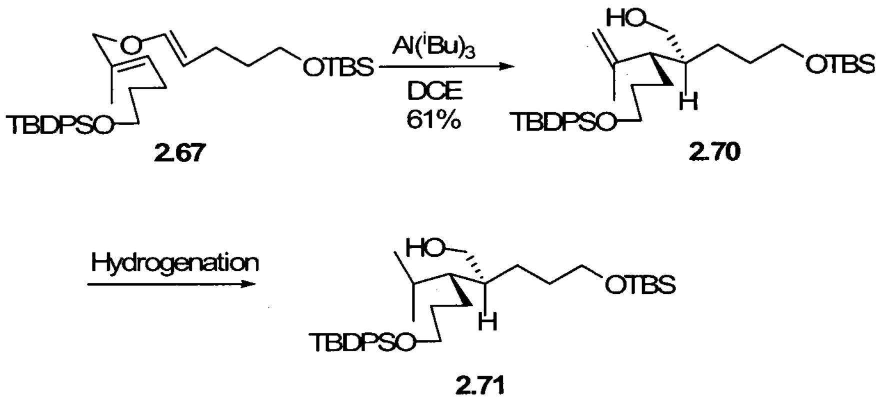


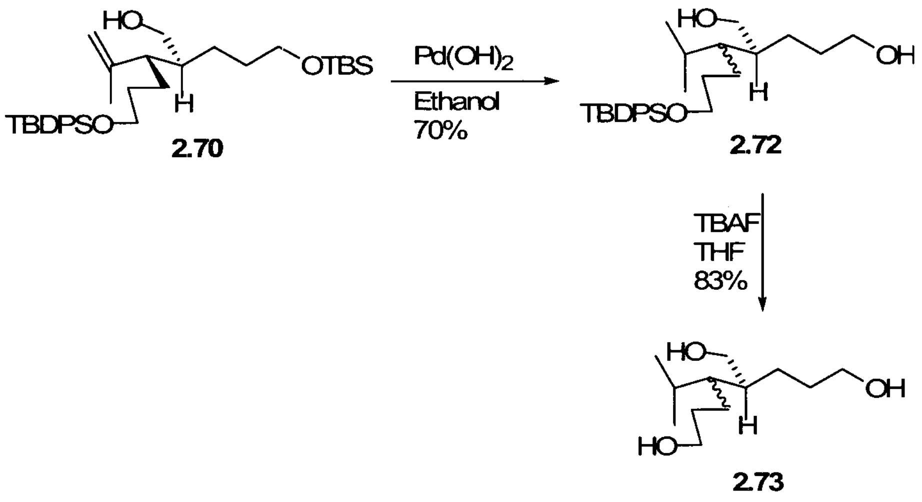
*Table 2.3-Hydrogenation of alkene **2.70***

Entry	Catalyst (mol%)	Hydrogen source	Solvent	Result
1	Pd/C (1)	H_2 (1 atm)	MeOH	SM
2	Pd/C (10)	H_2 (1 atm)	EtOH	50% conversion
3	Raney Nickel (110)	H_2 (1 atm)	EtOH	85% conversion
4	Pd/C (10)	Ammonium formate (40 °C)	MeOH	SM
5	$Pd(OH)_2$ (10)	H_2 (1 atm)	EtOH	75% conversion but cleaves TBS group[a]
6	$Pd(OH)_2$ (15)	H_2 (1 atm)	EtOAc	50% conversion
7	$Pd(OH)_2$ (20)	H_2 (1 atm)	ACN	100% conversion 64% yield (mix)[a]
8	PtO_2 (50)[b]	H_2 (1 atm)	EtOAc	100% conversion 63% yield (clean)

[a] A mixture of isomers was detected by C^{13} NMR.

[b] It was not intended to put 50 mol% but it was a very small amount of catalyst

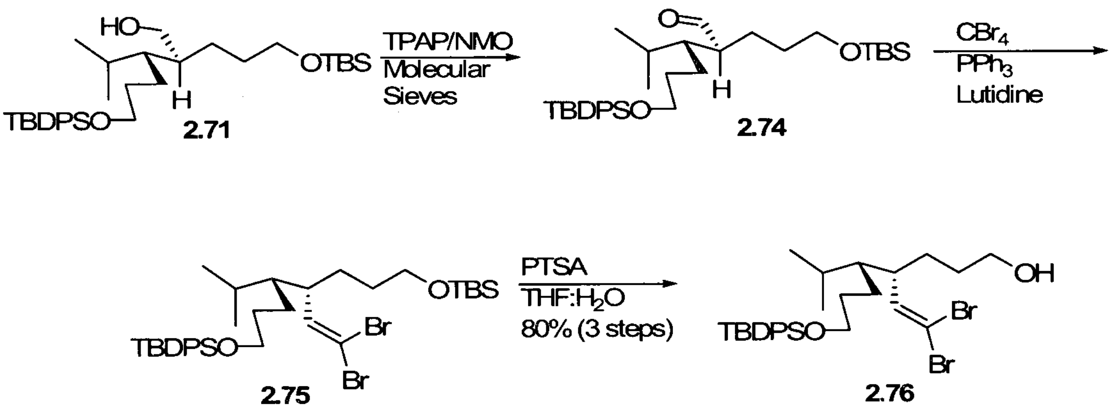
Scheme 2.21-Hydrogenation using palladium hydroxide



At that point in the synthesis, the two stereogenic centers had been introduced using the Claisen rearrangement and conditions to perform the hydrogenation had been found. To synthesize the precursor for the enyne metathesis, functionalization was needed. Firstly, alcohol **2.71** was oxidized using a ruthenium-catalyzed method to unstable aldehyde **2.74** that was used directly in the next step (Scheme 2.22). The aldehyde functionality needed to be converted into an alkyne. The first attempt using the dimethyl (1-diazo-2-oxo-propyl)-phosphonate (Ohira's reagent) and sodium methoxide as the base yielded only 33% of the desired product with 34% of recovered starting material.[64] The 2-step protocol to generate alkynes from aldehydes developed by Corey and Fuchs was thus investigated.[75] The first step was the formation of dibromide **2.75**. Due to the acid sensitive TBS protecting group, it was necessary to add a base in order to prevent deprotection of the primary alcohol.[76] However, addition of a base was problematic since it slowed down the reaction and could potentially racemize the chiral center adjacent to the aldehyde. 2,6-Lutidine proved to be superior to triethylamine. In addition, the number of equivalents had a considerable effect on the yield. The optimal conditions were 2.0 equivalents of 2,6-lutidine, 2.0 equivalents of carbon tetrabromide and 4.2 equivalents of triphenylphosphine. The second step of the Corey-Fuchs was transformation of the dibromide into the alkyne using *n*-BuLi. This reaction was sensitive to the purity of the dibromide. However, purification of dibromide

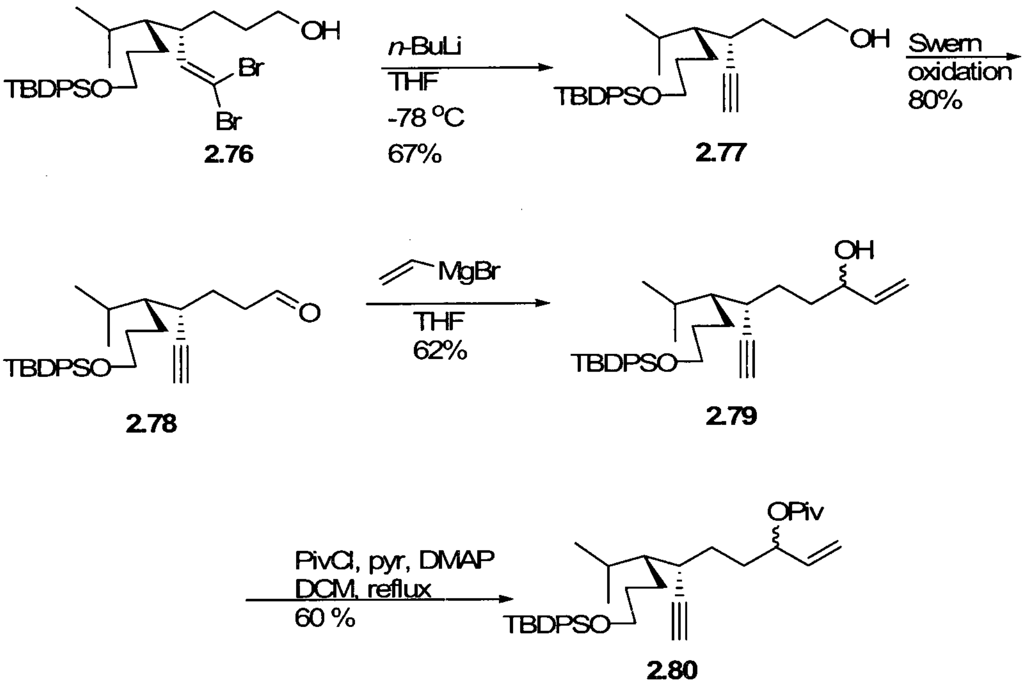
2.75 gave low yields. Thus, selective deprotection of the TBS group using PTSA in THF and water gave dibromide **2.76** in 80% yield over three steps.

*Scheme 2.22-Formation of dibromide **2.76***



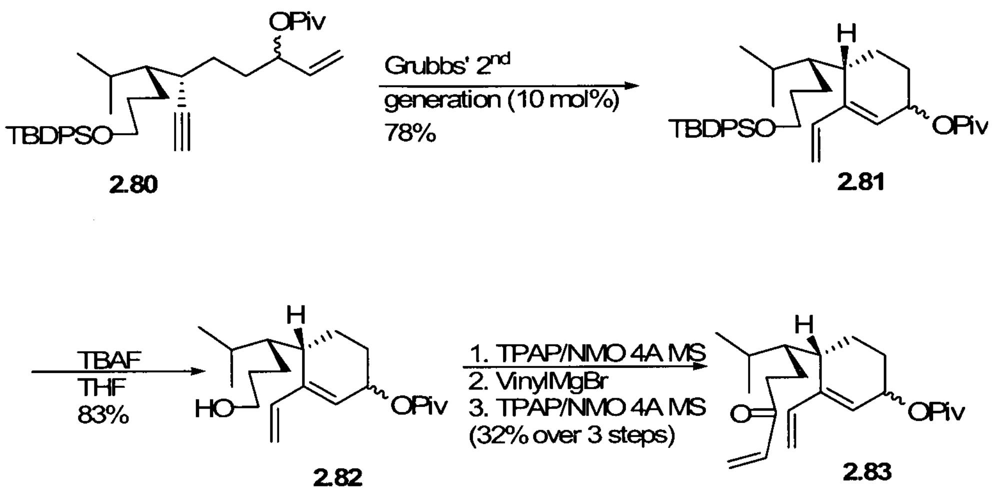
Having pure dibromide **2.76**, the second step of the Corey-Fuchs was accomplished using an excess of *n*-BuLi at -78 °C in 67% yield (Scheme 2.23). Oxidation of the alcohol using a Swern oxidation gave aldehyde **2.77** in 80% yield, which was vinylated to provide **2.78** in 62% yield as a mixture of diastereoisomers. Protection of the secondary alcohol proved to be more difficult than initially anticipated. The alcohol was treated with 2-methoxy-propene in the presence of PTSA to install a MOP group but no desired product was observed. Next, various conditions were tried in order to install a PMB group (PMBCl/NaH; PMBCl/NaH/NaI; PMBCl/KOH/DMSO) but only starting material was recovered. Fortunately, it was possible to install a pivaloyl ester using pivaloyl chloride, pyridine and DMAP and heating at reflux in dichloromethane for 18 hours. The desired product was obtained in 60% yield. It was later found that better yields were obtained if alcohol **2.76** was subjected to all the steps leading to product **2.80** and only one purification at the end (35-37% yield over 4 steps).

Scheme 2.23-Further functionalization



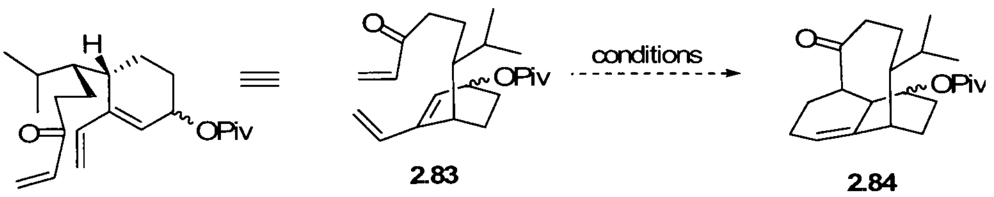
The synthesis of precursor **2.80** being complete, the first key step was tested with a functionalized precursor. Gratifyingly, enyne metathesis of **2.80** with Grubbs' second-generation catalyst in an ethylene atmosphere provided diene **2.81** in 78% yield (Scheme 2.24). Next, the protected alcohol needed to be converted into the dienophile. This was accomplished by deprotection of **2.81** with TBAF to yield alcohol **2.82**. Finally, this alcohol was converted into α,β-unsaturated ketone **2.83** by oxidation with TPAP/NMO, alkylation with vinyl magnesium bromide and oxidation with TPAP/NMO in 32% yield over three steps.

Scheme 2.24-Enyne metathesis of ***2.80***



The necessary substituted Diels-Alder precursor **2.83** had been successfully synthesized in nineteen steps from commercially available material. At that point, the second key step was examined (Scheme 2.25). Unfortunately, heating triene **2.83** in toluene at temperatures ranging from 72 to 110 °C or treating the triene with $BF_3{\cdot}OEt_2$ at -78 °C did not give any of the cycloadduct **2.84**. It was hypothesized that the pivaloate group might not be the best protecting group due to its steric bulk. Furthermore, the electron-withdrawing ester probably deactivated the diene thus enhancing the activation barrier of the Diels-Alder reaction. It was also rationalized that the allylic pivaloate was not stable toward strong Lewis acids. This route confirmed that it was possible to generate the functionalized Diels-Alder precursor using the enyne metathesis as a key step. However, a protecting group other than the pivaloate was needed for the intramolecular Diels-Alder reaction.

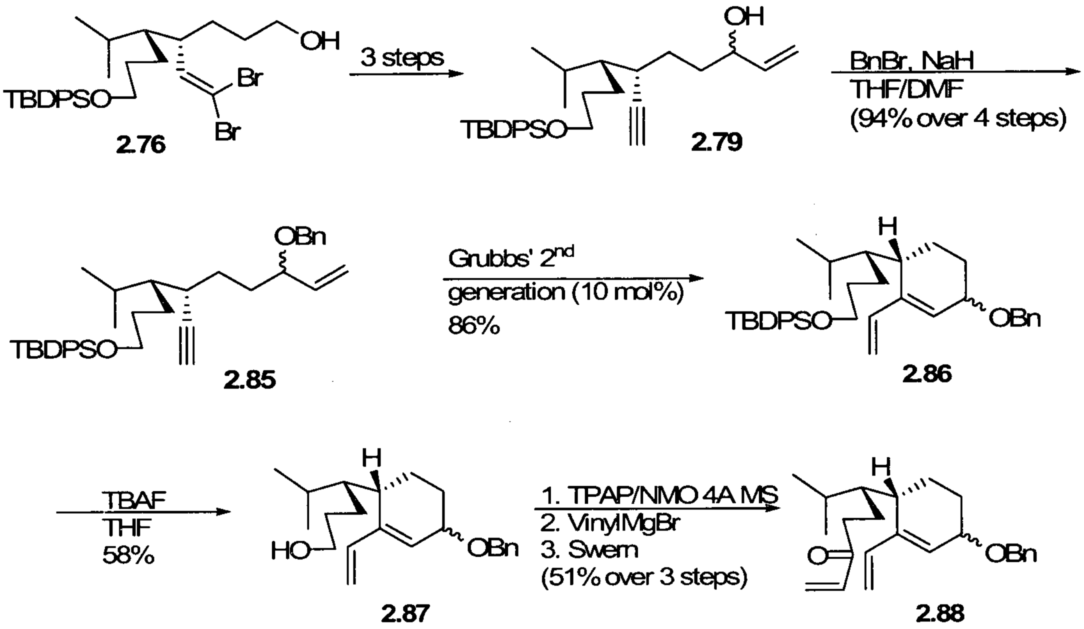
Scheme 2.25-Intramolecular Diels-Alder reaction of ***2.83***



Route 2: Benzyl as a protecting group

In order to change the protecting group, it was necessary to go back to alcohol **2.79** and install a different protecting group. Although a PMB group could not be installed, protection with a benzyl group was done easily (Scheme 2.26). Treating alcohol **2.79** with benzyl bromide and sodium hydride in THF/DMF gave desired benzyl ether **2.85** in 94% over four steps (from dibromide **2.76**). The same sequence of steps was done with the benzyl protecting group that had been done with the pivaloate. Enyne metathesis of compound **2.85** with Grubbs' second-generation catalyst in an ethylene atmosphere gave cyclic diene **2.86** in 86% yield. Deprotection of the alcohol was done with TBAF in 58% yield. Oxidation with TPAP/NMO followed by treatment with vinyl magnesium bromide yielded the allylic alcohol. Although, the last oxidation to give the α,β-unsaturated ketone worked well in the case of the pivaloate group with TPAP/NMO, the reaction never went to completion in the case of the benzyl group (17% product, 39% recovered starting material). Other oxidation methods such as Dess-Martin periodinane or manganese oxide only gave recovered starting material. The method of choice was a Swern oxidation since the desired triene **2.88** was obtained in 51% yield over three steps.

Scheme 2.26-Functionalization and enyne metathesis (benzyl group)



Intramolecular Diels-Alder reaction of triene **2.88** was then studied under various conditions (Scheme 2.27). As shown in Table 2.4, only starting material was observed when triene **2.88** was treated with $BF_3{\cdot}OEt_2$ at -78 °C (entry 1). Heating the Diels-Alder precursor at reflux in toluene also gave recovered starting material (entry 2). Satisfyingly, the desired product **2.89** was obtained in 44% yield when the reaction was performed in the microwave at 200 °C in toluene for 2 hours (entry 3). More importantly, only one regioisomer could be observed. Based on the work done on the unsubstituted core, it was believed that the desired regioisomer was obtained. In order to optimize the reaction conditions, different temperatures, time and solvents were tried (entries 4,5 and 9). Running the reaction in toluene for 4 hours at 200 °C proved to give the best yield. Different additives were also surveyed (entries 6-8). The best reaction conditions found were toluene as the solvent and triethylamine as the additive and heating at 200 °C for 4 hours (52% isolated yield). After careful analysis of the NMR, it was clear that only one isomer of **2.88** reacted to give **2.89**. Since there was a 1:1 ratio of both isomers in **2.88**, it explained that the maximum yield would be 50% (with experimental error). This could be explained by steric effects and it was hypothesized that the benzyl ether with the substituent down would be the one that reacted. The NMR data was not sufficient to prove the stereochemistry of the Diels-Alder product. Since the Diels-Alder product was an oil, functionalization of substrate **2.89** was done in order to generate a crystalline product.

Scheme 2.27-Intramolecular Diels-Alder reaction with benzyl protecting group

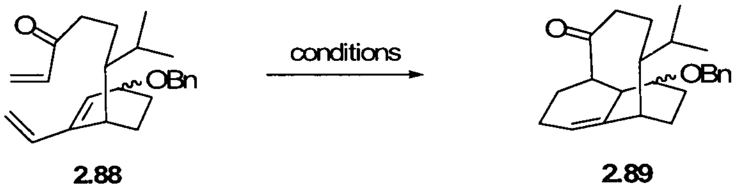


Table 2.4-Intramolecular Diels-Alder reaction

Entry	Conditions	Additive	Result
1	$BF_3{\cdot}OEt_2$, -78 °C, DCM	-	Starting material only
2	Sealed tube, 115 °C, toluene	-	Starting material only
3	Microwave 200 °C (2 hrs), toluene	-	44%
4	Microwave 220 °C (2 hrs), toluene	-	Decomposition
5	Microwave 200 °C (4 hrs), toluene	-	48%
6	Microwave 200 °C (4 hrs), toluene	BHT	34%
7	Microwave 200 °C (4 hrs), toluene	NEt_3	52%
8	Microwave 200 °C (4 hrs), toluene	Proton sponge	21%
9	Microwave 200 °C (4 hrs), acetonitrile	-	36%

In order to prove the structure of **2.89**, dihydroxylation using osmium tetraoxide and *N*-methylmorpholine-*N*-oxide gave diol **2.90** in low yield. It was believed that the diol would facilitate hydrogen bonding and thus, crystals would be obtained. Yet, all attempts at crystallizing **2.90** were unsuccessful. Therefore, removal of the benzyl group was attempted to give triol **2.91**. Many conditions were tried to remove the protecting group (Table 2.5). Using the typical hydrogenolysis conditions did not remove the benzyl group (entries 1-3). Only palladium hydroxide gave some product but the amount recovered was too small to characterize or to grow crystals. Hydrogenolysis with RaneyNickel provided a new product but it did not correspond to triol **2.91** (entry 5). Other benzyl deprotection conditions were attempted (entries 6-7) only to recover starting material. Although triol **2.91** was not needed for the synthesis of vinigrol, another protecting group should be considered since the benzyl group proved to be very difficult to remove. Even though it was not possible to prove the structure by crystal structure, NMR analysis of **2.90** proved with certainty that the right regioisomer was observed and that the stereochemistry at the oxygen was α (Figure 2.7).

Scheme 2.28-Functionalization of Diels-Alder product ***2.89***

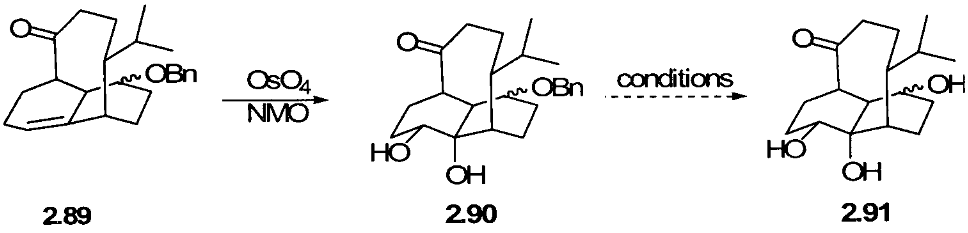
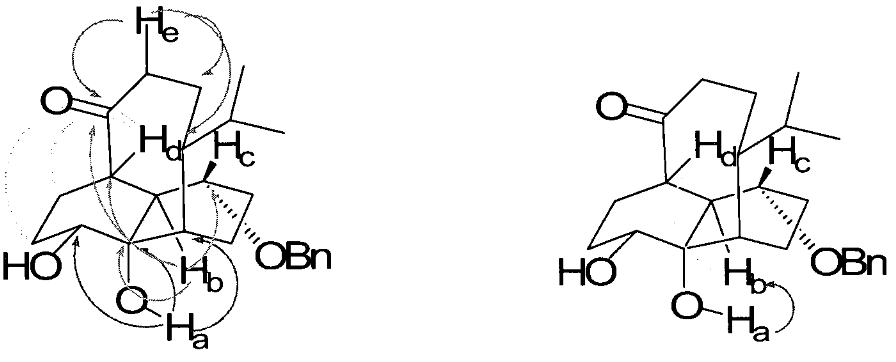


Table 2.5-Removal of the benzyl protecting group

Entry	Conditions	Result
1	Pd/C, H_2, EtOH	SM only
2	Pd/C, H_2, MeOH	SM only
3	Pd/C, ammonium formate, MeOH	SM only
4	$Pd(OH)_2$, H_2, EtOH	Approx. 10% conversion
5	RaneyNi, H_2, EtOH	No desired product
6	DDQ, DCM/H_2O, RT to reflux	SM only
7	I_2, MeOH	SM only

Figure 2.7-Proof of the stereochemistry



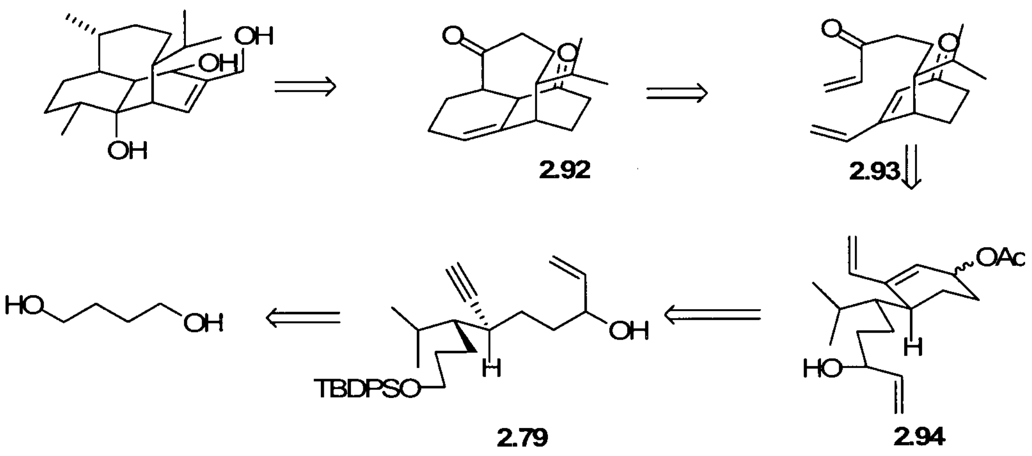
2.90, HMBC

2.90, NOESY

Route 3: Keto-derivative

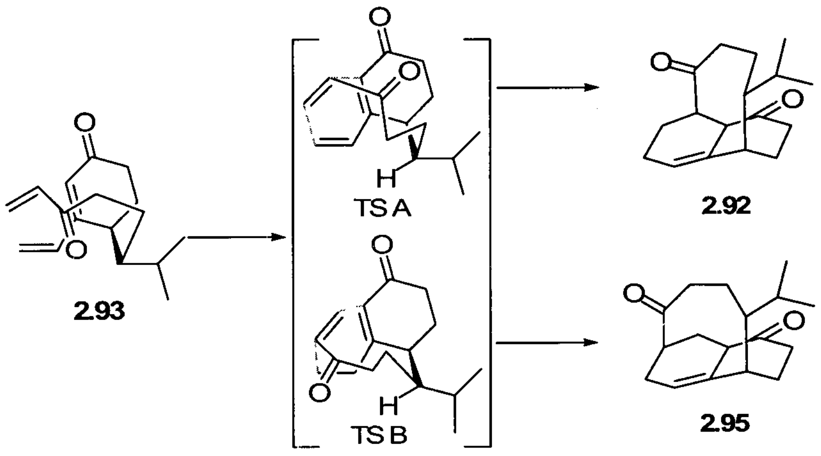
At the same time as the route with the benzyl group was developed, another possibility was studied. As mentioned previously, the pivaloate protecting group was not successful since it was bulky and electron-withdrawing (*Route 1: Pivaloate as a protecting group*). To remove steric bulk of a protected alcohol, it was hypothesized that a ketone might be a good solution (Figure 2.8). This ketone could arise from deprotection of the acetyl group and oxidation of an intermediate such as **2.94**. In turn, triene **2.94** should be easily obtained using the same type of technology used for the synthesis of related molecules from alcohol **2.79**.

Figure 2.8-Retrosynthetic analysis (keto-derivative)



The effect of a conjugating group (the ketone) on the regiochemistry of the intramolecular Diels-Alder reaction was unclear at that point (Figure 2.9). For the *endo* approach, there were two possible transition states, A and B, leading to the desired product **2.92** or its regioisomer **2.95**, respectively. All the other successful examples of intramolecular Diels-Alder reactions had an electron-donating group or neutral group adjacent to the diene. This type of functionality favored TS A over TS B. To study the effect of a conjugating group on the regioselectivity of the intramolecular Diels-Alder reaction, calculations were done with the help of Professor Tom Woo and Ph.D. student James Hooper.

*Figure 2.9-Intramolecular Diels-Alder reaction of the keto-derivative **2.93***



At the beginning of the project, Dr. Effie Sauer had performed DFT calculations of the Diels-Alder reaction of unsubstituted triene **2.30** (Figure 2.3). Since our experimental findings for the unsubstituted intramolecular Diels-Alder reaction were in agreement with the DFT calculations, we planned to use a similar type of analysis for the keto-derivative.

As a starting point, calculations done by Ms. Sauer were repeated. DFT calculations of gas-phase relative free energies at 298 K were obtained on the Jaguar 6.0 program using Khon-Sham DFT at the B3LYP level of theory with a 6-31G** basis set. The free energies of the starting material (**2.30**) as well as both possible products (**2.31** and **2.32**) were calculated (Figure 2.10, Figure 2.11). Then, using the structures that Effie had previously found, TSA, TSB1 and TSB2 were found as possible transition states leading to **2.31** in the case of TSA and to **2.32** in the case of TSB1 and TSB2. As shown in Figure 2.11, TSB1 and TSB2 had very similar energies. The major difference between both transition states is the ring conformation. The transition state A corresponding to the other ring conformation was also searched but it was not found after many attempts. All transition states had frequency calculations performed to confirm that the saddle points had only one imaginary frequency. With a 6-31G** basis set, the difference between TSA and TSB1 (the lower of the possible transition states) was 10.1 kcal/mol. Having described the potential energy surface for the unsubstituted triene **2.30**, calculations to study the keto-derivative **2.93** were performed.

Figure 2.10- Intramolecular Diels-Alder reaction of unsubstituted triene ***2.30***

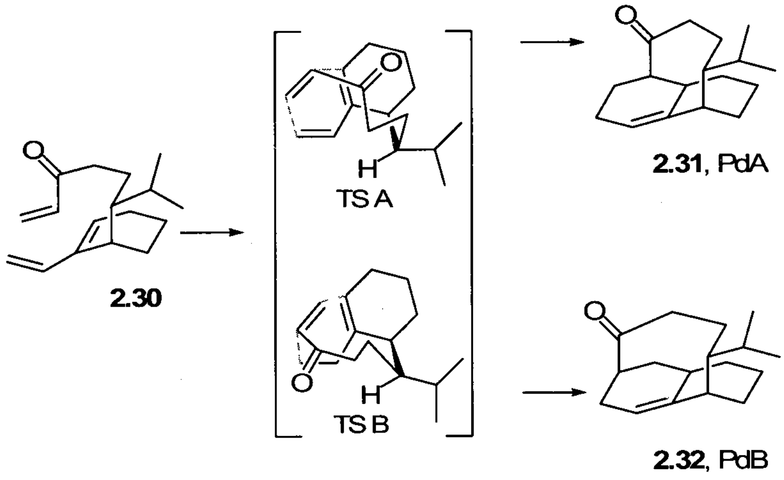
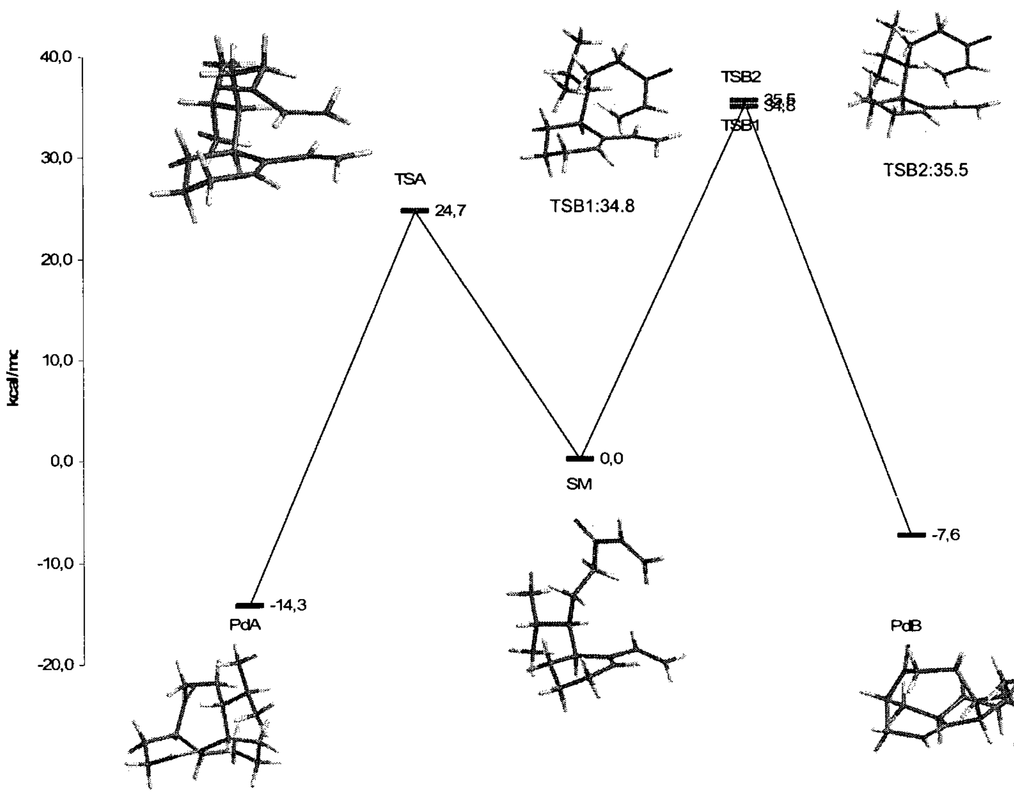


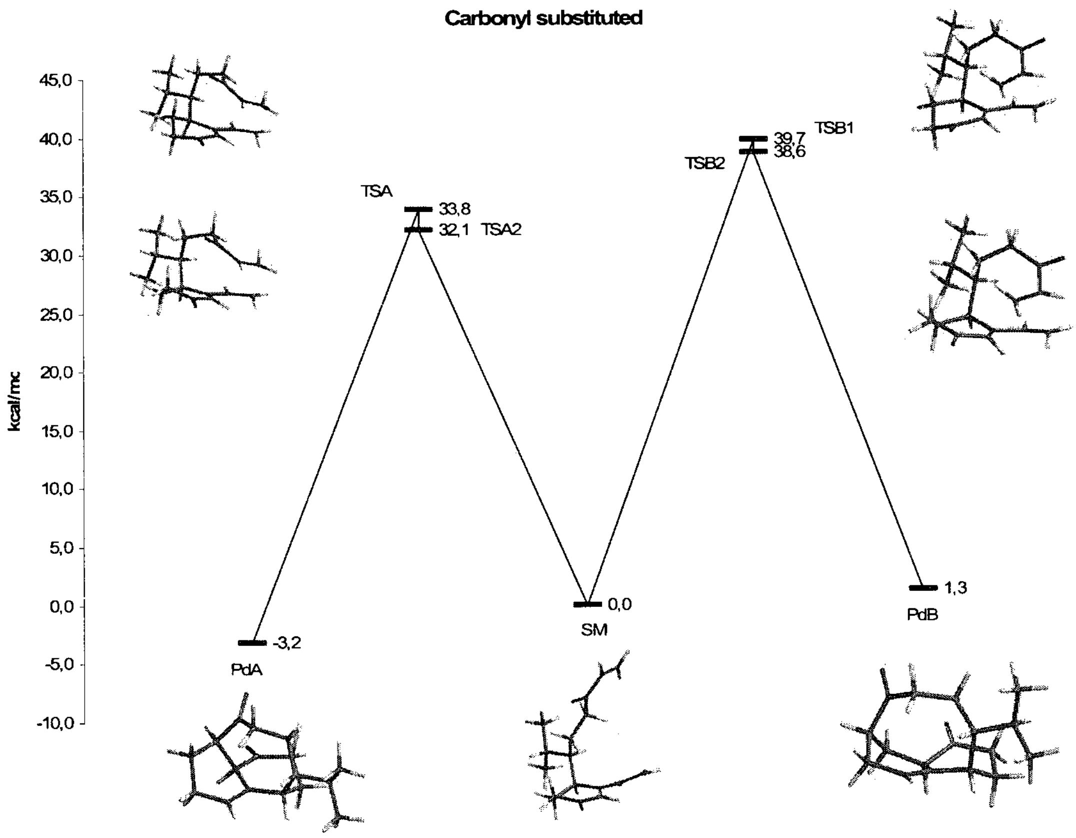
Figure 2.11-Energy potential diagram for the intramolecular Diels-Alder reaction of the unsubstituted triene (PdA corresponds to ***2.31*** *and PdB corresponds to* ***2.32****) (B3LYP/6-31G**)*



Calculations for the keto-derivative were done in a very similar manner to the unsubstituted case. First, we studied the effect of the basis set on the keto-derivative. We compared the 6-31G* to the 6-311G** and 6-311G**$^{++}$ basis sets. To this end, we took the three lowest energy conformation found for **2.93**, **2.92** and **2.95** and looked at the energy with the different basis sets. In all cases, the lowest energy conformation found at the 6-31G** was the same at the 6-311G** and 6-311G**$^{++}$ levels. As predicted, the energy found was slightly lower at the higher-level basis sets. Since we are looking at the relative energy, any basis set seemed to be acceptable to study this reaction.[77]

For the keto-derivative, we used the B3LYP level of theory with a 6-311G**$^{++}$ basis set. The relative free energy of the starting material (**2.93**) and the two potential products (**2.92** and **2.95**) were calculated (Figure 2.9, Figure 2.12). In the case of the unsubstituted reaction, there was a large difference in energy between the starting material and the products (-14.3 and -7.6 kcal/mol). However, in the case of the keto-derivative, product **2.92** was only 3.2 kcal/mol more stable than the starting material and product **2.95** was 1.3 kcal/mol higher in energy compared to the starting material.

Figure 2.12- Energy potential diagram for the intramolecular Diels-Alder reaction of the keto-derivative (PdA corresponds to ***2.92*** *and PdB corresponds to* ***2.95****) (B3LYP/6-311G**$^{++}$)*

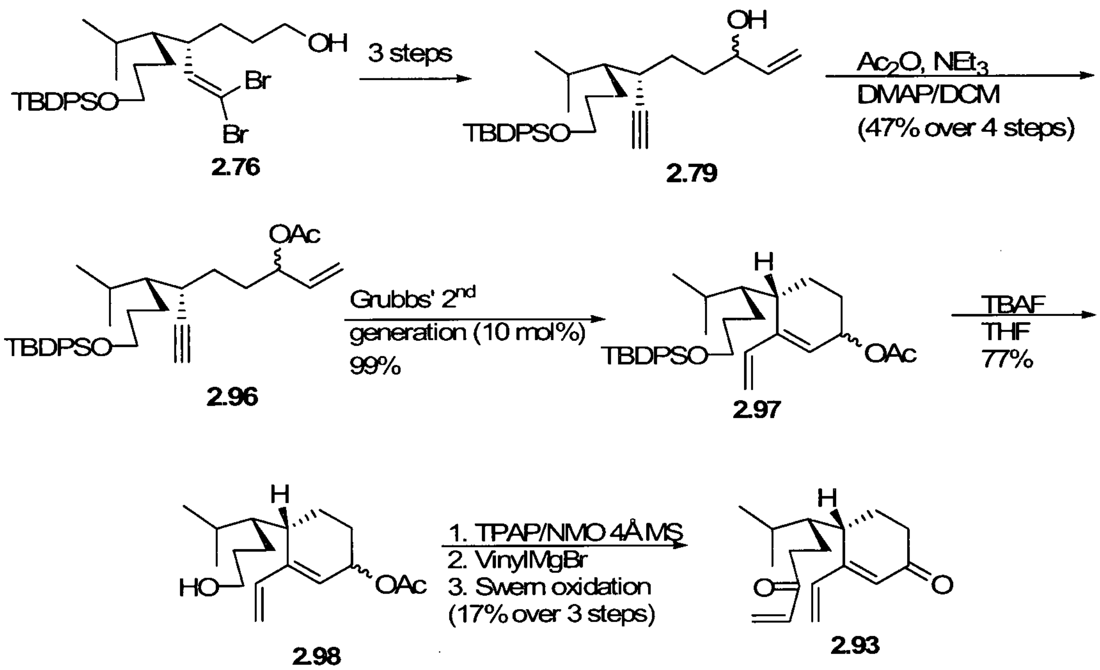


At last, the potential transition states for the intramolecular Diels-Alder reaction of the keto-derivate were studied. For the mode of attack A, which led to the desired product **2.92** (PdA), two possible transition states were found corresponding to both conformations of the ring (TSA, 33.8 kcal/mol and TSA2, 32.1 kcal/mol).[78] It is important to note that in the case of the unsubstituted triene, only one transition state was found for this mode of attack. There was a 1.7 kcal/mol difference in energy between the two transitions states. For the mode of attack B, which led to the undesired product **2.95** (PdB), again two possible transitions states were found corresponding to both conformations (TSB1, 39.7 kcal/mol and TSB2, 38.6 kcal/mol).[79] The lowest energy transition state was TSA2 (32.1 kcal/mol) leading to the desired product **2.92**. The difference in energy between TSB2 and TSA2 was 6.5 kcal/mol.

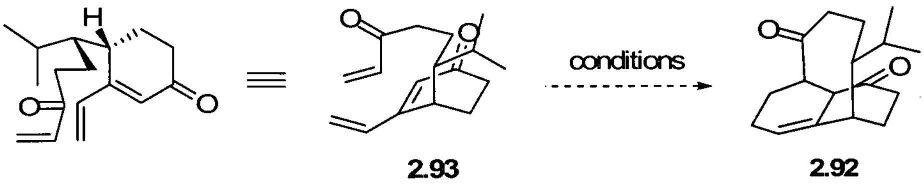
In conclusion, the calculations performed enabled us to produce the energy potential of the intramolecular Diels-Alder reaction for the keto-derivative. Having a ketone conjugated with the diene increased the barrier of energy to reach the transition state from 24.7 kcal/mol to 32.1 kcal/mol. Thus, the reaction would need to be heated to a much higher temperature to have enough energy to undergo the rearrangement. Although transition state A2 should also be favored in the case of the keto-derivative, the difference in energy between both mode of attacks (A and B) was lower than in the case of the unsubstituted triene (6.5 kcal/mol versus 10.1 kcal/mol). Nevertheless, a difference of energy of 6.5 kcal/mol was large enough that the major product should be the desired regioisomer **2.92**. Thus, the synthesis of keto-derivative **2.93** was undertaken.

The synthesis of the keto-derivative **2.93** was similar to the synthesis of the benzyl derivative **2.88** (see p. 42). An analysis of the different protecting groups was done and the acetyl protecting group was chosen because it could potentially be removed in the alkylation step with vinyl magnesium bromide. If not, an easy deprotection step would be possible. The acetyl protecting group was installed using acetic anhydride with triethylamine and DMAP in dichloromethane (47% over 4 steps from **2.76**) (Scheme 2.29). Enyne metathesis occurred in nearly quantitative yield to give cyclic diene **2.97**. Deprotection of the primary alcohol was performed using TBAF in THF to give alcohol **2.98** in 77% yield. Oxidation with TPAP/NMO gave the aldehyde that was used directly in the next step. Addition of 5.0 equivalents of vinyl magnesium bromide enabled two reactions to occur at once: alkylation of the aldehyde and deprotection of the acetate protection group. The resulting diol was very unstable and used directly in the next oxidation step to give keto-derivative **2.93** in 17% over three steps. Having the Diels-Alder precursor in hand, the key step was tested (Scheme 2.30). There was not a lot of material; thus, only two reaction conditions were tested. Keto-derivative **2.93** was heated in the microwave in toluene with 10 equivalents of triethylamine at 200 °C for 4 hours. Unfortunately, no desired product **2.92** was observed. It was thought that the base might be detrimental to the starting material. Therefore, the reaction was performed by heating the starting material in toluene at 200 °C for 2 hours. Again, no desired product was observed. It is true that the reaction was only performed on small scale but it seemed that the intramolecular Diels-Alder reaction of the keto-derivative was problematic since no desired product was observed. Looking at the calculations, this could be explained by the large activation energy.

*Scheme 2.29-Synthesis of the keto-derivative **2.93***



*Scheme 2.30-Intramolecular Diels-Alder reaction of keto-derivative **2.93***



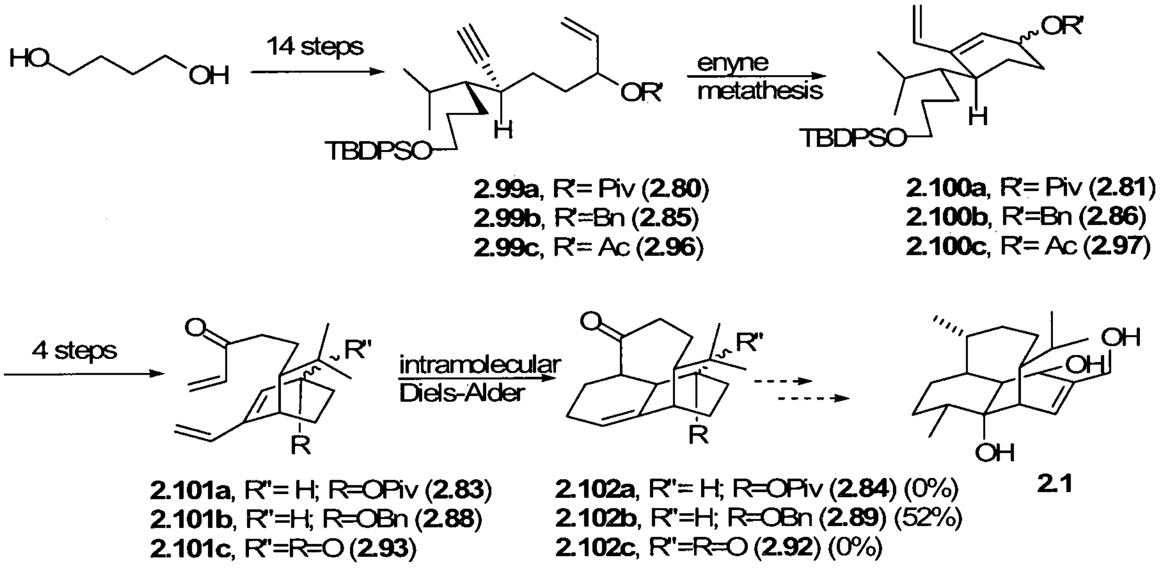
In summary, a synthetic route to the keto-derivative was developed. The intramolecular Diels-Alder reaction of this product was studied by DFT calculations and experimentally. It was found that the conjugating group had an effect on the energy of the possible transition states. The activation energy was higher and there was a smaller difference in the energy between transition A and B as compared to the unsubstituted triene.

Experimentally, it was found that the reaction did not proceed under the conditions found for the benzyl-protected precursor. Since the calculations and the preliminary result indicated that the intramolecular Diels-Alder reaction of the keto-derivate was difficult, efforts were concentrated on other routes.

Summary of the first approach to the functionalized core of vinigrol

Three routes have been explored in order to synthesize the functionalized core of vinigrol. All the routes used the same general approach where the relative stereochemistry was installed using a Claisen rearrangement. The key steps were the enyne metathesis to generate the cyclic diene and the intramolecular Diels-Alder reaction. The three different routes were different in the protecting group used for the oxygen adjacent to the diene (Scheme 2.31). The first route used a pivaloate protecting group, the second route had a benzyl group and the last route had a ketone functionality. In all cases, it was possible to synthesize the precursor needed for the Diels-Alder reaction. It was determined that the intramolecular Diels-Alder reaction was very sensitive to the nature of the protecting group as only the substrate with the benzyl-protecting group underwent a successful intramolecular Diels-Alder reaction. With this substituted tricyclic core of vinigrol, we were confident that the natural product could be obtained after manipulations of product **2.102b**. Since the synthesis to the functionalized core was twenty steps from commercially available material, it was difficult to make a large amount of material to explore the further reactions. In addition, the benzyl group was very difficult to remove and might cause problems at the end of the synthesis. For these reasons, a new approach was devised.

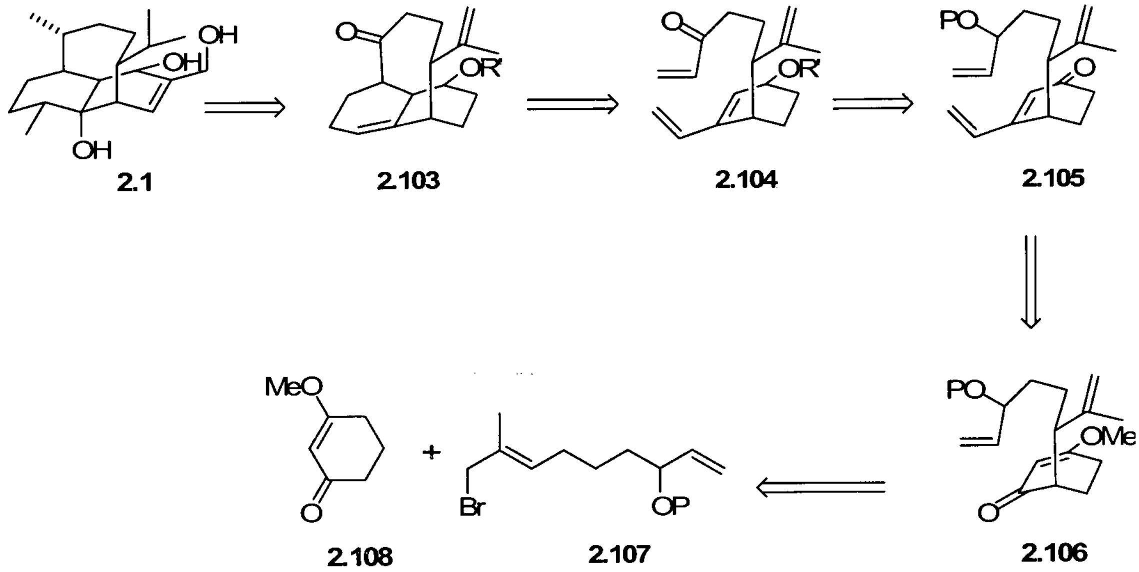
Scheme 2.31-Summary of the first approach to the functionalized core of vinigrol



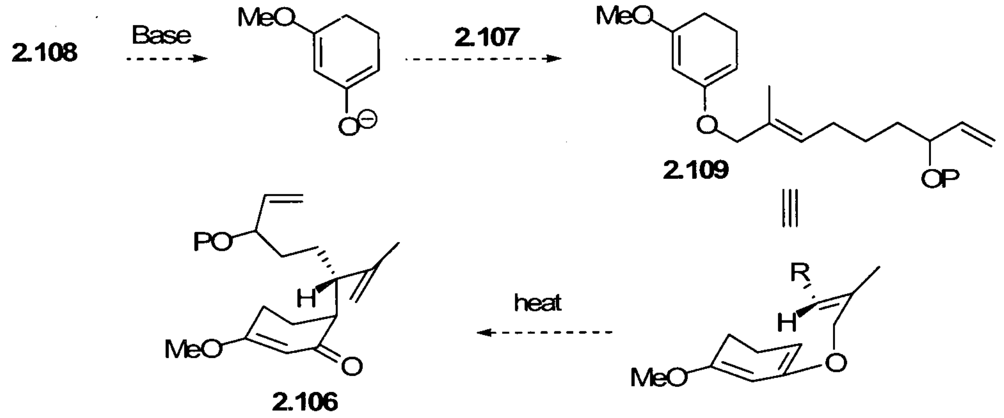
Second approach to the functionalized core of vinigrol

During the first approach, we established that the best way to introduce both necessary stereogenic centers was by a sigmatropic rearrangement. In order to have a more efficient synthesis, a new approach to the Diels-Alder precursor was investigated where the starting material already contained the six-membered ring (Figure 2.13). From a retrosynthetic point-of-view, triene **2.104** could be obtained by functionalization of **2.105**. The diene moiety could be obtained by treating compound **2.106** with vinyl magnesium bromide followed by acidic work-up. The key step would be the *O*-alkylation of the enolate generated from **2.108** with bromide **2.107** followed by an in-situ Claisen rearrangement (Scheme 2.32). It was predicted that the sigmatropic rearrangement would occur in a chair-like transition state to generate **2.106**. The *O*-alkylation would be the greatest challenge of this approach. There were no references at the time demonstrating the *O*-alkylation of simple ketones with allyl bromide or related compounds.[80] Even though there was not any precedence, this route was very attractive since it was convergent. In order to test this approach, allyl bromide **2.107** needed to be synthesized.

Figure 2.13-Retrosynthesis for second approach



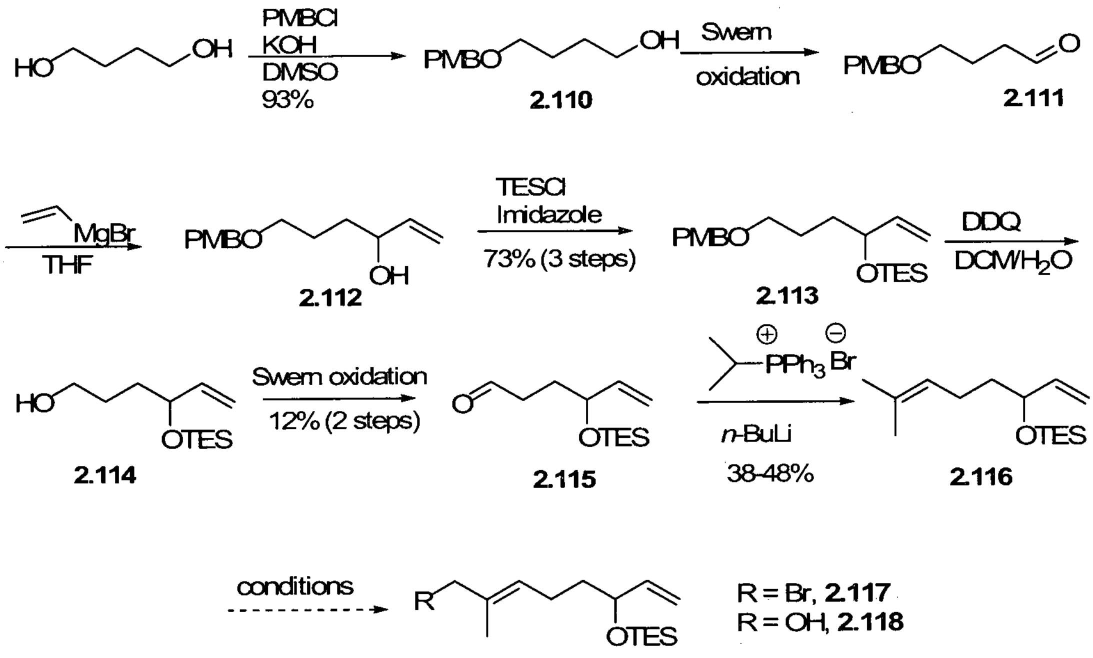
Scheme 2.32-First key step: O-Alkylation and Claisen rearrangement



O-Alkylation approach (version 1)

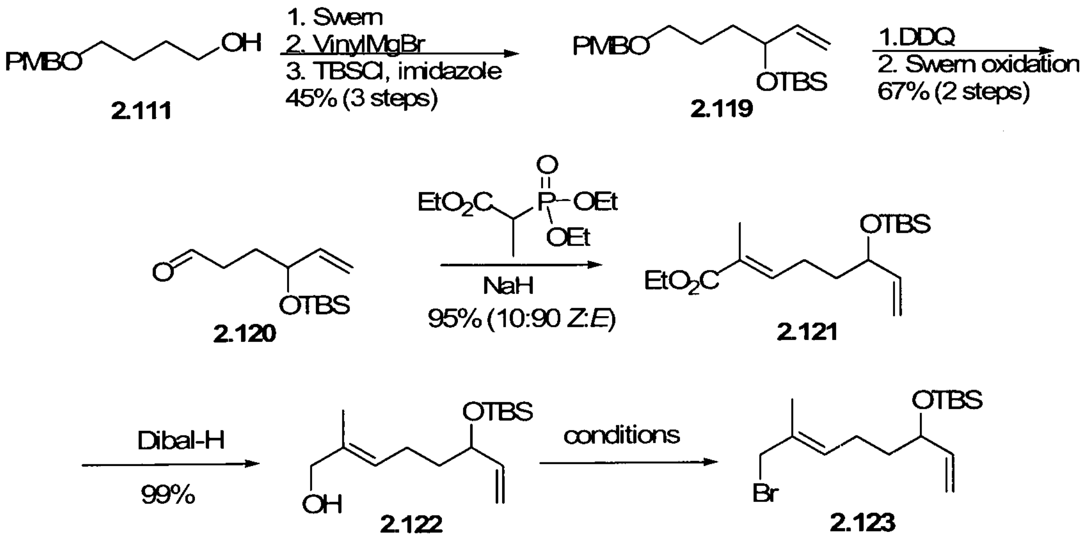
The synthesis of allyl bromide **2.117** started with commercially available 1,4-butanediol (Scheme 2.33). Monoprotection using PMBCl and KOH in DMSO gave alcohol **2.110** in 93% yield. Next, oxidation, Grignard addition and protection gave olefin **2.113** in 73% yield over three steps. In order to introduce the other olefin, **2.113** was deprotected with DDQ and the resulting alcohol was oxidized. Unfortunately, the TES group was not resistant to the Swern conditions and only 12% of the desired aldehyde was obtained. With enough material to test the next steps, olefination was done although in modest yields (38-48%).[81] In order to make the allyl bromide, olefin **2.116** was treated with *N*-bromosuccinimide in the presence of a catalytic amount of AIBN.[82] The starting material was completely consumed but no desired product was obtained. NMR analysis of the major product showed that the monosubstituted alkene was no longer present. It was concluded that the reaction conditions were not compatible with the substrate. To solve this problem, we envisioned an allylic oxidation to give alcohol **2.118** that could be transformed into bromide **2.117** with PPh_3 and CBr_4. Treating olefin **2.116** with selenium dioxide with *tert*-butyl hydroperoxide gave a mixture of products but the TES group was not present anymore. It was clear that a more robust protecting group was needed. Since the direct bromination was unsuccessful, we used this opportunity to explore a different route to obtain the necessary alcohol.

*Scheme 2.33-Synthesis of bromide **2.117***



A better route to generate allyl alcohol **2.122** was investigated where a Wadsworth-Horner-Emmons would be used to introduce the olefin and the necessary functionality in one step (Scheme 2.34). It was based on the previous synthesis of a similar allylic alcohol (see, Scheme 2.18). Starting from alcohol **2.111**, it was possible to generate the protected alcohol **2.119** in three steps. A TBS protecting group was chosen since it was more robust than the TES group. Removal of the PMB group with DDQ and subsequent oxidation of the resulting alcohol gave aldehyde **2.120** in 67% yield over two steps. Next, the Wadsworth-Horner-Emmons reaction was performed with triethyl phosphonoproprionate and sodium hydride to give the desired α,β-unsaturated ester **2.121** in 95% yield but as a 90:10 (E:Z) ratio. The mixture was directly reduced using Dibal-H to give the alcohol in quantitative yield. The two isomers could be separated at that point. Finally, the alcohol needed to be converted to the bromide. This type of reaction can usually be performed with triphenylphosphine and carbon tetrabromide. In our case, using the standard conditions did not give any desired product since deprotection of the TBS group occurred. Deprotection could be due to the HBr generated during the reaction. To solve this problem, addition of a base in the reaction mixture was explored. It was found that an excess of 2,6-lutidine (compared to the other reagent) was necessary to suppress TBS deprotection. Yet, the base slowed down the reaction and the bromination would not go to completion. After optimization, the best conditions were CBr_4 (2.3 eq.), PPh_3 (2.5 eq.) and 2,6-lutidine (3.0 eq.) in dichloromethane which gave the desired product in 71% yield.

*Scheme 2.34-Synthesis of allyl bromide **2.123***



An efficient synthesis of allyl bromide **2.123** had been achieved. Hence, the key step involving the *O*-alkylation/Claisen reaction could be studied. Firstly, different reaction conditions were attempted for the *O*-alkylation step of the domino reaction (Scheme 2.35, Table 2.6). Unfortunately, treating enone **2.108** with KHMDS and adding 18-crown-6 and allyl bromide **2.123** did not give the desired product (entries 1-2). Different additives were then added in order to promote the desired reaction (entries 3-6). In all cases, only recovered starting material **2.108** was observed. Interestingly, allyl bromide **2.123** was not present at the end of the reaction. The crude NMR seemed to indicate that the allyl bromide rearranged in the reaction mixture. In fact, an elimination reaction could be imagined when allyl bromide **2.123** was treated under basic conditions (Figure 2.14). The preliminary trials with allyl bromide **2.123** did not give any of the desired *O*-alkylation product.

Scheme 2.35-O-alkylation reaction

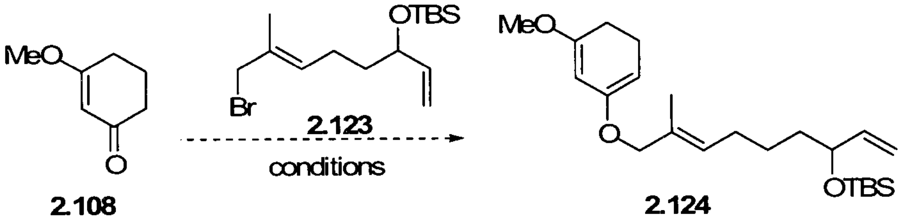
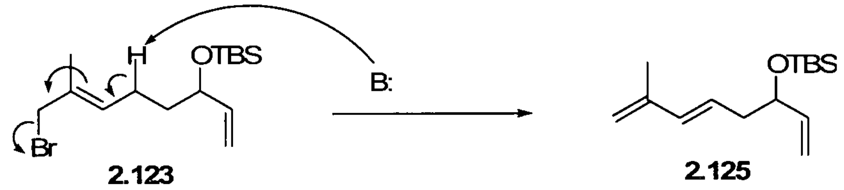


Table 2.6-O-alkylation reaction

Entry	Base (equiv)	Additives (equiv)	Conditions	Result
1	KHMDS (1.5)	18-crown-6 (3.0)	-78 °C to -50 °C THF	SM
2	KHMDS (1.3)	18-crown-6 (3.0)	-78 °C to 0 °C THF	SM
3	KHMDS (1.2)	HMPA (excess)	-78 °C to RT THF	SM
4	NaHMDS (1.2)	HMPA (excess) 4Å MS	-78 °C to RT THF	SM
5	KHMDS (1.2)	NaI (1.4) HMPA (excess)	-78 °C to RT THF	SM
6	KHMDS (1.2)	NaI (1.4) HMPA (excess) 4Å MS	-78 °C to RT THF	SM

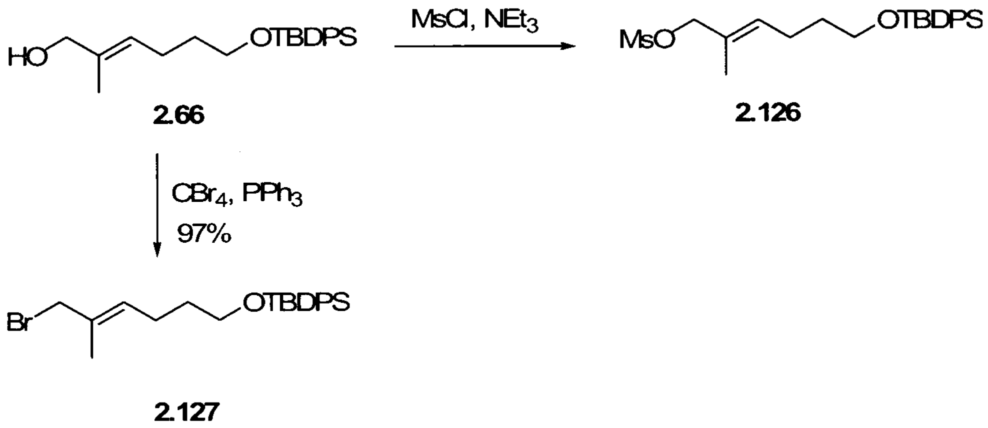
*Figure 2.14-Potential side reaction of allyl bromide **2.123** with a base*



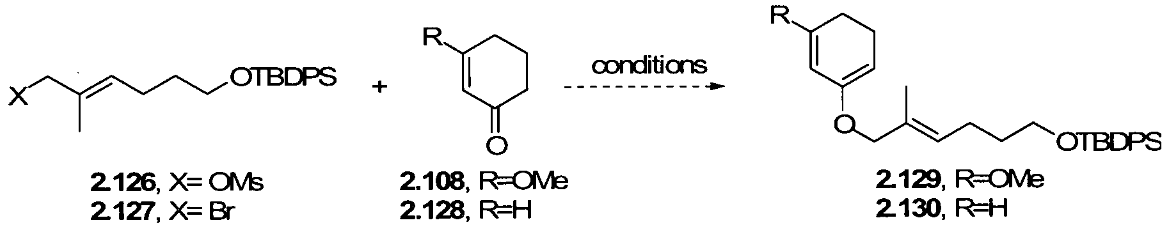
***O*-Alkylation approach (version 2)**

A report by Stephen Ley and co-workers encouraged us to try other conditions for the *O*-alkylation/Claisen reaction.[83] They successfully did the *O*-alkylation of the enolate of a ketone with a propargyl mesylate in their synthesis of azadirachtin. We decided to try their reaction conditions with a simpler substrate than compound **2.123**. Thus, we synthesized mesylate **2.126** and bromide **2.127** to test the *O*-alkylation conditions mentioned in the Ley report (Scheme 2.36). Accordingly, substrate **2.108** was deprotonated with NaH in the presence of 15-crown-5 followed by the addition of mesylate **2.126** (Scheme 2.37). Unfortunately, no desired product was observed. Using the bromide instead of the mesylate did not provide the desired product. Different bases, temperatures and additives were tested with the bromide and the mesylate without success. Finally, *O*-alkylation of substrate **2.128** was also fruitless. Although Ley and co-workers successfully did the *O*-alkylation of their ketone with a propargyl mesylate, it was clear that the conditions were not compatible for our system.

*Scheme 2.36-Synthesis of mesylate **2.126** and bromide **2.127***



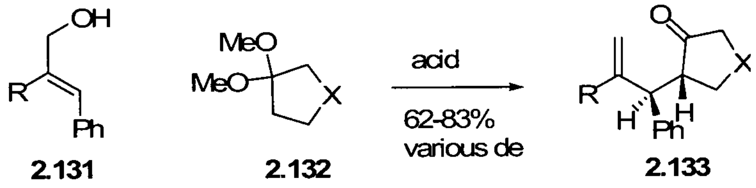
Scheme 2.37-O-alkylation (version 2)



Ketal Claisen rearrangement

In 1986, Daub and Griffith reported a study of the stereoselectivity of the ketal Claisen rearrangement.[84] Their investigation showed that good selectivity could be obtained with carefully substituted allylic alcohols. The major product resulted from a chair-like transition state where the steric interactions were minimized. As a result, they were able to obtain functionalized ketones **2.133** in good yield and moderate diastereoselectivity (Scheme 2.38). It was found that the intrinsic selectivity was high but the ratio decreased with time. This was attributed to epimerization of the chiral center alpha to the ketone under the reaction conditions.

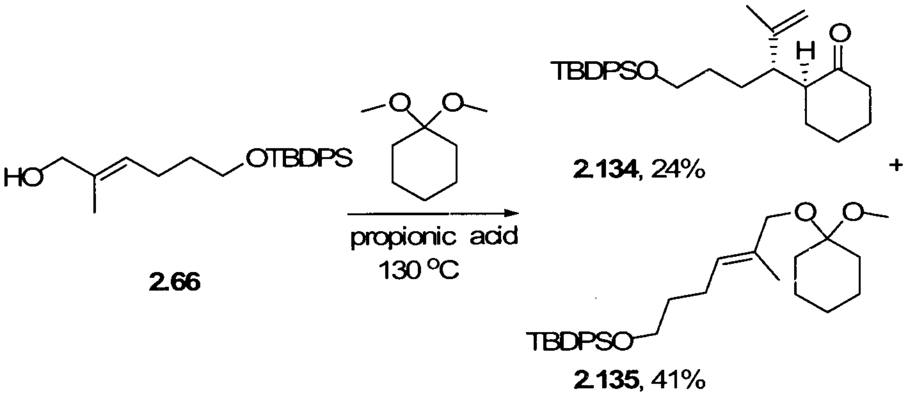
Scheme 2.38-Ketal Claisen rearrangement (Daub and Griffith)



It was thought that the ketal Claisen rearrangement might be a solution to the problematic *O*-alkylation/Claisen route. To test the application of their method toward the synthesis of vinigrol, cyclohexanone dimethylketal was heated with alcohol **2.66** in the presence of a catalytic amount of acid (Scheme 2.39). Satisfyingly, ketone **2.134** and ketal **2.135** were obtained in 24 and 41% yield respectively. Treating the ketal **2.135** with the same reaction conditions gave ketone **2.134**. Only one isomer was visible by NMR and it is predicted to be **2.134** due to the chair-like transition state proposed by Daub and Griffith

(Figure 2.15). Since epimerization occurred under the reaction conditions, the time of the reaction was crucial. The optimal reaction conditions were found to be heating at 125-133 °C for 8 hours. The protected alcohol was converted into *para*-nitrobenzoate **2.136** in the hope of the generating a crystalline compound and prove the relative stereochemistry of the **2.134** (Scheme 2.40). Deprotection using TBAF was done in 78% yield and acylation using *para*-nitrobenzoylchloride and pyridine in DCM gave the desired product in 64% yield. Unfortunately, compound **2.136** was an oil and it was not possible to grow crystals. The synthesis was continued with the assumption that the Claisen rearrangement afforded the correct stereochemistry. The stereochemistry was eventually proven with an advanced intermediate (see, Scheme 2.70).

*Scheme 2.39-Ketal Claisen rearrangement with alcohol **2.66***

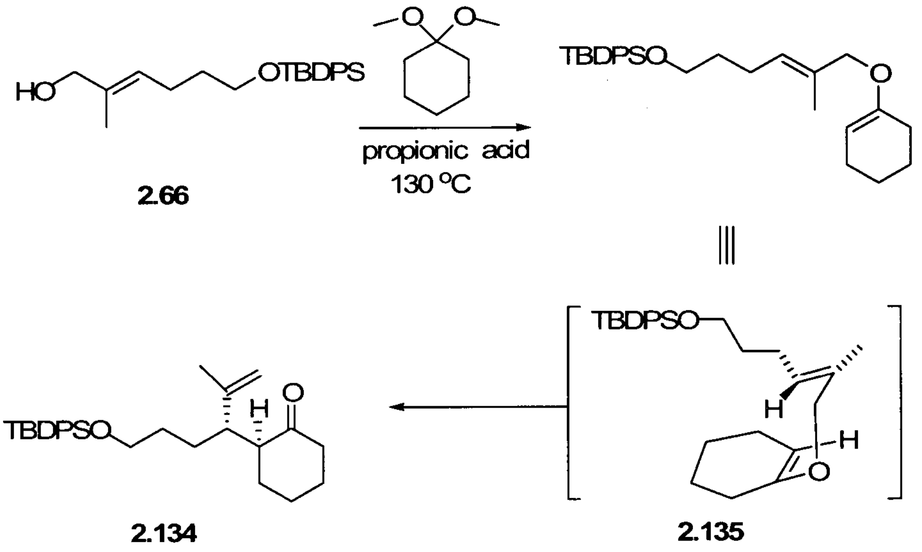


2.66

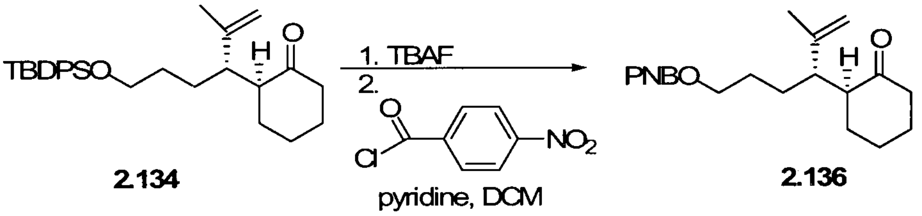
2.134, 24%

2.135, 41%

Figure 2.15-Proposed mechanism for ketal Claisen rearrangement

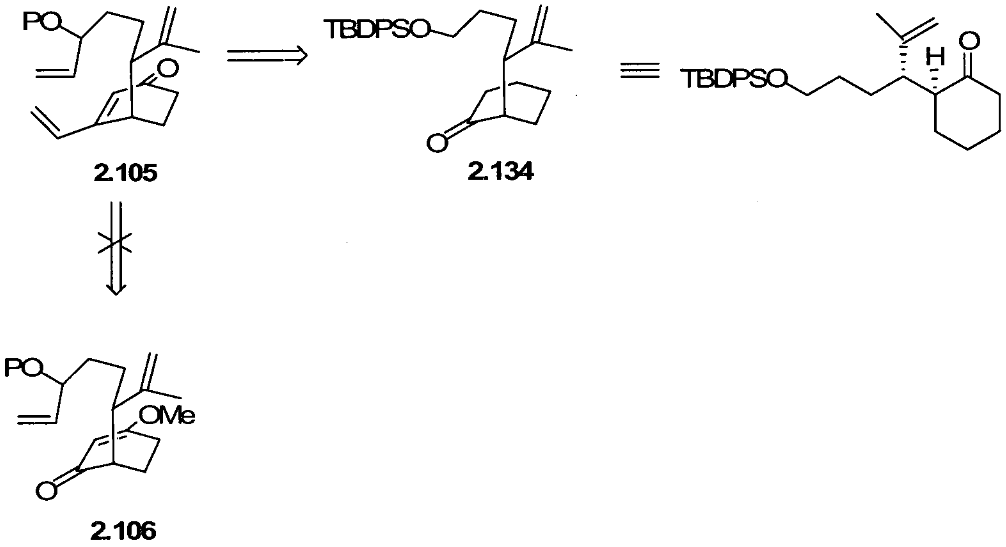


*Scheme 2.40-Transformation of silyl alcohol **2.134** into para-nitrobenzoate **2.136***



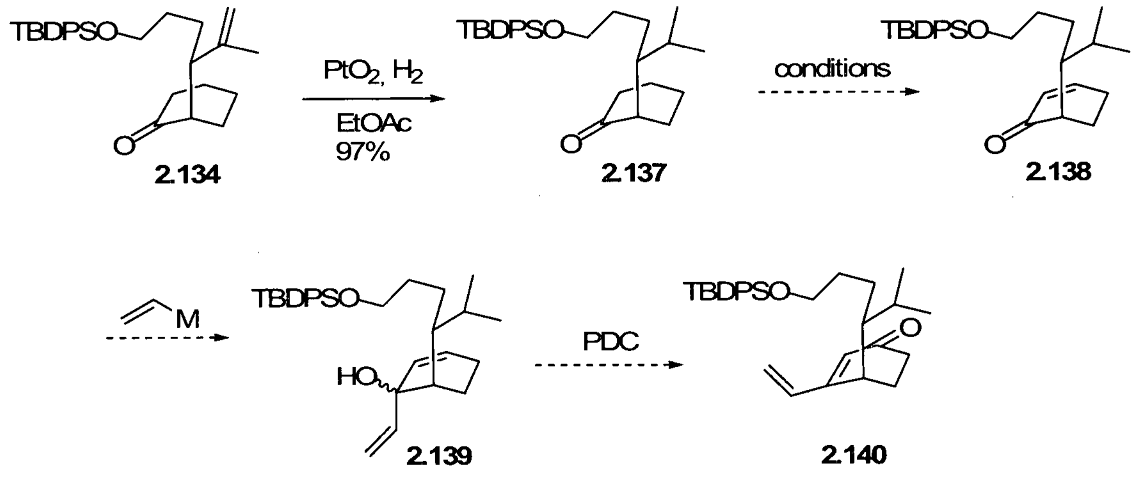
Having found a method to generate the two key stereocenters starting from a six-membered ring precursor, the retrosynthesis of **2.105** needed to be revised. In the original retrosynthetic plan (Figure 2.13), it was imagined that advanced intermediate **2.105** would come from **2.106** via an alkylation and acid treatment (Figure 2.16). In order to access a compound similar to **2.106** with the ketal Claisen rearrangement, the reaction would have to be performed with 1,3,3-trimethoxy-cyclohexene. However, a mixture of products was envisioned since the enol ether would not be stable to the reaction conditions. Instead, it was judged that intermediate **2.105** could be obtained by functionalization of **2.134**.

Figure 2.16-Adapted retrosynthesis



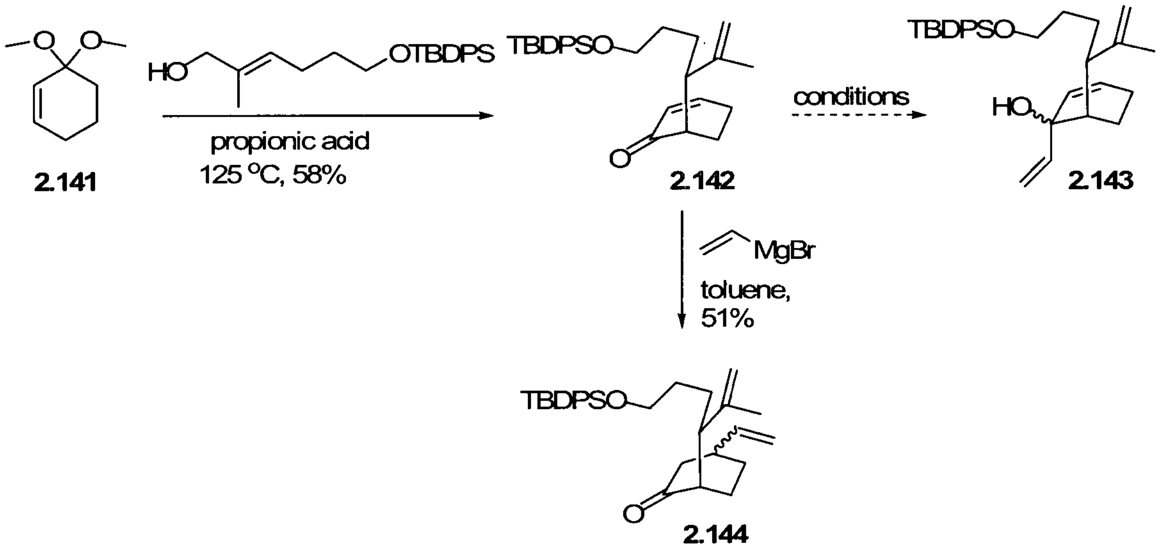
The first strategy explored to generate a derivative of compound **2.105** is shown in Scheme 2.41. It was imagined that alkylation of an α,β-unsaturated ketone followed by an allylic transposition should provide the desired functionalized diene (**2.140**). Hydrogenation of **2.134** with Adams' catalyst in ethyl acetate gave **2.137** in 66% yield. To convert the ketone into the α,β-unsaturated ketone, the silyl enol ether was formed and treated with palladium acetate and benzoquinone. Unfortunately, only ketone **2.137** was recovered. To solve this problem, a new route to α,β-unsaturated ketone **2.138** was investigated (Scheme 2.42).

Scheme 2.41-Strategy for the installation of the functionalized diene

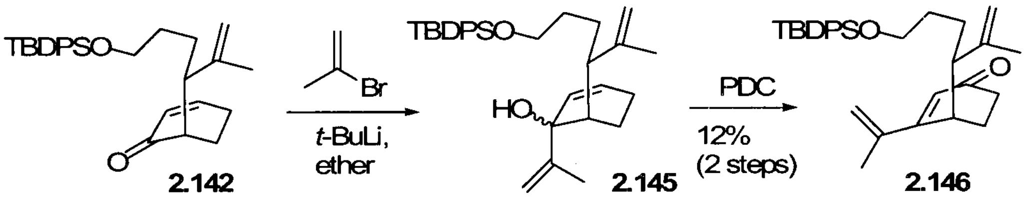


Starting with cyclohexenone-dimethylketal **2.141**, Claisen product **2.142** was obtained in 58% yield (Scheme 2.42). In was not possible to hydrogenate selectively the isopropenyl moiety at this point. Thus, vinylation was attempted directly on the Claisen product. Many conditions were attempted to alkylate the α,β-unsaturated ketone in order to generate allylic alcohol **2.143**. When the reaction was performed with vinyl magnesium bromide in toluene, only 1,4-addition occurred to give product **2.144**. Other solvents did not give any product. Adding cerium chloride is known to favor 1,2-addition over 1,4-addition but only starting material was recovered in our case. Alkylation with the vinyl lithium species generated from tributylvinyl tin and *n*-BuLi did not provide any product. Fortunately, alkylation with the lithium reagent generated from isopropenyl bromide and *t*-BuLi did provide allylic alcohol **2.145** (Scheme 2.43). The mixture was used directly in the next step. It was possible to promote the allylic transposition using PDC but the desired product was only obtained in 12% yield (over 2 steps) with 42% of recovered allylic alcohol. Additives such as molecular sieves and silica were tested but the conversion did not increase.[85] Although this route did provide the desired functionalized diene in a short sequence, the low yields were not acceptable for the total synthesis. Thus, a new approach of converting ketone **2.134** into **2.105** was investigated.

*Scheme 2.42-Synthesis of enone **2.142** and alkylation*



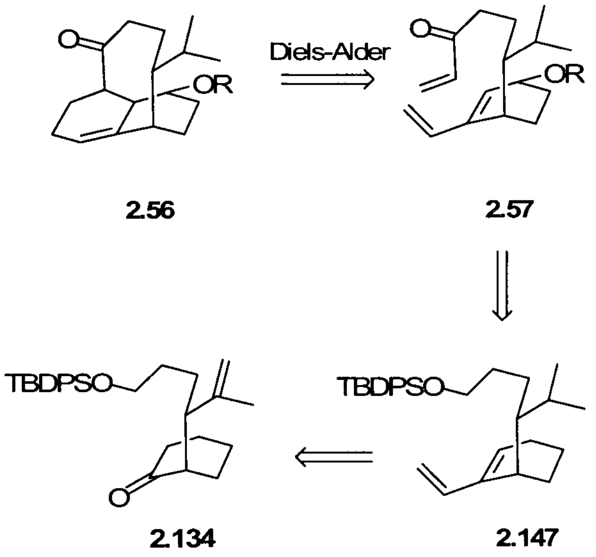
Scheme 2.43-Synthesis of a functionalized diene



Allylic oxidation route

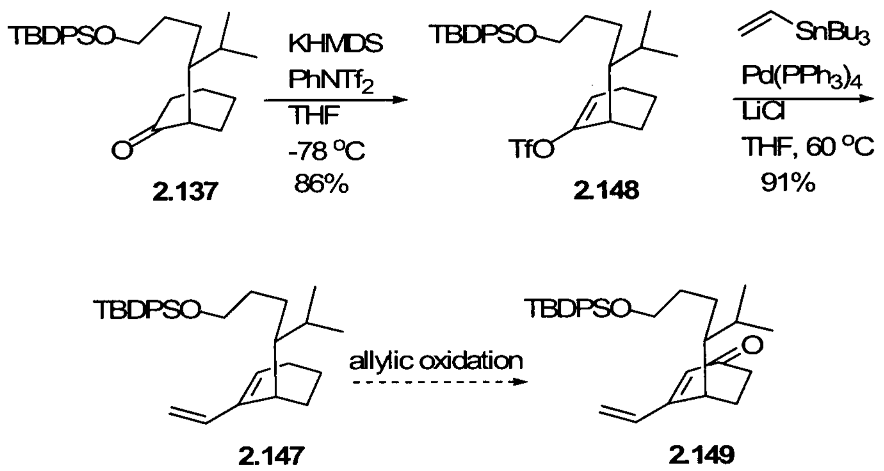
Since the allylic transposition route gave the desired product in low yield, an alternative route was conceived. It was imagined that ketone **2.134** could be transformed into diene **2.147** that could undergo an allylic oxidation to furnish the functionalized diene of **2.57**.

Figure 2.17-Retrosynthesis using an allylic oxidation



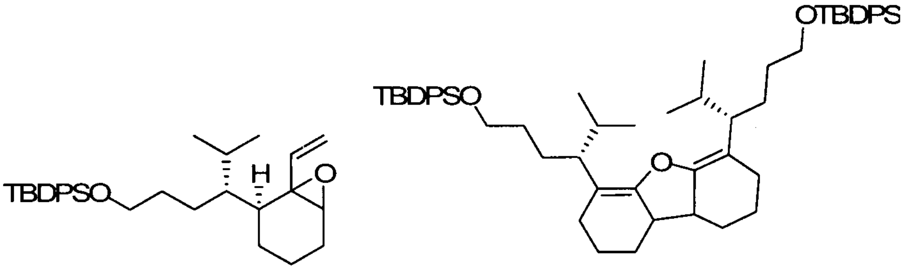
To determine the feasibility of this route, diene **2.147** needed to be synthesized. To this end, ketone **2.137** was deprotonated with KHMDS and *O*-alkylated with *N*-phenyltriflimide to give vinyl triflate **2.148** in 86% yield (Scheme 2.44). Next, the Stille coupling occurred in 91% yield with tributylvinyl tin to give diene **2.147** in 91% yield. Allylic oxidation was attempted with selenium dioxide and *t*-butylhydroperoxide in dichloromethane. A new product was obtained in 40% yield but it did not correspond to **2.149** or the corresponding alcohol. The NMR data indicated that epoxide **2.150** was the product obtained (Figure 2.18). It was believed that this product resulted from the *t*-butylhydroperoxide added as the co-oxidant in the reaction. Thus, oxidation with a stoichiometric amount of selenium dioxide was attempted. Again, no desired product was observed but a new compound was isolated. The structure was believed to be compound **2.151** (Figure 2.18). It is not clear at this point how this product was formed under the reaction conditions. In a report by Yang *et al.*, allylic oxidation of dienes was accomplished using $CaCl_2$ or $MgCl_2$ and *t*-butylhydroperoxide.[86] Unfortunately, under these reaction conditions, only compound **2.151** was isolated. Allylic oxidation was also tried using chromium oxide and 3,5-dimethylpyrazole but again compound **2.151** was observed. Clearly, allylic oxidation of diene **2.147** was problematic.

*Scheme 2.44-Synthesis of functionalized diene **2.149***



2.137 2.148 2.147 2.149

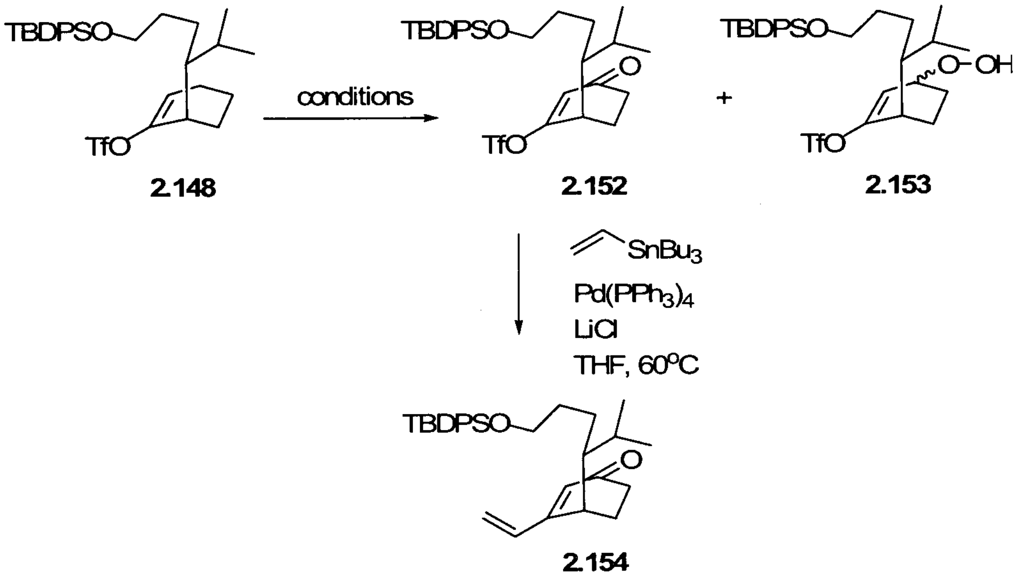
*Figure 2.18-Possible products in the allylic oxidation of **2.147***



2.150 2.151

In order to circumvent the allylic oxidation of diene **2.147**, the oxidation of triflate **2.148** was attempted (Scheme 2.45). The typical conditions for allylic oxidation of alkenes (selenium dioxide or CrO_3/dimethylpyrazole) did not provide any of the desired product. Using the conditions of Yang and co-workers,[86] promising results were obtained. Although the reaction only gave a trace of product with calcium chloride and *t*-butylhydroperoxide in water, magnesium chloride and dry *t*-butylhydroperoxide in acetonitrile at 60 °C did give the desired product **2.152** in 22% yield.

*Scheme 2.45-Allylic oxidation of triflate **2.148***



To optimize the yield of the allylic oxidation, various reaction conditions were scanned (Table 2.7). The reaction was performed in a variety of solvents (acetonitrile, DCE, acetone, mixture with water) at temperatures ranging from 60 to 80 °C (entries 2-5, 7). With all the different conditions, the yield varied between 21 and 31% yield, where the best yield was obtained with dichloroethane. Other efforts were made to optimize the yield by increasing the concentration, performing the reaction in the presence of air or oxygen or by adding a base (entries 6, 8-10). In call cases, the desired product was observed in lower yields. During these reactions, hydroperoxide **2.153** was isolated and characterized. The hydroperoxide could be transformed into the desired enone but in low yield. The mechanism proposed by Yang and co-workers for the allylic oxidation of dienes with magnesium chloride involved radical species. Therefore, it was reasonable that the radical intermediate reacted with O_2 to form the hydroxyperoxide product.

Different metals ($RuCl_3$, CuCl, $CuCl_2$, $Pd(OH)_2$[87]) were also explored (entries 11-14) Only palladium hydroxide gave similar results to magnesium chloride. Allylic oxidation with palladium trifluoroacetate, *o*-methoxyacetophenone and acetic acid was also attempted but no reaction occurred (entry 15).[88] The best conditions remained the allylic oxidation with magnesium chloride in dichloroethane at 60 °C (entry 3). Although the yield was not high, there was enough material to test the next steps toward tricyclic compound **2.56**. Coupling of triflate **2.152** with tributylvinyl tin occurred in low yield (13 to 40%). It was believed that enone **2.154** might be unstable and it was thought that reduction and protection of the ketone before the coupling might be favorable.

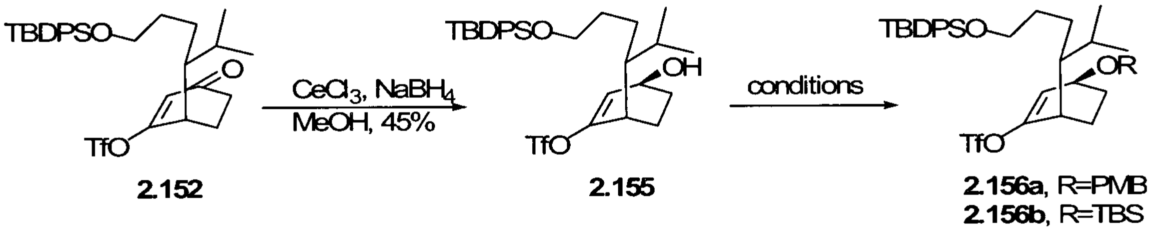
Table 2.7-Allylic oxidation of triflate ***2.152***

Entry	Metal	Oxidant	Conditions	Result
1	$CaCl_2$	TBHP[b]	Acetonitrile, 60 °C	Trace of product
2	$MgCl_2$	TBHP[a]	Acetonitrile, 60 °C	22% yield
3	$MgCl_2$	TBHP[a]	DCE, 60 °C	31% yield
4	$MgCl_2$	TBHP[a]	Acetone, 60 °C	21% yield
5	$MgCl_2$	TBHP[a]	DCE, H_2O, 60 °C	26% yield
6	$MgCl_2$	TBHP[a]	DCE, 60 °C, 0.2 M	19% yield
7	$MgCl_2$	TBHP[a]	DCE, 80 °C	21% yield
8	$MgCl_2$	TBHP[a]	DCE, 60 °C, air	16% yield (+10% peroxide)
9	$MgCl_2$	TBHP[a]	DCE, 60 °C, O_2	26% yield
10	$MgCl_2$	TBHP[a]	K_2CO_3 (3 eq), DCE, 60 °C, air	11% yield
11	$CuCl_2$	TBHP[a]	Acetonitrile, 60 °C	SM only
12	$RuCl_3$	TBHP[b]	Cyclohexane, H_2O, 60 °C	5% conversion
13	CuCl	TBHP[a]	Acetonitrile, 60 °C	SM only
14	$Pd(OH)_2$	TBHP[a]	K_2CO_3, DCM, air	27% yield
15	$Pd(OCOCF_3)_2$	Benzoquinone	methoxyacetophenone, acetic acid (90 °C)	SM only

Otherwise indicated, all reactions were performed under argon atmosphere at 0.1 M. [a] TBHP, 5M in decane [b] TBHP 70% in water

It was necessary to choose a protecting group very carefully. The requirements were that the group had to be easily installed and had to stay in place at the TBDPS deprotection step. First, enone **2.152** was reduced using the Luche conditions ($CeCl_3$/$NaBH_4$) to afford **2.155** in 45% yield (Scheme 2.46). Under the reaction conditions, only one diastereoisomer could be detected. Reduction with Dibal-H was attempted in order to improve the yield of the reaction. However, two diastereoisomers were detected in that case (the major diastereoisomer was the same as the one obtained with Luche reaction). Due to the higher stereoselectivity, reduction using the Luche conditions was preferred. It was suspected that the hydride attacked from the least hindered to give the stereochemistry shown in **2.155**. In order to prove the stereochemistry, either an X-ray of a crystal or extensive NMR spectroscopy of the tricyclic core of vinigrol needed to be performed. The second option was chosen since the material was not crystalline.

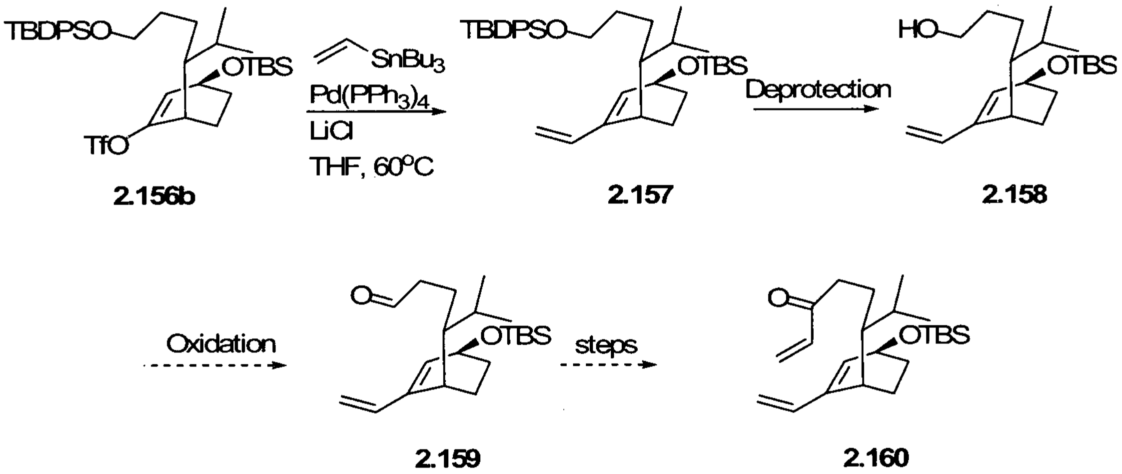
Scheme 2.46-Reduction and protection



A PMB group seemed to satisfy the requirements mentioned above. However, treatment of alcohol **2.155** with NaH and PMBCl in DMF did not give the desired product **2.156a**. Other conditions including NaH, PMBCl and tetrabutylammonium iodide or PMB-Br were investigated but no desired product was observed. The starting material disappeared but no desired product could be detected. A crude NMR showed that no alkene peak was present. It was believed that the starting material was not compatible with sodium hydride.[89] Thus, a TBS group was installed with imidazole and TBSCl in THF in 46% yield. Since the stability of the allylic alcohol was suspected to be low, protection was done on crude alcohol **2.155** to afford **2.156b** in 59% yield over two steps.

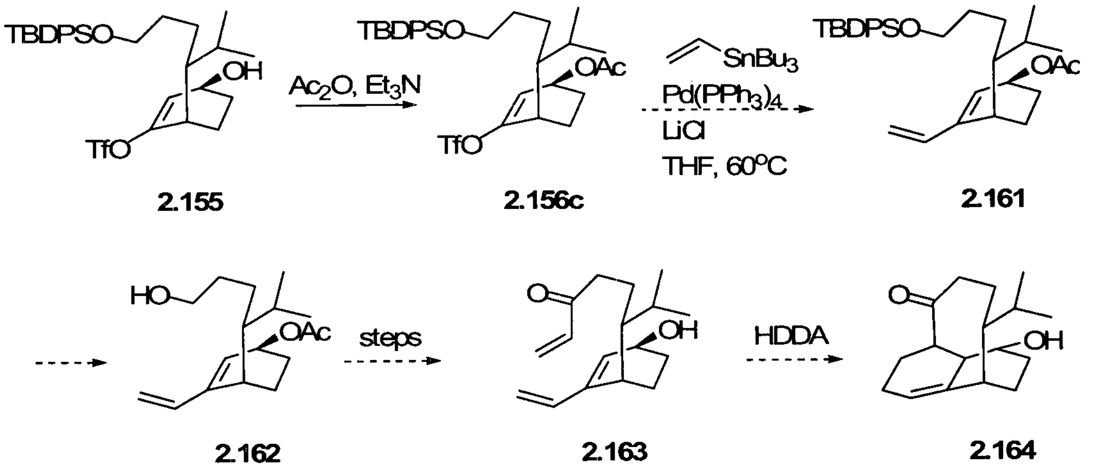
Once the secondary alcohol had been protected, the Stille coupling with tributylvinyl tin proceeded in 100% conversion to diene **2.157** (Scheme 2.47). The crude diene was used in the next deprotection step. In a first trial, the TBDPS group was selectively removed under basic conditions with sodium hydroxide in methanol to give **2.158** in 12% yield over two steps. In a second trial, selective deprotection was attempted with TBAF. The primary alcohol was deprotected before the secondary alcohol. This method gave primary alcohol **2.158** in 16% yield over two steps. Problems arose with the oxidation of **2.158**. Under the TPAP/NMO conditions used for other similar substrates, no desired product was obtained. Although we were very close to synthesizing functionalized diene **2.160**, it was not possible to access it using this route.

Scheme 2.47-Further functionalization of ***2.156b***



A possible solution was to synthesize the acetyl derivative **2.156c** and carry out the same steps as mentioned for the silyl ether (Scheme 2.48). From our previous studies, we suspected that an acetyl group was not compatible with the intramolecular Diels-Alder reaction (see, p. 31). However, functionalization and deprotection of **2.162** could afford **2.163**, which could be used in a hydroxy-directed Diels-Alder reaction[23] to promote the intramolecular cycloaddition. Protection of alcohol **2.155** with acetyl anhydride gave compound **2.156c** in 32% yield over two steps (from **2.152**). Unfortunately, there was not enough material to continue with this route. Moreover, another route was studied simultaneously and provided results that were more promising.

Scheme 2.48-Synthesis with acetyl protecting group

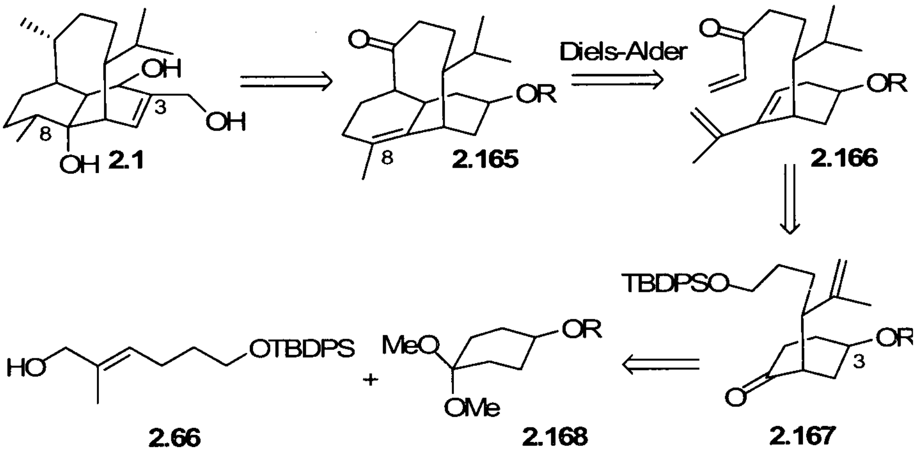


The allylic oxidation route did generate the functionalionalized cyclic diene. However, this route was plagued with the low yielding allylic oxidation making it difficult to access a large amount of material to synthesize the Diels-Alder precursor. To solve this problem, one can imagine performing the coupling reaction with a substituted ketal.

Ketal Claisen rearrangement with a substituted precursor

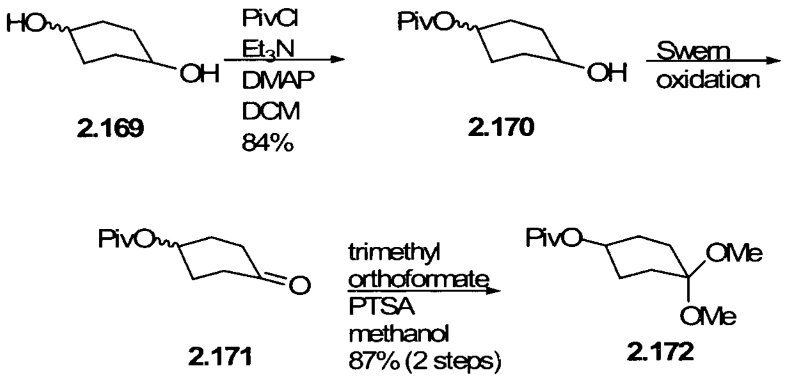
The ketal Claisen rearrangement provided a very efficient way to introduce the necessary stereocenters. This approach was advantageous over the enyne metathesis route (see, Synthesis of the functionalized tricyclic core of vinigrol, p.31) since it was convergent and it was possible to access the six-membered ring rapidly. However, it was found that functionalization of the Claisen product into the substituted diene by various methods gave the desired product in low yield. To avoid these problems, a new route was devised (Figure 2.19). The synthetic plan started with the Claisen rearrangement of meso ketal **2.168** and allylic alcohol **2.66**. This reaction should allow the formation of ketone **2.167** with the substituent at C3. The conversion of this ketone into the Diels-Alder precursor **2.166** should be straightforward. Then, the intramolecular Diels-Alder reaction should afford substituted tricyclic compound **2.165**. The substituent at C3 could operate as the handle to install the functionalities found on the natural product. In this synthetic plan, the methyl at C8 was installed before the Diels-Alder reaction. A model study performed by Patrick Levesque had indicated that it was best to install the methyl earlier in the synthesis (see, *Opening of the epoxide*, p. 88).

Figure 2.19-Retrosynthesis using a substituted precursor



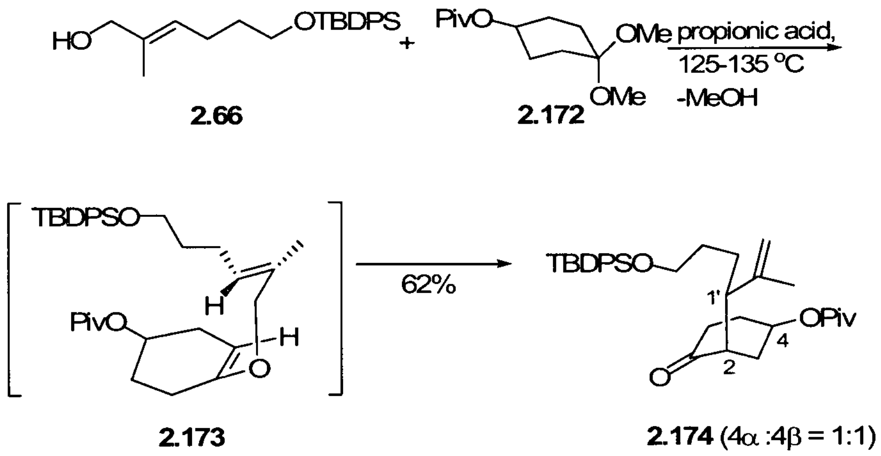
To start the synthesis, substituted ketal **2.172** was obtained in three steps from the commercially available diol (Scheme 2.49). Cyclohexane-1,4-diol **2.169** was mono-protected with pivaloyl chloride. A pivaloate protecting group was selected due to its robustness and ease of removal. Oxidation of the secondary alcohol with the Swern conditions gave ketone **2.171** that was immediately transformed into the dimethoxy ketal upon treatment with trimethyl orthoformate in methanol and a catalytic amount of PTSA. The high yielding steps gave the desired meso ketal efficiently.

Scheme 2.49-Synthesis of meso ketal ***2.172***

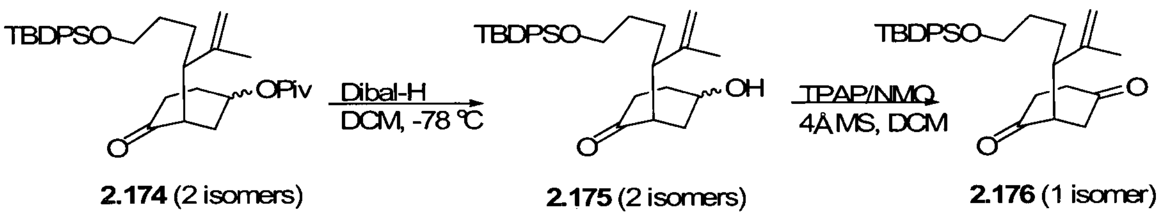


With the ketal in hand, the ketal Claisen rearrangement was tested. Alcohol **2.66** and ketal **2.172** were heated at 125-135 °C in the presence of catalytic amount of propionic acid. Enol ether **2.173** was generated in situ and it rearranged via a Claisen rearrangement to compound **2.174** (Scheme 2.50). Two diastereoisomers were obtained after the reaction. It was suspected that the two diastereoisomers corresponded to the two possible isomers at the pivaloate position (α and β). To identify the nature of the diastereoisomers, the mixture was treated with Dibal-H to remove the pivaloate and oxidized using TPAP/NMO (Scheme 2.51). Since only one stereoisomer was detected after the oxidation, it was possible to confirm that the diastereoisomers correspond to both isomers at the pivaloate position. Hence, the pivaloate does not control the reaction as both isomers are obtained in a 1:1 ratio. Gratifyingly, the stereochemistry at the 2 and 1' positions was controlled as only one stereoisomer at these positions was observed. It is important to note that the epimerization at C2 was possible if the reaction was left for a long period of time. It was found that the optimal reaction time was eight hours.

Scheme 2.50-Ketal Claisen rearrangement with pivaloyl substituted ketal

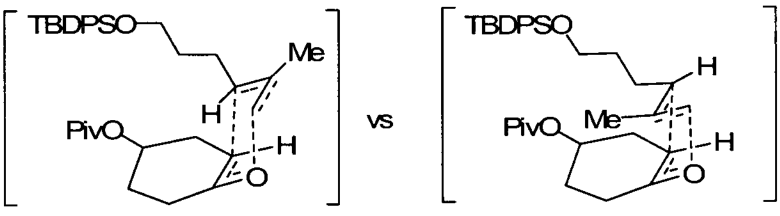


Scheme 2.51-Determination of the nature of the diastereoisomers



The stereoselectivity of the ketal Claisen rearrangement can be explained by the lower energy transition state of the chair-like transition state (**2.177A**) in comparison to the boat-like transition state (**2.177B**) that suffers from major steric interactions (Figure 2.20). In the report of Daub and Griffith, they have not looked at the influence of substituents on the cyclohexane ring.[84] Although possible steric interactions between the developing side chain and the pivaloate might have influenced the reaction, the results indicate that a substituent at the 4-position did not create a remote stereoselectivity.

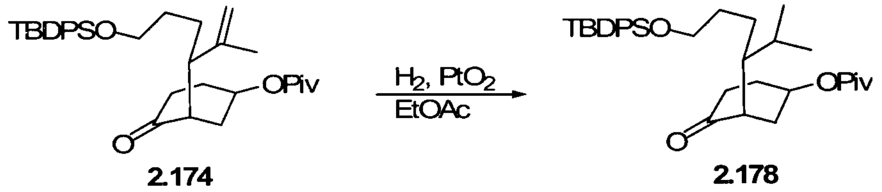
Figure 2.20-Possible transition states for the ketal Claisen rearrangement



2.177A **2.177B**

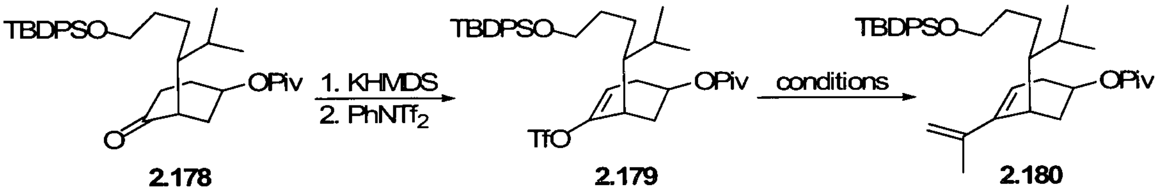
The Claisen rearrangement with the substituted ketal gave successfully the functionalized ketone **2.174**. At that point, the ketone needed to be converted into the diene and the silyl ether into the dienophile in order to form the necessary Diels-Alder reaction precursor (**2.166**). Most of the steps had already been described for similar compounds. Hydrogenation of compound **2.174** was attempted with Adams' catalyst in ethyl acetate (Scheme 2.52). Surprisingly, the reaction did not proceed on the first trial. Fortunately, the reaction did proceed the second time to give isopropyl ketone **2.178** in 76% yield. A thorough analysis of the reaction showed that ketone **2.174** was contaminated with a small amount of ketal **2.172**. Upon the first hydrogenation, the ketal was converted to ketone **2.171** and was removed during the purification. Although the source of the problem was found, a simple purification of ketone **2.174** would not satisfy since ketone **2.174** and ketal **2.172** co-eluted. To solve this problem, the Claisen rearrangement mixture was stirred with oxalic acid in THF and water. These conditions were mild enough that no epimerization occurred. After stirring for 18 hours, most of the ketal was converted into its corresponding ketone (**2.171**). Purification by flash chromatography gave product **2.174** that could be used for the hydrogenation reaction. (Note that even with this removal of the ketal, on larger scale, the hydrogenation needed to be done twice in order to have complete conversion).

Scheme 2.52-Hydrogenation of substrate ***2.174***

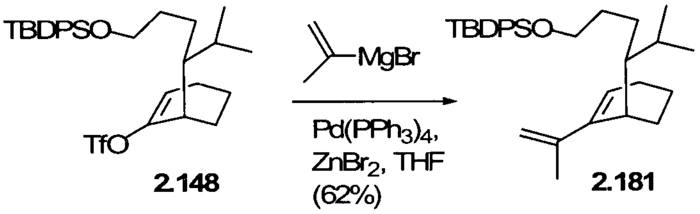


Next, triflate **2.179** was generated under standard conditions in almost quantitative yield. The generation of the diene was envisaged to arise from a cross-coupling reaction (Scheme 2.53). A Negishi cross-coupling seemed the most convenient method to install the isopropenyl unit. In order to find good conditions, the Negishi coupling was tested on unsubstituted triflate **2.148** (Scheme 2.54). It was found that the reaction did not work with $ZnCl_2$ but using $ZnBr_2$ and $Pd(PPh_3)_4$ in THF,[90] the desired product (**2.181**) was obtained in 62% yield. When these conditions were applied to substituted triflate **2.179** (the α isomer was used), the desired product was obtained but as a 7:3 mixture with cyclohexene **2.182** (Scheme 2.55). To explain this product, a proposed mechanism is shown in Figure 2.21. Oxidative insertion of Pd(0) into the vinyl triflate generates intermediate **2.183**. Then, transmetallation with the zinc reagent forms intermediate **2.184**. Next, reductive elimination (Path A) gives the desired product **2.180**. However, due to the steric bulk, this step is in competition with β-hydride elimination (Path B) to generate **2.185**. Then, a reductive elimination gives the cyclohexene product (**2.182**). To minimize this side reaction, it was hypothesized that bidentate ligands would promote the reductive elimination step and minimize pathway B. Different ligands were tested including 1,4-(diphenylphosphino)butane (DPPB), 1,2-(diphenylphosphino)ethane (DPPE) and Xantphos (4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene). It was found that an equimolar quantity of palladium acetate and DPPB gave the desired product **2.180** in 93% yield with only a trace amount of the undesired cyclohexene (Scheme 2.56).

*Scheme 2.53-Conversion of the ketone into diene **2.180***



Scheme 2.54-Negishi coupling with unsubstituted triflate



Scheme 2.55-Negishi coupling with pivaloyl substrate

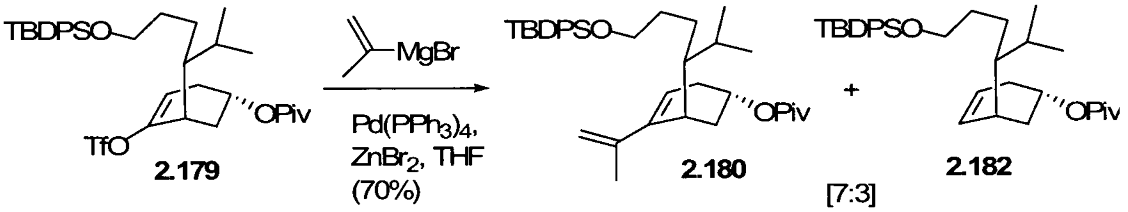
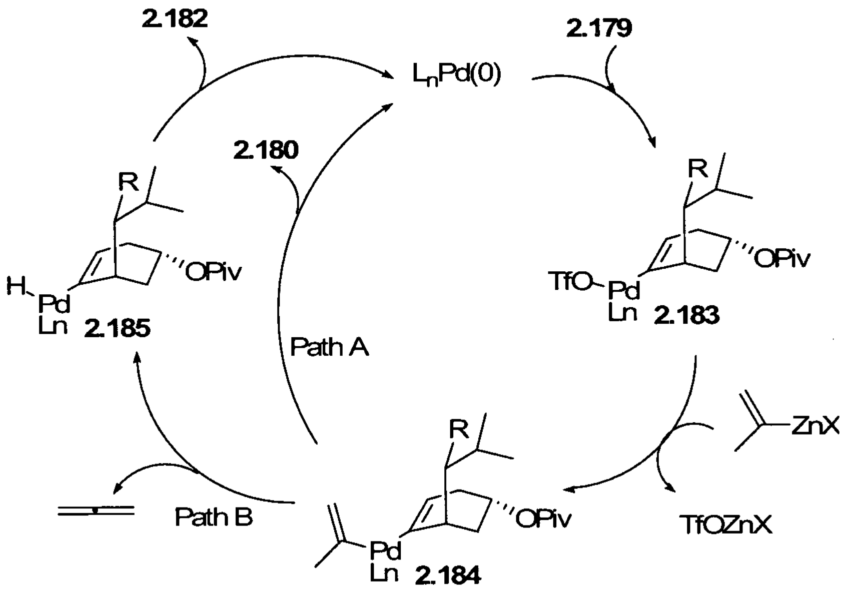
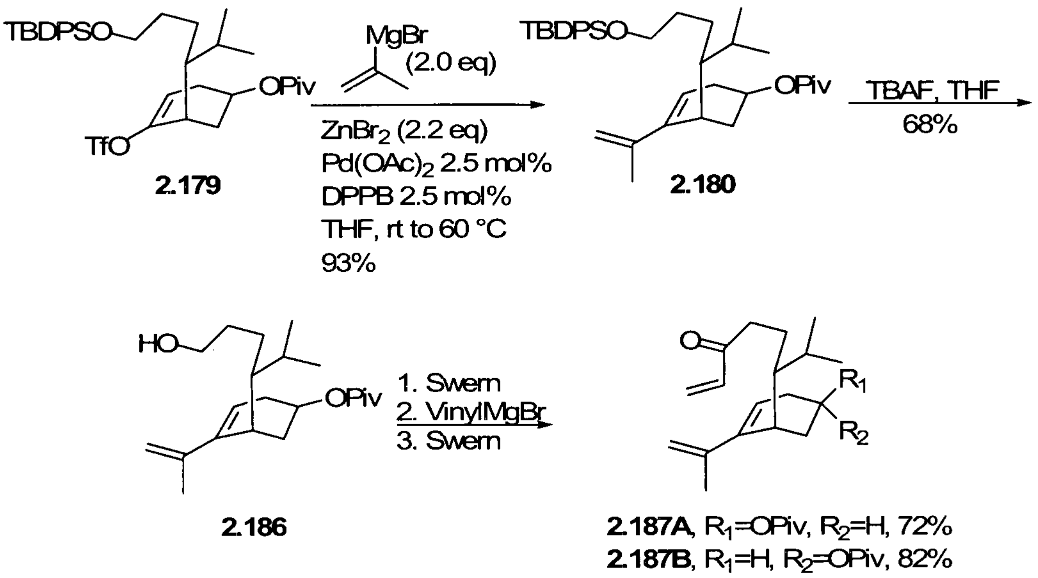


Figure 2.21-Proposed mechanism for Negishi coupling (Path A= Reductive elimination and Path B=β-Hydride elimination pathway)



Diene **2.180** was easily converted to the Diels-Alder precursor by straightforward manipulations of the side chain. Deprotection of **2.180** using TBAF gave **2.186** in 68% yield. It was possible to separate both isomers at this point and carry the following steps separately. Oxidation, alkylation with vinyl magnesium bromide and oxidation of the resulting allylic alcohol gave **2.187** in 72-82% yield. In previous routes, a TPAP/NMO oxidation was used in both instances. However, it was found that higher yields were obtained using a Swern oxidation.

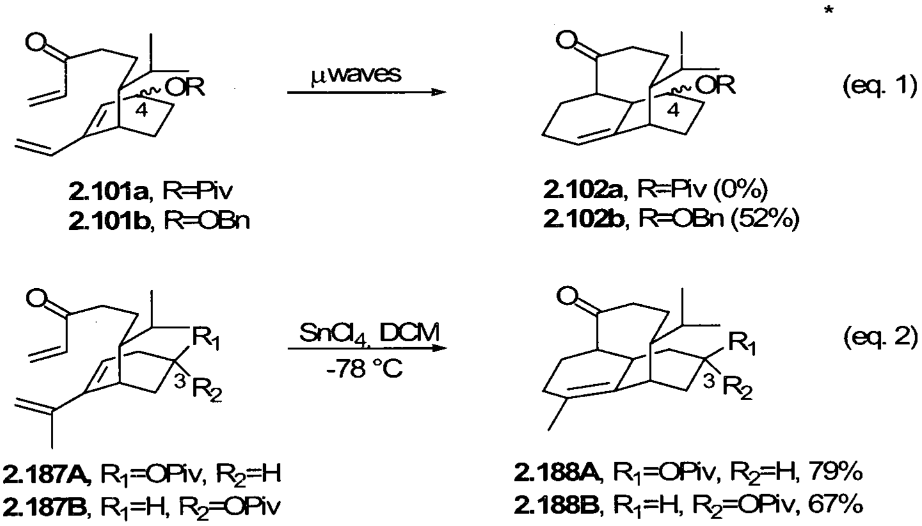
Scheme 2.56-Negishi and functionalization



Our previous studies indicated that the intramolecular Diels-Alder reaction of an unsubstituted triene was very rapid and gave the desired product as a sole diastereoisomer (Proof of principle: Synthesis of the tricyclic core of vinigrol, p.25). In the case of the first generation substituted precursor, the functionality was adjacent to the diene (at C4). The reaction did not work in the case of the pivaloate but the desired product was obtained with a benzyl-protecting group (Scheme 2.57, eq. 1). In the case of substituted triene **2.187**, the functionality was now at C3 and it was hard to anticipate the effect of the pivaloate (eq. 2). There was a risk of steric interactions affecting the reaction. This was especially worrisome for substrate **2.187A**, where the side chain was situated on the same side as the pivaloate.

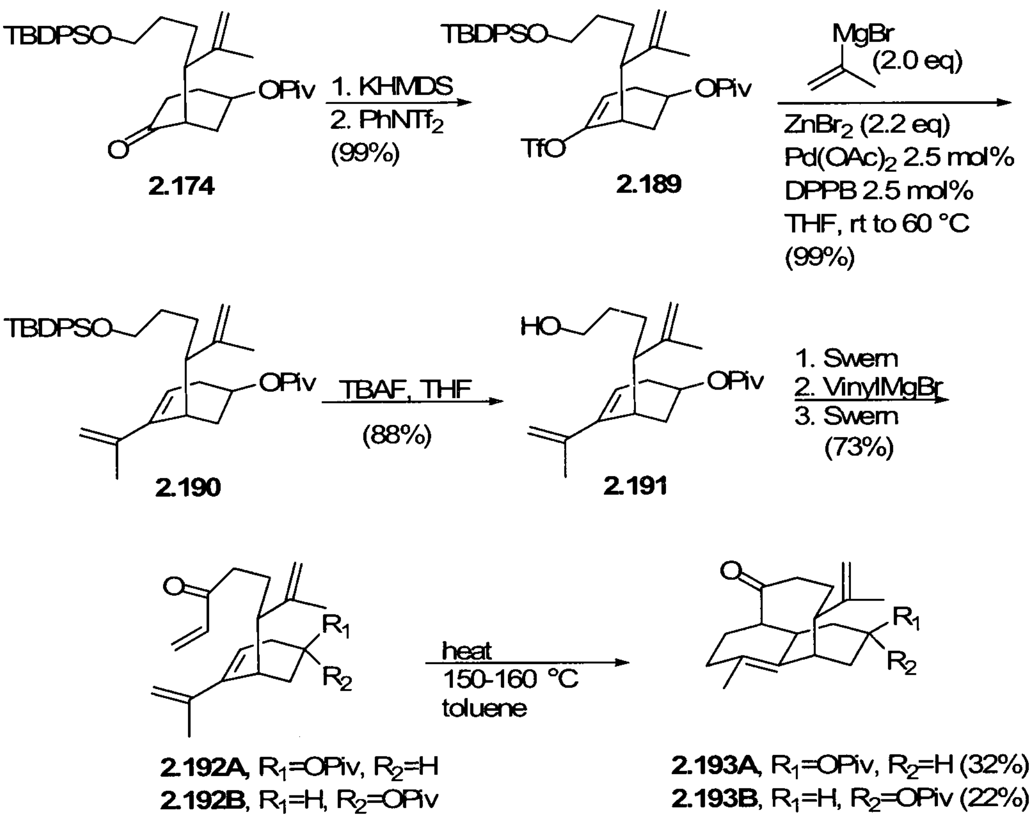
Satisfyingly, treating triene **2.187** with a Lewis acid provided the tricyclic core **2.188**. Different Lewis acids were tested including $BF_3{\cdot}OEt_2$, TMSOTf, $SnCl_4$ and $Sc(OTf)_3$. In all cases except $Sc(OTf)_3$, the desired product was obtained in moderate yield (35-46%). The reaction could also be performed in the microwave at 200 °C to provide **2.188** in 32% yield. It was found that the best Lewis acid was tin tetrachloride in dichloromethane. After optimization of the reaction conditions, the tricyclic core could be obtained in high yield. In both cases, a single diastereoisomer of the Diels-Alder product was observed and it was possible to isolate the valuable intermediate in 67 and 79% depending on the orientation of the protected alcohol. Furthermore, the intramolecular Diels-Alder reaction was performed on a scale up to 0.5 g with similar yields.

Scheme 2.57-Intramolecular Diels-Alder reaction



In summary, we had found a new efficient synthesis to a functionalized core of vinigrol. The synthesis was short and most reactions were high yielding. The only problematic step was the hydrogenation. Although it was possible to get the reaction to go to completion after two trials, we wanted to explore another solution. One can imagine that performing all the steps with the isopropenyl group instead of the isopropyl group and carry out the hydrogenation after the generation of the tricyclic core. The advantage of this approach was that the hydrogenation of the isopropenyl group could be performed simultaneously with the hydrogenation of the other alkene (see Scheme 2.75) and thus, the overall sequence would be one step shorter. Using the optimized conditions, ketone **2.174** was transformed into triflate **2.189** in quantitative yield (Scheme 2.58). The Negishi coupling gave diene **2.190** in 99% yield. Next, the silyl ether was deprotected to afford alcohol **2.191** that was modified into Diels-Alder precursor **2.192** in three steps. For this series, it was found that both isomers could be separated after the last oxidation step and taken separately into the intramolecular Diels-Alder reaction. Unfortunately, the key step did not work as well when the isopropenyl group was present. Under Lewis acid catalysis, the desired product was not observed. Only heating the substrates in toluene at high temperatures could promote the desired cycloaddition (150-160 °C in a sealed tube or microwave at 200 °C). It was possible to isolate the desired product in 22-32% yield. Although the sequence was one step shorter, the lower yield of the key step was unfavorable. For this reason, the synthesis using the isopropyl group was used for the remainder of the research.

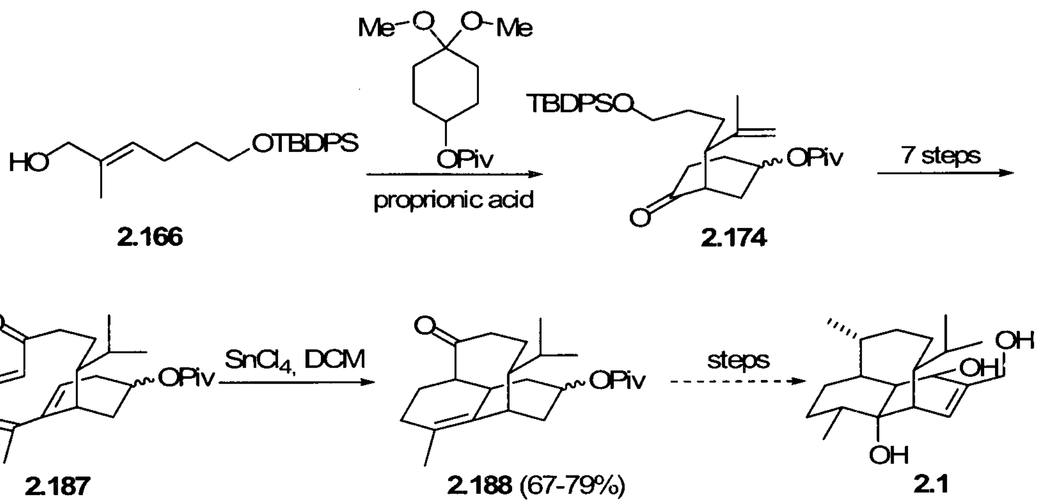
Scheme 2.58-Sequence with the isopropenyl moiety



Summary

In brief, the second approach to the substituted tricyclic core of vinigrol was much more efficient than the first route. A Claisen rearrangement of a functionalized ketal with the appropriate alcohol successfully installed the correct relative stereochemistry. Furthermore, this convergent route had the 6-membered ring already installed from the beginning. Therefore, there were only nine steps in order to generate the tricyclic core of vinigrol (**2.188**) from alcohol **2.166**. With this efficient route to a functionalized core of vinigrol, the next steps toward the natural product were explored.

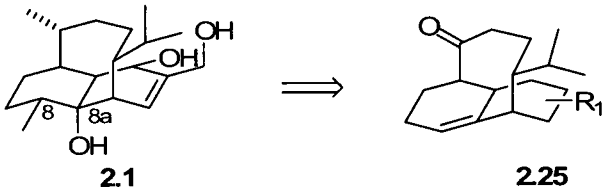
Scheme 2.59-Summary of the second approach



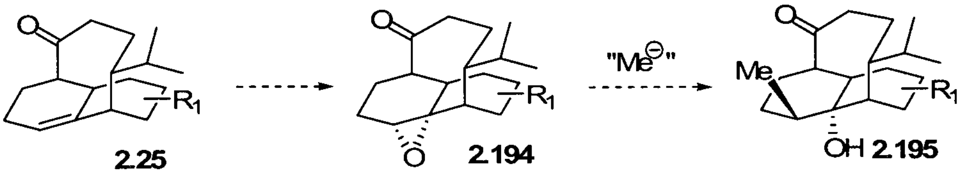
Functionalization at the C8-C8a positions

In the original retrosynthetic analysis, it was imagined that vinigrol (**2.1**) could come from functionalization of tricyclic core **2.25** (Figure 2.22). All the efforts up to this point had been dedicated to the synthesis of the tricyclic core. One of the challenges in the total synthesis of vinigrol was the synthesis of the C8-C8a moiety. As shown in Figure 2.22, the methyl and the hydroxyl group were both syn. The obvious way of installing a methyl adjacent to a tertiary alcohol was to generate the trisubstituted epoxide and open it with a nucleophilic methyl reagent (Scheme 2.60). However, this method would afford the anti relationship between the two functional groups. It is important to note that only the group of Madsuda and co-workers were able to install the correct functionalization (see Scheme 2.3) at C8 and C8a using their Barbier SmI_2-mediated cyclization.[49m,n] However, they did not have the complete core of vinigrol as they were only able to synthesize two of the three rings.

*Figure 2.22-Vinigrol from intermediate **2.25***



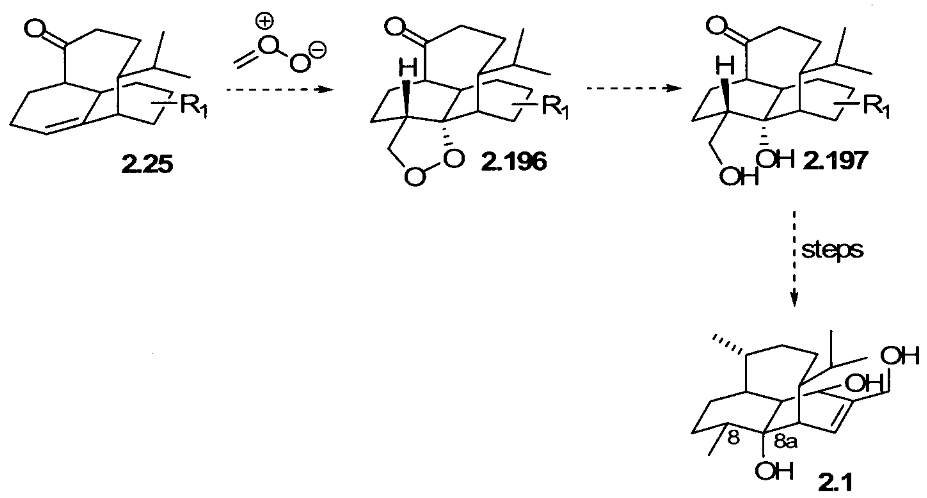
Scheme 2.60-Potential synthesis of the anti isomer



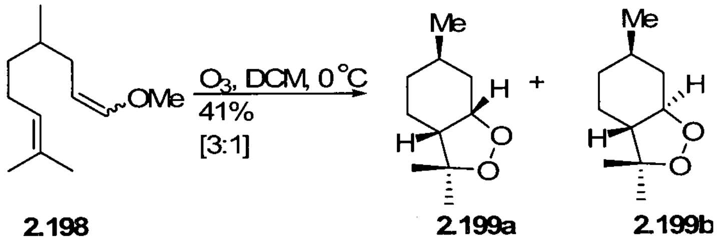
Cycloaddition

From our retrosynthesis, it was believed that the alkene at C8-C8a could be used to install the methyl and the alcohol moieties with the correct stereochemistry. Our first approach was to use a [3+2]-cycloaddition to install the functionalities (Scheme 2.61). We envisioned that the cycloaddition of **2.25** with carbonyl oxide should afford **2.196** since the cycloaddition should occur from the least hindered face of the molecule. The weak peroxide bond could then be cleaved easily to generate diol **2.197**. Finally, a deoxygenation reaction could produce the methyl group at C8. Carbonyl oxides are unstable intermediates that can be generated from ozonolysis of vinyl ethers.[91] Examples of cycloadditions of carbonyl oxides with alkenes are limited.[92] Furthermore, there are no examples in the context of the synthesis of natural products. The only example of a stereoselective cycloaddition was reported by Casey and Culshaw (Scheme 2.62) where they did an intramolecular cycloaddition to afford **2.199a** as the major product.[93]

Scheme 2.61-Functionalization using a [3+2]-cycloaddition

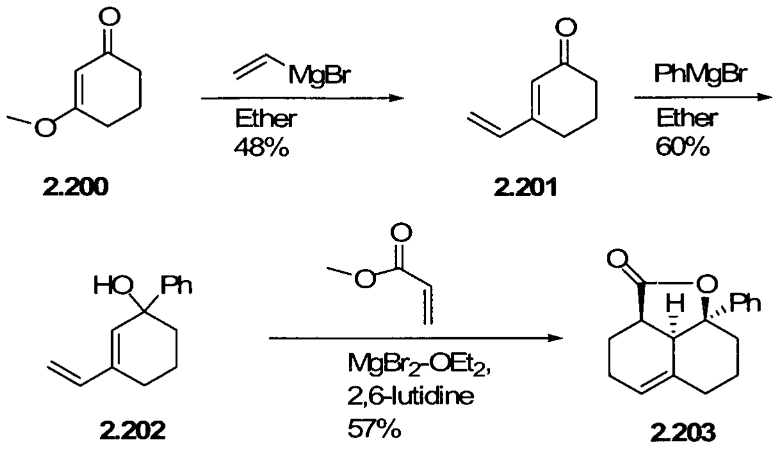


Scheme 2.62-Cycloaddition with a carbonyl oxide (Casey and Culshaw)

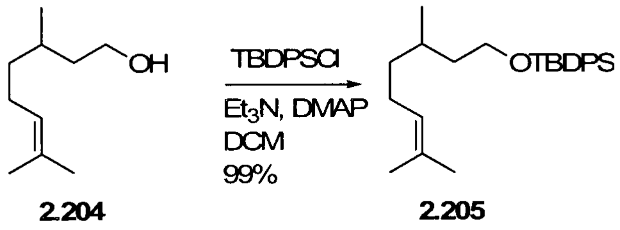


In order to study the feasibility of our approach, the cycloaddition of carbonyl oxide with two different models was tested. This work has been performed by a co-op student, Patrick Levesque under my supervision. Firstly, model substrates **2.203** and **2.205** were synthesized using known procedures (Scheme 2.63 and Scheme 2.64).[23,94] Next, the reaction conditions used by Casey and Culshaw were tested with the model substrates and ethyl vinyl ether (Scheme 2.65). Ozone reacted with ethyl vinyl ether to generate the carbonyl oxide that could react with the tri-substituted alkene. Different reaction conditions including different solvents, temperature, order of addition and number of equivalents were attempted but none gave the desired product.

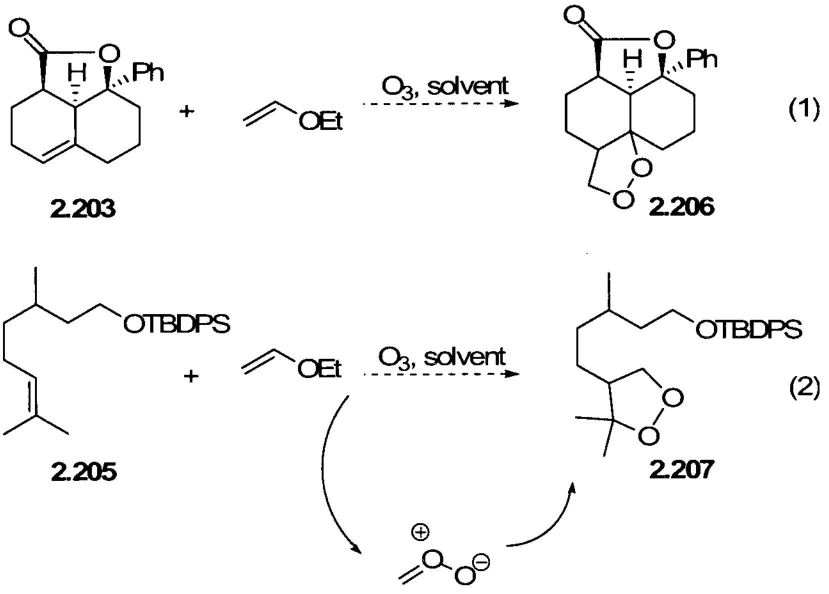
Scheme 2.63-Synthesis of model ***2.203***



Scheme 2.64-Synthesis of model ***2.205***

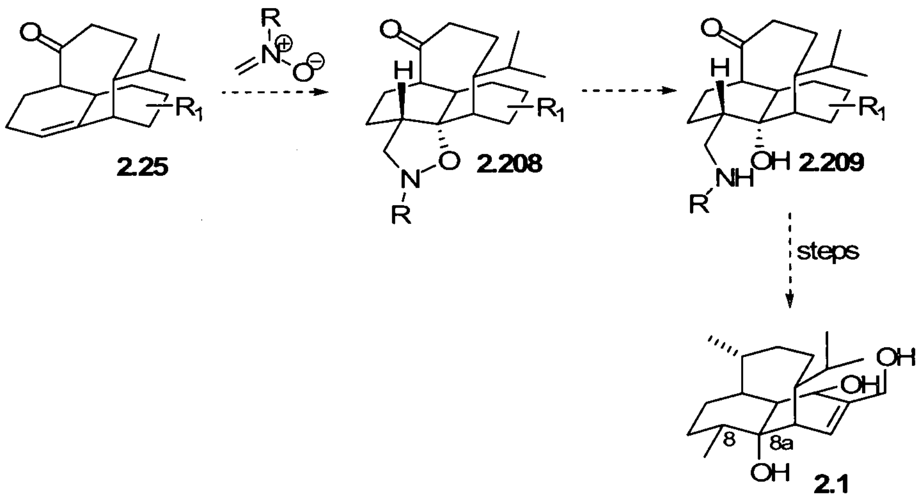


Scheme 2.65-[3+2]-Cycloaddition with carbonyl oxide

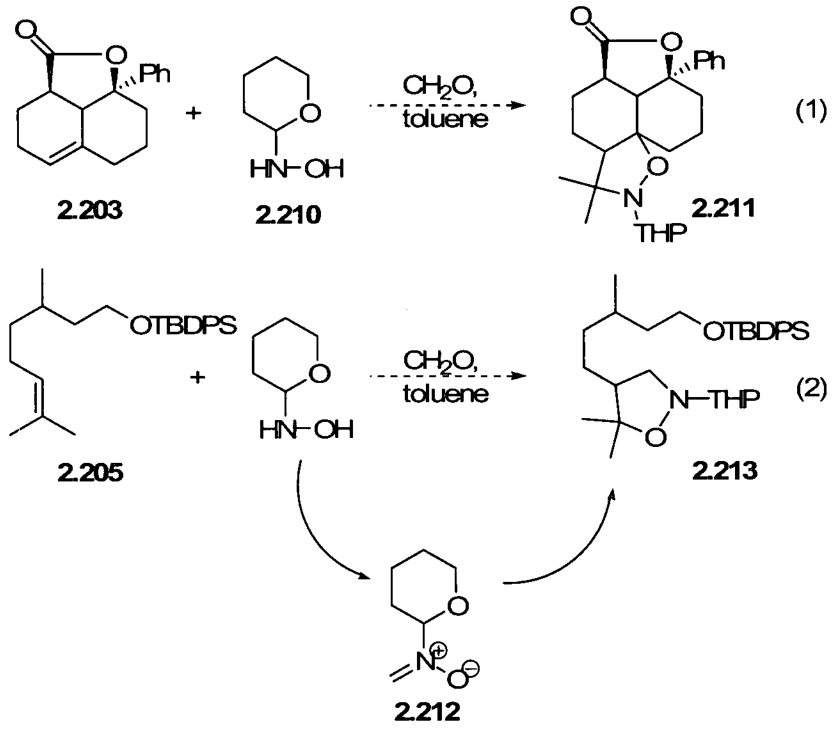


The cycloaddition with a carbonyl oxide was problematic since no desired product was observed. An alternative was the cycloaddition of the alkene with a nitrone to generate an isoxazolidine. A similar strategy to access the functionalities at C8 and C8a could then be used (Scheme 2.66). It might be more difficult to remove the NHR substituent but Nickon and Hill showed that a reductive deamination of aliphatic amines was possible.[95] Since this method removed NH_2, the R group was chosen in a way that it could be replaced easily by a proton. To this end, a tetrahydropyran was chosen as a protecting group. It was known that amino-alcohol **2.210** reacted with paraformaldehyde to generate in situ nitrone **2.212**.[96] The reaction was tried with both models at different temperatures, with or without aluminum oxide. Unfortunately, only starting material was recovered. It was suspected that the non-activated alkenes were just not reactive enough to undergo the cycloaddition.

Scheme 2.66-Isoxazolidine route



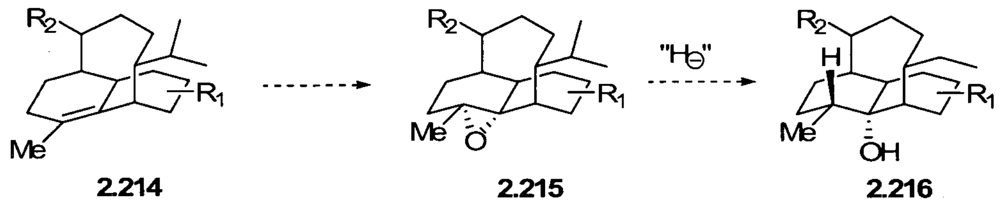
Scheme 2.67-[3+2]-Cycloaddition with nitrone



Opening of the epoxide

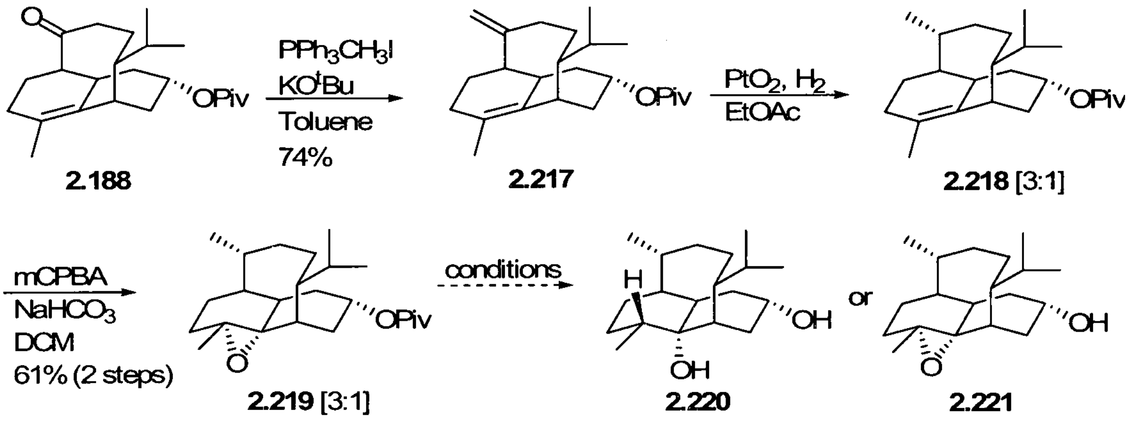
The strategy of installing the methyl and the hydroxyl group in one-step with a cycloaddition was unsuccessful due to the unreactive alkene. Consequently, a new approach to the C8-C8a functionalities was considered. By installing the methyl group from the beginning, one can imagine the opening of epoxide **2.215** with a source of hydride (Scheme 2.68). There are only a limited number of examples where this type of reaction was possible on tetrasubstituted epoxides. In 2004, Kraft and Popaj reported the epoxide opening with three equivalents of Super-Hydride in the last step of their synthesis of limdrostanol.[97] Others have used $LiAlH_4$ in refluxing ether or THF in order to open tetrasubstituted epoxides.[98] These examples gave us the confidence to try this challenging reaction.

Scheme 2.68-Opening of the epoxide strategy



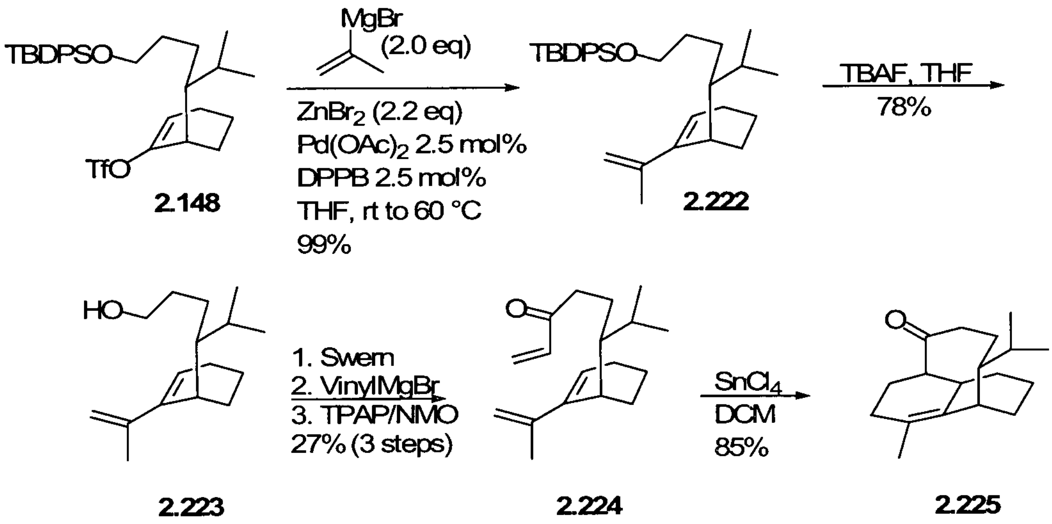
To test the feasibility of this epoxide opening strategy, epoxide **2.219** was prepared (Scheme 2.69). Since the key step used a hydride source as the reagent, it was necessary to protect or convert the ketone moiety. Because the natural product has a methyl at C9, it was judged best to convert the ketone into the necessary methyl group. Accordingly, ketone **2.188** was transformed into **2.217** using the conditions developed by Conia (this exploration was done on the substrate with the α-pivaloate).[66] Next, hydrogenation using Adams' catalyst gave product **2.218** in a 3:1 to 6.3:1 ratio at C9 favoring the desired stereochemistry. The relative stereochemistry was proven later by the synthesis of derivatives (see, Figure 2.25). It was not possible separate the isomers. Therefore, both were transformed into epoxide **2.219** in 61% yield over two steps. Epoxide **2.219** was treated with Super-Hydride in refluxing THF but only starting material was recovered. Next, compound **2.219** was treated with an excess of $LiAlH_4$ in refluxing THF. There was no more starting material but the products obtained did not correspond to **2.220** or **2.221**. It was expected that the pivaloate protecting group would be removed under the reaction conditions. However, the products obtained after the reaction with $LiAlH_4$ did not have any alcohol. In addition, they were not stable and decomposed easily. To test the stability of hydroxy-epoxide **2.221**, substrate **2.219** was treated with Dibal-H to remove the pivaloate. Again, decomposition was observed. These preliminary results indicated that the pivaloate might be interfering in the epoxide opening reaction. At that point, a model study with the unsubstituted core of vinigrol was undertaken by Patrick Levesque.

Scheme 2.69-First trial at the opening of the epoxide



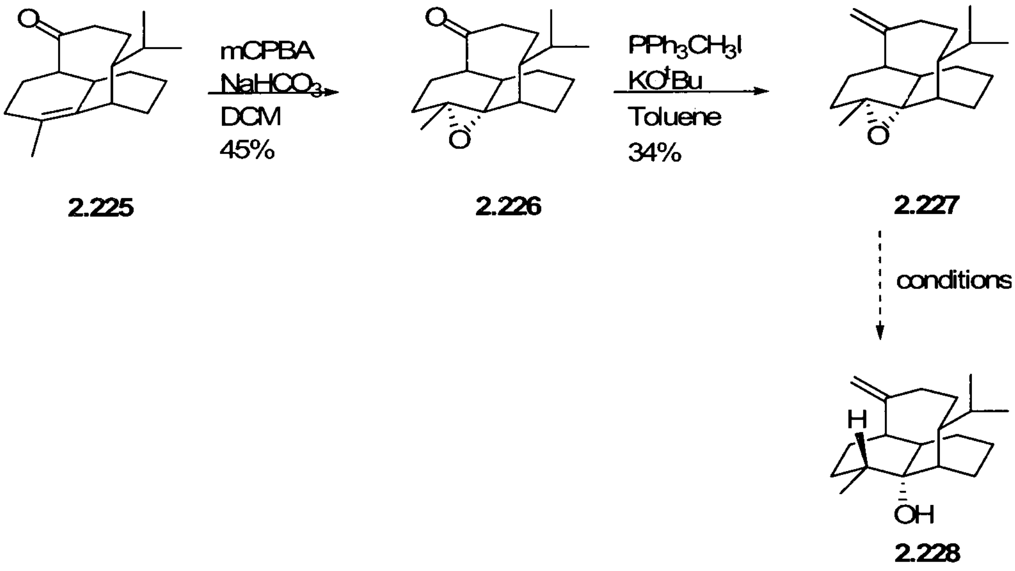
A rapid synthesis of tricyclic core **2.225** was designed based on the previous work done on similar molecules (Scheme 2.70). Triflate **2.148** had been previously synthesized using a ketal Claisen rearrangement and functionalization. Then, Negishi coupling of triflate **2.148** and isopropenyl zinc bromide gave **2.222** in quantitative yield. Although this reaction worked well on small scale using $Pd(PPh_3)_4$, it was found that the cyclohexene impurity was obtained when the reaction was performed on larger scale. Gratifyingly, the optimized conditions using the bidentate ligand DPPB gave the desired product. At that point, the silyl-protecting group was removed using a fluorine source (TBAF) and the resulting alcohol was transformed into the enone in a three step procedure. Better yields were obtained when the second oxidation was done using TPAP and NMO instead of a Swern oxidation. The intramolecular Diels-Alder reaction of **2.224** proceeded smoothly with tin tetrachloride to provide the unsubstituted core of vinigrol with the methyl at C8 already installed (**2.225**).

Scheme 2.70-Synthesis of core ***2.225***



To test the key epoxide opening reaction, alkene **2.225** was converted to epoxide **2.226** using *m*CPBA with sodium bicarbonate as a buffer at 0 °C in 45% yield (Scheme 2.71). Ketone **2.226** was then converted into the olefin in 34% yield. Since the hydrogenation of **2.217** gave a mixture of products, we decided to test the key step on substrate **2.227** to avoid working with mixtures. Firstly, the epoxide was treated with $LiAlH_4$ in refluxing THF. Only starting material was recovered. In a second trial, the epoxide was treated with $LiAlH_4$ in refluxing diethyl ether in the presence of $AlCl_3$.[99] There was no more starting material. However, the products observed did not correspond to the desired product **2.228**. It was believed that elimination of the alcohol occurred under the reaction conditions. At least two inseparable products were obtained and it was hypothesized that this was due to the migration of the new double bond. These experiments indicated that the opening of the epoxide might be happening but side reactions were occurring. One could imagine that the exocyclic alkene might be interfering with the reaction, thus the hydrogenated product was needed.

Scheme 2.71-Second trial of the epoxide opening



Substrate **2.231** was synthesized to study the epoxide opening reaction (Scheme 2.72). Olefination of ketone **2.225** provided **2.229** in 62% yield. Hydrogenation with Adams' catalyst gave a mixture of product as predicted. The ratio was approximately 2:1. Epoxidation with *m*CPBA gave the desired epoxide **2.231** in 59% yield over two steps. Various conditions were attempted to generate the desired product **2.232** (Table 2.8). Treating epoxide **2.231** with an excess of $LiAlH_4$ in THF gave compound **2.230** in 99% yield (entry 1). Under these reaction conditions, the epoxide was probably opened with the hydride source but elimination occurred to provide the alkene (**2.230**). Dibal-H also gave an elimination product but it was different from **2.230** (entry 2). Characterization indicated that diene **2.233** was obtained in quantitative yield. A proposed mechanism for this reaction might be deprotonation of the proton adjacent to the epoxide with concomitant opening of the epoxide. Then, elimination of the alcohol and isomerization provides the diene. Other reducing agents, Red-Al and sodium borohydride, only gave recovered starting material (entries 3 and 4). The base promoted epoxide opening was also attempted using LDA. Only recovered starting material or diene **2.233** were observed under various conditions. Finally, the opening of the epoxide was attempted with TMSI (generated in situ from TMSCl and NaI) but no desired product was observed.

Scheme 2.72-Third trial at opening of the epoxide

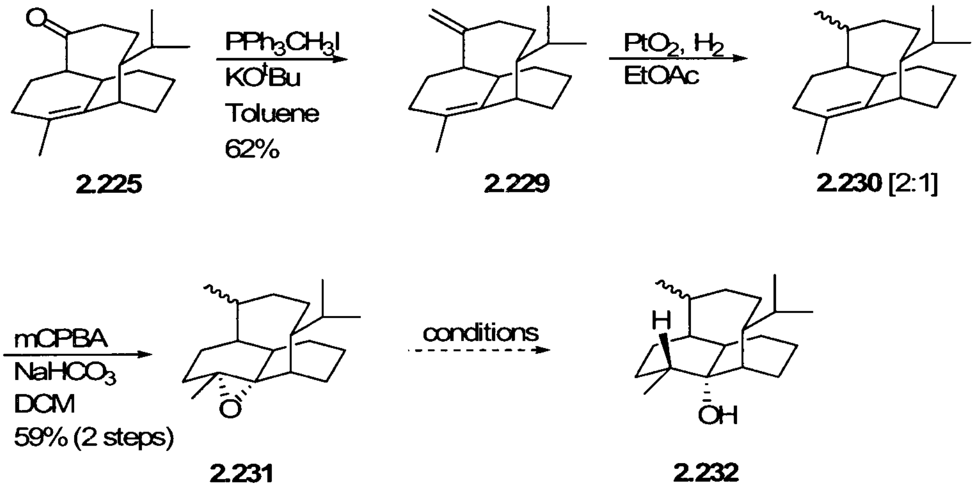
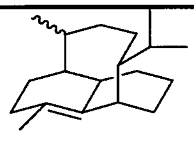
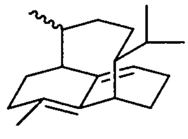


Table 2.8-Opening of the epoxide ***2.23***

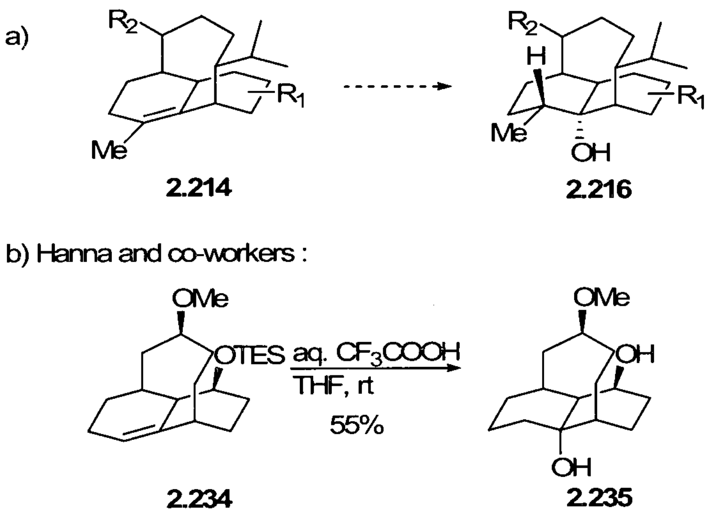
Entry	Hydride source (equiv)	Solvent	Temperature (°C)	Product	Yield
1	LiAlH$_4$ (20)	Et$_2$O	40	 **2.230**	99%
2	Dibal-H (5)	Et$_2$O	-78 to 23	 **2.233**	99%
3	Red-Al (12)	THF	0 to 60	SM	-
4	NaBH$_4$ (5)	Ethanol	80	SM	-

In summary, it was not possible to isolate the desired product from all the epoxide opening attempts. The isolated products (alkene **2.230** and diene **2.233**) are probably derived from the desired alcohol but the rearrangement was rapid since the desired product was never observed. To solve this problem, a new approach to the C8-C8a functionality was imagined.

Direct functionalization of the alkene

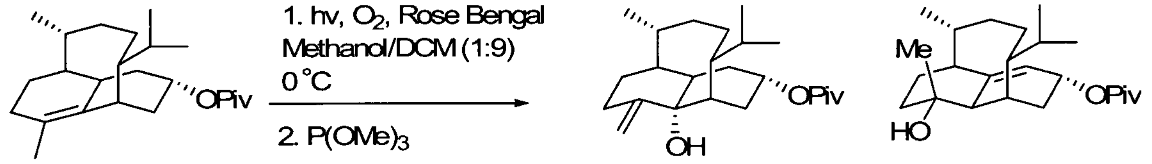
A careful analysis of vinigrol indicated that the methyl group at C8 was positioned in the more stable equatorial position. Thus, under thermodynamic conditions it might be possible to access the desired stereochemistry. Thus, we hypothesized that thermodynamic hydration of **2.214** with water and an acid could generate **2.216** (Scheme 2.73, (a)). Although both possible carbocation at C8 and C8a would be tertiary, the carbocation at C8a might have extra stability due to the adjacent substituent (via hyperconjugation). Hanna and co-workers reported the hydration of **2.234** with trifluoroacetic acid (Scheme 2.73, (b)).[49c] Unfortunately, applying their conditions to our system did not promote the reaction. Various acidic conditions were also tested but only recovered starting was observed.

Scheme 2.73-Direct hydration of the alkene



In a last attempt to functionalize the alkene, an ene reaction with singlet oxygen was imagined. [100] The reaction was done with substrate **2.218** and a mixture of products was observed. However, it was possible to isolate **2.237** as the major product. Based on this result, this route was abandoned.

Scheme 2.74-Functionalization via an ene reaction

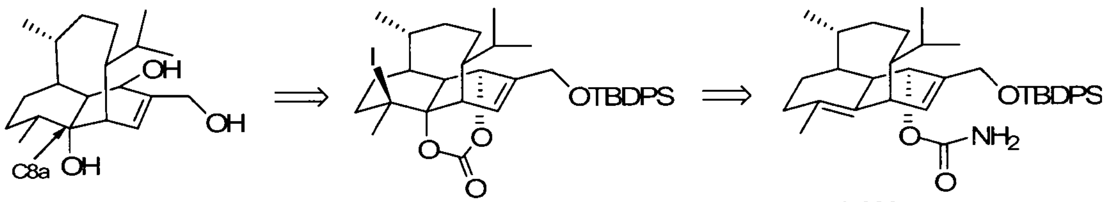


2.188 [3:1] **2.236** [3:1] **2.237** [3:1]

Three different routes have been explored to install the correct functionalities at C8 and C8a. The cycloaddition strategy was unsuccessful due to the unreactive double bond. Alternatively, it was possible to make the epoxide. However, attempts to open the epoxide with various hydride sources did not give the desired product. It was possible that the desired reaction occurred but elimination of the resulting alcohol was very fast. Finally, other methods to open the epoxide or to functionalize directly the alkene were unsuccessful.

It was hypothesized that installing a protected form of the alcohol might minimize the elimination problems. Therefore, a new retrosynthesis for the end of the synthesis was conceived (Figure 2.23). Vinigrol (**2.1**) could be obtained by reduction and deprotection of **2.238**. It was envisioned that the reduction of the C-I bond with Bu_3SnH and a radical initiator would provide the thermodynamic product. Compound **2.238** could be obtained via the iodocyclization of carbamate **2.239**. This strategy should not be plagued by the elimination problems since the necessary alcohol at C8a is revealed only at the last step of the synthesis.

Figure 2.23-Iodocyclization/reduction strategy



2.1 **2.238** **2.239**

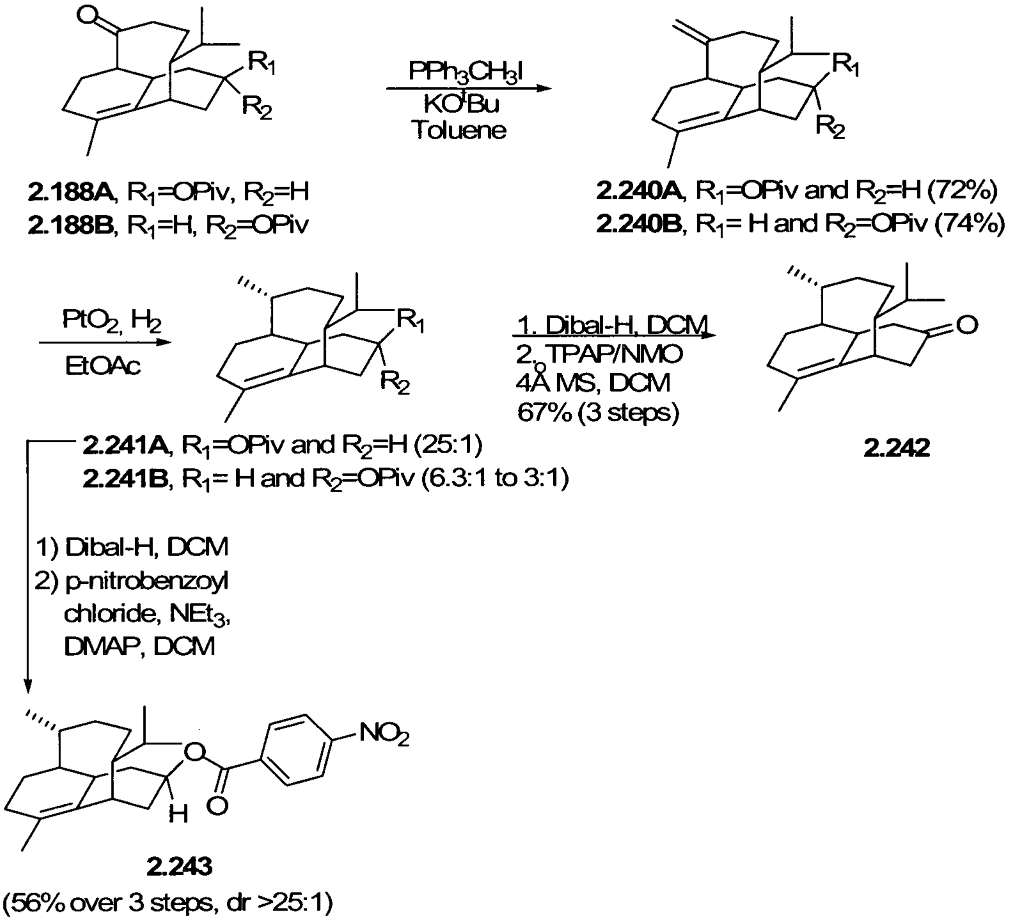
Functionalization of ring B

At that point, an efficient synthesis for the functionalized core of vinigrol had been developed. The results obtained while trying to install the C8-C8a functionalities required us to establish a new synthetic plan for the end of the total synthesis. In order to investigate the iodocyclization/reduction strategy, we needed to synthesize carbamate **2.239** starting from the Diels-Alder product **2.188** (Figure 2.24).

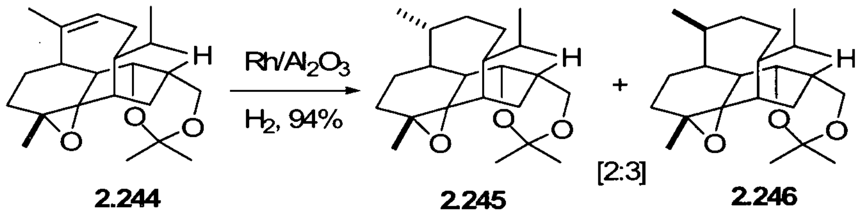
Figure 2.24-Synthesis of carbamate 2.239

During the work on the functionalization of C8 and C8a, a method for converting the ketone at C9 into the methyl group had been established. At that point, the reactions had only been done on substrate **2.188B** (Scheme 2.69). To rectify this issue, both isomers A and B were separately converted to olefins **2.240 A** and **B** in 72-74% yield (Scheme 2.75). As mentioned previously, hydrogenation of olefin **2.240B** using Adams' catalyst gave product **2.241B** in a 6.3:1 to 3:1 ratio. Using the same reaction conditions with olefin **2.240A**, compound **2.241A** was obtained as the sole diastereoisomer (ratio > 25:1). This stereoselectivity was not expected since the pivaloate is far from the olefin. In addition, Hanna *et al* reported that the hydrogenation of **2.244** led to mixture of **2.245** and **2.246** (dr = 2:3) where the major isomer **2.246** possesses the wrong stereochemistry at C9 (Scheme 2.76).[49a] In our case, a cursory inspection of **2.240A** and **2.240B** indicates no apparent conformational preference of the four carbons bridge favoring the olefin hydrogenation to take place only or mainly from the β-face.

*Scheme 2.75-Functionalization of **2.188** into **2.242***



Scheme 2.76-Hydrogenation by Hanna and co-workers



The relative stereochemistry of **2.241A** was established without ambiguity by X-ray crystallography of the benzoate derivative **2.243** (Figure 2.25). A careful examination of **2.243** reveals that the B ring is locked in a half chair conformation and the 8-membered ring adopts a crown conformation (Figure 2.26). This conformation is also found in compound

2.245. In contrast, the crystal structure of a vinigrol derivative (**2.1a**) demonstrates that the 8-membered ring of the natural product adopts a rare boat half-chair conformation (Figure 2.26).

The high diastereoselectivity observed for the hydrogenation reaction of **2.240A** can be rationalized if one assumes that **2.240A** adopts a conformation similar to **2.243**. In this case, the axial hydrogens H1 and H2 are in close proximity to the olefin thereby preventing hydrogenation to occur from the α-face. In the case of **2.240B**, one might propose that pivaloate group is oriented in the equatorial position in a manner to minimize steric interactions. As a result, this could slightly change the conformation of the ansa belt and partially expose the α-face to hydrogenation.

Figure 2.25-Crystal structure of ***2.243***

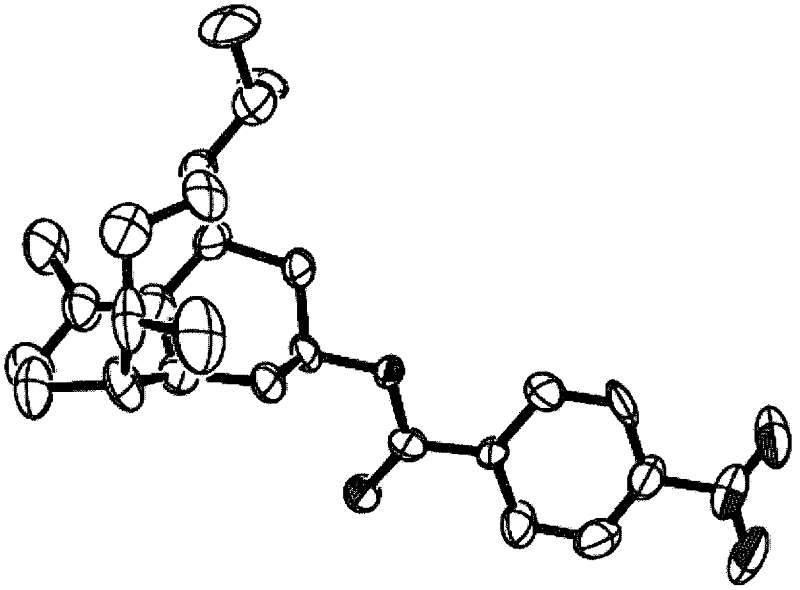
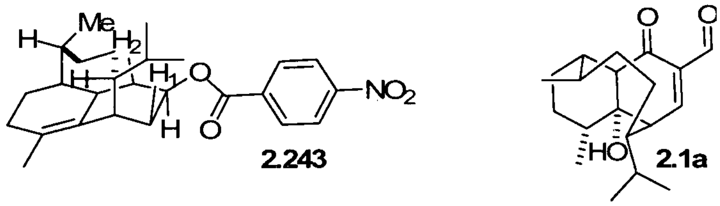
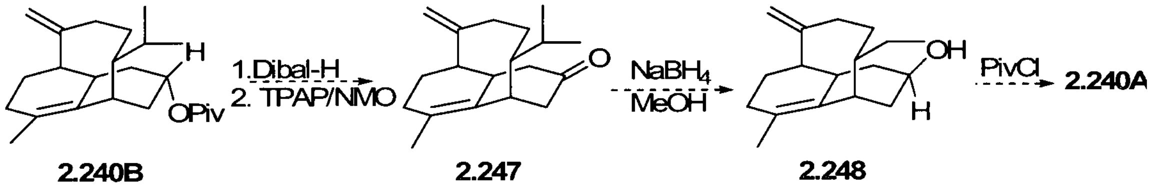


*Figure 2.26-Comparison between substrate **2.243** and vinigrol derivative **2.1a***



To confirm the relative stereochemistry of **2.241B**, it was converted to ketone **2.242** (Scheme 2.75). Firstly, the pivaloate was deprotected using Dibal-H and the resulting alcohol was oxidized using TPAP and NMO. The desired product **2.242** was obtained in 67% yield. The same sequence was performed with **2.241A** to afford **2.242** in 57% yield that time. By comparing the NMR spectra (^{1}H and ^{13}C) of the product obtained in both cases, it was clear that the major isomer in **2.241B** had the same stereochemistry at C9 as **2.241A**. Although an overall selectivity of 86:14 to 93:7 (calculated assuming a 1:1 ratio of A:B) was acceptable, one could also imagine the transformation of **2.240B** into **2.240A** in a four steps procedure (Scheme 2.77). In brief, we found an efficient method to convert the substrate **2.188** into the advanced intermediate **2.242**.

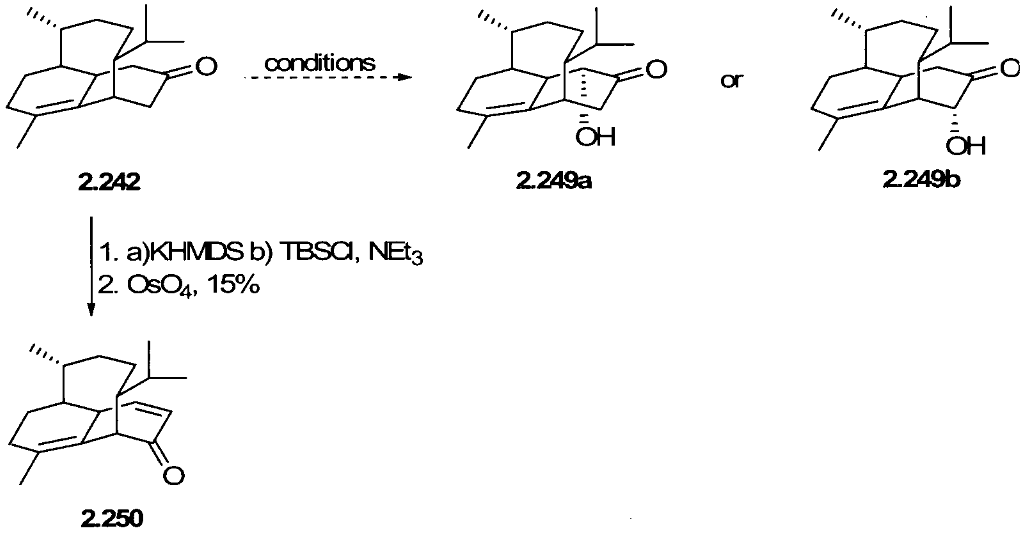
*Scheme 2.77-Transformation of **2.240B** into **2.240A***



Alpha-oxygenation

With ketone **2.242** in hand, it was possible to use that functionality in order to introduce the substituents on the B ring. The first transformation attempted was the alpha-oxygenation. We anticipated a selective deprotonation due to that the conformation of the molecule. It was hard to predict with a molecular model if **2.249a** or **2.249b** was going to be the major product. Ketone **2.242** was deprotonated with KHMDS and treated with Davis' oxaziridine.[101] Many products were obtained and it was not possible to isolate any of them for characterization. In another trial, ketone **2.242** was converted into its silyl enol ether and treated with osmium tetraoxide to promote the Rubottom oxidation.[102] Unfortunately, no desired product was observed. The only product that was isolated in 15% yield was characterized as α,β-unsaturated ketone **2.250**. At the point of the studies, the crystal structure of **2.243** was not available. As this information became available, it became evident that the deprotonation of **2.242** was problematic (Figure 2.25). The protons that are aligned with the π-system of the carbonyl are the two protons on the top of the molecule. Due to the ansa bridge, these protons are very sterically encumbered and the deprotonation cannot occur. In order for the deprotonation to occur, the molecule needed to adopt a different conformation. In brief, these results indicated that the alpha-oxygenation of ketone **2.242** was not feasible and another strategy had to be adopted.

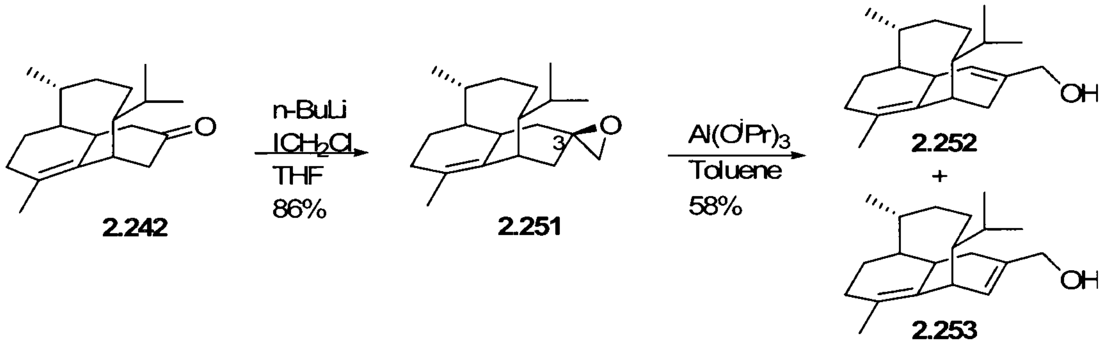
*Scheme 2.78-Alpha-oxygenation of ketone **2.242***



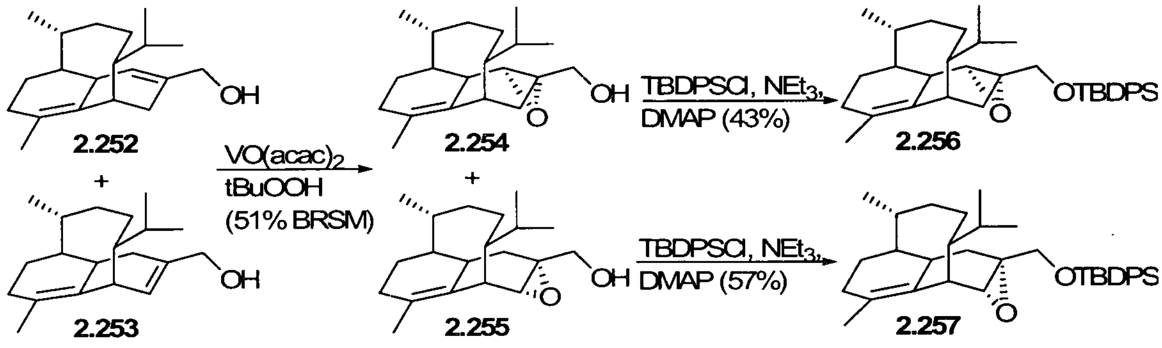
Epoxide-opening strategy

To circumvent the deprotonation issues, ketone **2.242** was transformed into epoxide **2.251** with chloroiodomethane and *n*-BuLi (Scheme 2.79). The method gave **2.251** in 86% yield in a 4:1 ratio at C3. The preference of the attack of the nucleophile from the bottom face was explained by the steric effects of the ansa bridge. The mixture was inconsequential since the chiral center was destroyed in the next step. The base promoted opening of the epoxide was tested with LDA[103] or LDA and TMEDA.[104] Only stating material was recovered in both cases. Fortunately, the epoxide was opened under the Lewis acidic conditions.[105] Epoxide **2.251** was treated with aluminum isopropoxide in toluene at 80 °C to afford an inseparable mixture (approximately 2:1) of alcohols **2.252** and **2.253** in 58% yield. It was envisioned that both products could be transformed into the natural product. A hydroxy-directed epoxidation gave compounds **2.254** and **2.255** in 42% yield (BRSM) (Scheme 2.80). The sensitive hydroxy-epoxides were separated by a rapid purification. Protection with a silyl protecting group provided **2.256** and **2.257** in 57 and 43% yield respectively. Since the stability of the epoxides was unknown, it was judged best to transform them directly into the allylic alcohol to characterize fully the products (note that characterization of product **2.266** enabled to determine the regiochemistry of the epoxide, see Figure 2.27). The Lewis acid conditions previously found to open epoxide **2.251** were applied to the opening of epoxides **2.256** and **2.257**. Compound **2.256** was treated with three equivalents of aluminum isopropoxide in toluene at reflux. A new major product appeared but it did not correspond to allylic alcohol **2.258**. Instead, a very non-polar product was present with extra olefinic peaks indicating that the alcohol might have eliminated. In the case of substrate **2.257** under the same reaction conditions, deprotection of the silyl group was the only reaction occurring after four days of heating. These disappointing results indicated that the endocyclic epoxide could not be opened under Lewis acid conditions. In addition, the stability of alcohol **2.258** was questionable. Therefore, a different method of opening of the epoxide with concomitant protection of the alcohol was explored.

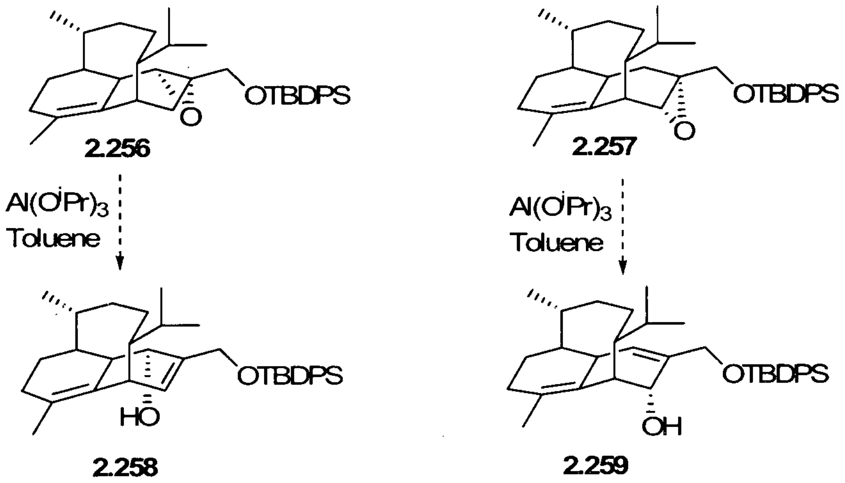
Scheme 2.79-Functionalization of ketone ***2.242***



Scheme 2.80-Selective epoxidation and protection



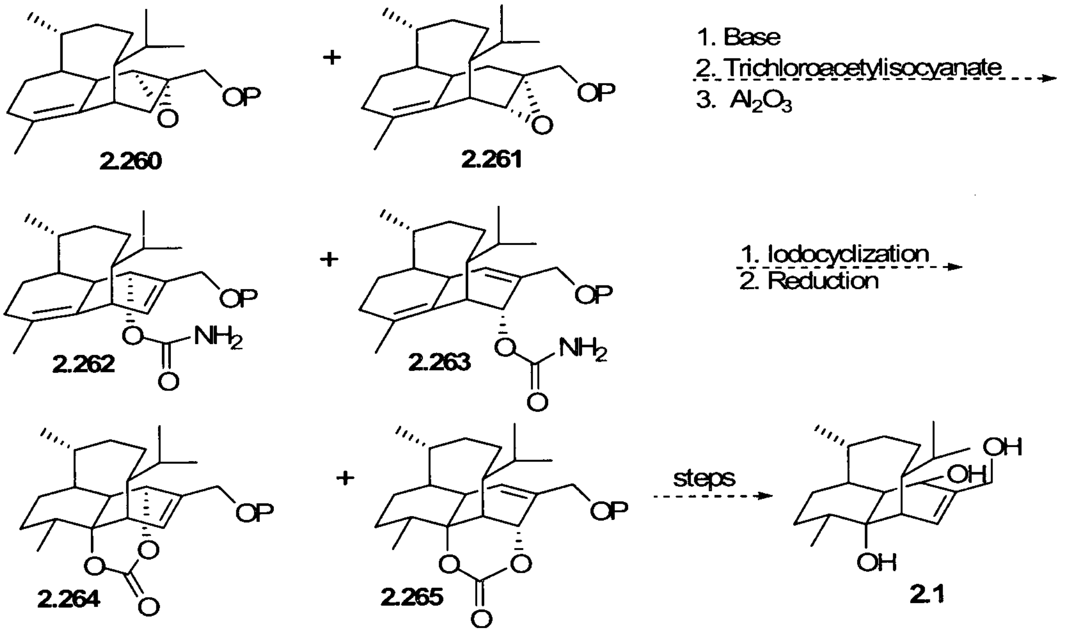
Scheme 2.81-Allylic alcohol formation



Since the goal of functionalizing the B ring was to synthesize carbamate **2.239** (Figure 2.24), a direct route was considered (Scheme 2.82). It was known that alcohols are transformed into carbamates by treatment with trichloroacetyl isocyanate followed by a base (Al_2O_3 can be used for the one-pot procedure).[106] One can imagine opening the epoxide with a base and treating the resulting alkoxide with trichloroacetyl isocyanate followed by aluminum alkoxide. The one-pot procedure should afford carbamates **2.262** and **2.263** and minimize side reactions. Both carbamates could be used in the iodocyclization/reduction sequence to afford **2.264** and **2.265** that should eventually provide the natural product. In the Lewis acid opening of the epoxide, the acid resistant protecting group TBDPS was selected. However, this group was not ideal for the base catalyzed opening of the epoxide.

Therefore, *tert*-butyldimethylsilyl ether **2.266** was synthesized (note that the other regioisomer **2.254** was also treated with the same conditions but there was not enough material to characterize it) (Scheme 2.83). Characterization of **2.266** confirmed the regiochemistry of epoxide **2.255** (Figure 2.27). Protons H_a and H_b were identified by their characteristic chemical shift. A NOESY interaction between H_a and the allylic methyl group confirmed its position. H_a and H_b coupled together as seen in the COSY and there was a weak NOESY interactions between the two protons. These correlations were only possible with regioisomer **2.266**. To promote the opening of the epoxide, activated bases were considered. In a first trial, a mixture of LDA and isopropyl magnesium bromide was tested but only starting material was recovered.[107] In another attempt, a combination of $LiNEt_2$ and potassium *tert*-butoxide was attempted.[108] The strong base generated under the reaction conditions did promote a rearrangement reaction. However, the desired product **2.267** was not observed; instead, aldehyde **2.269** was isolated in 97% yield (the reaction was performed on very small scale). Even with the sterically encumbered TBS protecting group, the deprotonation occurred on the exocyclic methylene group. It was proposed that silyl enol ether **2.268** rearranged to afford the α,β-unsaturated aldehyde **2.269**. In summary, the desired base-promoted opening of the epoxide was not feasible due to important steric interactions in the B ring generated by the ansa belt.

Scheme 2.82-Proposed synthetic plan



Scheme 2.83-Base-promoted opening of the epoxide

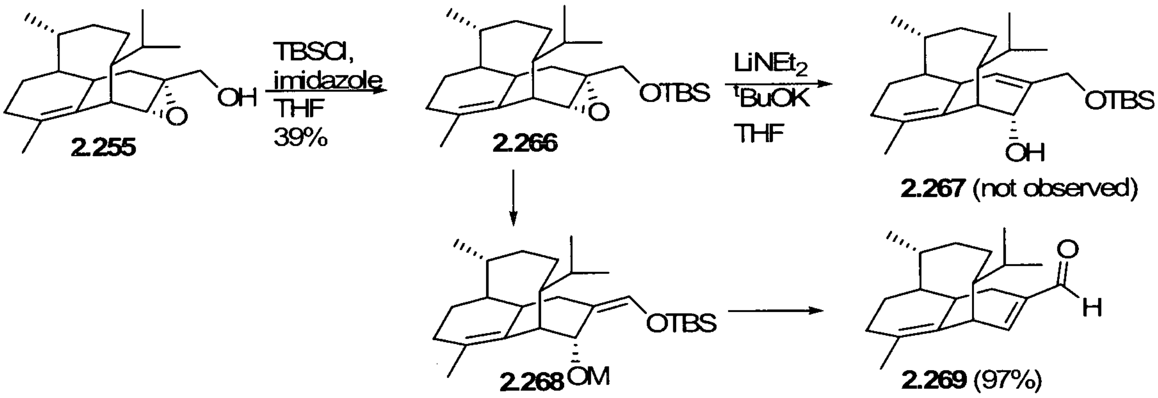
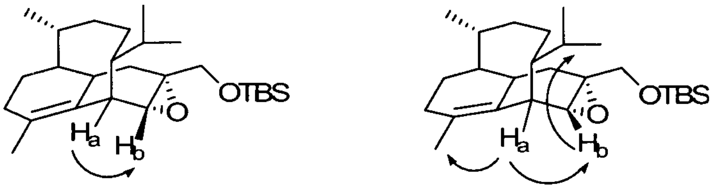


Figure 2.27-Structure elucidation for ***2.266***

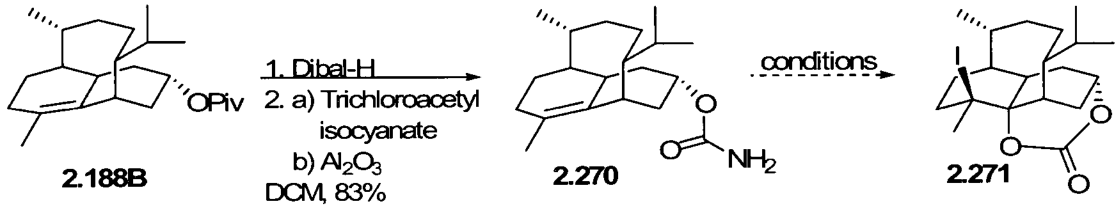


COSY **2.266** NOESY

Iodocyclization

In the iodocyclization synthetic plan, the carbamate moiety was positioned on C4 (Figure 2.23). Since the pivaloate was present on C3, we hypothesized that carbamate **2.270** should be easy to synthesize and it could do the iodocyclization to install the oxygen at C8a (Scheme 2.84). Deprotection of pivaloate **2.188B** and formation of carbamate **2.270** proceeded smoothly in 83% yield over two steps. The iodocyclization was attempted with iodine and sodium bicarbonate with or without silver triflate but no desired product was observed.[109] This investigation was ended since there was likely too much conformational strain for the desired iodocyclization to occur.

Scheme 2.84-Carbamate formation and iodocyclization



Allylic oxidation

Another synthetic plan was explored based on the similarity of compound **2.253** and the natural product (**2.1**). Compound **2.253** was the major product (2:1 ratio) obtained from the epoxide opening of **2.251** (see the *Epoxide-opening strategy* section) and it was only a molecule of H_2O_2 away from the natural product. Thus, selective allylic oxidation at C4 would introduce the necessary alcohol at that position. Since a hydroxy-directed allylic oxidation of alkene does not exist yet, the tetrasubstituted double bond had to be masked. One way to approach this problem is presented in Scheme 2.85. An acetate group was introduced under standard conditions to afford **2.272** and **2.273** that are still inseparable. The acetate group was chosen since it was believed that it would deactivate the adjacent trisubstituted alkene in order to do selective epoxidation of the tetrasubstituted alkene. In a first trial, the reaction did give products **2.274** and **2.275** in 48% yield (un-optimized). It was clear that the oxidation was selective since the characteristic alkene peak was still present by ^{1}H NMR. The product was used directly in the allylic oxidation step. The alkenes were treated with selenium dioxide with an excess of *t*-BuOOH in dichloromethane. It was envisioned that the allylic oxidation would occur from the least hindered side of the molecule. In the final step toward the natural product, it was envisioned that the opening of the epoxide with a hydride source with concomitant deprotection of the acetate would occur to give the stable natural product. Unfortunately, the allylic oxidation only led to decomposition and no desired product was observed. In order to test different reaction conditions, alkenes **2.272** and **2.273** were synthesized again and treated with *m*CPBA in the same conditions as the first trial. That time, the epoxidation was not selective and epoxidation of both alkenes occurred (Figure 2.28). Products **2.276** and **2.277** could not be transformed into the natural product. A possible solution to the problematic epoxidation would be to convert the allylic alcohol to α,β-unsaturated aldehyde **2.280** (Scheme 2.86). After the selective epoxidation, the aldehyde could be reduced to the alcohol and protected before the allylic oxidation.[110] Preliminary literature research resulted in finding one example of an allylic oxidation reaction proceeding in the presence of a trisubstituted epoxide.[111] Alternatively, with a benzoate (instead of an acetate), it might also be possible to promote the selective epoxidation of the tetrasubstituted olefin.[112] Although a viable route, it was not tested yet.

Scheme 2.85-Allylic oxidation strategy

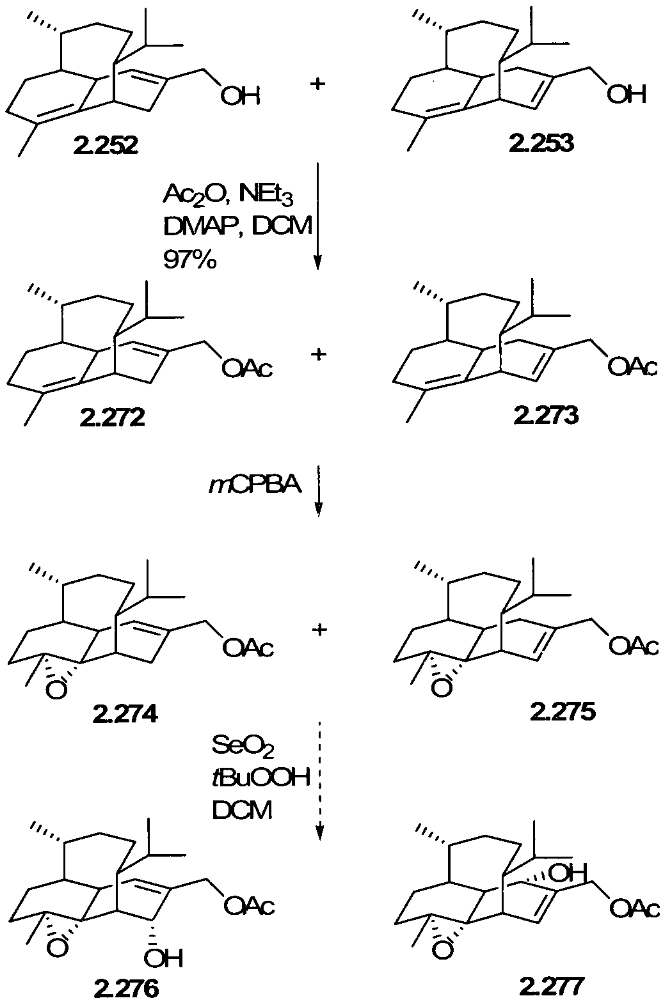
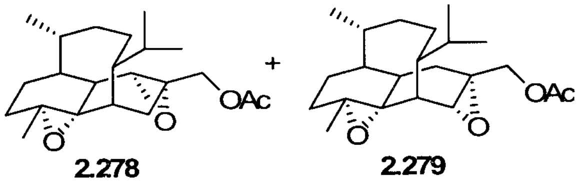
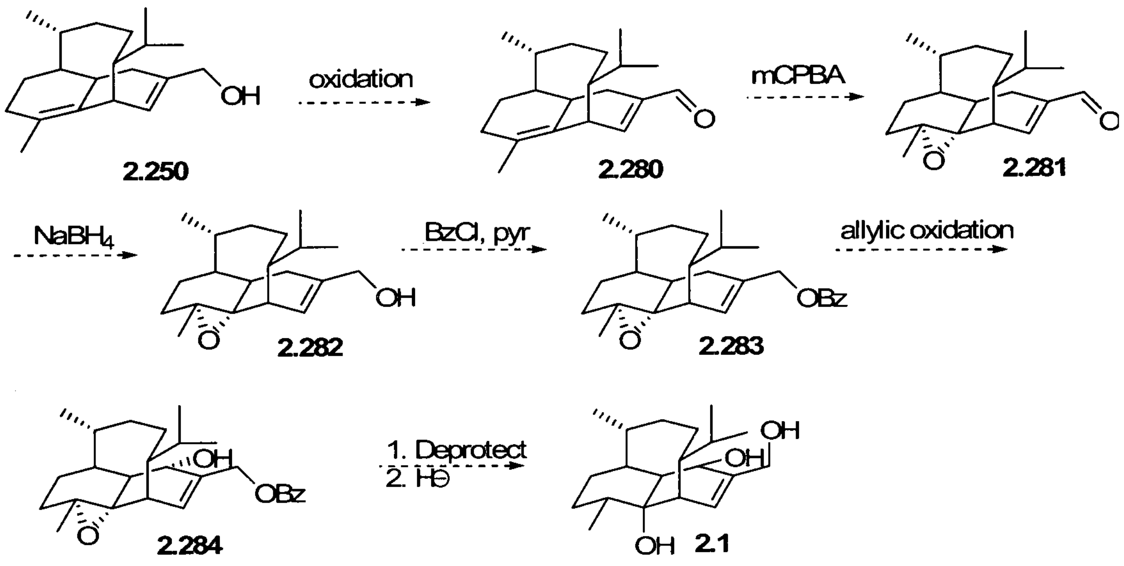


Figure 2.28-Epoxidation products (second trial)



Scheme 2.86-Alternative allylic oxidation route



In summary, the derivatization of the functionalized tricyclic core of vinigrol was explored. It was possible to install the methyl at C9 using a stereoselective hydrogenation. Then, the pivaloate was transformed into the corresponding ketone. Although, alpha-oxygenation was not possible, the ketone was used to install the allylic alcohol. At that point, the complete carbon skeleton of vinigrol was present. An epoxidation/rearrangement strategy was investigated in order to generate the allylic diol and the necessary carbamate. The sterically encumbered B ring did not reacted in the desired fashion. A different strategy to install the allylic diol was explored based on an allylic oxidation reaction but the preliminary results were unfavorable. All the experiments performed gave valuable information for the total synthesis of vinigrol. The reactivity of the molecule was not predictable and could be explained by the highly compact nature of the tricyclic core of vinigrol.

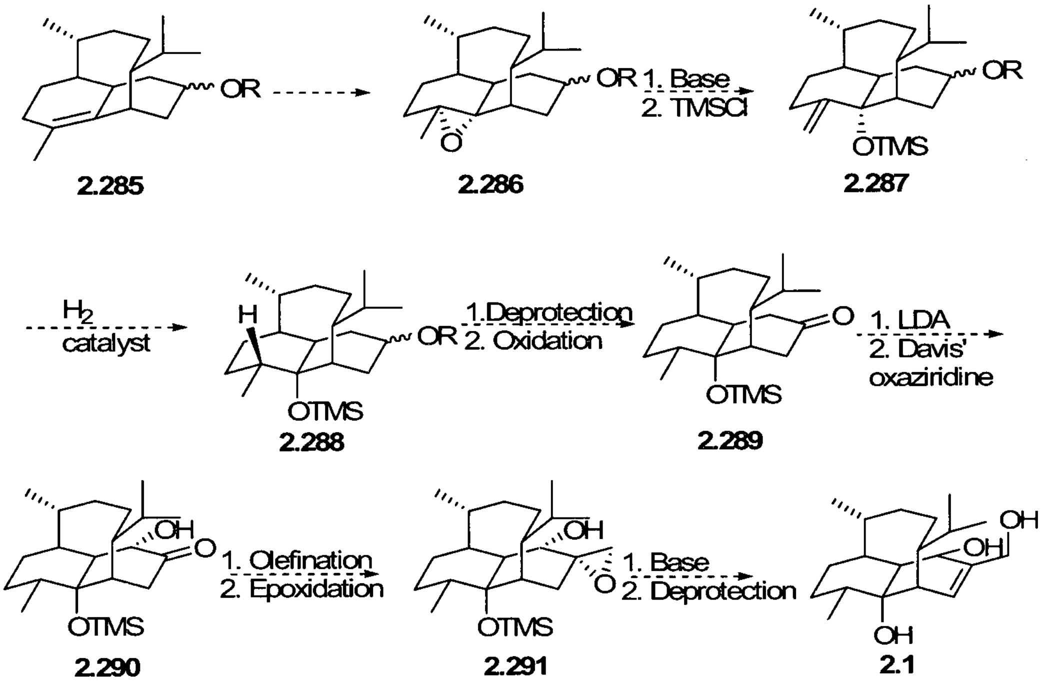
Outlook

The crystal structure of **2.243** was useful to confirm the stereochemistry of the methyl group at C9. By comparison with the crystal structure of the natural product, it was clear that the ansa bridge is in a different conformation in both cases (Figure 2.26). Thus, the substituents on the core of vinigrol influence the preferred conformation of the ansa belt.

In the case of **2.242**, the predominant conformation has the top hydrogen aligned with the pi-system of the carbonyl. Analysis with a molecular model suggests that having a sp^3-hydridized carbon (other than an epoxide) at C8a made the ansa bridge adopt the boat-half chair conformation resulting in the bottom hydrogen being aligned with carbonyl. Therefore, a synthetic plan to access the desired functionalities at C8 and C8a were conceived (Scheme 2.87). The opening of the epoxide had proven to be difficult in the past but other conditions could be tested to generate the protected allylic alcohol (**2.287**). Hydrogenation should occur from the least hindered top face. Next, alpha-oxygenation and functionalization should give the natural product.

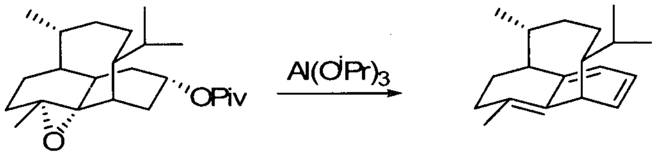
With a small quantity of epoxide **2.219** available, preliminary tests were performed. Treating the epoxide with LDA and potassium *tert*-butoxide only gave recovered starting material. On the other hand, a rearrangement occurred when the epoxide was treated with aluminum isopropoxide in refluxing toluene to provide triene **2.292** (Scheme 2.88). In a last attempt, a different protecting group and base were tested (Scheme 2.89). To this end, epoxide **2.295** was synthesized from alcohol **2.293** in two steps. Satisfyingly, it was possible to open the exoxide with $LiNEt_2$ and *t*-BuOK to provide allylic alcohols **2.296a** and **2.296b** in 74% as a 1:1 ratio. These allylic alcohols have been fully characterized. This is the first report of the complete tricyclic core of vinigrol with the alcohol installed at the C8a position. Protection of the alcohol was possible using KHMDS and TMSCl to provide silyl ethers **2.297a** and **2.297b** in 97% yield. Hydrogenation was quickly attempted with palladium on carbon, Adams' catalyst or Raney nickel but only recovered starting material was obtained at atmospheric pressure. Future work to access the hydrogenated product is currently underway and will be reported in due course.

Scheme 2.87-Future work (optimal)



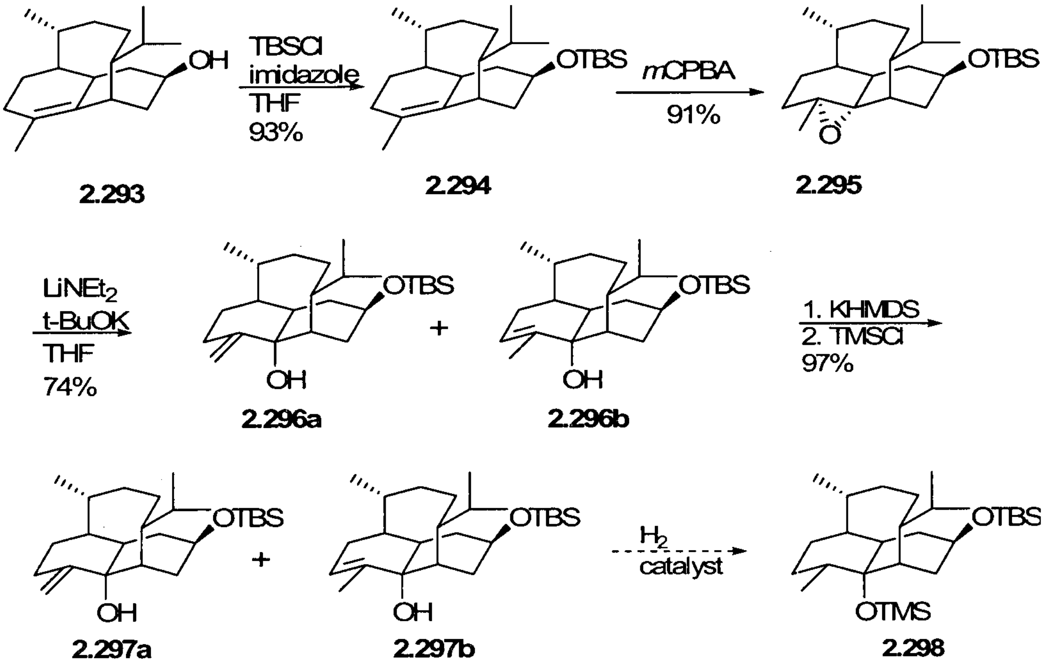
2.285 **2.286** **2.287** **2.288** **2.289** **2.290** **2.291** **2.1**

*Scheme 2.88-Opening of epoxide **2.219** with aluminum isopropoxide*



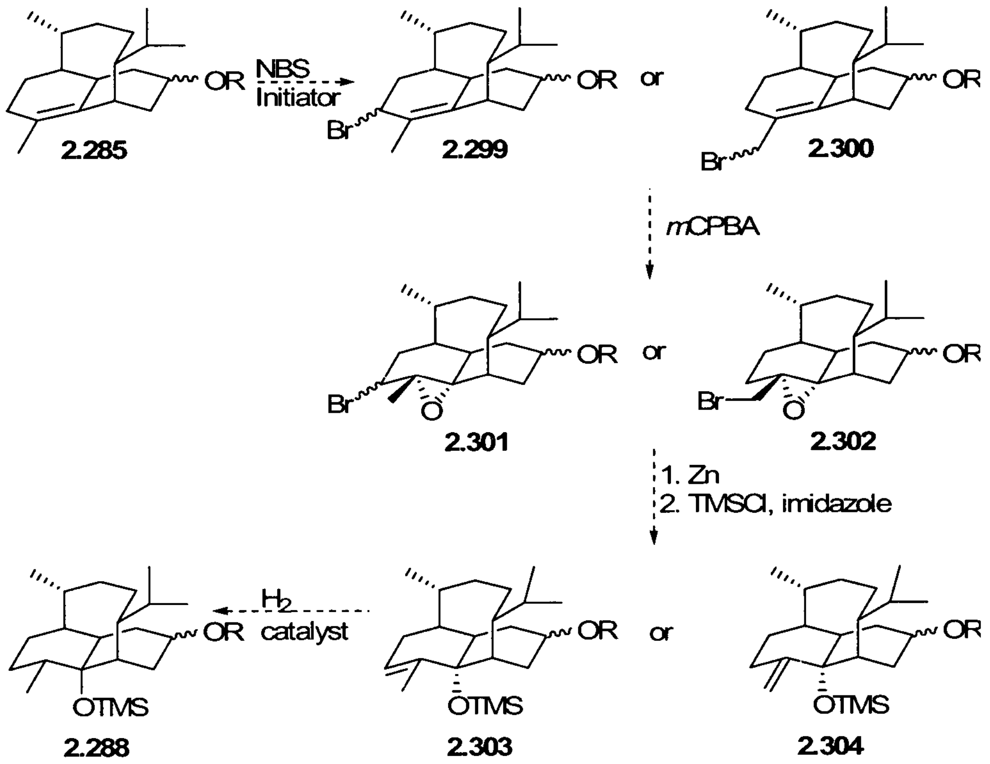
2.219 [3:1] **2.292**

*Scheme 2.89-Opening of epoxide **2.295***



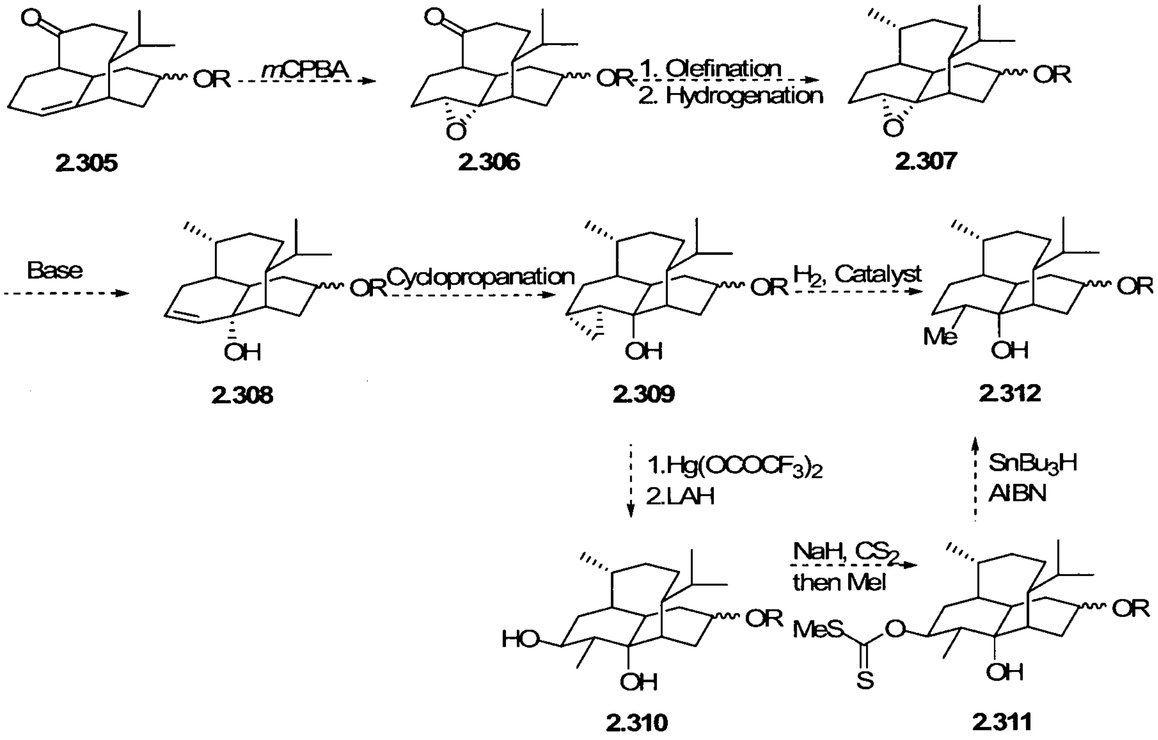
A back-up strategy was also imagined starting from alkene **2.285** (Scheme 2.90). Bromination with NBS and a radical initiator should provide **2.299** as the major product along with **2.300**.[113] Epoxidation and opening of the epoxide with zinc should provide the allylic alcohol that could be protected to afford **2.303** and **2.304**.[114] Hydrogenation should then occur from the least hindered top face to give **2.288** that can be converted into the natural product with the sequence described in Scheme 2.87.

Scheme 2.90-Future work (option 2)



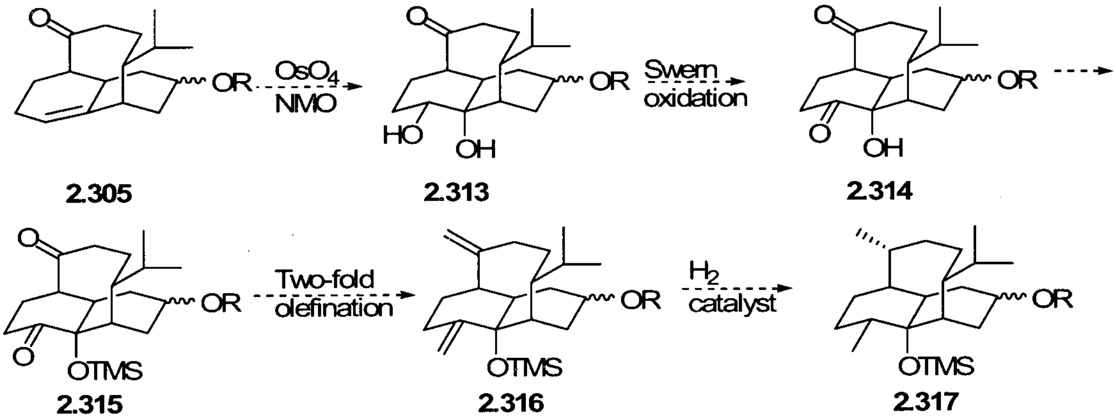
Another way to access the necessary functionalities at C8 and C8a is via a cyclopropane (Scheme 2.91). To access **2.305**, a route similar to the one previously used to synthesize **2.188** could be used with a vinyl coupling partner during the cross-coupling reaction. Epoxide **2.307** could be accessed readily and opening of the epoxide should provide **2.308**. Hydroxy-directed cyclopropanation would generate **2.309** preferentially. Next, the direct hydrogenation will be attempted but regioselectivity in the bond cleavage might be an issue. An alternative is the regioselective opening of cyclopropanes using mercury acetate developed by Still and co-workers.[115] Deoxygenation following standard conditions should give the desired product (**2.312**).

Scheme 2.91-Cyclopropane route to the C8-C8a functionalities



Another possibility for the formation of functionalized molecule **2.317** is using a dihydroxylation strategy (Scheme 2.92). Dihydroxylation of substrate **2.305** should generate diol **2.313**. Then, a Swern oxidation could give the diketone (**2.314**). Protection and a two-fold olefination should give **2.316**. Finally, hydrogenation of both olefins could provide the desired product **2.317**.

Scheme 2.92-Dihydroxylation route to vinigrol



In summary, new routes to install the C8 and C8a functionalities have been planned. This work is currently being conducted by Dr. Minaruzaman in our laboratory.

Conclusions

The studies presented in this chapter represent great advancement toward the total synthesis of vinigrol. Indeed, the intramolecular Diels-Alder reaction was an effective approach to construct the tricyclic core of vinigrol. The strategy was first demonstrated by the synthesis of the unsubstituted core of vinigrol. The Lewis acid promoted intramolecular Diels-Alder reaction generated both the eight-membered and six-membered ring of the tricyclic core in the key step. A functionalized precursor was then synthesized having either a protected alcohol or a ketone at C4. The intramolecular Diels-Alder reaction was possible for the benzyl derivative giving access to the functionalized core of vinigrol (**2.242**).

A more efficient route to a functionalized carbon skeleton was then investigated where a Claisen rearrangement was used to install the desired stereochemistry. After exploring various *O*-alkylation methods, it was found that the ketal Claisen rearrangement gave the desired product. A short thirteen-step sequence was developed, giving access to the functionalized core of vinigrol.

Different routes were examined in order to transform the alkene at C8-C8a into the desired substituents. Cycloadditions, opening of an epoxide and direct functionalization were all explored but it was found that the tertiary alcohol was not very stable. Therefore, efforts were concentrated on functionalization of the B ring before installing the tertiary alcohol. Although it was possible to synthesize the allylic alcohol portion of the B ring, it was not possible to install the other necessary alcohol. Nevertheless, the exploration gave new insights into the reactivity of the functionalized core and the effect of the substituents on the conformation of the molecule. With this information, new routes toward the final functionalization of molecule have been conceived and are presently being explored in order to reach the first total synthesis of vinigrol.

Chapter 3

The Oxy-Cope/Claisen/Ene/Hydroxy-Directed Diels-Alder Reaction: Optimization and Application Towards the Synthesis of Digitoxigenin

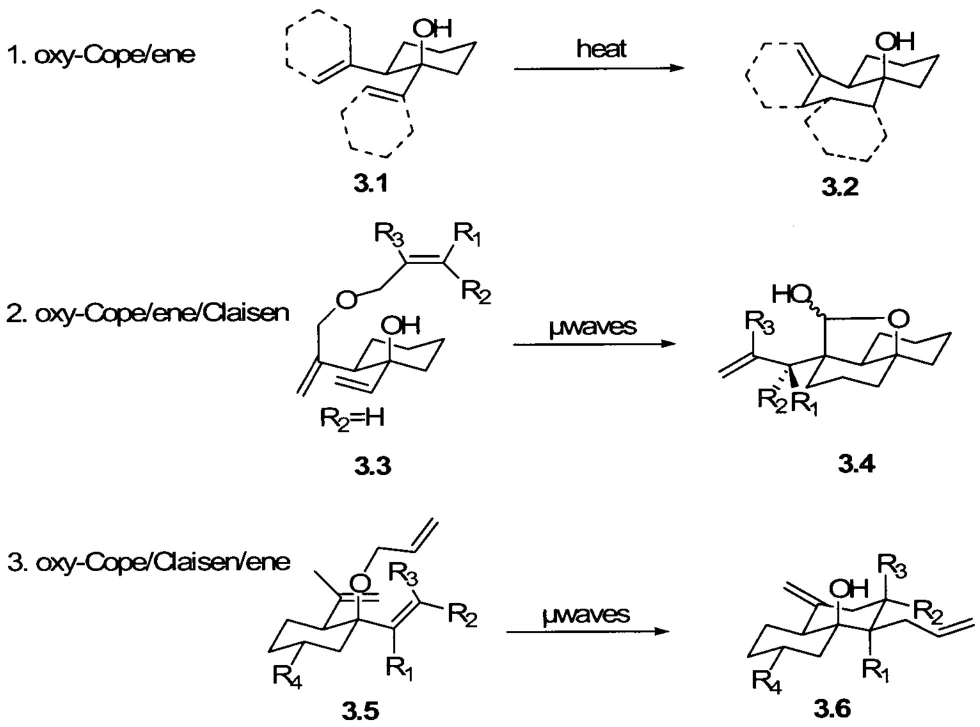
Introduction to domino pericyclic reactions

In the twentieth century, organic chemistry has evolved tremendously. Improved instrumentation, new reagents and catalysts, a century of novel reactions and the emergence of asymmetric catalysis have all contributed to the advancement of the science. Now, the challenge remains of making the reactions as efficient as possible. Domino reactions are a great way to maximize efficiency since it is possible to access complex molecule from simple precursors.

The research in our laboratory has focused on the development and application of cascading pericyclic reactions.[116] In 2000, Warrington and Barriault reported a rapid access to bi- and tricyclic molecules by a cascading oxy-Cope/ene reaction of 1,2-

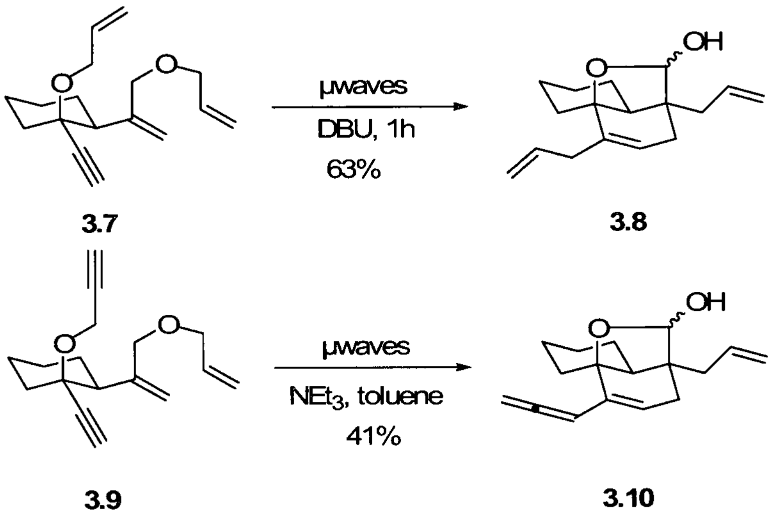
divinylcyclohexanols (Scheme 3.1, eq. 1).[117] This methodology was applied to the total synthesis of (+)-arteannuin-M.[118] In order to increase the molecular complexity achieved during the course of the reaction, the oxy-Cope/ene/Claisen reaction was developed (eq. 2). It was possible to obtain diastereoselectivity molecules of the type **3.4** that contained a quaternary carbon center.[119] This methodology was used towards the total synthesis of tetrodecamycin.[120] Further development led to the oxy-Cope/Claisen/ene domino reaction (eq. 3). This reaction used a preferential macrocyclic conformation in order to generate decalins in a diastereoselective way bearing two adjacent quaternary centers.[121] This methodology was used as the key step towards wiedemannic acid[122] and teucrolivin A.[123]

Scheme 3.1-Cascading pericyclic reactions



In an accidental discovery, Dr. Jeff Warrington was able to isolate and characterize decalin **3.8** (Scheme 3.2). This reaction was the result of an oxy-Cope/Claisen/ene/Claisen domino reaction of substrate **3.7**. Danny Gauvreau studied the scope of this reaction and found that the reaction was very sensitive to functionalization.[124] It was found that propargyl ether **3.9** could undergo the domino reaction to afford allene **3.10**. Optimization was done by Danny Gauveau and myself to determine that the yield could be increased by using triethylamine instead of DBU as a base. Roxanne Clément also investigated other functionalities in systems related to **3.7** and **3.9** but it was found that the reaction was very sensitive to the substitution patterns and the scope of the reaction was limited.[125] With the goal of building as much complexity as possible from simple precursors, Clément investigated other domino and sequential reactions.

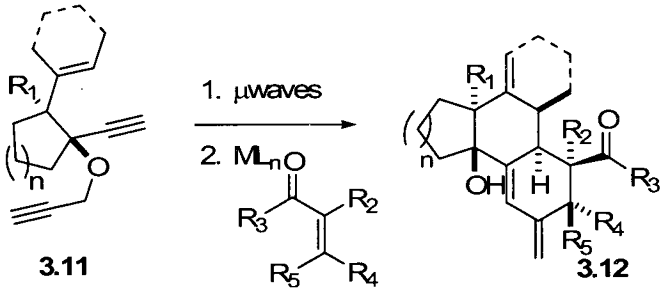
Scheme 3.2-The oxy-Cope/Claisen/ene/Claisen reaction



Introduction to the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction

In 2004, a sequential oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction was developed by Barriault and Clément (Scheme 3.3).[125] The methodology consisted of heating the propargyl ethers (**3.11**) in the microwave to promote the oxy-Cope/Claisen/ene reaction. This domino reaction generates dienes that subsequently react with a dienophile via a hydroxy-directed Diels-Alder reaction.[23] The newly developed method was a very efficient way to access carbocycles (**3.12**) from simple substrates. The importance of the process came from the diastereoselective formation of only one carbocycle having up to four new contiguous chiral centers. Furthermore, the technology was shown to be applicable to a variety of propargyl ethers and dienophiles.[125,126]

Scheme 3.3-Stereoselective synthesis of carbocycles



The proposed mechanism is shown in Figure 3.1 and Figure 3.2 (the specific example of propargyl ether **3.13** and methyl acrylate as the dienophile was chosen for clarity). Submitting propargyl ether **3.13** to microwave irradiation (160-165 °C) for 3 hours led to the isolation of allene **3.16** in yields ranging between 24-27%.[127] The formation of **3.16** can be explained by an oxy-Cope/Claisen/ene reaction. The domino sequence is triggered by an oxy-Cope rearrangement of **3.13** to give the highly strained macrocycle **3.14**. The latter is poised to rearrange via a Claisen rearrangement to provide enone **3.15**. The sequence finishes with a transannular ene reaction to provide the bicyclic allene **3.16**.

In past studies, the dienophile (methyl acrylate) was added to the propargyl ether in toluene before heating in the microwave. A cascade reaction consisting of an oxy-Cope/Claisen/ene/Diels-Alder reaction occurred. However, there was not any selectivity in the Diels-Alder reaction and the four possible diastereoisomers were obtained in a combined yield of 63%.[125] To circumvent this problem, a sequential method was devised using the hydroxy-directed Diels-Alder (HDDA) reaction (Figure 3.2).[23] Thus, the crude allene **3.16** was treated with vinyl magnesium bromide to give the corresponding alkoxide. Subsequent addition of the dienophile allowed for the formation of a complex with the magnesium alkoxide. This tether allowed the reaction to occur with facial selectivity. Although there were two possible transition states for the cycloaddition (TS-A or TS-B), only one isomer was observed. Diels-Alder adduct **3.17** was isolated in 35% yield [dr > 25:1].[128] The high regioselectivity of the HDDA reaction is explained by the HOMO-LUMO interactions between the allene and dienophile.[129] Since there was only one diastereoisomer observed (**3.17**), TS-A must be the lowest energy transition state.

Figure 3.1-Mechanism of oxy-Cope/Claisen/ene reaction

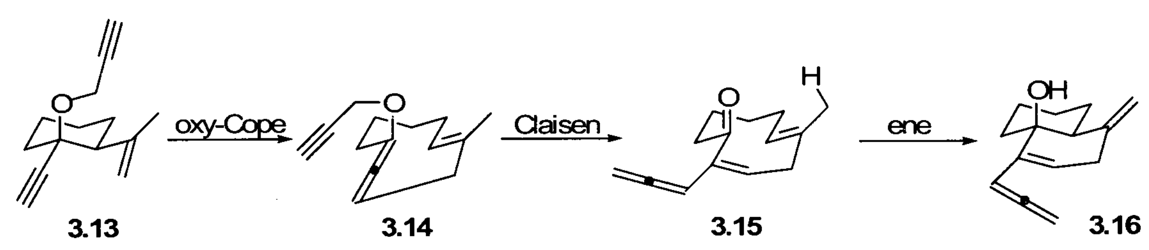
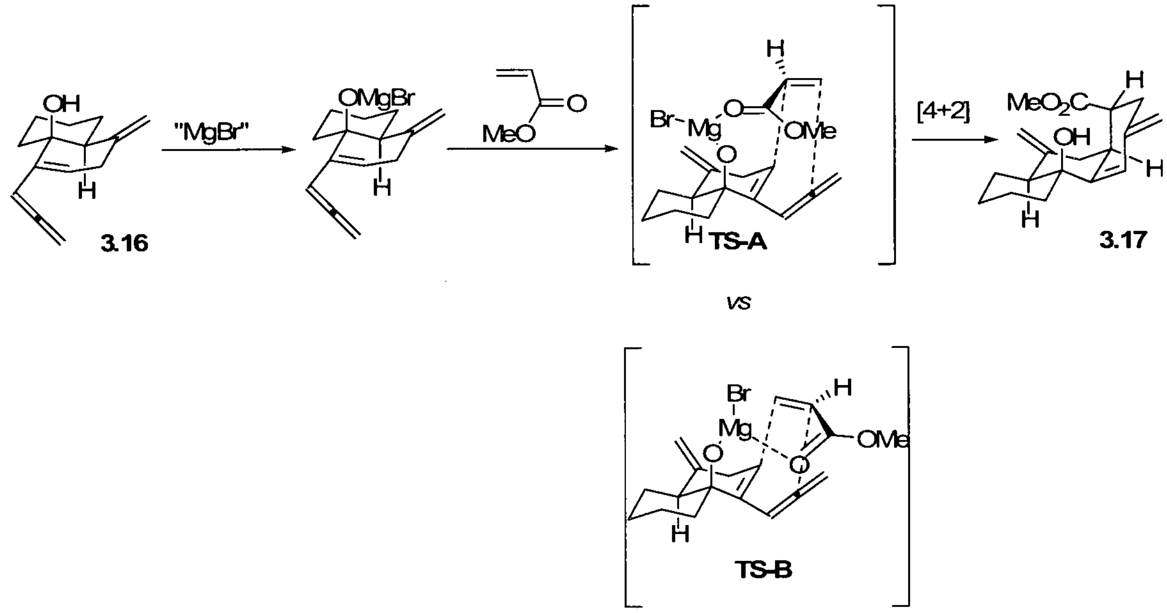


Figure 3.2- Mechanism of hydroxy-directed Diels-Alder reaction



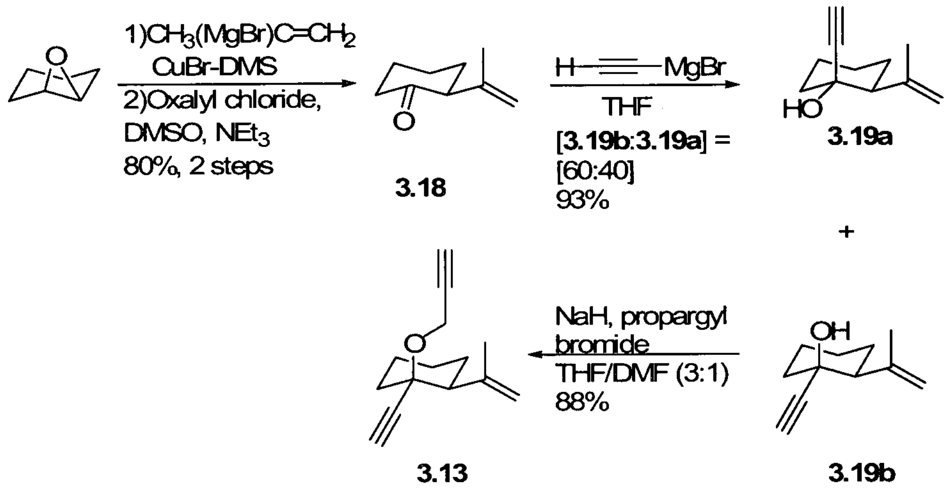
In the initial investigation, it was found that the quality of the organomagnesium reagent greatly influenced the yield of the reaction (only freshly prepared reagent gave reproducible yields). Thus, an alternative method of generating the magnesium alkoxide was preferred ($MgBr_2{\cdot}OEt_2$ in conjunction with 2,6-lutidine[130]). Everything considered, the methodology for the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction developed by Clément and Barriault can be described as follows.[125] A solution of the propargyl ether

(**3.11**) and triethylamine in toluene was degassed and heated in the microwave at 200 °C for 2 hours. Subsequently, the solvent was removed *in vacuo*. The crude allene was dissolved in dichloromethane and added to a pre-mixed solution of $MgBr_2{\cdot}OEt_2$ and 2,6-lutidine in dichloromethane. After stirring the reaction for 2 hours (this time proved to be crucial for the generation of the magnesium alkoxide), the appropriate dienophile was added and the resulting solution was stirred overnight to give the desired carbocycle (**3.12**).

Having a practical and reproducible method for the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction, optimization of the chemical yield was undertaken. Although a yield of 35% was acceptable in view of the four chemical steps, the four new C-C bonds and up to four new chiral centers generated during the one-pot reaction (average of 77% per step): We still judged it necessary to try to increase the yield as high as possible for the eventual application of the methodology as a key step for the total synthesis of a natural product.

For simplicity and comparability, optimization was done using propargyl ether **3.13** and methyl acrylate as the dienophile. This precursor could be obtained in four steps from commercially available cyclohexene oxide (Scheme 3.4). Treatment of known ketone **3.18**[117] with ethynyl magnesium bromide afforded a mixture of diastereoisomers that could be separated to give the major diastereoisomer **3.19b** (59% isolated yield). Subsequent treatment of alcohol **3.19b** with propargyl bromide and sodium hydride in THF/DMF (3:1) gave the desired propargyl ether (**3.13**) in 88% yield.

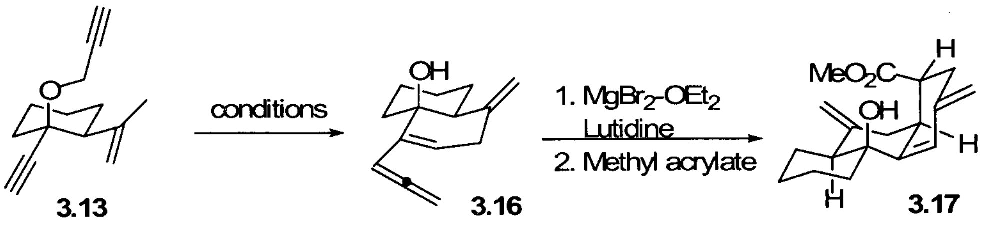
*Scheme 3.4-Synthesis of propargyl ether **3.13***



Optimization of the oxy-Cope/Claisen/ene sequence

Optimization was started by finding the most favorable conditions for the oxy-Cope/Claisen/ene sequence (Scheme 3.5). As mentioned above, the resulting allene (**3.16**) was not stable on silica and its isolation led to low yields. Thus, it was necessary to perform the hydroxy-directed Diels-Alder reaction and isolate the product (**3.17**) in order to get a meaningful yield. In order to compare the yields, the same reaction conditions for the hydroxy-directed Diels-Alder reaction were used throughout the first study.

Scheme 3.5-Optimization of oxy-Cope/Claisen/ene sequence



As mentioned previously, the microwave reaction conditions that promoted the oxy-Cope/Claisen/ene cascade (200 °C for 2 hours in toluene) used triethylamine in excess. It has been hypothesized that the role of the base was to neutralize any acid that could be formed at high temperatures. In a control experiment, it was found that performing the reaction without a base led to 5 to 10% lower yields. The first step in the optimization was to modify the additive. A variety of bases were examined including tetramethylethylenediamine, sparteine, *N*,*O*-bis(trimethylsilyl)acetamide, DBU and 2,6-lutidine. Unfortunately, the yield of the reaction was lowered in comparison to triethylamine. These bases could not be removed *in vacuo* and were present in the hydroxy-directed Diels-Alder step. The lower yield observed could be due to the fact that these bases interfered with the complexation of the magnesium alkoxide to the dienophile. In the past, higher yields of microwave reaction have been observed in certain cases when a radical scavenger was added to the reaction conditions.[131] However, in the case of the oxy-Cope/Claisen/ene reaction of propargyl ether **3.13**, addition of a catalytic amount BHT did not increase the yield but led to an 8-10% decrease of yield. Therefore, these results indicate that the best additive was triethylamine and ruled out the interference of radicals in the reaction.

Next, the temperature and time of the microwave reaction were modified (Table 3.1). The reaction was performed in toluene with 10 equivalents of triethylamine. Decreasing the reaction time to 30 minutes led to an increase of yield to 40% (entry 2). A similar yield (42%) was obtained by increasing the reaction temperature to 207 °C and changing the reaction time to 60 minutes. It was believed that shorter reaction time prevented decomposition and resulted in higher yields. It was also important to note that previous studies by Clément showed that the domino reaction occurred at lower reaction temperature (165-190 °C) but the reaction times were long and the yield was also 35%.[125] Thus, the optimal conditions for the microwave reaction in toluene seemed to be at 200-207 °C for 30-60 minutes.

Table 3.1-Effect of time and temperature on the yield[a]

Entry	Temperature (°C)	Time (min)	Isolated Yield (%)
1	200	120	35
2	200	30	40
3	207	60	42

[a] Microwave reaction was done in toluene with 10 equiv of triethylamine. HDDA reaction was performed with $MgBr_2{\cdot}OEt_2$ and 2,6-lutidine in dichloromethane at room temperature.

Different high boiling point solvents were explored for the microwave reaction (Table 3.2). Chlorobenzene gave lower yields than toluene (entries 2 & 3). Again, a higher yield was observed by decreasing the reaction time to 30 minutes. However, this yield was still lower than the one obtained with toluene. On the other hand, acetonitrile proved to be comparable to toluene. A yield of 42% yield was obtained for the microwave reaction performed at 200 °C for 35 minutes (entry 4). Since acetonitrile absorbed the microwaves, it was possible to increase the reaction temperature to 220 °C. Even by reducing the reaction time to 15 minutes, the product was only isolated in 30% yield (entry 5). Lastly, 1,2-dimethoxyethane (DME) gave low yields due to decomposition (visible by TLC) and 1,2-dichloroethane gave a sluggish mixture and no desired product (entries 6 & 7). Thus, the best solvents for the microwave reaction are toluene and acetonitrile.

Table 3.2-Effect of the solvent of the microwave reaction on the yield[a]

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	Toluene	207	60	42
2	Chlorobenzene	200	120	21
3	Chlorobenzene	200	30	31
4	Acetonitrile	200	35	42
5	Acetonitrile	220	15	30
6	DME	200	35	20
7	1,2-dichloroethane	200	30	0[b]

[a] Microwave reaction done with triethylamine. Diels-Alder reaction was performed with $MgBr_2 \cdot OEt_2$ and 2,6-lutidine in dichloromethane at room temperature .

[b] A sluggish reaction mixture was obtained after irradiation in the microwave. No desired product was obtained.

During the optimization studies, two side products were observed during the microwave reaction and characterized (Scheme 3.6). Tricyclic compounds **3.20** and **3.21** were identified by extensive NMR studies. Under the typical reaction conditions (toluene, triethylamine, 200 °C, 30-60 minutes), alcohol **3.20** and macrocycle **3.21** were isolated in 4% and 27% yield, respectively. It was assumed that compound **3.20** was obtained from product **3.16** via a four-π-electron electrocyclization (Figure 3.3). Theoretically, this process should be reversible and it was expected that allene **3.16** could be regenerated by a ring opening electrocyclization. Thus, the 10:1 ratio between **3.16** and **3.20** should represent the thermodynamic stability of both compounds. Calculations done by Effie Sauer determined that the k_{rel} value for **3.16** and **3.20** are 0 and 6.0 kcal/mol respectively. To determine if it was indeed the thermodynamic ratio observed, minor product **3.20** was resubmitted to the reaction conditions. Agreeably, a mixture of compounds **3.16** and **3.20** were obtained in a 10:1 ratio.

Scheme 3.6-Side products observed

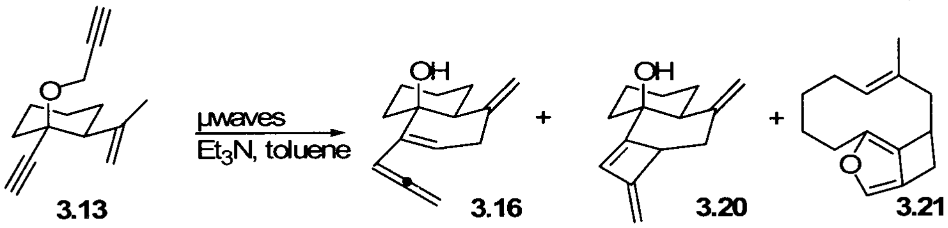
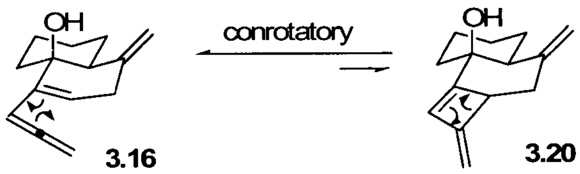
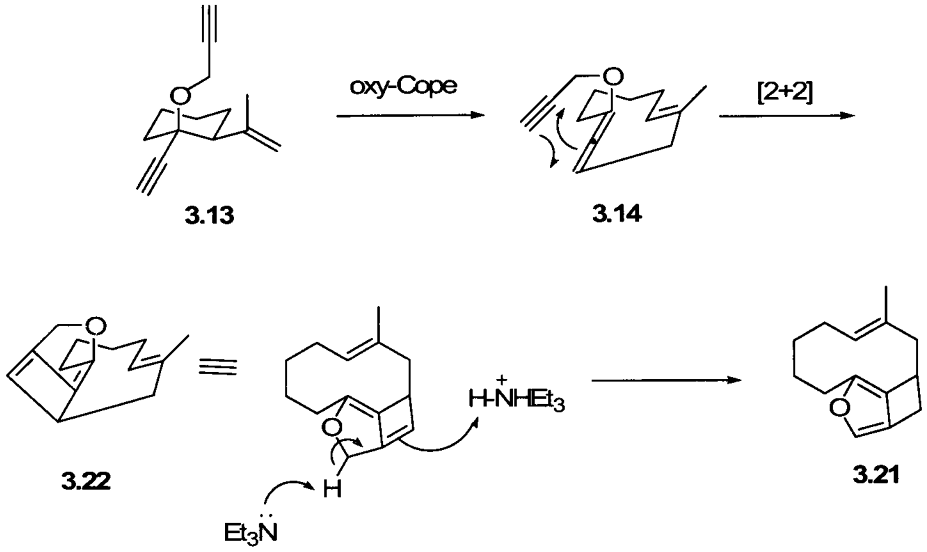


Figure 3.3-Mechanism of electrocyclization



Tricyclic compound **3.21** was proposed to arise from the mechanism shown in Figure 3.4 . Propargyl ether **3.13** rearranges normally to macrocycle **3.14** by an oxy-Cope reaction. In the oxy-Cope/Claisen/ene sequence, intermediate **3.14** undergoes the Claisen rearrangement (Figure 3.1). But, a [2+2] cycloaddition is also possible from that same intermediate. Due to the extra orbital present in the alkyne, the $[2\pi_s+2\pi_a]$ cycloaddition between this moiety and the allene[132] is rather facile to access the strained intermediate **3.22**.[133] Following aromatization, furanyl compound **3.21** was obtained. Although the structure of **3.20** and **3.21** are unique, there are other examples in the literature of tricyclic compounds bearing a cyclobutane or a cyclobutene.[134] The identification of the side products allows a better understanding of the reactivity of propargyl ether **3.13** at high temperatures.

*Figure 3.4-Proposed mechanism for **3.21***



Optimization of the hydroxy-directed Diels-Alder reaction

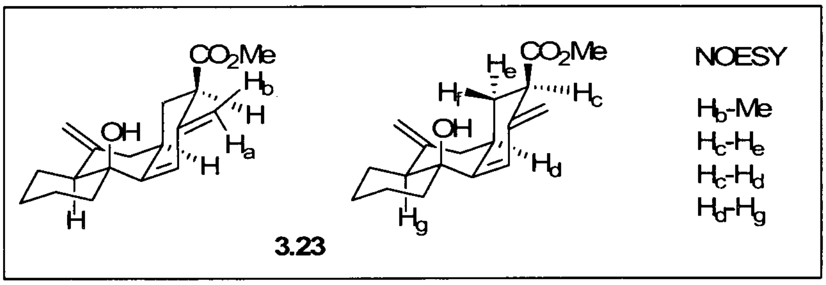
To further increase the yield, we focused our attention on the hydroxy-directed Diels-Alder step of the sequential reaction. Firstly, the solvent of the reaction was examined. The optimization done by Clément showed that dichloromethane was satisfactory but toluene gave a mixture of diastereoisomers. It was postulated that the poor solubility of magnesium bromide dietherate in toluene explained the low diastereoselectivity observed.[125] There is only a limited choice of solvents that could solubilize the magnesium bromide for the HDDA. Thus, the hydroxy-directed Diels-Alder step was performed in 1,2-dichloroethane, chlorobenzene, acetonitrile and a 3:1 mixture of dichloromethane-pyridine. None of these solvent systems proved to increase the yield of the reaction.

For the hydroxy-directed Diels-Alder methodology, a base is necessary. This base is crucial to generate the necessary magnesium alkoxide.[135] It was shown previously that triethylamine or 2,6-lutidine could be used but the developed protocol called for 2,6-luditine due to the higher yields. In the hope of increasing the yield, other bases were investigated such as 2,6-di-*t*-butyl-4-methyl-pyridine and TMEDA. Unfortunately, yields of 25 and 35% were observed respectively.

A crucial element to the HDDA reaction was the Lewis acid used to make the metal alkoxide. As mentioned above, magnesium bromide dietherate was superior to vinyl magnesium bromide. Still within the goal of increasing the yield of the reaction, other Lewis acids were investigated. Firstly, other magnesium Lewis acids were studied. In 2005, Carreira and co-workers reported the formation of magnesium alkoxides with ethyl magnesium bromide in the presence of isopropanol.[136] Using the same conditions in our HDDA reaction did not give any desired product. Nicolaou and Harrison developed conditions for a Diels-Alder reaction using a magnesium tether. [137] Their methodology used methyl magnesium bromide and a ligand (2-pyrrolidin-1-yl-phenol) to generate the magnesium alkoxide complex. When these conditions were applied to allene **3.16**, the desired product was obtained but in low yield. Secondly, different elements were surveyed. A quick investigation of catecholborane did not give promising results. However, when Dibal-H was added directly to the reaction mixture (microwave reaction performed in toluene and then cooled at -78 °C), the desired product was obtained in 33% yield.

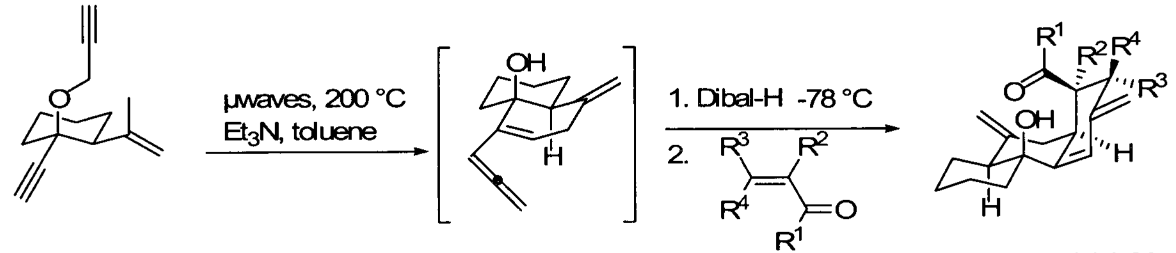
Optimization of the conditions for the reaction using Dibal-H as a Lewis acid was completed. Different equivalents of Dibal-H, different temperatures, stirring time, solvents, concentration and the addition of a base were examined. It was found that in order to have a higher yield, allene **3.16** must be stirred with Dibal-H for at least two hours. Using dichloromethane as the solvent for the Diels-Alder reaction and 1.3 equivalents of Dibal-H, the desired product was obtained in 40% yield. In contrast to the magnesium bromide method, using Dibal-H as a Lewis acid gave a second isomer that could be detected in a diastereomeric ratio of 8:1. The minor isomer was characterized as regioisomer **3.23** (Figure 3.5) using key NOESY interactions (H_b-Me, H_c-He, H_c-H_d, and H_d-H_g) and analogy to **3.27** (see below for in depth analysis). The lower diastereoselectivity of Dibal-H in comparison to magnesium bromide might be due to the weaker Lewis acidity of the aluminum. In turn, this affects the electronic density at the terminal carbons of the diene (the coefficient) making the reaction less regioselective. Another possibility is that the energy difference between the 8-membered (TS-A) and 9-membered (TS-B) tether's transition states (Figure 3.2) was smaller in the case of the aluminum Lewis acid due to steric effects of Dibal-H.

Figure 3.5-Structure assignment of ***3.23***



To establish the scope of the reaction, the sequential oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder was done using Dibal-H with a variety of dienophiles (Scheme 3.7, Table 3.3). As a comparison, the results obtained previously with $MgBr_2{\cdot}OEt_2$ are also included in the table.[125] Using methyl methacrylate as a dienophile gave the desired product **3.24** as the only diastereomer in 41 and 35% yield respectively with magnesium bromide and Dibal-H as Lewis acids (entry 2). Using methyl vinyl ketone (entry 3) with magnesium bromide gave product **3.25** in 49% yield with a diastereomeric ratio greater than 25:1. In contrast, the same dienophile with Dibal-H gave product **3.25** in a yield of 26% but as a mixture of isomers (2:1). The minor isomer was identified as regioisomer **3.27** (Figure 3.6). Proton H_c was identified by COSY interactions with H_a, H_b, H_e and H_f and a characteristic chemical shift at 3.25. A nOe between H_b and the methyl group (1.4%) confirmed the structure of regioisomer **3.27**. The stereochemistry of the product was determined by the various nOe interactions. Protons Hc and Hd had a nOe of 1.8%. This was only possible by having both protons down. Since proton Hc had a nOe of 2.0% with H_e and 0% with H_f, the two protons on the methylene carbon were assigned. Finally, there was a nOe between H_d and H_e (3.4%) and between H_d and H_g (the value cannot be determined because of superimposing peaks). All the spectroscopic data corresponded to the presence of regioisomer **3.27**.

Scheme 3.7-Scope of oxy-Cope/Claisen/ene/HDDA using Dibal-H as the Lewis acid



3.13 **3.16** **3.17, 3.24-3.26**

Table 3.3- Scope of oxy-Cope/Claisen/ene/HDDA using Dibal-H as the Lewis acid

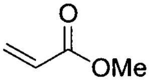
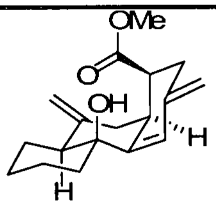
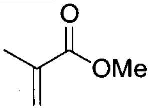
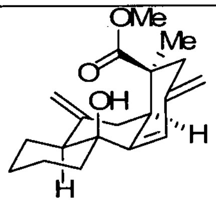
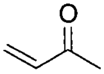
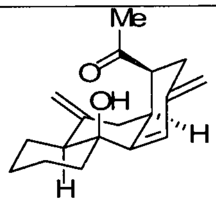
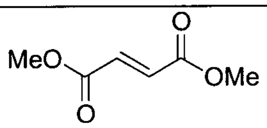
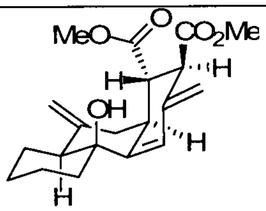
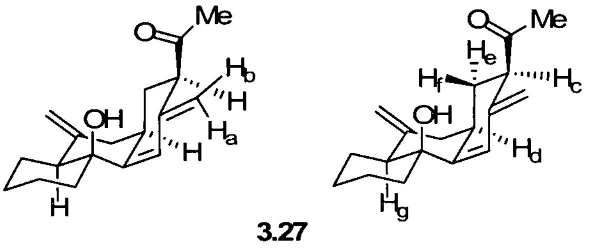
Entry	Dienophile	Product	Yield (%) [dr]	
			$MgBr_2{\cdot}OEt_2$	Dibal-H
1		 **3.17**	35 [> 25:1]	40 [8:1]
2		 **3.24**	41 [> 25:1]	31 [>25:1]
3		 **3.25**	49 [> 25:1]	26 [2:1]
4		 **3.26b**	34 [> 25:1]	32 [>25:1]

Figure 3.6-Structure assignment of ***3.27***



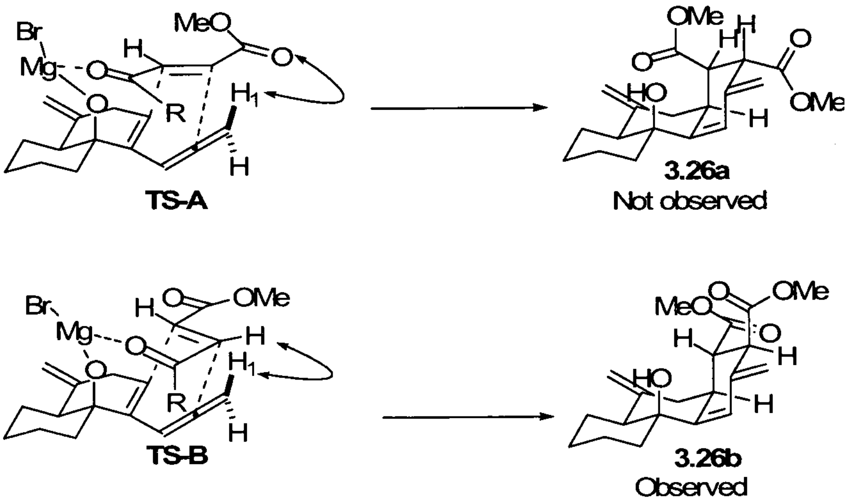
3.27

nOe

H_b-Me = 1.4%
H_c-H_d = 1.8%
H_c-H_e = 2.0%
H_c-H_f = 0%
H_d-H_e = 3.4%
H_d-H_g = nOe present

Cycloadduct **3.26b** resulted from the sequential oxy-Cope/Claisen/ene/HDDA reaction of allene **3.16** with dimethyl fumarate (entry 4). In both cases, magnesium bromide and Dibal-H, the ester group at C-14 was anti to the hydroxyl group. This preferred regiochemistry is attributed to the steric interactions present in TS-A which are not present in TS-B (Figure 3.7). Both methods gave the desired adduct in comparable yields (magnesium bromide: 34% yield /Dibal-H: 31%). The use of acrolein as the dienophile with magnesium bromide led to the formation of two diastereoisomers in 39% overall yield.[125] Using the same dienophile under the Dibal-H conditions did not give the desired product. Other dienophiles did not react either with magnesium bromide or with Dibal-H. These include methyl crotonate, dimethyl maleate, *p*-benzoquinone and benzaldehyde.

Figure 3.7-Mechanism for HDDA with dimethyl fumarate



Overall, it was found that magnesium bromide was superior to Dibal-H for the hydroxy-directed Diels-Alder reaction step since the chemical yield and the selectivity are better with the first reagent. However, the discovery of Dibal-H as a Lewis acid for the hydroxy-directed Diels-Alder still has significance. With the goal of applying the methodology to the synthesis of a natural product, it is desirable to have a variety of reaction conditions to test in order to optimize the reaction with the key substrate.

In summary, the optimization study allowed to gather important information about the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction. It was possible to increase the yield by decreasing the irradiation time from 2 hours to 30-60 minutes at 200-207 °C (the optimized yield was 42%, dr > 25:1). It was found that the microwave reaction could be performed in toluene as well as acetonitrile without loss in the yield. Furthermore, it was found that Dibal-H could replace magnesium bromide etherate giving the desired product again in 40% yield but with a dr of 8:1.

Mechanistic studies

The proposed mechanism for the formation of allene **3.16** from propargyl ether **3.13** was described as a domino reaction consisting of an oxy-Cope/Claisen/ene sequence (Figure 3.1). This proposal was based on previous work in our laboratory concerning the oxy-Cope/Claisen/ene reaction of 1,2-divinylcyclohexanol allyl ethers.[116,121,138] Also, there have been reports of oxy-Cope rearrangements of 1-ethynyl-2-vinylcycloalkanols.[120,139] In order to get a better understanding of the reaction mechanism, allyl ether **3.28** was synthesized from alcohol **3.19b** in 89% yield. When this allyl ether was heated in the microwave in toluene with triethylamine at 207 °C for 60 minutes, products **3.29** and **3.30** were obtained (Scheme 3.8). It was found that the concentration of the reaction influenced the product distribution. When the reaction was done more concentrated (44.7 mg in 3 mL), product **3.30** was predominant. However, when the reaction was done in a less concentrated medium (13 mg in 3 mL), the expected product **3.29** was obtained almost exclusively. A proposed mechanism is shown in Figure 3.8. Product **3.29** results from the domino reaction started by an oxy-Cope followed by a Claisen rearrangement and finally, an ene reaction. To explain the formation of product **3.30**, it is proposed that isomerization occurs faster than the Claisen rearrangement (Figure 3.8). The concentration effect could be due to the fact that the isomerization occurs by deprotonation with triethylamine and reprotonation. The bimolecular process is probably favored in a more concentrated medium. Since this type of side product was not observed in the case of propargyl ether **3.13**, it is possible to conclude that the Claisen rearrangement occurs faster with a propargyl ether than an allyl ether. The rearrangement of allyl ether **3.28** supported the proposed mechanism in the sense that an oxy-Cope/Claisen/ene sequence explained entirely the formation of products **3.29** and **3.30**.

*Scheme 3.8-The oxy-Cope/Claisen/ene reaction of allyl ether **3.28***

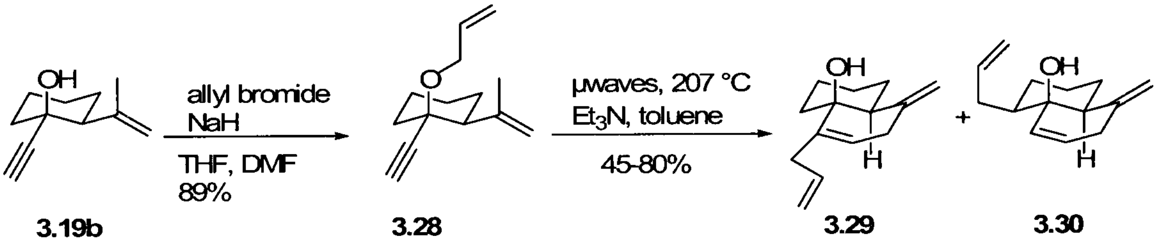
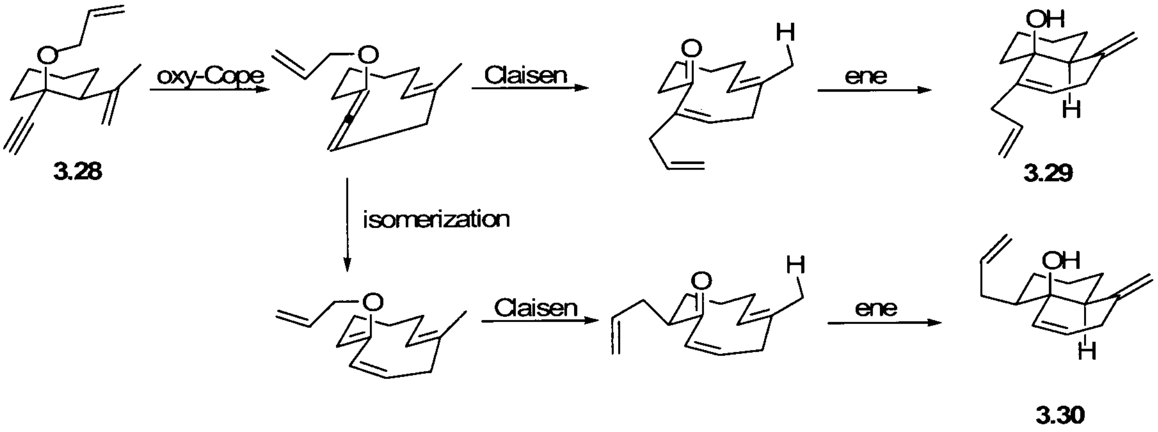
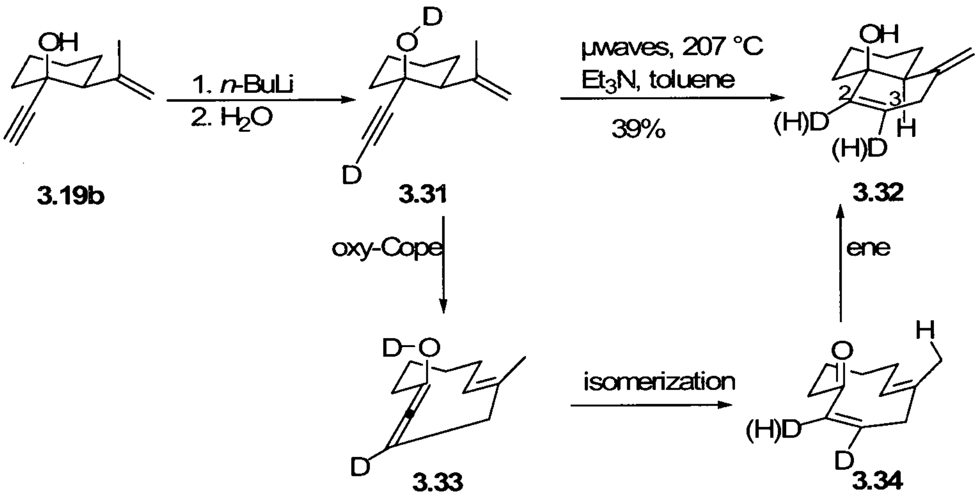


*Figure 3.8-Proposed mechanism of the domino reactions of allyl ether **3.28***



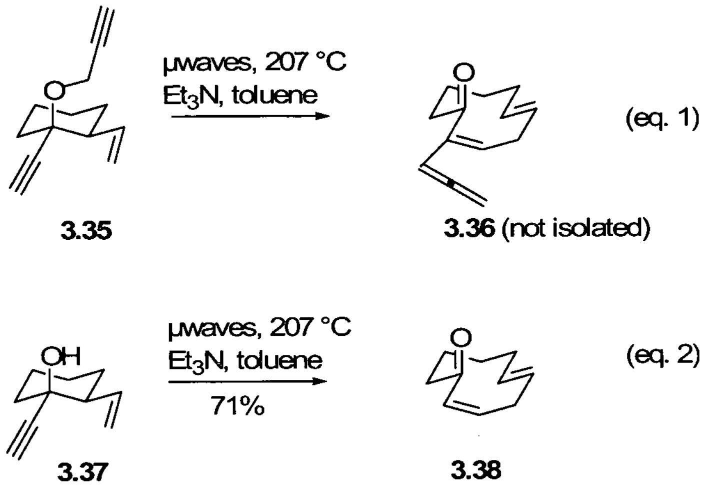
Next, we looked at deuteration studies (Scheme 3.9). Alcohol **3.19b** was deprotonated with *n*-BuLi and treated with D_2O to give deuterated alcohol **3.31**. A crude NMR revealed that there was no more alkyne proton and the MS confirmed the structure. The crude deuterated alcohol **3.31** was submitted to the microwave conditions (toluene, triethylamine (10 equiv), 207 °C for 60 min.). The desired decalin **3.32** was obtained but it was not fully deuterated as expected. The reaction was repeated many times but it was not possible to obtain the fully deuterated product **3.32**. Since there was no propargyl ether, the reaction sequence involves an oxy-Cope followed by an isomerization and finally an ene reaction.[139a] Since the tautomerization between **3.33** and **3.34** is an intermolecular process, the non-complete deuteration at C-2 is reasonable. However, there was only 30% deuteration at C-3. According to the proposed mechanism, the deuterium at C-3 comes from the alkyne terminal position and should not be able to easily exchange. However, the reaction was done at high temperature and one could conceive that deuterium-hydrogen exchange occurred during the reaction. Unfortunately, no conclusions from these experiments can be drawn at this point.

Scheme 3.9-Deuteration studies



To further study the reaction mechanism, we investigated the outcome of the reaction when the isopropenyl was replaced by a vinyl group (Figure 3.9). When propargyl ether **3.35** was submitted to the reaction conditions, the oxy-Cope/Claisen product could not be isolated (eq. 1). As mentioned before, the allenes generated are not very stable. In the case of allene **3.36**, it was too unstable to isolate. To avoid this problem, alcohol **3.37** was heated in the microwave under the typical reaction conditions (eq. 2). Macrocycle **3.38** was detected by NMR as a mixture with the starting material. This macrocycle was the result of the oxy-Cope reaction of alcohol **3.37**.

Figure 3.9-Microwave reaction of vinyl precursors



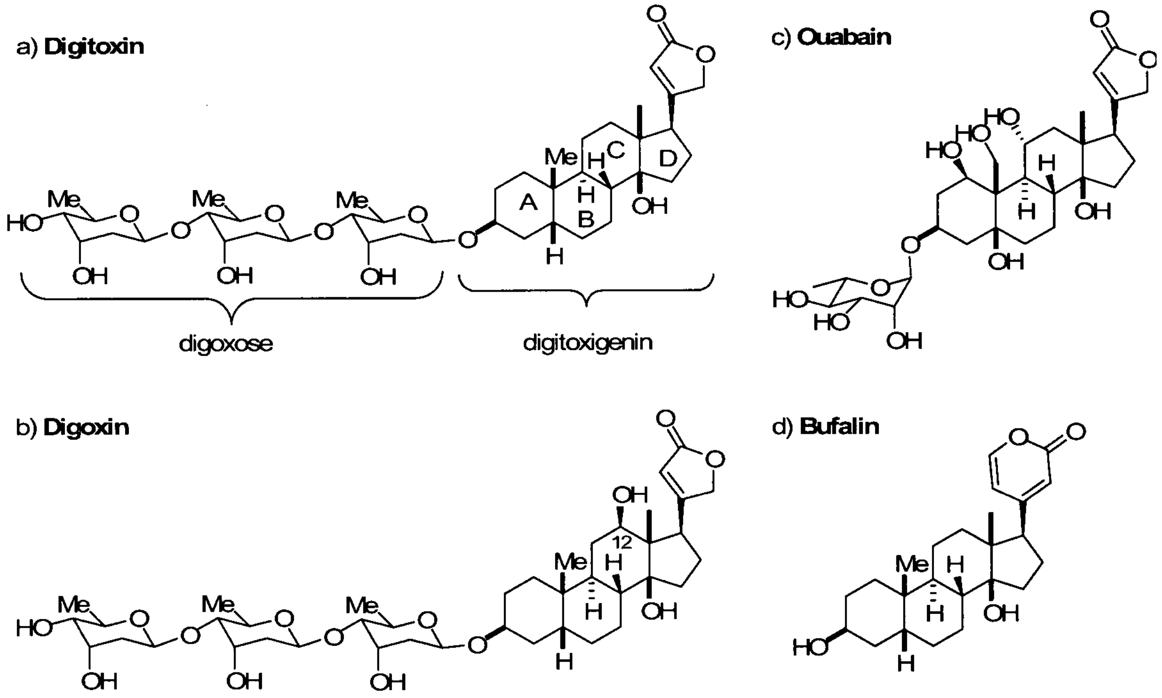
In summary, the mechanistic studies confirm that the microwave reaction of propargyl ethers such as **3.11** consists of an oxy-Cope/Claisen/ene sequence. It has been shown that thermal rearrangement of allyl ether **3.28** produced **3.29** and **3.30** via an oxy-Cope/Claisen/ene and an oxy-Cope/isomerization/Claisen/ene reaction, respectively. Furthermore, the thermal rearrangement of alcohol **3.31** gave the oxy-Cope/ene product **3.32**. Although the deuteration studies were not conclusive, the fact that the oxy-Cope/ene product was isolated gave evidence towards the proposed mechanism. Finally, the oxy-Cope rearrangement of alcohol **3.37** to macrocycle **3.38** confirmed the first step of domino reaction.

Introduction to digitoxigenin

The extracts of the plants *Digitalis purpurea* and *Digitalis lunata* have been used to treat congestive heart failure for over 200 years.[140] The active compounds are digitoxin and digoxin. These natural products are from the cardiac glycosides family of steroids. By definition, cardiac glycosides have a steroid genin, a sugar attached at the 3β-OH and an unsaturated lactone at the 17β position. There are two classes that are distinguished by the unsaturated lactone: cardenolide have a butyrolactone whereas bufadienolide have a pyrone at the 17β position. Cardenolide are extracted from plants and include digoxin, digitoxin and ouabain whereas bufadienolide are present in frog poison (for example, bufalin) (Figure 3.10).

The cardiac glycosides have unique structural features that distinguish them from other steroids: There is a *cis* C/D ring junction instead of the typical trans ring junction and there is a 14β-hydroxyl group. Within the cardenolides, the aglycons have different substitution patterns and the sugar moiety varies also. The structure of digitoxin consists of a trisaccharide (digoxose) and digitoxigenin. Digoxin is very closely related to digitoxin but it has an extra hydroxyl group at C12. Ouabain has an ouabagenin core and a rhamnoside sugar.

Figure 3.10-Selected cardiac glycosides



a) **Digitoxin**

c) **Ouabain**

b) **Digoxin**

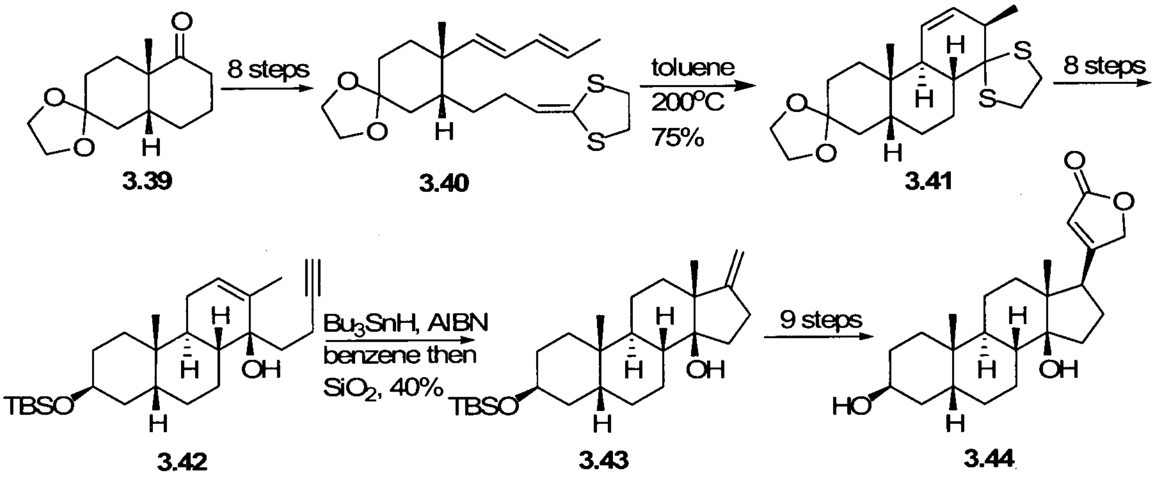
d) **Bufalin**

The digitalis cardiac glycosides have been used to treat heart failure by improving myocardial contractility.[141] This is attributed to the inhibition of the Na^+/K^+ ATPase.[142] However, recent research has demonstrated that this inhibition occurs only at high concentration of digitoxin. Pollard and co-workers have shown that at low concentrations (near the therapeutic index), digitoxin increases the intracellular concentration of calcium by influx through digitoxin calcium channels.[143] The higher concentration of calcium in the myocardial cells results in a more efficient contraction of the heart muscle. Evidently, more research has to be done to better understand the mechanism of action of digitoxin and digoxin.

It has also been demonstrated that digitoxin could be used as a potential anticancer agent due to its interesting biological activity.[142] Although the mechanism of action is still unclear, it is known that the digitoxin increases the intracellular concentration of calcium. This affects signaling pathways and can lead to apoptosis. The biological activity was shown in studies such as the blockade of TNF-α (tumor necrosis factor) and NF-κB (nuclear factor) signaling pathways by cardiac glycosides.[144] Also, these natural products regulate the amount of FGF-2 (fibroblast growth factor) that is crucial to angiogenesis.[142] Since apoptosis, TNF-α, NF-κB and FGF-2 are all targets for anticancer drugs, it is clear that digitoxin and other cardenolides have the possibility of treating more than heart failure.

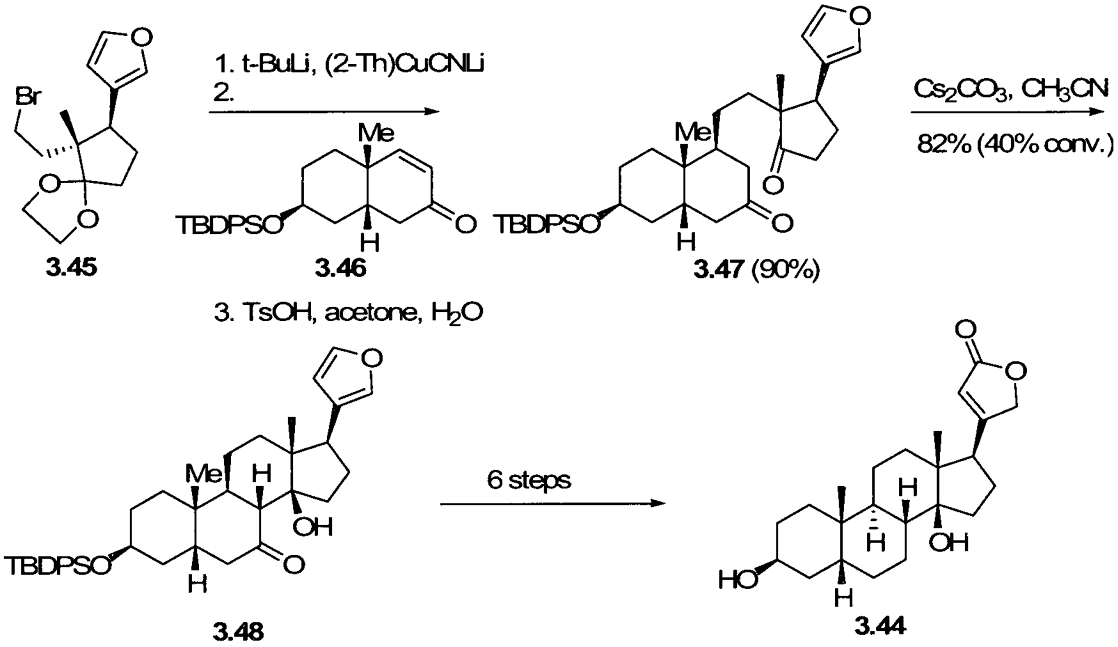
The interesting biological activity and the unique structure of digitoxin sparked our interest in synthesizing the aglycon moiety (digitoxigenin). There have been many syntheses of digitoxigenin. However, most reported syntheses started from steroids.[145] In 1996, the first total synthesis was reported by Stork and co-workers (Scheme 3.10).[146] Starting from the (*S*)-enantiomer of the Wieland Miescher ketone **3.39**, they were able to synthesize precursor **3.40** in eight steps. Their first key step was a stereoselective intramolecular Diels-Alder reaction to afford **3.41** in 75% yield This product was converted in **3.42** in eight steps. The second key step was a radical cyclization in order to install the D ring with the desired *cis* ring junction between rings C and D. The natural product, (+)-digitoxigenin, was obtained after nine steps to introduce the butenolide moiety.

Scheme 3.10-Stork's digitoxigenin synthesis



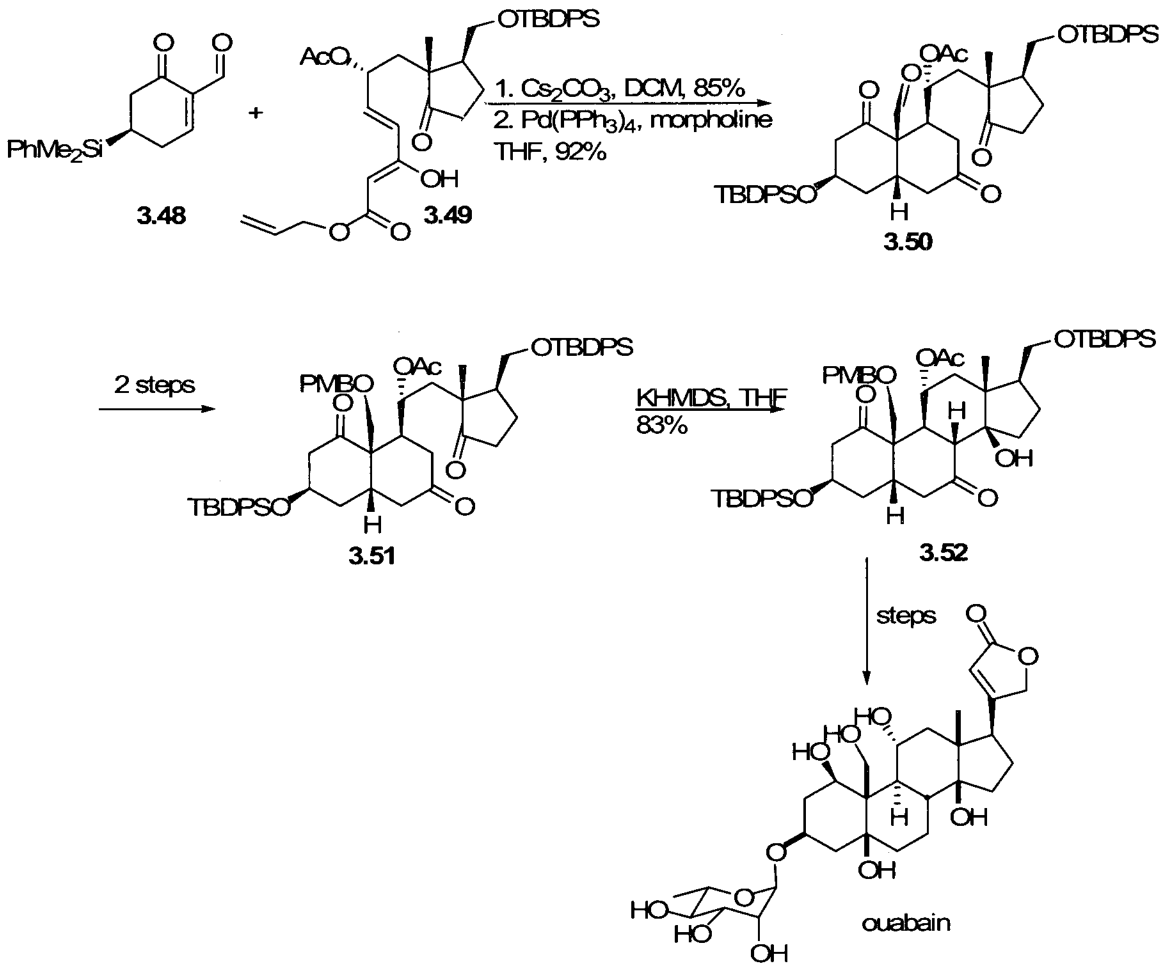
In 2007, Honma and Nakada also reported the total synthesis of (+)-digitoxigenin (Scheme 3.11).[145] They used their catalytic asymmetric intramolecular cyclopropanation[147] in order to generate a substrate that was then converted to **3.46** in six steps. They also synthesized bromide **3.45** in fifteen steps from a readily available starting material. The first key step consisted of a conjugate addition of the cuprate derived from bromide **3.45** onto enone **3.46**. After deprotection of the ketal, they obtained compound **3.47** as a single diastereoisomer. Next, they did an intramolecular aldol reaction and obtained **3.48** again as a single product. After functional group manipulations, they were able to synthesize (+)-digitoxigenin.

Scheme 3.11-Nakada's digitoxigenin synthesis



In 2008, Deslongchamps and co-workers were the first to report the total synthesis of ouabain (Scheme 3.12).[148] Since the aglycon moiety of ouabain is related to digitoxigenin, their synthesis will be briefly described. The key step involves a double Michael addition of substrates **3.48** and **3.49** to give tricycle **3.50** after decarboxylation. Next, the intramolecular Aldol reaction of **3.51** afforded the carbon skeleton of ouabain (**3.52**). There were still twenty-two steps needed to reach the natural product. The highly oxygenated molecule was finally obtained in a synthetic laboratory.

Scheme 3.12-Deslongchamps's synthesis of ouabain



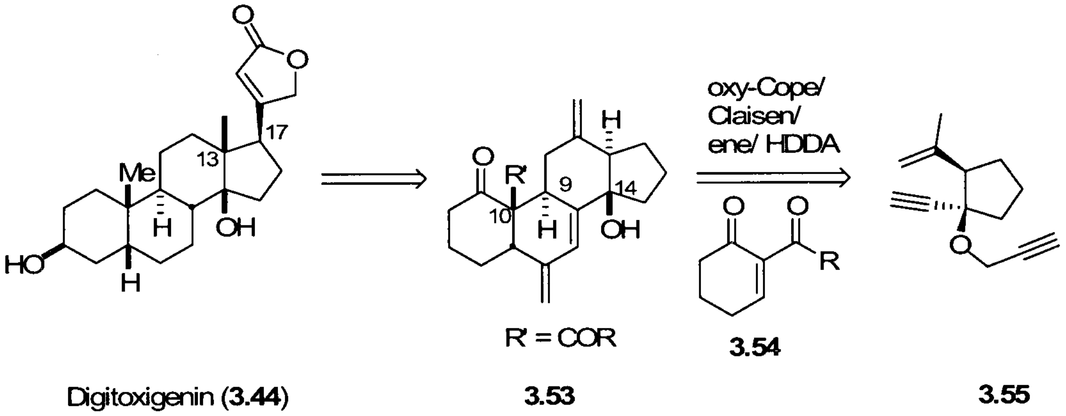
The interesting biological properties of the cardenolides motivate chemists to develop new and concise routes to these natural products. Although digitoxigenin and ouabain have been synthesized, there is still a need for shorter and more flexible routes in order to do structural modification for structure-activity relationship studies. Also, the remarkable structures present the opportunity to develop new methodologies or adapt known methodologies.

Retrosynthetic analysis

To validate the new sequential methodology, we wanted to apply the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction to the synthesis of digitoxigenin.

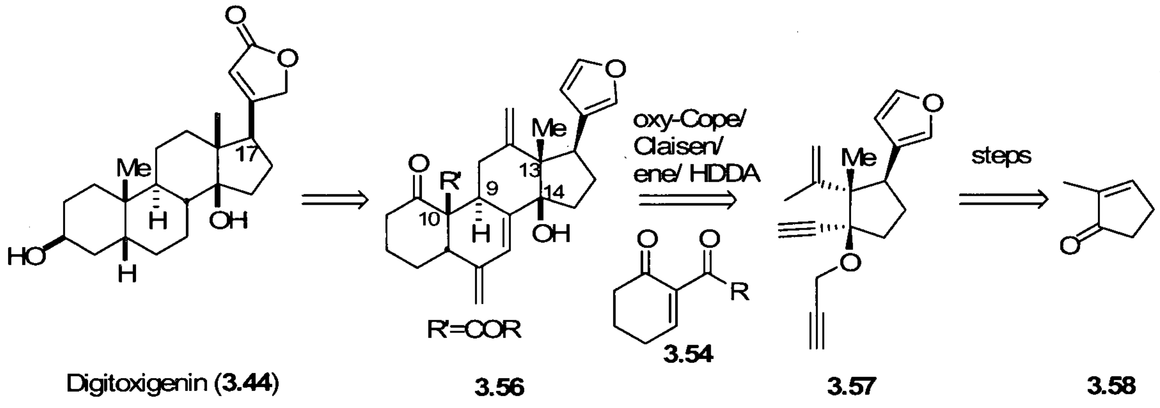
From a retrosynthetic point of view, it was clear that the method could be used to construct rings B, C and D having the proper stereochemistry at C9, C10 and C14 (Figure 3.11). Using a cyclic dienophile such as **3.54**, it would be possible to construct the four rings of the natural product in one step. In the beginning, it was thought that five-membered ring propargyl ether **3.55** should be the necessary precursor. Looking closely at the structure of digitoxigenin (**3.44**), we saw that a *cis* geometry existed between the hydroxyl group on C14 and the methyl group on C13. Although it would be possible to imagine that the functionalities present on compound **3.53** could be used to install the methyl C13; Problems were envisaged in the generation of a quaternary carbon center at a sterically encumbered position. Also, it might be difficult to install the butenolide at C17 at a late stage.

Figure 3.11-Retrosynthesis



All these factors taken into account, we revised our retrosynthesis (Figure 3.12). Digitoxigenin could come from cycloadduct **3.56** after functionalization. By doing so, the key step would install the right stereochemistry at the C9, C10, C13 and C14 positions. Also, the functionalization should be much easier and shorter since the methyl at C13 and a furan at C17 would be installed already. Thus, the precursor for the key step would be **3.57** and it should be possible to synthesize it from commercially available 2-methyl-cyclopentenone (**3.58**). Although this approach seemed to be the most direct route to digitoxigenin, there was the limitation that the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction methodology was only applied, up to now, to *trans* propargyl ethers (the isopropenyl and ethynyl groups were *trans* one to another). Thus, efforts were concentrated on applying the methodology to *cis* precursors.

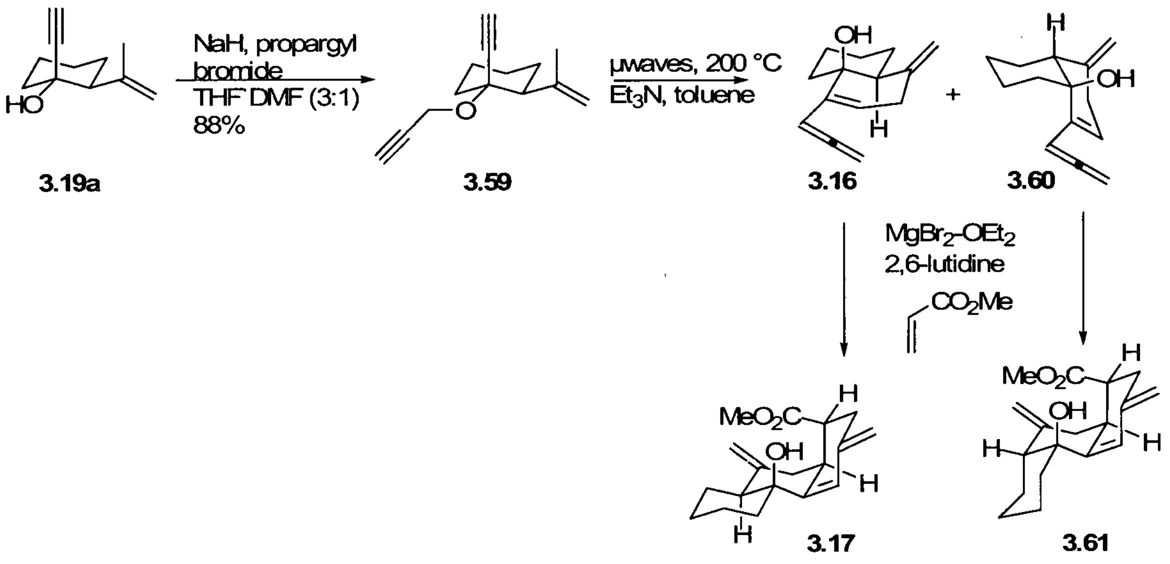
Figure 3.12-Revised retrosynthesis



The oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction of cis precursors

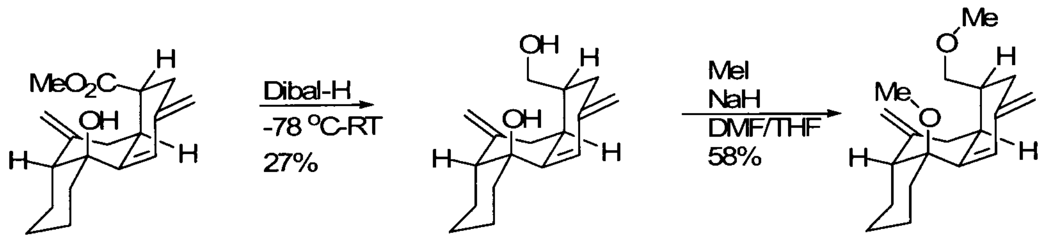
To test the feasibility of applying the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction to *cis* precursors, compound **3.59** was obtained from alcohol **3.19a** in 88% yield (Scheme 3.13). Irradiation of substrate **3.59** with microwaves at 200 °C for 60 minutes in toluene gave a mixture of the *cis* (**3.60**) and the *trans* allenes (**3.16**) (It is important to note that the starting precursor **3.59** was racemic, thus the products **3.16** and **3.60** were racemic as well). The two allenes were separated by flash chromatography and it was determined that the ratio was 1:2.6 in favor of the *trans* isomer. Since the allenes were not stable on silica, the isolated yield was very low (6%). Still, it was possible to perform the hydroxy-directed Diels-Alder reaction on the isolated *cis* allene **3.60**. A single product was obtained in 29% yield and it corresponded to **3.61**. Next, the sequential oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction was done on substrate **3.59**. It was difficult to isolate the desired product since the two cycloadducts (*cis* and *trans*) were present as well as side products (believed to be **3.20**, **3.21** and their isomers). Cycloadducts **3.17** and **3.61** were isolated in 17 and 8% yield, respectively. A slightly better yield of the *cis* cycloadduct was obtained when the crude microwave reaction mixture was passed through a plug of silica before the hydroxy-directed Diels-Alder reaction. Product **3.61** was obtained in 12% isolated yield.

*Scheme 3.13-Synthesis and reaction of cis precursor **3.59***



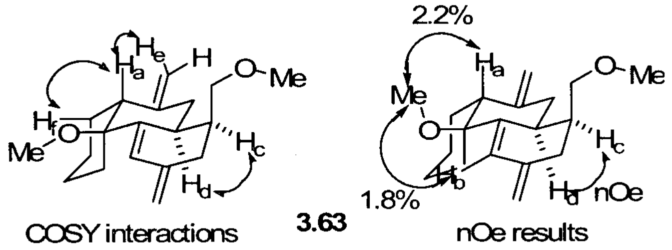
To demonstrate the relative stereochemistry of **3.61**, the ester was reduced to diol **3.62** in 27% yield (Scheme 3.14). Then, diol **3.62** was treated with iodomethane and sodium hydride to generate the methylated product **3.63** in 58% yield. The *cis* ring junction was demonstrated through extensive NMR spectroscopy of **3.63**. According to the correlations found, compound **3.63** must exist as the conformer shown in Figure 3.13. The proton at the *cis* ring junction (Ha) was identified by the multiple COSY interactions (Ha-He and Ha-Hf). This proton had a 2.2% nOe with the methyl of the methoxy group at the ring junction. If the ring junction was *trans*, there would not be this important interaction. Since the methyl at the ring junction can rotate, there is a 1.8% nOe interaction with Hb. Finally, Hc and Hd must be on the same side of the molecule as seen by COSY and nOe interactions (a precise number was not possible because of superimposing peaks).

Scheme 3.14- Transformation of ***3.61*** into ***3.63***



3.61 **3.62** **3.63**

Figure 3.13-Structure assignment of ***3.63***



Based on previous work in our laboratory, it was not surprising that the *cis* and *trans* isomers (**3.16** and **3.60**) were obtained from the *cis* precursor **3.59**. Morency and Barriault had previously researched domino reaction of analogous *cis* precursors.[149] They looked at the oxy-Cope/Claisen/ene reaction of allyl ethers (Figure 3.14). In the case of the unsubstituted *cis* precursor **3.64**, a trace of amount product might have formed but it was not characterizable (eq. 1). In the case of methoxy precursor **3.66**, only *trans* isomer **3.67** was isolated (eq. 2). They proposed a mechanism to account for the formation of the *trans* product from the *cis* precursor based on the facile interconversion of the reaction intermediates.[149] A similar explanation can account for the formation of **3.16** and **3.60** from precursor **3.59**. The mechanism is shown in Figure 3.15. By heating precursor **3.59**, an oxy-Cope rearrangement occurs via the two possible transitions states (A and B). A close inspection of the two transition states shows that TS-A has one pseudo-axial group whereas TS-B has two pseudo-axial substituents. After the oxy-Cope, the Claisen rearrangement and the ene reaction gave allenes **3.16,** ent-**3.16, 3.60** and ent-**3.60.** There are two possible transition states for the ene for each pathway giving rise to four possible products (two diastereomers and their enantiomers). Since the starting material was racemic, only the ratio of *cis* and *trans* allenes is significant. Thus, a 2.6:1 ratio favoring the *trans* allene **3.16** indicates that the difference in energy between TS-A and TS-B is relatively small favoring transition state B.

Figure 3.14-Morency and Barriault's exploration of cis precursors in domino reactions

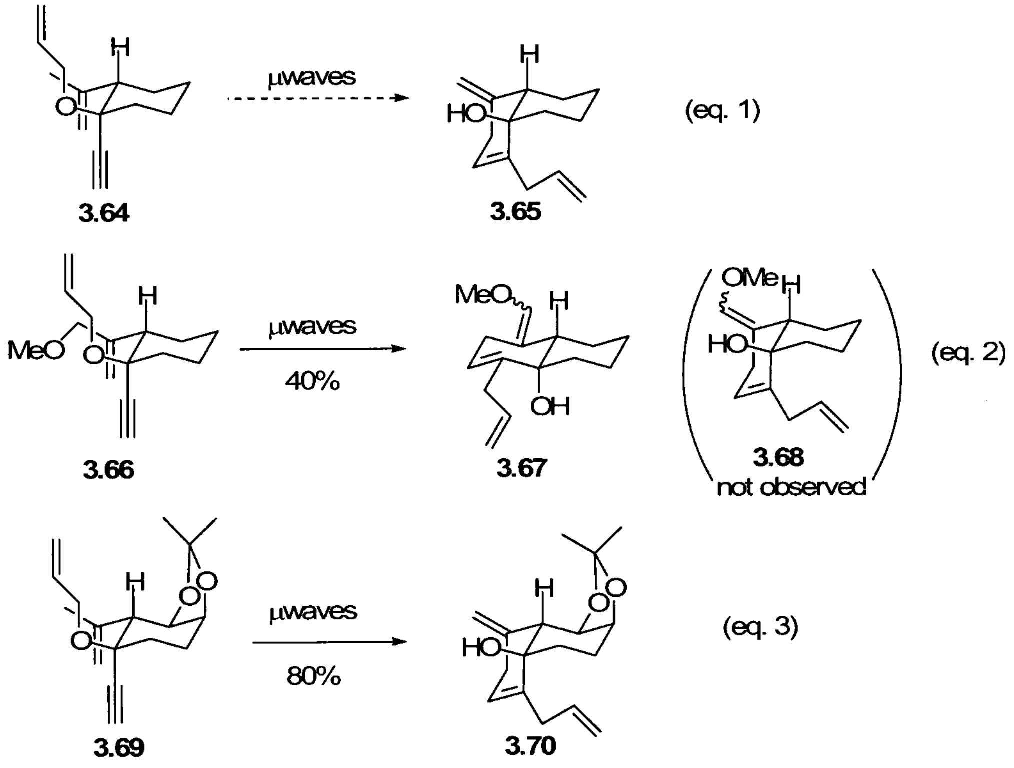
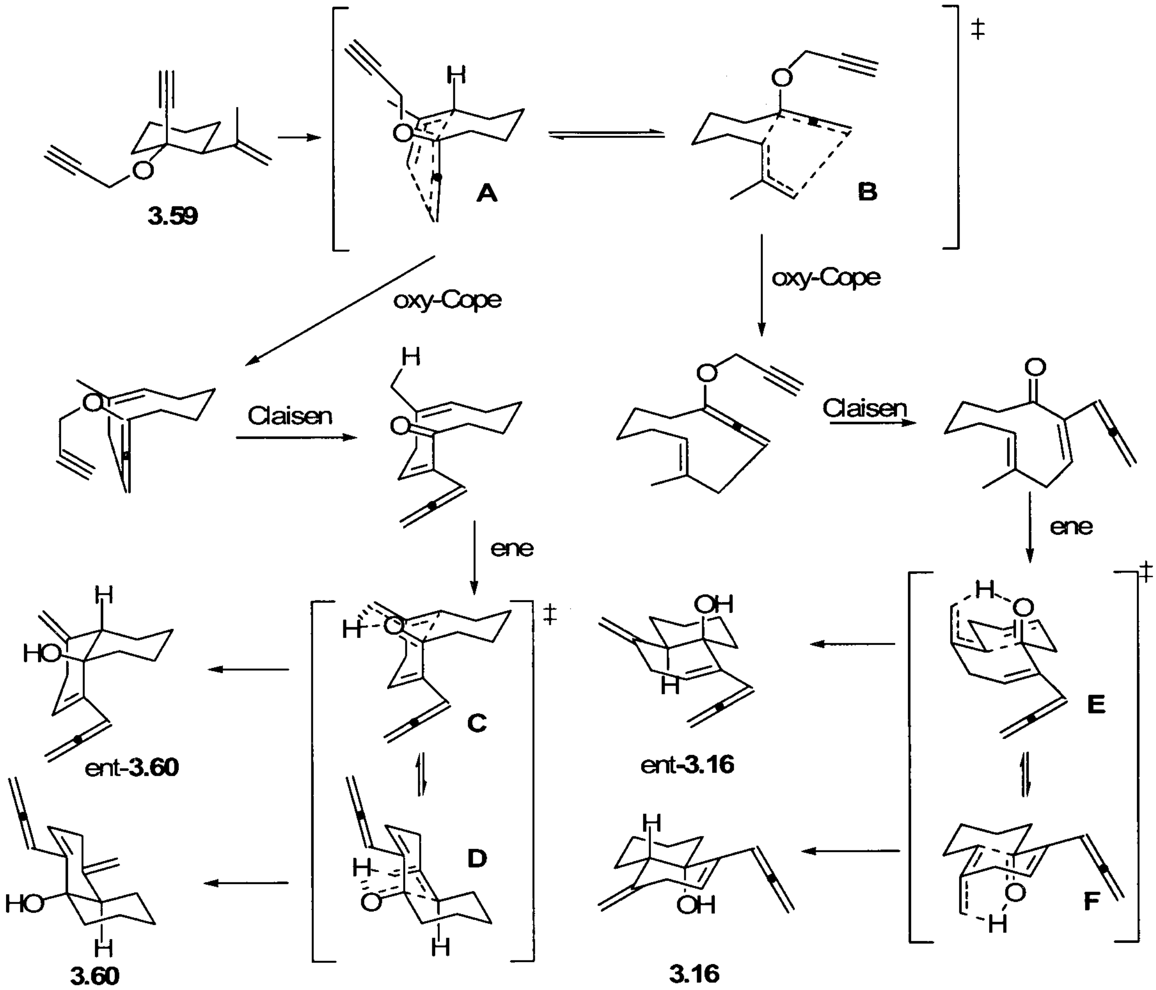
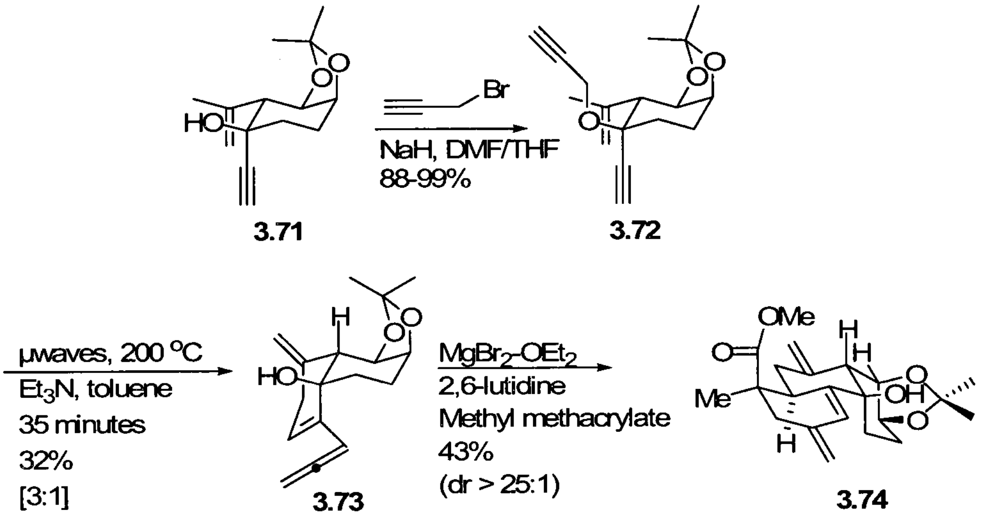


Figure 3.15-Proposed mechanism for rearrangement of ***3.59***



Fortunately, Morency and Barriault have reported that installing a substituent strategically on the microwave precursor results in the stereoselective formation of one *cis*-decalin product (Figure 3.14, eq. 3).[150] The acetonide moiety serves as a directing group by favoring one pathway. In order to see the effect of this directing group on our system, propargyl ether **3.72** was synthesized from known alcohol **3.71**[149] in 88 to 99% yield. Irradiation of propargyl ether **3.72** with microwaves at 200 °C for 35 minutes in toluene gave *cis* allene **3.73** in 32% yield (Scheme 3.15). A minor isomer could be detected by crude NMR of reaction mixture in a 3:1 ratio. It is important to note that reaction conditions for the microwave were not optimized at this point since the goal of this study was to see the effect of the directing group on the selectivity of the oxy-Cope/Claisen/ene reaction of *cis* propargyl ethers. Having shown that a directing group did in fact favor one isomer, the hydroxy-directed Diels-Alder reaction was performed with allene **3.73** and methyl methacrylate. Gratifyingly, only one isomer of **3.74** was detected (dr >25:1) and it was isolated in 43% yield (based on recovered SM).

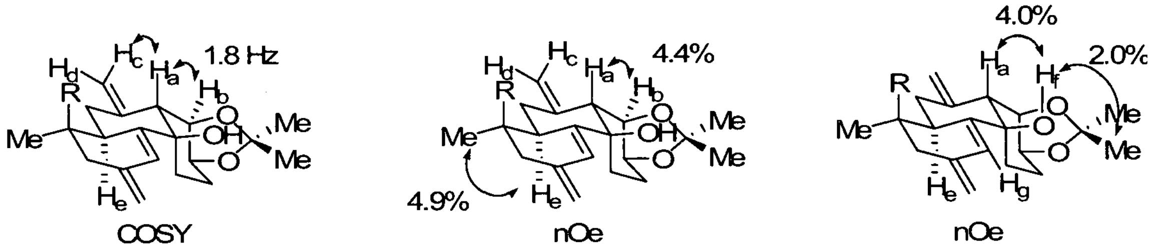
Scheme 3.15-Synthesis and reaction of functionalized cis precursor 3.72



The stereochemistry of compound **3.74** was established by NMR studies (Figure 3.16). There are two possible conformers for the *cis* decalin **3.74**. However, only one conformation was visible by NMR and it is the one shown. This conformation was determined by the interactions of protons H_a and H_b (1.8 Hz coupling constant and a 4.4% nOe interaction). Once proton H_e was identified by the COSY interactions, it was possible to identify a nOe interaction of 4.9% with the methyl on the adjacent carbon. This clearly indicates that proton H_e and the methyl group were on the same side of the molecule. Furthermore, no nOe interactions were present between H_e and H_a or H_f indicating that these protons were on opposite sides of the molecule. The proton of the hydroxyl group was identified by exchange with D_2O. Proton H_f was used to determine the stereochemistry at the ring junction. In fact, there were nOe interactions between H_f and H_a (4.0%), H_f and H_g

(1.7%) and H_f and the methyl group (2.0%). Overall, the results from the NMR studies prove the stereochemistry of compound **3.74**.

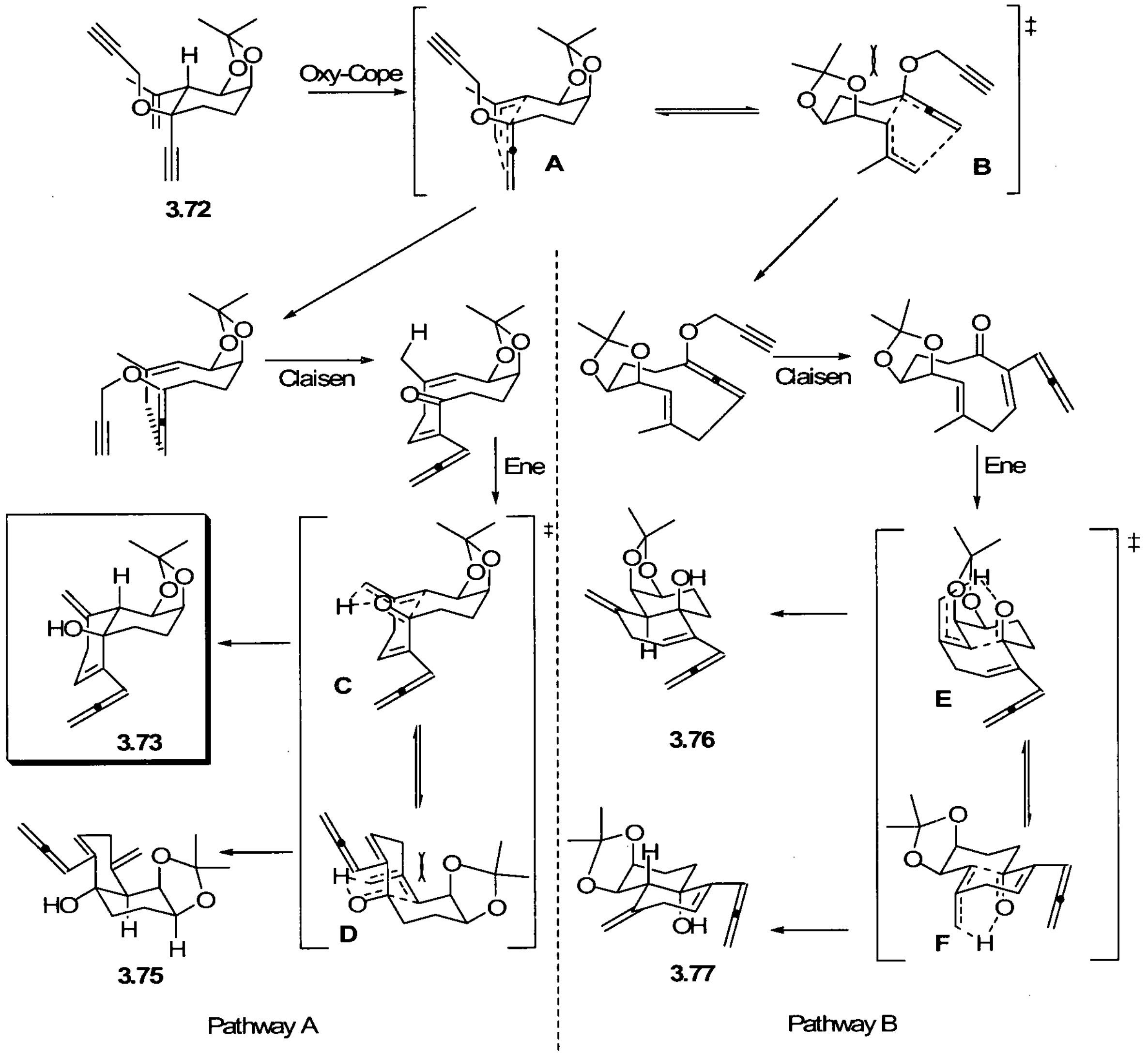
Figure 3.16-Structure assignment of 3.74



3.74 (R=CO_2Me)

As stated previously, Morency and Barriault studied the effect of the acetonide directing group on the oxy-Cope/Claisen/ene reaction of allyl ethers.[150] It was possible to adapt their proposed mechanism to explain that propargyl ether **3.72** gave **3.73** as the major product (3:1 ratio with a *trans* product) (Figure 3.17). The oxy-Cope reaction can proceed through TS-A and TS-B. The large 1,3-diaxial interaction observed in transition state B raise the energy of the transition state thus favoring the reaction to proceed via transition state A. Pathway A can lead to the formation of two products (**3.73** and **3.75**) following the Claisen and ene reactions. There are two possible transition states for the ene reactions. A close inspection shows that TS-D has important steric interactions that raise the energy of the transition state. Consequently, product **3.75** was not observed and product **3.73** was the major product of the reaction. In summary, it was demonstrated that a *cis* decalin could be obtained by the oxy-Cope/Claisen/ene reaction of propargyl ethers possessing a directing group. Furthermore, it was demonstrated that the *cis* allenes could undergo the hydroxy-directed Diels-Alder reaction to give the exclusive formation of one diastereoisomer.

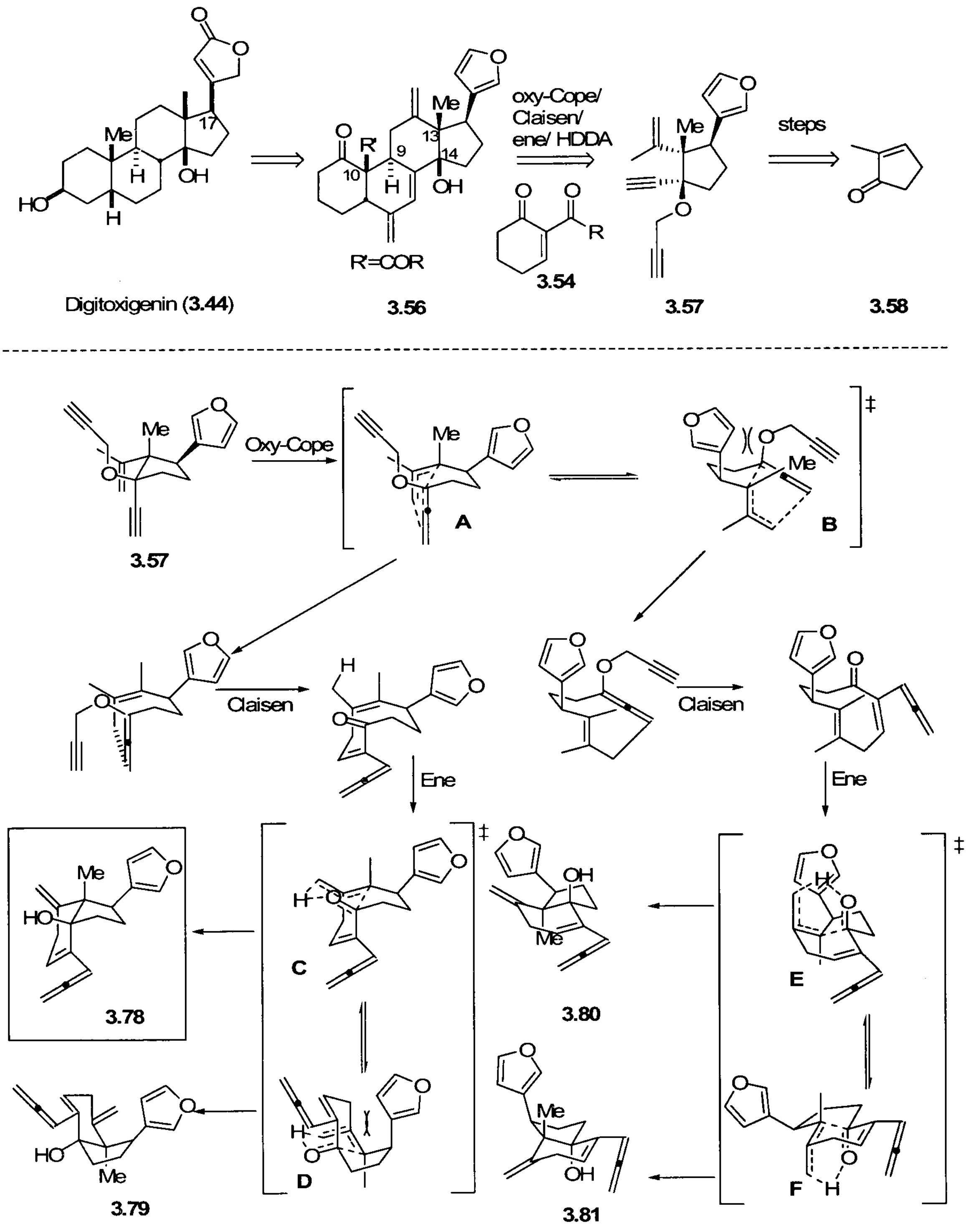
*Figure 3.17-Proposed mechanism for the formation of **3.73***



Synthesis of digitoxigenin: Furan as a directing group

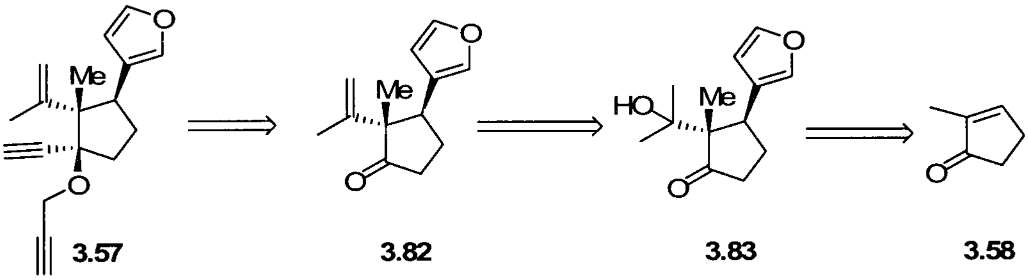
The studies performed on the six-membered ring *cis* propargyl ethers demonstrated that generating selectively a *cis* ring junction with the oxy-Cope/Claisen/ene reaction was feasible provided that a directing group was present. Looking at the proposed retrosynthesis for digitoxigenin, we see that the furan group could serve as the directing group in order to achieve the desired *cis* ring junction between ring C and D and the correct stereochemistry at C17 (Figure 3.18). A proposed mechanism is also shown in Figure 3.18 where the furan acts as the directing group in a similar way to the acetonide in precursor **3.72**. The reaction should favor the formation of product **3.78** that can react under the hydroxy-directed Diels-Alder conditions to provide **3.56**.

Figure 3.18-Furan as the directing group



A more detailed retrosynthesis of propargyl ether **3.57** was formulated (Figure 3.19). It was proposed that propargyl ether **3.57** could come from ketone **3.82** that could be obtained by dehydration of alcohol **3.83**. A sequential diastereoselective 1,4-addition/alkylation of 3-furanyl cuprate to cyclopentenone **3.58** followed by the addition of acetone should provide **3.83**. The diastereoselectivity of the 1,4-addition/alkylation (the alkylating group *trans* to the nucleophilic group) is favored due to steric effects and there are many examples in literature for related systems.[151]

Figure 3.19-Retrosynthesis of propargyl ether 3.57



The synthesis started with commercially available 2-methylcyclopentenone (**3.58**) and 3-bromofuran.[152] At first, efforts were targeted at the 1,4-addition reaction of the sequential reaction (Table 3.4). Two organometallic species were investigated: the Grignard and the lithio-species. Firstly, the Grignard reagent was made using 1,2-dichloroethane as an activator and used immediately since it was not very stable.[153] Then, the cuprate reagent was made in situ either by adding CuI or CuBr-SMe_2. The first attempt at the cuprate addition on the cyclopentenone using standard conditions (CuI)[154] did not give any reaction (entry 1). By adding TMSCl, triethylamine and TMEDA to the reaction,[155] only starting material was recovered (entry 2). Changing the copper source to CuBr-SMe_2 and using a variety of additives only led to recovered starting material or decomposition (entries 3-5).[156] Secondly, the 3-lithiofuran was obtained by treating 3-bromofuran with *t*-BuLi. With the organolithium, the same copper sources were tested in the presence of various additives but the desired product was not detected (entries 6 & 7).[157] In a recent paper, lithium 2-thienylcyanocuprate (ThCuCNLi)[158] was used to generate a second order cuprate[159] from 3-bromofuran and it was reacted with a doubly activated cyclopentenone.[160] Using the same conditions for our substrate only gave recovered starting material (entry 8). Unfortunately, the addition of additives did not promote the reaction (entry 9). Also, it was found that boron trifluoroetherate could be used to activate the other copper-catalyzed conjugate addition with lithiofuran.[161] In our case, only starting material was recovered. The results obtained in this study can attest to a statement by Lipshutz that classifies furans as difficult substrates for 1,4-additions.[162]

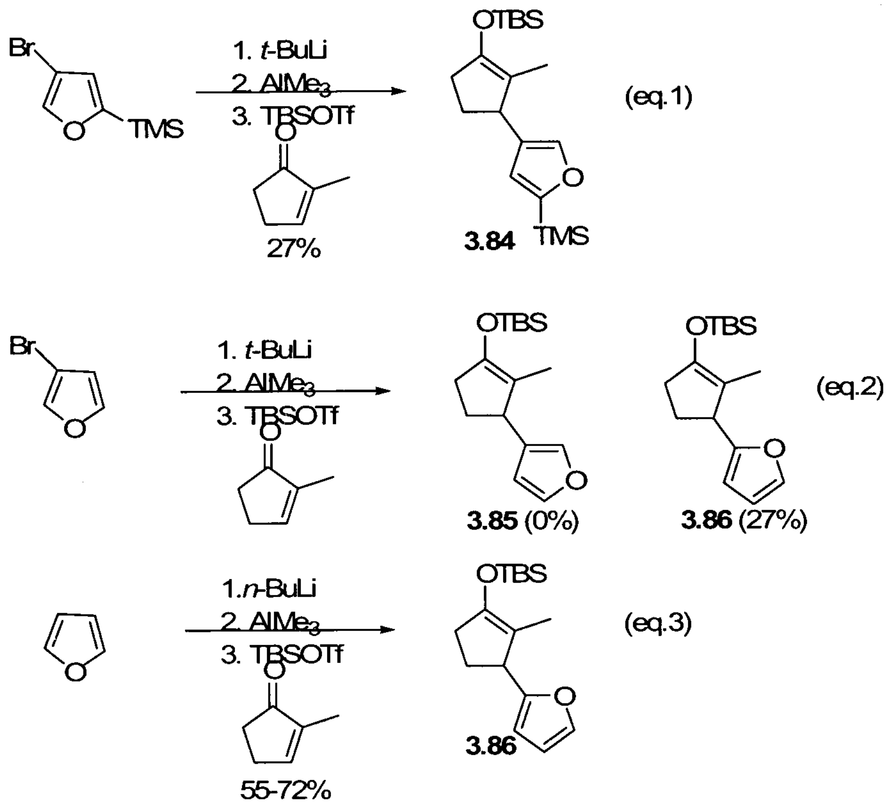
Table 3.4-Copper catalyzed 1,4-addition

Entry	Organometallic Species	Copper reagent	Additives	Conditions	Result
1	Grignard	CuI	-	-78 to -30 °C	SM
2	Grignard	CuI	TMSCl, NEt_3 TMEDA	-78 °C to RT	SM
3	Grignard	$CuBr{\cdot}SMe_2$	TMSCl, NEt_3	-78 °C to RT	SM
4	Grignard	$CuBr{\cdot}SMe_2$	DMPU, TMSCl, NEt_3	-78 °C to RT	SM
5	Grignard	$CuBr{\cdot}SMe_2$	HMPA, TMSCl	-78 to -20 °C	SM
6	Lithium	CuI	TMEDA, TMSCl	-78 to -45 °C	Not desired product[a]
7	Lithium	$CuBr{\cdot}SMe_2$	HMPA, TMSCl, NEt_3	-78 to -45 °C	Not desired product[a]
8	Lithium	ThCuCNLi	-	-78 to RT	SM
9	Lithium	ThCuCNLi	TMEDA, TMSCl	-78 to -20 °C	SM

[a] The products isolated did not have any of the furanyl peaks or the characteristic peaks of the starting material by NMR.

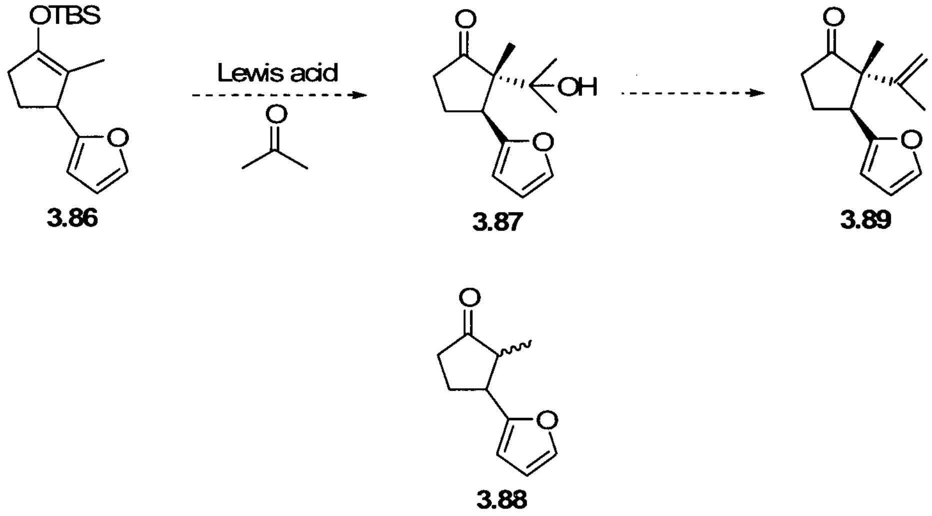
Since all attempts to achieve the copper-mediated 1,4-addition of 3-bromofuran to 2-methylcyclopentenone were unsuccessful, other methods were investigated. In a report by Jung and Davidov,[163] they formed silyl enol ether **3.84** (Scheme 3.16, eq. 1) using a modified procedure of Kim and Park.[164] Using 3-bromofuran and the same conditions as Jung and Davidov gave us a surprising result (eq. 2). The expected silyl enol ether **3.85** was not obtained: instead, the reaction gave silyl enol ether **3.86** in 27% yield. To prove the structure unambiguously, it was compared to the product of the reaction performed using furan (eq. 3). Deprotonation of furan with *n*-BuLi gave the 2-lithiofuran. Then, trimethylaluminum followed by 2-methylcyclopentenone and TBSOTf were added and silyl enol ether **3.86** was obtained in 55 to 72% yield. Thus, starting from 3-bromofuran or furan gave the same product. Since clean halogen-metal exchange with 3-bromofuran was known in our laboratory in THF or ether at -78°C, [165] the problematic step must be the exchange with trimethylaluminum. Under the reaction conditions, the 3-aluminum-furan must rearrange to the more stable 2-aluminum-furan. In the case of Jung and Davidov, this rearrangement was not observed. It was hypothesized that the TMS group at the 2-position must prevent this rearrangement. To the best of our knowledge, there is no literature on the rearrangement of 3-aluminum-furan species. In an attempt to minimize this rearrangement, the reaction conditions were modified. Using *n*-BuLi and ether as the solvent gave the same regioisomer (**3.86**). Also, the reaction was done at –90 °C but no reaction occurred. The best solution was to synthesize the 2-TMS-3-bromofuran and repeat the work of Jung and Davidov. However, at that point, the immediate goal was to determine if the furan group could serve as a good directing group for the oxy-Cope/Claisen/ene reaction of a *cis* propargyl ether. Since it was five steps to synthesize the protected bromo-furan,[166] we judged it more advantageous to use a model where the furan was attached by its C2 instead of its C3 since it was possible to access **3.86** easily. It was anticipated that the regiochemistry of the furan group would not affect the outcome of the domino microwave reaction. Thus, once the effectiveness of the furan group as a directing group will be established, efforts will be directed to fix the regioselectivity problem of the furan. Solutions include the use of the 2-TMS-3-bromofuran or use of a rhodium catalyzed 1,4-addition with the boronic acid of 3-bromofuran.

Scheme 3.16-Aluminum catalyzed 1,4-addition of furan reagents



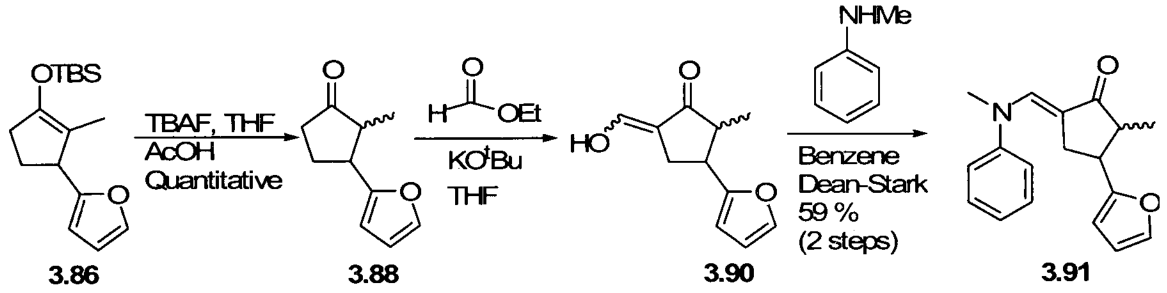
Having installed the furan on the molecule, the next step was to install the quaternary carbon center alpha to the carbonyl (Scheme 3.17). Since the aluminum based 1,4-addition gave a silyl enol ether, it was thought that a Mukaiyama aldol[167] reaction with acetone could generate compound **3.87,** that could be dehydrated to alkene **3.89**. It was predicted that the electrophile would be added from the least hindered side to give desired relative stereochemistry (methyl and furan are *cis*). The Mukaiyama reaction was attempted with several Lewis acids ($TiCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$, $MgBr_2{\cdot}OEt_2$) and under different reaction conditions (time, temperature, solvent, with or without a base). Unfortunately, none of the reaction conditions gave the desired compound **3.87**. Either, starting material was recovered or the silyl enol ether was transformed into its corresponding ketone **3.88**. It was believed that the aldol was unsuccessful due to the steric demands of the reaction and the unreactive electrophile.

Scheme 3.17-Installation of the quaternary carbon center (Mukaiyama aldol)



To avoid the challenging Mukaiyama aldol reaction, a different strategy was examined to introduce stereoselectively the isopropenyl group. Buchwald and co-workers developed a new method to generate quaternary carbon centers by an asymmetric arylation[168] or vinylation of ketones.[169] The coupling of an enolate with an aryl or vinyl halide in the presence of catalyst (palladium and an appropriate ligand) gave the desired α-vinyl or aryl ketone. To apply the methodology to our system, it was important to protect one side of the ketone (Scheme 3.18). The protection of the methylene can be done by installing a substituted enone that can be removed in two steps. Ketone **3.88** was obtained quantitatively from silyl enol ether **3.86** by treatment with TBAF and acetic acid in THF. A mixture of *cis* and *trans* isomers was obtained. However, that was unimportant since both isomers will form the same tetrasubstituted enolate during the coupling reaction. Next, ketone **3.88** was treated with ethyl formate and potassium *t*-butoxide to generate hydroxy-enone **3.90**. The crude material was dissolved in benzene and treated with *N*-methylaniline. Using a Dean-Stark trap, the water was azeotropically removed and protected ketone **3.91** was obtained in 59% yield (2 steps).

Scheme 3.18-Protection of ***3.88***



Buchwald and co-workers investigated various aryl and vinyl groups when they developed their methodology. However, they did not look at isopropenyl groups. Thus, a first attempt was tried using one of their arylation conditions.[170] Ketone **3.91** was treated with 2-bromopropene, NaHMDS, $Pd_2(dba)_3$ and 2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl in toluene to afford the desired product **3.92** in 18% yield (Scheme 3.19). Although the yield was low, the relative stereochemistry observed was the desired one as demonstrated by nOe studies (Figure 3.20). The proton H_a was identified from the proton NMR as a multiplet between the region of 3.51-3.48 ppm. Irradiation of that proton gave a nOe of 2.3% with the methyl of the isopropenyl group (Me_c can be differentiated from the methyl on the quaternary carbon center (Me_b) by the characteristic chemical shift). In order to have a nOe of 2.3%, the proton and the isopropenyl group must be *cis* one to another. In comparison, a very weak nOe interaction was detected between Me_b and the proton (0.3%).

Scheme 3.19- Installation of the quaternary carbon center (enolate coupling)

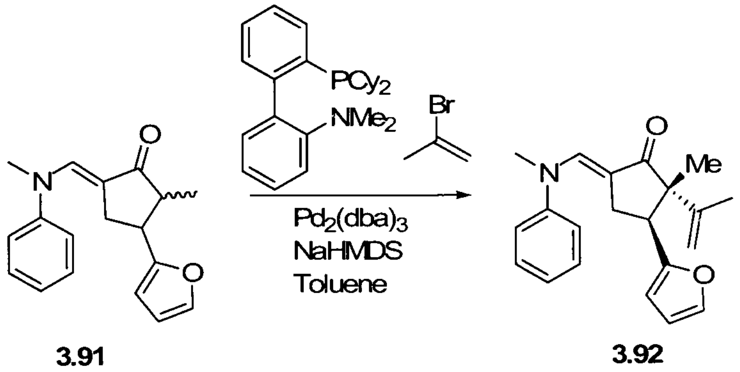
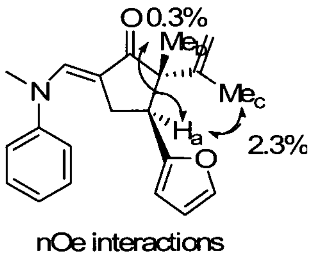


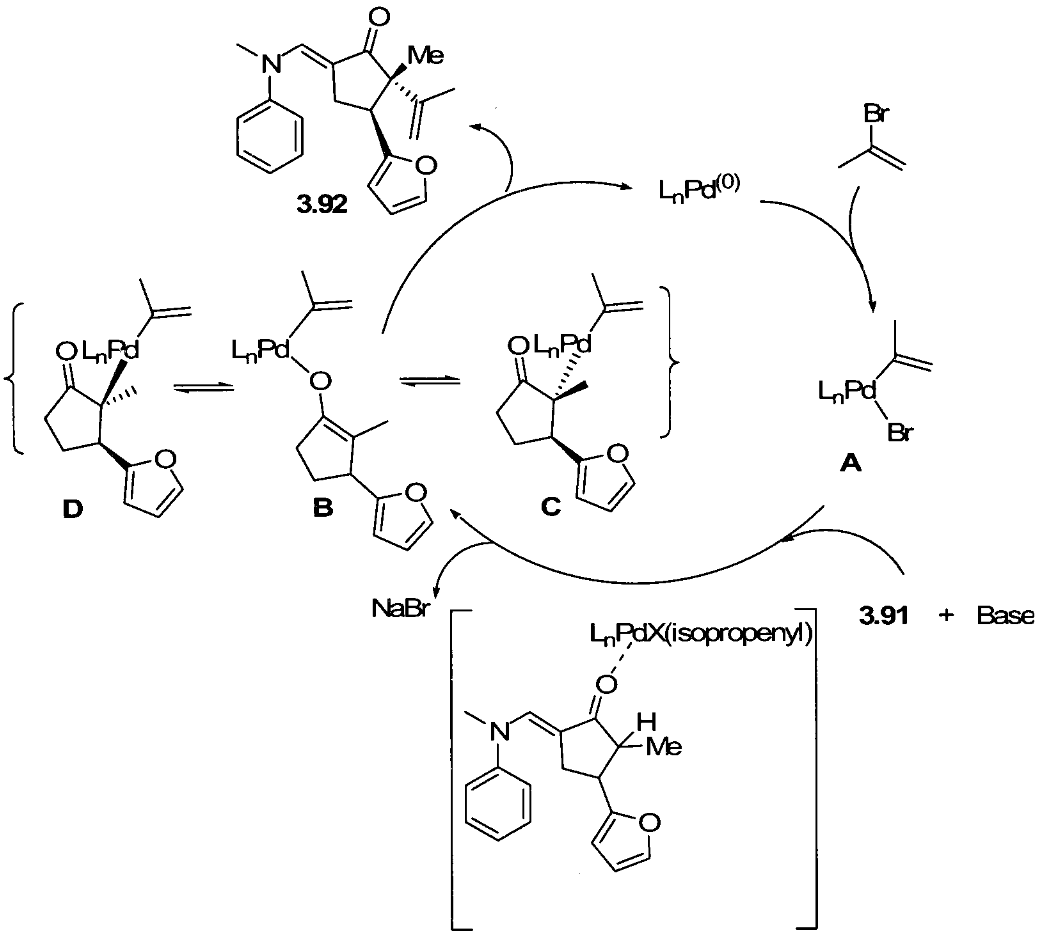
Figure 3.20-Relative stereochemistry of ***3.92***



3.92

The observed stereochemistry was explained by the adapted mechanism[170] shown in Figure 3.21. Oxidative insertion of isopropenyl bromide into the palladium(0) catalyst provides intermediate **A**. It has been suggested that the palladium catalyst then coordinates to the ketone to facilitate deprotonation by the base and provide **B**. In the proposed mechanism by Buchwald, an equilibrium between the Pd-O and the Pd-C linked species is invoked. Likewise, an equilibrium between Pd-O species **B** and Pd-C species **C** and **D** is possible. If there is a rapid equilibrium between these species then it is the energy of the transition state for the reductive elimination that dictates the observed stereochemistry (**3.92** only) (Curtin-Hammet conditions[171]). However, it is also possible that the equilibrium between **B**, **C** and **D** leaned towards **B** and **C** due to the diminished steric interactions in those isomers. Thus, reductive elimination occurs only from intermediate **C** and stereoisomer **3.92** was the only product obtained. At this point, it was not possible to dissociate between both mechanisms.

*Figure 3.21-Proposed mechanism for the formation of **3.92***



It was shown that the enolate coupling gave the desired product. However, the yield was low and needed to be improved (Table 3.5). The initial conditions consisted of using 2.0 equivalents of NaHMDS, 2.0 equivalents of 2-bromopropene, 3 mol% of $Pd_2(dba)_3$, 3.6 mol% of ligand and heating in toluene (0.1 M) at 80 °C for 24 hours (entry 1, 18% yield). Increasing the amount of base and 2-bromopropene was beneficial. Still, the reaction did not go to completion. By increasing the temperature to 90 °C it was possible to get the reaction to go almost to completion (entry 2, 15% yield). However, if the reaction was performed at 100 °C, another inseparable isomer was detected (entry 4). Increasing the amount of the catalyst did not affect the yield (entry 3). It was noticed that the conversion, as seen by TLC analysis, did not correspond to the isolated yield. The purification consisted of a flash chromatography of the reaction mixture. The yield was increased by pre-treating the silica with triethylamine (entry 5, 35% yield). The modest yield was partially explained by the detection of a more polar product. Characterization determined that enone **3.93** was obtained (Figure 3.22). It is hypothesized that a slow reductive elimination led to a competing pathway. Intermediate **D** underwent β-hydride elimination to provide the side product. The active catalyst was regenerated via a reductive elimination. It was thought that an equivalent of Bu_4NBr could assure that the palladium is always coordinatively saturated. Thus, β-hydride elimination could not occur. Unfortunately, adding Bu_4NBr to the coupling reaction did not improve the yield. In summary, the optimization studies led to an increased yield of the reaction and an understanding of the limitation of the method (more sterically encumbered substrates led to side reactions).

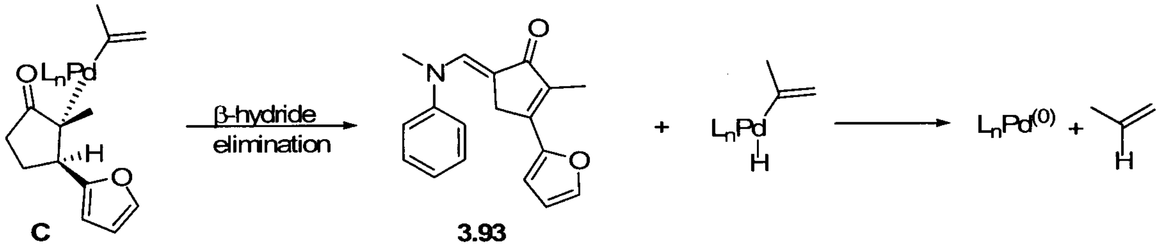
Table 3.5-Enolate coupling

Entry	Equivalents of reagents[a]	Other modification[b]	Temperature (°C)	Time (Days)	Isolated yield (%)
1	2.0	-	80	1	18
2	5.0	-	90	3	15
3	5.0	$Pd_2(dba)_3$-5% Ligand-12.5%	90	2	14
4	5.0	-	100	1	49 (mixture of isomers)
5	5.0	Used NEt_3 on column	90	3	35

[a] NaHMDS and 2-bromopropene

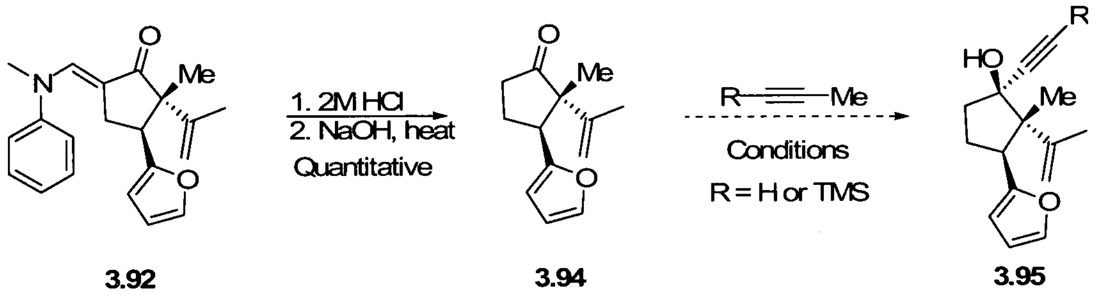
[b] Typical conditions: $Pd_2(dba)_3$ 3% mol, ligand 3.6% mol, toluene (1 mL-concentration approximately 0.1 to 0.2 M). Reaction was done in a schlenk tube.

Figure 3.22-Side reaction in enolate coupling



With some material in hand, the next steps were examined (Scheme 3.20). Removal of the methylene protecting group was done by treating with an acid followed by a base and heating to promote the retro-Claisen reaction. This reaction occurred in quantitative yield giving the necessary ketone **3.94** having the quaternary and tertiary carbon centers in the desired relative stereochemistry. Next, the ketone needed to be acetylated. To this end, the ketone was treated with a variety of nucleophiles (ethynyl magnesium bromide or lithium trimethylsilylacetylene) with different reaction conditions (temperature and equivalents). The acetylenation proved to be much harder than initially anticipated. A molecular model of ketone **3.94** shows that the isopropenyl group was positioned in a way that it is blocking the necessary angle for the approach of the nucleophile (Bürgi-Dunitz[172]). A related example in the literature showed that a similar ketone with a vinyl group alpha to the ketone was successfully acetylated.[173] Thus, the methyl group of the isopropenyl group must have hindered the necessary approach. Furthermore, 5-membered ketones can exist in the enol and keto forms rendering the attack of a nucleophile much more difficult as compared to 6-membered rings.[174] Complexation of ketone **3.94** with $CeCl_3$ might have favored the keto form but only starting material was observed. To remove the enolization problem, it was thought that 1,2-addition could be done directly on ketone **3.92** with lithium trimethylsilylacetylene. A mixture of products was obtained but the NMR clearly showed that the *N*-methylaniline substituent was missing. Therefore, the lithium reagent attacked the enone in a 1,4-manner and the *N*-methylaniline substituent was removed. This 1,4-addition is not typical of lithium reagent that usually attack in a 1,2-manner. This is yet another proof that the carbonyl adjacent to the quaternary carbon center was very sterically encumbered.

Scheme 3.20-Attempted synthesis of ***3.95***

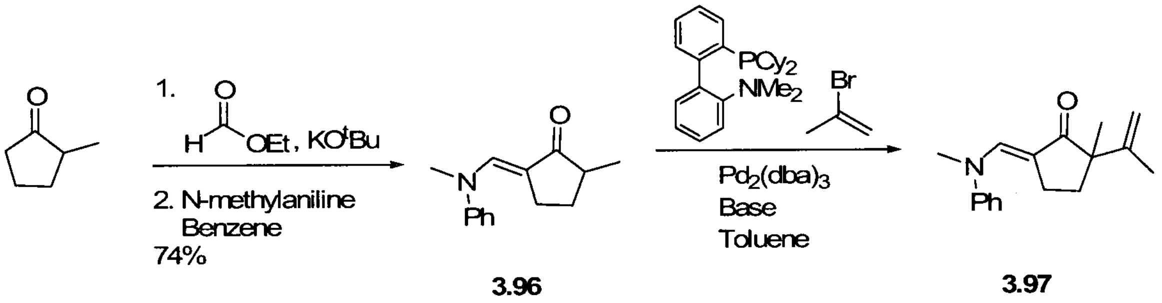


Synthesis of digitoxigenin: model study

In the previous section, attempts to generate a five-membered ring *cis* precursor with a furan directing group were discussed. Although, it was not possible to get the desired propargyl ether **3.57** at that point, it was found that the enolate coupling reaction was the best way to introduce the quaternary carbon center with the desired stereochemistry. Yet, the method had its limitations since it was low yielding. In the original publication by Buchwald and co-workers, yields above 90% were obtained.[169] However, they did not use a substrate with a substituent at C-3 and they did not try to couple 2-bromopropene. Since we got yields from 14 to 35% in our case, we decided to explore the enolate coupling and the subsequent reactions with a simple model substrate (no C-3 substituent).

To this end, 2-methylcyclopentanone was protected using the standard conditions giving known ketone **3.96** in 74% yield (Scheme 3.21). It was then possible to do the enolate coupling with 2-bromopropene under a variety of conditions. It is clear that without the substituent at C-3, the enolate coupling with 2-bromopropene was much more efficient. Using 2 equivalents of NaHMDS, 2 mol% of $Pd_2(dba)_3$, 5 mol% of the ligand and 2 equivalents of 2-bromopropene gave the desired product with a 81% isolated yield. More importantly, the coupling reaction was done at room temperature and it was complete after 24 hours. Changing the base to NaO^{t}Bu gave similar yields (71-75% when the reaction was done on a 200-750 mg scale). Overall, these results confirmed that the low yield observed previously was due to the C-3 substituent.

*Scheme 3.21-Enolate coupling with simple substrate **3.96***



To better understand the problem with the acetylenation observed in the case of furan-substituted ketone **3.94**, the reactivity of the non-substituted substrates was studied (Scheme 3.22). The removal of the protecting group was done by treating substrate **3.97** with 2 M HCl followed by 1 M NaOH at 90 °C. Acetylenation of ketone **3.98** was done by treatment with ethynyl magnesium bromide in THF and stirring for 18 hours. The success of this reaction gave insights into the failure of the acetylenation reaction of **3.94**. Both five-membered ring substrates, **3.98** and **3.94**, had a quaternary carbon center adjacent to the carbonyl. Thus, the quaternary carbon center by itself and enolization can both be ruled out as the reasons why the reaction did not work for the furanyl substrate **3.94**. Instead, it was postulated that the bulky substituent at C-3 forced the molecule into an unfavorable conformation for a carbonyl attack by the nucleophile.

Acetylenation of the non-substituted substrate gave an inseparable mixture of *cis* and *trans* isomers (**3.99**) (Scheme 3.22) (**A**:**B**=65:35). Treatment with propargyl bromide in the presence of sodium hydride gave propargyl ethers **3.100A** and **3.100B** in 41% yield over three steps. The identity of both isomers was determined by NOESY experiments (Figure 3.23). For compound **3.100A**, the methyl at the quaternary carbon center (Me$_z$, δ = 1.15 ppm) had interactions with H$_c$ and H$_f$ whereas the CH$_2$ of the propargyl group saw H$_a$ by nOe. In contrast, the alkene proton in compound **3.100B** saw H$_c$ and H$_f$ while the CH$_2$ of the propargyl group saw H$_a$ by nOe.

Scheme 3.22-Functionalization of non-substituted substrates

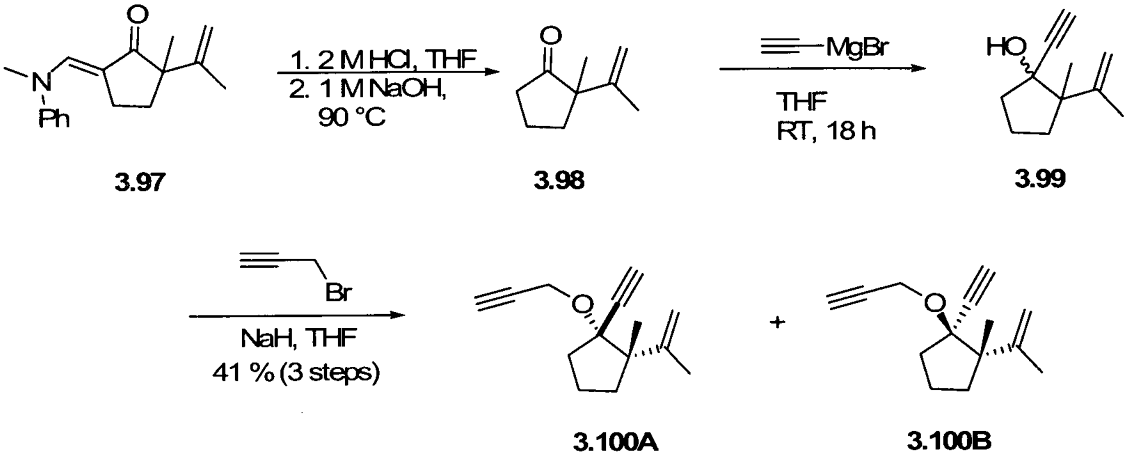
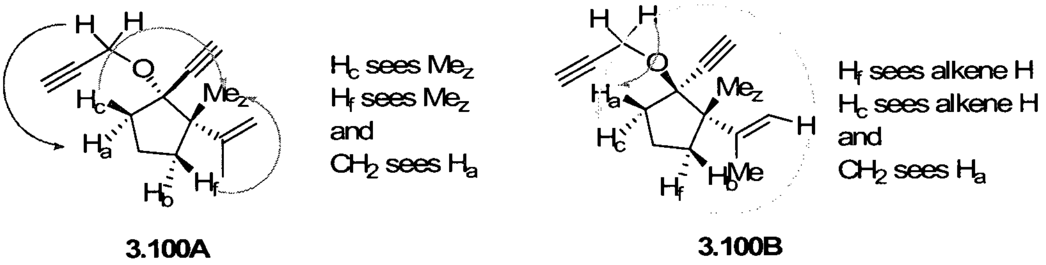


*Figure 3.23-Structure differentiation between **3.100A** and **3.100B***

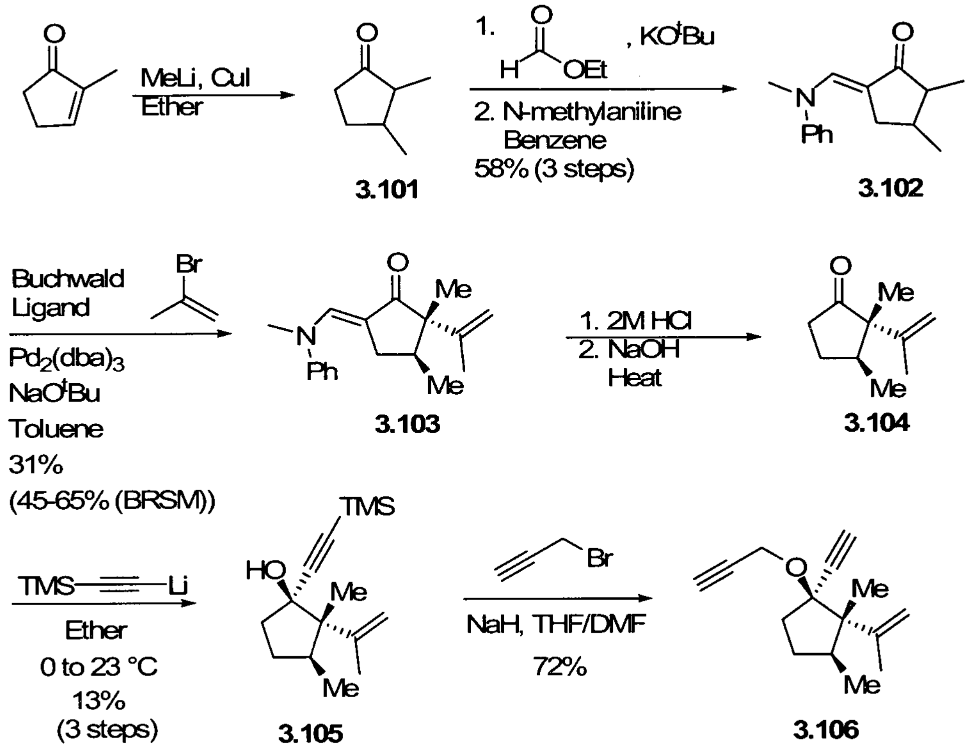


With the substrates in hand, the oxy-Cope/Claisen/ene reaction of the unsubstituted 5-membered ring was studied. The microwave reaction of *trans* propargyl ether **3.100A** gave a mixture of products. The desired product could be detected by proton NMR but it was not reproducible from one reaction to another. Next, *cis* propargyl ether **3.100B** was submitted to microwaves at 210 °C for 120 minutes: at least nine spots were visible by TLC with no major product. From the previous studies on *cis* precursors, it had been predicted that two products should be observed (at the most, four products). The methodology was not compatible to substrates **3.100A** and **3.100B**. It was clear that a directing group was necessary for the reaction *cis* precursors. However, our previous attempts at synthesizing the furanyl-substituted propargyl ether were unsuccessful due to the unreactive ketone. The model study determined that it was possible to do the acetylenation in the non-substituted case. Thus, it was essential to find a directing group that could be functionalized to the butenolide but it cannot be too bulky in order for the acetylenation to occur. At that point in the project, we were not sure how the substituted *cis* five-membered precursor would react in the sequential oxy-Cope/Claisen/ene/HDDA reaction. Since it might take many efforts to find the perfect directing group, the simplest directing group (a methyl group) was chosen to validate the key step towards digitoxigenin.

Synthesis of digitoxigenin: second model study

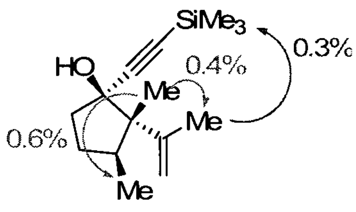
A new *cis* precursor with a methyl directing group was synthesized in order to test the key oxy-Cope/Claisen/ene/HDDA reaction (Scheme 3.23). Using a known procedure, 2-methylcyclopentenone was transformed to 2,3-dimethylcyclopentanone.[175] Since the compound was volatile, it was used directly in the next two steps. Protected ketone **3.102** was obtained in 58% yield over three steps. Next, the enolate coupling was explored. As in the case of the furanyl, the yield was modest. Using sodium *tert*-butoxide as the base, it was possible to isolate the desired product in 29% yield (65% BRSM). Thus, the size of the substituent was not very important as any substituent at C-3 affected tremendously the enolate coupling reaction. The protecting group was removed by treating substrate **3.103** with 2 M HCl followed by 1 M NaOH and heating. This compound was volatile and was used directly in the following acetylenation and propargylation steps. Alkylation of the lithium species of trimethylsilylacetylene was done in ether at room temperature for 18 hours before the reaction went to completion to give alcohol **3.105** in 13% yield over 3 steps (a small amount of the other isomer was also observed but there was not enough to characterize it).

Scheme 3.23-Synthesis of propargyl ether ***3.106***



The stereochemistry of alcohol **3.105** was proven by nOe experiments (Figure 3.24). The methyls of the silyl protecting group on the alkyne are very far from the rest of the molecule as seen with a molecular model yet there is a 0.3% nOe with the methyl of the isopropenyl group. Also, the methyl on the quaternary carbon center has a 0.6% nOe with the C-3 methyl and a 0.4% nOe with the methyl on the isopropenyl group. The only possible stereochemistry was the one where the methyl and the alcohol are *cis* one to another. Treating alcohol **3.105** with sodium hydride and propargyl bromide did two reactions in one: the propargylation and the deprotection of the alkyne were done in the same reaction conditions with a yield of 72%.

*Figure 3.24-Structure determination of **3.105***



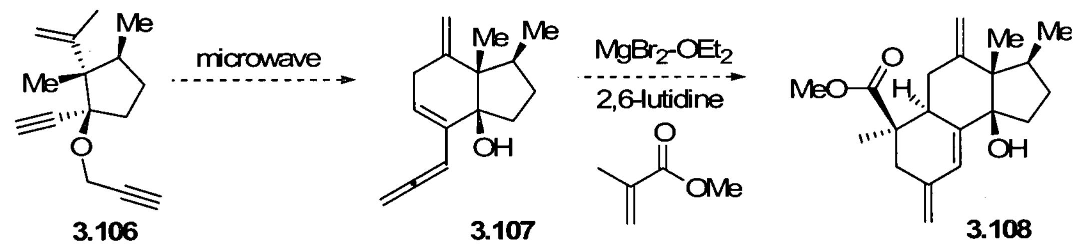
NOE

3.105

Having the propargyl ether **3.106** in hand, it was possible to test the oxy-Cope/Claisen/ene/HDDA reaction (Scheme 3.24). Submitting the starting material to microwave irradiation at 200 °C in toluene with triethylamine only gave a trace amount of a product that could be desired intermediate **3.107** (crude proton NMR). From previous studies, it was known that allenes of the type **3.107** were not very stable on silica and had to be used crude in the next step. Taking the crude material into the hydroxy-directed Diels-Alder reaction using methyl methacrylate as the dienophile did not give any of the desired product **3.108**. Various microwave reaction conditions were tested in order to get the desired product. In the past, acetonitrile was found to be a good alternative to toluene for the microwave reaction. However, it did not give the desired product in the case of propargyl ether **3.106**. By crude NMR, it was clear that allene **3.107** was not generated by heating the substrate yet there was no more starting material. The major compound was purified and characterized as tricyclic compound **3.109** (Figure 3.25). This compound was isolated in 33% yield when toluene was used as the solvent.

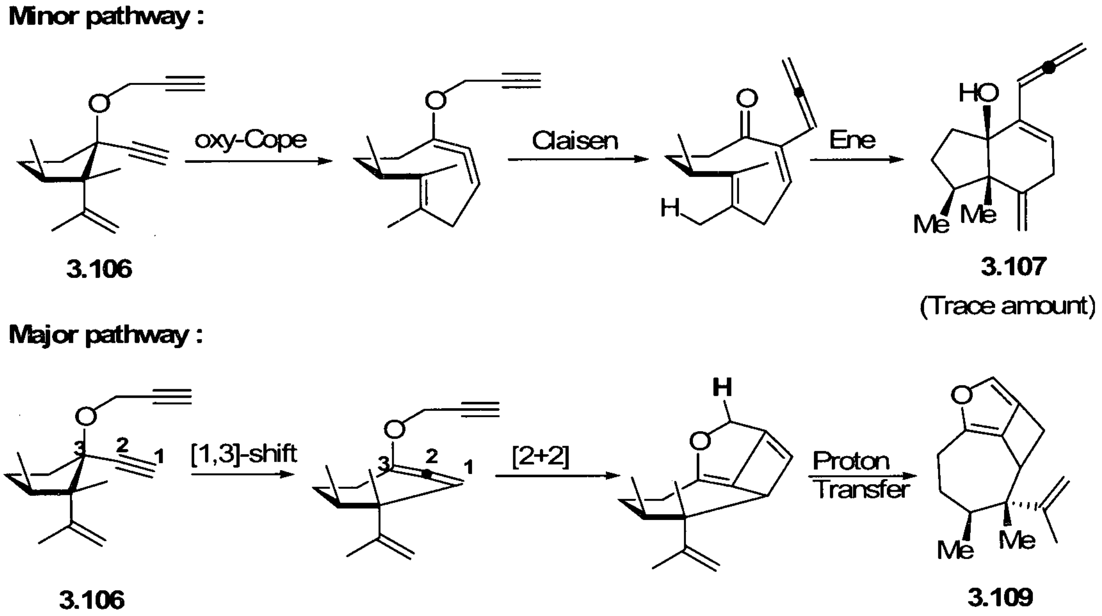
A proposed mechanism for the microwave reaction of propargyl ether **3.106** is shown in Figure 3.25. The minor pathway consisted of the oxy-Cope/Claisen/ene reaction (simplified mechanism, see Figure 3.18 for a complete mechanism with a directing group). Since the major product was **3.109**, the major pathway was a 1,3-shift followed by a [2+2] involving the alkyne and finally aromatization to give the tricyclic compound.[176] Although 1,3-shifts had never been observed in the microwave reaction of propargyl ethers, it was believed that the starting material was very sterically encumbered and the 1,3-shift was favorable since it led to steric decompression.[177]

*Scheme 3.24-Oxy-Cope/Claisen/ene/HDDA of propargyl ether **3.106***



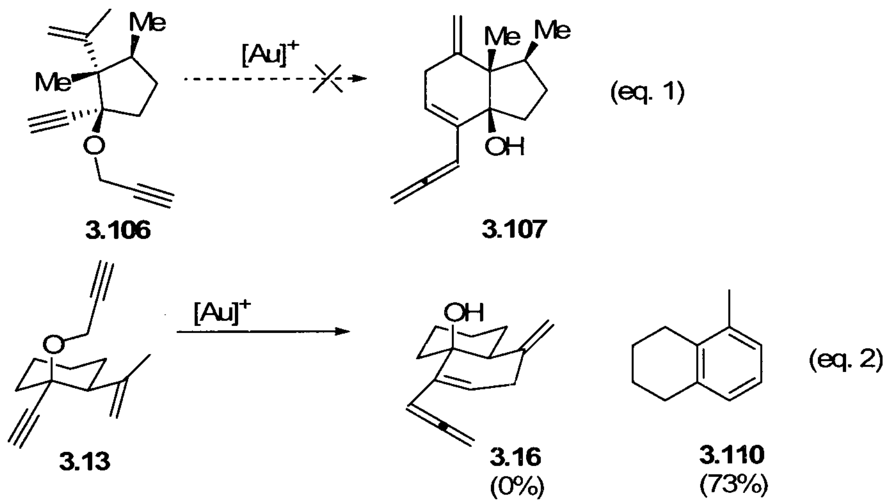
3.106 **3.107** **3.108**

*Figure 3.25-Proposed mechanism for the microwave reaction of **3.106***



Since there were two competing pathways, other temperatures and various solvents were tried but the major compound was constantly tricyclic compound **3.109**. Conventional heating was also attempted but only a trace amount of **3.107** was detected, as the major product was **3.109**. Finally, gold catalysis was attempted since it is known that cationic gold catalysts can activate alkyne towards nucleophilic attacks.[178] Furthermore, Toste and Sherry demonstrated that cationic gold catalysts could promote the Claisen rearrangement of propargyl vinyl ether.[179] Unfortunately, catalyst systems consisting of Au(PPh$_3$)Cl and a silver salt (AgOTf, AgBF$_4$ or AgSbF$_6$) did not promote the desired reaction (Scheme 3.25, eq. 1). Simultaneously, the oxy-Cope/Claisen/ene reaction of propargyl ether **3.13** was studied using the same cationic gold catalysts. The desired product, allene **3.16**, was not observed but tetrahydronaphthalene **3.110** was obtained in 73% yield. This gold-catalyzed benzannulation will be discussed in the next chapter.

Scheme 3.25-Gold-catalyzed attempt at the oxy-Cope/Claisen/ene reaction

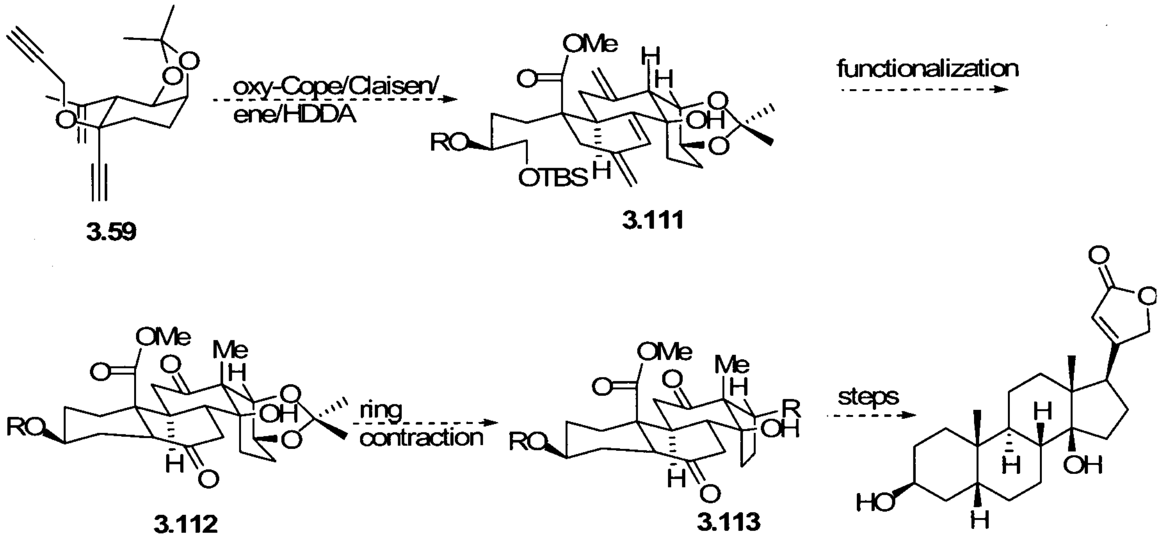


This model study, with the methyl group as a directing group, addressed many issues. Although the enolate coupling reaction was an efficient way to introduce quaternary carbon centers, if there is a substituent at C-3 (furanyl or methyl), the yield suffers noticeably. Also, the acetylenation reaction was feasible with a methyl directing group but not in the case of the furanyl directing group. Most importantly, the limitations of oxy-Cope/Claisen/ene/HDDA have been found. If the precursor was sterically encumbered, the desired reaction was not observed. In the case of propargyl ether **3.106**, three consecutive chiral centers (two quaternary centers, 1 tertiary) on a five-membered ring caused major steric hindrance. Thus, heating this precursor led to a side reaction due to steric decompression instead of the oxy-Cope/Claisen/ene reaction. It is not believed that having a furanyl instead of the methyl group would change the outcome of the domino reaction. Thus, the retrosynthesis needs to be revised in order to apply the oxy-Cope/Claisen/ene/HDDA to the total synthesis of digitoxigenin.

Outlook

The studies towards the total synthesis of digitoxigenin have demonstrated the scope and limitations of the oxy-Cope/Claisen/ene/HDDA reaction. The sequential reaction worked in the case of the *cis* six-membered ring propargyl ether having a directing group (Scheme 3.15). However, the five-membered ring *cis* functionalized precursors were too hindered and led to difficult acetylenation and an undesired rearrangement during the key step. Thus, if the oxy-Cope/Claisen/ene/HDDA reaction were to be used towards the total synthesis of digitoxigenin, it would be necessary to do a ring contraction in order to generate the five-membered ring (Scheme 3.26). The sequential reaction could be done with precursor **3.59** with an appropriate dienophile[180] in order to form substrate **3.111**. Then, functionalization would be needed to introduce the methyl at the ring junction and close the A ring. Next, a ring contraction could be imagined to achieve **3.113** that could be further functionalized to the natural product.

Scheme 3.26-Alternative synthetic plan


3.59

3.111

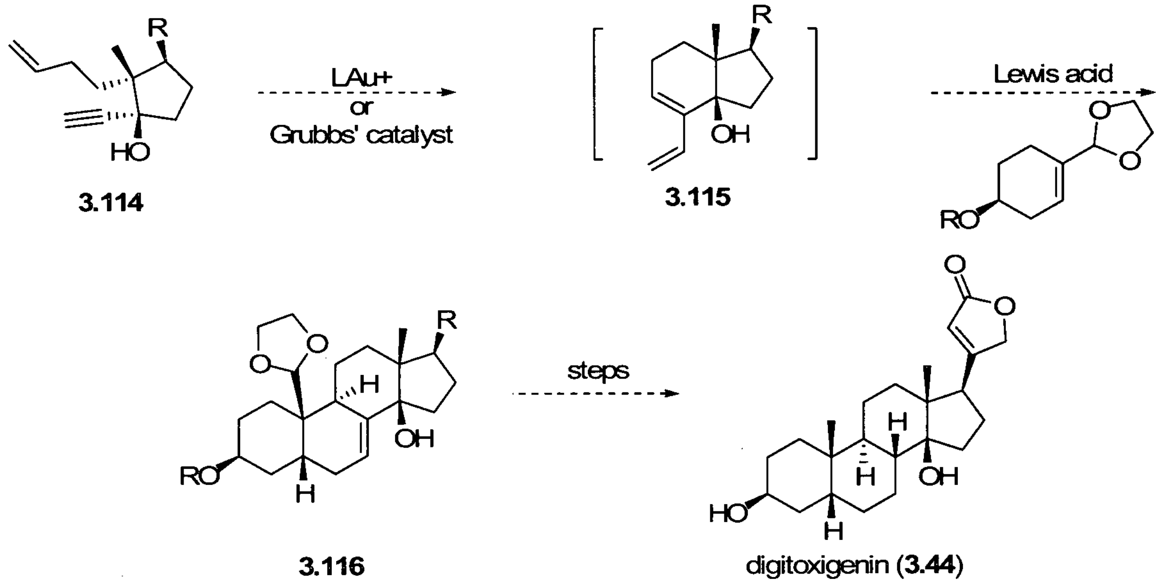
3.112

3.113

In reality, it was decided that it would be best to use another key step for the total synthesis of digitoxigenin (Scheme 3.27). Colleague Jason Poulin has been working on this project. It was imagined that substrate **3.114** could undergo a gold-catalyzed 1,7-cycloisomerization or a ruthenium-catalyzed metathesis to afford diene **3.115**. Then, a

Gassman-type dienophile[181] would be added to the reaction mixture and a Lewis-acid mediated Diels-Alder reaction could provide the tetracyclic core of digitoxigenin (**3.116**). Efforts to make this reaction one-pot are underway as well as the efforts towards the total synthesis. The advantage of this approach is that the key step should be done at much lower temperature and thus, avoids the side reaction observed in the oxy-Cope/Claisen/ene/HDDA reaction.

Scheme 3.27-Jason Poulin's synthetic plan towards digitoxigenin



Conclusions

The oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction of propargyl ethers is a powerful method to construct carbocycles in a diastereoselective way. It was possible to optimize the reaction conditions in order to increase the yield. During these studies, it was discovered that the hydroxy-directed Diels-Alder reaction could be done using Dibal-H, albeit with a lower diastereoselectivity. Also, mechanistic studies have confirmed that the domino reaction does proceed through a oxy-Cope/Claisen/ene sequence of reactions.

The application of the method towards the total synthesis of digitoxigenin allowed to expand the scope to *cis* precursors. Unfortunately, the oxy-Cope/Claisen/ene reaction was not compatible with highly substituted five-membered ring *cis* precursors. Nevertheless, the studies allowed the development of an approach to the *cis* precursors using an enolate coupling reaction. In addition, a gold-catalyzed benzannulation has been discovered. Finally, these studies have brought about a new approach to cardenolides that is presently being pursued by a colleague.

Chapter 4

Gold-Catalyzed Benzannulation of 3-Hydroxy-1,5-Enynes

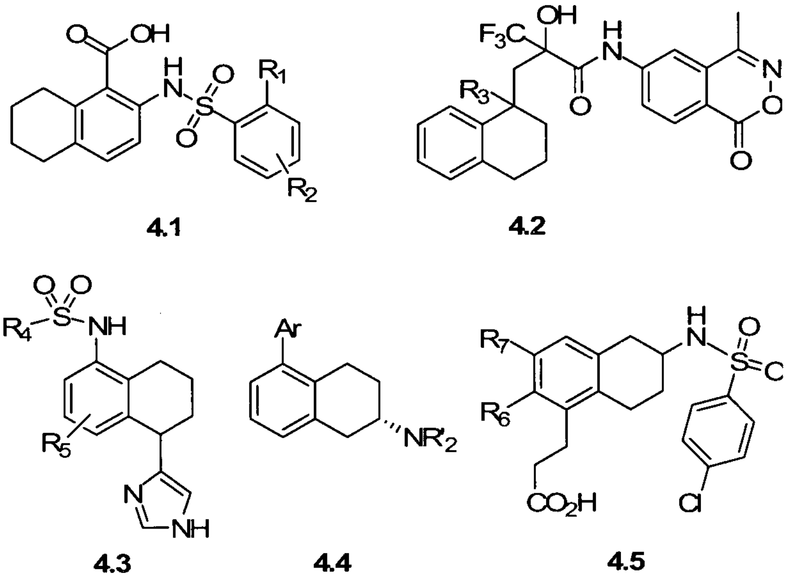
Introduction

Substituted aromatic compounds have a fundamental importance in organic chemistry. They are found in natural products, medicinally important molecules, as well as in materials. Although there are many methods to functionalize aromatic rings, one must also consider a benzannulation reaction as an efficient approach to access these substituted aromatic compounds. Various strategies have been developed for acyclic precursors to be transformed into aromatic rings. Generally, these methods have the advantages that the substituted aromatic compounds are accessed in few steps and with high regioselectivity. Examples of benzannulation reactions include the Dötz reaction of Fisher carbene complexes, acid promoted benzannulation, anionic cyclization, [4+2] cycloaddition, metal-catalyzed carbocyclization and metal-catalyzed cyclotrimerization of alkynes.[182]

Taking into account the peculiar reactivity of gold salts to activate alkynes, allenes and alkenes towards nucleophilic attack,[183] one can imagine the use of gold complexes to catalyze benzannulation and related reactions. For instance, Hashmi and co-workers described a selective synthesis of substituted phenols using 2 mol% of $AuCl_3$ in acetonitrile.[184] Subsequently, Asao and coworkers have developed a gold catalyzed-[4+2] benzannulation between enynals and carbonyl compounds.[185] From that point, the number reports on gold-catalyzed benzannulation reactions have increased dramatically. It was shown that the cycloisomerization of aromatic enynes gave an access to substituted phenanthrenes,[186] naphthalenes[187] or styrenes.[188] Toste *et al.* provided a new approach to form substituted naphthalenes via a metal-catalyzed tandem [3,3]-sigmatropic rearrangement/formal Myers-Saito cyclization.[189] Liu and coworkers disclosed the synthesis of various arenes using an intramolecular [3+2]-cycloaddition of arenyne-yne substrates.[190]

1,2,3,4-Tetrahydronaphthalenes and related derivatives are key fragments of medicinally important molecules. Selected examples are shown in Figure 4.1. Methionine aminopeptidase-2 reversible inhibitor **4.1**, glucocorticoid receptor agonist **4.2**, α_{1A}-adronoceptor selective agonist **4.3**, serotonin 5-HT_7 receptor agonist **4.4** and thromboxane receptor antagonist **4.5** are just a few of the biologically active compounds that were identified.[191] Numerous syntheses to obtain this important class of molecules have been developed. One of the most common ways to access these molecules is hydrogenation of naphthalenes.[192] Alternatively, the cyclohexane ring can be generated via a Friedel-Crafts alkylation.[193] Another frequent approach is the use of [4+2] cycloadditions to form the aromatic ring of the tetrahydronaphthalenes.[194] These approaches are limited due to the regioselectivity problems, the restricted scope and/or low yields. Thus, gold-catalyzed benzannulation of hydroxy-enynes represents an attractive alternative for *de novo* synthesis of the tetrahydronaphthalene framework.

Figure 4.1-Selected biologically active molecules containing a tetrahydronaphthalene



4.1 **4.2** **4.3** **4.4** **4.5**

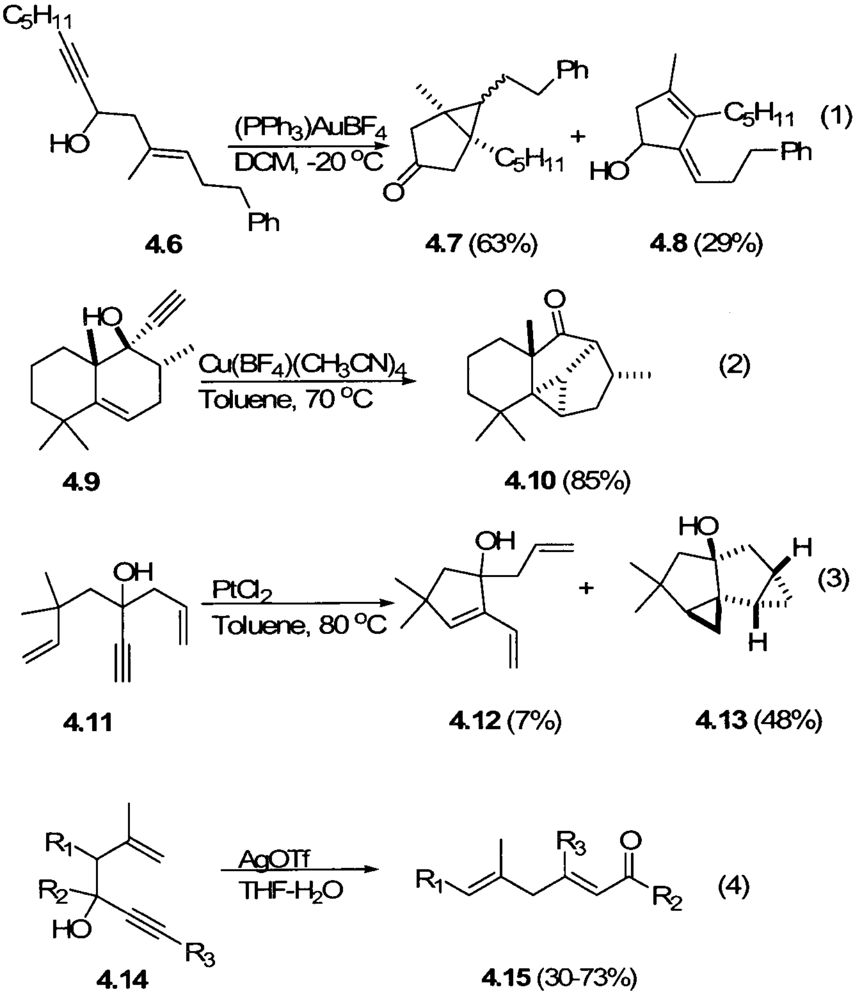
It has been demonstrated that 3-hydroxy-1,5-enynes undergo cycloisomerization when they were treated with Cu, Pt or Au salts.[195] Typically, the products generated were either metathesis-type or polycyclic compounds. For example, Gagosz has shown that enyne **4.6** rearranged to give bicyclic compound **4.7** and cyclopentenol **4.8** (Scheme 4.1, eq. 1).[195c] In 2006, Fehr and coworkers reported that ring expansion of hydroxy-enyne **4.9** to polycyclic compound **4.10** occurs in 85% yield (eq. 2).[195b] Also, Malacria *et al.* established that polycyclic compound **4.13** was the major product when dienyne **4.11** was treated with $PtCl_2$ (eq. 3).[195h]

3-Hydroxy-1,5-enynes were also shown to rearrange via the oxy-Cope reaction in the presence of soft Lewis acid. Gore *et al.* reported the Ag(I)-mediated sigmatropic rearrangement of 3-hydroxy-1,5-enynes **4.14** to provide the desired enone **4.15** (eq. 4).[196] This reaction proved to be limited in scope since some of the substrates gave a mixture of products.

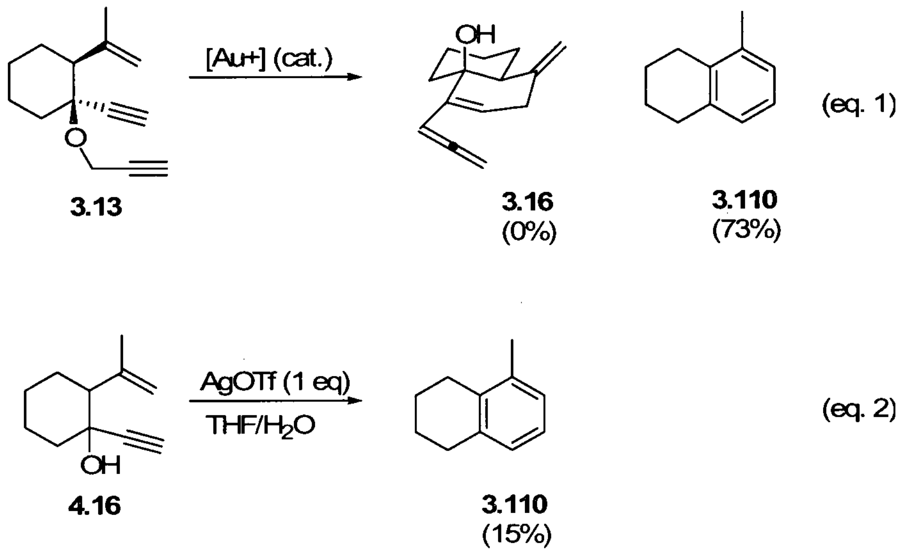
During our studies on the oxy-Cope/Claisen/ene/HDDA reaction, we were intrigued by the possibility of promoting the desired rearrangement using gold catalysis. As mentioned in the previous chapter, treating propargyl ether **3.13** with $Au(PPh_3)Cl$ and AgOTf in dichloromethane did not promote the desired oxy-Cope/Claisen/ene reaction

(Scheme 4.2, eq. 1). Instead, tetrahydronaphthalene **3.110** was obtained in 73% yield. At that point, a more thorough search in the literature showed that this product was observed, among many other side products, by Gore and co-workers. When the correspondent 3-hydroxy-1,5-enyne **4.16** was treated with a stoichiometric amount of silver triflate in THF/H_2O the tetrahydronaphthalene was isolated in only 15% yield (Scheme 4.2, eq.2).[196a] With our promising preliminary results, we decide to explore a catalytic version of this unusual benzannulation.[197]

Scheme 4.1-Metal-catalyzed rearrangement of hydroxy-enynes



Scheme 4.2-Benzannulation of enynes

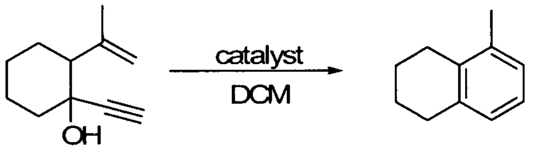


Optimization

Based on the work of Gore and co-workers,[196] we suspected that the propargyl group was not necessary for the benzannulation. To our delight, subjection of a *cis* and *trans* mixture of **4.16** to 1 mol% Au(PPh_3)Cl and 1 mol% AgOTf in dichloromethane gave **4.17** in 72% yield (Scheme 4.3). To optimize the reactions conditions, other catalyst systems were explored (Table 4.1).

Treatment of alcohol **4.16** with 5 mol% Au(PPh_3)Cl and 5 mol% $AgBF_4$ (entry 1) gave **4.17** in 42% yield. Changing the silver salt to $AgSbF_6$ gave the desired product in 22% yield (entry 2). A catalytic amount of $AuCl_3$ and AuCl also catalyzed the benzannulation, albeit in low conversion (entry 3-4), while $PdCl_2(PhCN)_2$ did not promote the reaction (entry 5). A control experiment employing 2.5 mol% Au(PPh_3)Cl only (entry 6) did not give any desired tetrahydronaphthalene **4.16**. However, 2.5 mol% AgOTf (entry 7) or 2.5 mol% AgOTf and 2.5% PPh_3 (entry 8) did promote the reaction although with a 48 and 45% conversion respectively after 18 h. The best catalyst system was a combination of Au(PPh_3)Cl and AgOTf. The use of 2.5 mol% of both catalysts led to the desired product in 84% yield. A reduction of catalyst loading to 0.1 mol% of Au(PPh_3)Cl and AgOTf, however, led to a significant loss in yield (58%) along with a longer reaction time (96 h).

Scheme 4.3-Metal-mediated benzannulation



4.16 **4.17**

Table 4.1-Au- and Ag-catalyzed tetrahydronaphthalene synthesis

Entry	**Catalyst**[a]	**Result**[b]
1	5 mol% $Au(PPh_3)Cl$, 5 mol% $AgBF_4$	42% isolated yield
2	5 mol% $Au(PPh_3)Cl$, 5 mol% $AgSbF_6$	22% isolated yield
3	2.5 mol% $AuCl_3$	22% conversion
4	2.5 mol% AuCl	22% conversion
5	2.5 mol% $PdCl_2(PhCN)_2$	SM only
6	2.5 mol% $Au(PPh_3)Cl$	SM only
7	2.5 mol% AgOTf	48% conversion
8	2.5 mol% AgOTf, 2.5 mol% PPh_3	45% conversion
9	2.5 mol% $Au(PPh_3)Cl$, 2.5 mol% AgOTf	84% isolated yield

[a] Reactions run at 23 °C for 18 h. [b] conversion was determined by H^1 NMR

Mechanism

To gain more insight into the reaction mechanism, compound **4.18** was synthesized from alcohol **4.16** and treated with a catalytic amount of $Au(PPh_3)Cl$ and AgOTf (Scheme 4.4). The only detectable product was tetrahydronaphthalene **4.17** and it was isolated in 70% yield. There is much precedence for the gold-catalyzed rearrangement of propargylic esters that include 1,2- and 1,3-migrations.[198] Surprisingly, acetate **4.18** did not form any products resulting from these pathways (carbene-type reactivity or allene activation). This result in combination with the fact that propargyl ether **3.13** also rearranged to the same tetrahydronaphthalene (Scheme 4.2), seemed to indicate that the substitution on the alcohol did not influence the benzannulation. Based on these results, we proposed the following mechanism illustrated in Figure 4.2.

Scheme 4.4-Benzannulation of the acetoxy-derivative

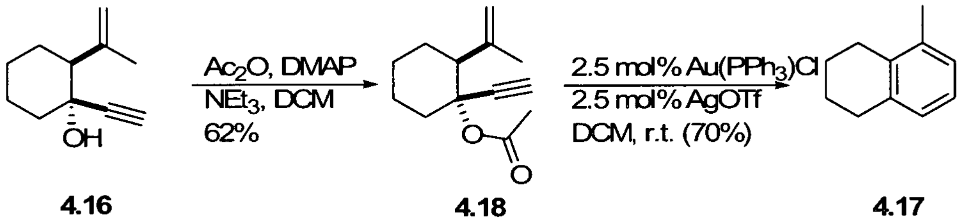
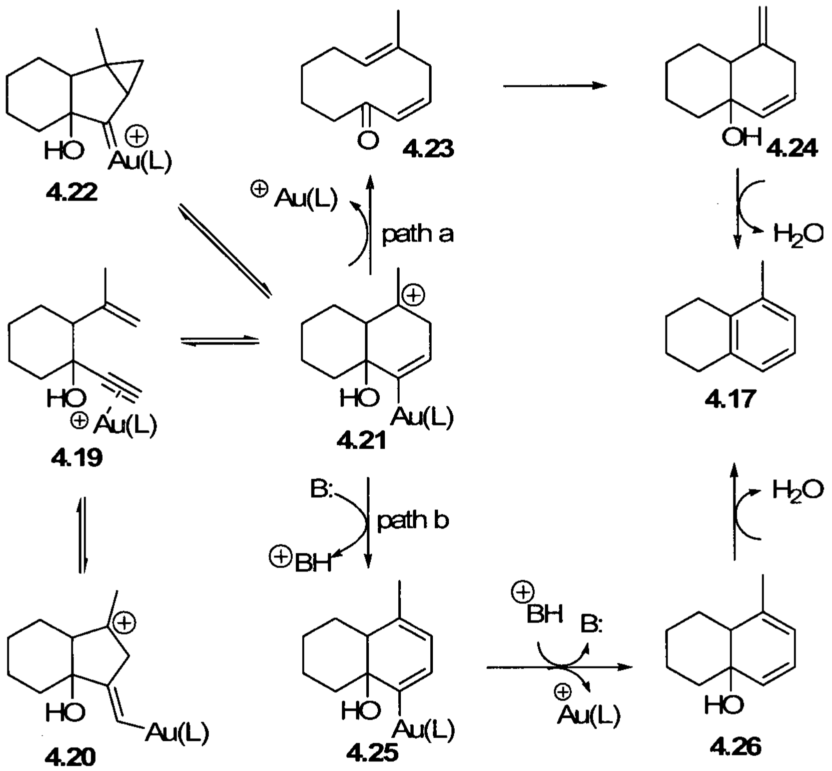


Figure 4.2-Proposed mechanism

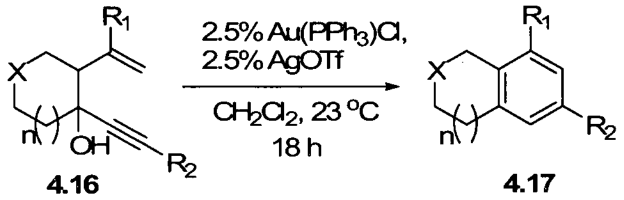


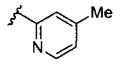
The combination of the pre-catalysts Au(PPh$_3$)Cl and AgOTf produces a cationic gold species which coordinates to the alkyne in a reversible manner. This enables the nucleophilic attack of the alkene onto the alkyne via a 5-*exo*-dig[199] or 6-*endo*-dig[187b,188,195b,200] mode to afford **4.20** and **4.21** respectively.[201] Intermediate **4.21** could be in equilibrium with **4.22**. Examples of polycyclic products arising from a 1,2-hydride shift of intermediates analogous to **4.22** have been demonstrated.[195a,c,f] However in the present case, the formation of such polycyclic products was not possible due to the tertiary alcohol. From intermediate **4.21**, two possible pathways are considered. The first scenario (pathway a) could be a ring expansion of **4.21** to give the formal oxy-Cope product **4.23**.[195c] At that point, **4.23** could undergo a transannular ene reaction to give **4.24** which upon loss of water followed by aromatization would give **4.17**. Alternatively, intermediate **4.21** could undergo a subsequent deprotonation, protonation and aromatization sequence to afford tetrahydronaphthalene **4.17** (pathway b). To determine which pathway, A or B, was involved in the reaction mechanism, we treated alcohol **4.24**[202] with 2.5 mol% of Au(PPh_3)Cl and AgOTf in dichloromethane at room temperature. After stirring for 3 hours, **4.24** was slowly converted to **4.17**.[203] One might propose that pathway A could be involved in the reaction mechanism. However, we did not detect any products in the crude reaction mixture resulting from an oxy-Cope reaction when **3.13** and **4.18** were treated a catalytic amount of Au(I) and Ag(I) (Scheme 4.2 and Scheme 4.4). The slow conversion of **4.24** to **4.17** combined by the absence of any oxy-Cope products during the benzannulation process suggest that the reaction proceeds through pathway B.

Scope and limitations of the benzannulation reaction

Having found the optimal reaction conditions, the scope of the reaction was then examined (Table 4.2 and Table 4.3). The substrates (**4.16a-t**) were generally obtained in two to three steps from commercially available materials. In a method similar to the synthesis of alcohol **4.16**, alcohols **4.16a**, **4.16b**, **4.16d** and **4.16j** were obtained by the alkylation of a Grignard reagent onto ketone **4.27** that was obtained in two steps from a cyclic epoxide (Scheme 4.5). Substrates **4.16c**, **4.16i**, **4.16o**, **4.16p** and **4.16q** were obtained in two steps from 2-chlorocyclohexan-1-one (Scheme 4.6). First, the chloro-ketone was alkylated with the appropriate organolithium species. Then, ethynylmagnesium bromide deprotonates the alcohol that undergoes a 1,2-migration to generate the corresponding ketone *in situ*; subsequently, the ketone is alkylated by the Grignard reagent to afford the desired product. A Sonogashira coupling was used to install a phenyl or a substituted-phenyl group at the terminal alkyne position (Scheme 4.7). Thus, it was possible to generate alcohols **4.16e**, **4.16f**, **4.16g**, **4.16h** and **4.16k** efficiently.

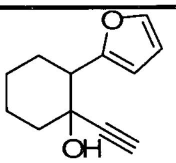
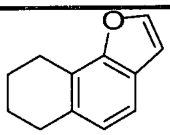
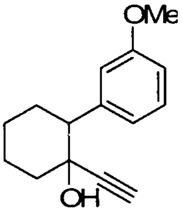
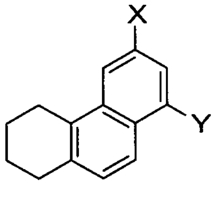
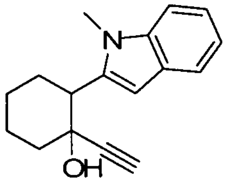
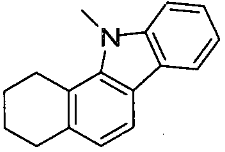
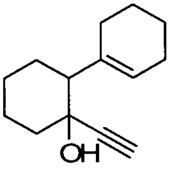
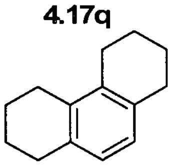
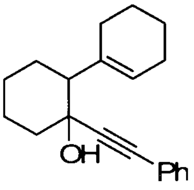
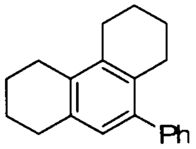
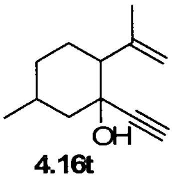
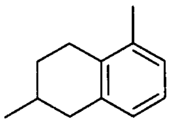
Table 4.2-Scope of the gold-catalyzed benzannulation



Entry	R_1	R_2	n	X	Yield%[a]
1	Me	H	0	CH_2	**4.17a**, 28
2	H	H	1	CH_2	**4.17b**, 10
3	Ph	H	1	CH_2	**4.17c**, 84
4	Me	Me	1	CH_2	**4.17d**, 77
5	Me	Ph	1	CH_2	**4.17e**, 86
6	Me	4-$NO_2C_6H_4$	1	CH_2	**4.17f**, 73
7	Me	4-$NHAcC_6H_4$	1	CH_2	**4.17g**, 66
8	Me		1	CH_2	**4.17h**, 75[b]
9	OEt	H	1	CH_2	**4.17i**, 12
10	Me	H	2	CH_2	**4.17j**, 51
11	Me	Ph	2	CH_2	**4.17k**, 65
12	Me	H	1	NTs	**4.17l**, 49
13	Me	Ph	1	NTs	**4.17m**, 67
14	Me	H	1	O	**4.17n**, 51

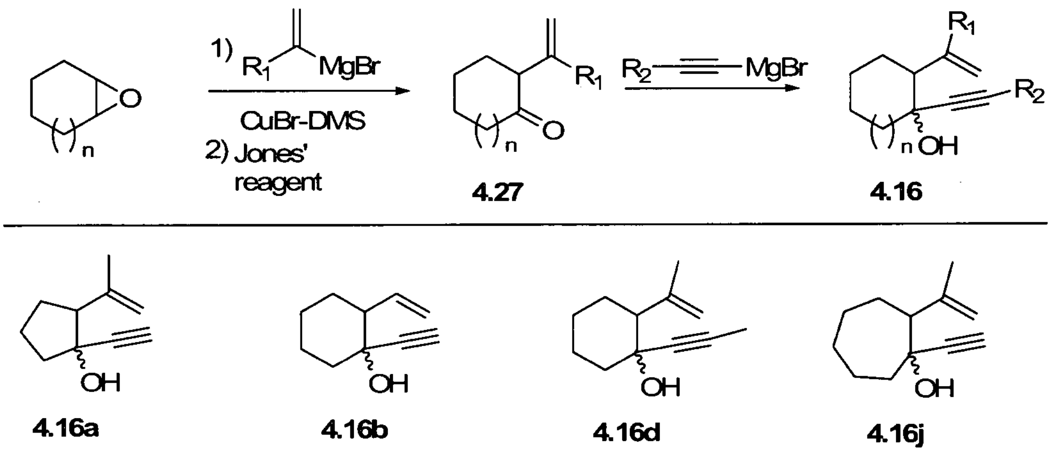
[a]Isolated yield after column chromatography. [b]1.5 equiv of PTSA was added and 10 mol% of Au(I) and Ag(I) were used.

Table 4.3- Scope of the gold-catalyzed benzannulation[a]

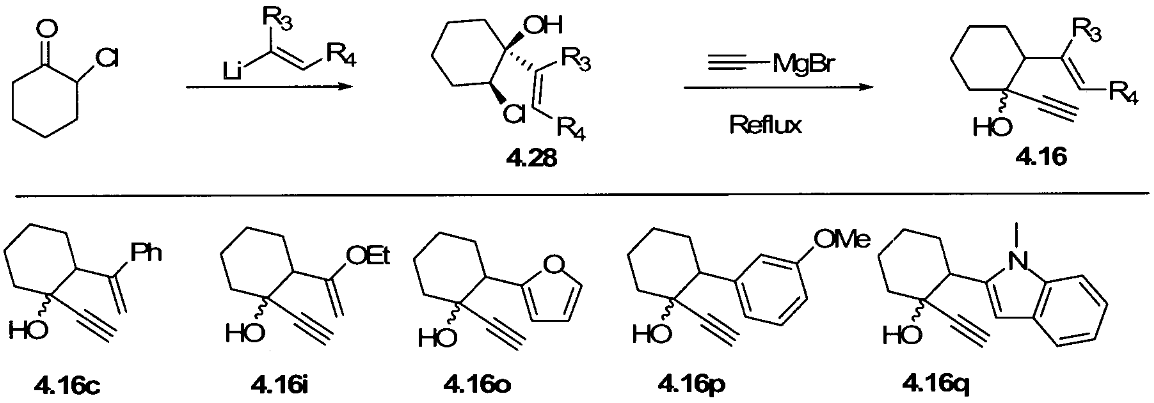
Entry	Substrate	Product	Yield (%)[b]
1	 **4.16o**	 **4.17o**	57
2	 **4.16p**	 **4.17pI** X = OMe, Y = H (1.5) **4.17pII** X = H, Y = OMe (1)	76
3	 **4.16q**	 **4.17q**	81
4	 **4.16r**	 **4.17r**	70
5	 **4.16s**	 **4.17s**	81
6	 **4.16t**	 **4.17t**	74

[a] The reaction conditions are 2.5 mol% of each Au(PPh_3)Cl and AgOTf in DCM at 23 °C for 18 hours. [b]Isolated yield after column chromatography.

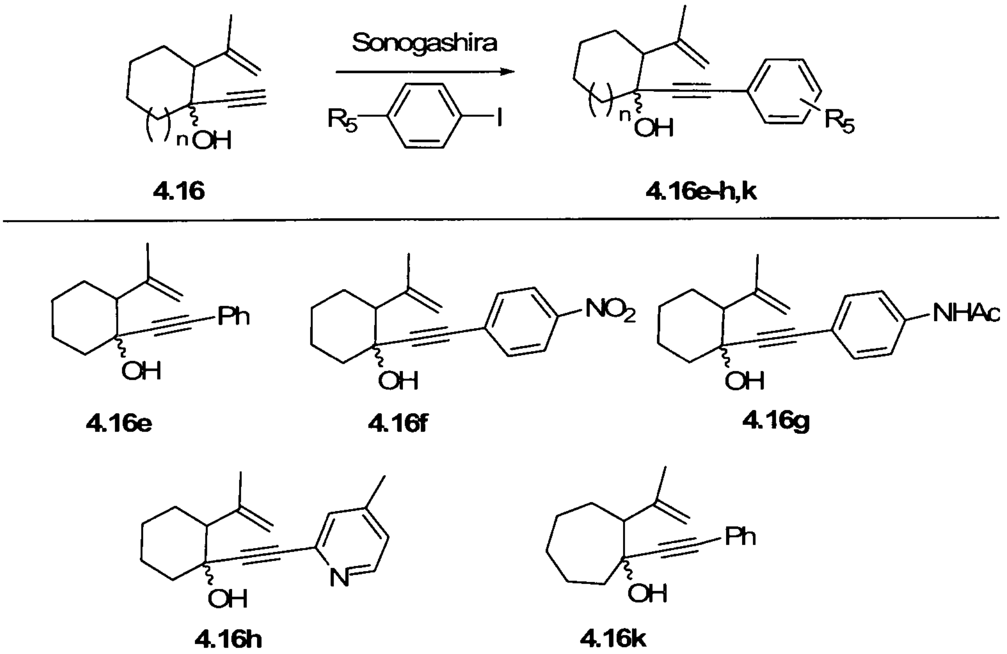
Scheme 4.5-Synthesis of substrates ***4.16a, 4.16b, 4.16d*** *and* ***4.16j***



Scheme 4.6-Synthesis of substrates ***4.16c, 4.16i, 4.16o, 4.16p*** *and* ***4.16q***

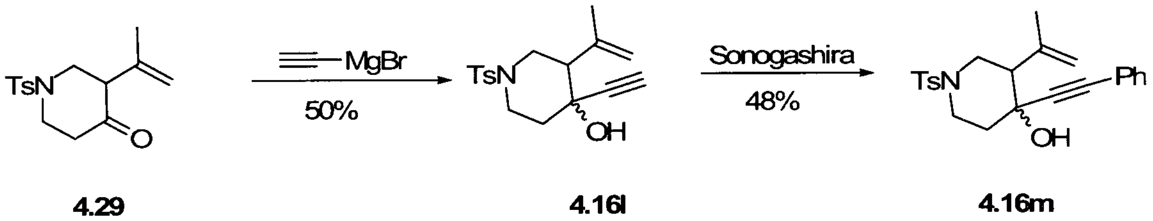


*Scheme 4.7-Sonogashira coupling to obtain substrates **4.16e-h,k***

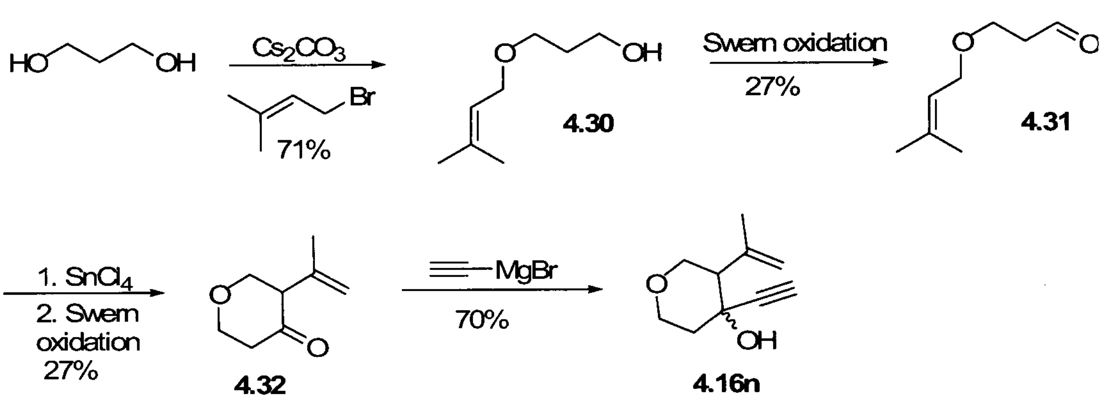


The nitrogen containing substrates **4.16l** and **4.16m** were obtained from known ketone **4.29** (Scheme 4.8). In a similar strategy, it was possible to synthesize cyclic ether **4.16n**. Ketone **4.32** was not known in the literature; thus, it was synthesized in four steps from 1,3-propanediol (Scheme 4.9). The sequence was developed by analogy to the synthesis of ketone **4.29**.[204] Mono-allylation of propanediol afforded alcohol **4.30** in 73% yield that was oxidized to aldehyde **4.31** using a Swern oxidation. In the paper of Bahia and co-workers, they obtained ketone **4.29** by a one-pot ene/oxidation reaction promoted by triflic acid and PCC. However, these conditions were not suitable for the cyclization of aldehyde **4.31**. Thus, a two-step procedure was devised where the ene reaction was catalyzed by tin tetrachloride and a Swern oxidation gave the desired ketone **4.32**. Following alkylation with ethynylmagnesium bromide, it was possible to obtain substrate **4.16n**.

*Scheme 4.8-Synthesis of the nitrogen containing substrates **4.16l** and **4.16m***

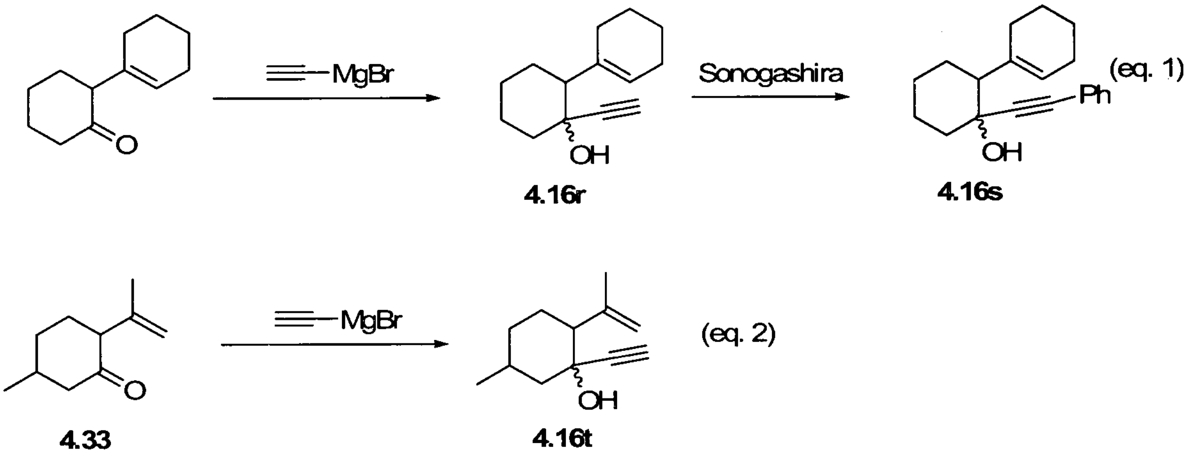


*Scheme 4.9-Synthesis of cyclic ether **4.16n***



Compounds **4.16r**, **4.16s** and **4.16t** were synthesized according to approaches previously described for other substrates (Scheme 4.10). Commercially available 2-(1-cyclohexenyl)-cyclohexanone was alkylated with ethynylmagnesium bromide to give **4.16r**. Next, Sonogashira coupling with phenyliodide provided **4.16s**. Alkylation of isopulegone (**4.33**)[205] with ethynylmagnesium bromide gave substrate **4.16t** (Scheme 4.10, eq. 2).

*Scheme 4.10-Synthesis of compounds **4.16r**, **4.16s** and **4.16t***



A cursory inspection of the results illustrated in the Table 4.2 revealed that the ring size and the substitution at R_1 influenced the reaction yield. A low yield of 28% was observed when the reaction was performed on a substrate having a 5-membered ring (Table 4.2, entry 1). When R_1 was a hydrogen, the desired product **4.17b** was obtained in 10% yield (Table 4.2, entry 2). One might assume that the stability of the carbocation in **4.21** affected the process. Thus, the substituents at R_1 were chosen for their ability to stabilize the carbocation. Although enol ether **4.16i** did satisfy this criterion, the benzannulation gave the desired product **4.17i** in only 12% yield (Table 4.1, entry 9). In contrast, substrates bearing a phenyl (Table 4.2, entry 3), a methyl (Table 4.2, entries 4-6) or a methylene (Table 4.3, entry 4) substituent on the alkene gave the desired benzannulation product in good yields. Also, electron rich aromatic ring system such as furan **4.16o**, aryl **4.16p** and indole **4.16q** proceeded in 57, 76 and 81% yield respectively (Table 4.3, entries 1-3). Satisfyingly, the benzannulation occurred in good yields with substrates having an internal alkyne (Table 4.2, entries 4-8 and 11 and Table 4.3, entry 5). This generates meta-substituted aromatic rings, which are rather difficult to obtain via cross-coupling reactions. However, benzannulation of the pyridine derivative **4.16h** did not take place under the typical reaction conditions as only starting material was recovered. One might propose that the pyridine group could bind on the gold complex thereby inhibiting the benzannulation. Addition of 1.5 equivalents of PTSA proved to be necessary to obtain **4.17h** (Table 4.2, entry 8).

Lastly, we investigated substitution on the cyclohexane ring. Protected piperidine **4.16l** and **4.16m** were treated under the benzannulation conditions to give the corresponding tetrahydroisoquinolines **4.17l** and **4.17m** in 49 and 67% yield respectively (Table 4.2, entries 12-13). The method was also extended to cyclic ether **4.16n** (Table 4.2, entry 14) and methyl-substituted cyclohexane **4.16t** (Table 4.3, entry 6). Thus, the gold-catalyzed benzannulation can be utilized to generate many different tetrahydronaphthalene scaffolds.

Role of acid in the benzannulation reaction

As previously mentioned, the reaction with pyridine substrate **4.16h** only proceeded in the presence of an excess of acid. This result suggests that acid might play a role in the other benzannulation reactions. One might assume that a trace of triflic acid could be present in the typical reaction conditions due to the presence of silver triflate. From a mechanistic point of view, one might propose that elimination of water could be assisted with acid (**4.26**→**4.17**, Figure 4.2). Alternatively, one might suggest that the elimination of water occurs initially to generate a diene-yne intermediate that undergoes a gold-catalyzed benzannulation.

To clarify the role of the protic acid, hydroxy-enyne **4.16** was treated with 2.5 mol% each of $Au(PPh_3)Cl$ and AgOTf in the presence of a hindered base such as 2,6-di-*t*-butyl-4-methylpyridine (DTBMP, 1.05 equiv.) (Table 4.4, entry 1). After 18 hours, only starting material was recovered. However, a low conversion was observed when the reaction was carried out in the presence of 5 mol% DTBMP (entry 2). In 2006, Hartwig reported examples of reaction catalyzed by metal triflates that are the result from simple protic acid catalysis.[206] In our case, exposure of alcohol **4.16** to 5 mol% TfOH, PTSA or chloroacetic acid did not give any desired product **4.17**. Only starting material was recovered, thus it was possible to rule out simple Brønsted acid catalyzed benzannulation or formation of a diene-yne intermediate.[207]

Table 4.4-Investigation into the reactive species

Entry	Catalyst[a]	Additive (equiv)	Conversion (%)[b]
1	Au(PPh_3)Cl, AgOTf	DTBMP (1.05)	0
2	Au(PPh_3)Cl, AgOTf	DTBMP (0.05)	31-50
3	TfOH[c]	-	0
4	Au(PPh_3)Cl, AgOTf	4Å molecular sieves	> 95
5	Au(PPh_3)Cl, TfOH	-	95
6	AuCl, TfOH	-	29

[a]Reactions done with 2.5 mol% of each species in DCM at 23 °C for 18 hours. [b]Determined by ^1H NMR. [c]5 mol% was used.

To explore the effect of water in the reaction, hydroxy-enyne **4.16** was treated with the standard conditions but molecular sieves were added. The conversion was greater than 95%, thus it is possible to exclude the role of water in the mechanism other than a leaving group. In order to further investigate the reactive species, hydroxy-enyne **4.16** was treated with 2.5 mol% of each Au(PPh_3)Cl and TfOH (Table 4.4, entry 5). Surprisingly, tetrahydronaphthalene **4.17** was obtained in 95% conversion. In contrast, 2.5 mol% of each AuCl and TfOH only gave 29% conversion to the desired tetrahydronaphthalene. It is important to note that Au(PPh_3)Cl alone did not catalyze the reaction whereas AuCl alone gave a 22% conversion. To the best of our knowledge, this is first report of an active catalyst generated from Au(PPh_3)Cl and triflic acid.

Benzannulation catalyzed by Au(PPh_3)Cl and an acid: Optimization

To study this novel catalytic system, we investigated different sources of protic acid. This investigation was done in conjunction with a co-op student, Eric Rodrigue. Weak organic acids (acetic acid, tartaric acid, trichloroacetic acid, trifluoroacetic acid, phenyl phosphonic acid and mineral acids (HBr, HCl, H_3PO_4, and H_2SO_4) did not catalyze the reaction. Nonetheless, PTSA and CSA in combination with Au(PPh_3)Cl did promote the benzannulation with good conversion. However, the results were not reproducible. It was later found that reactions performed with freshly recrystallized PTSA or CSA did not produce the desired product. Only starting material was recovered. One might propose that the commercial acids were contaminated with a stronger acid that was responsible for the catalysis. This suggests that an active catalyst could only be generated when Au(PPh$_3$)Cl was in the presence of a very strong acid.

We also studied the use of Lewis acids as potential activators of Au(PPh$_3$)Cl. Hydroxy-enyne **4.16** was submitted to conditions consisting of 5 mol% Au(PPh$_3$)Cl and 5 mol% BF$_3$·OEt$_2$ or TMSOTf. In both cases, the benzannulation occurred in 83% and 80% conversion respectively. However, we must take into consideration the possible presence of protic acids in the reaction mixture. To avoid background reactions created by the presence of protic acids, the reactions were performed by pre-mixing the Lewis acid (5 mol%), Au(PPh$_3$)Cl (5 mol%) and DTBMP (20 mol%) followed by the addition of substrate **4.16**. Four Lewis acids were tested under these conditions (BF$_3$·OEt$_2$, TMSOTf, MgBr$_2$·OEt$_2$ and SnCl$_4$). In all cases, we recovered only starting material. These results show that Au(PPh$_3$)Cl can only be activated by a strong protic acid. Undoubtedly, triflic acid was the best acid to use in combination with Au(PPh$_3$)Cl since it gave the best conversion (95%). We found that an increase of the triflic acid loading while keeping constant Au(PPh$_3$)Cl at 2.5 mol% was detrimental to the reaction. This resulted in low conversions to tetrahydronaphthalene **4.17**. Thus, a 1:1 ratio of triflic acid to Au(I) proved to be optimal.

Next, we carried out the benzannulation reactions in various solvents at room temperature for 18 hours. Reactions run in toluene, methanol, THF, diethyl ether, acetonitrile, water and a dichloromethane/water combination showed very low conversions. Changing the solvent for dichloroethane and heating to reflux proved to be successful as a 100% conversion was observed (Table 4.5, entry 1). Gratifyingly, we were able decrease the catalyst loading to 1 mol% without affecting the conversion (entry 2). A quantitative conversion was observed when the reaction was performed using 1 mol% of AuCl, TfOH and PPh$_3$ (entry 3). Unexpectedly, treating substrate **4.16** with Au(PPh$_3$)Cl in dichloroethane at 80 °C did give the desired product in 43% conversion (entry 4). In contrast, only starting material was recovered when hydroxy-enyne **4.16** was treated with Au(PPh$_3$)Cl in dichloroethane at room temperature. Also, it was noticed that no desired product was observed when the substrate was heated alone or in the presence of triflic acid (entries 5 and 6).[208] One hypothesis to explain the formation of the desired product using only Au(PPh$_3$)Cl in DCE at 80 °C was there was some HCl present in the solvent at that temperature. Thermal decomposition of DCE to vinyl chloride and HCl is known to happen at very high temperature (576-791 °C).[209] But, reports showed that decomposition can occur at lower temperature in the presence of a catalyst.[210] One can postulate that the gold catalyst promoted the decomposition of the solvent to HCl and vinyl chloride. Then, activation of the gold pre-catalyst with HCl promoted the benzannulation.

Table 4.5-Optimization of the catalyst system

Entry	Catalyst[a]	Loading (mol%)	Conversion (%)[b]
1	Au(PPh_3)Cl, TfOH	2.5	100
2	Au(PPh_3)Cl, TfOH	1.0	100
3	AuCl, TfOH, PPh_3	1.0	100
4	Au(PPh_3)Cl	1.0	43
5	TfOH	1.0	0
6	None	-	0

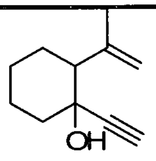
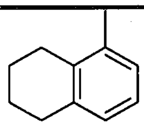
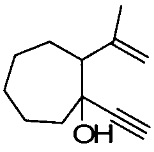
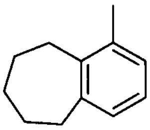
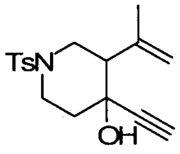
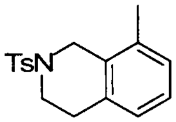
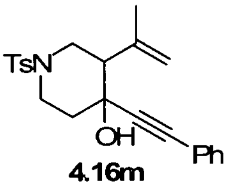
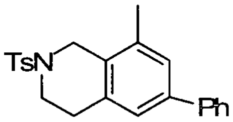
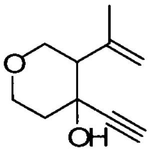
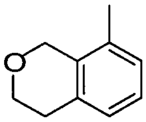
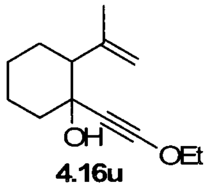
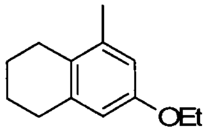
[a]Reactions done in DCE at 80 °C for 18 hours. [b]Determined by GC.

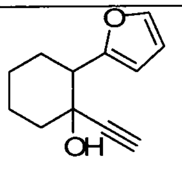
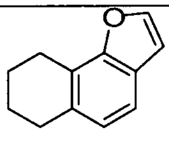
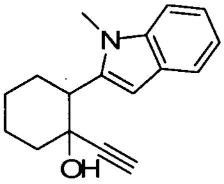
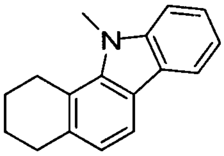
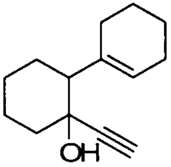
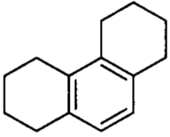
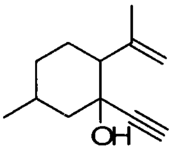
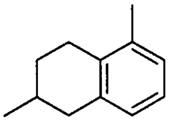
In summary, it was possible to promote the benzannulation of hydroxy-enynes using Au(PPh_3)Cl and an acid. The optimal conditions consisted of using 1 mol% of each, Au(PPh_3)Cl and TfOH and heating at 80 °C in dichloromethane.

Benzannulation catalyzed by Au(PPh_3)Cl and an acid: Scope and limitations

Having established the optimal reaction conditions, we investigated the scope of the Au(I)/TfOH-catalyzed benzannulation using selected hydroxy-enynes (Table 4.6). Cyclization of 6 and 7-membered hydroxy-enynes **4.16**, **4.16j** and **4.16t** gave the corresponding aromatic compounds **4.17**, **4.17j** and **4.17t** in 48, 68 and 82% yield respectively (entries 1-2 and 10). *N*-Tosyl-piperidine **4.16l** and **4.16m** and tetrahydropyrane **4.16n** were easily transformed to the corresponding tetrahydroisoquinolines **4.17l**, **4.17m** and isochromane **4.17n** in good yields (entries 3-5). To our delight, the highly acid sensitive ynol ether **4.16u** was converted to the corresponding phenol ether **4.17u** in 51% yield (entry 6).[211] Under these conditions, electron rich aromatics **4.16o** and **4.16p** gave the desired tetrahydronaphthalenes **4.17o** and **4.17p** in 64 and 76% yield respectively (entries 6 and 7). Benzannulation of cyclic olefin **4.16r** occurred smoothly, providing **4.17r** in 82% yield (entry 9). With the exception of substrates **4.16** and **4.16n**, the yields were higher when the benzannulation was catalyzed with Au(PPh_3)Cl and TfOH in comparison with Au(PPh_3)Cl and AgOTf. Overall, we have shown that 1 mol% Au(PPh_3)Cl and triflic acid generated an effective catalyst system for benzannulation of 3-hydroxy-1,5-enynes.

Table 4.6-Au(PPh_3)Cl/TfOH catalyzed benzannulation[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **4.16**	 **4.17**	48
2	 **4.16j**	 **4.17j**	68
3	 **4.16l**	 **4.17l**	65
4	 **4.16m**	 **4.17m**	56
5	 **4.16n**	 **4.17n**	62
6	 **4.16u**	 **4.17u**	51

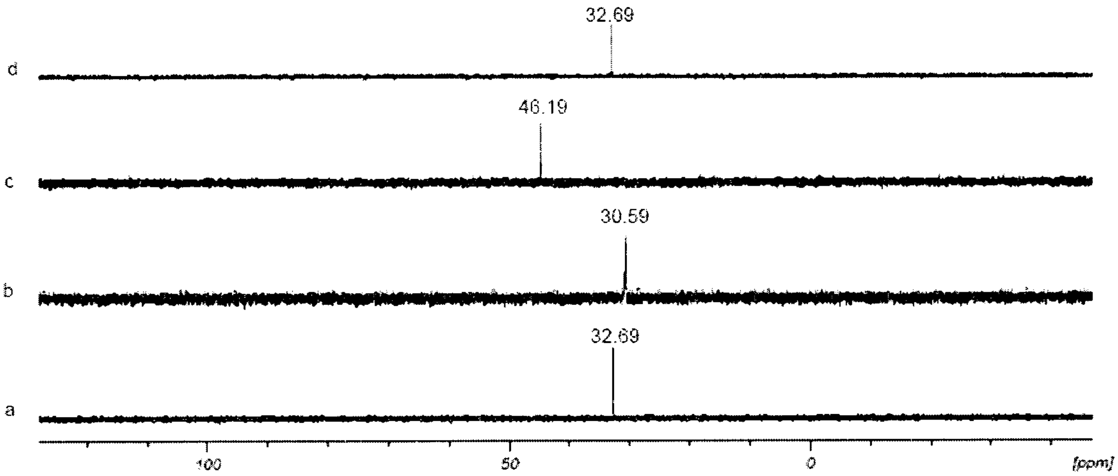
7	 **4.16o**	 **4.17o**	64
8	 **4.16q**	 **4.17q**	76
9	 **4.16r**	 **4.17r**	82
10	 **4.16t**	 **4.17t**	82

[a] The reaction conditions are 1 mol% of each TfOH and Au(PPh$_3$)Cl in dichloroethane at 80 °C for 18 hours. [b] Isolated yield after column chromatography.

Au(PPh$_3$)Cl and an acid: Insights into the active catalyst

Since neither Au(PPh$_3$)Cl and TfOH catalyzed the benzannulation reaction on their own (at room temperature), an active catalyst must be generated when these two species are in contact. Teles and co-workers reported that a cationic gold complex is generated by protonolysis of Au(PPh$_3$)Me by methanesulfonic acid.[212] By analogy, one might suggest that protonolysis of Au(PPh$_3$)Cl by triflic acid might give the cationic gold catalyst, Au(PPh$_3$)OTf. ^{31}P NMR studies were performed to gain insight into the reactive species (Figure 4.3). Different Au(I) complexes were detected when Au(PPh$_3$)Cl and AgOTf were mixed alone to form Au(PPh$_3$)OTf (spectra b) or in the presence of substrate **4.16** (spectra c). In the latter case, the complex generated could be [Au(PPh3)-Ar]+ (Ar=tetrahydronaphthalene) since the benzannulation occurred in the NMR tube. In contrast, Au(I) cationic species were not identified when Au(PPh$_3$)Cl and TfOH were combined in the presence of the substrate **4.16** (spectra d). In fact, the chemical shift of the single peak (32.7 ppm) correspond to that of Au(PPh$_3$)Cl (spectra a). Based on the NMR data, one might suggest that the active catalyst, in the case of Au(PPh$_3$)Cl and TfOH, might not be a cationic gold complex A possible reversible complexation between the Au(PPh$_3$)Cl and TfOH created a highly reactive gold complex that could be responsible for the catalysis but could not be detected by the NMR.

Figure 4.3-^{31}P NMR studies for benzannulation



^{31}P NMR study at 23 °C in CDCl$_3$ (PPh$_3$ used as a standard at -6.0 ppm). (a) Au(PPh$_3$)Cl; (b) Au(PPh$_3$)Cl (2.5 mol%) and AgOTf (2.5 mol%) after 16 hours; (c) Au(PPh$_3$)Cl (2.5 mol%), AgOTf (2.5 mol%) and alcohol **4.16** (59% conversion); (d) Au(PPh$_3$)Cl (5 mol%), TfOH (5 mol%) and alcohol **4.16** (37% conversion).

One can postulate that triflic acid protonated the bound triphenylphosphine, and the active catalyst was in fact AuCl (Equation 4.1). It was found that only Au(PPh$_3$)Cl was detected by NMR when the gold pre-catalyst was treated with TfOH (Figure 4.4). Based on this result, if an equilibrium between Au(PPh$_3$)Cl and AuCl exists, then it must be shifted to the left. Thus, treatment of AuCl with protonated triphenylphosphine should give Au(PPh$_3$)Cl and it should be the only the species detectable by ^{31}P NMR. In a first trial, 10 equivalents of TfOH were added to a solution of triphenylphosphine in chloroform (Figure 4.5 and Figure 4.6). After 1 hour, there was complete protonation of the phosphine as single peak at 6.8 ppm was present (Figure 4.5, equation (b)).[213] Then, AuCl was added and the reaction was monitored after 1 and 24 hours. There was no appearance of Au(PPh$_3$)Cl (Figure 4.6, equations (c) and (d)) as the only phosphorus species detectable was the protonated triphenylphosphine (Figure 4.5, equations (c) and (d)). This experiment seems to indicate that Equation 4.1 was not reversible.

Equation 4.1-Possible protonation of the phosphine ligand

$$\mathrm{Au(PPh_3)Cl} + \mathrm{TfOH} \rightleftharpoons \mathrm{AuCl} + \mathrm{PPh_3} + \mathrm{TfOH} \rightleftharpoons {}^{\oplus}\mathrm{PPh_3H} + \mathrm{TfO}^{\ominus} + \mathrm{AuCl}$$

Figure 4.4-Au(PPh$_3$)Cl and TfOH after 3 days

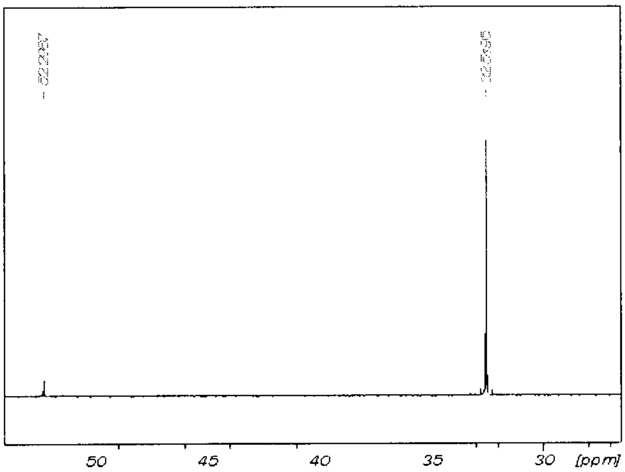
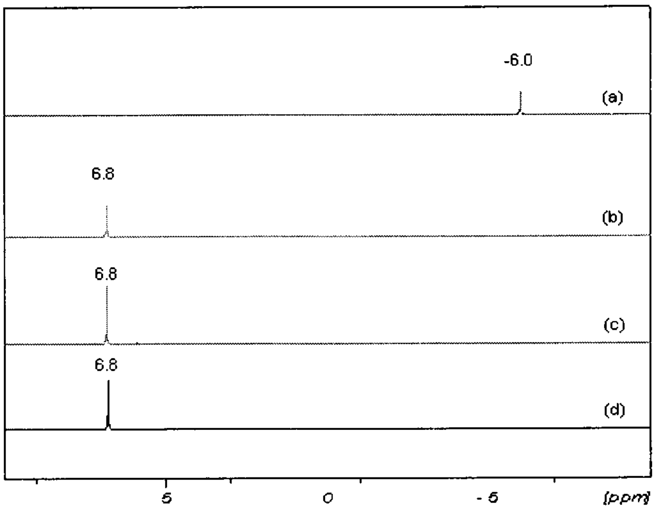
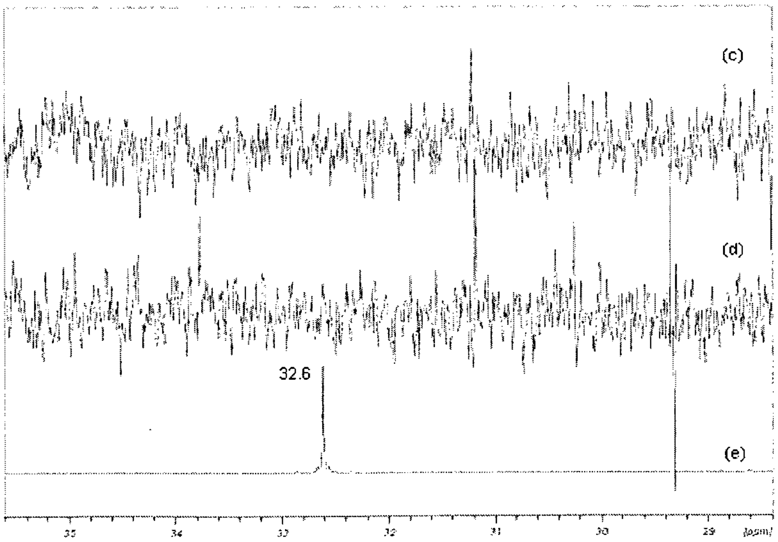


Figure 4.5-^{31}P NMR studies of AuCl in the presence of PPh$_3$ and TfOH (10 equiv)



^{31}P NMR study at 23 °C in CDCl$_3$ (PPh$_3$ used as a standard at -6.0 ppm). (a) PPh$_3$ (1.0 equiv); (b) PPh$_3$ (1.0 equiv) and TfOH (10.0 equiv) after 1 hour; (c) PPh$_3$ (1.0 equiv), TfOH (10.0 equiv) and AuCl (0.22 equiv) after 1 hour; (d) PPh$_3$ (1.0 equiv), TfOH (10.0 equiv) and AuCl (0.22 equiv) after 24 hours.

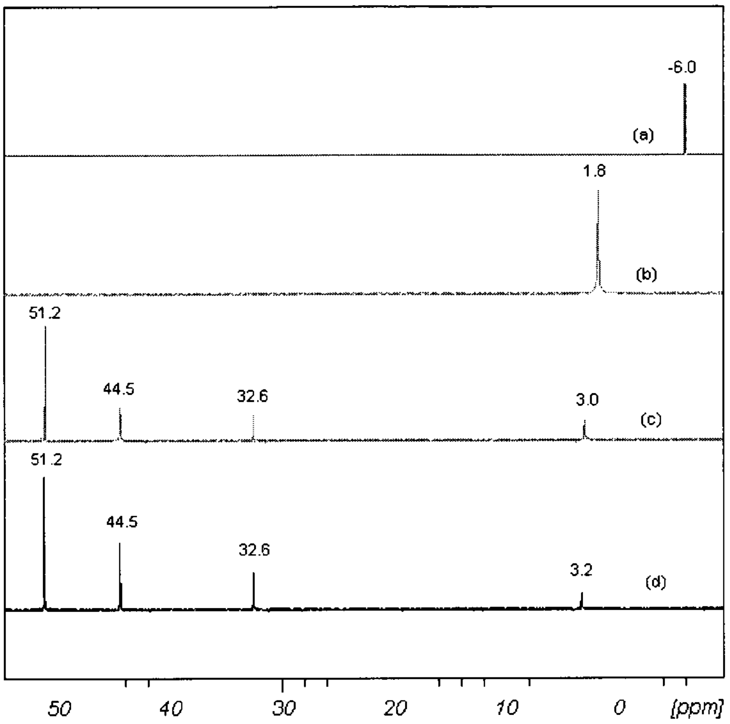
Figure 4.6-^{31}P NMR studies of AuCl in the presence of PPh$_3$ and TfOH (10 equiv)



^{31}P NMR study at 23 °C in CDCl$_3$ (PPh$_3$ used as a standard at -6.0 ppm). (Expansion) (c) PPh$_3$ (1.0 equiv), TfOH (10.0 equiv) and AuCl (0.22 equiv) after 1 hour; (d) PPh$_3$ (1.0 equiv), TfOH (10.0 equiv) and AuCl (0.22 equiv) after 24 hours; (e) Au(PPh$_3$)Cl.

In the previous example, the phosphine was completely protonated due to the excess of triflic acid present in the reaction medium. To see the effect of the number of equivalents of TfOH, a similar experiment was done using 1 equivalent of each, PPh_3, TfOH and AuCl. In contrast to the results obtained with a large excess of acid, many species were detected (Figure 4.7). When the triphenylphosphine was treated with 1 equivalent of triflic acid, a peak at 1.8 ppm was present (Figure 4.7, (b)). It was suspected that the triphenylphosphine was not completely protonated in this case. Next, the addition of 1 equivalent of AuCl created three new species at 51.2, 44.5 and 32.6 ppm. The nature of the major complex at 51.2 was not known. However, the peak at 44.5 ppm could be assigned to $Au(PPh_3)_2Cl$ by analogy with the work reported by Dake and co-workers[214] and the peak at 32.6 ppm corresponded to $Au(PPh_3)Cl$. It is known that AuCl and PPh_3 form the $Au(PPh_3)Cl$ complex.[214] Therefore, it possible that these particular reaction conditions made it in sort that a portion of the triphenylphosphine was not protonated and it reacted with AuCl to produce a small amount $Au(PPh_3)Cl$. Nevertheless, the major phosphorus species generated from AuCl, PPh_3 and TfOH had chemical shifts of 51.2 and 44.5 ppm.

Figure 4.7-^{31}P NMR studies of AuCl in the presence of PPh_3 and TfOH (1 equiv)



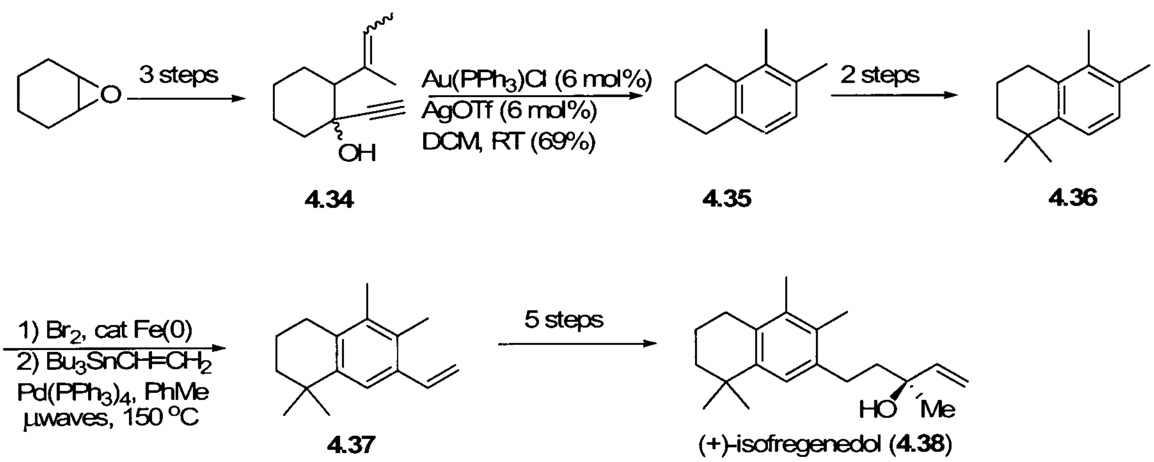
^{31}P NMR study at 23 °C in $CDCl_3$ (PPh_3 used as a standard at -6.0 ppm). (a) PPh_3 (1.0 equiv); (b) PPh_3 (1.0 equiv) and TfOH (1.1 equiv) after 1 hour; (c) PPh_3 (1.0 equiv), TfOH (1.1 equiv) and AuCl (1.0 equiv) after 1 hour; (d) PPh_3 (1.0 equiv), TfOH (1.1 equiv) and AuCl (1.0 equiv) after 48 hours.

As a summary, two experiments were done in order to determine if the reactive species was AuCl in reactions catalyzed by $Au(PPh_3)Cl$ and TfOH. When the triphenylphosphine was fully protonated (10 equivalents of TfOH), no $Au(PPh_3)Cl$ was detected. In the second case, an equimolar combination of TfOH, AuCl and PPh_3 gave a mixture of products where the minor product was $Au(PPh_3)Cl$. It is possible to conclude that an equilibrium between $Au(PPh_3)Cl$ and AuCl does not exist under the reaction conditions. Therefore, another species was in equilibrium with $Au(PPh_3)Cl$/TfOH and this species was responsible for the catalysis observed. Further investigations are still needed to elucidate the exact nature of the reactive species.

Total synthesis of (+)-isofrenegedol

In an effort to demonstrate the usefulness of the new gold-catalyzed benzannulation reaction, my colleague Dr. Maxime Riou synthesized the natural product (+)-isofrenegedol.[215] The de-novo synthesis clearly showed the value of the method since the diterpene was obtained in thirteen steps from commercially available material (Scheme 4.11). Starting from cyclohexene oxide, alcohol **4.34** was obtained in three steps. The benzannulation reaction was performed with Au(PPh_3)Cl and AgOTf to afford tetrahydronaphthalene **4.35** in 69% yield. The gem-dimethyl was then introduced in two steps. Bromination of **4.36** followed by a Stille cross-coupling reaction provided selectively **4.37**. It was possible to transform **4.37** into the natural product in five steps. Since a Sharpless asymmetric epoxidation was used to introduce the chiral center, the enantiopure (+)-isofregenedol was obtained.

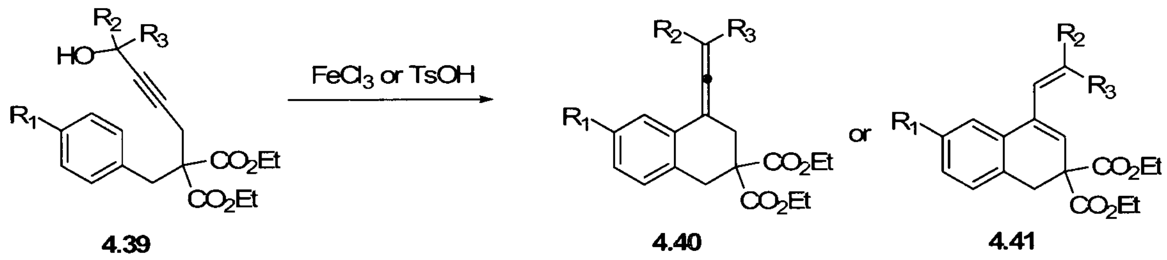
Scheme 4.11-Synthesis of (+)-isofrenegedol (Riou and Barriault, 2008)



Recent developments

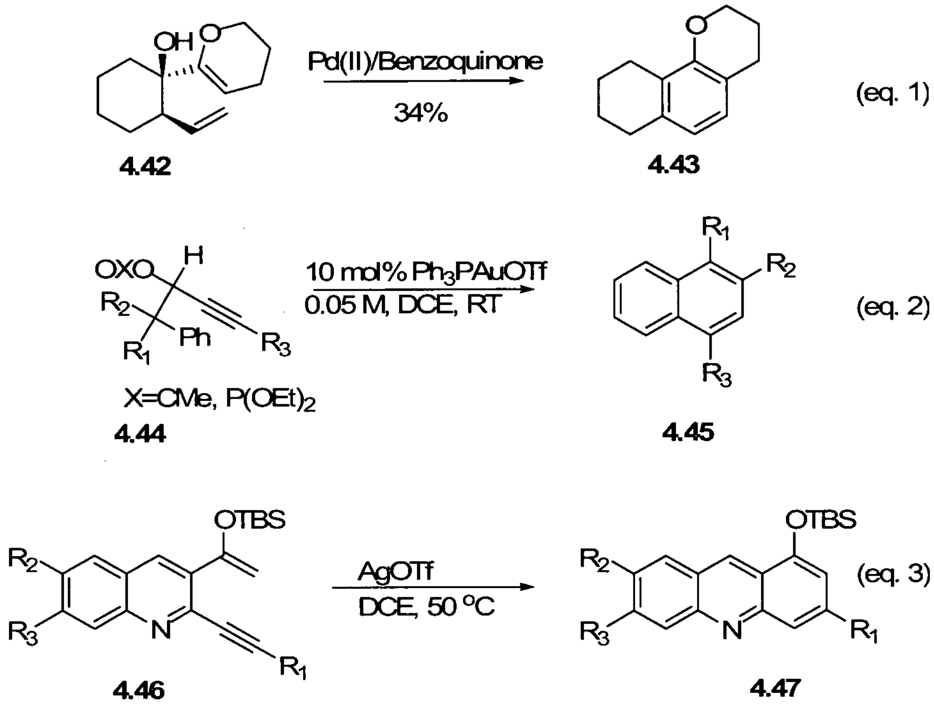
Since our publication in 2008,[197] new developments in the field of metal-catalyzed benzannulation and the efficient synthesis of aromatic compounds took place. Zhou and co-workers reported the selective synthesis of tetrahydronaphthalenes **4.40** or **4.41** when propargyl alcohol **4.39** was treated with iron trichloride or *para*-toluene sulfonic acid in nitromethane at 80 °C, respectively (Scheme 4.12).[216] A Friedel-Craft like mechanism has been proposed to explain the products observed.

Scheme 4.12-Iron or acid catalyzed synthesis of tetrahydronaphthalenes



Recently, Gagné and Korotchenko studied the cyclization of 1,ω-dienols using palladium as the catalyst.[217] They found that substrates having electron rich alkenes, such as **4.42** (Scheme 4.13, eq.1) gave tetrahydronaphthalenes, such as **4.43**. They proposed a cyclization/aromatization sequence that is catalyzed by the Pd(II) catalyst. In 2008, Gevorgyan and co-workers developed a double migration/benzannulation cascade catalyzed by gold.[218] Treating substrate **4.44** with a gold(I) catalyst gave naphthalene **4.45** in good yield (Scheme 4.13, eq. 2). They suggest a 1,3-shift followed by a 1,2-migration to provide a 1,3-diene that cyclizes and aromatizes to give the product. In addition, Godet and Belmont showed that silver salts catalyzed the benzannulation of silyl enol ether **4.46** giving access to polycyclic aromatic compounds (Scheme 4.13, eq. 3).[219] This type of cyclization had been previously demonstrated by Dankwardt and co-workers using $AuCl_3$.[187b]

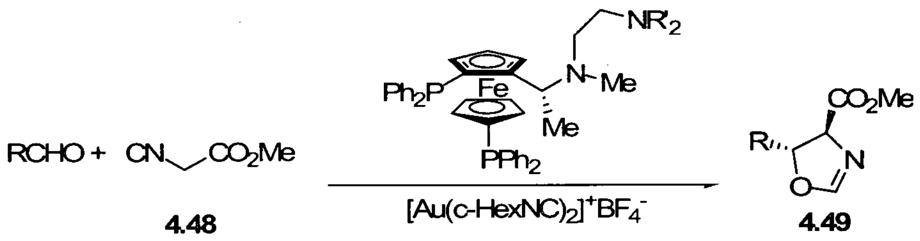
Scheme 4.13-Recent examples of benzannulation reactions



Introduction to stereoselective gold-catalyzed reactions

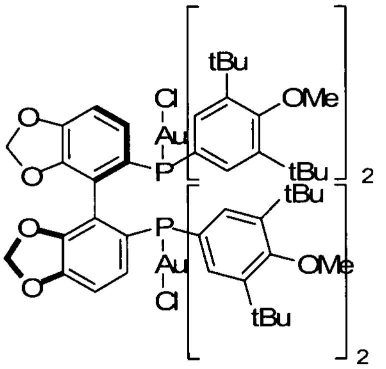
Interest in gold-catalyzed reactions has increased tremendously since the new millennium. The mild conditions and the unique reactivity of gold have driven the research in the area. However, the reports of asymmetric gold-catalyzed reactions are limited.[220] This is surprising since the first example of enantioselective gold catalysis was in 1986. Ito and co-workers showed an enantioselective aldol reaction between an isocyanate (**4.48**) and an aldehyde was possible using a gold catalyst and a ferrocenyl ligand (Figure 4.8).[221] The diastereoselectivity was good and the desired product (**4.49**) was obtained in 72 to 97% ee.

Figure 4.8-First example of asymmetric gold catalysis (Ito and co-workers)



Almost twenty years after the first report of asymmetric gold-catalyst, Echavarren and co-workers published the use of a chiral gold catalyst for the alkoxycyclization of enynes with moderate enantioselectivity.[222] The catalyst was of $Au_2(P\text{-}P)Cl_2$ stoichiometry. Similarly, Toste and co-workers demonstrated the use of catalyst **4.50** (Figure 4.9) in an enantioselective cyclopropanation.[223] The reason for these elaborated catalysts is that the linear gold complexes cause the ligand to be relatively far from the site of the catalysis. Furthermore, it was demonstrated that bidentate phosphine or related ligands bind to gold atoms with only one phosphine.

Figure 4.9-Example of a $Au_2(P\text{-}P)Cl_2$ catalyst



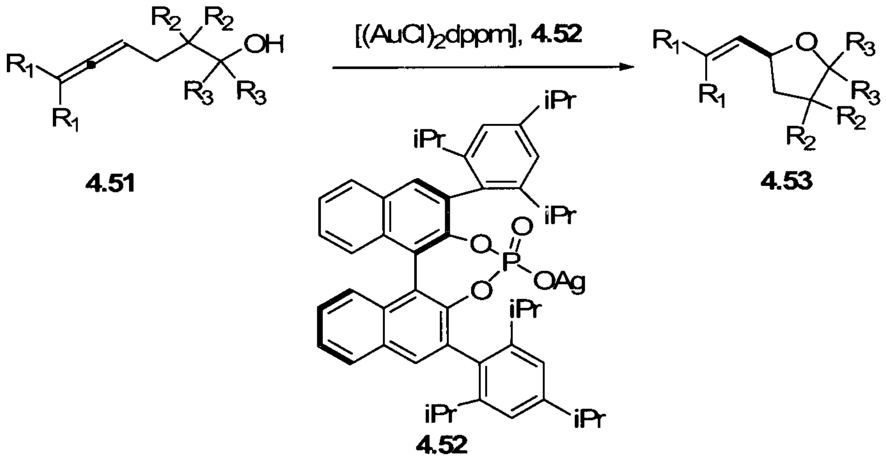
4.50

Due to the limited catalyst scope for enantioselective gold-catalyzed reactions, we believed that our $Au(PPh_3)Cl$/acid catalyst system might provide a solution to this problem. As mentioned previously, the exact nature of the reaction species was not determined.

However, the NMR studies seemed to indicate that Au(PPh$_3$)Cl and the acid formed, reversibly, an active complex. Thus, one could imagine that interaction of the Au(PPh$_3$)Cl with a chiral acid should provide a chiral complex that could catalyze the reaction. By choosing the appropriate acid, this chiral complex could lead to enantioselectivity in the reaction.

As our study of chiral acids and Au(PPh$_3$)Cl was progressing, Toste and co-workers published their solution to asymmetric gold catalysis. They reported the use of a chiral counterion with an achiral gold catalyst to promote the cycloisomerization of hydroxy-allenes to provide the cyclic product in good yield and ee (Scheme 4.14).[224] They proposed that the high ee (90-99%) observed was due to the fact that the chiral anion was positioned close to the cationic gold. Thus, the chiral information was close to the reactive center and good enantioselectivities were obtained.

Scheme 4.14-Chiral counterion for enantioselective gold catalysis (Toste, 2007)



The report by Toste confirmed that chiral gold complexes could promote enantioselective reaction. Since it was believed that an active complex was formed when Au(PPh$_3$)Cl and acid were combined, we were confident to pursue our hypothesis that our new catalyst system could lead to asymmetric induction with the appropriate choice of acid and conditions.

Rearrangement of 1,6-enynes catalyzed by Au(PPh$_3$)Cl and an acid

The first task in applying our new catalyst system to asymmetric catalysis was to determine if the new catalyst system was applicable to gold-catalyzed reactions other than the benzannulation of 3-hydroxy-1,5-enynes. The rearrangement of 1,6-enynes was chosen due to the ease of the synthesis of substrates. This study was performed by two undergraduate students, Eric Rodrigue and Catherine Séguin.

The cyclization of enynes can be catalyzed by a variety of electrophilic metals.[225] The mild conditions exhibited by cationic gold catalysts have driven the development of gold-catalyzed rearrangements of enynes.[226] There are three possible products arising from the rearrangement of 1,6-enynes (Scheme 4.15): the single *exo*-cleavage product **4.55**, the double *exo*-cleavage product **4.56** and the single *endo*-cleavage product **4.57** (if the alkene is cleaved only, it is a single cleavage whereas a double cleavage refers to both the alkyne and the alkene being cleaved during the reaction) . The product distribution has been shown to be influenced by the substituents R and R' and the catalyst used for the reaction. The proposed mechanism for the formation of the products is depicted in Figure 4.10. The cationic gold catalyst, generated by the activation of the neutral LAuCl pre-catalyst with a silver salt, activates the alkyne. It has been proposed that the alkyne and alkene react in a 5-*exo*-dig manner to produce cyclopropyl gold carbene **4.59**. Although it has been shown that this type of intermediate have carbene-like properties,[227] it has recently been proposed that these types of intermediates might also be of carbocationic nature.[201, 228] Intermediate **4.59** rearranged following three possible pathways depending on the substitution pattern. In pathway *a*, the cyclopropyl carbene intermediate **4.59** rearranges to generate carbocation **4.60.** Subsequently, metal elimination affords diene **4.55**. In the double cleavage pathway (b), a diotropic rearrangement[229] occurs to form carbene **4.41** that gives **4.56** after a hydride-shift and a demetallation sequence. For the formation of endocyclic product **4.57**, the cyclopropyl carbene intermediate rearranges to produce cation **4.62** that undergoes a metal elimination.

Scheme 4.15-Skeletal rearrangement of 1,6-enynes

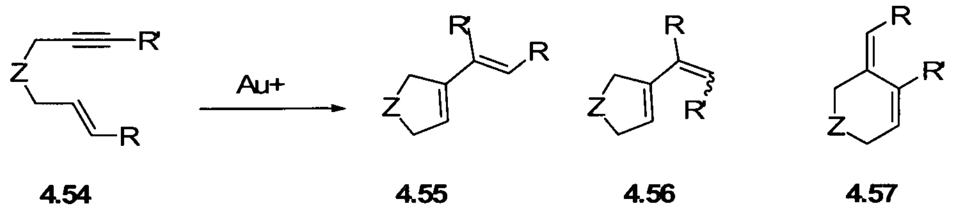
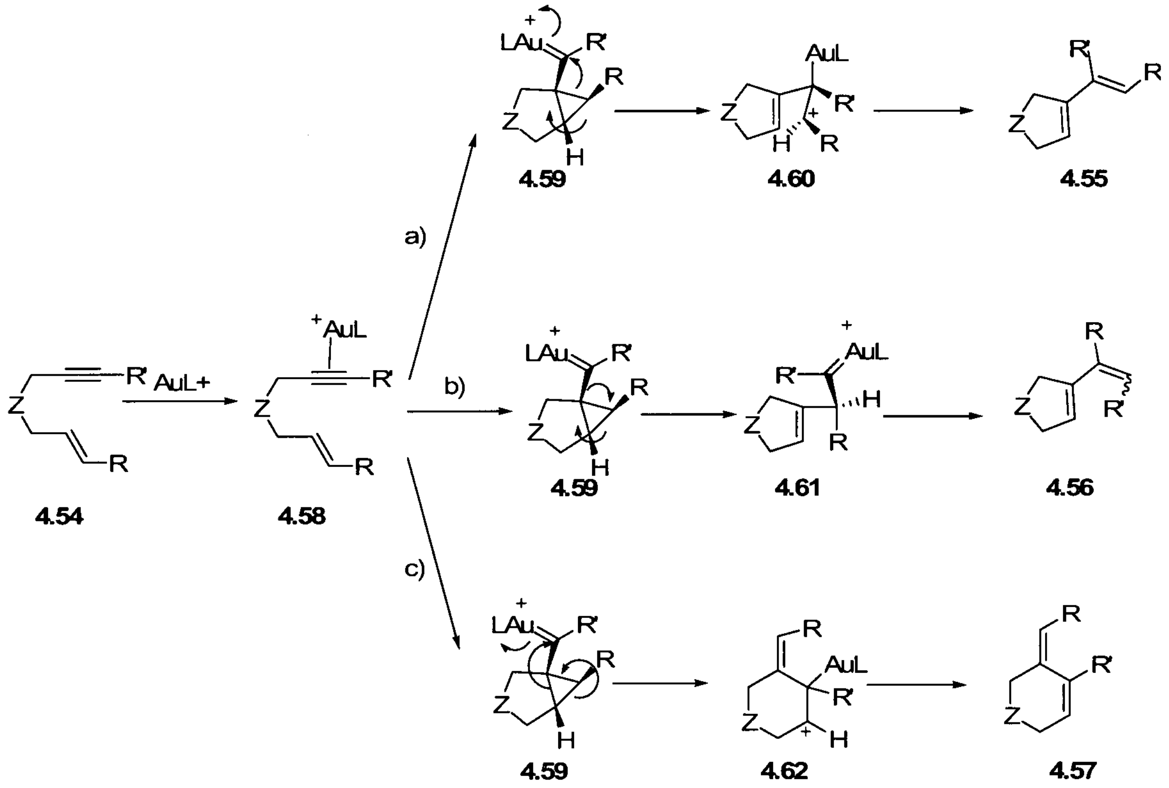
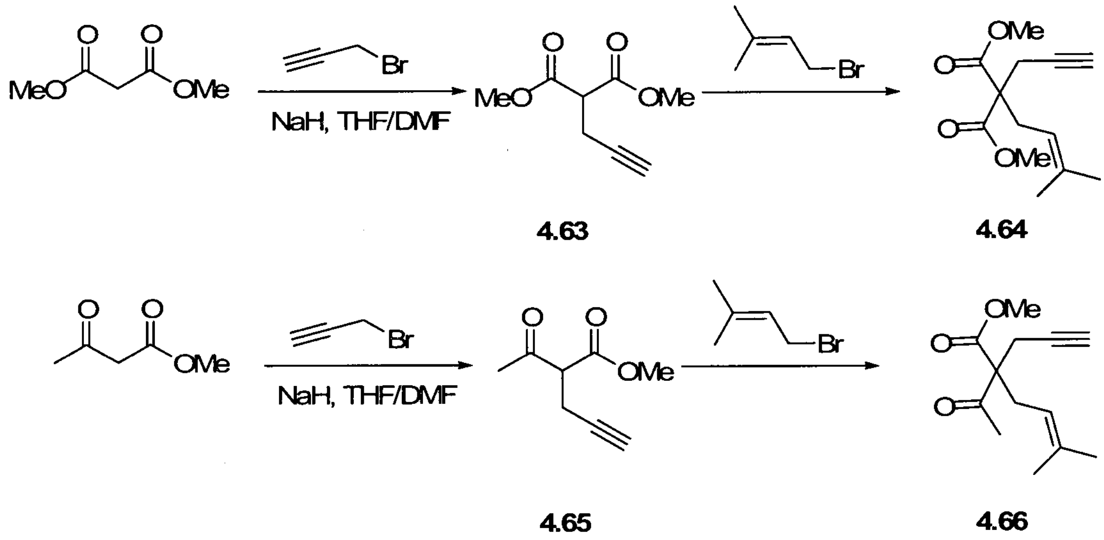


Figure 4.10-Proposed mechanism for the rearrangement of 1,6-enynes



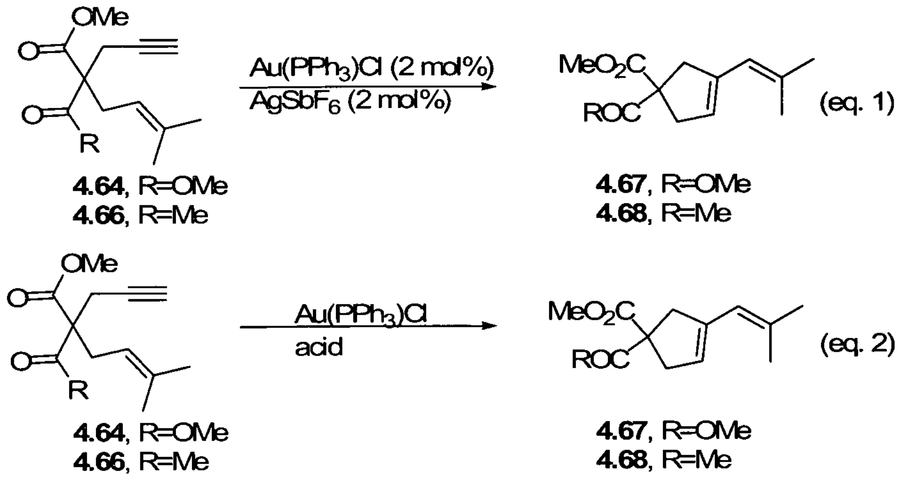
For our study of the skeletal rearrangement of 1,6-enynes with Au(PPh_3)Cl and an acid, substrates that cyclize to give products of the type **4.55** were selected. Thus, known substrate **4.64** was synthesized in two steps from commercially available dimethylmalonate (Scheme 4.16). With the eventual goal of obtaining chiral products using a chiral acid, substrate **4.66** was also synthesized in a similar way.

Scheme 4.16-Synthesis of the necessary precursors



Echavarren and co-workers demonstrated that enyne **4.64** rearranged to diene **4.67** in the presence of a cationic gold catalyst (generated from Au(PPh$_3$)Cl and AgSbF$_6$) (Scheme 4.17, eq. 1).[227] It was hypothesized that the new Au(PPh$_3$)Cl/acid catalyst system would also catalyze this reaction to afford the same product (Scheme 4.17, eq. 2) In a preliminary trial, substrate **4.64** was treated with 2.5 mol% of each, Au(PPh$_3$)Cl and TfOH in dichloroethane at room temperature. The reaction went to completion and it was possible to isolate the desired product (**4.67**) in 70% yield. Moreover, the Au(PPh$_3$)Cl/TfOH catalyzed cycloisomerization of **4.66** gave **4.68** in 60% yield. Even though the optimization of the reaction conditions was done for the benzannulation, we wanted to study the effect of the different acids on the rearrangement of 1,6-enynes. The goal of this investigation was to find other acids than TfOH that could catalyze the reaction.

Scheme 4.17-Gold-catalyzed rearrangement of ***4.64*** *and* ***4.66***

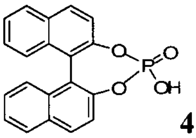


The cycloisomerization of enyne **4.64** was studied with a variety of acids in the presence of Au(PPh$_3$)Cl (Table 4.7). At the beginning of the exploration, the results were not reproducible. It was found that residual acid on the side of the reaction flasks could affect the reaction. In order to have valid and reproducible results, all the glassware had to be washed in a base bath (KOH in isopropanol) prior to use. Different acids were scanned to see the effect of the strength of the acid. When 5 mol% of Au(PPh$_3$)Cl and 5 mol% of TfOH were added to a solution of the enyne **4.64** in dichloromethane, 100% conversion was obtained after 2 hours (entry 1). Under these reaction conditions, products **4.67** and its isomer **4.69** were obtained in a 4:1 ratio. Isomer **4.69** was also observed as a minor product when Echavarren and co-workers performed the reaction with Au(PPh$_3$)Cl and AgSbF$_6$.[230] Weaker acids were tested but the cycloisomerization did not occur in the case of acetic acid (entry 2), pyridinium p-toluenesulfonate (entry 3) or trichloroacetic acid (entry 4). Although PTSA did give 100% conversion to the product, it was suspected that the impurity in the acid catalyzed the reaction (see, p. 189). Trifluoroacetic acid in conjunction with Au(PPh$_3$)Cl could be used to promote the cycloisomerization (entries 8-9). It was found that the reaction was longer than in the case of TfOH and the reaction went to completion after 40 hours.

Chiral phosphoric acids have been used in various reactions to access enantiomerically pure products from achiral substrates through hydrogen bonding.[231] Based on these precedents, binol-derived phosphoric acid **4.70** was tested and the desired product was obtained in 7 to 22% conversion (entry 6). Although the conversion was not very high, we were hopeful that modification of the reaction conditions could allow higher conversions. Also, one could imagine using a homochiral binol-derived phosphoric acid for asymmetric induction.

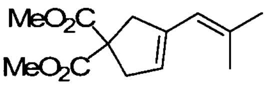
In a recent report by Jacobsen and co-workers, it was shown that hydrogen bond catalysis was feasible by anion binding (Scheme 4.18).[232] They showed that the Pictet-Spengler reaction of substrate **4.71** was catalyzed by TMSCl and a thiourea. The chiral thiourea was bound to the chlorine anion and created chiral environment around intermediate **4.72**. The desired product (**4.74**) was obtained in yields up to 94% and with excellent ee's. Inspired by this report of anion binding, we were curious to see if a substituted urea could complex with the chlorine of the $Au(PPh_3)Cl$ pre-catalyst and render an active catalyst. To this end, *N,N'*-di(4-fluorophenyl)urea was synthesized and tested under the typical reaction conditions (entry 7). Unfortunately, no desired product was obtained, even with 20 mol% of the urea. In order to see if there was a cooperative effect between TFA and the urea, both additives were used (entry 10). After 18 hours, the conversion was higher than with TFA alone.

Table 4.7-Cycloisomerization catalyzed by Au(PPh$_3$)Cl and an acid

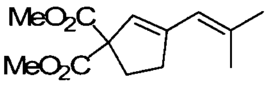
Entry	**Acid**	**Change in typical conditions^a**	**Conversion (%)^b**
1	TfOH	2 hours	100^c
2	Acetic acid	-	0
3	PPTS	-	0
4	Trichloroacetic acid	-	0
5	PTSA	-	100^c
6	 **4.70**	-	7-22
7	*N,N'*-Di(4-fluorophenyl)urea	20 mol% of acid	0
8	TFA	-	41
9	TFA	40 hours	100^d
10	TFA + *N,N'*-Di(4-fluorophenyl)urea	-	69

^{a}Typical reaction conditions, 5 mol% AuPPh$_3$Cl, 5 mol% acid in dichloromethane at room temperature for 18 hours (0.06 M concentration) ^{b}Determined by ^{1}H NMR. ^{c}Mixture of product and the isomer ^{d} Isolated yield was 100%.

*Figure 4.11-Products of the cycloisomerization of **4.64***

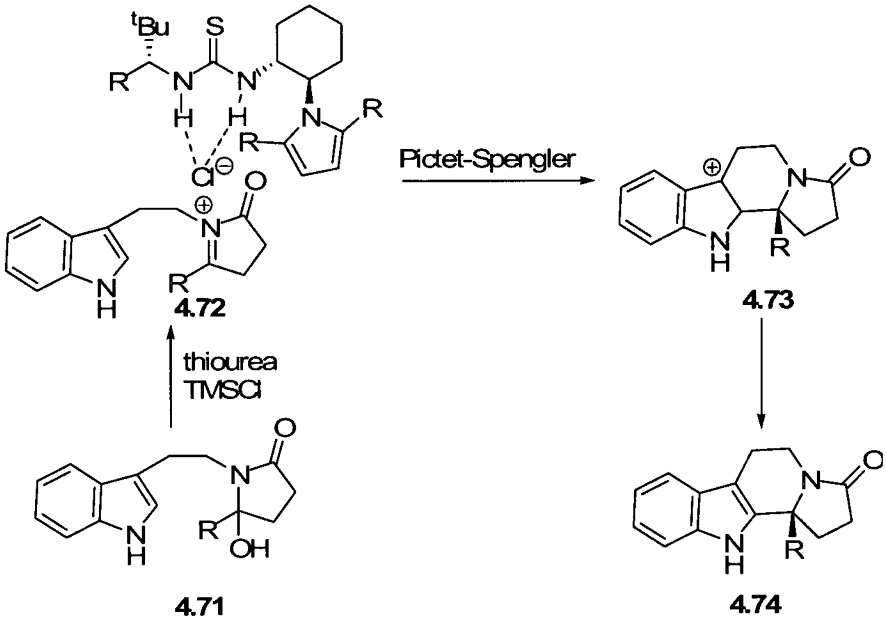


4.67



4.69

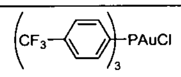
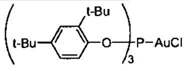
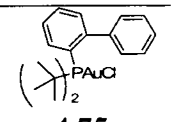
Scheme 4.18-H-bond donor catalysis by anion binding (Jacobsen, 2007)



The results indicate that there were different acids that could be used in conjunction with Au(PPh$_3$)Cl to catalyze the cycloisomerization. TfOH, TFA and phosphoric acid **4.70** were all compatible with the reaction although the reaction went to completion only in the case of TfOH and TFA. To confirm that that reaction was catalyzed by a combination of Au(PPh$_3$)Cl and an acid, control experiments were performed. There was no desired product observed when the reaction was done in the presence of only Au(PPh$_3$)Cl. In addition, only enyne **4.64** was recovered when the substrate was treated with TFA, phosphoric acid **4.70** or TfOH alone. Thus, it was the complex formed by the interaction of Au(PPh$_3$)Cl and the acid that catalyzed the reaction.

Next, the reaction conditions were optimized. Firstly, the proportion of gold versus acid was modified. In the case of TFA, it was found that there was no difference in the conversion between 1 mol% Au(PPh$_3$)Cl/5 mol% of TFA and 5 mol% Au(PPh$_3$)Cl/1 mol% of TFA. However, the conversion was approximately half as compared to 5 mol% Au(PPh$_3$)Cl/5 mol% of TFA for the same amount of time. In the case of TfOH, 100% conversion was observed with 5 mol% Au(PPh$_3$)Cl/1 mol% of TfOH but there was decomposition with 1 mol% Au(PPh_3)Cl/5 mol% of TfOH. Secondly, different ligands on the gold catalyst were investigated (Table 4.8). In all cases, there was no conversion when the gold catalyst was used without the presence of an acid (entry 1). It had been shown that the cycloisomerization was very facile with TfOH. Accordingly, conversions of 100, 78, 38 and 50% were observed when substrate **4.64** was reacted with TfOH and gold catalyst **4.75a, 4.75b**, Au(PEt_3)Cl and **4.75c**,[233] respectively (entry 2). In the case of the weaker acid, TFA, a marked difference was observed between the different catalysts (entry 3). When the ligand was either triphenylphosphine, triethylphosphine or the trifluoro derivative **4.75a**, similar conversions were obtained (41, 60 and 54%, respectively). However, in the case of catalyst **4.75b**, there was almost no conversion. Echavarren has categorized the cationic gold catalyst generated from **4.75b** and a silver salt has the most electrophilic gold catalyst that they tested for the rearrangement of enynes.[234] Since the conversion was low in the case of **4.75a** with TFA, it is believed that a cationic gold species was not generated in this case. Furthermore, this result seems to indicate that strongly electron-withdrawing ligands are not suitable with the gold/acid catalyst system. In contrast, the reaction performed with the bulky, diphenyl gold catalyst **4.75c** and TFA gave the desired product in 100% conversion. In this case, the electron-donating ligands are facilitating the reaction. However, the discrepancy between the results with triflic acid and TFA make it difficult to draw conclusions from these results. With the even weaker acid, phosphoric acid, there was no conversion for gold catalyst **4.75a** and **4.75b** and low conversions for Au(PEt_3)Cl and **4.75c** (entry 4).

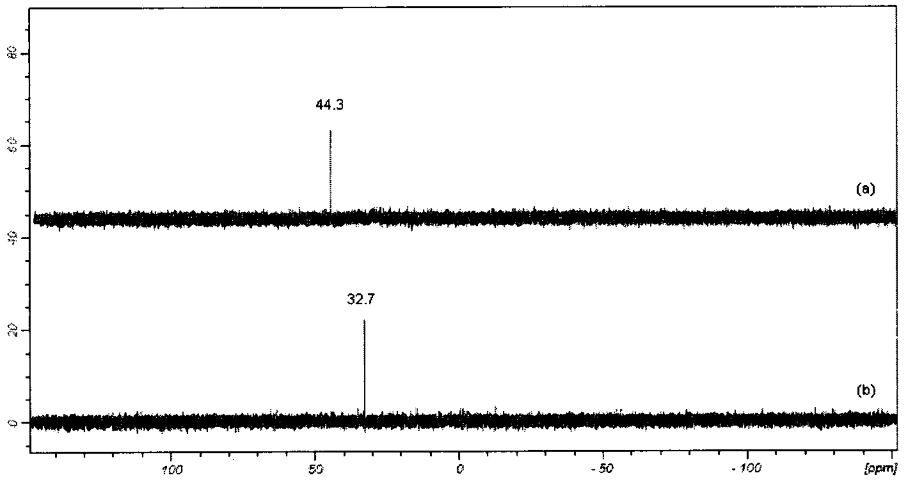
Table 4.8-Effect of the ligand on the conversion with various acids[a]

		Conversion (%)[b]				
Entry	**Acid**	Au(PPh_3) Cl	 **4.75a**	 **4.75b**	Au(PEt_3) Cl	 **4.75c**
1	None	0	0	0	21	0
2	TFOH	100	100	78	38	50
3	TFA	41	54	2	60	100
4	Phosphoric Acid **4.70**	7-22	0	0	12	10

[a]Typical reaction conditions, 5 mol% LAuCl, 5 mol% acid in dichloromethane at room temperature for 18 hours (0.06 M concentration) [b]Determined by ^{1}H NMR.

In order to have a better understanding of the nature of the catalyst system, the cycloisomerization of **4.64** was performed with Au(PPh)$_3$Cl and AgOTf in deuterated dichloromethane (Figure 4.12, (a)) and followed by ^{31}P NMR. There was a single peak present at 44.3 ppm. However, when the reaction was performed with Au(PPh)$_3$Cl and TfOH, a different peak was present (Figure 4.12, (b)). The peak at 32.7 ppm corresponded to Au(PPh$_3$)Cl. These results are similar to the ones obtained in the case of the benzannulation (the peak observed in the case of Au(PPh)$_3$Cl and AgOTf was at 46.2, see p. 193) and reiterate the reversible formation of an active species between the gold and the acid pre-catalysts.

Figure 4.12-NMR study of the cycloisomerization of ***4.64***



^{31}P NMR study at 23 °C in CD_2Cl_2 (PPh_3 used as a standard at -6.0 ppm). (a) substrate **4.64**, 5 mol% Au(PPh$_3$)Cl and 5 mol% AgOTf; (b) substrate **4.64**, 5 mol% Au(PPh$_3$)Cl and 5 mol% TfOH.

Application of the Au(PPh$_3$)Cl and acid catalyst system to the Conia-ene reaction

In the previous section, it was possible to identify three acids (TfOH, TFA and phosphoric acid **4.70**) that could be used in conjunction with Au(PPh$_3$)Cl to catalyze the cycloisomerization of 1,6-enynes. Since the phosphoric acid **4.70** was available in an enantiomerically pure form, we were anxious to determine if the gold/acid catalyst system could lead to asymmetric induction. Since the asymmetric rearrangement of 1,6-enynes was not known, it was best to focus on a reaction that had been already performed with a catalyst in a enantioselective fashion. Therefore, the Conia-ene reaction of substrate **4.76** came to our attention (Scheme 4.19). Toste and co-workers demonstrated that β-ketoester **4.76** reacted with the intramolecular alkyne when it was treated with Au(PPh_3)Cl and AgOTf.[235] They performed studies to support their proposed mechanism (Figure 4.13). The cationic gold catalyst generated from Au(PPh_3)Cl and AgOTf activated the alkyne towards nucleophilic attack of the enol. Following proto-demetallation, the desired product was obtained. When they tried to the reaction with a chiral gold catalyst, they obtained the desired product but with 0% ee. The lack of enantioselection was explained by the "linear geometry of the gold complex".[236] After scanning various catalysts, they found that palladium catalyst **4.79** promoted the asymmetric reaction in good yield and ee when the reaction was performed in the presence of a ytterbium Lewis acid (Scheme 4.19, eq. 2). The Conia-ene reaction was a good reaction to study with our gold/acid catalyst since it had been demonstrated that the reaction was catalyzed by gold catalysts and it was possible to render the reaction enantioselective using a chiral palladium catalyst. Furthermore, Toste and co-workers were not able to get enantioselectivity with their cationic gold catalyst. Since we believe that a complex is formed between the acid and the gold catalyst, the chiral environment created by the complex should be closer to the reaction center. One could postulate that with a chiral acid under the right conditions, enantioselective Conia-ene should be observed (Scheme 4.19, eq. 3).

Scheme 4.19-Conia-ene reaction

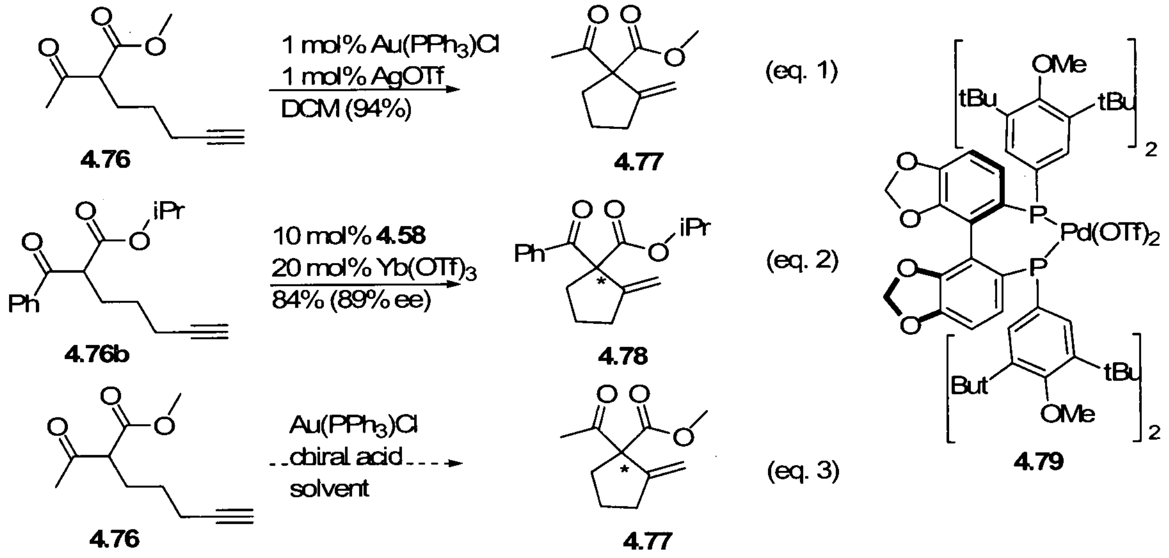
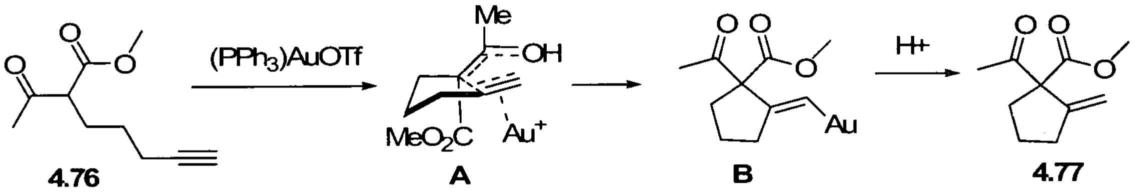


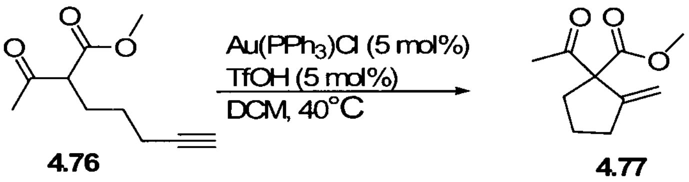
Figure 4.13-Proposed mechanism for the Conia-ene reaction



First of all, it was necessary to determine that the Conia-ene reaction of substrate **4.76** did occur under the standard Au(PPh$_3$)Cl/TfOH conditions. Satisfyingly, the desired product **4.77** (racemic) was obtained in 69% isolated yield (Scheme 4.20). Importantly, there was no reaction when TfOH was used without the gold catalyst. Secondly, the Conia-ene reaction was tested using Au(PPh$_3$)Cl and phosphoric acid **4.70**. When the reaction was performed at 40 °C in DCM with 5 mol% of each pre-catalyst, the desired product was obtained in 35% yield. In a control experiment, no conversion was observed when the substrate was stirred with phosphoric acid alone.

In order to optimize the reaction conditions, various solvents were tested (Table 4.9). It was not possible to use DCE since a 20% conversion to the desired product was observed without any phosphoric acid at 80 °C. As in the case of the benzannulation, it was suspected that HCl was formed by the catalyst and the solvent (see, p. 189). Toluene, acetonitrile, THF and acetone at 40 °C gave low conversions (entries 2, 4-6). Unexpectedly, toluene at 110 °C gave a 100% conversion after 18 hours. However, it was found that a 34% conversion occurred when the substrate was heated at 110 °C in toluene without any phosphoric acid. In contrast, a 3% conversion was observed when the substrate was heated at 110 °C in toluene with phosphoric acid without any gold catalyst. Since there was an important background reaction with Au(PPh$_3$)Cl alone, conditions consisting of heating toluene at 110 °C were incompatible to enantioselective catalysis.

Scheme 4.20-Conia-ene catalyzed by the gold/acid conditions



Scheme 4.21- Conia-ene catalyzed by the gold/phosphoric acid conditions

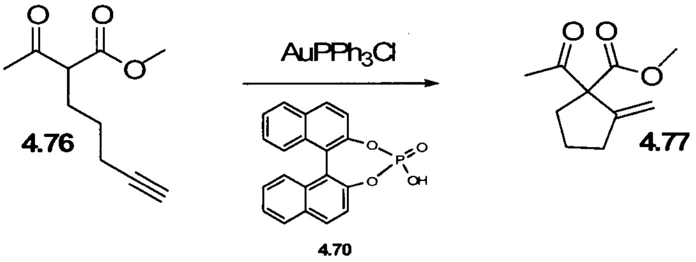


*Table 4.9-Effect of the solvent on the Conia-ene reaction with AuPPh$_3$Cl and phosphoric acid **4.70***

Entry	Solvent	Time	Temp. (°C)	Conversion (%)
1	DCM	18 hrs	40	35
2	Toluene	18 hrs	40	4
3	Toluene	18 hrs	110	100
4	MeCN	18 hrs	40	3
5	THF	18 hrs	40	0
6	Acetone	18 hrs	40	5

[a] Typical condition, 0.05 M with 5 mol% AuPPh$_3$Cl and 5 mol% phosphoric acid **4.70**

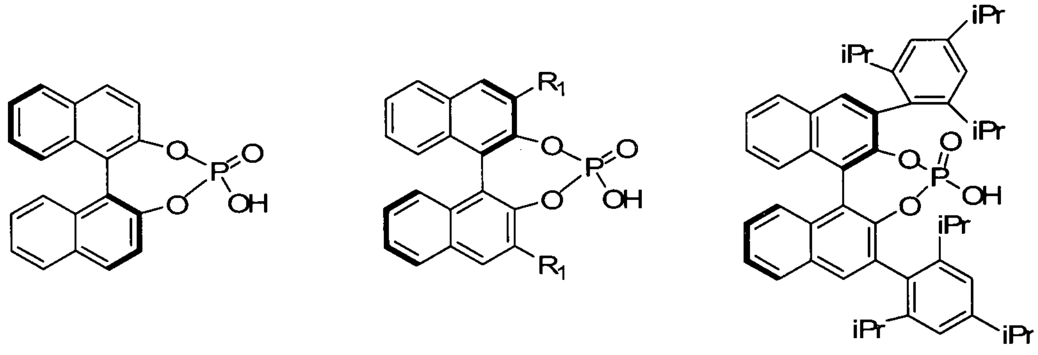
From the previous study, the best solvent was dichloromethane (and heating at 40 °C). To further optimize the reaction conditions, the ratio of gold to phosphoric acid was varied but there was no effect on the conversion. However, increasing the amount to 10 mol% of each Au(PPh$_3$)Cl and phosphoric acid did increase the conversion to 49%. There was also an increase of the conversion by 18% when the concentration was increased to 0.25 M. To increase the conversion, the reaction was performed in a microwave. Although the conversion was higher, it was found that there was important background reaction with only Au(PPh$_3$)Cl (no phosphoric acid).

In summary, the best conditions found were to heat the substrate at 40 °C in dichloromethane (0.25 M) in the presence of 10 mol% of each, Au(PPh$_3$)Cl and phosphoric acid.

With these optimal conditions, the reaction was tested with the commercially available chiral derivative of phosphoric acid **4.70**. The reaction was performed with 5 mol% Au(PPh$_3$)Cl and 5 mol% (*S*)-phosphoric acid **4.70** at 0.25 M in dichloromethane (40 °C for 18 hours). A 38% conversion to the desired product was observed. The product was isolated in 31% yield. However, preliminary results indicated that the product obtained was racemic. In general, enantioselective reactions catalyzed by chiral binol-phosphoric acid do not use the unsubstituted phosphoric acid (**4.70**).[237] Most catalysts have a substituent at R$_1$ (Figure 4.14). The effect of the substitution at R$_1$ was demonstrated by Uraguchi and Terada in 2004.[238] In their study of a direct enantioselective mannich reaction catalyzed by chiral phosphoric acids, a low ee was observed (12%) with the unsubstituted phosphoric acid

(R_1=H). Yet, high ee's were possible when R_1 was an aromatic ring (up to 95% ee). It is believed that the R_1 substituent created a chiral environment that led to highly enantioselective reactions. In the case of Toste and co-workers, they used the silver salt of phosphoric acid **4.81** in their counterion controlled enantioselective gold cyclization of hydroxy-allenes (Scheme 4.14). For this reason, in order to see if enantioselectivity is feasible with a chiral phosphoric acid and Au(PPh_3)Cl, phosphoric acid **4.81** will need to be synthesized and tested under the optimized reaction conditions.

Figure 4.14-Phosphoric acids



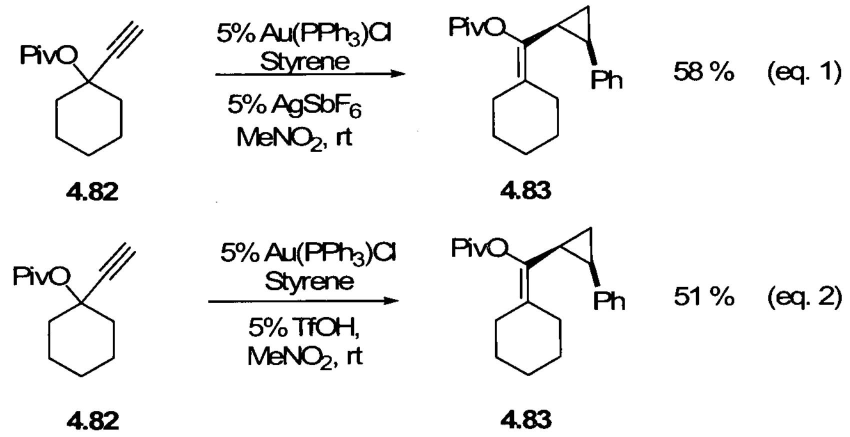
(S)-4.70 **(R)-4.80** **(R)-4.81**

Application of the gold-acid catalyst system to other reactions

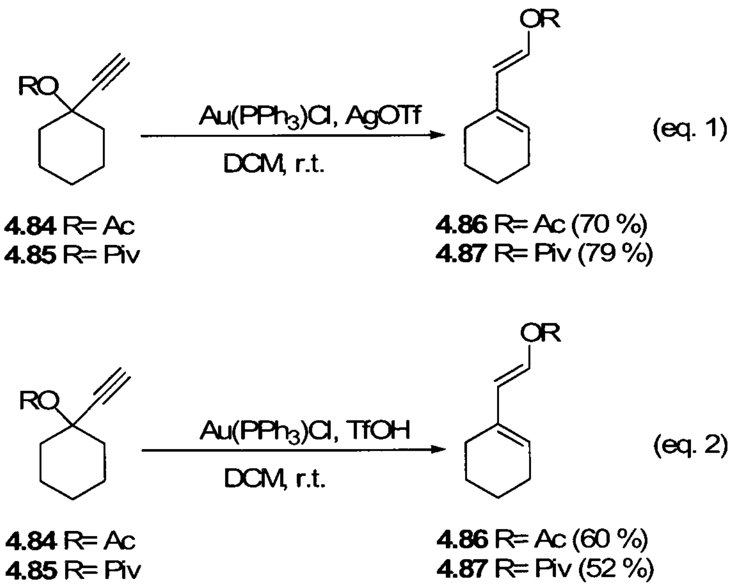
The Au(PPh_3)Cl and acid catalyst system was also used in the context of other reactions. Anik Chartrand and Anne-Catherine Bédard have applied the catalyst system to known and novel reaction systems that can otherwise be catalyzed by cationic gold species. Toste and co-workers demonstrated the gold-catalyzed transformation of propargylic pivaloate **4.82** into product **4.83** (Scheme 4.22) in 58% yield.[239] Treating the same substrate with 5 mol% of Au(PPh_3)Cl and TfOH furnished the desired product in 51% yield (Scheme 4.22, eq. 2). A novel gold-catalyzed rearrangement of propargylic acetates and pivaloates was discovered in our laboratory. Using 5 mol% each of Au(PPh_3)Cl and silver triflate, the acetoxy- and pivaloxy-dienes are obtained in good yield (70-79%) (Scheme 4.23). It was found that the same rearrangement could be catalyzed by Au(PPh_3)Cl and triflic acid (Scheme 4.23, eq. 2). The desired products (**4.86** and **4.87**) were obtained in 60 and 52%

yield, respectively. These examples demonstrate the generality of the gold-acid catalyst system.

Scheme 4.22-Olefin cyclopropanation



Scheme 4.23-Synthesis of acetoxy-dienes



Outlook

It was an important milestone that was achieved when phosphoric acid **4.70** was identified as a good co-catalyst in reactions catalyzed by the Au(PPh$_3$)Cl/acid system. Even though the conversions were moderate, we are hopeful that further investigations will rectify this problem. More mechanistic studies are needed in order to determine the nature of the complex or the reactive species that is responsible for the catalysis provided by the Au(PPh_3)Cl/acid system. This information could help design better functionalized acids or find better conditions for the reaction. Also, substituted phosphoric acids, such as **4.80** (R_1=Ar) or **4.81**, will need to be synthesized and tested in their ability to catalyze enantioselective gold reactions.

The fact that the only species detected by ^{31}P NMR of Au(PPh_3)Cl/acid catalyzed reactions was Au(PPh_3)Cl suggests that a reversible complex was formed in situ. A possible application of our Au(PPh_3)Cl/acid catalyst system is a recyclable gold catalyst. If the Au(PPh_3)Cl pre-catalyst could be grafted onto a solid support, it might be possible to recover the pre-catalyst by a simple filtration at the end of the reaction. Although this methodology needs to be developed, the industrial application of this Au(I) on solid support with acid as a activator should be large. The recyclable catalyst would desirable since it would lower costs, decrease waste, facilitate the work-up and finally, decrease the amount of residual metal in the final product.

Application of the novel Au(PPh_3)Cl/acid catalyst system toward the development of new domino reactions are also being investigated. Jason Poulin's one-pot cycloisomerization/Diels-Alder reaction is one example (see, Scheme 3.27).

Conclusions

In summary, we disclosed a gold-catalyzed benzannulation of 3-hydroxy-1,5-enynes. The reaction conditions were compatible to a variety of functional groups proving to be an effective method to generate substituted tetrahydronaphthalenes. In the course of the study, we discovered that the combination 1 mol% of Au(PPh_3)Cl and TfOH in dichloroethane emerged as a novel and effective catalyst for the benzannulation process. In general, the tetrahydronaphthalenes were obtained in higher yields.

The mechanistic studies done on the Au(PPh_3)Cl and TfOH catalyst system insinuate that a reversible complex between the two species was the active species. Therefore, it was hypothesized that using a chiral acid could lead to enantioselective reactions. The Au(PPh_3)Cl/acid catalyst system was applied to the cycloisomerization of 1,6-enynes and the

Conia-ene reaction. In both cases, it was possible to identify other acids than TfOH that could activate Au(PPh$_3$)Cl. Preliminary results indicated that phosphoric acid **4.70** in conjunction with Au(PPh$_3$)Cl did catalyze both reactions. Further investigations are needed to identify the conditions and chiral phosphoric acid that will give an enantioselective reaction.

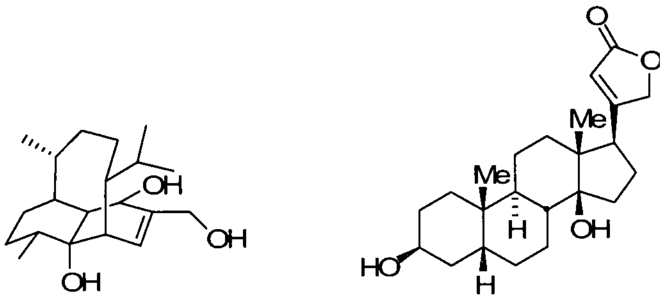
Chapter 5

Summary

Summary of work

The total syntheses of two natural products have been investigated in this thesis (Figure 5.1). The synthesis of both molecules relied on the Diels-Alder reaction in the key step to generate molecular complexity in a stereoselective fashion.

Figure 5.1-Natural products of interest

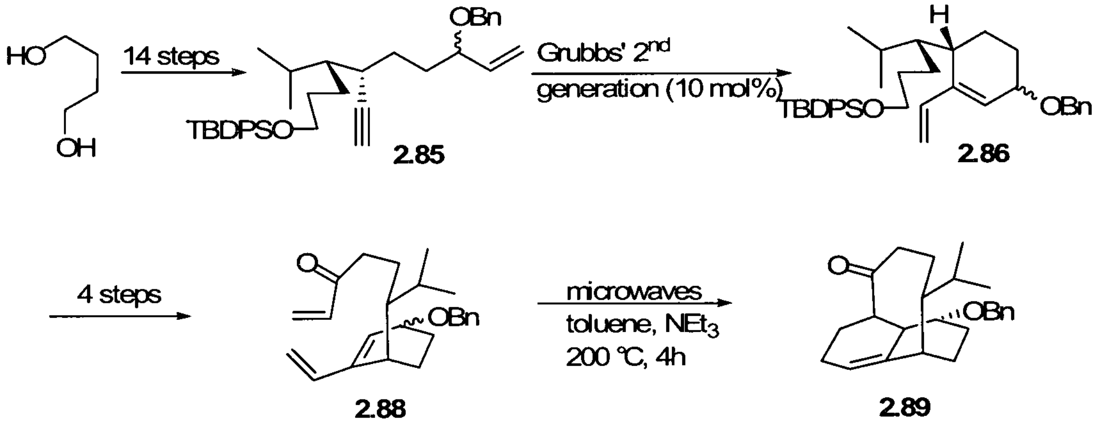


2.1 :
vinigrol

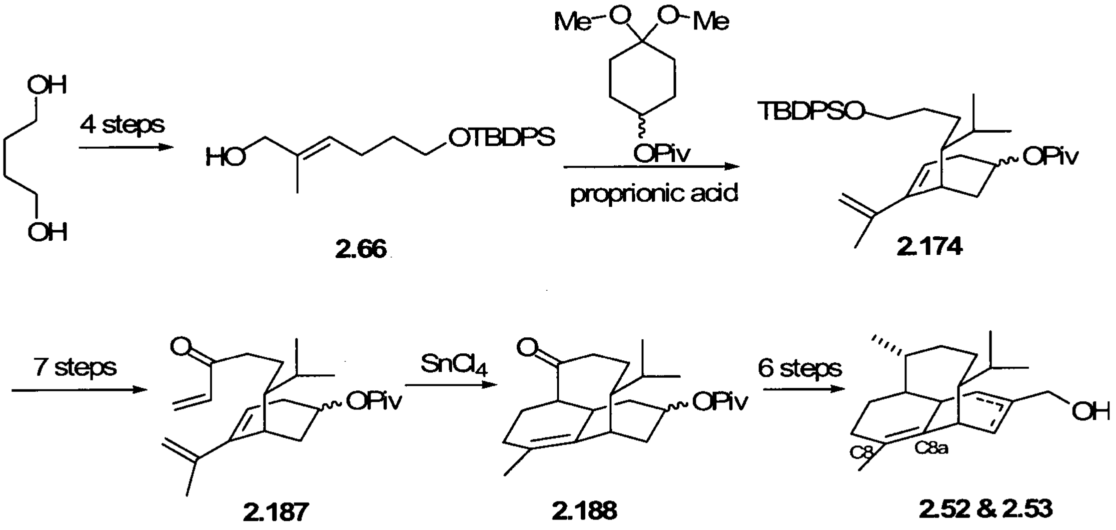
3.44 :
digitoxigenin

In the first case, an intramolecular Diels-Alder reaction was used to synthesize the tricyclic core of vinigrol, a diterpenoid with an interesting biological activity. In order to prove the concept, a non-functionalized Diels-Alder precursor was initially synthesized. During these studies, a diastereoselective Claisen rearrangement and an enyne metathesis were found to be reliable methods to access the necessary precursor. The intramolecular Diels-Alder reaction produced the desired tricyclic core in good yield and as a sole diastereoisomer. Based on these results, the synthesis of the functionalized precursor was done in nineteen steps from commercially available 1,4-butanediol (Scheme 5.1). The intramolecular Diels-Alder reaction proceeded by heating in the microwave at high temperatures to provide the functionalized core in 52% yield. A shorter route to a functionalized precursor (**2.187**) was then developed taking advantage of the diastereoselective ketal Claisen rearrangement (Scheme 5.2). It was possible to generate the tricyclic carbon skeleton (**2.188**) using the intramolecular Diels-Alder methodology. Using a Lewis acid to catalyze the reaction, the desired product was obtained in good yield.

Scheme 5.1-First approach to a functionalized core of vinigrol



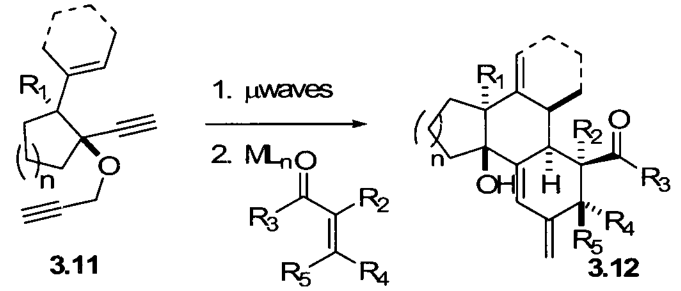
Scheme 5.2-Second approach to a functionalized core of vinigrol



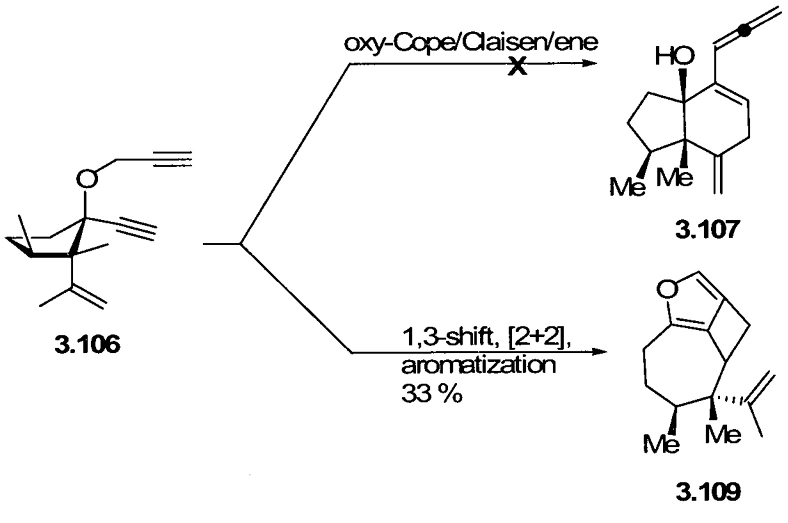
Many approaches to install the desired substituents at C8 and C8a were explored but the desired product could not be isolated. For this reason, functionalization of ring B of molecule **2.188** was investigated. It was possible to obtain allylic alcohols **2.52** and **2.53** as a mixture. However, it was not possible to transform the allylic alcohol to the allylic diol at that point. Different routes and approaches have been considered to finish the total synthesis of vinigrol and they are currently being explored.

In the second case, the synthesis of digitoxigenin was based on a domino reaction containing a Diels-Alder reaction. Optimization of the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction was necessary before it could be applied to a total synthesis (Scheme 5.3). During these studies, it was found that $MgBr_2 \cdot OEt_2$ or Dibal-H could promote the hydroxy-directed Diels-Alder reaction and better results were obtained with the magnesium Lewis acid. The methodology was then expanded to *cis* precursor. This was done with the total synthesis of digitoxigenin in mind. The reaction was possible for functionalized *cis* precursors having a six-membered ring. Next, many approaches to the synthesis of a functionalized *cis* five-membered ring precursor were investigated. Eventually, the synthesis of a *cis* precursor with a methyl group as a functional group was possible. Unfortunately, this precursor did not undergo the desired oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction (Scheme 5.4). Another rearrangement occurred to provide **3.109** instead. This ended our efforts towards digitoxigenin using the described domino reaction. A new approach to this natural product based on a cycloisomerization/Diels-Alder reaction is currently being studied.

Scheme 5.3-The oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction

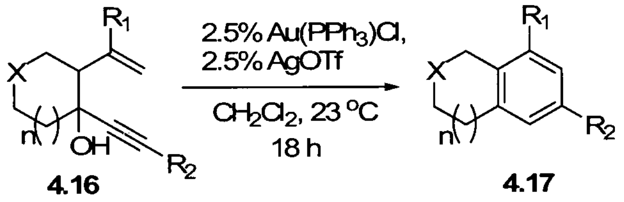


*Scheme 5.4-Thermal rearrangement of propargyl ether **3.106***



The survey of gold reagents as possible catalysts for the oxy-Cope/Claisen/ene reaction of propargyl ethers led to the discovery of a gold-catalyzed benzannulation reaction. The method proved to be an efficient way to generate tetrahydronaphthalenes from 3-hydroxy-1,5-enynes (Scheme 5.5). Mechanistic studies were done and this led to the discovery of a new catalyst system. It was found that Au(PPh$_3$)Cl and triflic acid catalyzed the benzannulation reaction. Furthermore, this catalyst system also promoted other reactions generally catalyzed by cationic gold species. Preliminary research in the application of this new catalyst system to stereoselective synthesis was also discussed.

Scheme 5.5-Gold-catalyzed benzannulation reaction



Claims to original research

1. Investigations into the synthesis of the tricyclic core of vinigrol using an intramolecular Diels-Alder reaction.
2. Development of two routes to a functionalized core of vinigrol.
3. Exploration of the transformation of the functionalized core into the natural product.
4. Optimization of the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction.
5. Investigations of the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction on *cis* precursors.
6. Research into the application of the oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder reaction towards the total synthesis of digitoxigenin.
7. Synthesis of tetrahydronaphthalenes using the gold-catalyzed benzannulation of 3-hydroxy-1,5-enynes.
8. Discovery of the activation of Au(PPh$_3$)Cl using an acid.

Publications from this work

Grisé-Bard, C.M.; Barriault, L. "**Stereoselective Synthesis of the Carbocyclic Core of Vinigrol**" Submitted.

Clément, R.; Grisé, C.M.; Barriault, L. "**Stereocontrolled Synthesis of Carbocycles via Four Successive Pericyclic Reactions**" *Chem. Comm.* **2008**, 3004.

Grisé, C.M.; Rodrigue, E.M.; Barriault, L. "**Gold(I)-catalyzed benzannulation of 3-hydroxy-1,5-enynes: an efficient synthesis of substituted tetrahydronaphthalenes and related compounds**" *Tetrahedron-Symposium-in-Print* **2008**, *64*, 797.

Grisé, C.M.; Tessier, G.; Barriault, L. "**Synthesis of the Tricyclic Core of Vinigrol via an Intramolecular Diels-Alder Reaction**" *Org. Lett.* **2007**, *9*, 1545.

Grisé, C.M.; Barriault, L. "**Gold-catalyzed Synthesis of Substituted Tetrahydronaphthalenes**" *Org. Lett.* **2006**, *8*, 5905.

Presentations from this work

Oral: "**Towards the Total Synthesis of Vinigrol**" Organic08, Hobart, Australia. December 2008.

Oral: "**Towards the Total Synthesis of Vinigrol**" Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, Toronto, Canada. November 2008.

Poster: "**Towards the Total Synthesis of Vinigrol**" AstraZeneca Symposium, Montréal, Canada. Poster. October 2008.

Poster: "**Towards the Total Synthesis of Vinigrol**" University of Ottawa Synthesis Day, Ottawa, Canada. Poster. June 2008.

Poster: "**Towards the Total Synthesis of Vinigrol**" Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, Montreal, Canada. November 2007.

Oral: "**Gold Catalyzed Synthesis of Substituted Tetrahydronaphthalenes**" Organic Reactions & Processes Gordon Conference, Bryant University, United-States. July 2007.

Poster: "**Gold Catalyzed Synthesis of Substituted Tetrahydronaphthalenes**" Organic Reactions & Processes Gordon Conference, Bryant University, United-States. July 2007.

Poster: "**Towards the Total Synthesis of Vinigrol**" University of Ottawa Synthesis Day, Ottawa, Canada. June 2007.

Oral: "**Towards the Total Synthesis of Vinigrol**" Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, London, Canada. November 2006.

Poster: "**Gold-Catalyzed Synthesis of Substituted Tetrahydronaphthalenes**" Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, London, Canada. November 2006.

Poster: "**Further Developments of the Tandem Oxy-Cope/Claisen/Ene/ Hydroxy-Directed Diels-Alder Reaction and Gold-Catalyzed Benzannulation of Hydroxy-Enynes**" University of Ottawa Synthesis Day, Ottawa, Canada. August 2006.

Poster: "**Further Developments of the Tandem Oxy-Cope/Claisen/Ene/ Hydroxy-Directed Diels-Alder Reaction**" Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, Ste-Adèle, Canada. November 2005.

Poster: "**Further Developments of the Tandem Oxy-Cope/Claisen/Ene/Hydroxy-Directed Diels-Alder Reaction**" University of Ottawa Synthesis Day, Ottawa, Canada. June 2005.

Poster: "**Further Developments of the Tandem Oxy-Cope/Claisen/ene/ hydroxy-directed Diels-Alder reaction**" 4th Symposium International en Synthèse Organique de l'Université de Montréal, Montréal, Canada. April 2005.

Chapter 6

Experimental

General Experimental

All reactions were performed under argon in flame-dried glassware equipped with a magnetic stirbar and a rubber septum unless otherwise indicated. Solvents used were freshly distilled prior to use: ether and THF over sodium and benzophenone; dichloromethane, toluene and DMF over calcium hydride. Triethylamine was distilled prior to use. All other commercial reagents were used without purification unless specified.

Microwave reactions were preformed using a CEM Model ESP-1500 Plus microwave oven equipped with a pressure monitoring device and an EST-300 Plus fiber optic temperature probe or the CEM Discovery microwave. The reaction vessel was a quartz tube, and in each case was added a carboflon^{TM} to aid in the absorption of microwave radiation.

Reactions were monitored by TLC analysis using glass plates precoated (250 µm thickness) with silica gel 60 F_{254} (E. Merck). TLC plates were viewed using UV light, *p*-anisaldehye staining solution, phosphomolybdic acid staining solution or potassium permanganate staining solution. Flash chromatography was carried out on 230-400 mesh silica gel 60.

^1H and ^{13}C NMR spectra were recorded on Bruker AMX 300 MHz, Bruker AMX 500 MHz and Bruker AMX 400 MHz spectrometers in the specified deuterated solvent. IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer. HRMS spectra were obtained using a Kratos Analytical Concept spectrometer, and melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus.

Procedures-Chapter 2

General Procedures

A) Swern oxidation (concentrated procedure for larger scale reactions): To a solution of oxalyl chloride (12.2 mL, 140 mmol) in dichloromethane (350 mL) was added a solution of dimethyl sulfoxide (14.6 mL, 206 mmol) in dichloromethane (75 mL) at -60 °C. The mixture was stirred for 30 minutes and then cooled to -78 °C before a solution of the alcohol (82.5 mmol) in dichloromethane (75 mL) was added. The mixture was stirred for 60 minutes at -78 °C before triethylamine (57.5 mL, 413 mmol) was added. The mixture was stirred for 15 minutes then warmed up to 0 °C and further stirred for 45 minutes. The reaction was quenched by adding water at 0°C. The aqueous layer was extracted with dichloromethane (2x) and ethyl acetate (1x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.*

B) Swern oxidation (regular scale): To a solution of oxalyl chloride (0.012 mL, 0.134 mmol) in dichloromethane (1 mL) was added dimethyl sulfoxide (0.014 mL, 0.200 mmol) at -60 °C. The mixture was stirred for 30 minutes and then cooled to -78 °C before a solution of alcohol (0.040 mmol) in dichloromethane (1 mL) was added. The mixture was stirred for 60 minutes at -78 °C before triethylamine (0.056 mL, 0.400 mmol) was added. The mixture was stirred for 15 minutes then warmed up to 0 °C and further stirred for 45 minutes. The reaction was quenched by adding water at 0°C. The aqueous layer was extracted with dichloromethane (2x) and ethyl acetate (1x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.*

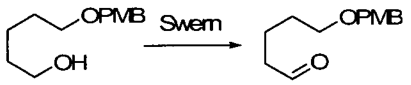
C) TPAP/NMO oxidation: Molecular sieves 4 Å (1.19 g) were flame-dried under vacuum. A solution of alcohol (1.01 mmol) in dichloromethane (10 mL) was cannulated into the flask containing the sieves. NMO (237 mg, 2.02 mmol) was added, followed by TPAP (17.7 mg, 0.05 mmol). The reaction was stirred for 1h, then filtered on a silica gel pad (elution with ethyl acetate) and concentrated *in vacuo*.

Detailed experimental

2.29A **2.29B**

5-((4-Methoxyphenoxy)methoxy)pentan-1-ol (2.29B). To a solution of 1,5-pentanediol (31.1 mL, 297 mmol) in dimethyl sulfoxide (120 mL) was added grinded potassium hydroxide (15.9g, 284 mmol) portionwise at 0°C. The mixture was stirred for 15 minutes at 0°C before 1-(chloromethyl)-4-methoxybenzene (PMB-Cl) (21.2g, 135 mmol) was added. The mixture was stirred at ambient temperature for 16 h prior to being quenched with saturated NH_4Cl solution and extracted with diethyl ether (3x). The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30-40% ethyl acetate in hexanes) afforded 27.0g (89%) of **2.29B** as a light yellow oil.

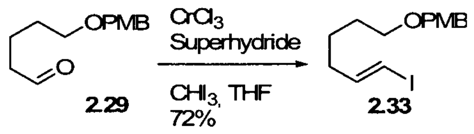
Full characterization is available through the literature.[240]



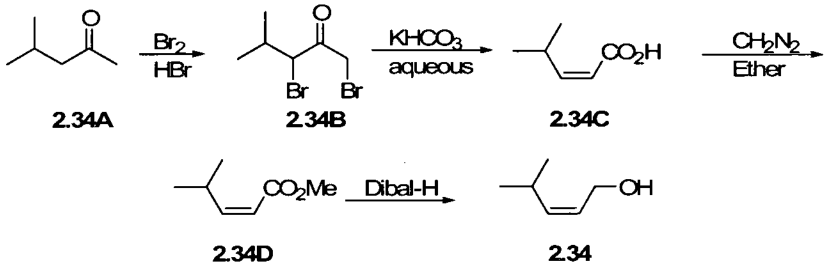
2.29B **2.29**

5-(4-Methoxybenzyloxy)pentanal (2.29). Procedure A: oxalyl chloride (12.2 mL, 140 mmol), dimethyl sulfoxide (14.6 mL, 206 mmol), alcohol **2.29B** (18.5 g, 82.5 mmol), dichloromethane (350+75+75 mL), triethylamine (57.5 mL, 413 mmol). Purification of the residue on silica gel (elution with 20-40% ethyl acetate in hexanes) afforded 17.6 g (96%) of **2.29** as a light yellow oil.

Full characterization is available through the literature.[240]



(*E*)-1-(5-Iodo-pent-4-enyloxymethyl)-4-methoxy-benzene (2.33). To a suspension of chromium(III) chloride (95.3 g, 602 mmol) in tetrahydrofuran (1000 mL) at 0 °C was added a 1M solution of super hydride (451 mL, 451 mmol). The purple mixture was stirred at ambient temperature for 3h and evolved to a dark grey suspension. The mixture was cooled to 0 °C and a solution of aldehyde **2.29** (16.7g, 75.2 mmol) and iodoform (59.8g, 150 mmol) in tetrahydrofuran (375 mL) was added dropwise and stirred at 0°C for 3h. The mixture was poured into water and extracted with diethyl ether (3x). The ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-20% ethyl acetate in hexanes) afforded 18.8g (72%) of **2.33** as a yellow oil: IR (neat, cm^{-1}) 2934 (s), 2858 (s), 1613 (m), 1586 (w), 1513 (s), 1247 (s), 1099 (m), 1036 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.48(ddd, *J*=14.3, 7.1, 7.1 Hz, 1H), 5.96 (ddd, *J*=14.3, 1.3, 1.3 Hz, 1H) 4.41 (s, 2H), 3.79 (s, 3H), 3.42 (t, *J* = 6.2 Hz, 2H), 2.05 (dddd, *J* = 7.3, 7.3, 7.3, 1.3 Hz, 2H), 1.64-1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (C_{quat}), 146.4 (CH), 130.6 (C_{quat}), 129.3 (CHx2), 113.8 (CHx2), 74.8 (CH), 72.6 (CH_2), 69.6 (CH_2), 55.3 (CH_3), 35.8 (CH_2), 29.1 (CH_2), 25.0 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{19}O_2I$ [M^+] 346.0430, found 346.0404.

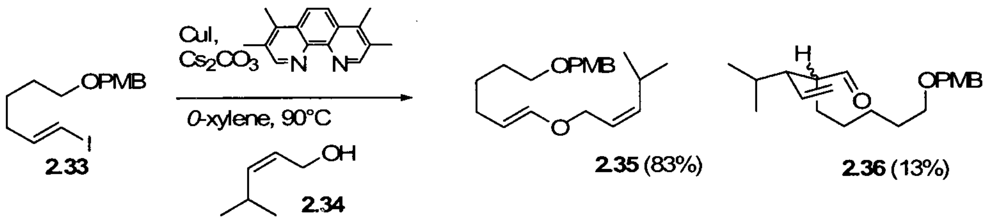


1,3-Dibromo-4-methylpentan-2-one (2.34B). (Powerful lachrymator!!). To a solution of 4-methylpentane-2-one (25.0 mL, 198 mmol) in hydrobromic acid 48% (28 mL) in a 3-neck flask equipped with a condenser and a bubbling trap filled with sodium hydroxide was added bromine (20.3 mL, 396 mmol) at 0°C over 30 minutes. The mixture was stirred 1h before the heavier organic phase was separated. The product was used without further purification.[241]

(Z)-4-Methylpent-2-enoic acid (2.34C). Dibromoketone **2.34B** (51.13g, 198 mmol (assuming 100% yield from ketone to **2.34B**)) was added to a 1M aqueous solution of potassium carbonate (1000 mL) at 0°C. The mixture was stirred 16h at ambient temperature under a condenser. The aqueous solution was extracted with diethyl ether (3x) to remove unreacted material. The aqueous phase was then acidified with hydrochloric acid 37% to a pH of 2 and extracted with diethyl ether (4x). The ethereal layers were dried over anhydrous magnesium sulfate and filtrated. The product was used without further purification.

(Z)-Methyl 4-methylpent-2-enoate (2.34D). To a solution of acid **2.34C** (22.6 g, 198 mmol (assuming 100% yield from **2.34B** to **2.34C**)) in diethyl ether was added a solution diazomethane in diethyl ether until the mixture became yellow. Silica was added until the yellow color disappeared. The mixture was filtrated and used without further purification.

(Z)-4-Methylpent-2-en-1-ol (2.34). To a solution of ester **2.34D** in diethyl ether (25.4g, 198 mmol (assuming 100% yield from **2.34C** to **2.34D**)) at -78 °C was added a 1M solution of diisobutylaluminum hydride in dichloromethane (595 mL, 595 mmol). The mixture was stirred at -78 °C for 1h before being quenched with 1M HCl. The mixture was extracted with diethyl ether (3x) and the etheral layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30-50% diethyl ether in petroleum ether) afforded 13.2g (66% over 4 steps) of **2.34** as a colorless oil. Full characterization is available through the literature.[242]



(5*E*,2'*Z*)-1-Methoxy-4-[6-(4-methyl-pent-2-enyloxy)-hex-5-enyloxymethyl]-benzene (2.35). A sealed tube was loaded with allylic alcohol **2.34** (8.68g, 86.7 mmol), vinyl iodide **2.33** (10.0g, 28.9 mmol), copper (I) iodide (550 mg, 2.89 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (1.37g, 5.78 mmol), cesium carbonate (28.3g, 86.7 mmol) and *o*-xylene (30 mL). The mixture was stirred for 60h at 90 °C, filtered over a pad of silica gel (elution with ethyl acetate) and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-20% ethyl acetate in hexanes) afforded 7.47g (83%) of **2.35** as a light yellow oil and 1.21 g (13%) of **2.36** also as a light yellow oil.

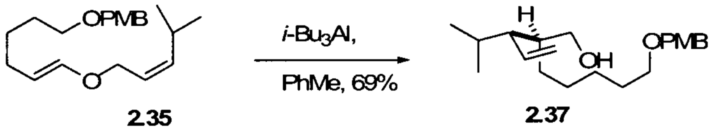
2.35: IR (neat, cm^{-1}) 2955(s), 2934(s), 2859(s), 1651 (m), 1613 (m), 1513 (s), 1464 (m), 1247 (s), 1171 (m), 1100 (m), 1037 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.21 (d, *J*=12.6 Hz, 1H), 5.43-5.40 (m, 2H) 4.76 (ddd, *J*=12.6, 7.4, 7.4 Hz, 1H), 4.41 (s, 2H), 4.21 (d, *J* = 4.9 Hz, 2H), 3.78 (s, 3H), 3.42 (dd, *J* = 6.5 Hz, 2H), 2.66-2.50 (m, 1H), 1.91 (ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H),1.64-1.55 (m, 2H), 1.50-1.34 (m, 2H), 0.96 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (C_{quat}), 145.9 (CH), 141.4 (CH), 130.8 (C_{quat}), 129.3 (CHx2), 122.6 (CH), 113.8 (CHx2), 104.3 (CH), 72.6 (CH_2), 70.1 (CH_2), 65.0 (CH_2), 55.3 (CH_3), 29.2 (CH_2), 27.7 (CH_2), 27.3 (CH_2), 27.1 (CH), 23.1 (CH_3x2); HRMS (EI) m/z calcd for $C_8H_{13}O$ [$(M-C_{12}H_{17}O_2)^+$] 125.0961, found 125.0946.

(±)-(2*R*,1'*S*)-2-(1-Isopropyl-allyl)-6-(4-methoxy-benzyloxy)-hexanal and (±)-(2*S*,1'*S*)-2-(1-Isopropyl-allyl)-6-(4-methoxy-benzyloxy)-hexanal (2.36).

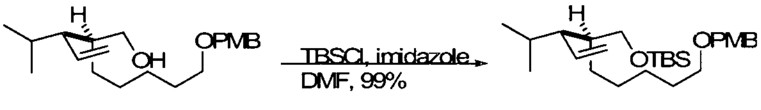
Product was isolated as mentioned above. Both epimers were obtained in a 1:1 ratio and were not separable by flash chromatography. (Note: each isomer is considered as one in the following characterization).

IR (neat, cm^{-1}) 2957(s), 2934(s), 2865(s), 1723 (s), 1613 (m), 1513 (s), 1463 (m), 1098 (w), 1037 (w); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, *J*=4.1 Hz, 1H), 9.46 (d, *J*=4.0 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 4H), 6.84 (d, *J* = 8.3 Hz, 4H), 5.56 (ddd, *J*=17.0, 10.0, 10.0 Hz, 1H), 5.46 (ddd, *J*=17.0, 10.0, 10.0 Hz, 1H), 5.09 (d, *J*=10.2 Hz, 1H), 5.08 (d, *J*=10.2 Hz, 1H), 4.98 (dd, *J*=17.0, 2.2 Hz, 1H), 4.97 (dd, *J*=17.0, 2.2 Hz, 1H), 4.38 (s, 2H), 4.37 (s, 2H), 3.76 (s, 6H), 3.41-3.35 (m, 4H), 2.42-2.27 (m, 2H), 2.17-2.09 (m, 1H), 1.99 (ddd, *J*=10.0, 6.7, 6.7 Hz, 1H), 1.80-1.73 (m, 1H), 1.66-1.38 (m, 8H), 1.35-1.15 (m, 5H), 0.91 (d, *J*=6.6 Hz, 3H), 0.86 (d, *J*=6.7 Hz, 3H), 0.80 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7 (CH), 205.5 (CH), 159.2 (C_{quat}x2), 136.7 (CH), 135.9 (CH), 130.6 (C_{quat}x2), 129.3 (CHx4), 118.4 (CH_2), 118.1 (CH_2), 113.8 (CHx4), 72.6 (CH_2x2), 69.8 (CH_2), 69.7 (CH_2), 55.3 (CH_3x2), 53.5 (CH), 53.0 (CH), 52.0 (CH), 50.8 (CH), 29.9 (CH_2), 29.8 (CH_2), 29.1 (CH), 28.3 (CH), 27.5 (CH_2), 26.2 (CH_2), 24.4 (CH_2), 24.0 (CH_2), 21.4 (CH_3), 21.3

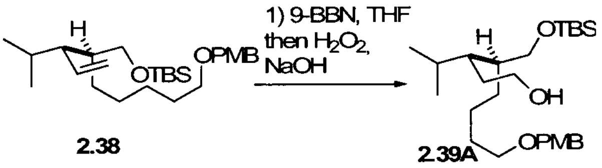
(CH_3), 19.0 (CH_3), 17.9 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{30}O_3$ [M^+] 318.2195, found 318.2181.



(±)-(2*R*,1'*S*)-2-(1-Isopropyl-allyl)-6-(4-methoxy-benzyloxy)-hexan-1-ol (2.37). To a solution enol ether **2.35** (1.74 g, 5.46 mmol) in dichloroethane (55 mL) was added a 1 M solution of tri-isobutlyaluminium (16.4 mL, 16.4 mmol) in toluene. The mixture was stirred for 18 hours under argon atmosphere before being diluted in hexane (30 mL) and poured over a 1M aq. solution of tartaric acid (33 mL). The resulting solution was vigorously stirred for 20 min. and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20-30% ethyl acetate in hexanes) afforded 1.21 g (69%) of **2.37** as a light yellow oil: IR (neat, cm^{-1}) 3417 (br), 2954 (s), 2840 (s), 1613 (s), 1586 (m), 1513 (s), 1420 (m), 1248 (s), 1173 (m), 1098 (s), 1037 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.54 (ddd, J=17.0, 10.0, 10.0 Hz, 1H), 5.05 (d, J=10.2 Hz, 1H) 4.97 (d, J=17.0 Hz, 1H), 4.40 (s, 2H), 3.78 (s, 3H), 3.64-3.47 (m, 2H), 3.41 (dd, J=6.3, 6.3 Hz, 2H), 1.88-1.05 (m, 10H), 0.87 (d, J=6.6 Hz, 3H), 0.80 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C_{quat}), 139.3 (CH), 130.7 (C_{quat}), 129.4 (CHx2), 117.0 (CH_2), 113.8 (CHx2), 72.7 (CH_2), 70.1 (CH_2), 64.1 (CH_2), 55.4 (CH_3), 52.6 (CH), 41.1 (CH), 30.2 (CH_2), 28.0 (CH), 26.3 (CH_2), 24.6 (CH_2), 21.3 (CH_3), 20.5 (CH_3); HRMS (EI) m/z calcd for $C_{14}H_{19}O_2$ [$(M- C_6H_{13}O)^+$] 219.1380, found 219.1402.



(±)-(2*R*,1'*S*)-*tert*-Butyl-[2-(1-isopropyl-allyl)-6-(4-methoxy-benzyloxy)-hexyloxy]-dimethyl-silane (2.38). To a solution of alcohol **2.37** (3.20g, 10 mmol) in *N,N*-dimethylformamide (50 mL) was added imidazole (1.70g, 25 mmol) followed by *tert*-butyldimethylchlorosilane (1.81g, 12 mmol). The mixture was stirred for 16h at ambient temperature before it was poured over water and extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-10% ethyl acetate in hexanes) afforded 4.38g (100%) of **2.38** as a light yellow oil: IR (neat, cm^{-1}) 2954 (s), 2927 (s), 2857 (s), 1613 (m), 1513 (s), 1463 (m), 1248 (s), 1098 (s), 836 (s), 774 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.46 (ddd, J=17.0, 10.2, 10.2 Hz, 1H), 5.01 (dd, J = 10.2, 2.6 Hz, 1H), 4.90 (dd, J = 17.1, 2.6 Hz, 1H), 4.41 (s, 2H), 3.78 (s, 3H), 3.52 (dd, J = 9.9, 4.7 Hz, 1H), 3.50-3.35 (m, 3H), 1.94-1.86 (m, 1H), 1.72-1.61 (m, 1H), 1.58-1.45 (m, 3H), 1.42-1.20 (m, 3H), 1.07-0.96 (m, 1H), 0.87 (s, 9H), 0.85 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H), 0.00 (s, 6H); ^{13}C NMR δ 159.2 (C_{quat}), 138.8 (CH), 130.9 (C_{quat}), 129.3 (CHx2), 116.8 (CH_2), 113.8 (CHx2), 72.6 (CH_2), 70.2 (CH_2), 63.6 (CH_2), 55.4 (CH_3), 51.4 (CH), 41.2 (CH), 30.4 (CH_2), 27.9 (CH), 27.4 (CH_2), 26.0 (CH_3x3), 24.8 (CH_2), 21.5 (CH_3), 20.1 (CH_3), 18.3 (C_{quat}), -5.3 (CH_3x2); HRMS (EI) m/z calcd for $C_{18}H_{37}O_2Si$ ($(M-C_6H_9O)^+$) 313.2557, found 313.2549.

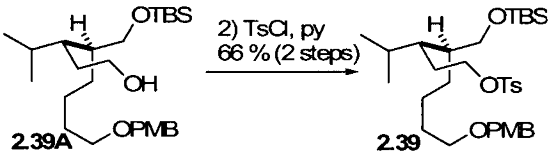


2.38

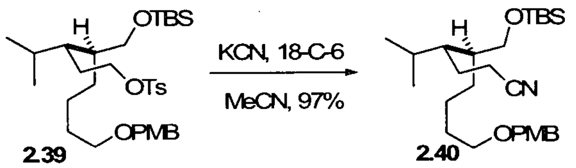
2.39A

(±)-(3*R*,4*S*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-3-isopropyl-8-(4-methoxybenzyloxy)octan-1-ol (2.39A). To a 0 °C solution of 9-BBN dimer (990 mg, 4.06 mmol) in THF (25 mL) was added alkene **2.38** (1.47 g, 3.38 mmol) in THF (8 mL) via cannula. The resulting solution was stirred 18 hours at room temperature. The solution was cooled to 0 °C and sodium hydroxide 3 M (2.25 mL) and hydrogen peroxide 30% (2.25 mL, 20 mmol) were added. The solution was stirred 8 hours at room temperature before being extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The product was used without further purification in the next step. Purification of an aliquot was done on silica gel (elution with 10-30% ethyl acetate in hexanes) to afford **2.39A** as a colorless liquid: IR (neat, cm^{-1}) 3417 (br), 2954 (s), 2934(s), 2853(s), 1611(w), 1511(s), 1469 (m), 1249(s), 1172 (w), 1095 (s), 836 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.41 (s, 2H), 3.78 (s, 3H), 3.64-3.59 (m, 1H), 3.61 (dd,

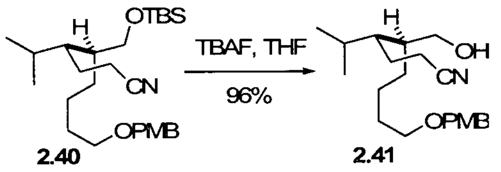
J=10.5, 5.0 Hz, 1H), 3.56-3.53 (m, 1H), 3.47 (dd, J=10.4, 8.6, 1H), 3.41 (dd, J=6.5, 6.5 Hz, 2H), 2.38 (br, 1H), 1.66-1.45 (m, 5H), 1.42-1.34 (m, 3H), 1.28-1.20 (m, 2H), 1.08-0.99 (m, 1H), 0.88 (d, J=8.0 Hz, 3H), 0.87 (s, 9H), 0.84 (d, J=6.7 Hz, 3H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C_{quat}), 130.9 (C_{quat}), 129.4 (CHx2), 113.9 (CHx2), 72.7 (CH_2), 70.1 (CH_2), 64.5 (CH_2), 63.9 (CH_2), 55.3 (CH_3), 41.4 (CH), 41.2 (CH), 31.1 (CH_2), 30.8 (CH), 30.4 (CH_2), 26.7 (CH_2), 26.0 (CH_3x3), 25.1(CH_2), 21.2 (CH_3), 21.1 (CH_3), 18.4 (C_4), -5.3 (CH_3), -5.4 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{23}O$ [(M-$C_{14}H_{25}O_2Si)^+$] 183.1743, found 183.1762.



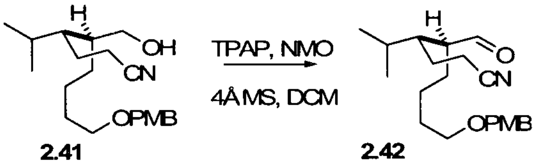
(±)-(3*R*,4*S*)-Toluene-4-sulfonic acid 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-isopropyl-8-(4-methoxy-benzyloxy)-octyl ester (2.39). To a solution of crude alcohol **2.39A** (3.38 mmol) in pyridine (18 mL) at 0 °C was added toluene sulfonyl chloride (1.29 g, 6.76 mmol) and the mixture was stirred 16h at ambient temperature. The mixture was diluted with diethyl ether and poured over HCl 1N at 0°C. The aqueous layer was extracted with diethyl ether (3x). The etheral layers were washed with HCl 1N, then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 10-20% ethyl acetate in hexanes) afforded 1.35 g (66% over 2 steps) of **2.39** as a colorless oil: IR (neat cm^{-1}) 2954 (s), 2930 (s), 2857 (s), 1613 (w), 1513 (s), 1464 (m), 1362 (s), 1248 (s), 1177 (s), 1097 (s), 836 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H) 7.31 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.40 (s, 2H), 4.00-3.94 (m, 2H), 3.78 (s, 3H), 3.48-3.29 (m, 4H), 2.41 (s, 3H), 1.66-1.48 (m, 6H), 1.37-0.88 (m, 5H), 0.82 (s, 9H), 0.77 (d, J=6.7 Hz, 6H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C_{quat}), 144.6 (C_{quat}), 133.4 (C_{quat}), 130.8 (C_{quat}), 129.9 (CHx2), 129.4 (CHx2), 128.0 (CHx2), 113.8 (CHx2), 72.7 (CH_2), 71.0 (CH_2), 70.1 (CH_2), 64.1 (CH_2), 55.4 (CH_3), 41.3 (CH), 40.5 (CH), 30.3 (CH_2), 29.4 (CH), 27.3 (CH_2), 27.3 (CH_2), 26.0 (CH_3x3), 25.0 (CH_2), 21.7 (CH_3), 20.8 (CH_3), 20.3 (CH_3), 18.3 (C_{quat}), -5.3 (CH_3), -5.4 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{23}O_2$ [(M- $C_{21}H_{31}O_4SSi)^+$] 199.1693, found 199.1702.



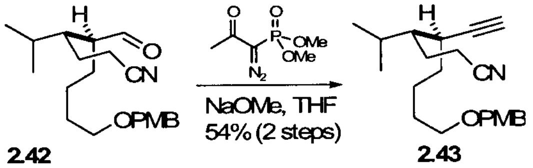
(±)-(4*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-4-isopropyl-9-(4-methoxybenzyloxy) nonanenitrile (2.40). To a solution of tosylate **2.39** (3.00g, 4.9 mmol) in acetonitrile (50 mL) was added 18-crown-6 (3.89g, 14.7 mmol) followed by potassium cyanide (957 mg, 14.7 mmol). The mixture was stirred 16h at ambient temperature, then diluted with diethyl ether and poured over water. The aqueous phase was extracted with diethyl ether (3x). The etheral layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 10-30% ethyl acetate in hexanes) afforded 2.20g (97%) of **2.40** as a light yellow oil: IR (neat, cm^{-1}) 2954 (s), 2930 (s), 2857 (s), 2247 (w), 1612 (m), 1513 (s), 1464 (m), 1248 (s), 1172 (w), 1092 (s), 836 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.41 (s, 2H), 3.78 (s, 3H), 3.54-3.44 (m, 2H), 3.41 (dd, J = 6.5, 6.5 Hz, 2H), 2.32 (dd, J = 7.9, 7.9 Hz, 2H), 1.76-1.64 (m, 2H), 1.60-1.46 (m, 4H), 1.42-1.05 (m, 5H), 0.87 (d, J=8.4 Hz, 3H), 0.86 (s, 9H), 0.85 (d, J=6.9 Hz, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C_{quat}), 130.7 (C_{quat}), 129.4 (CHx2), 120.3 (C_{quat}), 113.8 (CHx2), 72.7 (CH_2), 70.0 (CH_2), 64.4 (CH_2), 55.4 (CH_3), 44.3 (CH), 41.0 (CH), 30.3 (CH_2), 29.1 (CH), 27.4 (CH_2), 26.0 (CH_3x3), 25.0 (CH_2), 24.1 (CH_2), 20.7 (CH_3), 20.5 (CH_3), 18.3 (C_{quat}), 17.2 (CH_2), -5.3 (CH_3), -5.4 (CH_3); HRMS (EI) m/z calcd for $C_{15}H_{28}NOSi$ [(M- $C_{12}H_{19}O_2$) $^+$] 266.1935, found 266.1917.



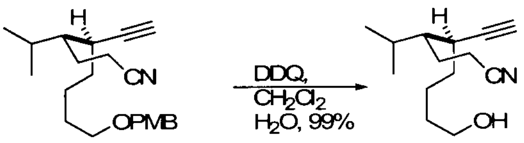
(±)-(4*R*,5*S*)-5-(Hydroxymethyl)-4-isopropyl-9-(4-methoxybenzyloxy)nonanenitrile (2.41). To a solution of silylated enol ether **2.40** (117 mg, 0.253 mmol) in tetrahydrofuran (2.5 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.759 mL, 0.759 mmol). The mixture was stirred for 3 h at ambient temperature before water was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in* *vacuo*. Purification of the residue on silica gel (elution with 10-50% ethyl acetate in hexanes) afforded 84.6 mg (96%) of **2.41** as a light yellow oil: IR (neat, cm^{-1}) 3448(br), 2936 (s), 2868 (s), 2245(w), 1613 (m), 1513 (s), 1465 (m), 1248 (s), 1174 (m), 1095 (m), 1035 (s), 821 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.61-3.46 (m, 2H), 3.41 (dd, J = 6.3, 6.3 Hz, 2H), 2.35 (dd, J = 7.7, 7.7 Hz, 2H), 1.76-1.47 (m, 7H), 1.45-1.05 (m, 5H), 0.89 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (C_{quat}), 130.7 (C_{quat}), 129.4 (CHx2), 120.5 (C_{quat}), 113.9 (CHx2), 72.7 (CH_2), 70.0 (CH_2), 64.0 (CH_2), 55.4 (CH_3), 43.9 (CH), 41.4 (CH), 30.2 (CH_2), 29.4 (CH), 27.3 (CH_2), 25.0 (CH_2), 24.0 (CH_2), 20.9 (CH_3), 20.4 (CH_3), 17.6 (CH_2); HRMS (EI) m/z calcd for $C_{21}H_{33}NO_3$ [M^+]: 347.2460, found 347.2453.



(±)-(4*R*,5*S*)-5-Formyl-4-isopropyl-9-(4-methoxybenzyloxy)nonanenitrile (2.42). Procedure C: Molecular sieves 4 Å (1.19 g), alcohol **2.41** (3445 mg, 1.01 mmol), dichloromethane (10 mL), NMO (237 mg, 2.02 mmol) , TPAP (17.7 mg, 0.05 mmol), elution with 70% ethyl acetate in hexanes. The product was used without further purification in the next step.

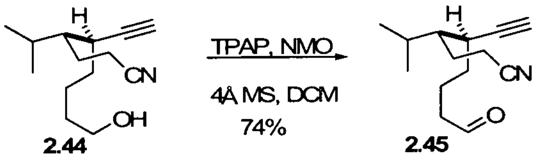


(±)-(4*R*,5*S*)-5-Ethynyl-4-isopropyl-9-(4-methoxy-benzyloxy)-nonanenitrile (2.43). To a -78 °C solution of sodium methoxide (109 mg, 2.02 mmol) in THF (5 mL) was added dimethyl-1-diazo-2-oxopropylphosphonate[243] (388 mg, 2.02 mmol). The resulting yellow solution was stirred 20 minutes. Crude aldehyde **2.42** (1.01 mmol) in THF (2.5 mL) was cannulated and the resulting solution was allowed to reach room temperature slowly and stirred overnight. The reaction mixture was quenched with a saturated solution of sodium bicarbonate and extracted 3x with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 25% ethyl acetate in hexanes) afforded aldehyde **2.42** (52.6 mg) and 188 mg (54%, 64% BRSM) of **2.43** as a light yellow oil: IR (neat, cm^{-1}) 3290 (m), 2938 (s), 2865 (s), 2244 (w), 1613 (m), 1513 (s), 1484 (m), 1247 (s), 1173 (w), 1098 (m), 1035 (m), 820 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.44 (dd, J = 6.3, 6.3 Hz, 2H), 2.50-2.41 (m, 2H), 2.39-2.30 (m, 1H), 2.06 (d, J=2.6 Hz, 1H), 1.95-1.87 (m, 2H), 1.81-1.71 (m, 2H), 1.67-1.57 (m, 3H), 1.51-1.36 (m, 3H), 0.92 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (C_{quat}), 130.8 (C_{quat}), 129.4 (CHx2), 119.9 (C_{quat}), 113.9 (CHx2), 86.1(C_{quat}), 72.7 (CH_2), 71.4 (CH), 70.0 (CH_2), 55.4 (CH_3), 46.0 (CH), 33.3 (CH), 31.6 (CH_2), 29.7 (CH_2), 28.6 (CH), 24.9 (CH_2), 24.1 (CH_2), 22.2 (CH_3), 18.6 (CH_3), 16.8 (CH_2); HRMS (EI) m/z calcd for $C_{22}H_{31}NO$ [M^+]: 341.2355, found 341.2365.

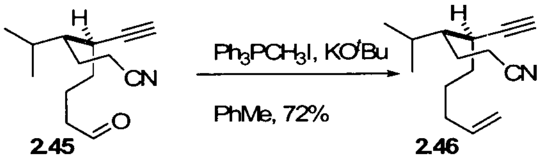


2.43 2.44

(±)-(4*R*,5*S*)-5-Ethynyl-9-hydroxy-4-isopropylnonanenitrile (2.44). To a solution of alkyne **2.43** (72.7 mg, 0.213 mmol) in dichloromethane (2.2 mL) and water (0.125 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (72.5 mg, 0.319 mmol) . The mixture was stirred at ambient temperature for 1h before a saturated solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane and the organic layers were washed with a saturated solution of sodium bicarbonate, then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 10-40% ethyl acetate in hexanes) afforded 49.8 mg (100%) of **2.44** as a yellow oil: IR (neat, cm^{-1}) 3428 (br), 3299 (m), 2919 (s), 2855 (m), 2246 (w), 1463 (m), 1053 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (dd, J=6.4, 6.4 Hz, 2H), 2.51-2.43 (m, 2H), 2.41-2.32 (m, 1H), 2.06 (d, J=2.6 Hz, 1H), 1.96-1.88 (m, 1H), 1.82-1.69 (m, 2H), 1.66-1.37 (m, 8H), 0.92 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.9 (C_{quat}), 86.0 (C_{quat}), 71.5 (CH), 62.9 (CH_2), 45.9 (CH), 33.4 (CH), 32.6 (CH_2), 31.5 (CH_2), 28.6 (CH), 24.3 (CH_2), 24.1 (CH_2), 22.2 (CH_3), 18.5 (CH_3), 16.7 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{22}NO$ [$(M-H)^+$]: 220.1696, found 220.1690.

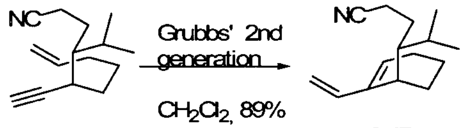


(±)-(4*R*,5*S*)-5-Ethynyl-8-formyl-4-isopropyloctanenitrile (2.45). Procedure C: Molecular sieves 4 Å (411 mg), alcohol **2.44** (77.0 mg, 0.348 mmol), dichloromethane (3.5 mL), NMO (81.5 mg, 0.696 mmol), TPAP (6.1 mg, 0.017 mmol). The reaction was stirred for 1h and directly purified by flash chromatography (elution with 30% ethyl acetate in hexanes). The desired aldehyde **2.45** was obtained (56.8 mg, 74%) as a colorless oil: IR (neat, cm^{-1}) 3302 (m), 2958 (s), 2925 (s), 2873 (m), 2242 (w), 1723 (s), 1457 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (dd, *J*=1.6, 1.6 Hz, 1H), 2.52-2.33 (m, 5H), 2.09 (d, *J*=2.6 Hz, 1H), 1.96-1.88 (m, 2H), 1.80-1.76 (m, 2H), 1.75-1.64 (m, 1H), 1.52-1.37 (m, 3H), 0.93 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2 (CH), 119.8 (C_{quat}), 85.4 (C_{quat}), 71.9 (CH), 46.0 (CH), 43.6 (CH_2), 33.3 (CH), 31.1 (CH_2), 28.6 (CH), 24.0 (CH_2), 22.1 (CH_3), 20.6 (CH_2), 18.5(CH_3), 16.7 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{20}NO$ [(M-H)$^+$]: 218.1539 , found 218.1570.



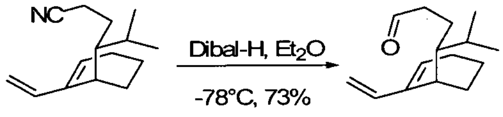
(±)-(4*R*,5*S*)-5-Ethynyl-4-isopropyldec-9-enenitrile (2.46). To a suspension of methyltriphenylphosphonium iodide (314.1 mg, 0.777 mmol) in toluene (2 mL) was added potassium *tert*-butoxide (1 M solution in THF, 0.777 mL, 0.777 mmol). The resulting yellow suspension was stirred 20 minutes. A solution of aldehyde **2.45** (56.8 mg, 0.259 mmol) in toluene (1 mL) was then cannulated and the reaction was stirred at reflux for 45 minutes. After the reaction was cooled to room temperature, the reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-10% ethyl acetate in hexanes) afforded 40.6 mg (72%) of **2.46** as a colorless oil: IR (neat, cm^{-1}) 3307 (m), 2929 (s), 2874 (m), 2247 (w), 1723 (m), 1639 (w), 1462 (m); ^{1}H

NMR (500 MHz, $CDCl_3$) δ 5.83-5.75 (m, 1H), 5.01 (dd, *J*=17.1, 1.6 Hz, 1H), 4.95 (dd, *J*=10.2, 1.2 Hz, 1H), 2.51-2.42 (m, 2H), 2.40-2.33 (m, 1H), 2.10-2.05 (m, 3H), 1.94-1.90 (m, 1H), 1.81-1.66 (m, 3H), 1.50-1.23 (m, 4H), 0.92 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6 (CH), 120.3 (C_{quat}), 115.0 (CH_2), 86.1 (C_{quat}), 71.4 (CH), 46.0 (CH), 33.6 (CH_2), 33.2 (CH), 31.1 (CH_2), 28.6 (CH), 27.3 (CH_2), 24.1 (CH_2), 22.3 (CH_3), 18.6 (CH_3), 16.8 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{23}N$ [M^+]: 217.1830, found 217.1701.



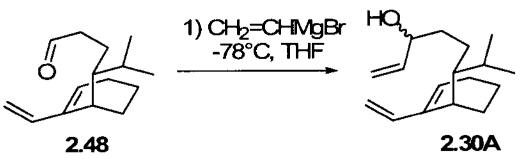
2.46 2.47

(±)-(4*S*,1'*R*)-5-Methyl-4-(2-vinylcyclohex-2-enyl)hexanenitrile (2.47). A solution of ene-yne **2.46** (128 mg, 0.59 mmol) in dichloromethane (20 mL) was degassed with argon for 30 min. 2nd generation Grubb's catalyst (51 mg, 0.06 mmol) was added and the mixture was stirred under ethylene atmosphere (1 atm.) for 16 h. The solvent was evaporated and the residue was purified on silica gel (elution with 0-10% ethyl acetate in hexanes) afforded 115 mg (89%) of **2.47** as a colorless oil: IR (neat, cm^{-1}) 2930 (s), 2870 (m), 2248 (s), 1728 (m), 1632 (w), 1463 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, *J*=17.7, 11.1 Hz, 1H), 5.98 (dd, *J*=4.3, 4.3 Hz, 1H), 5.06 (d, *J*=17.7 Hz, 1H), 4.94 (d, *J*=11.1 Hz, 1H), 2.76 (br, 1H), 2.22-2.17 (m, 2H), 2.13-1.97 (m, 2H), 1.77-1.58 (m, 4H), 1.52-1.43 (m, 2H), 1.38-1.26 (m, 2H), 0.96 (d, *J*=6.6 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (CH), 139.1 (C_{quat}), 131.7 (CH), 120.4 (C_{quat}), 111.8 (CH_2), 45.9 (CH), 35.8 (CH), 30.9 (CH), 26.0 (CH_2), 25.8 (CH_2), 23.6 (CH_2), 21.8 (CH_3), 21.5 (CH_2), 21.3 (CH_3), 18.0 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{23}N$ [M^+]: 217.1830, found 217.1818.

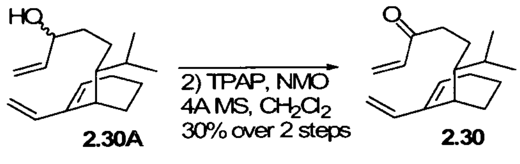


2.47 2.48

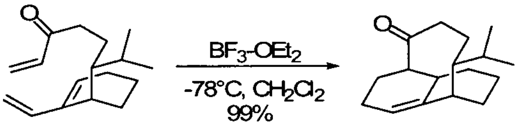
(±)-(4*S*,1'*R*)-5-Methyl-4-(2-vinyl-cyclohex-2-enyl)-hexanal (2.48). To a solution of nitrile **2.47** (60 mg, 0.28 mmol) in diethyl ether (3 mL) was added a 1M solution of di-isobutylaluminium hydride in dichloromethane (0.840 mL, 0.84 mmol) at -78 °C. The mixture was stirred for 3h before being quenched at 0 °C with a 1M aqueous solution of tartaric acid. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with a saturated solution of sodium bicarbonate, then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Aldehyde **2.48** was found to be analytically pure and 44 mg (73%) of **2.48** as a colorless oil was obtained. IR (neat, cm^{-1}) 2956 (m), 2929 (s), 1725 (s), 1462 (m); ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.62 (t, J=1.8 Hz, 1H), 6.15 (dd, J=17.7, 11.0 Hz, 1H), 5.94 (dd, J=4.6, 4.6 Hz, 1H), 5.05 (d, J=17.7 Hz, 1H), 4.91 (d, J=11.1 Hz, 1H), 2.80-2.72 (m, 1H), 2.38-2.30 (m, 2H), 2.06-2.02 (m, 2H), 1.75-1.56 (m, 3H), 1.51-1.30 (m, 5H), 0.95 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 203.5 (CH), 139.6 (C$_{\text{quat}}$), 139.4 (CH), 131.2 (CH), 111.5 (CH$_2$), 45.5 (CH), 45.3 (CH$_2$), 36.1 (CH), 31.2 (CH), 25.8 (CH$_2$), 23.5 (CH$_2$), 21.9 (CH$_3$), 21.8 (CH$_2$), 21.6 (CH$_2$), 21.4 (CH$_3$); HRMS (EI) m/z calcd for C$_{14}$H$_{21}$O [(M-CH$_3$)$^+$]: 205.1587, found 205.1573.



(±)-(3*R*,6*S*,1'*R*)-7-Methyl-6-(2-vinylcyclohex-2-enyl)oct-1-en-3-ol and (±)-(3*S*,6*S*,1'*R*)-7-Methyl-6-(2-vinylcyclohex-2-enyl)oct-1-en-3-ol (2.30A). To a -78 °C solution of aldehyde **2.48** (5.7 mg, 0.026 mmol) in tetrahydrofuran (1 mL) was added a 1M solution of vinylmagnesium bromide in tetrahydrofuran (129 μL, 0.129 mmol). The mixture was stirred for 2 hours during which time the solution warmed up to -20 °C before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The material was used crude in the next step.

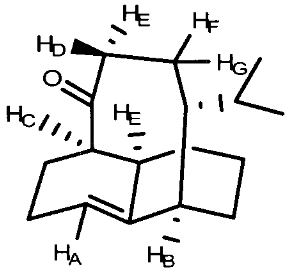


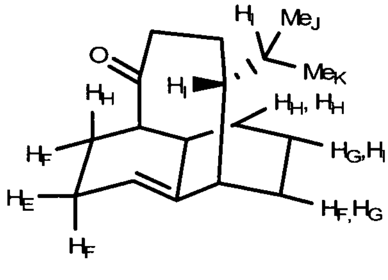
(±)-(6*S*,1'*R*)-7-Methyl-6-(2-vinylcyclohex-2-enyl)oct-1-en-3-ol (2.30). Procedure C: Molecular sieves (72 mg), alcohol **2.30A** (crude, 0.026 mmol), dichloromethane (1 mL), NMO (6.1 mg, 0.052 mmol), TPAP (0.5 mg, 0.0013 mmol), elution with ethyl acetate. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 1.9 mg (30% over 2 steps) of **2.30** as a colorless oil. IR (neat, cm^{-1}) 2932 (s), 2871 (m), 1681 (m), 1461 (m), 1402 (m), 989 (m); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.30-6.09 (m, 3H), 5.94 (s, 1H), 5.76 (dd, *J*=10.3, 1.4 Hz, 1H), 5.06 (d, *J*=17.3 Hz, 1H), 4.91 (d, *J*=11.2 Hz, 1H), 2.79-2.68 (m, 1H), 2.49 (dd, *J*=7.3, 7.3 Hz, 1H), 2.36-2.32 (m, 1H), 2.05-2.03 (m, 2H), 1.75-1.56 (m, 3H), 1.51-1.27 (m, 5H), 0.95 (d, *J*=6.5 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.1 (C$_{quat}$), 140.0 (C$_{quat}$), 139.9 (CH), 137.0 (CH), 131.5 (CH), 128.2 (CH$_2$), 111.6 (CH$_2$), 46.1 (CH$_2$), 41.5 (CH), 36.4 (CH$_2$), 31.6 (CH$_2$), 26.1 (CH), 24.4 (CH), 23.9 (CH$_3$), 22.3 (CH$_2$), 21.9 (CH$_3$), 21.7 (CH$_2$); HRMS (EI) m/z calcd for $C_{17}H_{26}O$ [M$^+$]: 246.1984, found 246.1968.

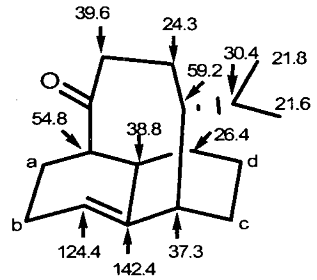


2.30 **2.31**

(±)-(5*R*,9*R*,10*S*,14*R*)-9-Isopropyl-tricyclo[8.4.0.0^{5,14}]tetradec-1-en-6-one (2.31). To a solution of triene **2.30** (1.1 mg, 0.004) in dichloromethane (1 mL) was added trifluoroborane etherate (1 drop) at -78 °C. The mixture was stirred for 30 min. before being quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with dichloromethane and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 1.1 mg (100%) of **2.31** as a colorless oil. IR (neat, cm^{-1}): 2927 (s), 2870 (m), 1729 (w), 1688 (s), 1462 (m), 1272 (w). HRMS (EI) m/z calcd for $C_{17}H_{26}O$ [M$^+$]: 246.1984, found 246.1975.







carbons a,b,c and d : 23.1, 23.1, 22.9, 22.7

H^1: C_6D_6, 300 MHz

H	Chemical shift (δ)	COSY	NOESY	HMQC	HMBC
A	5.55-5.52 (m, 1H)	E	B(s), D(w), E(s), I(s)	124.4	-
B	2.91-2.87 (m, 1H)	G, I	G(s), I(s), J(s)	37.3	-
C	2.77-2.74 (m, 1H)	F	E(s), F(s), H(w)	54.8	142.4, 38.8, 22.9 (v.w.)
D	2.34 (dd, *J*=11.6, 8.1 Hz, 1H)	E, G	E(s), F(w), H(s), I(s)	39.6	59.2, 24.3
E	2.07-1.94 (m, 3H)	A, D, F, H	C(w), D(s), F(s), H(w)	39.6, 38.8, 23.1	142.4, 124.4, 59.2, 54.8, 24.3, abcd
F	1.75-1.54 (m, 4H)	C, E, G, H	C (m), E (s), G (s), H (s), K (m)	24.3, 23.1, 23.1, 22.9, 22.7	124.4, 59.2, 54.8, 39.6, 37.3, 30.4, abcd
G	1.53-1.33 (m, 3H)	B, D, F, I	B(m), F(s), H(w), I(s)		59.2, 39.6, 37.3, 30.4, 26.4, abcd
H	1.29-1.18 (m, 3H)	E, F	D (s), E(w), F(s), G(w)	26.4, 23.1	54.8, 38.8, abcd
I	1.17-0.85 (m, 3H)	B, G, J, K	B(w), D(s), G (s), H(w), J(s), K(s)	59.2, 30.4, 23.1	59.2, 39.6, 37.3, 30.4, 26.4, abcd, 21.8, 21.6
J	0.80 (d, *J*=6.2 Hz, 3H)	I	B(s), I(s)	21.8	59.2, 30.4, 21.8, 21.6
K	0.77 (d, *J*=6.1 Hz, 3H)	I	F(s), I(s)	21.6	59.2, 30.4, 21.8, 21.6

[a] Abbreviations used: (s) = strong, (m)= medium, (w)= weak and (v.w.)= very weak; abcd = 23.1, 23.1, 22.7 and/or 22.9.

C^{13}: C_6D_6, 75 MHz

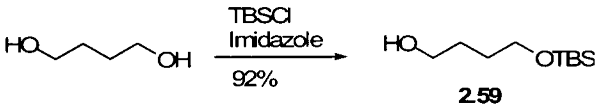
Chemical shift (δ)	Multiplicity	HMBC interactions
214.2	C_{quat}	-
142.4	C_{quat}	C, E
124.4	CH	E, F
59.2	CH	D, E, F, G, I, J, K
54.8	CH	E, F, H
39.6	CH_2	F, G, I
38.8	CH	C, H
37.3	CH	F, G, I
30.4	CH	F, G, I, J, K
26.4	CH_2	E, G, I
24.3	CH_2	D, E, I
23.1	CH_2	E, F, G, H, I
23.1	CH_2	
22.9	CH_2	
22.7	CH_2	
21.8	CH_3	I, J, K
21.6	CH_3	

Determination of this regio-isomer:

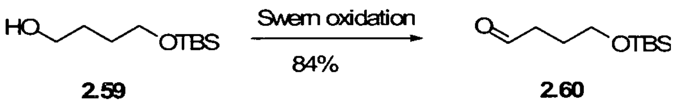
1- Carbon 142.4 sees proton H_c by HMBC. Only possible if H_c is 2 carbons away from alkene carbon.

2- Carbon 38.8 sees protons H_c and H_H by HMBC. Further proof that H_c is on the carbon adjacent to the ring junction.

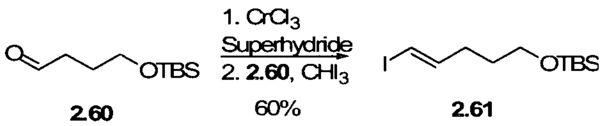
3- By NOESY, H_A, H_B, H_D all see each other meaning that H_D is the proton facing the 6-membered ring. Since H_D and H_H see each other by NOESY this means that the carbon a has the H_H up. This NOESY interaction is impossible in the other regio-isomer.



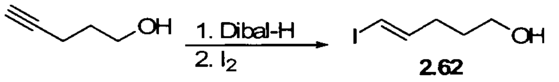
4-(*tert*-Butyl-dimethyl-silanyloxy)-butan-1-ol (2.59). To a solution of 1,4-butanediol (30.0 g, 333 mmol) in *N,N*-dimethylformamide (60 mL) was added imidazole (5.11 g, 75 mmol) followed by *tert*-butyldimethylchlorosilane (9.04 g, 60 mmol). The mixture was stirred for 1.5h at ambient temperature before it was poured over a saturated solution of ammonium chloride and extracted with diethyl ether (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30% diethyl ether in petroleum ether) afforded 11.24 g (92%) of **2.59** as a colorless oil. Full characterization is available through the literature.[244]



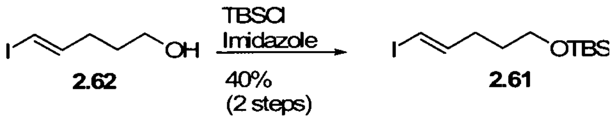
4-(*tert*-Butyl-dimethyl-silanyloxy)-butyraldehyde (2.60). Procedure A: oxalyl chloride (0.733 mL, 8.4 mmol), dimethyl sulfoxide (0.874 mL, 12.4 mmol), alcohol **2.59** (1.01 g, 4.94 mmol), dichloromethane (18.6+5.6+4.4 mL), triethylamine (3.4 mL, 24.7 mmol). Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 834.8 mg (84%) of **2.60** as a yellow oil. Full characterization is available through the literature.[245]



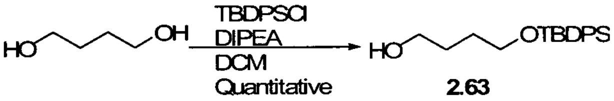
(*E*)-*tert*-Butyl-(5-iodo-pent-4-enyloxy)-dimethyl-silane (2.61). To a suspension of chromium(III) chloride (3.97 g, 25.1 mmol) in tetrahydrofuran (41 mL) at 0 °C was added a 1M solution of super hydride (18.8 mL, 18.8 mmol). The purple mixture was stirred at ambient temperature for 18 h and evolved to a dark grey suspension. The mixture was cooled to 0 °C and a solution of aldehyde **2.60** (634.8 mg, 3.14 mmol) and iodoform (2.50 g, 6.28 mmol) in tetrahydrofuran (16 mL) was added dropwise and stirred at 0°C for 3h. The mixture was poured into water and extracted with diethyl ether (3x). The ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-20% ethyl acetate in hexanes) afforded 609 mg (60%) of **2.61** as a yellow liquid. Full characterization is available through the literature.[71]



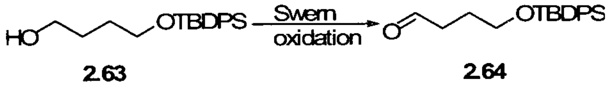
(*E*)-5-Iodo-pent-4-en-1-ol (2.62). Followed the procedure described by Kelly and co-workers.[70]



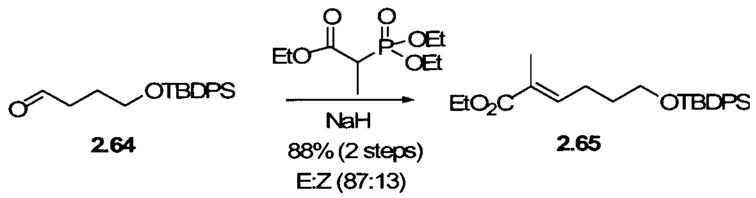
(*E*)-*tert*-Butyl-(5-iodo-pent-4-enyloxy)-dimethyl-silane (2.61). To a crude mixture of alcohol 2.62 (21.5 mmol) in THF (110 mL) was added imidazole (3.66 g, 53.7 mmol) then TBSCl (3.88 g, 25.8 mmol). The heterogeneous solution was stirred overnight before quenching with a saturated solution of ammonium chloride. The mixture was extracted 3x with diethyl ether. The ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-5% ethyl acetate in hexanes) afforded 2.80 g of **2.61** as a yellow liquid. Full characterization is available through the literature.[71]



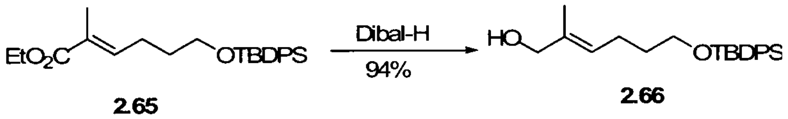
4-(*tert*-Butyl-diphenyl-silanyloxy)-butan-1-ol (2.63). To a solution of 1,4-butanediol (5.0 g, 55 mmol) in DCM (10 mL) was added DIPEA (10 mL, 57 mmol) followed by *tert*-butyldiphenylchlorosilane (5 mL, 18 mmol). The mixture was stirred for 18 hrs at ambient temperature. The solvent was removed *in vacuo*. Purification of the residue on silica gel (elution with 20-30% ethyl acetate in hexanes) afforded 6.64 g (quantitative) of **2.63** as a colorless oil. Full characterization is available through the literature.[246]



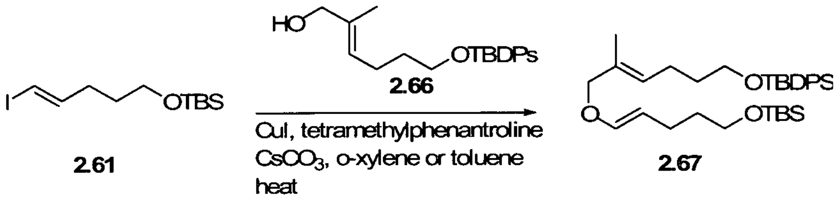
4-(*tert*-Butyl-diphenyl-silanyloxy)-butyraldehyde(2.64). Procedure A: oxalyl chloride (10.6 mL, 121 mmol), dimethyl sulfoxide (12.6 mL, 178 mmol), alcohol **2.63** (23.4 g, 71.2 mmol), dichloromethane (269+81+63 mL), triethylamine (49.6 mL, 356 mmol). The mixture was used crude in the next step.



(*E*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-2-methyl-hex-2-enoic acid ethyl ester (2.65). To a 0 °C solution of triethyl-2-phosphonoproprionate (18.6 mL, 85.4 mmol) in THF (437 mL) was added NaH (3.42 g, 142 mmol). The resulting solution was stirred for 1 hour at room temperature before adding aldehyde **2.64** (crude mixture) in THF (131 mL). The solution was left warming up overnight before the reaction was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with diethyl ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The reaction mixture was used crude in the next step. However, purification of an aliquot on silica gel (elution with 5% ethyl acetate in hexanes) afforded **2.65** (87:13; E:Z) as a yellow oil. Full characterization is available through the literature.[246]

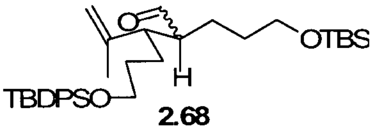


(*E*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-2-methyl-hex-2-en-1-ol (2.66). To a -78 °C solution of ester **2.65** (crude mixture, 71.2 mmol) in DCM (690 mL) was added Dibal-H in toluene (1.0 M, 251 mL, 251 mmol). The solution was stirred 30 minutes and quenched at -78 °C with water (25 mL) followed by NaOH 4 M (25 mL) and finally, more water (50 mL). The mixture was left warming up to room temperature before magnesium sulfate was added. The mixture was then filtered (rinsing with DCM). Magnesium sulfate was added once more to the filtrate before the mixture was filtered and concentrated *in vacuo*. Flash chromatography (elution with 15% ethyl acetate in hexanes) afforded alcohol **2.66** (13.1 g, 50%) and a 2:1 mixture of alcohol **2.66** and its *Z* isomer (8.18 g, 31%) as yellow oils. IR (neat, cm^{-1}) 3334 (br), 2931 (s), 2858 (s), 1428 (m), 1112 (s), 702 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.43-7.34 (m, 6H), 5.35 (t, *J*=6.0 Hz, 1H), 3.96 (s, 2H), 3.66 (t, *J*=6.3 Hz, 2H), 2.12 (ddd, *J*=7.4, 7.4, 7.4 Hz, 2H), 1.63 (s, 3H), 1.63-1.58 (m, 2H), 1.31 (br, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CHx4), 135.5 (C_{quat}), 134.2 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 126.0 (CH), 69.1 (CH_2), 63.4 (CH_2), 32.5 (CH_2), 27.0 (CH_3x3), 24.0 (CH_2), 19.3 (C_{quat}), 13.7 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{23}O_2Si$ [$(M-C_4H_9)^+$] 311.1462, found 311.1459.



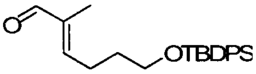
(1'*E*,4*E*)-6-(5-(*tert*-Butyl-dimethyl-silanyloxy)-pent-1-enyloxy)-5-methyl-hex-4-en-1-(*tert*-butyl-diphenyl-silanyl)alcohol (2.67). A sealed tube was loaded with allylic alcohol **2.66** (954 mg, 2.59 mmol), vinyl iodide **2.61** (276.4 mg, 0.847 mmol), copper (I) iodide (16.1 mg, 0.085 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (40.0 mg, 0.169 mmol), cesium carbonate (843 mg, 2.59 mmol) and toluene (0.850 mL). The mixture was stirred for 18 h at 80 °C, filtered over a pad of silica gel (elution with ethyl acetate) and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 0-5% ethyl acetate in hexanes) afforded 314.0 mg (65%) of **2.67** as a light yellow oil. IR (neat, cm^{-1}) 2930 (s), 2857 (s), 1652 (m), 1472 (m), 1255 (m), 1110 (s), 836 (s), 702 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.43-7.34 (m, 6H), 6.19 (d, *J*=12.5 Hz, 1H), 5.40 (dd, *J*=6.6 Hz, 1H), 4.78 (dt, *J*=12.5, 7.4 Hz, 1H), 3.99 (s, 2H), 3.65 (t, *J*=6.3 Hz, 2H), 3.59 (t, *J*=6.4 Hz, 2H), 2.13 (ddd, *J*=7.3, 7.3, 7.3 Hz, 2H), 1.95 (ddd, *J*=7.3, 7.3, 7.3 Hz, 2H), 1.63 (s, 3H), 1.63-1.57 (m, 2H), 1.56-1.50 (m, 2H), 1.04 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1 (CH), 135.7 (CHx4), 134.2 (C_{quat}x2), 131.9 (C_{quat}), 129.7 (CHx2), 128.6 (CH), 127.7 (CHx4), 104.3 (CH), 75.6 (CH_2), 63.5 (CH_2), 62.5 (CH_2), 33.8 (CH_2), 32.4 (CH_2), 27.0 (CH_3x3), 26.1 (CH_3x3), 24.2 (CH_2), 24.1 (CH_2), 19.4 (C_{quat}), 18.5 (C_{quat}), 13.9 (CH_3), -5.1 (CH_3x2); HRMS (EI) m/z calcd for $C_{30}H_{45}O_3Si_2$ [$(M-C_4H_9)^+$] 509.2902, found 509.2907.

Other products that were observed while doing the coupling reaction:



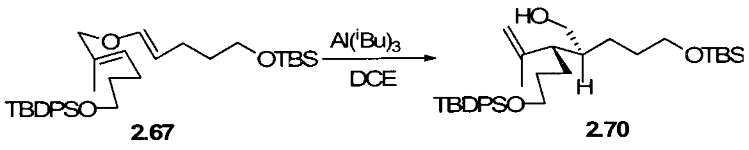
2.68

(±)-(2*S*,3*S*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(tert-butyl-diphenyl-silanyloxy)-3-isopropenyl-hexanal and (±)-(2*R*,3*S*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(tert-butyl-diphenyl-silanyloxy)-3-isopropenyl-hexanal (2.68)
Both epimers were obtained in a 2:1 ratio and were not separable by flash chromatography. (Note: each isomer is considered as one in the following characterization). IR (neat, cm^{-1}) 2930 (s), 2857 (s), 1725 (s), 1428 (m), 1111(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J*=4.6 Hz, 1H), 9.41 (d, *J*=4.4 Hz, 1H), 7.66-7.61 (m, 8H), 7.42-7.34 (m, 12H), 4.85 (s, 1H), 4.80 (s, 1H), 4.72 (s, 1H), 4.69 (s, 1H), 3.68-3.53 (m, 8H), 2.34-2.24 (m, 2H), 1.83-1.32 (m, 18H), 1.56 (s, 3H), 1.55 (s, 3H), 1.04 (s, 9H), 1.02 (s, 9H), 0.86 (s, 18H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5 (CH), 204.8 (CH), 144.6 (C_{quat}), 143.5 (C_{quat}), 135.7 (CHx8), 134.2 (C_{quat}x2), 134.0 (C_{quat}x2), 129.7 (CHx4), 127.7 (CHx8), 115.0 (CH_2), 114.3 (CH_2), 63.7 (CH_2), 63.6 (CH_2), 62.8 (CH_2), 62.6 (CH_2), 54.8 (CH_2), 54.3 (CH_2), 47.6 (CH), 47.3 (CH), 30.5 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 27.0 (CH_3x6), 26.1 (CH_3x3), 26.0 (CH_3x3), 25.7 (CH_2), 25.3 (CH_2), 24.2 (CH_2), 24.2 (CH_2), 19.3 (C_{quat}x4), 18.1 (CH_3), 19.1 (CH_2), -5.2 (CH_3x4); HRMS (EI) m/z calcd for $C_{30}H_{45}O_3Si_2$ [$(M-C_4H_9)^+$] 509.2902, found 509.2927.

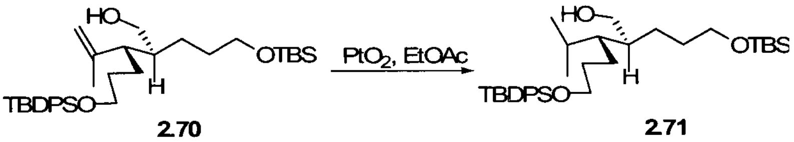


2.69

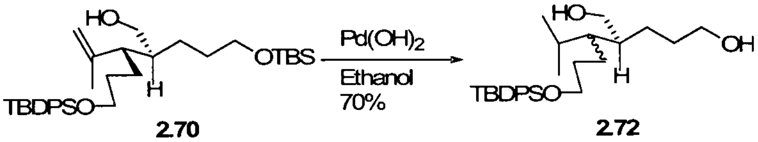
(*E*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-2-methyl-hex-2-enal (2.69). IR (neat, cm^{-1}) 2931 (br), 2857 (s), 2858 (s), 1692 (s), 1428 (m), 1111 (s), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.65-7.62 (m, 4H), 7.44-7.34 (m, 6H), 6.44 (td, *J*=7.4, 1.3 Hz, 1H), 3.69 (t, *J*=6.0 Hz, 2H), 2.44 (ddd, *J*=7.2, 7.2, 7.2 Hz, 2H), 1.75-1.69 (m, 2H), 1.72 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4 (CH), 154.6 (CH), 139.7 (C_{quat}), 135.7 (CHx4), 133.8 (C_{quat}x2), 129.8 (CHx2), 127.8 (CHx4), 63.1 (CH_2), 31.3 (CH_2), 27.0 (CH_3x3), 25.6 (CH_2), 19.3 (C_{quat}), 9.7 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{21}O_2Si$ [$(M-C_4H_9)^+$] 309.1305, found 309.1315.



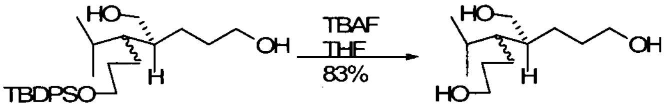
(±)-(2*S*,3*S*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(*tert*-butyl-diphenyl-silanyloxy)-3-isopropenyl-hexan-1-ol (2.70). To a solution enol ether **2.67** (271.2 mg, 0.478 mmol, 9:1 ratio of isomers) in dichloroethane (5 mL) was added a 1 M solution of tri-isobutylaluminum (1.44 mL, 1.44 mmol) in toluene. The mixture was stirred for 18 hours under argon atmosphere before being diluted in hexane (3 mL) and poured over a 1M aq. solution of tartaric acid (3 mL). The resulting solution was vigorously stirred for 20 min. and the organic layer separated. The aqueous layer was extracted with dichloromethane (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 145.8 mg of **2.70** and 18.8 mg of a mixture of isomers (61%) as a light yellow oil. IR (neat, cm^{-1}) 3412 (br), 2930 (s), 2857 (s), 1472 (m), 1428 (m), 1254 (m), 1109 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65-7.62 (m, 4H), 7.42-7.33 (m, 6H), 4.79 (s, 1H), 4.69 (s, 1H), 3.66-3.46 (m, 6H), 2.00-1.94 (m, 1H), 1.63-1.42 (m, 7H), 1.60 (s, 3H), 1.39-1.24 (m, 3H), 1.02 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.2 (C$_{quat}$), 135.7 (CHx4), 134.2 (C$_{quat}$), 134.2 (C$_{quat}$), 129.6 (CHx2). 127.7 (CHx4), 113.1 (CH$_2$), 64.0 (CH$_2$), 63.9 (CH$_2$), 63.6 (CH$_2$), 48.6 (CH), 42.4 (CH), 30.7 (CH$_2$), 30.0 (CH$_2$), 27.0 (CH$_3$x3), 26.1 (CH$_3$x3), 25.8 (CH$_2$), 24.5 (CH$_2$), 19.3 (C$_{quat}$), 18.7 (CH$_3$), 18.5 (C$_{quat}$), -5.2 (CH$_3$x2); HRMS (EI) m/z calcd for $C_{30}H_{47}O_3Si_2$ [(M-C$_4$H$_9$)$^+$] 511.3058, found 511.3080.



(±)-(2*S*,3*R*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(*tert*-butyl-diphenyl-silanyloxy)-3-isopropyl-hexan-1-ol (2.71). Platinum oxide (13.9 mg, 0.0612 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.70** (696.6 mg, 1.220 mmol) in freshly distilled ethyl acetate (12.2 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. Purification of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 652.0 mg of **2.71** (94%) as a light yellow oil. IR (neat, cm^{-1}) 3382 (br), 2954 (s), 2930 (s), 2857 (s), 1471 (m), 1254 (m), 1106 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 4H), 7.42-7.33 (m, 6H), 3.63-3.50 (m, 6H), 1.76-1.56 (m, 3H), 1.52-1.32 (m, 4H), 1.30-1.11 (m, 4H), 1.03 (s, 9H), 0.94 (s, 1H), 0.87 (s, 9H), 0.85 (d, *J*=6.8 Hz, 3H), 0.84 (d, *J*=6.8 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (CHx4), 134.2 (C_{quat}x2), 129.7 (CHx2). 127.7 (CHx4), 64.9 (CH_2), 64.4 (CH_2), 63.6 (CH_2), 44.3 (CH), 42.2 (CH), 33.1 (CH_2), 31.6 (CH_2), 29.5 (CH), 27.0 (CH_3x3), 26.1 (CH_3x3), 24.2 (CH_2), 23.9 (CH_2), 21.2 (CH_3), 20.4 (CH_3), 19.3 (C_{quat}), 18.5 (C_{quat}), -5.1 (CH_3x2); HRMS (EI) m/z calcd for $C_{30}H_{49}O_3Si_2$ [$(M-C_4H_9)^+$] 513.3215, found 513.3239.

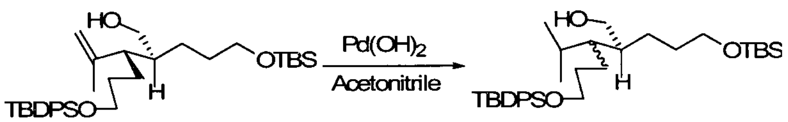


(±)-(2*R*,1'*R*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-pentane-1,5-diol and (±)-(2*S*,1'*R*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-pentane-1,5-diol (2.72). Palladium hydroxide (5.9 mg, 0.008 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.70** (47.7 mg, 0.084 mmol) in ethanol (1 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. Hydrogen was bubbled into the reaction mixture for 15 min. then the reaction was stirred overnight under an atmosphere of hydrogen. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. Purification of the residue on silica gel (elution with 70% ethyl acetate in hexanes) afforded 33.5 mg of **2.72** (70%) as a light yellow oil. Each isomer is considered as one in the following characterization: IR (neat, cm^{-1}) 3337 (br), 2929 (s), 2858 (s), 1472 (m), 1091 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 8H), 7.43-7.34 (m, 12H), 3.69-3.39 (m, 12H), 2.03-1.97 (m, 2H), 1.70 (d, *J*=4.5 Hz, 6H), 1.73-1.67 (m, 2H), 1.60-1.21 (m, 22H), 1.03 (s, 18H), 0.85 (d, *J*=5.8 Hz, 3H), 0.84 (d, *J*=5.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CHx8), 134.2 (C_{quat}), 134.0 (C_{quat}), 131.4 (C_{quat}), 130.6 (C_{quat}), 129.7 (CHx2). 129.6 (CHx2), 127.7 (CHx8), 65.0 (CH_2), 64.8 (CH_2), 64.4 (CH_2), 64.3 (CH_2), 63.3 (CH_2), 63.2 (CH_2), 44.5 (CH), 44.4 (CH), 42.0 (CHx2), 33.2 (CH_2), 33.1 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 29.4 (CHx2), 27.0 (CH_3x6), 25.8 (CH_2x2), 24.2 (CH_2), 23.9 (CH_2), 21.3 (CH_3x2), 20.6 (CH_3), 20.3 (CH_3), 19.3 (C_{quat}x2); HRMS (EI) m/z calcd for $C_{24}H_{33}O_2Si$ [$(M-C_4H_{11}O)^+$] 381.2244, found 381.2203.



2.72 2.73

(±)-(4*R*,5*R*)-4-Hydroxymethyl-5-isopropyl-octane-1,8-diol and (±)-(4*S*,5*R*)-4-Hydroxymethyl-5-isopropyl-octane-1,8-diol (2.73). To a solution of diol **2.72** (10.2 mg, 0.022 mmol) in THF (1 mL) was added a 1.0 M solution of TBAF in THF (0.067 mL, 0.067 mmol). The mixture was stirred overnight before being quenched with water. The aqueous layer was extracted with ethyl acetate (4x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 2-4% methanol in ethyl acetate) afforded 4.0 mg of **2.73** (83%) as a light yellow oil. Each isomer is considered as one in the following characterization: IR (neat, cm^{-1}) 3337 (br), 2926 (s), 2857 (m), 1463 (m), 1056 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 3.67 (m, 12H), 2.02 (s, 2H), 1.74 (s, 2H), 1.71 (s, 2H), 1.67-1.20 (m, 22H), 0.88 (d, *J*=6.8 Hz, 6H), 0.88 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.1 (CH_2), 64.9 (CH_2), 63.5 (CH_2), 63.3 (CH_2x2), 63.2 (CH_2), 44.6 (CH), 44.3 (CH), 41.9 (CHx2), 33.3 (CH_2), 32.9 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 29.7 (CHx2), 25.9 (CH_2x2), 23.9 (CH_2x2), 21.5 (CH_3), 21.2 (CH_3), 20.7 (CH_3), 20.6 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{24}O_3$ [$(M-H_2)^{+}$] 216.1714, found 216.1807.

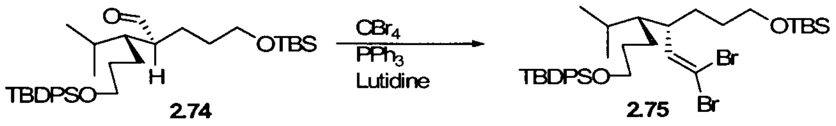


2.70 2.71(mixed)

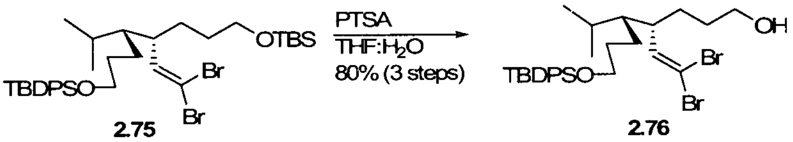
(±)-(2*R*,3*R*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(*tert*-butyl-diphenyl-silanyloxy)-3-isopropyl-hexan-1-ol and (±)-(2*S*,3*R*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(*tert*-butyl-diphenyl-silanyloxy)-3-isopropyl-hexan-1-ol (2.71).

Palladium hydroxide (6.6 mg, 0.009 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.70** (26.7 mg, 0.047 mmol) in acetonitrile (2 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. Hydrogen was bubbled into the reaction mixture for 45 min. then the reaction was stirred overnight under an atmosphere of hydrogen. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. Purification of the residue on silica gel (elution with 12-15% ethyl acetate in hexanes) afforded 17.3 mg of **2.71** (mixed) (64%) as a colorless oil. Each isomer is considered as one in the following characterization: IR (neat, cm^{-1}) 3391 (br), 2930 (s), 1472 (m), 1254 (m), 1106 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 8H), 7.42-7.34 (m, 12H), 3.64-3.37 (m, 12H), 2.01-1.97 (m, 2H), 1.70 (d, *J*=5.2 Hz, 6H), 1.73-1.67 (m, 2H), 1.60-1.24 (m, 20 H), 1.04 (s, 18H), 0.87 (s, 18H), 0.86 (d, *J*=5.8 Hz, 3H), 0.84 (d, *J*=5.8 Hz, 3H), 0.03 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CHx8), 134.2 (C_{quat}), 134.1 (C_{quat}), 131.3 (C_{quat}), 130.8 (C_{quat}), 129.7 (CHx2). 129.6 (CHx2), 127.7 (CHx8), 65.1 (CH_2), 64.9 (CH_2), 64.4 (CH_2), 64.3 (CH_2), 63.6 (CH_2), 63.4 (CH_2), 44.5 (CH), 44.3 (CH), 42.2 (CHx2), 33.3 (CH_2), 33.1 (CH_2), 31.6 (CH_2), 31.0 (CH_2), 29.5 (CHx2), 27.0 (CH_3x6), 26.1 (CH_3x6), 25.9 (CH_2x2), 24.2 (CH_2), 23.9 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 20.6 (CH_3), 20.4 (CH_3), 19.3 (C_{quat}x2), 18.5 (C_{quat}x2), -5.1 (CH_3x4); HRMS (EI) m/z calcd for $C_{30}H_{49}O_3Si_2$ [$(M-C_4H_9)^+$] 513.3215, found 513.3168.

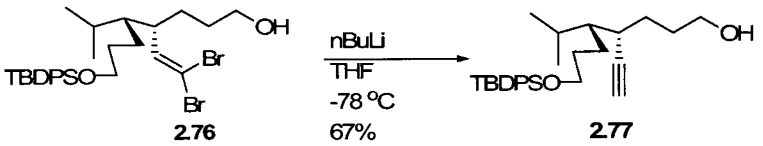
(±)-(2*S*,3*R*)-2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-6-(*tert*-butyl-diphenyl-silanyloxy)-3-isopropyl-hexanal (2.74). Procedure C: Molecular sieves 4 Å (270.8 mg), alcohol **2.71** (124.8 mg, 0.195 mmol), dichloromethane (2.2 mL), NMO (51.3 mg, 0.438 mmol), TPAP (3.8 mg, 0.011 mmol), elution with ethyl acetate. The aldehyde was used crude in the next step.



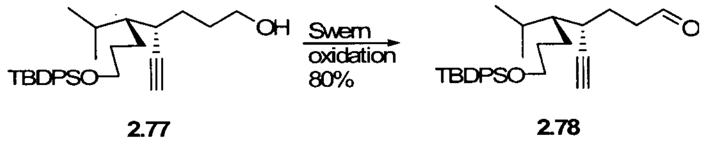
(±)-(4*S*,5*R*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-4-(2,2-dibromo-vinyl)-5-isopropyl-octan-1-(*tert*-butyl-dimethylsilanyl)alcohol (2.75). To a flame-dried flask, carbon tetrabromide (129.3 mg, 0.395 mmol) was diluted in dichloromethane (1 mL). The mixture was cooled to 0 °C before adding triphenylphosphine (217.7 mg, 0.830 mmol). The resulting yellow solution was stirred for 10 minutes before a solution of the crude aldehyde and 2,6-lutidine (0.046 mL, 0.395 mmol) in dichloromethane (1.5 mL) was cannulated. The solution was stirred for 1 hour at 0 °C and 1 hour at RT until the reaction was complete by TLC. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with dichloromethane (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.



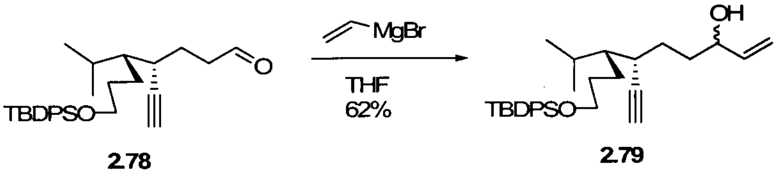
(±)-(4*S*,5*R*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-4-(2,2-dibromo-vinyl)-5-isopropyl-octan-1-ol (2.76). The crude product **2.75** was dissolved in 2 mL of THF and 0.1 mL of H_2O. PTSA (7.5 mg, 0.040 mmol) was added to the reaction and the mixture was stirred overnight. The reaction was quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30% ethyl acetate in hexanes) afforded 95.2 mg of **2.75** (80% over 3 steps) as a light yellow oil. IR (neat, cm^{-1}) 3327 (br), 2955 (s), 2858 (s), 1471 (m), 1427 (m), 1111 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H), 7.42-7.35 (m, 6H), 6.18 (d, J=10.3 Hz, 1H), 3.64-3.58 (m, 4H), 2.42-2.40 (m, 1H), 1.74-1.13 (m, 11H), 1.05 (s, 9H), 0.88 (d, J=6.9 Hz, 3H), 0.82 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9 (CH), 135.7 (CHx4), 134.1 (C_{quat}x2), 129.4 (CHx2). 127.5 (CHx4), 88.1 (C_{quat}), 64.2 (CH_2), 63.0 (CH_2), 48.0 (CH), 46.3 (CH), 33.3 (CH_2), 30.6 (CH_2), 29.3 (CH), 27.8 (CH_2), 27.0 (CH_3x3), 24.0 (CH_2), 22.1 (CH_3), 19.3 (C_{quat}), 18.8 (CH_3); HRMS (EI) m/z calcd for $C_{25}H_{33}O_2SiBr_2$ [$(M-C_4H_9)^+$] 551.0611, found 551.0603.



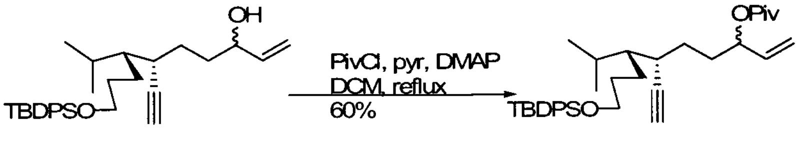
(±)-(4*S*,5*R*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-4-ethynyl-5-isopropyl-octan-1-ol (2.77). To a -78 °C solution of dibromide **2.76** (95.2 mg, 0.156 mmol) in THF (1.6 mL) was added *n*-BuLi (0.312 mL, 0.624 mmol). The reaction was stirred for 2 hours at the same temperature before being quenched with water and warmed to RT. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30% ethyl acetate in hexanes) afforded 47.1 mg of **2.77** (67%) as a light yellow oil. IR (neat, cm^{-1}) 3306 (br), 2955 (s), 2859 (s), 1472 (w), 1427 (w), 1111 (s), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 4H), 7.40-7.36 (m, 6H), 3.67-3.62 (m, 4H), 2.45-2.39 (m, 1H), 2.00 (d, *J*=2.5 Hz, 1H), 1.97-1.90 (m, 1H), 1.81-1.65 (m, 1H), 1.64-1.38 (m, 7H), 1.24-1.20 (m, 2H), 1.03 (s, 9H), 0.88 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CHx4), 134.9 (C_{quat}), 134.2 (C_{quat}), 129.6 (CHx2). 127.7 (CHx4), 87.2 (C_{quat}), 70.6 (CH), 64.3 (CH_2), 62.9 (CH_2), 47.1 (CH), 34.3 (CH), 32.5 (CH_2), 31.4 (CH_2), 29.0 (CH), 28.6 (CH_2), 27.0 (CH_3x3), 24.2 (CH_2), 22.3 (CH_3), 19.3 (C_{quat}), 18.3 (CH_3); HRMS (EI) m/z calcd for $C_{25}H_{33}O_2Si$ [$(M-C_4H_9)^+$] 393.2244, found 393.2250.



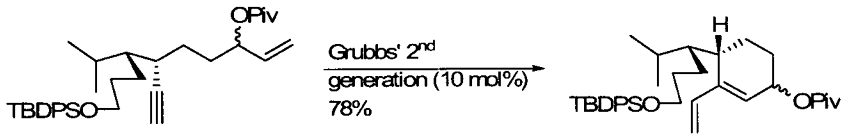
(±)-(4*S*,5*R*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-4-ethynyl-5-isopropyl-octanal (2.78). Procedure B: oxalyl chloride (0.012 mL, 0.134 mmol), dimethyl sulfoxide (0.014 mL, 0.200 mmol), alcohol **2.77** (17.9 mg, 0.040 mmol), dichloromethane (1+1 mL), triethylamine (0.056 mL, 0.400 mmol). Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 14.3 mg (80%) of **2.78** as a light yellow oil. The structure of the aldehyde was confirmed by proton NMR and used directly in the next step.



(±)-(3*R*,6*S*,7*R*)-10-(*tert*-Butyl-diphenyl-silanyloxy)-6-ethynyl-7-isopropyl-dec-1-en-3-ol and (±)-(3*S*,6*S*,7*R*)-10-(*tert*-Butyl-diphenyl-silanyloxy)-6-ethynyl-7-isopropyl-dec-1-en-3-ol (2.79). To a -78 °C solution of aldehyde **2.78** (14.3 mg, 0.032 mmol) in THF (1 mL) was added vinylmagnesium bromide (0.096 mL, 0.096 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 9.5 mg of **2.79** (62%) as a yellow oil. (Each isomer is one.) IR (neat, cm^{-1}) 3306 (br), 2955 (s), 2859 (s), 1470 (w), 1427 (m), 1111(s), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.65 (m, 8H), 7.40-7.34 (m, 12H), 5.90-5.82 (m, 2H), 5.21 (d, *J*=17.2 Hz, 2H), 5.09 (d, *J*=10.4 Hz, 2H), 4.13-4.08 (m, 2H), 3.64 (t, *J*=6.0 Hz, 4H), 2.45-2.38 (m, 2H), 2.00-1.92 (m, 4H), 1.83-1.76 (m, 2H), 1.68-1.35 (m, 16H), 1.26-1.19 (m, 2H), 1.03 (s, 18H), 0.88 (d, *J*=6.7 Hz, 6H), 0.88 (d, *J*=7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3 (CH), 141.2 (CH), 135.7 (CHx8), 134.3 (C_{quat}x4), 129.7 (CHx4), 127.7 (CHx8), 115.0 (CH_2), 114.8 (CH_2), 87.2 (C_{quat}), 87.1 (C_{quat}), 73.4 (CH), 73.0 (CH), 70.7 (CHx2), 64.4 (CH_2x2), 47.1 (CHx2), 35.6 (CH_2), 35.4 (CH_2), 34.4 (CH), 34.3 (CH), 32.5 (CH_2x2), 29.1 (CH), 29.0 (CH), 28.3 (CH_2), 27.9 (CH_2), 27.0 (CH_3x6), 24.2 (CH_2x2), 22.4 (CH_3x2), 19.4 (C_{quat}x2), 18.3 (CH_3x2); HRMS (EI) m/z calcd for $C_{27}H_{35}O_2Si$ [$(M-C_4H_9)^+$] 419.2401, found 419.2377.



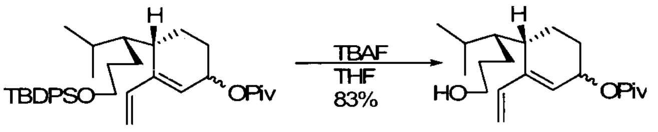
(±)-(1*R*,4*S*,5*R*)-2,2-Dimethyl-propionic acid 8-(*tert*-butyl-diphenyl-silanyloxy)-4-ethynyl-5-isopropyl-1-vinyl-octyl ester and (±)-(1*S*,4*S*,5*R*)-2,2-Dimethyl-propionic acid 8-(*tert*-butyl-diphenyl-silanyloxy)-4-ethynyl-5-isopropyl-1-vinyl-octyl ester (2.80). To a solution of alcohol **2.79** (44.9 mg, 0.094 mmol) in dichloromethane (0.5 mL) was added DMAP (2.3 mg, 0.022 mmol) and pyridine (0.024 mL, 0.282 mmol) followed by pivaloyl chloride (0.027 mL, 0.216 mmol). The solution was stirred at 40 °C for 18 hours. The reaction was quenched with a saturated solution of ammonium chloride, extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 31.7 mg of **2.80** (60%) as a yellow oil. (Each isomer is one) IR (neat, cm^{-1}) 2959 (s), 2866 (m), 1726 (s), 1474 (w), 1426 (w), 1277 (w), 1153 (s), 1111 (s), 700 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 8H), 7.40-7.34 (m, 12H), 5.81-5.71 (m, 2H), 5.27-5.18 (m, 2H), 5.13 (d, J=10.7 Hz, 2H), 3.65-3.60 (m, 4H), 2.46-2.34 (m, 2H), 2.00 (d, J=2.2 Hz, 1 H), 1.99 (d, J=2.2 Hz, 1H), 1.94-1.86 (m, 4H), 1.70-1.31 (m, 16H), 1.25 (s, 18H), 1.19 (s, 18H), 0.87 (d, J=6.8 Hz, 6H), 0.87 (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (C_{quat}), 174.1 (C_{quat}), 136.8 (CH), 136.7 (CH), 135.7 (CHx8), 134.2 (C_{quat}x4), 129.6 (CHx4), 127.7 (CHx8), 116.4 (CH_2), 116.2 (CH_2), 86.9 (C_{quat}), 86.8 (C_{quat}), 74.3 (CH), 73.7 (CH), 70.8 (CH), 70.7 (CH), 64.3 (CH_2x2), 47.0 (CHx2), 40.3 (C_4), 39.0 (C_4), 34.4 (CH), 34.1 (CH), 32.9 (CH_2), 32.6 (CH_2), 32.5 (CH_2x2), 29.1 (CHx2), 27.9 (CH_2), 27.5 (CH_2), 27.0 (CH_3x6), 26.6 (CH_3x6), 24.3 (CH_2x2), 22.3 (CH_3x2), 19.3 (C_{quat}x2), 18.4 (CH_3x2); HRMS (EI) m/z calcd for $C_{32}H_{43}O_3Si$ [$(M-C_4H_9)^+$] 503.2976, found 503.2978.



2.80 **2.81**

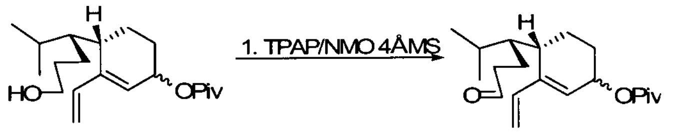
(±)-(1*S*,4*S*,1'*R*) 2,2-Dimethyl-propionic acid 4-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-vinyl-cyclohex-2-enyl ester and (±)-(1*R*,4*S*,1'*R*)- 2,2-Dimethyl-propionic acid 4-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-vinyl-cyclohex-2-enyl ester (2.81). A solution of ene-yne **2.80** (57.5 mg, 0.103 mmol) in dichloromethane (3.4 mL) was degassed with argon for 30 min. 2nd generation Grubb's catalyst (8.7 mg, 0.010 mmol) was added and the mixture was stirred under ethylene atmosphere (1 atm.) for 16 h. The solvent was evaporated and the residue was purified on silica gel (elution with 10% ethyl acetate in hexanes) afforded 46.3 mg of **2.80** and **2.81**.

The mixture of **2.80** and **2.81** was resubmitted to reaction conditions and after purification on silica gel, 45.0 mg of **2.81** as a colorless oil was obtained (78%). (Ratio of 1:1 of isomers) **2.80a**: IR (neat, cm^{-1}) 2960 (s), 2867 (m), 1724 (s), 1471 (m), 1423 (m), 1278 (m), 1154 (s), 1105 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.61 (m, 4H), 7.41-7.34 (m, 6H), 6.12 (dd, *J*=17.5, 11.2 Hz, 1H), 5.71 (s, 1H), 5.26-5.10 (m, 1H), 5.17 (d, *J*=17.8 Hz, 1H), 4.97 (d, *J*=11.0 Hz, 1H), 3.66-3.45 (m, 2H), 2.69-2.63 (m, 1H), 2.03-1.97 (m, 1H), 1.83-1.73 (m, 1H), 1.64-1.32 (m, 8H), 1.18 (s, 9H), 1.02 (s, 9H), 0.93 (d, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C_{quat}), 142.9 (C_{quat}), 138.3 (CH), 135.6 (CHx4), 134.3 (C_{quat}x2), 129.6 (CHx2), 128.7 (CH), 127.7 (CHx4), 113.9 (CH_2), 69.8 (CH), 64.5 (CH_2), 45.8 (CH), 38.8 (C_4), 36.7 (CH), 33.8 (CH_2), 31.1 (CH), 27.5 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 25.6 (CH_2), 21.8 (CH_3), 21.4 (CH_3), 20.2 (CH_2), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{32}H_{43}O_3Si$ [$(M-C_4H_9)^+$] 503.2976, found 503.2952. **2.80b:** IR (neat, cm^{-1}) 2961 (s), 2861 (m), 1722 (s), 1474 (m), 1427 (m), 1282 (m), 1155 (s), 1108 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.60 (m, 4H), 7.41-7.31 (m, 6H), 6.13 (dd, *J*=17.7, 11.1 Hz, 1H), 5.93 (d, *J*=5.6 Hz, 1H), 5.24-5.16 (m, 1H), 5.19 (d, *J*=17.6 Hz, 1H), 5.00 (d, *J*=11.0 Hz, 1H), 3.65-3.42 (m, 2H), 2.65-2.63 (m, 1H), 1.78-1.74 (m, 1H), 1.67-1.15 (m, 9H), 1.09 (s, 9H), 1.01 (s, 9H), 0.94 (d, *J*=6.6 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C_4), 146.0 (C_4), 138.3 (CH), 135.7 (CHx4), 134.3 (C_4x2), 129.6 (CHx2), 127.7 (CHx4), 125.3 (CH), 114.6 (CH_2), 67.1 (CH), 64.7 (CH_2), 45.6 (CH), 38.9 (C_{quat}), 37.1 (CH), 33.8 (CH_2), 31.3 (CH), 27.3 (CH_3x3), 27.0 (CH_3x3), 27.0 (CH_2), 25.3 (CH_2), 21.9 (CH_3), 21.4 (CH_3), 19.3 (C_{quat}), 18.4 (CH_2); HRMS (EI) m/z calcd for $C_{32}H_{43}O_3Si$ [$(M-C_4H_9)^+$] 503.2976, found 503.2946.



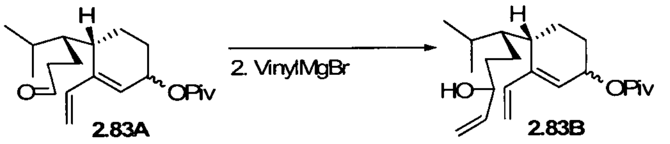
2.81 **2.82**

(±)-(1*S*,4*S*,1'*R*) 2,2-Dimethyl-propionic acid 4-(4-hydroxy-1-isopropyl-butyl)-3-vinyl-cyclohex-2-enyl ester and (±)-(1*R*,4*S*,1'*R*)- 2,2-Dimethyl-propionic acid 4-(4-hydroxy-1-isopropyl-butyl)-3-vinyl-cyclohex-2-enyl ester (2.82). To a solution of silylated enol ether **2.81** (33.6 mg, 0.060 mmol) in tetrahydrofuran (1 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.180 mL, 0.180 mmol). The mixture was stirred for 3 h at ambient temperature before a solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 15.7 mg (83%) of **2.82** as a colorless oil. (Ratio of 1:1 of isomers) **2.82a**: IR (neat, cm^{-1}) 3434 (br), 2958 (s), 2869 (m), 1722 (s), 1284 (m), 1154 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J*=17.8, 11.1 Hz, 1H), 5.99 (s, 1H), 5.24 (dd, *J*=17.6, 1.2 Hz, 1H), 5.20-5.17 (m, 1H), 5.06 (dd, *J*=11.0, 1.1 Hz, 1H), 3.51-3.41 (m, 2H), 2.69-2.67 (m, 1H), 1.80-1.76 (m, 1H), 1.68-1.21 (m, 10H), 1.16 (s, 9H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7 (C_{quat}), 145.9 (C_{quat}), 138.3 (CH), 125.7 (CH), 114.7 (CH_2), 67.1 (CH), 63.5 (CH_2), 45.6 (CH), 38.9 (C_{quat}), 36.9 (CH), 33.9 (CH_2), 31.4 (CH), 27.3 (CH_3x3), 26.9 (CH_2), 25.3 (CH_2), 22.0 (CH_3), 21.4 (CH_3), 18.3 (CH_2); HRMS (EI) m/z calcd for $C_{20}H_{34}O_3$ [M^+] 322.2508, found 322.2518. **2.82b**: IR (neat, cm^{-1}) 3409 (br), 2959 (s), 2870 (m), 1724 (s), 1278 (m), 1151 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, *J*=17.9, 11.2 Hz, 1H), 5.76 (s, 1H), 5.28-5.20 (m, 2H), 5.03 (d, *J*=11.0 Hz, 1H), 3.64-3.44 (m, 2H), 2.76-2.70 (m, 1H), 2.04-1.97 (m, 1H), 1.83-1.32 (m, 10H), 1.17 (s, 9H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7 (C_{quat}), 142.7 (C_{quat}), 138.3 (CH), 129.2 (CH), 114.0 (CH_2), 69.9 (CH), 63.5 (CH_2), 45.8 (CH), 38.8 (C_{quat}), 36.7 (CH), 33.8 (CH_2), 31.1 (CH), 27.8 (CH_2), 27.3 (CH_3x3), 25.4 (CH_2), 21.9 (CH_3), 21.4 (CH_3), 20.3 (CH_2); HRMS (EI) m/z calcd for $C_{20}H_{34}O_3$ [M^+] 322.2508, found 322.2519.

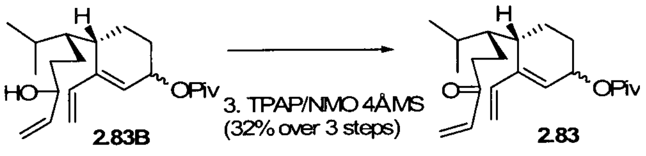


2.82 2.83A

(±)-(1*S*,4*S*,1'*R*) 2,2-Dimethyl-propionic acid 4-(1-isopropyl-4-oxo-butyl)-3-vinyl-cyclohex-2-enyl ester and (±)-(1*R*,4*S*,1'*R*)- 2,2-Dimethyl-propionic acid 4-(1-isopropyl-4-oxo-butyl)-3-vinyl-cyclohex-2-enyl ester (2.83A). Procedure C: Molecular sieves 4 Å (60.5 mg), alcohol **2.82** (15.7 mg, 0.050 mmol), dichloromethane (1 mL), NMO (11.7 mg, 0.100 mmol), TPAP (0.9 mg, 0.003 mmol), elution with ethyl acetate. The aldehyde was used crude in the next step. An aliquot was purified and characterized. (colorless oil and ratio of 1:1 of isomers) IR (neat, cm^{-1}) 2958 (s), 2872 (m), 2716 (w), 1725 (s), 1280 (m), 1157 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.61 (t, *J*=1.8 Hz, 1H), 9.60 (t, *J*=1.8 Hz, 1H), 6.22-6.12 (m, 2H), 6.00 (d, *J*=5.5 Hz, 1H), 5.77 (s, 1H), 5.27-5.03 (m, 6H), 2.74-2.69 (m, 2H), 2.42-2.29 (m, 4H), 2.05-1.37 (m, 16H), 1.17 (s, 18H), 0.97 (d, *J*=6.3 Hz, 3H), 0.97 (d, *J*=6.1 Hz, 3H), 0.96 (d, *J*=6.0 Hz, 3H), 0.95 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.8 (CH), 202.6 (CH), 178.3 (C$_{quat}$x2), 145.5 (C$_{quat}$), 142.3 (C$_{quat}$), 138.1 (CHx2), 129.4 (CH), 125.8 (CH), 115.0 (CH$_2$), 114.3 (CH$_2$), 69.7 (CH), 66.8 (CH), 45.4 (CH), 45.2 (CH), 44.9 (CH$_2$), 44.8 (CH$_2$), 38.9 (C$_{quat}$), 38.8 (C$_{quat}$), 36.8 (CH), 36.7 (CH), 31.2 (CH), 30.9 (CH), 27.7 (CH$_2$), 27.3 (CH$_3$x3), 27.2 (CH$_3$x3), 26.9 (CH$_2$), 21.9 (CH$_3$), 21.8 (CH$_3$), 21.4 (CH$_2$x2), 21.3 (CH$_3$), 21.2 (CH$_3$), 20.2 (CH$_2$), 18.1 (CH$_2$); HRMS (EI) m/z calcd for $C_{20}H_{32}O_3$ [M$^+$] 320.2351, found 320.2348.

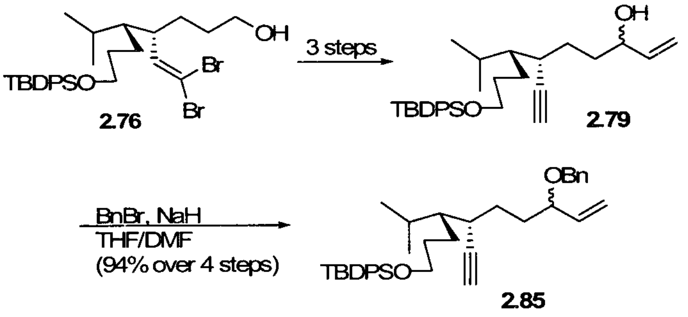


(±)-(1*S*,4*S*,1'*R*,4'*R*)-and (1*R*,4*S*,1'*R*,4'*R*)-and (1*S*,4*S*,1'*R*,4'*S*)- and (1*R*,4*S*,1'*R*,4'*S*)-2,2-Dimethyl-propionic acid 4-(4-hydroxy-1-isopropyl-hex-5-enyl)-3-vinyl-cyclohex-2-enyl ester (2.83B). To a -78 °C solution of aldehyde **2.83A** (crude, 0.050 mmol) in THF (1 mL) was added vinylmagnesium bromide (0.092 mL, 0.092 mmol). The reaction was stirred for 2 hours at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.



(±)-(1*S*,4*S*,1'*R*)-2,2-Dimethyl-propionic acid 4-(1-isopropyl-4-oxo-hex-5-enyl)-3-vinyl-cyclohex-2-enyl ester and (±)-(1*R*,4*S*,1'*R*)-2,2-Dimethyl-propionic acid 4-(1-isopropyl-4-oxo-hex-5-enyl)-3-vinyl-cyclohex-2-enyl ester (2.83). Procedure C: Molecular sieves 4 Å (37.5 mg), alcohol **2.83B** (crude mixture), dichloromethane (1 mL), NMO (11.7 mg, 0.100

mmol), TPAP (0.9 mg, 0.003 mmol), elution with ethyl acetate. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 3.5 mg (32% over 3 steps) of **2.83** as a colorless oil.(Ratio of 2:1 of isomers) IR (neat, cm^{-1}) 2964 (s), 2876 (m), 1724 (s), 1283 (m), 1156 (s); ^1H NMR (500 MHz, C_6D_6) δ 6.14-5.88 (m, 8H), 5.44-5.40 (m, 1H), 5.36-5.30 (m, 1H), 5.21 (dd, *J*=10.7, 1.1 Hz, 2H), 5.15 (dd, *J*=17.4, 12.3 Hz, 2H), 4.89 (dd, *J*=9.8, 9.8 Hz, 2H), 2.53-2.43 (m, 2H), 2.39-2.28 (m, 2H), 2.01-1.92 (m, 2H), 1.79-1.32 (m, 16H), 1.20 (s, 18H), 0.85 (d, *J*=6.1 Hz, 2H), 0.83 (d, *J*=6.4 Hz, 4H), 0.81 (d, *J*=6.1 Hz, 2H), 0.77 (d, *J*=6.3 Hz, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.0 (C_{quat}), 198.9 (C_{quat}), 177.6 (C_{quat}), 177.4 (C_{quat}), 145.6 (C_{quat}), 142.7 (C_{quat}), 138.7 (CH), 138.6 (CH), 136.8 (CH), 136.7 (CH), 129.6 (CH), 126.8 (CH_2), 126.7 (CH_2), 126.3 (CH), 114.5 (CH_2), 113.9 (CH_2), 69.9 (CH), 66.9 (CH), 45.7 (CH), 45.6 (CH), 40.9 (CH_2), 40.8 (CH_2), 39.0 (C_{quat}), 38.8 (C_{quat}), 37.1 (CH), 36.9 (CH), 31.4 (CH), 31.0 (CH), 28.0 (CH_2), 27.3 (CH_3x6), 27.1 (CH_2), 23.8 (CH_2x2), 21.9 (CH_3), 21.8 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.3 (CH_2), 18.4 (CH_2); HRMS (EI) m/z calcd for $C_{22}H_{34}O_3$ [M^+] 346.2508, found 346.2494.

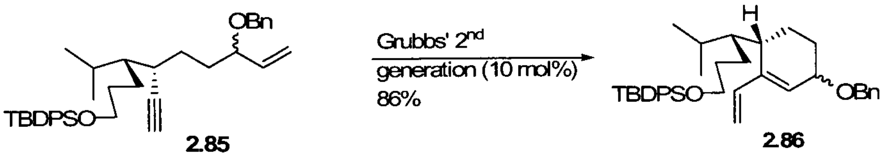


(±)-(4*R*,5*S*,8*R*)-(8-Benzyloxy-5-ethynyl-4-isopropyl-dec-9-enyloxy)-*tert*-butyl-diphenyl-silane and (4*R*,5*S*,8*S*)-(8-Benzyloxy-5-ethynyl-4-isopropyl-dec-9-enyloxy)-*tert*-butyl-diphenyl-silane (2.85). To a -78 °C solution of dibromide **2.76** (546.9 mg, 0.896 mmol) in THF (9 mL) was added *n*-BuLi (1.79 mL, 3.58 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with water and warmed to RT. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The mixture was used crude in the next step.

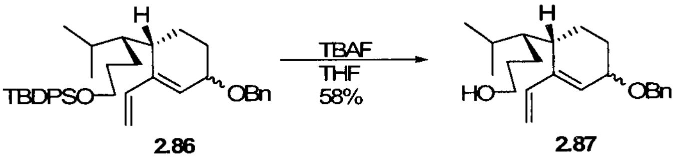
Procedure B: oxalyl chloride (0.133 mL, 1.52 mmol), dimethyl sulfoxide (0.158 mL, 2.24 mmol), alcohol **2.77** (crude), dichloromethane (5+4 mL), triethylamine (0.624 mL, 4.48 mmol).The mixture was used directly in the next step.

To a -78 °C solution of crude aldehyde **2.78** in THF (9 mL) was added vinylmagnesium bromide (2.69 mL, 2.69 mmol). The reaction was stirred for 45 minutes at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.

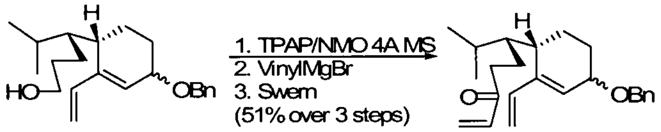
To a 0 °C solution of the crude alcohol **2.79** in THF (1.5 mL) and DMF (1.5 mL) was added sodium hydride (86.0 mg, 2.15 mmol) followed by benzyl bromide (0.277 mL, 2.33 mmol). The solution was stirred overnight at room temperature before being quenched with water. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 479.8 mg (94% over 4 steps) of **2.85** as a colorless oil. (Ratio of 1:1 of isomers) IR (neat, cm^{-1}) 3304 (m), 2955 (s), 2858 (s), 1454 (m), 1110 (s), 700 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 8H), 7.43-7.27 (m, 22H), 5.82-5.67 (m, 2H), 5.24-5.16 (m, 4H), 3.78-3.71 (m, 2H), 3.70-3.61 (m, 4H), 2.42-2.37 (m, 2H), 1.99 (d, *J*=2.5 Hz, 2H), 1.99-1.87 (m, 2H), 1.86-1.76 (m, 2H), 1.74-1.19 (m, 20H), 1.05 (s, 18H), 0.89 (d, *J*=6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (CH), 139.1 (CH), 138.9 (C_{quat}), 138.4 (C_{quat}), 135.7 (CHx8), 134.3 (C_{quat}x4), 129.6 (CHx2), 128.5 (CHx4), 128.5 (CHx2), 127.9 (CHx4), 127.9 (CH), 127.8 (CH), 127.7 (CHx8), 117.3 (CH_2), 117.2 (CH_2), 87.2 (C_{quat}), 87.1 (C_{quat}), 80.7 (CH), 80.1 (CH), 72.3 (CH_2x2), 70.6 (CHx2), 64.4 (CH_2x2), 47.0 (CHx2), 34.4 (CH), 34.2 (CH), 34.0 (CH_2), 33.8 (CH_2), 32.5 (CH_2x2), 29.0 (CHx2), 28.4 (CH_2), 27.9 (CH_2), 27.0 (CH_3x6), 24.2 (CH_2x2), 22.4 (CH_3x2), 19.3 (C_{quat}x2), 18.3 (CH_3x2); HRMS (EI) m/z calcd for $C_{19}H_{19}OSi$ [$(M-C_{19}H_{31}O)^+$] 291.1200, found 291.1047.



(±)-(4*S*, 1'*R*, 1*R*)-[4-(4-Benzyloxy-2-vinyl-cyclohex-2-enyl)-5-methyl-hexyloxy]-*tert*-butyl-diphenyl-silane and (±)-(4*S*, 1'*R*, 1*S*)-[4-(4-Benzyloxy-2-vinyl-cyclohex-2-enyl)-5-methyl-hexyloxy]-*tert*-butyl-diphenyl-silane (2.86). A solution of ene-yne **2.85** (100.2 mg, 0.177 mmol) in dichloromethane (5.9 mL) was degassed with argon for 30 min. 2nd generation Grubb's catalyst (15.0 mg, 0.018 mmol) was added and the mixture was stirred under ethylene atmosphere (1 atm.) for 16 h. The solvent was evaporated and the residue was purified on silica gel (elution with 5 to 10% ethyl acetate in hexanes) afforded 85.7 mg of **2.86** (86%) as a colorless oil. (Each isomer is one) IR (neat, cm^{-1}) 2954 (s), 2931 (s), 2858 (s), 1427 (w), 1110 (s), 700 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71-7.62 (m, 8H), 7.41-7.21 (m, 22H), 6.20-6.10 (m, 2H), 5.97-5.94 (m, 2H), 5.22-5.13 (m, 2H), 4.99-4.94 (m, 2H), 4.56 (s, 2H), 4.51 (s, 2H), 3.96-3.94 (m, 2H), 3.66-3.47 (m, 4H), 2.77-2.55 (m, 2H), 2.11-2.01 (m, 2H), 1.87-1.17 (m, 18H), 1.02 (s, 18H), 0.94 (d, *J*=6.6 Hz, 12H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.6 (C$_{quat}$), 141.7 (C$_{quat}$), 139.4 (C$_{quat}$), 139.1 (C$_{quat}$), 138.8 (CH), 138.7 (CH), 135.7 (CHx8), 134.4 (C$_{quat}$x4), 131.1 (CH), 129.6 (CH), 129.5 (CH), 128.6 (CHx4), 128.5 (CH), 128.4 (CHx2), 127.9 (CHx2), 127.8 (CH), 127.7 (CHx9), 127.6 (CH), 127.4 (CH), 113.9 (CH$_2$), 113.3 (CH$_2$), 74.6 (CH), 71.2 (CH), 70.2 (CH$_2$), 70.0 (CH$_2$), 64.7 (CH$_2$), 64.6 (CH$_2$), 45.9 (CH), 45.8 (CH), 37.1 (CHx2), 33.8 (CH$_2$), 33.7 (CH$_2$), 31.3 (CH), 31.2 (CH), 28.4 (CH$_2$), 27.2 (CH$_2$), 27.0 (CH$_3$x6), 25.7 (CH$_2$), 25.4 (CH$_2$), 21.9 (CH$_3$), 21.8 (CH$_3$), 21.5 (CH$_3$), 21.4 (CH$_3$), 20.5 (CH$_2$), 19.3 (C$_{quat}$x2), 19.1 (CH$_2$); HRMS (EI) m/z calcd for C$_{19}$H$_{19}$OSi [(M-C$_{19}$H$_{31}$O)$^+$] 291.1200, found 291.1016.



(±)-(4*S*, 1'*R*, 1*R*)-4-(4-Benzyloxy-2-vinyl-cyclohex-2-enyl)-5-methyl-hexan-1-ol and (±)-(4*S*, 1'*R*, 1*S*)-4-(4-Benzyloxy-2-vinyl-cyclohex-2-enyl)-5-methyl-hexan-1-ol (2.87). To a solution of silylated enol ether **2.86** (352.2 mg, 0.621 mmol) in tetrahydrofuran (6 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.86 mL, 1.86 mmol). The mixture was stirred for 18 h at ambient temperature before a solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20-30% ethyl acetate in hexanes) afforded 119.2 mg (58%) of **2.86** as a colorless oil. (Each isomer is one) IR (neat, cm^{-1}) 3397 (br), 2953 (s), 2869 (m), 1457 (w), 1061 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10H), 6.20(ddd, *J*=17.6, 10.6, 10.6 Hz, 2H), 6.02 (d, *J*=5.2 Hz, 1H), 5.98 (s, 1H), 5.21 (dd, *J*=17.6, 17.6 Hz, 2H), 5.04 (dd, *J*=11.0, 1.3 Hz, 1H), 5.00 (d, *J*=11.1 Hz, 1H), 4.58 (d, *J*=12.6 Hz, 2H), 4.57 (d, *J*=10.0 Hz, 2H), 3.99-3.96 (m, 2H), 3.51-3.44 (m, 4H), 2.73-2.64 (m, 2H), 2.11-2.05 (m, 2H), 1.91-1.05 (m, 20H), 0.97 (d, *J*=6.6 Hz, 6H), 0.96 (d, *J*=6.0Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C_{quat}), 141.6 (C_{quat}), 139.2 (C_{quat}), 139.0 (C_{quat}), 138.8 (CH), 138.6 (CH), 131.4 (CH), 128.5 (CHx4), 127.9 (CH), 127.8 (CHx2), 127.7 (CHx2), 127.6 (CHx2), 114.0 (CH_2), 113.4 (CH_2), 74.5 (CH), 71.1 (CH), 70.2 (CH_2), 70.1 (CH_2), 63.5 (CH_2x2), 45.7 (CHx2), 37.1 (CH), 36.8 (CH), 33.8 (CH_2), 33.7 (CH_2), 31.4 (CH), 31.1 (CH), 28.4 (CH_2), 26.9 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 21.4 (CH_3x2), 20.5 (CH_2), 18.8 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{23}O$ [$(M-C_7H_9O)^+$] 219.1743, found 219.1759.



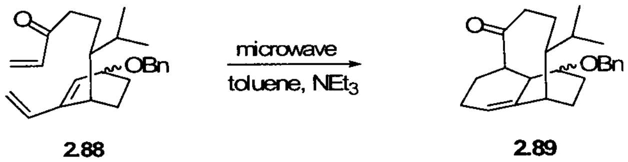
2.87 2.88

(±)-(6*R*,1'*S*,4'*R*)-6-(4-Benzyloxy-2-vinyl-cyclohex-2-enyl)-7-methyl-oct-1-en-3-one and (±)-(6*R*,1'*S*,4'*S*)-6-(4-Benzyloxy-2-vinyl-cyclohex-2-enyl)-7-methyl-oct-1-en-3-one (2.88). Procedure C: Molecular sieves 4 Å (203.2 mg), alcohol **2.88** (55.3 mg, 0.168 mmol), dichloromethane (2 mL), NMO (39.4 mg, 0.336 mmol), TPAP (3.0 mg, 0.008 mmol), elution with ethyl acetate. The aldehyde was used crude in the next step.

To a -78 °C solution of the crude aldehyde in toluene (3 mL) was added vinylmagnesium bromide (0.504 mL, 0.504 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.

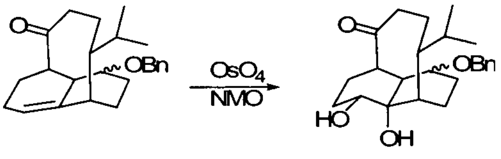
Procedure B: oxalyl chloride (0.050 mL, 0.571 mmol), dimethyl sulfoxide (0.059 mL, 0.840 mmol), crude alcohol, dichloromethane (1+1 mL), triethylamine (0.234 mL, 1.68 mmol).

Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 29.1 mg (51% over 3 steps) of **2.88** as a colorless oil. (Ratio of 1:1 of isomers) IR (neat, cm^{-1}) 2955 (s), 2870 (m), 1733 (s), 1456 (m); ^{1}H NMR (500 MHz, C_6D_6) δ 7.39-7.36 (m, 4H), 7.26-7.18 (m, 6H), 6.18-5.88 (m, 8H), 5.24-5.16 (m, 4H), 4.96 (dd, *J*=11.1, 1.4 Hz, 1H), 4.93 (d, *J*=10.4 Hz, 1H), 4.41 (d, *J*=6.3 Hz, 4H), 3.87-3.79 (m, 2H), 2.63-2.52 (m, 2H), 2.46-2.33 (m, 2H), 2.00-1.28 (m, 18H), 0.89 (d, *J*=6.6 Hz, 3H), 0.86 (d, *J*=6.3 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 3H), 0.82 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.4 (C_{quat}), 199.2 (C_{quat}), 144.4 (C_{quat}), 140.9 (C_{quat}), 139.9 (C_{quat}x2), 139.2 (CH), 139.1 (CH), 136.8 (CHx2), 135.3 (CH), 132.7 (CHx2), 129.8 (CH), 128.6 (CHx2), 128.5 (CHx2), 127.7 (CHx2), 127.5 (CHx2), 126.7 (CH_2x2), 113.9 (CH_2), 113.2 (CH_2), 74.8 (CH), 71.0 (CH), 70.3 (CH_2x2), 45.9 (CH), 45.7 (CH), 41.1 (CH_2), 40.4 (CH_2), 37.2 (CH), 37.1 (CH), 31.4 (CH), 31.1 (CH), 28.7 (CH_2), 26.7 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 21.8 (CH_3x2), 21.4 (CH_3), 21.2 (CH_3), 20.6 (CH_2), 18.7 (CH_2); HRMS (EI) m/z calcd for $C_{24}H_{32}O_2$ [M$^+$] 352.2402, found 352.2398.



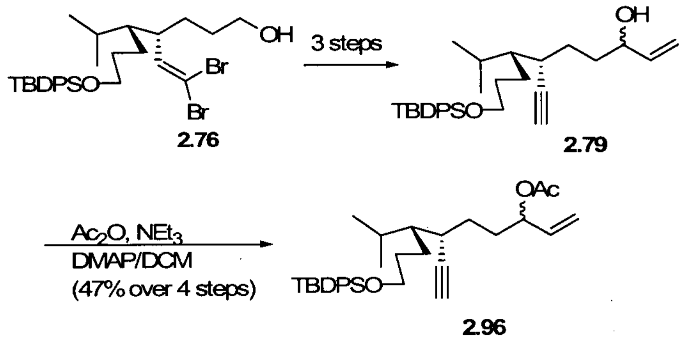
(±)-(5*R*,9*R*,10*S*,14*R*,13*R*)-13-Benzyloxy-9-isopropyl-tricyclo[8.4.0.0^{5,14}]tetradec-1-en-6-one (2.89). Triene **2.88** (5.6 mg, 0.016) was dissolved in 1 mL of benzene. The solvent was removed *in vacuo* and the triene was left on the pump for 10 minutes. Once the triene was very dry, it was cannulated to a flame-dried microwave cell using toluene (3 mL). Triethylamine (0.022 mL, 0.159 mmol) was added and the resulting solution was degassed with argon for 30 minutes. Irradiation with microwaves (200 °C for 4 hrs, watts=300, pressure=250 psi) was done. The solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 2.9 mg (52%) of **2.89** as a yellow oil. IR (neat, cm^{-1}) 2931 (s), 2869 (m), 1686 (s), 1455 (m), 1363 (w), 1098 (m), 1068 (m); ^{1}H NMR (500 MHz, C_6D_6) δ 7.73-7.71 (m, 1H), 7.51 (d, *J*=7.9Hz, 2H), 7.25-7.19 (m, 2H), 5.54-5.53 (m, 1H), 4.65 (d, J_{AB}=11.5 Hz, 1H), 4.61 (d, J_{AB}=11.3 Hz, 1H), 3.47-3.42 (m, 2H), 2.80-2.78 (m, 1H), 2.44-2.43 (m, 1H), 2.34 (dd, *J*=9.5, 9.5 Hz, 1H), 2.02-1.87 (m, 3H), 1.75-1.66 (m, 3H), 1.62-1.55 (m, 1H), 1.51-1.44 (m, 1H), 1.40-1.32 (m, 1H), 1.27-1.18 (m, 2H), 1.14-1.04 (m, 1H), 0.98-0.89 (m, 1H), 0.81 (d, *J*=6.5 Hz, 3H), 0.79 (d,

J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 215.2 (C_{quat}), 142.4 (C_{quat}), 140.0 (C_{quat}), 135.3 (CH), 129.8 (CH), 128.6 (CHx2), 127.6 (CH), 124.9 (CH), 78.1 (CH), 71.8 (CH_2), 58.6 (CH), 51.8 (CH), 47.3 (CH), 39.4 (CH_2), 36.8 (CH), 30.5 (CH), 28.7 (CH_2), 24.9 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 20.7 (CH_2); HRMS (EI) m/z calcd for $C_{24}H_{32}O_2$ [M^+] 352.2402, found 352.2340.



2.89 **2.90**

(±)-(1*S*,2*R*,5*R*,9*R*,10*S*,14*S*,13*R*)-13-Benzyloxy-1,2-dihydroxy-9-isopropyl-tricyclo[8.4.0.0^{5,14}]tetradecan-6-one (2.90). To a solution of alkene **2.89** (11.1 mg, 0.031 mmol) in THF (0.5 mL) and water (0.25 mL) was added NMO (7.3 mg, 0.062 mmol) followed by OsO_4 (0.019 mL, 0.006 mmol) in a sealed tube. The solution was stirred at room temperature for 18 hours and at 100 °C for 18 hours. The solution was cool to room temperature and quenched with a saturated solution of sodium sulfite. The mixture was stirred for 15 minutes. The aqueous layer was extracted with diethyl ether (3x) and ethyl acetate (1x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20-40% ethyl acetate in hexanes) afforded 1.0 mg (8%) of **2.90** as a yellow oil. IR (neat, cm^{-1}) 3431 (br), 2924 (s), 2872 (m), 1677 (s), 1454 (m), 1048 (w); ^{1}H NMR (500 MHz, C_6D_6) δ 7.14-7.10 (m, 5H), 5.80 (s, 1H), 4.13 (d, J_{AB}=11.7Hz, 1H), 4.05 (d, J_{AB}=11.4Hz, 1H), 3.96 (s, 1H), 3.86 (s, 1H), 3.73 (s, 1H), 2.70 (dd, J=5.4, 5.4 Hz, 1H), 2.49 (d, J=6.8 Hz, 1H), 2.28-2.24 (m, 2H), 2.12-2.02 (m, 5H), 1.65-1.12 (m, 8H), 0.77 (d, J=6.6 Hz, 3H), 0.76 (d, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 216.2 (C_{quat}), 138.2 (C_{quat}), 127.9 (CHx2), 127.1 (CH), 126.9 (CHx2), 78.3 (CH), 75.1 (C_{quat}), 71.2 (CH_2), 70.6 (CH), 52.7 (CH), 44.1 (CH), 41.9 (CH_2), 41.9 (CH), 41.3 (CH), 35.8 (CH), 27.1 (CH_2), 26.4 (CH_2), 23.2 (CH_2), 21.9 (CH_3), 21.6 (CH_3), 20.3 (CH_2), 16.9 (CH_2); HRMS (EI) m/z calcd for $C_{24}H_{34}O_4$ [M^+] 386.2457, found 386.2445.



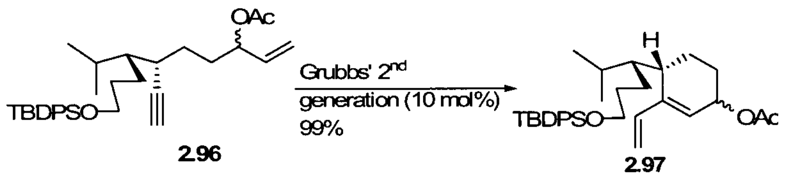
(±)-(1*R*,4*S*,5*R*)-Acetic acid 8-(*tert*-butyl-diphenyl-silanyloxy)-4-ethynyl-5-isopropyl-1-vinyl-octyl ester and (1*S*,4*S*,5*R*)-Acetic acid 8-(*tert*-butyl-diphenyl-silanyloxy)-4-ethynyl-5-isopropyl-1-vinyl-octyl ester (2.96). To a -78 °C solution of dibromide **2.76** (373.2 mg, 0.611 mmol) in THF (6.1 mL) was added *n*-BuLi (1.22 mL, 2.44 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with water and warmed to RT. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The mixture was used crude in the next step.

Procedure C: Molecular sieves 4 Å (758 mg), crude alcohol, dichloromethane (6 mL), NMO (143.2 mg, 1.22 mmol), TPAP (10.7 mg, 0.0310 mmol), elution with ethyl acetate. The mixture was used directly in the next step.

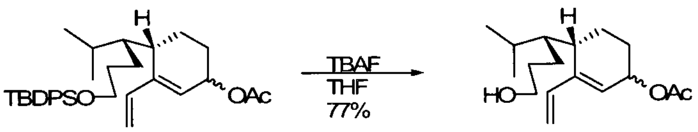
To a -78 °C solution of crude aldehyde in THF (6.1 mL) was added vinylmagnesium bromide (1.83 mL, 1.83 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.

To a solution of the crude alcohol in dichloromethane (6 mL) was added triethylamine (0.255 mL, 1.83 mmol), acetic anhydride (0.133 mL, 1.41 mmol) and DMAP (1 crystal). The solution was stirred at RT for 18 hours. The reaction was quenched with a saturated solution of ammonium chloride, extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 8-10% ethyl acetate in hexanes) afforded 150.5 mg of **2.96** (47% over 4 steps) as a yellow oil. (Each isomer is one.) IR (neat, cm^{-1}) 3306 (m), 2956 (s), 2859 (s), 1739 (s), 1428 (m), 1239 (s), 1111 (s); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 8H), 7.42-7.33 (m, 12H), 5.80-5.71 (m, 2H), 5.27-5.13 (m, 6H), 3.65-3.59 (m, 4H), 2.52-2.34 (m, 2H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02-1.99 (m, 2H), 1.97-1.82 (m, 4H), 1.69-1.59 (m, 4H), 1.49-1.19 (m, 12H), 1.03 (s, 18H), 0.88 (d, J=6.8 Hz, 6H), 0.87 (d, J=6.8Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C_{quat}x2), 136.6 (CH), 136.5 (CH), 135.7 (CHx8), 134.2 (C_{quat}x4), 129.7 (CHx4), 127.7 (CHx8), 117.1 (CH_2), 116.8 (CH_2), 86.8 (C_{quat}x2), 75.0 (CH), 74.5 (CH), 70.9 (CH), 70.8 (CH), 64.3 (CH_2x2), 47.0 (CHx2), 34.4 (CH), 34.1 (CH), 32.8 (CH_2), 32.6 (CH_2), 32.4 (CH_2x2), 29.0 (CHx2), 28.0 (CH_2), 27.6 (CH_2), 27.0 (CH_3x6), 24.1 (CH_2x2), 22.4 (CH_3), 22.3 (CH_3), 21.4 (CH_3x2), 19.4 (C_{quat}x2), 18.3 (CH_3x2); HRMS (EI) m/z calcd for $C_{27}H_{34}OSi$ [$(M-C_6H_{12}O_2)^+$] 402.2373, found 402.2319.

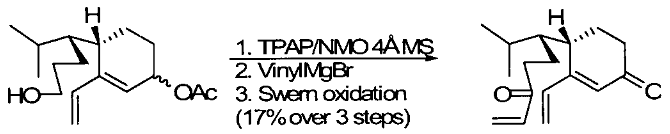


(±)-(1*R*,4*S*,1'*R*)-Acetic acid 4-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-vinyl-cyclohex-2-enyl ester and (±)-(1*S*,4*S*,1'*R*)-Acetic acid 4-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-vinyl-cyclohex-2-enyl ester (2.97). A solution of ene-yne **2.96** (9.3 mg, 0.018 mmol) in dichloromethane (0.6 mL) was degassed with argon for 30 min. 2nd generation Grubb's catalyst (1.5 mg, 0.002 mmol) was added and the mixture was stirred under ethylene atmosphere (1 atm.) for 16 h. The solvent was evaporated and the residue was purified on silica gel (elution with 10% ethyl acetate in hexanes) afforded 11.4 mg of **2.97** (99%) as a yellow oil. (Each isomer is one) IR (neat, cm^{-1}) 2954 (s), 2860 (m), 1734 (s), 1427 (m), 1239 (s), 1108 (s), 703 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.63 (m, 8H), 7.41-7.33 (m, 12H), 6.20-6.08 (m, 2H), 5.92 (d, J=5.3 Hz, 1H), 5.74 (s, 1H), 5.27-5.16 (m, 4H), 5.02 (dd, J=11.0, 1.3 Hz, 1H), 4.98 (d, J=11.0 Hz, 1H), 3.66-3.47 (m, 4H), 2.68-2.62 (m, 2H), 2.04 (s, 3H), 2.03-1.98 (m, 2H), 1.93 (s, 3H), 1.83-1.70 (m, 2H), 1.68-1.09 (m, 16H), 1.03 (s, 18H), 0.96 (d, J=6.6 Hz, 3H), 0.94 (d, J=5.8 Hz, 3H), 0.93 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C_{quat}), 170.8 (C_{quat}), 146.0 (C_{quat}), 143.2 (C_{quat}), 138.2 (CHx2), 135.4 (CHx8), 134.3 (C_{quat}x4) 129.6 (CHx4), 128.2 (CH), 127.8 (CHx8), 125.1 (CH), 114.4 (CH_2), 114.1 (CH_2), 70.2 (CH), 67.8 (CH), 64.6 (CH_2), 64.5 (CH_2), 45.8 (CH), 45.5 (CH), 37.1 (CH), 36.8 (CH), 33.8 (CH_2), 33.5 (CH_2), 31.2 (CH), 31.1 (CH), 27.8 (CH_2), 27.0 (CH_3x6), 27.0 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 21.9 (CH_3), 21.8 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 21.4 (CH_3x2), 20.2 (CH_2), 19.3 (C_{quat}x2), 18.8 (CH_2); HRMS (EI) m/z calcd for $C_{29}H_{37}O_3Si$ [$(M-C_4H_9)^+$] 461.2506, found 461.2423.



2.97 2.98

(±)-(1*R*,4*S*,1'*R*)-Acetic acid 4-(4-hydroxy-1-isopropyl-butyl)-3-vinyl-cyclohex-2-enyl ester and (±)-(1*S*,4*S*,1'*R*)-Acetic acid 4-(4-hydroxy-1-isopropyl-butyl)-3-vinyl-cyclohex-2-enyl ester (2.98). To a solution of silylated enol ether **2.97** (102.3 mg, 0.197 mmol) in tetrahydrofuran (2 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.592 mL, 0.592 mmol). The mixture was stirred for 3 h at ambient temperature before a solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30-40% ethyl acetate in hexanes) afforded 42.3 mg (77%) of **2.98** as a yellow oil. (Each isomer is one) IR (neat, cm^{-1}) 3420 (br), 2953 (s), 2870 (m), 1734 (s), 1371 (w), 1242 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 6.18 (ddd, J=17.6, 11.5 Hz, 2H), 5.97 (d, J=5.5 Hz, 1H), 5.78 (s, 1H), 5.28-5.15 (m, 4H), 5.06 (dd, J=12.0, 1.3 Hz, 1H), 5.03 (d, J=11.0 Hz, 1H), 3.64-3.44 (m, 4H), 2.73-2.65 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 1.81-1.74 (m, 4H), 1.65-1.11 (m, 18H), 0.96 (d, J=6.7 Hz, 6H), 0.95 (d, J=6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C_{quat}x2), 145.8 (C_{quat}), 143.0 (C_{quat}), 138.2 (CH), 138.1 (CH), 128.7 (CH), 125.5 (CH), 114.8 (CH_2), 114.1 (CH_2), 70.3 (CH), 67.8 (CH), 63.6 (CH_2), 63.4 (CH_2), 45.7 (CH), 45.5 (CH), 36.8 (CH), 36.7 (CH), 33.8 (CH_2), 33.6 (CH_2), 31.3 (CH), 31.1 (CH), 27.9 (CH_2), 26.9 (CH_2), 25.3 (CH_2x2), 21.9 (CH_3x2), 21.5 (CH_3x2), 21.4 (CH_3x2), 20.2 (CH_2), 18.6 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{24}O$ [$(M-C_2H_4O_2)^+$] 220.1827, found 220.1804.

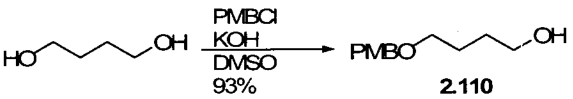


2.98 2.93

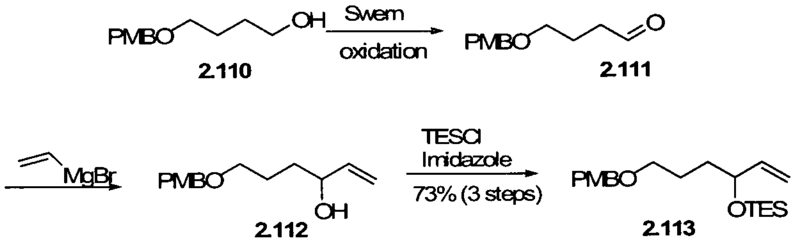
(±)-(4*S*,1'*R*)-4-(1-Isopropyl-4-oxo-hex-5-enyl)-3-vinyl-cyclohex-2-enone (2.93). Procedure C: Molecular sieves 4 Å (100.0 mg), alcohol **2.98** (23.1 mg, 0.082 mmol), dichloromethane (2 mL), NMO (19.3 mg, 0.164 mmol), TPAP (1.4 mg, 0.004 mmol), elution with ethyl acetate. The aldehyde was used crude in the next step.

To a -78 °C solution of the crude aldehyde in toluene (2 mL) was added vinylmagnesium bromide (0.410 mL, 0.410 mmol). The reaction was stirred for 18 hours at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic diol was used directly in the next step.

Procedure B: oxalyl chloride (0.050 mL, 0.571 mmol), dimethyl sulfoxide (0.059 mL, 0.840 mmol), crude alcohol, dichloromethane (1+2 mL), triethylamine (0.234 mL, 1.68 mmol). Purification of the residue on silica gel (elution with 30% ethyl acetate in hexanes) afforded 3.6 mg (17% over 3 steps) of **2.93** as a colorless oil. IR (neat, cm^{-1}) 2954 (w), 2917 (s), 2849 (m), 1715 (s), 1669 (s), 1462 (w); ^{1}H NMR (500 MHz, C_6D_6) δ 6.17 (d, *J*=11.8 Hz, 1H), 6.03 (dd, *J*=17.6, 10.6 Hz, 1H), 5.94 (dd, *J*=17.7, 11.2 Hz, 1H), 5.84 (dd, *J*=17.6, 1.1 Hz, 1H), 5.22 (dd, *J*=17.5, 0.8 Hz, 1H), 5.18 (dd, *J*=10.6, 1.2 Hz, 1H), 4.91 (d, *J*=10.2 Hz, 1H), 2.54-2.49 (m, 1H), 2.35-2.21 (m, 2H), 2.19-2.11 (m, 2H), 2.07-2.03 (m, 2H), 2.00-1.92 (m, 1H), 1.48-1.20 (m, 3H), 0.75 (d, *J*=6.6 Hz, 3H), 0.69 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 198.2 (C_{quat}), 197.4 (C_{quat}), 159.6 (C_{quat}), 137.2 (CH), 136.2 (CH), 127.1 (CH), 126.5 (CH_2), 118.5 (CH_2), 45.6 (CH), 40.0 (CH_2), 37.0 (CH), 35.3 (CH_2), 30.6 (CH), 23.5 (CH_2), 23.0 (CH_2), 21.0 (CH_3), 20.4 (CH_3); HRMS (EI) m/z calcd for $C_{14}H_{17}O_2$ [$(M-C_3H_7)^+$] 217.1223, found 217.1224.



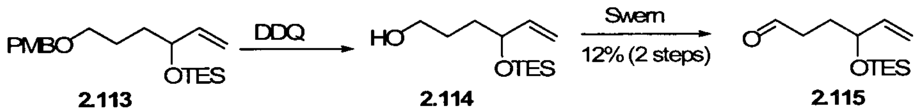
4-(4-Methoxy-benzyloxy)-butan-1-ol (2.110). To a 0 °C solution of 1,4-butanediol (7.30 g, 81.0 mmol) in DMSO (33 mL) was added finely grinded KOH (4.34 g, 77.5 mmol). The mixture was stirred for 15 minutes at 0°C before 1-(chloromethyl)-4-methoxybenzene (PMB-Cl) (5 mL, 36.8 mmol) was added. The mixture was stirred at ambient temperature for 3 h prior to being quenched with saturated NH_4Cl solution and extracted with diethyl ether (3x). The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 50-60% ethyl acetate in hexanes) afforded 7.21g (93%) of **2.110** as a light yellow oil. Full characterization is available through the literature.[247]



(±)-Triethyl-[4-(4-methoxy-benzyloxy)-1-vinyl-butoxy]-silane(2.113). Procedure A: oxalyl chloride (1.15 mL, 13.2 mmol), dimethyl sulfoxide (1.37 mL, 19.4 mmol), alcohol **2.110** (1.63 g, 7.75 mmol), dichloromethane (29+9+7 mL), triethylamine (5.4 mL, 38.8 mmol). The crude aldehyde was used directly in the next step.

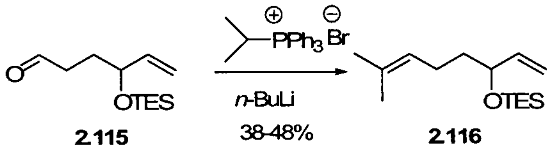
The crude aldehyde **2.111** was dissolved in THF (60 mL) and cooled to -78 °C. Vinyl magnesium bromide (1.0 M in THF, 11.6 mL, 11.6 mmol) was added dropwise and the resulting solution was stirred 2h30 (the reaction mixture warmed to -10 °C) before being quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

The crude alcohol **2.112** was dissolved in DMF (18 mL) and cooled to 0 °C. Imidazole (844 mg, 12.4 mmol) and TESCl (1.56 mL, 9.3 mmol) were added sequentially and the mixture was stirred overnight. The reaction was quenched by adding water. The aqueous layer was diluted with sodium bicarbonate and then extracted with EtOAc (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 1.97 g (73%) of **2.113** as a light yellow oil. Full characterization is available through the literature.[248]



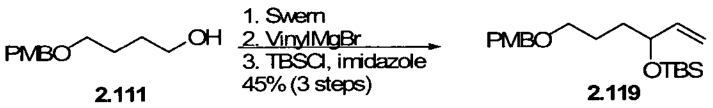
(±)-4-Triethylsilanyloxy-hex-5-enal(2.115). To a solution of alkene **2.113** (1.94 g, 5.62 mmol) in dichloromethane (56 mL) and water (3 mL) was added sodium acetate (314 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.40 g, 6.18 mmol) . The mixture was stirred at ambient temperature for 2 h before a saturated solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane and the organic layers were washed with a saturated solution of sodium bicarbonate, then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (eluting with 20% ethyl acetate in hexanes) gave a mixture of alcohol **2.114** and 4-methoxy-benzaldehyde (by-product of DDQ deprotection) that was used directly in the next step.

Procedure A: oxalyl chloride (0.833 mL, 9.55 mmol), dimethyl sulfoxide (0.994 mL, 14.1 mmol), crude alcohol **2.114**, dichloromethane (21+6.5+5.1 mL), triethylamine (3.9 mL, 28.1 mmol). Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 159 mg (12%) of **2.115** as a light yellow oil. Full characterization is available through the literature.[248]



(±)-Triethyl-(5-methyl-1-vinyl-hex-4-enyloxy)-silane(2.116). To a 0 °C solution of isopropyl-triphenyl-phosphonium bromide[81] (100.3 mg, 0.260 mmol) in THF (1.2 mL) was added *n*-BuLi (2.0 M in pentane, 0.124 mL, 0.249 mmol). The red solution was stirred 1 h at room temperature. The mixture was cooled to O °C before adding aldehyde **2.115** (54.0 mg, 0.237 mmol) in THF (1.2 mL) via cannula. The mixture was stirred 1 hour at room temperature before being quenched with a saturated solution of ammonium chloride and extracted with diethyl ether (3x). The combined ethereal layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (dry pack and elution with 2% ethyl acetate in hexanes) afforded

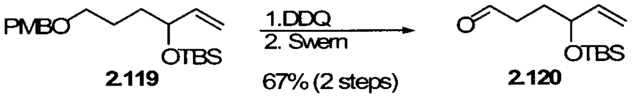
28.7 mg (48%) of **2.116** as a light yellow oil. IR (neat, cm^{-1}) 2955 (s), 2913 (s), 2877 (s), 1458 (m), 1239 (w), 1086 (m), 1007 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, *J*=16.8, 10.3, 6.4 Hz, 1H), 5.15-5.06 (m, 2H), 5.00 (d, *J*=10.3 Hz, 1H), 4.05 (ddd, *J*=6.3, 6.3, 6.3 Hz, 1H), 2.03-1.93 (m, 2H), 1.61 (s, 3H), 1.55 (s, 3H), 1.53-1.39 (m, 2H), 0.93 (t, *J*=8.1 Hz, 9H), 0.55 (q, *J*=7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8 (CH), 131.8 (C_{quat}), 124.4 (CH), 113.9 (CH_2), 73.7 (CH), 38.4 (CH_2), 25.9 (CH_3), 24.0 (CH_2), 17.9 (CH_3), 7.0 (CH_3x3), 5.1 (CH_2x3); HRMS (EI) m/z calcd for $C_{15}H_{30}OSi$ [M^+] 254.2066, found 254.2069.



(±)-*tert*-Butyl-[4-(4-methoxy-benzyloxy)-1-vinyl-butoxy]-dimethyl-silane (2.119). Procedure A: oxalyl chloride (0.719 mL, 8.25 mmol), dimethyl sulfoxide (0.858 mL, 12.1 mmol), alcohol **2.11** (1.02 g, 4.85 mmol), dichloromethane (18+5.6+4.4 mL), triethylamine (3.4 mL, 24.3 mmol).

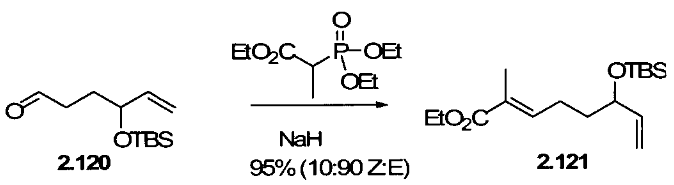
The crude aldehyde was dissolved in THF (40 mL) and cooled to -78 °C. Vinyl magnesium bromide (1.0 M in THF, 7.3 mL, 7.3 mmol) was added dropwise and the resulting solution was stirred 1h30 (the reaction mixture warmed to -40 °C) before being quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

The crude alcohol was dissolved in DMF (11 mL) and cooled to 0 °C. Imidazole (825 mg, 12.1 mmol) and TBSCl (877 mg, 5.8 mmol) were added sequentially and the mixture was stirred overnight. The reaction was quenched by adding water. The aqueous layer was extracted with EtOAc (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 764 mg (45%) of **2.119** as a light yellow oil. IR (neat, cm^{-1}) 2953 (s), 2930 (s), 2856 (m), 1613 (m), 1513 (s), 1463 (m), 1360 (m), 1248 (s), 1095 (s), 1038 (s), 835 (s), 775 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J*=8.7 Hz, 2H), 7.86 (d, *J*=8.7 Hz, 2H), 5.78 (ddd, *J*=16.4, 10.4, 6.0 Hz, 1H), 5.12 (ddd, *J*=17.2,1.7, 1.7Hz, 1H), 5.01 (ddd, *J*=10.4, 1.2, 1.2 Hz, 1H), 4.41 (s, 2H), 4.09 (ddd, J=6.0, 6.0, 6.0 Hz, 1H), 3.78 (s, 3H), 3.43 (t, J=6.2 Hz, 2H), 1.70-1.49 (m, 4H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C_{quat}), 141.7 (CH), 130.8 (C_{quat}), 129.3 (CHx2), 113.8 (CHx2), 113.8 (CH_2), 73.7 (CH), 72.6 (CH_2), 70.2 (CH_2), 55.3 (CH_3), 34.7 (CH_2), 26.0 (CH_3x3), 25.6 (CH_2), 18.3 (C_{quat}), -4.3 (CH_3), -4.7 (CH_3); HRMS (EI) m/z calcd for $C_{14}H_{18}O_2$ [$(M-C_6H_{16}OSi)^{+}$] 218.1301, found 218.1317.

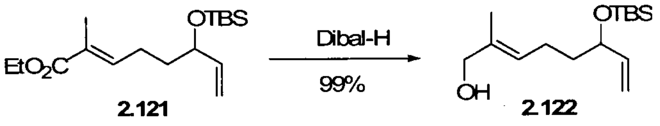


(±)-4-(*tert*-Butyl-dimethyl-silanyloxy)-hex-5-enal (2.120). To a solution of alkene **2.119** (660 mg, 1.88 mmol) in dichloromethane (19 mL) and water (1 mL) was added sodium acetate (105 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (449 mg, 1.98 mmol) . The mixture was stirred at ambient temperature for 2 h before a saturated solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane and the organic layers were washed with a saturated solution of sodium bicarbonate, then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (eluting with 15% ethyl acetate in hexanes) gave a mixture of alcohol and 4-methoxy-benzaldehyde (by-product of DDQ deprotection) that was used directly in the next step.

Procedure A: oxalyl chloride (0.222 mL, 2.55 mmol), dimethyl sulfoxide (0.265 mL, 3.75 mmol), crude alcohol, dichloromethane (5.6+1.7+1.4 mL), triethylamine (1.05 mL, 7.50 mmol). Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 231 mg (67%) of **2.120** as a yellow oil. IR (neat, cm^{-1}) 2955 (s), 2930 (s), 2857 (m), 2715 (w), 1727 (s), 1472 (w), 1253 (m), 1086 (m), 836 (s), 775 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J=1.6 Hz, 1H), 5.74 (ddd, J=17.0, 10.4, 5.7 Hz, 1H), 5.15 (d, J=17.2, 1H), 5.05 (d, J=10.4 Hz, 1H), 4.18 (ddd, J=5.7, 5.7, 5.7 Hz, 1H), 2.49-2.43 (m, 2H), 1.90-1.69 (m, 2H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8 (CH), 140.8 (CH), 114.7 (CH_2), 72.5 (CH), 39.4 (CH_2), 30.2 (CH_2), 25.9 (CH_3x3), 18.3 (C_{quat}), -4.3 (CH_3), -4.8 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{24}O_2Si$ [$(M-C_4H_9)^{+}$] 171.0836, found 171.0833.

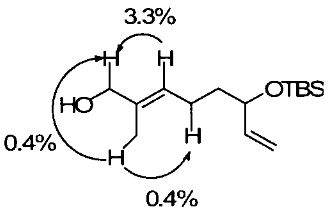


(±)-(*E*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-octa-2,7-dienoic acid ethyl ester (2.121). To 0 °C solution of triethyl-2-phosphonoproprionate (0.227 mL, 1.04 mmol) in 5 mL THF was added NaH (41.8 mg, 1.04 mmol). The resulting solution was stirred for 30 min. at room temperature. The reaction mixture was cooled to 0 °C before adding aldehyde **2.120** (159.0 mg, 0.696 mmol) in 2 mL THF. The solution was left warming up overnight before the reaction was quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 178.7 mg (95%) of **2.121** (90:10; E:Z) as a yellow oil. IR (neat, cm^{-1}) 2955 (s), 2930 (s), 2857 (m), 1712 (s), 1463 (w), 1258 (s), 835 (s), 775 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (ddd, *J*=7.5, 7.5, 1.4 Hz, 1H), 5.77 (ddd, *J*=17.1, 10.4, 6.0 Hz, 1H), 5.15 (ddd, *J*=17.2, 1.7, 1.7 Hz, 1H), 5.04 (ddd, *J*=10.4, 1.3, 1.3 Hz, 1H), 4.19-4.09 (m, 1H), 4.16 (q, *J*=7.1 Hz, 2H), 2.23-2.14 (m, 2H), 1.79 (s, 3H), 1.65-1.53 (m, 2H), 1.26 (t, *J*=7.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C_{quat}), 142.1 (CH), 141.3 (CH), 128.0 (C_{quat}), 114.3 (CH_2), 73.3 (CH), 60.5 (CH_2), 36.8 (CH_2), 26.0 (CH_3x3), 24.4 (CH_2), 18.4 (C_{quat}), 14.4 (CH_3), 12.5 (CH_3), -4.2 (CH_3), -4.7 (CH_3); HRMS (EI) m/z calcd for $C_{13}H_{21}O_3Si$ [$(M-C_4H_9)^+$] 255.1411, found 255.1415.

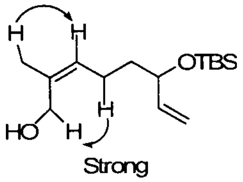


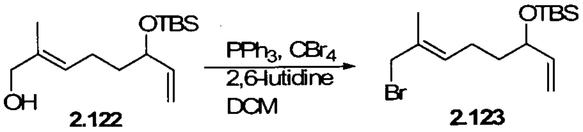
(±)-(*E*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-octa-2,7-dien-1-ol (2.122). To a -78 °C solution of ester **2.121** (178.7 mg, 0.572 mmol) in DCM (6 mL) was added Dibal-H in toluene (1.0 M, 1.72 mL, 1.72 mmol). The resulting solution was stirred for 1 hour before being quenched with a 1.0 M solution of sodium tartrate. The solution was stirred for 1h30, then the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in* *vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 93.3 mg of **2.122** and 63.5 mg of a mixture of *E* and *Z*-isomers (total: 154.8 mg, 100% yield) as yellow oils.

Major (2.122): IR (neat, cm^{-1}) 3335 (br), 2955 (s), 2929 (s), 2857 (s), 1472 (w), 1252 (m), 1081 (m), 836 (s), 775 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddd, *J*=17.1, 10.4, 6.1 Hz, 1H), 5.38 (dt, *J*=7.2, 1.2 Hz, 1H), 5.12 (ddd, *J*=17.1, 1.5, 1.5 Hz, 1H), 5.01 (ddd, *J*=10.4, 1.2, 1.2 Hz, 1H), 4.11-4.05 (m, 1H), 3.96 (s, 2H), 2.14-1.94 (m, 2H), 1.63 (s, 3H), 1.56-1.46 (m, 2H), 1.29 (br, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (CH), 135.0 (C_{quat}), 126.2 (CH), 113.9 (CH_2), 73.5 (CH), 69.1 (CH_2), 37.9 (CH_2), 25.9 (CH_3x3), 23.5 (CH_2), 18.4 (C_{quat}), 13.7 (CH_3) -4.2 (CH_3), -4.7 (CH_3); HRMS (EI) m/z calcd for $C_{11}H_{21}O_2Si$ [$(M-C_4H_9)^+$] 213.1305, found 213.1294.

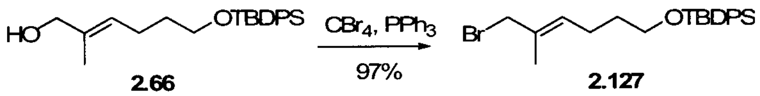


***Z*-isomer (minor):** IR (neat, cm^{-1}) 3326 (br), 2955 (s), 2929 (s), 2857 (s), 1472 (m), 1253 (s), 1083 (s), 1005 (s), 836 (s), 775 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, *J*=17.1, 10.4, 6.0 Hz, 1H), 5.28 (t, *J*=7.4 Hz, 1H), 5.12 (ddd, *J*=17.2, 1.4, 1.4 Hz, 1H), 5.02 (ddd, *J*=10.4, 1.2, 1.2 Hz, 1H), 4.11-4.08 (m, 1H), 4.10 (s, 2H), 2.13-1.98 (m, 2H), 1.77 (s, 3H), 1.53-1.47 (m, 2H), 1.23 (br, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6 (CH), 134.5 (C_{quat}), 128.4 (CH), 114.0 (CH_2), 73.4 (CH), 61.7 (CH_2), 38.4 (CH_2), 26.0 (CH_3x3), 23.4 (CH_2), 21.4 (CH_3), 18.4 (C_{quat}), -4.2 (CH_3), -4.7 (CH_3); HRMS (EI) m/z calcd for $C_{11}H_{21}O_2Si$ [$(M-C_4H_9)^+$] 213.1305, found 213.1316.

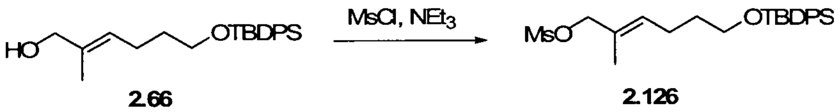




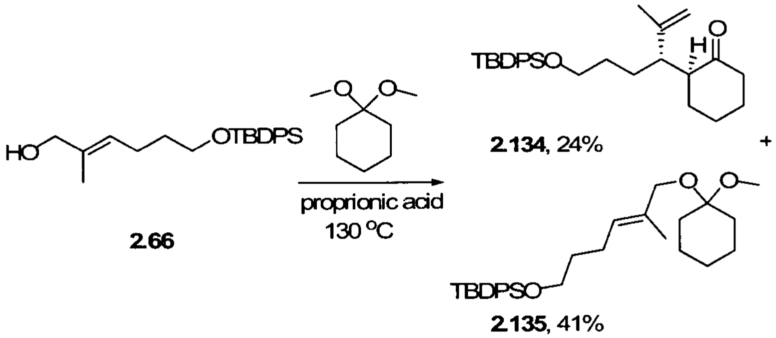
(±)-(*E*)-(6-Bromo-5-methyl-1-vinyl-hex-4-enyloxy)-*tert*-butyl-dimethyl-silane (2.123). To a solution of alcohol **2.122** (9.9 mg, 0.037 mmol) in DCM (0.5 mL) was added triphenylphosphine (24.3 mg, 0.093 mmol), 2,6-lutidine (0.013 mL, 0.111 mmol) and carbon tetrabromide (28.2 mg, 0.085 mmol) sequentially. The resulting solution was stirred 5 hours at room temperature. Silica was added to the reaction mixture and the solvent was evaporated. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 8.7 mg of **2.123** (71% yield) as a yellow oil. IR (neat, cm^{-1}) 2955 (s), 2929 (s), 2857 (s), 1471 (w), 1252 (m), 1084 (m), 836 (s), 775 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.77 (ddd, *J*=17.1, 10.4, 6.0 Hz, 1H), 5.58 (t, *J*=7.2 Hz, 1H), 5.13 (ddd, *J*=17.1, 1.4, 1.4 Hz, 1H), 5.02 (ddd, *J*=10.4, 1.2, 1.2 Hz, 1H), 4.11-4.06 (m, 1H), 3.95 (s, 2H), 2.13-1.96 (m, 2H), 1.73 (s, 3H), 1.56-1.48 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.5 (CH), 132.2 (C$_{quat}$), 131.4 (CH), 114.1 (CH$_2$), 73.4 (CH), 42.0 (CH$_2$), 37.4 (CH$_2$), 26.0 (CH$_3$x3), 24.2 (CH$_2$), 18.4 (C$_{quat}$), 14.8 (CH$_3$) -4.2 (CH$_3$), -4.7 (CH$_3$); HRMS (EI) m/z calcd for $C_{11}H_{20}O_2Si$ [(M-C$_4$H$_9$)$^+$] 275.0461, found 275.0492.



(*E*)-(6-Bromo-5-methyl-hex-4-enyloxy)-*tert*-butyl-diphenyl-silane (2.127). To a solution of alcohol **2.66** (1.09 g, 2.97 mmol) in DCM (30 mL) was added triphenylphosphine (1.95 g, 7.43 mmol), 2,6-lutidine (1.04 mL, 8.91 mmol) and carbon tetrabromide (2.27 g, 6.83 mmol) sequentially. The solution was stirred for 30 minutes before adding silica gel and evaporating the solvent *in vacuo*. Purification of the residue on silica gel (dry pack; elution with 5% ethyl acetate in hexanes) afforded 1.24 g (97%) of **2.127** as a yellow oil. IR (neat, cm^{-1}) 2928 (s), 2859 (m), 1585 (w), 1429 (w), 1112 (s), 704 (m); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.63-7.59 (m, 4H), 7.46-7.36 (m, 6H), 5.57 (t, *J*=7.3 Hz, 1H), 3.97 (s, 2H), 3.67 (t, *J*=6.2 Hz, 2H), 2.18-2.11 (m, 2H), 1.76 (s, 3H), 1.67-1.58 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.6 (CHx4), 134.0 (C$_{quat}$x2), 132.4 (C$_{quat}$), 131.2 (CH), 129.7 (CHx2), 127.7 (CHx4), 63.2 (CH$_2$), 41.9 (CH$_2$), 32.0 (CH$_2$), 27.0 (CH$_3$x3), 24.7 (CH$_2$), 19.3 (C$_{quat}$), 14.7 (CH$_3$); HRMS (EI) m/z calcd for $C_{19}H_{22}OSiBr$ [(M-C$_4$H$_9$)$^+$] 373.0618, found 373.0685.



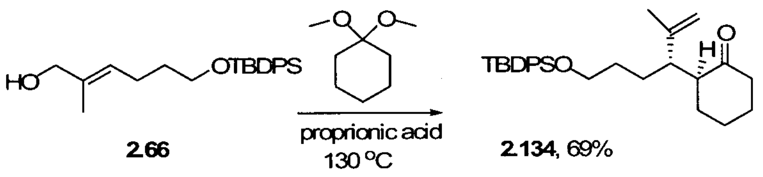
Methanesulfonic acid 6-(*tert*-butyl-diphenyl-silanyloxy)-2-methyl-hex-2-enyl ester (2.126). To a 0 °C solution of alcohol **2.66** (216.5 mg, 0.587 mmol) in dichloromethane (2 mL) was added triethylamine (0.246 mL, 1.76 mmol) then methanesulfonyl chloride (0.050 mL, 0.646 mmol). The solution was stirred for 35 minutes (not longer!) and quenched at 0 °C with a saturated solution of sodium bicarbonate. The mixture was extracted quickly 3x with dichloromethane. The resulting organic layers were dried with magnesium sulfate, filtered and concentrated *in vacuo*. A crude NMR indicated that the desired mesylate was present. It was found that purification of the product led to its decomposition. The mesylate was used directly or froze in benzene until it was used.



(±)-(2*S*,1'*S*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-cyclohexanone (2.134). To a solution of cyclohexanone dimethylketal (0.492 mL, 3.23 mmol) and alcohol **2.66** (595.6 mg, 1.62 mmol) was added propionic acid (0.018 mL, 0.242 mmol). The flask was mounted with a distillation apparatus and the solution was heated to 125 °C for 15 hours. The solution was cooled to room temperature and diluted with diethyl ether. The reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with diethyl ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 181.2 mg (24%) of **2.134** and 319.3 mg (41%) of **2.135** as yellow oils.

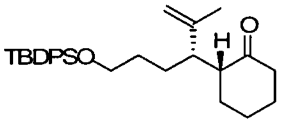
2.134: IR (neat, cm^{-1}) 2933 (s), 2858 (s), 1709 (s), 1428 (m), 1111 (s), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.61 (m, 4H), 7.47-7.34 (m, 6H), 4.77 (dd, J=1.6, 1.6 Hz,1H), 4.64 (s, 1H), 3.70-3.62 (m, 2H), 2.56-2.51 (m, 1H), 2.46-2.34 (m, 2H), 2.24-2.18 (m, 1H), 1.92-1.65 (m, 5H), 1.63 (s, 3H), 1.59-1.25 (m, 5H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (C_{quat}), 145.9 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 112.3 (CH_2), 64.0 (CH_2), 54.0 (CH), 44.8 (CH), 41.2 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 28.0 (CH_2), 27.0 (CH_3x3), 25.4 (CH_2), 23.1 (CH_2), 19.9 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{25}H_{31}O_2Si$ [$(M-C_4H_9)^+$] 391.2088, found 391.2063.

(±)-(*E*)-*tert*-Butyl-[6-(1-methoxy-cyclohexyloxy)-5-methyl-hex-4-enyloxy]-diphenyl-silane (2.135). IR (neat, cm^{-1}) 2934 (s), 2857 (s), 1738 (w), 1428 (m), 1105 (s), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.61 (m, 4H), 7.42-7.33 (m, 6H), 5.42-5.38 (m, 1H), 3.75 (s, 2H), 3.65 (t, J=6.3 Hz, 2H), 3.17 (s, 3H), 2.15-2.09 (m, 2H), 1.65 (s, 3H), 1.65-1.57 (m, 6H), 1.53-1.45 (m, 4H), 1.41-1.36 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CHx4), 134.2 (C_{quat}x2), 133.1 (C_{quat}), 129.6 (CHx2), 127.7 (CHx4), 126.8 (CH), 100.3 (C_{quat}), 65.9 (CH_2), 63.6 (CH_2), 47.7 (CH_3), 33.4 (CH_2x2), 32.6 (CH_2), 27.0 (CH_3x3), 25.8 (CH_2), 24.2 (CH_2), 23.1 (CH_2x2), 19.4 (C_{quat}), 14.4 (CH_3); HRMS (EI) m/z calcd for $C_{29}H_{40}O_2Si$ [$(M-CH_4O)]^+$ 448.2798, found 448.2794.

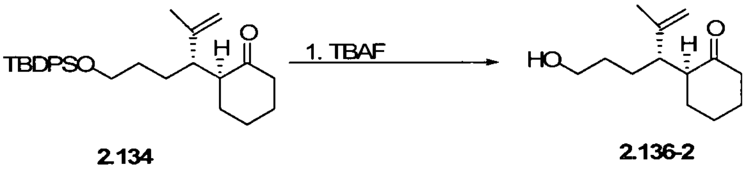


Better method to ketone **2.134**: To a solution of cyclohexanone dimethylketal (1.57 mL, 10.33 mmol) and alcohol **2.66** (1.90 g, 5.17 mmol) was added propionic acid (0.058 mL, 0.776 mmol). The flask was mounted with a distillation apparatus and the solution was heated to 125-133 °C for 8 hours. The solution was cooled to room temperature and diluted with diethyl ether. The reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with diethyl ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 1.59 g (69%) of **2.134** and 0.67 g of **2.134** and **2.134b** as yellow oils.

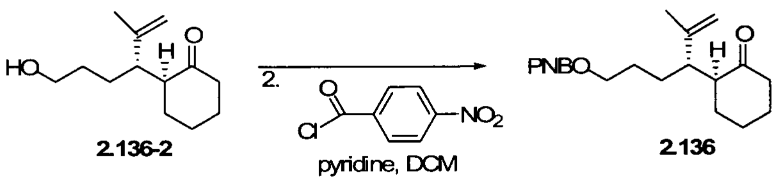
(±)-(2*R*,1'*S*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-cyclohexanone (2.134b)



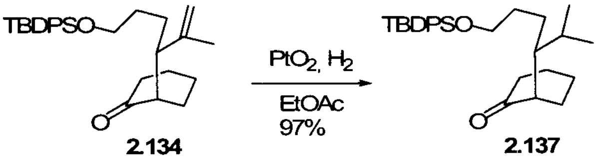
(characterized as mixture): IR (neat, cm^{-1}) 2932 (s), 2857 (s), 1707 (s), 1426 (s), 1109 (s), 702 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68-7.64 (m, 4H), 7.42-7.35 (m, 6H), 4.84 (dd, *J*=1.5, 1.5 Hz,1H), 4.73 (dd, *J*=2.2, 2.2 Hz, 1H), 3.69-3.56 (m, 2H), 2.56-2.18 (m, 4H), 1.91-1.65 (m, 4H), 1.61-1.19 (m, 6H), 1.53 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 214.4 (C$_{quat}$), 144.2 (C$_{quat}$), 135.7 (CHx4), 134.2 (C$_{quat}$x2), 129.7 (CHx2), 127.7 (CHx4), 114.6 (CH$_2$), 63.9 (CH$_2$), 53.7 (CH), 46.6 (CH), 41.8 (CH$_2$), 32.1 (CH$_2$), 30.7 (CH$_2$), 28.9 (CH$_2$), 27.1 (CH$_2$), 27.0 (CH$_3$x3), 23.2 (CH$_2$), 19.3 (C$_{quat}$), 17.6 (CH$_3$); HRMS (EI) m/z calcd for $C_{25}H_{31}O_2Si$ [(M-C$_4$H$_9$)$^+$] 391.2088, found 391.2095.



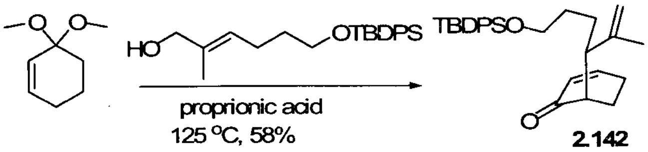
(±)-(2*S*,1'*S*)-2-(4-Hydroxy-1-isopropenyl-butyl)-cyclohexanone (2.136-2). To a solution of silylated enol ether **2.134** (34.7 mg, 0.077 mmol) in tetrahydrofuran (1 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.170 mL, 0.170 mmol). The mixture was stirred for 3 h at ambient temperature before a solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 40-50% ethyl acetate in hexanes) afforded 12.6 mg (78%) of **2.136-2** as a yellow oil. IR (neat, cm^{-1}) 3403 (br), 2938 (s), 2861 (m), 1707 (s), 1643 (w), 1449 (m), 1069 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.83 (dd, *J*=1.6, 1.6 Hz,1H), 4.69 (dd, *J*=0.9, 0.9Hz, 1H), 3.68-3.61 (m, 2H), 2.64-2.59 (m, 1H), 2.44-2.30 (m, 2H), 2.27-2.17 (m, 1H), 1.97-1.63 (m, 5H), 1.57 (s, 3H), 1.56-1.31 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 213.4 (C$_{quat}$), 145.6 (C$_{quat}$), 112.2 (CH$_2$), 62.6 (CH$_2$), 53.7 (CH), 43.4 (CH), 41.7 (CH$_2$), 30.2 (CH$_2$), 28.7 (CH$_2$), 27.8 (CH$_2$), 24.7 (CH$_2$), 23.9 (CH$_2$), 21.1 (CH$_3$); HRMS (EI) m/z calcd for $C_{13}H_{22}O_2$ [M$^+$] 210.1620, found 210.1637.



(±)-(4*S*,1'*S*)-4-Nitro-benzoic acid 5-methyl-4-(2-oxo-cyclohexyl)-hex-5-enyl ester (2.136). To a solution of alcohol **2.136-2** (6.7 mg, 0.032 mmol) in DCM (0.3 mL) was added triethylamine (0.022 mL, 0.159 mmol) and *p*-nitrobenzoylchloride (11.9 mg, 0.064 mmol) sequentially. The solution was stirred for 18 hours before it was purified directly by flash chromatography (20% ethyl acetate in hexanes) to give 7.4 mg (64%) of **2.136** as a yellow oil. IR (neat, cm^{-1}) 2940 (m), 2863 (w), 1724 (s), 1708 (s), 1528 (s), 1276 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.27 (d, *J*=9.0 Hz, 2H), 8.19 (d, *J*=9.0 Hz, 2H), 4.85 (dd, *J*=1.6, 1.6 Hz,1H), 4.70 (s, 1H), 4.36-4.32 (m, 2H), 2.66-2.61 (m, 1H), 2.44-2.36 (m, 2H), 2.27-2.20 (m, 1H), 1.98-1.69 (m, 5H), 1.68 (s, 3H), 1.66-1.52 (m, 4H), 1.45-1.35 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 212.5 (C$_{\text{quat}}$), 164.8 (C$_{\text{quat}}$), 150.6 (C$_{\text{quat}}$), 145.4 (C$_{\text{quat}}$), 136.0 (C$_{\text{quat}}$), 130.8 (CHx2), 123.7 (CHx2), 112.5 (CH$_2$), 66.1 (CH$_2$), 53.6 (CH), 44.1 (CH), 41.7 (CH$_2$), 28.9 (CH$_2$), 27.8 (CH$_2$), 26.7 (CH$_2$), 25.2 (CH$_2$), 23.8 (CH$_2$), 21.0 (CH$_3$); HRMS (EI) m/z calcd for $C_{20}H_{25}NO_5$ [M$^+$] 359.1733, found 359.1748.



(±)-(2*S*,1'*R*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-cyclohexanone (2.137). Platinum oxide (10.5 mg, 0.046 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.134** (0.83 g, 1.85 mmol) in ethyl acetate (19 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 808.5 mg of **2.137** (97%) as a colorless oil. IR (neat, cm^{-1}) 2931 (s), 2858 (s), 1705 (s), 1428 (w), 1106 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67-7.64 (m, 4H), 7.42-7.33 (m, 6H), 3.72-3.57 (m, 2H), 2.42-2.19 (m, 3H), 2.00-1.83 (m, 4H), 1.73-1.51 (m, 6H), 1.35-1.11 (m, 2H), 1.03 (s, 9H), 0.84 (d, *J*=6.8 Hz, 3H), 0.82 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.6 (CHx2), 127.6 (CHx4), 64.5 (CH_2), 52.9 (CH), 42.0 (CH), 40.7 (CH_2), 32.9 (CH_2), 30.3 (CH), 29.2 (CH_2), 27.6 (CH_2), 27.0 (CH_3x3), 25.3 (CH_2), 24.7 (CH_2), 20.7 (C_{quat}), 19.6(CH_3), 19.3 (CH_3); HRMS (EI) m/z calcd for $C_{25}H_{33}O_2Si$ [$(M-C_4H_9)^+$] 393.2244, found 393.2267.

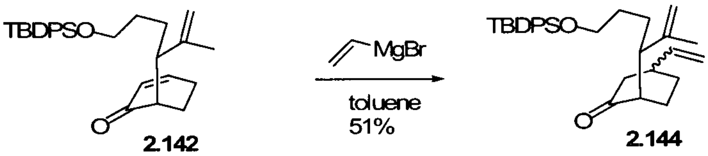


(±)-(6*S*,1'*S*)-6-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-cyclohex-2-enone (2.142). To a solution of cyclohexenone dimethylketal (0.475 mL, 2.78 mmol) and alcohol **2.66** (513 mg, 1.39 mmol) was added propionic acid (0.016 mL, 0.209 mmol). The flask was mounted with a distillation apparatus and the solution was heated to 125 °C for 24 hours. The solution was cooled to room temperature and diluted with diethyl ether. The reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with diethyl ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 362.7 mg (58%) of **2.142** (mixture of 2 isomers: 1:0.4) as colorless oils (characterized as a mixture)

(major): IR (neat, cm^{-1}) 2934 (s), 2861 (s), 1681 (s), 1427 (m), 1384 (w), 1109 (s), 707 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.42-7.33 (m, 6H), 6.88-6.83 (m, 1H), 5.95 (ddd, *J*=10.0, 1.9, 1.9 Hz, 1H), 4.82 (dd, *J*=1.6, 1.6 Hz, 1H), 4.63 (s, 1H), 3.68-3.56 (m, 2H), 2.70-2.65 (m, 1H), 2.45-2.19 (m, 4H), 1.99-1.79 (m, 2H), 1.68 (s, 3H), 1.43-1.35 (m, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0 (C_{quat}), 149.1 (CH), 145.7 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.9 (CH), 129.6 (CHx2), 127.7 (CHx4), 112.2 (CH_2), 64.1 (CH_2), 49.7 (CH), 44.1 (CH), 30.9 (CH_2), 27.7 (CH_3x3), 25.1 (CH_2), 24.9 (CH_2), 23.7 (CH_2), 21.1 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{25}H_{29}O_2Si$ [$(M-C_4H_9)^+$] 389.1931, found 389.1903.

(±)-(6*R*,1'*S*)-6-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-cyclohex-2-enone (2.142b)

(minor): IR (neat, cm^{-1}) 2934 (s), 2861 (s), 1681 (s), 1427 (m), 1384 (w), 1109 (s), 707 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.42-7.33 (m, 6H), 6.88-6.83 (m, 1H), 5.90(ddd, *J*=10.1, 1.8, 1.8 Hz, 1H), 4.86 (dd, *J*=1.4, 1.4 Hz, 1H), 4.75 (s, 1H), 3.68-3.56 (m, 2H), 2.45-2.19 (m, 4H), 1.99-1.79 (m, 2H), 1.56 (s, 3H), 1.43-1.35 (m, 4H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3 (C_{quat}), 149.3 (CH), 145.1 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.6 (CHx2), 129.0 (CH), 127.7 (CHx4), 114.4 (CH_2), 63.8 (CH_2), 48.8 (CH), 45.6 (CH), 30.7 (CH_2), 27.7 (CH_3x3), 26.6 (CH_2), 25.7 (CH_2), 23.2 (CH_2), 19.3 (C_{quat}), 17.7 (CH_3); HRMS (EI) m/z calcd for $C_{25}H_{29}O_2Si$ [$(M-C_4H_9)^+$] 389.1931, found 389.1903.

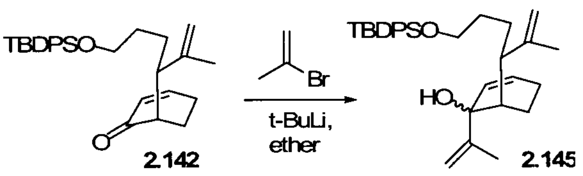


(±)-(2*S*,1'*S*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-5-vinyl-cyclohexanone (2.144). To a -78 °C solution of enone **2.142** (33.3 mg, 0.075 mL) in toluene (0.75 mL) was added vinylmagnesium bromide (0.224 mL, 0.224 mmol) dropwise. The solution was stirred for 1 hour before quenching with a saturated solution of ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 8.4 mg of **2.144a** and 9.9 mg of **2.144b** (51% yield) as colorless oils.

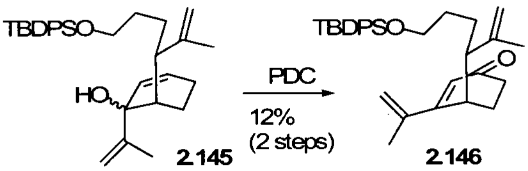
2.144a: IR (neat, cm^{-1}) 2934 (s), 2856 (s), 1712 (s), 1644 (w), 1428 (m), 1111 (s), 823 (w), 704 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.61 (m, 4H), 7.42-7.33 (m, 6H), 5.76(ddd, *J*=17.0, 10.4, 6.0 Hz, 1H), 5.00 (d, *J*=16.9 Hz, 1H), 4.98 (d, *J*=10.4 Hz, 1H), 4.80 (dd, *J*=1.5, 1.5 Hz, 1H), 4.63 (s, 1H), 3.68-3.57 (m, 2H), 2.56-2.51 (m, 1H), 2.46-2.41 (m, 2H), 2.37-1.91 (m, 4H), 1.66 (s, 3H), 1.55-1.32 (m, 6H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2 (C_{quat}), 146.7 (C_{quat}), 141.5 (CH), 135.7 (CHx4), 134.3 (C_{quat}x2), 129.6

(CHx2), 127.7 (CHx4), 113.7 (CH_2), 111.3 (CH_2), 64.3 (CH_2), 53.1 (CH), 47.5 (CH_2), 43.5 (CHx2), 31.1 (CH_2), 30.5 (CH_2), 27.7 (CH_2), 27.0 (CH_3x3), 25.4 (CH_2), 22.2 (CH_3), 19.4 (C_{quat}); HRMS (EI) m/z calcd for $C_{27}H_{33}O_2Si$ [$(M-C_4H_9)^+$] 417.2244, found 417.2241.

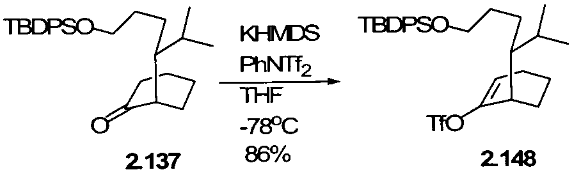
2.144b: IR (neat, cm^{-1}) 2929(s), 2859 (m), 1710 (s), 1426 (w), 1111(s), 703 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.60 (m, 4H), 7.42-7.34 (m, 6H), 5.76(ddd, *J*=16.5, 10.1, 6.6 Hz, 1H), 5.02-4.96 (m, 2H), 4.73 (dd, *J*=1.6, 1.6 Hz, 1H), 4.63 (s, 1H), 3.65-3.59 (m, 2H), 2.54-2.22 (m, 5H), 2.10-1.52 (m, 4H), 1.51 (s, 3H), 1.49-1.16 (m, 4H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7 (C_{quat}), 145.1 (C_{quat}), 141.5 (CH), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.7 (CHx2), 127.7 (CHx4), 113.9 (CH_2), 113.7 (CH_2), 63.8 (CH_2), 53.6 (CH), 46.1(CH), 44.9 (CH_2), 43.1 (CH), 30.3 (CH_2), 27.0 (CH_3x3), 26.8 (CH_2), 26.6 (CH_2), 25.5 (CH_2), 19.3 (C_{quat}), 17.7 (CH_3); HRMS (EI) m/z calcd for $C_{27}H_{33}O_2Si$ [$(M-C_4H_9)^+$] 417.2244, found 417.2267.



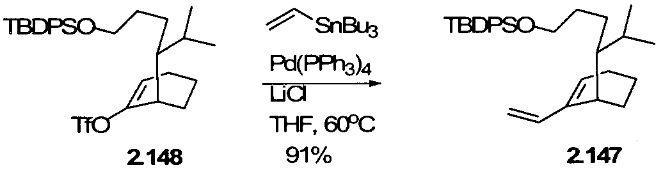
(±)-(1*R*,6*S*,1'*S*)-6-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-1-isopropenyl-cyclohex-2-enol or (±)-(1*S*,6*S*,1'*S*)-6-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-1-isopropenyl-cyclohex-2-enol (2.143). To a -78 °C solution of 2-bromopropene (0.067 mL, 0.770 mmol) in diethyl ether (1 mL) was added *t*-BuLi (1.056 mL, 1.542 mmol) and the resulting solution was stirred 30 minutes at the same temperature then 15 minutes at 0 °C. The clear solution was cooled back to -78 °C and a solution of enone **2.142** (114.6 mg, 0.257 mmol) in diethyl ether (1 mL) was cannulated. The solution was warmed slowly until -20 °C where TLC analysis showed complete disappearance of the starting material. The solution was quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was used in the next step but an aliquot was purified (flash chromatography: 10% ethyl acetate in hexanes) and characterized. IR (neat, cm^{-1}) 3513 (br), 2931 (s), 2858 (m), 1428 (m), 1112 (s), 702 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.41-7.35 (m, 6H), 5.86-5.81 (m, 1H), 5.45-5.41 (m, 1H), 5.16 (s, 1H), 4.95 (s, 1H), 4.68 (s, 1H), 4.61 (s,1H), 3.65-3.59 (m, 2H), 2.27-2.24 (m, 1H), 2.15-2.14 (m, 1H), 1.99-1.88 (m, 2H), 1.66 (s, 3H), 1.63 (s, 3H), 1.79-1.18 (m, 7H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (C_{quat}), 149.0 (C_{quat}), 135.7 (CHx4), 134.4 (C_{quat}x2), 133.3 (CH), 130.3(CH), 129.6 (CHx2), 127.7 (CHx4), 111.7 (CH_2), 110.7 (CH_2), 76.8 (C_4), 64.3 (CH_2), 44.3 (CH), 42.1 (CH), 31.1 (CH_2), 27.0 (CH_3x3), 26.2 (CH_2), 24.4 (CH_2), 20.6 (CH_3), 20.5 (CH_2), 19.9 (C_{quat}), 19.3 (CH_3); HRMS (EI) m/z calcd for $C_{28}H_{35}O_2Si$ [$(M-C_4H_9)^+$] 431.2401, found 431.2413.



(±)-(4*S*,1'*S*)-4-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-3-isopropenyl-cyclohex-2-enone (2.146). To a solution of allylic alcohol **2.145** (27.3 mg, 0.056 mmol) in dichloromethane (0.5 mL) was added PDC (42.0 mg, 0.112 mmol) and silica (25.9 mg). The mixture was stirred for 2 days before being filtered through celite using diethyl ether as a solvent. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 3.6 mg of **2.146** (13% over 2 steps) as a colorless oil and 7.9 mg (29%) of recovered starting material. IR (neat, cm^{-1}) 2931 (s), 2858 (s), 1665 (s), 1428 (m), 1112 (s), 703 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.60 (m, 4H), 7.40-7.33 (m, 6H), 6.00 (s, 1H), 5.24 (s, 1H), 5.14 (s, 1H), 4.81 (t, J=1.5 Hz, 1H), 4.65 (s, 1H), 3.65-3.57 (m, 2H), 2.83-2.79 (m, 1H), 2.51-2.42 (m, 1H), 2.35-1.91 (m, 4H), 1.88 (s, 3H), 1.79-1.17 (m, 4H), 1.65 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6 (C_{quat}), 165.6 (C_{quat}), 144.7 (C_{quat}), 143.1 (C_{quat}), 135.7 (CHx4), 134.1 (C_{quat}x2), 129.7 (CHx2), 127.8 (CHx4), 125.2 (CH), 117.4 (CH_2), 113.7 (CH_2), 63.9 (CH_2), 49.7 (CH), 37.6 (CH), 34.1 (CH_2), 31.1 (CH_2), 27.0 (CH_3x3), 25.6 (CH_2), 24.2 (CH_2), 21.1 (CH_3), 20.8 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{12}H_{11}OSi$ [$(M-C_{20}H_{31}O)^+$] 199.0574, found 199.0559.

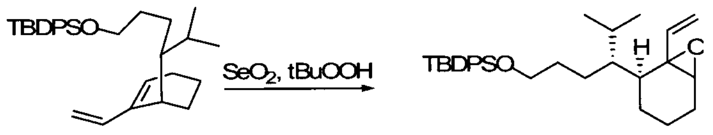


(±)-(6*S*,1'*R*)- Trifluoro-methanesulfonic acid 6-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-cyclohex-1-enyl ester (2.148). To a -78 °C solution of ketone **2.137** (0.67 g, 1.49 mmol) in 20 mL of THF was cannulated slowly a solution of KHMDS (889 mg, 4.46 mmol) in THF (20 mL). The resulting clear solution was stirred for 1 hour at the same temperature before adding *N*-phenyltrifluorosulfonimide (1.07 g, 2.98 mmol) in THF (5 mL). The solution was stirred for 1 hour during which the reaction turned orange. Silica gel was added to the solution and the solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 746.6 mg (86%) of **2.148** as colorless oil. IR (neat, cm^{-1}) 2933 (s), 2860 (m), 1412 (m), 1245 (w), 1210 (s), 1144 (m), 1112 (s), 1021 (w), 891 (w), 703 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.40-7.33 (m, 6H), 5.80-5.78 (m, 1H), 3.60 (t, *J*=6.0 Hz, 2H), 2.77-2.71 (m, 1H), 2.20-1.99 (m, 2H), 1.84-1.69 (m, 2H), 1.62-1.15 (m, 8H), 1.02 (s, 9H), 0.94 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 120.9 (CH), 64.1 (CH_2), 44.0 (CH), 40.3 (CH), 33.3 (CH_2), 30.7 (CH), 27.0 (CH_3x3), 25.4 (CH_2), 24.4 (CH_2), 24.1 (CH_2), 21.6 (CH_3), 21.2 (CH_2), 21.0 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{26}H_{32}O_4SiSF_3$ [$(M-C_4H_9)^+$] 525.1737, found 525.1720.



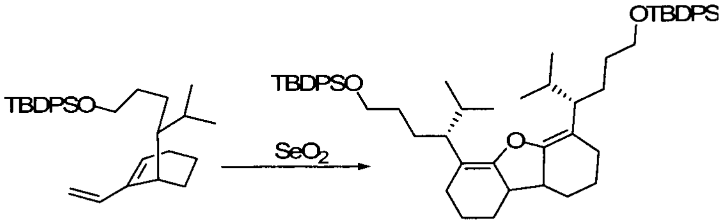
(±)-(1'*S*,4*R*)-*tert*-Butyl-[5-methyl-4-(2-vinyl-cyclohex-2-enyl)-hexyloxy]-diphenyl-silane (2.147). To a dry sealed tube was added LiCl (19.8 mg, 0.467 mmol) and was flame-dried. Once the flask was cooled to room temperature, a solution of triflate **2.148** (90.8 mg, 0.156 mmol) and tetrakis(triphenylphosphine) palladium (1.8 mg, 0.0016 mmol) in THF (0.85 mL) was cannulated. Tributylvinyltin (0.047 mL, 0.156 mmol) was added and the flask was sealed. The solution was heated to 60 °C for 18 hours. After cooling to room temperature, the reaction was quenched with water. The aqueous layer was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (dry pack; elution with 0 to 5% ethyl acetate in hexanes) afforded 65.2 mg of **2.147**

(91%) as a colorless oil. IR (neat, cm^{-1}) 2929 (s), 2859 (m), 1587 (w), 1426 (m), 1111(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.41-7.32 (m, 6H), 6.12 (dd, *J*=17.7, 11.0 Hz, 1H), 5.87 (dd, *J*=3.9, 3.9 Hz, 1H), 5.02 (d, *J*=17.5 Hz, 1H), 4.85 (d, *J*=10.7 Hz, 1H), 3.54 (d, J_{AB}=6.4 Hz, 1H), 3.51 (d, J_{AB}=6.3 Hz, 1H), 2.74-2.69 (m, 1H), 2.07-1.93 (m, 2H), 1.73-1.19 (m, 10H), 1.01 (s, 9H), 0.93 (d, *J*=6.6 Hz, 3H), 0.92 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (C_{quat}), 139.6 (CH), 135.7 (CHx4), 134.4 (C_{quat}x2), 130.6 (CH), 129.6 (CHx2), 127.7 (CHx4), 111.0 (CH_2), 64.7 (CH_2), 46.0 (CH), 36.3 (CH), 34.0 (CH_2), 31.3 (CH), 27.0 (CH_3x3), 26.0 (CH_2), 25.9 (CH_2), 23.7 (CH_2), 21.9 (CH_3), 21.6 (CH_2), 21.5 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{27}H_{35}OSi$ [$(M-C_4H_9)^+$] 403.2452, found 403.2467.



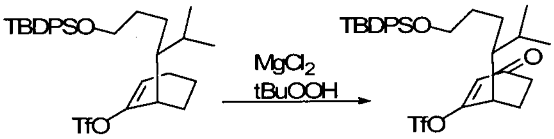
2.147 2.150

***tert*-Butyl-[5-methyl-4-(1-vinyl-7-oxa-bicyclo[4.1.0]hept-2-yl)-hexyloxy]-diphenyl-silane (2.150).** To a solution of diene 2.147 (5.4 mg, 0.012 mmol) in dichloromethane (0.5 mL) was added SeO_2 (0.9 mg, 0.008 mmol) then *t*-BuOOH (0.010 mL, 0.064 mmol). The mixture was stirred overnight at room temperature before quenching with sodium carbonate. The resulting mixture was extracted 3x with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20% ethyl acetate in hexanes) afforded 2.3 mg of **2.150** (46%) as a colorless oil. IR (neat, cm^{-1}) 2931 (s), 2858 (m), 1464 (w), 1426 (w), 1111 (s), 702 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.61 (m, 4H), 7.40-7.32 (m, 6H), 6.11 (dd, *J*=17.2, 11.0 Hz, 1H), 5.29 (dd, *J*=17.1, 1.7 Hz, 1H), 5.03 (dd, *J*=10.5, 1.6 Hz, 1H), 3.55 (t, *J*=6.5 Hz, 2H), 3.51 (s, 1H), 2.43 (s, 1H), 1.95 (s, 1H), 1.91-1.88 (m, 1H), 1.83-1.80 (m, 1H), 1.76-1.65 (m, 1H), 1.64-1.17 (m, 8H), 1.01 (s, 9H), 0.87 (d, *J*=6.9 Hz, 3H), 0.73 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (CH), 135.7 (CHx4), 134.3 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 114.6 (CH_2), 77.2 (C_{quat}), 74.6 (CH), 64.6 (CH_2), 40.0 (CH), 39.1 (CH), 32.0 (CH_2), 29.7 (CH), 29.4 (CH_2), 27.0 (CH_3x3), 26.3 (CH_2), 24.9 (CH_2), 21.6 (CH_2), 19.9 (CH_2), 19.3 (C_{quat}), 17.4 (CH_3); HRMS (EI) m/z calcd for $C_{27}H_{35}O_2Si$ [$(M-C_4H_9)^+$] 419.2401, found 419.2408.



2.147 2.151

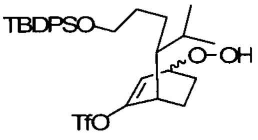
(±)-(1*S*,1*R*)-4,6-Bis-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-1,2,3,7,8,9,9a,9b-octahydro-dibenzofuran(2.151). Here is one of the methods that produced this product: To a flame-dried flask was added selenium dioxide (8.5 mg, 0.076 mmol) and diene **2.147** (32.2 mg, 0.070 mmol) in dichloromethane (0.7 mL). The resulting solution was stirred overnight at room temperature before quenching with sodium carbonate. The aqueous layer was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 7% ethyl acetate in hexanes) afforded 10.7 mg of **2.151** (35%) as a yellow oil. IR (neat, cm^{-1}) 2957 (s), 2861 (m), 1424 (s), 1212 (s), 1111(s), 703 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 8H), 7.40-7.34 (m, 12H), 3.64-3.53 (m, 4H), 2.87-2.82 (m, 2H), 2.46-2.42 (m, 4H), 1.87-1.79 (m, 4H), 1.63-1.49 (m, 8H), 1.41-1.19 (m, 8H), 1.03 (s, 18H), 0.95 (d, J=6.6 Hz, 6H), 0.87 (d, J=6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (C_{quat}x2), 135.7 (CHx8), 134.2 (C_{quat}x4), 129.7 (CHx4), 127.7 (CHx8), 127.4 (C_{quat}x2), 64.4 (CH_2x2), 44.4 (CHx2), 41.6 (CHx2), 33.4 (CH_2x2), 33.2 (CH_2x2), 31.1 (CHx2), 27.0 (CH_3x6), 25.5 (CH_2x2), 23.7 (CH_2x2), 22.0 (CH_2x2), 21.6 (CH_3x2), 21.0 (CH_3x2), 19.3 (C_{quat}x2); HRMS (EI) m/z calcd for $C_{27}H_{29}O_2Si$ $[(M-C_{31}H_{51}OSi)^+]$ 413.1931, found 413.1899.



2.148 2.152

(±)-(6*S*,1'*R*)-Trifluoro-methanesulfonic acid 6-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-oxo-cyclohex-1-enyl ester (2.152). To a solution of triflate **2.148** (52.0 mg, 0.089 mmol) in DCE (1.5 mL) was added $MgCl_2$ (20.4 mg, 0.214 mmol) and *t*-butylhydroperoxide (0.089 mL, 0.445 mmol). Balloon of oxygen was added (it was later found that just doing the reaction in air gave the same result) and the reaction was refluxed for 18 hours. The heterogeneous solution was filtered and silica gel was added before evaporation *in vacuo*. Purification of the residue on silica gel (dry pack; elution with 12% ethyl acetate in hexanes) afforded 13.6 mg (26%) of **2.152** as a colorless oil and 24.8 mg of recovered starting material (48%). IR (neat, cm^{-1}) 2964 (s), 2863 (m), 1693 (s), 1423 (s), 1216 (s), 1141 (m), 1108 (m), 704 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61-7.60 (m, 4H), 7.41-7.33 (m, 6H), 6.04 (d, *J*=2.0Hz, 1H), 3.59 (td, *J*=6.3, 2.3 Hz, 2H), 2.99-2.98 (m, 1H), 2.50 (ddd, *J*=17.0, 4.9, 4.9 Hz, 1H), 2.38-2.31 (m, 1H), 2.09-2.02 (m, 1H), 1.81-1.73 (m, 1H), 1.67-1.56 (m, 4H), 1.51-1.12 (m, 2H), 1.01 (s, 9H), 0.98 (d, *J*=6.5 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7 (C_{quat}), 170.4 (C_{quat}), 135.7 (CHx4), 134.0 (C_{quat}x2), 129.8 (CHx2), 127.8 (CHx4), 120.9 (CH), 64.0 (CH_2), 44.4 (CH), 41.3 (CH), 36.2 (CH_2), 33.0 (CH_2), 30.6 (CH), 27.0 (CH_3x3), 25.9 (CH_2), 21.7 (CH_2), 21.1 (CH_3), 21.0 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{26}H_{30}O_4SiSF_3$ [$(M-C_4H_9)^+$] 539.1530, found 539.1544.

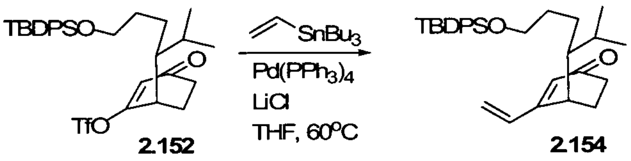
(±)-(3*R*,6*S*,1'*R*)-Trifluoro-methanesulfonic acid 6-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-hydroperoxy-cyclohex-1-enyl ester and (±)-(3*S*,6*S*,1'*R*)-Trifluoro-methanesulfonic acid 6-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-hydroperoxy-cyclohex-1-enyl ester (2.153)



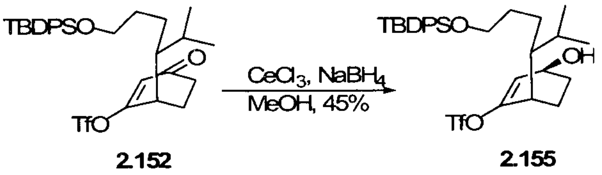
2.153

When the allylic oxidation was done on larger scale, peroxide **2.153** was observed as a yellow oil. IR (neat, cm^{-1}) 3429 (br), 2965 (s), 2856 (m), 1719 (w), 1263 (s), 1166 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (m, 8H), 7.42-7.34 (m, 12H), 5.99 (s, 1H), 5.90 (dd, *J*=5.5, 1.3 Hz, 1H), 4.62-4.61 (m, 2H), 3.61-3.57 (m, 4H), 2.82-2.75 (m, 1H), 2.74-2.67 (m, 1H), 2.13-2.03 (m, 2H), 2.02-1.98 (m, 2H), 1.92-1.83 (m, 2H), 1.67-1.22 (m, 16H), 1.02 (s, 18H), 0.95 (d, *J*=6.7 Hz, 3H), 0.94 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2 (C_{quat}), 154.4 (C_{quat}), 135.4 (CHx8), 134.0 (C_{quat}x2), 133.8 (C_{quat}x2), 129.4 (CHx4), 127.4 (CHx8), 119.8 (CH), 116.6 (CH), 79.0 (CH), 76.9 (CH), 64.0 (CH_2), 63.9 (CH_2), 43.6 (CH), 43.5 (CH), 40.6 (CH), 39.9 (CH), 32.9 (CH_2), 32.8 (CH_2), 30.4 (CH), 30.3 (CH), 26.7 (CH_3x6), 25.2 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 21.3

(CH$_3$), 21.2 (CH$_3$), 20.7 (CH$_3$), 20.7 (CH$_3$), 20.5 (CH$_2$), 19.0 (C$_{quat}$x2), 18.6 (CH$_2$); HRMS (EI) m/z calcd for $C_{26}H_{30}O_4SiSF_3$ [(M-C$_4$H$_{11}$O$_2$)$^+$] 523.1581, found 523.1582.

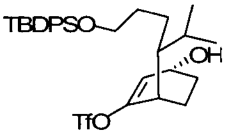


(±)-(4*S*,1'*R*)-4-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-vinyl-cyclohex-2-enone (2.154). To a dry sealed tube was added LiCl (3.0 mg, 0.070 mmol) and was flame-dried. Once the flask was cooled to room temperature, a solution of triflate **2.152** (14.0 mg, 0.023 mmol) and tetrakis(triphenylphosphine) palladium (0.3 mg, 0.0002 mmol) in THF (0.5 mL) was cannulated. Tributylvinyltin (0.007 mL, 0.024 mmol) was added and the flask was sealed. The solution was heated to 60 °C for 3 hours. After cooling to room temperature, the reaction was quenched with water. The aqueous layer was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 4.3 mg of **2.154** (40%) as a colorless oil and 2.1 mg of recovered starting material. IR (neat, cm^{-1}) 2957 (m), 2930 (s), 2853 (m), 1666 (s), 1466 (w), 1425 (w), 1112 (s); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61-7.59 (m, 4H), 7.41-7.33 (m, 6H), 6.31 (dd, *J*=17.5, 10.3 Hz, 1H), 6.05 (s, 1H), 5.59 (d, *J*=17.3 Hz, 1H), 5.32 (d, *J*=11.4 Hz, 1H), 3.58-3.47 (m, 2H), 2.82-2.79 (m, 1H), 2.47-2.41 (m, 1H), 2.32-2.26 (m, 1H), 1.97-1.92 (m, 2H), 1.71-1.29 (m, 6H), 1.00 (s, 9H), 0.96 (d, *J*=6.6 Hz, 3H), 0.93 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.9 (C$_{quat}$), 168.9 (C$_{quat}$), 137.0 (CH), 135.5 (CHx4), 134.6 (C$_{quat}$x2), 129.6 (CHx2), 127.6 (CH), 127.5 (CHx4), 119.9 (CH$_2$), 64.0 (CH$_2$), 46.4 (CH), 37.2 (CH), 35.3 (CH$_2$), 33.3 (CH$_2$), 30.8 (CH), 26.7 (CH$_3$x3), 25.7 (CH$_2$), 23.2 (CH$_2$), 21.3 (CH$_3$), 20.7 (CH$_3$), 19.0 (C$_{quat}$); HRMS (EI) m/z calcd for $C_{27}H_{33}O_2Si$ [(M-C$_4$H$_9$)$^+$] 417.2244, found 417.2235.



(±)-(3*S*,6*S*,1'*R*)-Trifluoro-methanesulfonic acid 6-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-hydroxy-cyclohex-1-enyl ester (2.155). To a solution of enone **2.152** (16.7 mg, 0.028 mmol) in methanol (0.3 mL) was added cerium chloride heptahydrate (15.6 mg, 0.042 mmol) and sodium borohydride (1.6 mg, 0.042 mmol). The solution was stirred for 4 hours before the reaction was quenched by adding ethyl acetate. The solvent was removed *in vacuo*. The mixture was diluted in water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30% ethyl acetate in hexanes) afforded 7.6 mg of **2.155** (45%) as a colorless oil. IR (neat, cm^{-1}) 3348 (br), 2962 (s), 2863 (s), 1673 (w), 1417 (s), 1213 (s), 1143 (m), 1110 (s), 903 (m), 704 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.62 (m, 4H), 7.41-7.34 (m, 6H), 5.81 (s, 1H), 4.31-4.29 (m, 1H), 3.59 (t, *J*=5.9 Hz, 2H), 2.79-2.77 (m, 1H), 2.13-2.07 (m, 1H), 1.87-1.81 (m, 1H), 1.64-1.14 (m, 9H), 1.02 (s, 9H), 0.94 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.7 (CHx2), 127.7 (CHx4), 124.7 (CH), 66.8 (CH), 64.2 (CH_2), 43.9 (CH), 40.2 (CH), 33.2 (CH_2), 31.7 (CH_2) 30.5 (CH), 27.0 (CH_3x3), 25.3 (CH_2), 21.6 (CH_3), 21.0 (CH_2), 20.9 (CH_3), 19.4 (C_{quat}); HRMS (EI) m/z calcd for $C_{26}H_{30}O_4SiSF_3$ [$(M-C_4H_{11}O)^+$] 523.1581, found 523.1612.

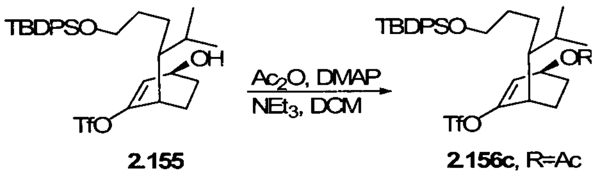
(±)-(3*R*,6*S*,1'*R*)-Trifluoro-methanesulfonic acid 6-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-hydroxy-cyclohex-1-enyl ester (2.155b).



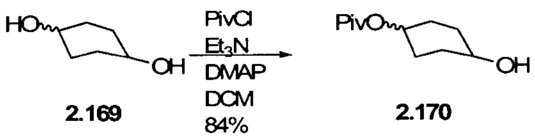
2.155b

When the reduction was done with Dibal-H, the other isomer was observed and characterized (colorless oil). IR (neat, cm^{-1}) 3419 (br), 2963 (s), 2929(s), 2861 (m), 1419 (m), 1213 (s), 1143 (m), 1111 (s), 703 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.64-7.62 (m, 4H), 7.41-7.33 (m, 6H), 5.89 (dd, *J*=6.4, 1.4 Hz, 1H), 4.38-4.37 (m, 1H), 3.61-3.58 (m, 2H), 2.72-2.68 (m, 1H), 1.81-1.78 (m, 1H), 1.69-1.20 (m, 10H), 1.02 (s, 9H), 0.96 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2 (C_{quat}), 135.6 (CHx4), 134.0 (C_{quat}x2), 129.4 (CHx2), 127.4 (CHx4), 121.0 (CH), 76.9 (CH), 64.0 (CH_2), 43.6

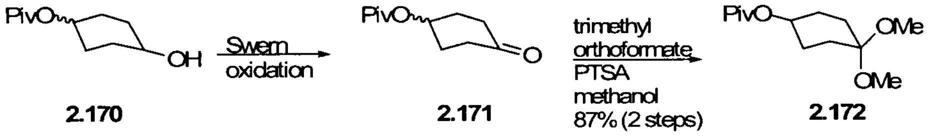
(CH), 40.6 (CH), 33.0 (CH_2), 30.5 (CH), 29.3 (CH_2), 26.7 (CH_3x3), 25.2 (CH_2), 21.3 (CH_3), 20.7 (CH_3), 19.1 (C_{quat}), 18.3 (CH_2); HRMS (EI) m/z calcd for $C_{26}H_{32}O_5SiSF_3$ [(M-$C_4H_{11}O)^+$] 541.1686, found 541.1670.



(±)-(1*S*,4*S*,1'*R*)- Acetic acid 4-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-3-trifluoromethanesulfonyloxy-cyclohex-2-enyl ester (2.156c). To a solution of alcohol 2.155 (crude, 0.059 mmol) in dichloromethane (0.5 mL) was added acetic anhydride (0.013 mL, 0.136 mmol) then triethylamine (0.025 mL, 0.177 mmol) and DMAP (1 crystal). The mixture was stirred at room temperature for 18 hours before quenching with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 30% ethyl acetate in hexanes) afforded 12.2 mg of **2.156c** (32% over 2 steps) as a colorless oil. IR (neat, cm^{-1}) 2959 (s), 2860 (m), 1742 (s), 1420 (s), 1214 (s), 1142 (m), 1112 (m), 703 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.42-7.33 (m, 6H), 5.76 (s, 1H), 5.34-5.32 (m, 1H), 3.62-3.57 (m, 2H), 2.81-2.79 (m, 1H), 2.08-2.02 (m, 1H), 2.06 (s, 3H), 1.87-1.84 (m, 1H), 1.60-1.20 (m, 8H), 1.02 (s, 9H), 0.95 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (C_{quat}), 154.3 (C_{quat}), 135.7 (CHx4), 134.3 (C_{quat}x2), 129.7 (CHx2), 127.7 (CHx4), 121.1 (CH), 68.5 (CH), 64.2 (CH_2), 43.9 (CH), 40.1 (CH), 33.2 (CH_2), 30.5 (CH), 27.4 (CH_2), 27.0 (CH_3x3), 25.3 (CH_2), 21.5 (CH_3), 21.3 (CH_3), 21.0 (CH_3), 20.8 (CH_2), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{28}H_{34}O_6F_3SSi$ [(M-$C_4H_9)^+$] 583.1792, found 583.1819.

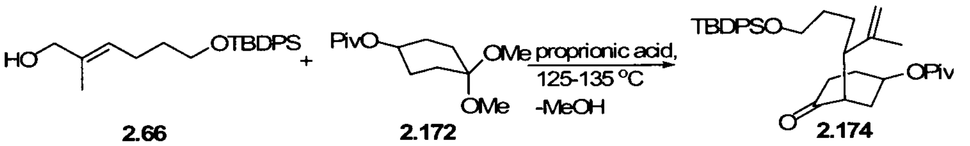


(±)-2,2-Dimethyl-propionic acid 4-hydroxy-cyclohexyl ester (2.170). To a solution of 1,4-cyclohexanediol (10.5 g, 90.4 mmol) in dichloromethane (213 mL) was added triethylamine (25.2 mL, 180.8 mmol), pivaloyl chloride (11.7 mL, 94.9 mmol) and DMAP (10 crystals) sequentially. The resulting suspension was stirred at 40 °C for 18 hours. The solution was cooled to room temperature and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 80% ethyl acetate in hexanes) afforded 15.18 g of **2.170** (84%) as a colorless oil. IR (neat, cm^{-1}) 3429 (br), 2942 (s), 2869 (m), 1726 (s), 1481 (m), 1286 (m), 1167 (s), 1069 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 4.75-4.71 (m, 1H), 4.61-4.60 (m, 1H), 3.64-3.58 (m, 4H), 1.92-1.26 (m, 16H), 1.08 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1 (C_{quat}), 178.0 (C_{quat}), 71.2 (CH), 69.0 (CH), 68.4 (CH), 68.2 (CH), 38.8 (C_{quat}), 38.7 (C_{quat}), 31.6 (CH_2x2), 30.2 (CH_2x2), 28.1 (CH_2x2), 27.5 (CH_2x2), 27.1 (CH_3x3), 27.1 (CH_3x3); HRMS (EI) m/z calcd for $C_{11}H_{18}O_2$ [$(M-H_2O)^+$] 182.1307, found 182.1311.



(±)-2,2-Dimethyl-propionic acid 4,4-dimethoxy-cyclohexyl ester (2.172). Procedure A: oxalyl chloride (5.05 mL, 57.9 mmol), dimethyl sulfoxide (6.02 mL, 85.1 mmol), alcohol **2.172** (6.82 g, 34.1 mmol), dichloromethane (165+36+36 mL), triethylamine (23.7 mL, 170.3 mmol).

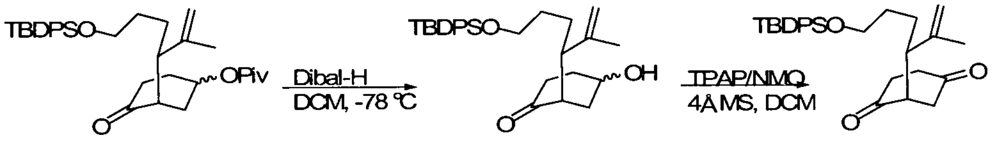
The crude ketone was dissolved in methanol (186 mL) and trimethylorthoformate (28 mL, 258.8 mmol) and *para*-toluenesulfonic acid (194 mg, 1.02 mmol) were added sequentially. The mixture was stirred for 18 hours and quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with dichloromethane (3x) and the organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 7.23 g of **2.172** (87% over 2 steps) as a yellow oil. IR (neat, cm^{-1}) 2959 (s), 2874 (m), 2829 (m), 1727 (s), 1481 (m), 1284 (s), 1000 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 4.76-4.75 (m, 1H), 3.10 (s, 3H), 3.08 (s, 3H), 1.75-1.56 (m, 8H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9 (C_{quat}), 99.2 (C_{quat}), 69.8 (CH), 47.8 (CH_3), 47.4 (CH_3), 38.8 (C_{quat}), 28.6 (CH_2x2), 27.2 (CH_3x3), 27.2 (CH_2x2); HRMS (EI) m/z calcd for $C_{12}H_{21}O_3$ [$(M-CH_3O)^+$] 213.1485, found 213.1491.



(±)-(1*R*,3*S*,1'*S*)-2,2-Dimethyl-propionic acid 3-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-4-oxo-cyclohexyl ester and (±)-(1*S*,3*S*,1'*S*)-2,2-Dimethyl-propionic acid 3-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-4-oxo-cyclohexyl ester (2.174). To a solution of cyclohexanone dimethylketal **2.172** (3.49 g, 14.3 mmol) and alcohol **2.66** (3.76 g, 10.2 mmol) was added propionic acid (0.114 mL, 1.53 mmol). The flask was mounted with a distillation apparatus and the solution was heated to 130-135 °C for 8 hours. The solution was cooled to room temperature and THF (16.2 mL) and water (4.5 mL) were added. Oxalic acid (180 mg) was added and the resulting mixture was stirred for 18 hours. Once the excess ketal had completely been converted to the ketone, the reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with diethyl ether (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 7 to 15% ethyl acetate in hexanes) afforded 3.47 g (62%) of a 1:1 mixture of isomers as a yellow oil. In a subsequent purification of an aliquot, it was possible to separate both isomers for characterization.

a: IR (neat, cm^{-1}) 2931 (s), 2858 (s), 1727 (s), 1714 (s), 1479 (m), 1428 (m), 1282 (m), 1158 (m), 1087 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.40-7.34 (m, 6H), 5.22-5.18 (m, 1H), 4.80 (t, *J*=1.5 Hz, 1H), 4.64 (s, 1H), 3.68-3.57 (m, 2H), 2.70-2.60 (m, 1H), 2.58-2.55 (m, 1H), 2.49-2.44 (m, 1H), 2.39-2.34 (m, 1H), 2.16-1.94 (m, 3H), 1.79-1.66 (m, 3H), 1.63 (s, 3H), 1.59-1.30 (m, 2H), 1.21 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9 (C_{quat}), 177.7 (C_{quat}), 145.5 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 112.1 (CH_2), 67.7 (CH), 64.1 (CH_2), 48.7 (CH), 43.8 (CH), 39.1 (C_{quat}), 37.2 (CH_2), 32.5 (CH_2), 31.1 (CH_2), 30.5 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 25.1 (CH_2), 21.2 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{34}H_{39}O_4Si$ [$(M-C_4H_9)^+$] 491.2612, found 491.2595.

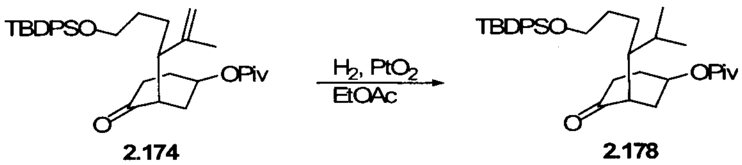
b: (characterized as a mixture with **a**) IR (neat, cm^{-1}) 2958 (s), 2933 (s), 2859 (m), 1725 (s), 1479 (m), 1428 (m), 1283 (m), 1158 (m), 1111 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.40-7.34 (m, 6H), 5.12-5.06 (m, 1H), 4.81 (t, *J*=1.5 Hz, 1H), 4.63 (s, 1H), 3.68-3.57 (m, 2H), 2.70-2.60 (m, 1H), 2.52-2.27 (m, 3H), 2.18-1.94 (m, 3H), 1.86-1.66 (m, 2H), 1.63 (s, 3H), 1.55-1.43 (m, 1H), 1.43-1.32 (m, 2H), 1.18 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3 (C_{quat}), 178.0 (C_{quat}), 145.7 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 112.3 (CH_2), 69.9 (CH), 64.3 (CH_2), 50.4 (CH), 44.5 (CH), 38.9 (C_{quat}), 37.7 (CH_2), 32.5 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 25.5 (CH_2), 21.2 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{34}H_{39}O_4Si$ [$(M-C_4H_9)^+$] 491.2612, found 491.2595.



2.174 (2 isomers) **2.175** (2 isomers) **2.176** (1 isomer)

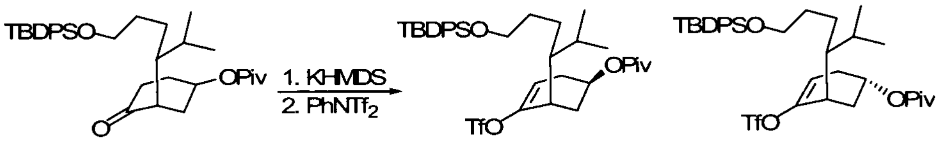
(±)-(2*S*,1'*S*)-2-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-cyclohexane-1,4-dione (2.176). To a -78 °C solution of pivaloate **2.174** (11.5 mg, 0.021 mmol) in dichloromethane (1 mL) was added Dibal-H (0.105 mL, 0.105 mmol) dropwise. The solution was stirred for 2 hours while the reaction mixture warmed to 0 °C. The reaction was quenched with 1M sodium tartrate and stirred overnight. The mixture was extracted three times using dichloromethane and the combined organic extracts were dried using magnesium sulfate. The crude diol was used directly in the next step. Molecular sieves 4 Å (26 mg) were flame-dried under vacuum. A solution of alcohol (crude mixture) in dichloromethane (1 mL) was cannulated into the flask containing the sieves. NMO (9.8 mg, 0.084 mmol) was added, followed by TPAP (0.7 mg, 0.002 mmol). The reaction was stirred for 6 hrs, then the mixture was purified using flash chromatography eluting with 20% ethyl acetate/ 80% hexanes to afford 2.3 mg of the desired diketone **2.176** (24%) and 2.4 mg of the mono-ketone (25%). IR (neat, cm^{-1}) 2931 (m), 2857 (m), 1716 (s), 1428 (w), 1111 (m), 703 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.61 (m, 4H), 7.41-7.34 (m, 6H), 4.87 (s, 1H), 4.67 (s, 1H), 3.65-3.56 (m, 2H), 2.70-2.49 (m, 7H), 1.65 (s, 3H), 1.42-1.20 (m, 5H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1 (C_{quat}), 208.5 (C_{quat}), 143.9 (C_{quat}), 135.5 (CHx4), 133.8 (C_{quat}x2), 129.4 (CHx2), 127.5 (CHx4), 112.9 (CH_2), 63.6 (CH_2), 49.1 (CH), 45.2

(CH), 39.2 (CH_2), 36.9 (CH_2), 36.8 (CH_2), 30.4 (CH_2), 26.7 (CH_3x3), 24.7 (CH_2), 21.1 (CH_3), 19.0 (C_{quat}); HRMS (EI) m/z calcd for $C_{29}H_{38}O_3Si$ [M^+] 462.2590, found 462.2617.



(±)-(1*S*,3*S*,1'*R*)- 2,2-Dimethyl-propionic acid 3-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-oxo-cyclohexyl ester and (1*R*,3*S*,1'*R*)- 2,2-Dimethyl-propionic acid 3-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-oxo-cyclohexyl ester (2.178). Platinum oxide (24.6 mg, 0.108 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.174** (2.37 g, 4.32 mmol) in ethyl acetate (14 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 2.19 g of the recovered starting material **2.174** (92%). Repeating the same method described above with the appropriate amount of catalyst (22.6 mg, 0.100 mmol) and solvent (13.5 mL) yielded 1.82 g of the desired hydrogenated product **2.178** (83%) as a colorless oil. (each isomer is one) IR (neat, cm^{-1}) 2962 (s), 2869 (m), 1726 (s), 1282 (m), 1159 (s), 1110 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 8H), 7.40-7.33 (m, 12H), 5.22-5.18 (m, 1H), 5.16-5.08 (m, 1H), 3.66-3.59 (m, 4H), 2.79-2.74 (m, 1H), 2.58-2.30 (m, 4H), 2.18-2.14 (m, 4H), 1.99-1.85 (m, 3H), 1.79-1.53 (m, 12H), 1.24-1.19 (m, 2H), 1.19 (s, 18H), 1.04 (s, 9H), 1.03 (s, 9H), 0.87 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.8Hz, 3H), 0.84 (d, J=6.8 Hz, 3H), 0.81 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2 (C_{quat}), 210.0 (C_{quat}), 178.0 (C_{quat}), 177.6 (C_{quat}), 135.7 (CHx8), 134.1 (C_{quat}x4), 129.6 (CHx4), 127.6 (CHx8), 70.4 (CH), 68.1 (CH), 64.4 (CH_2x2), 48.5 (CH), 46.2 (CH), 40.6 (CH), 39.9 (CH), 39.1 (C_{quat}), 38.8 (C_{quat}), 38.4 (CH_2), 37.1 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 30.4 (CH), 30.3 (CH_2), 30.3 (CH), 27.3 (CH_3x3), 27.2 (CH_3x3), 27.0 (CH_3x6), 26.2

(CH_2), 26.0 (CH_2), 20.7 (CH_3x2), 20.6 (CH_3), 20.2 (CH_3), 19.3 (C_{quat}x2); HRMS (EI) m/z calcd for $C_{25}H_{32}O_2Si$ [$(M-C_9H_{18}O_2)^+$] 392.2166, found 392.2112.

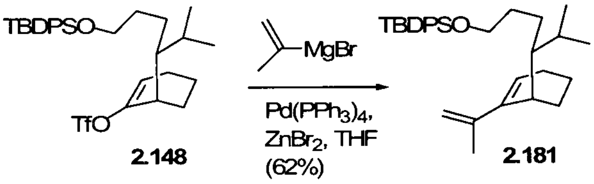


2.178 **2.179a** **2.179b**

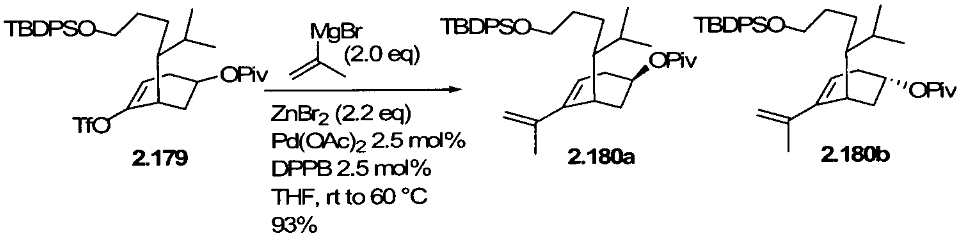
(±)-(1*R*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-trifluoromethanesulfonyloxy-cyclohex-3-enyl ester (a) and (±)-(1*S*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-trifluoromethanesulfonyloxy-cyclohex-3-enyl ester (b). To a -78 °C solution of ketone **2.178** (0.785 g, 1.42 mmol) in 19 mL of THF was cannulated slowly a solution of KHMDS (511 mg, 2.56 mmol) in THF (19 mL). The resulting clear solution was stirred for 1 hour at the same temperature before adding *N*-phenyltrifluorosulfonimide (1.02 g, 2.84 mmol) in THF (4.7 mL). The solution was stirred for 1 hour during which the reaction turned orange. Silica gel was added to the solution and the solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 1152 mg (quantitative) of **2.179** as colorless oil as a 1:1 mixture of isomers. In a subsequent purification of an aliquot, it was possible to separate both isomers for characterization.

a: IR (neat, cm^{-1}) 2959 (s), 2859 (m), 1729 (s), 1420 (m), 1212 (s), 1145 (s), 1111 (m), 703 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.42-7.35 (m, 6H), 5.72-5.68 (m, 1H), 4.98-4.88 (m, 1H), 3.68-3.61 (m, 2H), 3.02-3.00 (m, 1H), 2.56-2.33 (m, 2H), 2.18-1.97 (m, 2H), 1.75-1.33 (m, 6H), 1.20 (s, 9H), 1.06 (s, 9H), 0.97 (d, *J*=6.7 Hz, 3H), 0.91 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C_{quat}), 151.2 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.7 (CHx2), 127.7 (CHx4), 117.3 (CH), 68.2 (CH), 64.2 (CH_2), 43.8 (CH), 39.8 (CH), 38.8 (C_{quat}), 33.3 (CH_2), 30.8 (CH), 29.4 (CH_2), 29.0 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 25.5 (CH_2), 21.6 (CH_3), 21.0 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{26}H_{30}F_3O_4SSi$ [$(M-C_9H_{19}O_2)^+$] 523.1581, found 523.1517.

b: IR (neat, cm^{-1}) 2960 (s), 2860 (m), 1727 (s), 1419 (m), 1211 (s), 1145 (s), 1111 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.40-7.33 (m, 6H), 5.68-5.66 (m, 1H), 5.13-5.09 (m, 1H), 3.64-3.59 (m, 2H), 2.99-2.98 (m, 1H), 2.48-2.26 (m, 2H), 2.07-2.00 (m, 1H), 1.69-1.22 (m, 7H), 1.16 (s, 9H), 1.02 (s, 9H), 0.95 (d, J=6.1 Hz, 3H), 0.84 (d, J=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C_{quat}), 151.4 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.7 (CHx2), 127.7 (CHx4), 116.7 (CH), 66.2 (CH), 64.2 (CH_2), 43.3 (CH), 39.0 (C_{quat}), 36.1 (CH), 33.3 (CH_2), 30.8 (CH), 29.7 (CH_2), 27.6 (CH_2), 27.1 (CH_3x3), 27.0 (CH_3x3), 25.7 (CH_2), 21.7 (CH_3), 20.8 (CH_3), 19.4 (C_{quat}); HRMS (EI) m/z calcd for $C_{26}H_{30}F_3O_4SSi$ [$(M-C_9H_{19}O_2)^+$] 523.1581, found 523.1311.



(±)-(4*R*,1'*S*)-*tert*-Butyl-[4-(2-isopropenyl-cyclohex-2-enyl)-5-methyl-hexyloxy]-diphenyl-silane (2.181). $ZnBr_2$ (49.5 mg, 0.220 mmol) was weighed in a previously flame-dried flask. The $ZnBr_2$ was flame-dried until it started to melt. A stir bar was then added and the flask was flame-dried again. The flask was left to cool to room temperature before adding THF (0.4 mL). Once the $ZnBr_2$ had completely dissolved, the mixture was cooled to 0 °C and isopropenylMgBr (0.401 mL, 0.200 mmol) was added dropwise. While the solution stirred for 20 minutes at room temperature, a separate flask containing triflate **2.148** (58.4 mg, 0.100 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol) in 0.6 mL was prepared. After the 20 minutes, the solution of triflate and catalyst was cannulated to the reaction flask. The solution was stirred overnight at room temperature. The mixture was diluted with hexanes and filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc in hexanes-dry pack) to provide diene **2.181** (29.5 mg, 62%), as a colorless oil. IR (neat, cm^{-1}) 2933 (s), 2859 (s), 1473 (m), 1428 (m), 1265 (s), 1110 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.64 (m, 4H), 7.40-7.35 (m, 6H), 5.84 (s, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 3.55-3.52 (m, 2H), 2.76-2.71 (m, 1H), 2.04-1.91 (m, 2H), 1.77 (s, 3H), 1.72-1.21 (m, 10H), 1.03 (s, 9H), 0.92 (d, J=6.7 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6 (C_{quat}), 143.5 (C_{quat}), 135.6 (CHx4), 134.3 (C_{quat}x2), 129.5 (CHx2), 127.6 (CHx4), 126.2 (CH), 110.8 (CH_2), 64.7 (CH_2), 45.8 (CH), 36.7 (CH), 33.9 (CH_2), 31.1 (CH), 26.9 (CH_3x3), 25.9 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 21.7 (CH_2), 21.3 (CH_3), 19.2 (C_{quat}); HRMS (EI) m/z calcd for $C_{28}H_{37}OSi$ [$(M-C_4H_9)^+$] 417.2608, found 417.2608.

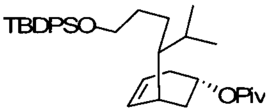


(±)-(1*R*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-isopropenyl-cyclohex-3-enyl ester (2.180a) and (±)-(1*S*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-isopropenyl-cyclohex-3-enyl ester (2.180b). $ZnBr_2$ (1.86 g, 8.27 mmol) was weighed in a previously flame-dried flask. The $ZnBr_2$ was flame-dried until it started to melt. A stir bar was then added and the flask was flame-dried again. The flask was left to cool to room temperature before adding THF (5.5 mL). Once the $ZnBr_2$ had completely dissolved, the mixture was cooled to 0 °C and isopropenylMgBr (15.0 mL, 7.52 mmol) was added dropwise. While the solution stirred for 20 minutes at room temperature, a separate flask containing triflate **2.179** (2.96 g, 3.76 mmol), $Pd(OAc)_2$ (21.1 mg, 0.094 mmol) and 1,4-bis(diphenylphosphino)butane (40.1 mg, 0.094 mmol) in 7.4 mL was prepared. After the 20 minutes, the solution of triflate and catalyst was cannulated to the reaction flask. Once combined, the resulting solution was stirred for 60 minutes at room temperature. Then, a reflux condenser was added and the solution was stirred overnight at 60 °C. The mixture was cooled to room temperature and filtered through a pad of silica using ethyl acetate as the eluent and concentrated *in vacuo*. The residue was purified by flash chromatography (3% ethyl acetate in hexanes-dry pack) to provide diene **2.180** (2.01 g, 93%), as a colorless oil. In a subsequent purification of an aliquot, it was possible to separate both isomers for characterization.

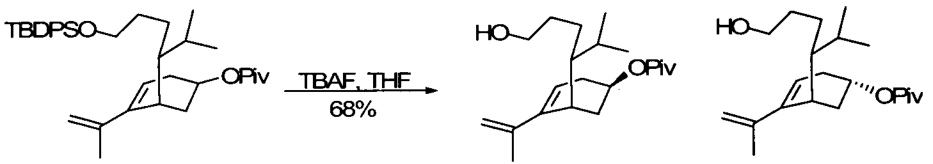
a: IR (neat, cm^{-1}) 2957 (s), 2859 (m), 1727 (s), 1282 (m), 1162 (s), 1111 (m), 702 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.40-7.33 (m, 6H), 5.65-5.63 (m, 1H), 4.79-4.76 (m, 3H), 3.55 (t, *J*=6.4 Hz, 2H), 2.98-2.88 (m, 1H), 2.41-2.30 (m, 1H), 2.00-1.77 (m, 2H), 1.75 (s, 3H), 1.64-1.23 (m, 7H), 1.18 (s, 9H), 1.03 (s, 9H), 0.92 (d, *J*=6.6 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C_{quat}), 145.0 (C_{quat}), 144.3 (C_{quat}), 135.7 (CHx4), 134.3 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 121.8 (CH), 112.1 (CH_2), 70.5 (CH), 64.8 (CH_2), 45.7 (CH), 38.8 (C_{quat}), 38.0 (CH), 33.9 (CH_2), 31.1 (CH), 31.0 (CH_2), 29.1 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 25.9 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 21.3 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{28}H_{35}OSi$ [$(M-C_9H_{19}O_2)^+$] 415.2452, found 415.2407.

b: IR (neat, cm^{-1}) 2958 (s), 2859 (m), 1725 (s), 1284 (m), 1163 (s), 1111 (m), 703 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.63 (m, 4H), 7.42-7.33 (m, 6H), 5.64-5.61 (m, 1H), 5.09-5.06 (m, 1H), 4.78 (s, 1H), 4.76 (s, 1H), 3.54 (t, *J*=6.4 Hz, 2H), 2.87-2.82 (m, 1H), 2.33-2.24 (m, 1H), 2.18-2.12 (m, 1H), 1.87-1.66 (m, 2H), 1.78 (s, 3H), 1.63-1.40 (m, 4H), 1.31-1.21 (m, 2H), 1.15 (s, 9H), 1.02 (s, 9H), 0.93 (d, *J*=6.6 Hz, 3H), 0.89 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C_{quat}), 145.5 (C_{quat}), 143.7 (C_{quat}), 135.7 (CHx4), 134.3 (C_{quat}x2), 129.6 (CHx2), 127.7 (CHx4), 121.3 (CH), 111.6 (CH_2), 68.2 (CH), 64.7 (CH_2), 45.3 (CH), 38.9 (C_{quat}), 34.3 (CH), 33.9 (CH_2), 31.2 (CH), 30.5 (CH_2), 27.5 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 26.1 (CH_2), 22.1 (CH_3), 21.9 (CH_3), 21.3 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{28}H_{35}OSi$ [$(M-C_9H_{19}O_2)^+$] 415.2452, found 415.2364.

(±)-(1*S*,5*S*,1'*R*)-2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-cyclohex-3-enyl ester (2.182).



Colorless oil. IR (neat, cm^{-1}) 2958 (s), 2859 (m), 1725 (s), 1284 (m), 1163 (s), 1111 (m), 703 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.63 (m, 4H), 7.42-7.33 (m, 6H), 5.52-5.36 (m, 2H), 5.22-5.12 (m, 1H), 3.64-3.56 (m, 2H), 2.87-2.82 (m, 1H), 2.33-2.24 (m, 1H), 2.18-2.12 (m, 1H), 1.87-1.66 (m, 2H), 1.63-1.40 (m, 4H), 1.31-1.21 (m, 2H), 1.15 (s, 9H), 1.02 (s, 9H), 0.88 (d, *J*=7.2 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C_{quat}), 135.7 (CHx4), 134.3 (C_{quat}x2), 132.4 (CH), 129.6 (CHx2), 127.7 (CHx4), 123.2 (CH), 68.4 (CH), 64.4 (CH_2), 48.3 (CH), 38.9 (C_{quat}), 33.5 (CH_2), 33.2 (CH), 30.4 (CH_2), 30.0 (CH), 28.5 (CH_2), 27.3 (CH_3x3), 27.0 (CH_3x3), 24.9 (CH_2), 21.4 (CH_3), 20.5 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{25}H_{31}OSi$ [$(M-C_9H_{19}O_2)^+$] 375.2139, found 375.2060.



2.180 2.186a 2.186b

(±)-(1*R*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-(4-hydroxy-1-isopropyl-butyl)-4-isopropenyl-cyclohex-3-enyl ester (2.186a) and (±)-(1*S*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-(4-hydroxy-1-isopropyl-butyl)-4-isopropenyl-cyclohex-3-enyl ester (2.186b). To a solution of silylated ether **2.180** (4.29 g, 7.46 mmol) in tetrahydrofuran (37 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (14.9 mL, 14.9 mmol). The mixture was stirred for 18 h at ambient temperature before a solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 0.74 g of top product **2.186a** and 0.95 g of bottom product **2.186b** as colorless oils (yield of 68%).

a: IR (neat, cm^{-1}) 3368 (br), 2958 (s), 2872 (m), 1727 (s), 1284 (m), 1162 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70-5.67 (m, 1H), 4.80 (s, 2H), 4.80-4.74 (m, 1H), 3.54-3.49 (m, 2H), 2.96-2.93 (m, 1H), 2.39-2.31 (m, 1H), 2.07-1.88 (m, 2H), 1.78 (s, 3H), 1.64-1.53 (m, 2H), 1.44-1.15 (m, 6H), 1.17 (s, 9H), 0.95 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C_{quat}), 145.1 (C_{quat}), 144.2 (C_{quat}), 122.1 (CH), 112.1 (CH_2), 70.4 (CH), 63.7 (CH_2), 45.7 (CH), 38.8 (C_{quat}), 38.0 (CH), 34.0 (CH_2), 31.2 (CH_2), 31.1(CH), 29.1 (CH_2), 27.3 (CH_3x3), 25.5 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 21.3 (CH_3); HRMS (EI) m/z calcd for $C_{16}H_{26}O$ [$(M-C_5H_{10}O_2)^+$] 234.1984, found 234.1974.

b: IR (neat, cm^{-1}) 3391 (br), 2958 (s), 2872 (m), 1725 (s), 1285 (m), 1164 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68-5.66 (m, 1H), 5.10-5.06 (m, 1H), 4.82 (s, 1H), 4.80 (s, 1H), 3.54-3.48 (m, 2H), 2.89-2.83 (m, 1H), 2.38-2.28 (m, 1H), 2.19-2.12 (m, 1H), 1.87-1.80 (m, 1H), 1.81 (s, 3H), 1.64-1.18 (m, 8H), 1.15 (s, 9H), 0.95 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7 (C_{quat}), 145.5 (C_{quat}), 143.8 (C_{quat}), 121.6 (CH), 111.8 (CH_2), 68.2 (CH), 63.8 (CH_2), 45.2 (CH), 39.0 (C_{quat}), 34.5 (CH), 33.8 (CH_2), 31.1 (CH), 30.6 (CH_2), 27.7 (CH_2), 27.2 (CH_3x3), 25.7 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 21.3 (CH_3); HRMS (EI) m/z calcd for $C_{16}H_{26}O$ [$(M-C_5H_{10}O_2)^+$] 234.1984, found 234.2016.

2.186a **2.187a**

(±)-(1*R*,5*S*,1'*R*)-2,2-Dimethyl-propionic acid 4-isopropenyl-5-(1-isopropyl-4-oxo-hex-5-enyl)-cyclohex-3-enyl ester (2.187a). Procedure B: oxalyl chloride (0.058 mL, 0.666 mmol), dimethyl sulfoxide (0.069 mL, 0.980 mmol), alcohol **2.186a** (65.9 mg, 0.196 mmol), dichloromethane (1+1 mL), triethylamine (0.273 mL, 1.96 mmol). The aldehyde was used crude in the next step.

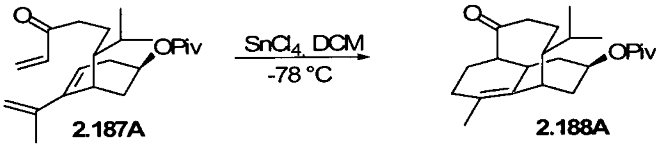
To a -78 °C solution of aldehyde (crude, 0.196 mmol) in toluene (2 mL) was added vinylmagnesium bromide (0.588 mL, 0.588 mmol). The reaction was stirred for 2 hours at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.

Procedure B: oxalyl chloride (0.058 mL, 0.666 mmol), dimethyl sulfoxide (0.069 mL, 0.980 mmol), crude alcohol, dichloromethane (1+1 mL), triethylamine (0.273 mL, 1.96 mmol). Rapid purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 50.9 mg of **2.187a** (72% yield over 3 steps) as a yellow oil. The triene was not very stable and it was used as quickly as possible in the next step. IR (neat, cm^{-1}) 2959 (s), 2873 (m), 1725 (s), 1684 (m), 1479 (w), 1283 (m), 1162 (s); ^1H NMR (500 MHz, C_6D_6) δ 6.10 (dd, *J*=17.7, 10.6 Hz, 1H), 5.90 (dd, *J*=17.7, 1.3 Hz, 1H), 5.54 (ddd, *J*=6.8, 1.7, 1.7 Hz, 1H), 5.18 (dd, *J*=10.6, 1.3 Hz, 1H), 5.04-4.99 (m, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 2.87-2.85 (m, 1H), 2.39-2.30 (m, 2H), 2.08-1.95 (m, 2H), 1.66 (s, 3H), 1.65-1.59 (m, 1H), 1.49-1.16 (m, 5H), 1.21 (s, 9H), 0.77 (d, *J*=6.8 Hz, 3H), 0.76 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.2 (C_{quat}), 177.9 (C_{quat}), 145.9 (C_{quat}), 144.3 (C_{quat}), 137.3 (CH), 126.7 (CH_2), 123.0 (CH), 112.1 (CH_2), 70.5 (CH), 45.9 (CH), 41.4 (CH_2), 38.8 (C_{quat}), 38.3 (CH), 31.4 (CH_2), 31.2 (CH), 29.5 (CH_2), 27.4 (CH_3x3), 23.7 (CH_2), 21.9 (CH_3), 21.8 (CH_3), 21.2 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{26}O$ $[(M-C_5H_{10}O_2)^+]$ 258.1984, found 258.2005.

(±)-(1*S*,5*S*,1'*R*)-2,2-Dimethyl-propionic acid 4-isopropenyl-5-(1-isopropyl-4-oxo-hex-5-enyl)-cyclohex-3-enyl ester (2.187b). Procedure B: oxalyl chloride (0.421 mL, 4.83 mmol), dimethyl sulfoxide (0.502 mL, 7.10 mmol), alcohol **2.186b** (0.950 g, 2.84 mmol), dichloromethane (9+5 mL), triethylamine (1.98 mL, 14.2 mmol). The aldehyde was used crude in the next step.

To a -78 °C solution of aldehyde (crude, 2.84 mmol) in toluene (14.2 mL) was added vinylmagnesium bromide (8.52 mL, 8.52 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.

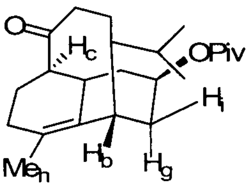
Procedure B: oxalyl chloride (0.421 mL, 4.83 mmol), dimethyl sulfoxide (0.502 mL, 7.10 mmol), alcohol **2.186b** (0.950 g, 2.84 mmol), dichloromethane (9+5 mL), triethylamine (1.98 mL, 14.2 mmol). Rapid purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 836.4 mg of **2.187b** (82% yield over 3 steps) as a yellow oil. The triene was not very stable and it was used as quickly as possible in the next step. IR (neat, cm^{-1}) 2959 (s), 2873 (m), 1723 (s), 1683 (m), 1479 (w), 1285 (m), 1164 (s); ^1H NMR (400 MHz, C_6D_6) δ 6.13 (dd, *J*=17.7, 10.5 Hz, 1H), 5.96 (dd, *J*=17.6, 1.4 Hz, 1H), 5.60-5.57 (m, 1H), 5.22 (dd, *J*=10.5, 1.4 Hz, 1H), 5.18-5.11 (m, 1H), 4.89 (d, *J*=1.9 Hz, 1H), 4.79 (dd, *J*=1.4, 1.4 Hz, 1H), 2.92-2.87 (m, 1H), 2.45-2.40 (m, 2H), 2.11-1.96 (m, 2H), 1.86-1.33 (m, 6H), 1.73 (s, 3H), 1.17 (s, 9H), 0.87 (d, *J*=6.6 Hz, 3H), 0.86 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.2 (C_{quat}), 177.3 (C_{quat}), 146.2 (C_{quat}), 143.7 (C_{quat}), 135.3 (CH), 126.7 (CH_2), 122.2 (CH), 111.7 (CH_2), 68.1 (CH), 45.4 (CH), 41.1 (CH_2), 38.9 (C_{quat}), 34.4 (CH), 31.2 (CH), 30.4 (CH_2), 27.4 (CH_2), 27.3 (CH_3x3), 24.0 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 21.2 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{26}O$ [$(M-C_5H_{10}O_2)^+$] 258.1984, found 258.1957.

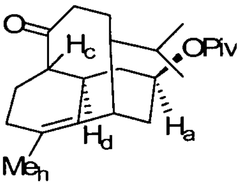


(±)-(1*S*,3*S*,5*S*,6*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-13-methyl-9-oxo-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.188a). To a -78 °C mixture of triene **2.187a** (204.8 mg, 0.568 mmol) in dichloromethane (9 mL) was added dropwise a 1.0 M solution of tin tetrachloride in dichloromethane (0.682 mL, 0.682 mmol). The solution was stirred for 1.5 h before it was quenched with Et_3N (1 drop) then with a saturated solution of sodium bicarbonate. The mixture was warmed to room temperature and extracted with dichloromethane (2x) and then with ethyl acetate (1x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to provide **2.188a** (162.8 mg, 79%) as a colorless oil. IR (neat, cm^{-1}) 2958 (s), 2873 (m), 1725 (s), 1691 (m), 1479 (w), 1283 (m), 1164 (s); ^{1}H NMR (500 MHz, $CDCl_3$) see table below; ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (C_{quat}), 178.3 (C_{quat}), 130.6 (C_{quat}), 130.3 (C_{quat}), 70.8 (CH), 55.0 (CH), 53.2 (CH), 39.2 (CH_2), 38.8 (C_{quat}), 38.1 (CH), 34.1 (CH), 32.4 (CH_2), 30.1 (CH), 29.7 (CH_2), 28.4 (CH_2), 27.3 (CH_3x3), 24.0 (CH_2), 22.2 (CH_2) 21.7 (CH_3), 21.4 (CH_3), 19.2 (CH_3); HRMS (EI) m/z calcd for $C_{23}H_{36}O_3$ [M$^+$] 360.2664, found 360.2643.

H	Chemical shift (δ)	COSY	HMQC	NOESY
A	4.74-4.67 (m, 1H)	G, I	70.8	D, G
B	3.44-3.40 (m, 1H)	G, I	34.1	G,H,I,K
C	2.76-2.74 (m, 1H)	G	55.0	D,G
D	2.56-2.50 (m, 1H)	G	38.1	A,C,F,G
E	2.44 (dd, *J*=11.7, 7.8 Hz, 1H)	F, I,	39.2 (with F)	F, I
F	2.15-2.10 (m, 3H)	E,G,I	39.2 (with E), 29.7	D,E,G,H,I
G	2.02-1.88 (m, 4H)	A,B,C,D,F, I	32.4 (with I), 28.4 (with I), 24.0 (with I), 22.2 (with I)	A,B,C,D,F,I,L
H	1.79 (s, 3H)	D (weak)	19.2	B,F,I
I	1.78-1.17 (m, 6H)	A,B,D,E,F,G, K,L	24.0 (with G), 22.2 (with G), 53.2, 32.4 (with G), 30.1, 28.4 (with G)	B,E,F,G,H,K,L
J	1.15 (s, 9H)	-	27.3	-
K	0.95 (d, *J*=6.3 Hz, 3H)	I	21.7 or 21.4	B,F,I
L	0.90 (d, *J*=6.2 Hz, 3H)	I	21.7 or 21.4	G,I

From COSY and HMQC; some of the assignment is the following:





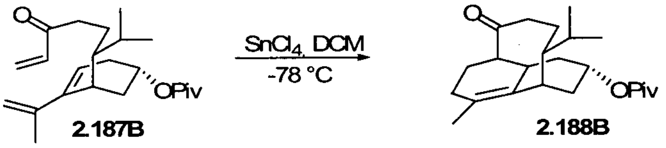
Important interactions by NOESY:

-H_a sees H_d

-H_d sees H_c

-Me$_h$ sees H$_b$

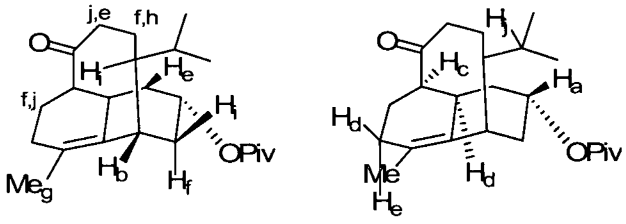
-isopropyl group sees H$_b$ but not H$_a$



(±)-(1*S*,3*R*,5*S*,6*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-13-methyl-9-oxo-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.188b). To a -78 °C mixture of triene **2.187b** (405 mg, 1.12 mmol) in dichloromethane (17 mL) was added dropwise a 1.0 M solution of tin tetrachloride in dichloromethane (1.35 mL, 1.35 mmol). The solution was stirred for 1.5 h before it was quenched with Et_3N (1 drop) then with a saturated solution of sodium bicarbonate. The mixture was warmed to room temperature and filtered through celite rinsing with dichloromethane. The mixture was extracted with dichloromethane (2x) and then with ethyl acetate (1x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to provide **2.188b** (270 mg, 67%) as a colorless oil. IR (neat, cm^{-1}) 2957 (s), 2871 (m), 1725 (s), 1688 (m), 1479 (w), 1284 (m), 1164 (s); ^{1}H NMR (500 MHz, $CDCl_3$) see table; ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.6 (C_{quat}), 178.0 (C_{quat}), 131.4 (C_{quat}), 128.7 (C_{quat}), 69.6 (CH), 54.7 (CH), 53.1 (CH), 39.2 (CH_2), 39.0 (C_{quat}), 34.5 (CH), 31.2 (CH), 30.2 (CH), 29.6 (CH_2), 29.5 (CH_2), 27.2 (CH_2), 27.1 (CH_3x3), 24.2 (CH_2), 22.4 (CH_2) 21.8 (CH_3), 21.4 (CH_3), 19.0 (CH_3); HRMS (EI) m/z calcd for $C_{23}H_{36}O_3$ [M$^+$] 360.2664, found 360.2637.

H	Chemical shift (δ)	COSY	HMQC	NOESY
A	5.09-5.08 (m, 1H)	E, I (weak)	69.6	E,F,I
B	3.28-3.27 (m, 1H)	F,I	31.2	F,G,I,M
C	2.73-2.71 (m, 1H)	F	54.7	D,E(weak), F
D	2.50-2.46 (m, 2H)	E,J	39.2 (with E), 34.5	C,E,H,I,L
E	2.15-2.06 (m, 3H)	D,F,H,J	39.2 (with D), 29.6 (with J), 29.5 (with J)	D,F,G,H,J
F	2.00-1.92 (m, 3H)	B,C,E,H,I,J	27.2 (with I), 24.2 (with J), 22.4 (with H)	B,C,E,H,I,J,M, N
G	1.81 (s, 3H)	-	19.0	B,D,E,I
H	1.55-1.45 (m, 1H)	E,F	22.4 (with F)	D,E,F
I	1.38-1.31 (m, 2H)	B,F,J	53.1, 27.2 (with F)	B,D,F,M
J	1.28-1.22 (m, 4H)	D,E,F,M	30.2, 29.6 (with E), 29.5(with E), 24.2 (with F)	E,F,M
K	1.08 (s, 9H)	-	27.1	D, E(weak)
L	0.93 (d, *J*=6.6 Hz, 3H)	J	21.8	B,F,I,J
M	0.89 (d, *J*=6.5 Hz, 3H)	J	21.4	F,I,J

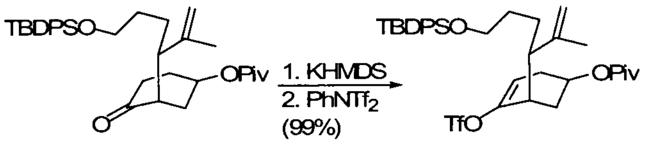
From COSY and HMQC; some of the assignment is the following:



Important interactions by NOESY:

- H_b sees Me_g
- H_b sees H_i
- H_i sees methyl is isopropyl group

- H$_d$ sees methyl of pivaloate group
- H$_d$ sees H$_c$

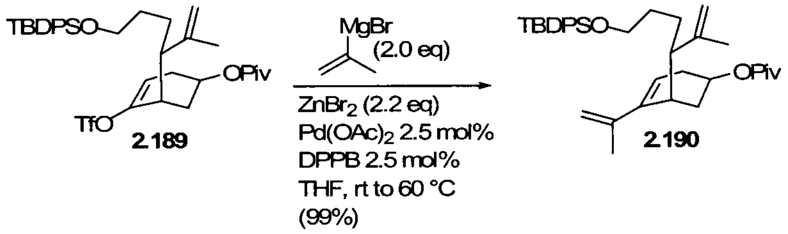


2.174 2.189

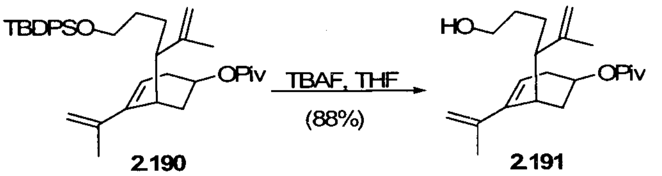
(±)-(1*R*,5*S*,1'*S*)- 2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-4-trifluoromethanesulfonyloxy-cyclohex-3-enyl ester (2.189a) and (±)-(1*S*,5*S*,1'*S*)- 2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-4-trifluoromethanesulfonyloxy-cyclohex-3-enyl ester (2.189b) To a -78 °C solution of ketone **2.174** (1.89 g, 3.44 mmol) in 46 mL of THF was cannulated slowly a solution of KHMDS (1.24 g, 6.20 mmol) in THF (46 mL). The resulting clear solution was stirred for 1 hour at the same temperature before adding *N*-phenyltrifluorosulfonimide (2.46 g, 6.88 mmol) in THF (11 mL). The solution was stirred for 1 hour during which the reaction turned orange. Silica gel was added to the solution and the solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 2.71 g (quantitative yield) of **2.189** as a colorless oil as a 1:1 mixture of isomers.

2.189a: IR (neat, cm^{-1}) 2959 (s), 2858 (m), 1728 (s), 1416 (m), 1211 (s), 1144 (s), 1110 (m), 700 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71-7.68 (m, 4H), 7.44-7.37 (m, 6H), 5.76-5.72 (m, 1H), 4.99 (s, 1H), 4.97-4.90 (m, 1H), 4.77 (s, 1H), 3.70 (t, *J*=5.9 Hz, 2H), 2.95-2.93 (m, 1H), 2.59-2.42 (m, 2H), 2.22-2.14 (m, 1H), 1.95-1.82 (m, 1H), 1.74 (s, 3H), 1.72-1.37 (m, 5H), 1.21 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.9 (C$_{quat}$), 150.4 (C$_{quat}$), 143.4 (C$_{quat}$), 135.7 (CHx4), 134.2 (C$_{quat}$x2), 129.7 (CHx2), 127.7 (CHx4), 117.9 (CH), 112.6 (CH$_2$), 68.3 (CH), 64.1 (CH$_2$), 44.8 (CH), 40.1 (CH), 38.8 (C$_{quat}$), 31.1 (CH$_2$), 29.8 (CH$_2$), 29.5 (CH$_2$), 27.3 (CH$_3$x3), 26.9 (CH$_3$x3), 23.0 (CH$_2$), 22.8 (CH$_3$), 19.3 (C$_{quat}$); HRMS (EI) m/z calcd for $C_{26}H_{28}F_3O_4SSi$ [(M-$C_9H_{19}O_2$)$^+$] 521.1424, found 521.1501.

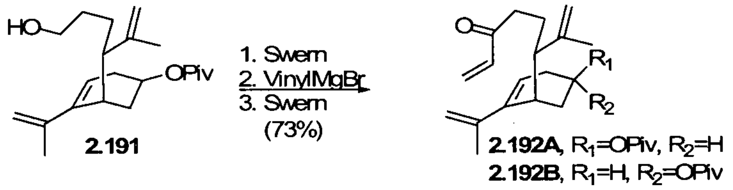
2.189b: IR (neat, cm^{-1}) 2959 (s), 2858 (m), 1728 (s), 1416 (m), 1211 (s), 1144 (s), 1110 (m), 700 (m); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66-7.64 (m, 4H), 7.39-7.36 (m, 6H), 5.73-5.72 (m, 1H), 5.12-5.08 (m, 1H), 4.96 (s, 1H), 4.74 (s, 1H), 3.66 (t, *J*=6.0 Hz, 2H), 2.92-2.88 (m, 1H), 2.49-2.42 (m, 2H), 2.34-2.28 (m, 1H), 1.91-1.85 (m, 1H), 1.70 (s, 3H), 1.65-1.33 (m, 5H), 1.17 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (C_{quat}), 150.4 (C_{quat}), 143.5 (C_{quat}), 135.7 (CHx4), 134.2 (C_{quat}x2), 129.7 (CHx2), 127.7 (CHx4), 117.1 (CH), 112.7 (CH_2), 66.0 (CH), 64.0 (CH_2), 44.8 (CH), 38.9 (C_{quat}), 37.2 (CH), 31.1 (CH_2), 29.8 (CH_2), 28.3 (CH_2), 27.2 (CH_3x3), 27.0 (CH_3x3), 23.3 (CH_2), 22.6 (CH_3), 19.3 (C_{quat}); HRMS (EI) m/z calcd for $C_{26}H_{28}F_3O_4SSi$ [$(M-C_9H_{19}O_2)^+$] 521.1424, found 521.1501.



(±)-(1*R*,5*S*,1'*S*)-2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-4-isopropenyl-cyclohex-3-enyl ester and (±)-(1*S*,5*S*,1'*S*)-2,2-Dimethyl-propionic acid 5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropenyl-butyl]-4-isopropenyl-cyclohex-3-enyl ester (2.190). $ZnBr_2$ (1.70 g, 7.57 mmol) was weighed in a previously flame-dried flask. The $ZnBr_2$ was flame-dried until it started to melt. A stir bar was then added and the flask was flame-dried again. The flask was left to cool to room temperature before adding THF (5 mL). Once the $ZnBr_2$ had completely dissolved, the mixture was cooled to 0 °C and isopropenylMgBr (13.8 mL, 6.88 mmol) was added dropwise. While the solution stirred for 20 minutes at room temperature, a separate flask containing triflate **2.189** (3.11 g, 3.44 mmol), $Pd(OAc)_2$ (19.3 mg, 0.086 mmol), 1,4-bis(diphenylphosphino)butane (36.7 mg, 0.086 mmol) in 7 mL was prepared. After the 20 minutes, the solution of triflate and catalyst was cannulated to the reaction flask. Once combined, the resulting solution was stirred for 60 minutes at room temperature. Then, a reflux condenser was added and the solution was stirred overnight at 60 °C. The mixture was cooled to room temperature and filtered through a pad of silica using ethyl acetate as the eluent and concentrated *in vacuo*. The residue was purified by flash chromatography (3% ethyl acetate in hexanes-dry pack) to provide diene **2.190** (1.99 g, 99%), as a colorless oil. IR (neat, cm^{-1}) 2956 (s), 1729 (s), 1473 (m), 1284 (m), 1163 (s), 1111 (m), 701 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.40-7.36 (m, 6H), 5.67-5.62 (m, 1H), 5.09-5.02 (m, 0.67H), 4.92-4.67 (m, 4H), 4.89-4.83 (m, 0.33H), 3.69-3.57 (m, 2H), 2.83-2.74 (m, 1H), 2.40-2.08 (m, 2H), 1.83 (s, 2H), 1.80 (s, 1H), 1.73 (s, 3H), 1.68-1.21 (m, 7H), 1.16 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) (each isomer is one) δ 178.2 (C$_{quat}$), 178.1 (C$_{quat}$), 145.2 (C$_{quat}$x2), 145.0 (C$_{quat}$x2), 144.0 (C$_{quat}$), 142.6 (C$_{quat}$), 135.7 (CHx8), 134.3 (C$_{quat}$x4), 129.6 (CHx4), 127.7 (CHx8), 122.0 (CH), 121.7 (CH), 112.1 (CH$_2$), 111.8 (CH$_2$), 111.6 (CH$_2$), 111.0 (CH$_2$), 70.6 (CH), 68.0 (CH), 64.7 (CH$_2$), 64.5 (CH$_2$), 47.0 (CH), 46.3 (CH), 38.8 (C$_{quat}$x2), 38.5 (CH), 35.7 (CH), 34.8 (CH$_2$), 31.7 (CH$_2$x2), 31.4 (CH$_2$), 30.8 (CH$_2$), 27.9 (CH$_2$), 27.2 (CH$_3$x6), 27.0 (CH$_3$x6), 25.4 (CH$_2$), 23.7 (CH$_2$), 23.4 (CH$_3$), 23.1 (CH$_3$), 21.9 (CH$_3$x2), 19.3 (C$_{quat}$x2); HRMS (EI) m/z calcd for $C_{28}H_{33}OSi$ [$(M-C_9H_{19}O_2)^+$] 413.2295, found 413.2302.



(±)-(1*R*,5*S*,1'*S*)- 2,2-Dimethyl-propionic acid 5-(4-hydroxy-1-isopropenyl-butyl)-4-isopropenyl-cyclohex-3-enyl ester and (±)-(1*S*,5*S*,1'*S*)- 2,2-Dimethyl-propionic acid 5-(4-hydroxy-1-isopropenyl-butyl)-4-isopropenyl-cyclohex-3-enyl ester (2.191). To a solution of silylated ether **2.190** (1.99 g, 3.47 mmol) in tetrahydrofuran (17 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (6.95 mL, 6.95 mmol). The mixture was stirred for 18 h at ambient temperature before a solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 1.02 g of **2.191** (88%) as colorless oil. Each isomer is one. IR (neat, cm^{-1}) 3400 (br), 2939 (s), 2874 (m), 1725 (s), 1700 (m), 1481 (m), 1164 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.66-5.64 (m, 2H), 5.05-5.00 (m, 2H), 4.89 (s, 2H), 4.85 (s, 2H), 4.82 (s, 2H), 4.71 (s, 2H), 3.51 (t, *J*=6.3 Hz, 4H), 2.77-2.73 (m, 2H), 2.38-2.30 (m, 2H), 2.25-2.22 (m, 2H), 2.13-1.98 (m, 6H), 1.83 (s, 6H), 1.70 (s, 6H), 1.62-1.23 (m, 10H), 1.13 (s, 18 H); ^{13}C NMR (100 MHz, CDCl$_3$) (each isomer is one) δ 178.6 (C$_{quat}$x2), 145.2 (C$_{quat}$x2), 145.1 (C$_{quat}$x2), 142.6 (C$_{quat}$x2), 123.2 (CH), 121.9 (CH), 111.8 (CH$_2$x2), 111.7 (CH$_2$x2), 68.1 (CHx2), 63.0 (CH$_2$x2), 47.0 (CHx2), 39.0 (C$_{quat}$x2), 35.8 (CHx2), 31.4 (CH$_2$x2), 30.9 (CH$_2$x2), 28.1 (CH$_2$x2), 27.2 (CH$_3$x6), 23.5 (CH$_2$x2), 23.0 (CH$_3$x2), 21.9 (CH$_3$x2); HRMS (EI) m/z calcd for $C_{28}H_{33}OSi$ [$(M-C_5H_{10}O_2)^+$] 232.1827, found 232.1848.



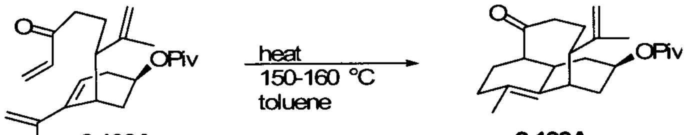
(±)-(1*R*,5*S*,1'*S*)-2,2-Dimethyl-propionic acid 4-isopropenyl-5-(1-isopropenyl-4-oxo-hex-5-enyl)-cyclohex-3-enyl ester (2.192A) and (±)-(1*S*,5*S*,1'*S*)-2,2-Dimethyl-propionic acid 4-isopropenyl-5-(1-isopropenyl-4-oxo-hex-5-enyl)-cyclohex-3-enyl ester (2.192B). Procedure B: oxalyl chloride (0.687 mL, 7.87 mmol), dimethyl sulfoxide (0.819 mL, 11.6 mmol), alcohol **2.191** (1.55 g, 4.63 mmol), dichloromethane (18+5 mL), triethylamine (3.20 mL, 23.2 mmol). The aldehyde was used crude in the next step.

To a -78 °C solution of aldehyde (crude, 4.63 mmol) in toluene (23 mL) was added vinylmagnesium bromide (13.9 mL, 13.9 mmol). The reaction was stirred for 1 hour at the same temperature before being quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude allylic alcohol was used directly in the next step.

Procedure B: oxalyl chloride (0.687 mL, 7.87 mmol), dimethyl sulfoxide (0.819 mL, 11.6 mmol), crude allylic alcohol, dichloromethane (18+5 mL), triethylamine (3.20 mL, 23.2 mmol). Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes-dry pack) afforded 0.34 g of top isomer **2.192A** and 0.88 g of bottom isomer **2.192B** (73% yield over 3 steps) as yellow oils.

2.192A: IR (neat, cm^{-1}) 2976 (s), 2875 (m), 1722 (s), 1400 (w), 1285 (m), 1163 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (dd, *J*=17.7, 10.4 Hz, 1H), 6.13 (dd, *J*=17.7, 1.3 Hz, 1H), 5.76 (dd, *J*=10.5, 1.3 Hz, 1H), 5.66-5.64 (m, 1H), 4.91 (s, 1H), 4.80 (br s, 3H), 4.67 (s, 1H), 2.85-2.82 (m, 1H), 2.62-2.52 (m, 1H), 2.38-1.98 (m, 5H), 1.81 (s, 3H), 1.75 (s, 3H), 1.67-1.32 (m, 3H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (C_{quat}), 178.2 (C_{quat}), 145.2 (C_{quat}), 144.4 (C_{quat}), 143.3 (C_{quat}), 136.8 (CH), 127.9 (CH_2), 122.6 (CH), 112.1 (CH_2), 111.3 (CH_2), 70.4 (CH), 46.0 (CH), 38.7 (C_{quat}), 38.5 (CH_2), 38.1 (CH), 31.3 (CH_2), 28.9 (CH_2), 27.2 (CH_3x3), 23.4 (CH_3), 21.9 (CH_3), 20.4 (CH_2); HRMS (EI) m/z calcd for $C_{18}H_{24}O$ [$(M-C_5H_{10}O_2)^+$] 256.1827, found 256.1878.

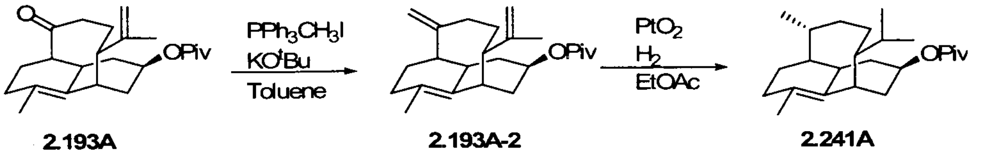
2.192B: IR (neat, cm^{-1}) 2971 (s), 2872 (m), 1719 (s), 1700 (s), 1396 (m), 1229 (w), 1161 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, *J*=16.9, 9.8 Hz, 1H), 6.12 (dd, *J*=17.7, 1.2 Hz, 1H), 5.79-5.66 (m, 2H), 5.13-4.64 (m, 5H), 2.85-1.86 (m, 8H), 1.81 (s, 3H), 1.71 (s, 3H), 1.68-1.50 (m, 2H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1 (C_{quat}), 178.2 (C_{quat}), 145.0 (C_{quat}), 144.7 (C_{quat}), 142.2 (C_4), 136.8 (CH), 127.8 (CH_2), 122.2 (CH), 111.9 (CH_2), 111.8 (CH_2), 67.9 (CH), 46.7 (CH), 39.1 (C_{quat}), 38.8 (CH_2), 35.3 (CH), 27.9 (CH_2), 27.8 (CH_2), 27.2 (CH_3x3), 22.6 (CH_3), 21.9 (CH_3), 21.8 (CH_2); HRMS (EI) m/z calcd for $C_{18}H_{25}O[(M-C_5H_9O_2)^+]$ 257.1900, found 257.1873.



2.192A 2.193A

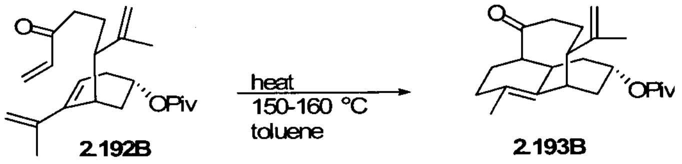
(±)-(1*S*,3*S*,5*S*,6*S*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropenyl-13-methyl-9-oxo-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.193A). To a solution of triene **2.192A** (58.6 mg, 0.163 mmol) in toluene (3 mL) in a seal tube was added triethylamine (0.114 mL, 0.817 mmol). The reaction was heated to 150-160 °C for 24 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded **2.193A** (18.6 mg, 32% yield) as a yellow oil. IR (neat, cm^{-1}) 2937 (s), 2872 (m), 1724 (s), 1688 (m), 1282 (w), 1164 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.74-4.65 (m, 1H), 4.54 (s, 1H), 3.44-3.38 (m, 1H), 2.78-2.74 (m, 1H), 2.58-2.52 (m, 1H), 2.50 (dd, *J*=11.9, 8.5 Hz, 1H), 2.35-2.33 (m, 1H), 2.17-2.13 (m, 3H), 1.98-1.92 (m, 3H), 1.87 (s, 3H), 1.76 (s, 3H), 1.74-1.47 (m, 5H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0 (C_{quat}), 178.3 (C_{quat}), 147.8 (C_{quat}), 131.1 (C_{quat}), 129.8 (C_{quat}), 111.3 (CH_2), 70.7 (CH), 54.9 (CH), 51.0 (CH), 38.8 (C_{quat}), 38.6 (CH_2), 38.2 (CH), 33.3 (CH), 32.3 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 27.3 (CH_3x3), 25.8 (CH_2), 22.9 (CH_3) 22.1 (CH_2), 19.1 (CH_3); HRMS (EI) m/z calcd for $C_{23}H_{34}O_3$ [M^+] 358.2508, found 358.2492.

To prove the stereochemistry, compound **2.193A** was transformed into the same hydrogenation product as obtained from hydrogenation of **2.240A** (see, below).



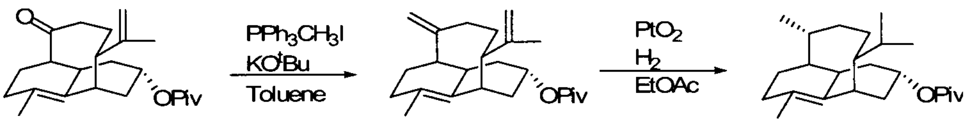
(±)-(1*S*,3*S*,5*S*,6*R*,10*R*)- 2,2-Dimethyl-propionic acid 6-isopropenyl-13-methyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.193A-2). To a flask containing CH_3PPh_3I (0.403 g, 0.998 mmol) was added dropwise KO^{t}Bu (1.0 M in THF, 1.10 mL, 1.10 mmol) and the resulting yellow solution was stirred for 20 minutes. A solution of ketone **2.193A** (0.120 g, 0.335 mmol) in toluene (1 mL) was added via cannula. The mixture was stirred at reflux for 1 h, cooled to r.t. and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (2% ethyl acetate in hexanes-dry pack) to provide **2.193A-2** (52.9 mg, 44%) as a colorless oil. IR (neat, cm^{-1}) 2934 (s), 1725 (s), 1480 (m), 1283 (w), 1164 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81-4.71(m,1H), 4.75 (s, 1H), 4.67 (d, *J*=2.7 Hz, 1H), 4.65 (dd, *J*=2.7, 1.0 Hz, 1H), 4.51 (s, 1H), 3.33-3.31 (m, 1H), 2.65-2.60 (m, 1H), 2.36-2.22 (m, 3H), 2.07-1.81 (m, 5H), 1.79 (s, 3H), 1.75 (s, 3H), 1.74-1.52 (m, 6H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5 (C_{quat}), 155.3 (C_{quat}), 148.9 (C_{quat}), 131.1 (C_{quat}), 129.9 (C_{quat}), 114.1 (CH_2), 110.6 (CH_2), 71.8 (CH), 52.2 (CH), 47.3 (CH), 38.9 (C_{quat}), 38.5 (CH), 33.2 (CH), 32.2 (CH_2), 32.2 (CH_2), 30.5 (CH_2), 30.2 (CH_2), 28.5 (CH_2), 27.3 (CH_3x3), 26.0(CH_2), 23.0 (CH_3), 18.9 (CH_3); HRMS (EI) m/z calcd for $C_{24}H_{36}O_2$ [M$^+$] 356.2715, found 356.2733.

Hydrogenation: the reaction was performed with compound **2.193B-2**.



(±)-(1*S*,3*R*,5*S*,6*S*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropenyl-13-methyl-9-oxo-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.193B). To a solution of triene **2.192B** (65.9 mg, 0.184 mmol) in toluene (3 mL) in a seal tube was added triethylamine (0.128 mL, 0.919 mmol). The reaction was heated to 150-160 °C for 24 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded **2.193B** (14.5 mg, 22% yield) as a yellow oil. IR (neat, cm^{-1}) 2939 (s), 2876 (m), 1721 (s), 1689 (m), 1283 (w), 1164 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.06-5.05 (m, 1H), 4.77 (s, 1H), 4.49 (s, 1H), 3.30-3.25 (m, 1H), 2.76-2.67 (m, 1H), 2.54 (dd, *J*=11.7, 8.5 Hz, 1H), 2.51-2.47 (m, 1H), 2.39-2.35 (m, 1H), 2.18-2.06 (m, 4H), 1.97-1.92 (m, 1H), 1.89 (s, 3H), 1.76 (s, 3H), 1.72-1.50 (m, 6H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 217.5 (C$_{quat}$), 177.9 (C$_{quat}$), 147.9 (C$_{quat}$), 130.6 (C$_{quat}$), 129.4 (C$_{quat}$), 111.1 (CH$_2$), 69.4 (CH), 54.6 (CH), 51.1 (CH), 39.0 (C$_{quat}$), 38.6 (CH$_2$), 34.4 (CH), 30.4 (CH), 29.6 (CH$_2$), 29.3 (CH$_2$), 27.3 (CH$_2$), 27.1 (CH$_3$x3), 25.9 (CH$_2$), 22.9 (CH$_3$) 22.2 (CH$_2$), 18.8 (CH$_3$); HRMS (EI) m/z calcd for $C_{23}H_{34}O_3$ [M$^+$] 358.2508, found 358.2390.

To prove the stereochemistry, compound **2.193B** was transformed into the same hydrogenation product as obtained from hydrogenation of **2.240B** (see, below).

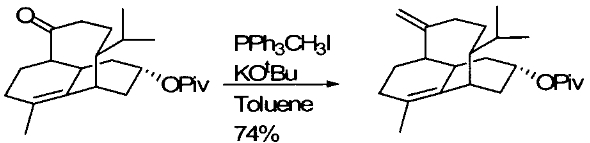


2.193B **2.193B-2** **2.241B**

(±)-(1*S*,3*R*,5*S*,6*R*,10*R*)- 2,2-Dimethyl-propionic acid 6-isopropenyl-13-methyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.193B-2). To a flask containing CH$_3$PPh$_3$I (0.143 g, 0.353 mmol) was added dropwise KO^{t}Bu (1.0 M in THF, 0.388 mL, 0.388 mmol) and the resulting yellow solution was stirred for 20 minutes. A solution of ketone **2.193B** (84.4 mg, 0.235 mmol) in toluene (0.5 mL) was added via cannula. The mixture was stirred at reflux for 1 h, cooled to r.t. and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (2% ethyl acetate in hexanes-dry pack) to provide **2.193B-2** (47.3 mg, 56%) as a colorless oil. IR (neat, cm^{-1}) 2936 (s), 1724 (s), 1478 (w), 1287 (m), 1165 (s); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.08-5.07 (m, 1H), 4.74 (s, 1H), 4.66 (d, *J*=2.7 Hz, 1H), 4.63 (dd, *J*=2.7, 1.1. Hz, 1H), 4.47 (s, 1H), 3.21-3.16 (m, 1H), 2.60 (ddd, *J*=10.8, 4.1, 4.1 Hz, 1H), 2.30-2.24 (m, 3H), 2.07-1.88 (m, 6H), 1.82 (s, 3H), 1.76 (s, 3H), 1.70-1.62 (m, 2H), 1.53 (dd, *J*=12.8, 12.8 Hz, 1H), 1.40-1.30 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.2 (C$_{quat}$), 155.6 (C$_{quat}$), 149.3 (C$_{quat}$), 131.7 (C$_{quat}$), 128.3

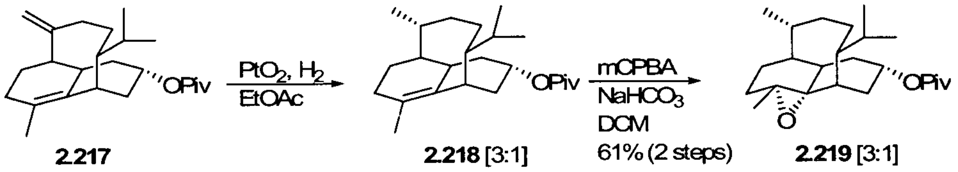
(C_{quat}), 114.1 (CH_2), 110.5 (CH_2), 70.5 (CH), 52.1 (CH), 46.9 (CH), 39.0 (C_{quat}), 34.2 (CH), 32.2 (CH_2), 30.4 (CH), 30.4 (CH_2), 30.3 (CH_2), 29.4 (CH_2), 27.6 (CH_2), 27.1 (CH_3x3), 26.0(CH_2), 23.0 (CH_3), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{27}$ $[(M-C_5H_9O_2)^+]$ 255.2107, found 255.2100.

(±)-(1*S*,3*S*,5*S*,6*R*,9*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.241A) and (±)-(1*S*,3*R*,5*S*,6*R*,9*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.241B). A solution of alkenes **2.193A-2** and **2.193B-2** (23.7 mg, 0.066 mmol) in 1.0 mL ethyl acetate was cannulated to a flask containing PtO_2 (0.8 mg, 0.003 mmol) under argon atmosphere. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. NMR analysis showed a mixture of hydrogenation products that corresponded to **2.241A** and **2.241B** that had been previously obtained via the isopropyl route (see description of the other method below).



2.188 2.217

(±)-(1*S*,3*R*,5*S*,6*R*,10*R*)- 2,2-Dimethyl-propionic acid 6-isopropyl-13-methyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.217). To a flask containing CH_3PPh_3I (0.430 g, 1.06 mmol) was added dropwise KO^{t}Bu (1.0 M in THF, 1.17 mL, 1.17 mmol) and the resulting yellow solution was stirred for 20 minutes. A solution of ketone **2.188B** (128 mg, 0.354 mmol) in toluene (1 mL) was added via cannula. The mixture was stirred at reflux for 1 h, cooled to r.t. and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10% ethyl acetate in hexanes-dry pack) to provide **2.217** (93.8 mg, 74%) as a colorless oil. IR (neat, cm^{-1}) 2929 (s), 1725 (s), 1479 (w), 1284 (m), 1164 (s); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.11-5.10 (m, 1H), 4.61-4.59 (m, 2H), 3.22-3.18 (m, 1H), 2.60-2.56 (m, 1H), 2.29-2.24 (m, 2H), 2.04-1.95 (m, 1H), 1.94-1.82 (m, 5H), 1.74 (s, 3H), 1.61-1.56 (m, 1H), 1.42-1.38 (m, 1H), 1.28-1.15 (m, 5H), 1.08 (s, 9H), 0.91 (d, J=6.4 Hz, 3H), 0.88 (d, J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 178.3 (C$_{quat}$), 155.9 (C$_{quat}$), 132.5 (C$_{quat}$), 127.6 (C$_{quat}$), 113.7 (CH$_2$), 70.7 (CH), 53.9 (CH), 47.0 (CH), 39.1 (C$_{quat}$), 34.2 (CH), 32.9 (CH$_2$), 31.2 (CH), 30.6 (CH), 30.3 (CH$_2$), 29.5 (CH$_2$), 28.6 (CH$_2$), 27.5 (CH$_2$), 27.1 (CH$_3$x3), 26.1(CH$_2$), 21.9 (CH$_3$), 21.3 (CH$_3$), 18.7 (CH$_3$); HRMS (EI) m/z calcd for $C_{24}H_{38}O_2$ [M$^+$] 358.2872, found 358.2896.



(±)-(1*R*,3*R*,5*S*,6*R*,9*R*,10*S*,13*R*,14*S*)-2,2-Dimethyl-propionic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}] -5-oxa-cyclopropa[d]tetradecen-3-yl ester and (±)-(1*R*,3*R*,5*S*,6*R*,9*S*,10*S*,13*R*,14*S*)-2,2-Dimethyl-propionic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}] -5-oxa-cyclopropa[d]tetradecen-3-yl ester (2.219). A solution of alkene **2.217** (39.7 mg, 0.111 mmol) in 1.2 mL ethyl acetate was cannulated to a flask containing PtO$_2$ (1.3 mg, 0.006 mmol) under argon atmosphere. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. NMR analysis showed a 3:1 ratio of isomers and the mixture was used directly in the next step.

To a 0 °C solution of alkene **2.218** (crude) in dichloromethane (1.1 mL) was added NaHCO$_3$ (39.2 mg, 0.466 mmol) and *m*CPBA (40.2 mg, 0.233 mmol) sequentially. The solution was stirred for 1 hour and quenched with a saturated solution of sodium sulfite. The mixture was extracted with dichloromethane (3x) and the organic layers were washed with a saturated solution of sodium bicarbonate, then, brine and finally, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 7% ethyl acetate in hexanes) afforded 25.7 mg of **2.219** (61% over 2 steps) as a colorless oil. IR (neat, cm^{-1}) 2955 (s), 1722 (s), 1482 (w), 1285 (m), 1164 (s);

^{1}H NMR (400 MHz, C_6D_6)

Major: δ 5.23-5.21 (m, 1H), 2.22-1.93 (m, 5H), 1.83-1.77 (m, 1H), 1.66-1.50 (m, 5H), 1.43-1.11 (m, 7H), 1.35 (s, 9H), 1.20 (s, 3H), 0.89 (d, *J*=7.1 Hz, 3H), 0.77 (d, *J*=6.4 Hz, 3H), 0.61 (d, *J*=6.6 Hz, 3H);

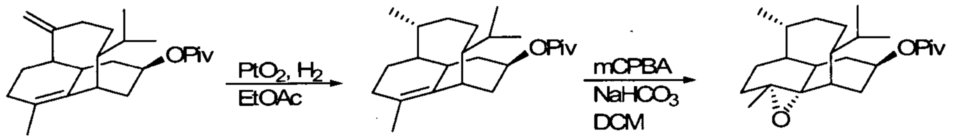
Minor: δ 5.37-5.33 (m, 1H), 2.22-1.93 (m, 5H), 1.83-1.77 (m, 1H), 1.66-1.50 (m, 5H), 1.43-1.11 (m, 7H), 1.40 (s, 9H), 1.22 (s, 3H), 0.89 (d, *J*=7.1 Hz, 3H), 0.77 (d, *J*=6.4 Hz, 3H), 0.61 (d, *J*=6.6 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6)

Major: δ 177.8 (C_{quat}), 68.9 (CH), 63.6 (C_{quat}), 60.0 (C_{quat}), 51.5 (CH), 41.1 (CH), 40.4 (CH), 39.3 (C_{quat}), 35.6 (CH), 34.8 (CH), 33.3 (CH_2), 31.9 (CH_2), 31.3 (CH), 31.1 (CH_2), 28.1 (CH_2), 27.5 (CH_3x3), 27.4 (CH_2), 23.7 (CH_3), 22.5 (CH_3), 21.8 (CH_3), 21.6 (CH_2), 21.1 (CH_3);

Minor: δ 177.9 (C_{quat}), 69.2 (CH), 62.8 (C_{quat}), 60.7 (C_{quat}), 49.4 (CH), 39.3 (C_{quat}), 39.1 (CH), 38.8 (CH), 35.9 (CH), 34.8 (CH), 32.8 (CH_2), 31.5 (CH), 30.9 (CH_2), 29.0 (CH_2), 27.7 (CH_2), 27.5 (CH_3x3), 26.9 (CH_2), 23.4 (CH_3), 22.3 (CH_2), 21.7 (CH_3), 21.3 (CH_3), 21.2 (CH_3);

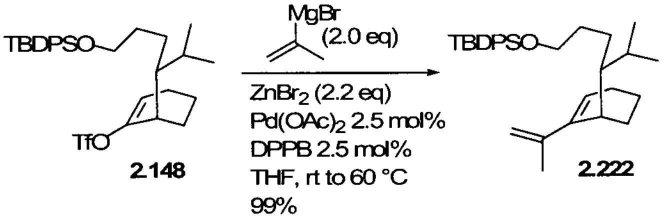
HRMS (EI) m/z calcd for $C_{21}H_{33}O_3$ [$(M-C_3H_7)^+$] 333.2424, found 333.2445.



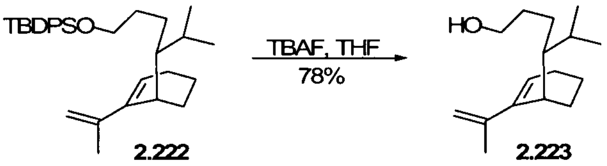
2.240A **2.218A** [25:1] 50% (2 steps) **2.219A** [25:1]

(±)-(1*R*,3*S*,5*S*,6*R*,9*R*,10*S*,13*R*,14*S*)-2,2-Dimethyl-propionic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}] -5-oxa-cyclopropa[d]tetradecen-3-yl ester (2.219A). A solution of alkene **2.240A** (see below for method) (10.9 mg, 0.030 mmol) in 1 mL ethyl acetate was cannulated to a flask containing PtO_2 (0.3 mg, 0.002 mmol) under argon atmosphere. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. NMR analysis showed only 1 isomer and was used directly in the next step.

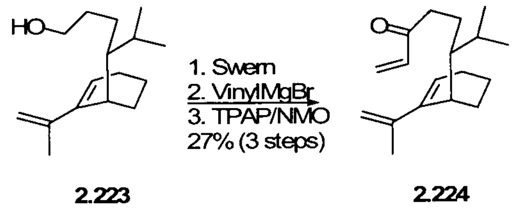
To a 0 °C solution of alkene **2.218A** (crude) in dichloromethane (1 mL) was added $NaHCO_3$ (10.6 mg, 0.126 mmol) and *m*CPBA (14.1 mg, 0.063 mmol) sequentially. The solution was stirred for 1 hour and quenched with a saturated solution of sodium sulfite. The mixture was extracted with dichloromethane (3x) and the organic layers were washed with a saturated solution of sodium bicarbonate, then, brine and finally, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 7% ethyl acetate in hexanes) afforded 5.7 mg of **2.219A** (50% over 2 steps) as a colorless oil. IR (neat, cm^{-1}) 2957 (s), 2873 (m), 1727 (s), 1283 (m), 1161 (s); ^1H NMR (400 MHz, C_6D_6) δ 5.36-5.27 (m, 1H), 2.29-2.11 (m, 3H), 1.98-1.92 (m, 2H), 1.79 (ddd, *J*=15.5, 7.7, 2.9 Hz, 1H), 1.68-1.34 (m, 10H), 1.24 (s, 3H), 1.24-1.05 (m, 2H), 1.23 (s, 9H), 0.93 (d, *J*=7.4 Hz, 3H), 0.80 (d, *J*=6.4 Hz, 3H), 0.65 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.2 (C_{quat}), 70.6 (CH), 63.7 (C_{quat}), 60.3 (C_{quat}), 50.4 (CH), 45.4 (CH), 40.4 (CH), 38.7 (C_{quat}), 38.3 (CH), 35.7 (CH), 33.8 (CH_2), 33.0 (CH_2), 31.7 (CH_2), 31.2 (CH), 28.4 (CH_2), 28.3 (CH_2), 27.4 (CH_3x3), 23.4 (CH_3), 22.2 (CH_3), 21.7 (CH_3), 21.7 (CH_2), 21.2 (CH_3); HRMS (EI) m/z calcd for $C_{21}H_{33}O_3$ [$(M-C_3H_7)^+$] 333.2424, found 333.2433.



(±)-(4*R*,1'*S*)-*tert*-Butyl-[4-(2-isopropenyl-cyclohex-2-enyl)-5-methyl-hexyloxy]-diphenyl-silane (2.222). In a glove box, $ZnBr_2$ (668 mg, 2.97 mmol) was weighed in a previously flame dried sealed tube. The sealed tube was then flame dried once more until the $ZnBr_2$ became liquid and then it is left to cool to about 60 °C. A stir bar is then added to the sealed tube and the latter was flame dried once more for a few seconds. The sealed tube was left to cool to room temperature before adding THF (3.2 mL) to dissolve $ZnBr_2$ and the resulting solution was cooled to 0 °C. Isopropenylmagnesium bromide (5.39 mL, 2.70 mmol) was added to the solution dropwise and the mixture was stirred at room temperature for 20 minutes. A solution of triflate **2.148** (786 mg, 1.35 mmol), $Pd(OAc)_2$ (14.4 mg, 0.0641mmol), DPPB (27.3 mg, 0.0641 mmol) in THF (4.90 mL) was stirred for 10 minutes before being cannulated into the sealed tube. The mixture was stirred overnight at 60 °C before being diluted with hexanes (31 mL), filtered through celite, rinsed with Et_2O and concentrated *in vacuo*. The residue was purified by flash chromatography (2% EtOAc in hexanes) to provide **2.222** (631.0 mg, 99%), as a colorless oil. The spectroscopic data corresponded to the one obtained for **2.181.**



(±)-(4*R*,1'*S*)- 4-(2-Isopropenyl-cyclohex-2-enyl)-5-methyl-hexan-1-ol (2.223). To a 0 °C solution of **2.222** (103 mg, 0.217 mmol) in THF (1.9 mL) was added TBAF (0.261 mL, 0.261 mmol). The mixture was stirred at room temperature overnight before it was quenched with $NaHCO_3$ and extracted with EtOAc (3X). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc in hexanes) to provide **2.223** (47.7 mg, 93%), as a colorless oil. IR (neat, cm^{-1}) 3403 (br), 2932 (s), 2868 (m), 1472 (w), 1384 (w), 1365 (w), 1142 (w), 1082 (w), 1065 (w), 1029 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.90 (m, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 3.57-3.46 (m, 2H), 2.71-2.79 (m, 1H), 2.10-1.93 (m, 2H), 1.83-1.82 (m, 3H), 1.78-1.08 (m, 11H), 0.96 (d, J=5.9 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.0 (C_{quat}), 143.8 (C_{quat}), 126.7 (CH), 111.2 (CH_2), 63.9 (CH_2), 46.1 (CH), 37.0 (CH), 34.3 (CH_2), 31.4 (CH), 26.0 (CH_2), 25.7 (CH_2), 24.1 (CH_2), 22.2 (CH_3), 22.1 (CH_3), 22.1 (CH_2), 21.6 (CH_3); HRMS (EI) m/z calcd for $C_{15}H_{25}O$ $[(M - CH_3)]^+$ 221.1900, found $C_{15}H_{25}O$ $[(M - CH_3)]^+$ 221.1890.

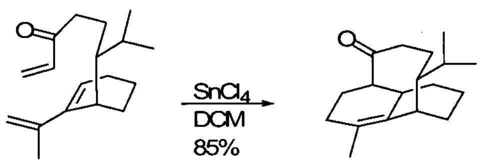


(±)-(6*R*,1'*S*)-6-(2-Isopropenyl-cyclohex-2-enyl)-7-methyl-oct-1-en-3-one (2.224). Procedure B: oxalyl chloride (0.131 mL, 1.51 mmol), dimethyl sulfoxide (0.157 mL, 2.21

mmol), alcohol **2.223** (209.4 mg, 0.886 mmol), dichloromethane (5+2.7 mL), triethylamine (0.617 mL, 4.43 mmol).

To a -78 °C mixture of crude aldehyde in toluene (6.1 mL) was added a solution of vinylMgBr 1.0 M in THF (2.66 mL, 2.66 mmol) dropwise. The mixture was stirred for 1 hour while warming up to about - 30°C before it was quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc (3X). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*.

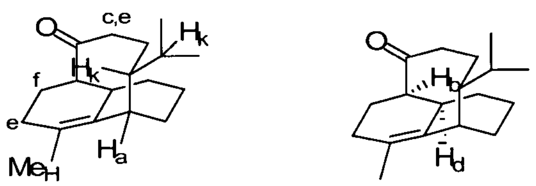
Procedure C: Molecular sieves 4 Å (1.83 g), crude alcohol, dichloromethane (8.9 mL), NMO (208 mg, 1.77 mmol), TPAP (7.80 mg, 0.0222 mmol). The solution was stirred overnight. The following morning, NMO (208 mg, 1.77 mmol) followed by TPAP (7.80 mg, 0.0222 mmol) were added once more and stirred for 6h. The mixture was then filtered through silica with EtOAc and then concentrated *in vacuo*. The residue was purified by flash chromatography (5% EtOAc in hexanes) to provide **2.224** (53.7 mg, 27% yield over 3 steps according to recovered starting material **2.223**), as a colorless oil. IR (neat, cm^{-1}) 3081 (w), 3024 (w), 2932 (s), 2870 (m), 1704 (m), 1682 (m), 1619 (m), 1399 (m), 959 (w), 883 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.29 (dd, *J*=17.7, 10.4 Hz, 1H), 6.15 (dd, *J*=17.7,1.4 Hz, 1H), 5.90-5.87 (m, 1H), 5.77 (dd, *J*=10.5, 1.4 Hz, 1H), 4.82-4.77 (m, 2H), 2.80-2.71 (m, 1H), 2.54-2.48 (m, 2H), 2.06-1.99 (m, 2H), 1.82-1.81 (m, 3H), 1.80-1.27 (m, 8H), 0.96 (d, *J*=1.0 Hz, 3H), 0.95 (d, *J*=1.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.9 (C_{quat}), 146.2 (C_{quat}), 143.5 (C_{quat}), 136.8 (CH), 127.6 (CH_2), 126.7 (CH), 111.2 (CH_2), 45.9 (CH), 41.1 (CH_2), 36.8 (CH), 31.3 (CH), 25.7 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 21.9 (CH_2), 21.4 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{28}O$ (M^+) 260.2140, found $C_{18}H_{28}O$ $(M)^+$ 260.2126.



2.224 **2.225**

(±)-(5*R*,9*R*,10*R*,14*R*)-2-methyl-9-Isopropyl-tricyclo[8.4.0.0^{5,14}]tetradec-1-en-6-one (2.225). To a -78 °C mixture of triene **2.224** (7.9 mg, 0.030 mmol) in DCM (0.30 mL) was added $SnCl_4$ (0.011 mL, 0.061 mmol). The solution was stirred for 3.5 h before it was quenched with Et_3N (1 drop) then with a saturated solution of sodium bicarbonate. The mixture was extracted with DCM (1X) and then with EtOAc (2X). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (7% EtOAc in hexanes) to provide **2.225** (6.7 mg, 85%) as a colorless oil. IR (neat, cm^{-1}) 2930 (s), 2869 (m), 1691 (s), 1474 (w), 1457 (w); ^1H NMR δ see table; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.7 (C_{quat}), 133.0 (C_{quat}), 129.8 (C_{quat}), 55.3 (CH), 53.4 (CH), 39.6 (CH), 39.4 (CH_2), 33.7 (CH), 30.3 (CH), 29.7 (CH_2), 27.1 (CH_2), 24.1 (CH_2), 23.2 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 21.8 (CH_3), 21.5 (CH_3), 19.2 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{28}O$ $(M)^+$ 260.2140, found $(M)^+$ 260.2159.

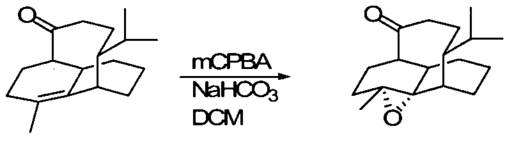
H	Chemical shift (δ) (CDCl$_3$, 400 MHz)	COSY	HMQC	HMBC	NOESY
A	3.30-3.29 (m, 1H)	H or G, K	33.7 (CH)	-	H or G, K,L
B	2.77-2.72 (m, 1H)	F	55.3 (CH)	-	D,F
C	2.46 (dd, J=8.0, 7.1 Hz, 1H)	E,J	39.4 (CH$_2$-E)	53.4, 2x, 218	E,I,J
D	2.44-2.35 (m, 1H)	H or G, K	39.6 (CH)	-	B,E,G
E	2.17-2.05 (m, 3H)	C,F,J	39.4 (CH$_2$-C), 29.7 (CH$_2$)	55.3, 133, 128, 218	C, I
F	1.96-1.86 (m, 2H)	B,E,J	24.1 (CH$_2$-J)	218, 33.7	B,I
G	1.83-1.73 (m, 2H)	A,D,K	27.1 (CH$_2$-K)	133, 128, 30.3, 29.7	A,B,C,D,E,F,J, K
H	1.79 (s, 3H)		19.3		
I	1.69-1.64 (m, 1H)	K	-	-	K
J	1.52-1.40 (m, 1H)	C,E,F	24.1 (CH$_2$-F)	-	C,E,F,G
K	1.38-1.01 (m, 6H)	A,D,G,I,L,M	53.4 (CH), 30.3 (CH), CH$_2$-G	2x	A,C,G,I
L	0.95 (d, J=6.2 Hz, 3H)	K	21.8	53.4, 29.7, 2x	F,K
M	0.89 (d, J=6.1, 3H)		21.5	53.4, 30.3	A,F,K



2.225

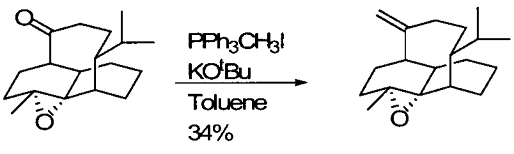
Important interactions for elucidation of the structure:

1. H_a sees Me_H
2. H_b sees H_d
3. methylene besides carbonyl has H_c and H_e. Only H_e sees H_b while H_k sees H_c.



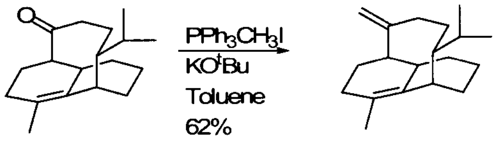
2.225 **2.226**

(±)-(1*S*,2*R*,5*S*,9*R*,10*R*,14*S*)-9-Isopropyl-2-methyl-tricyclo[8.4.0.0^{5,14}]-1-oxa-cyclopa[d]tetradec-1-en-6-one (2.226). To a 0 °C solution of alkene 2.225 (7.4 mg, 0.028 mmol) in dichloromethane (3.2 mL) was added sodium bicarbonate (10.0 mg, 0.119 mmol) then *m*CPBA (10.3 mg, 0.060 mmol). The solution was left for 1 hour before quenching with a saturated solution of sodium sulfite. The resulting mixture was stirred 20 minutes and extracted 3x with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (12% EtOAc in hexanes) to provide **2.226** (3.5 mg, 46%) as a colorless oil. IR (neat, cm^{-1}) 2933 (s), 2872 (m), 1727 (w), 1693 (s), 1458 (m), 901 (w); ^{1}H NMR (500 MHz, C_6D_6) δ 2.51-2.47 (m, 1H), 2.26-2.17 (m, 2H), 1.79-1.74 (m, 1H), 1.69-1.28 (m, 11H), 1.22 (s, 3H), 1.17-0.97 (m, 4H), 0.71 (d, J=6.6 Hz, 3H), 0.65 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 213.3 (C_{quat}), 62.7 (C_{quat}), 59.9 (C_{quat}), 52.1 (CH), 51.3 (CH), 42.8 (CH), 38.2 (CH_2), 37.9 (CH), 30.8 (CH_2), 30.7 (CH), 27.7 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 21.7 (CH_2), 21.6 (CH_3), 21.2 (CH_3), 21.2 (CH_3), 20.9 (CH_2); HRMS (EI) m/z calcd for $C_{18}H_{28}O_2$ [M^+] 276.2089, found 276.2086.



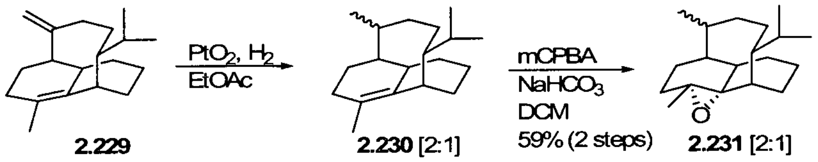
2.226 **2.227**

(±)-(1*S*,2*R*,5*S*,9*R*,10*R*,14*S*)-9-Isopropyl-2-methyl-6-methylene-tricyclo[8.4.0.0^{5,14}]-1-oxa-cyclopa[d]tetradec-1-ene (2.227). To a flask containing CH_3PPh_3I (51.2 mg, 0.127 mmol) was added dropwise KO^{t}Bu (1.0 M in THF, 0.137 mL, 0.137 mmol) and the resulting yellow solution was stirred for 20 minutes. A solution of ketone **2.226** (3.5 mg, 0.013 mmol) in toluene (0.3 mL) was added via cannula. The mixture was stirred at reflux for 1 h, cooled to r.t. and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (7% ethyl acetate in hexanes) to provide **2.227** (1.2 mg, 34%) as a colorless oil. IR (neat, cm^{-1}) 2931 (s), 2874 (m), 1456 (w); ^{1}H NMR (500 MHz, C_6D_6) δ 4.77 (d, *J*=2.8 Hz, 1H), 4.70 (d, *J*=2.9 Hz, 1H), 2.44 (t, *J*=13.2 Hz, 1H), 2.39-2.35 (m, 1H), 2.25-2.22 (m, 1H), 1.90-1.32 (m, 13H), 1.31 (s, 3H), 1.21-1.11 (m, 3H), 0.84 (d, *J*=6.4 Hz, 3H), 0.75 (d,*J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 154.0 (C_{quat}), 114.6 (CH_2), 63.5 (C_{quat}), 60.1 (C_{quat}), 52.1 (CH), 44.7 (CH), 42.8 (CH), 37.8 (CH), 33.3 (CH_2), 31.6 (CH_2), 31.4 (CH), 27.4 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 23.1 (CH_2), 21.8 (CH_3), 21.3 (CH_3), 21.0 (CH_3), 21.0 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{30}O$ [M^+] 274.2297, found 274.2323.



2.225 2.229

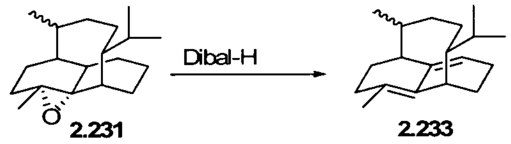
(±)-(5*R*,9*R*,10*R*,14*R*)-6-Methylen-2-methyl-9-isopropyl-tricyclo[8.4.0.0^{5,14}]tetradec-1-ene (2.229). To $IPPh_3CH_3$ (265 mg, 0.657 mmol) was added KO^{t}Bu dropwise and the solution was stirred for 20 minutes. A solution of ketone **2.225** in toluene (0.617 mL) was added via cannula. The mixture was stirred at reflux for 2 h, cooled to r.t. and quenched with NH_4Cl. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (0-15% EtOAc in hexanes) to provide **2.229** (19.1 mg, 62% according to recovered starting material) as a colorless oil. IR (neat, cm^{-1}) 2930 (s), 2870 (m), 1450 (m), 892 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61 (s, 2H), 3.29-3.19 (m, 1H), 2.69-2.62 (m, 1H), 2.33-2.25 (m, 1H), 2.25-2.15 (m, 1H), 2.02-1.54 (m, 7H), 1.77 (s, 3H), 1.44-1.11 (m, 8H), 0.97 (d, *J*=5.9 Hz, 3H), 0.92 (d, *J*=5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3 (C_{quat}), 134.3 (C_{quat}), 128.6 (C_{quat}), 112.7 (CH_2), 54.2 (CH), 47.5 (CH), 39.8 (CH), 33.6 (CH), 33.2 (CH_2), 30.5 (CH), 30.4 (CH_2), 28.3 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 23.3 (2xCH_2), 21.9 (CH_3), 21.4 (CH_3), 18.9 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{30}$ $(M)^+$ 258.2348, found $(M)^+$ 258.2340.



(±)-(1*R*,5*S*,6*R*,9*R*,10*S*,13*R*,14*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}] -5-oxa-cyclopropa[d]tetradecane (2.231). Platinum oxide (0.7 mg, 0.030 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.229** (38.2 mg, 0.148 mmol) in ethyl acetate (1 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*.

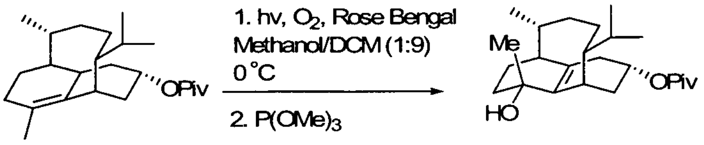
To a 0 °C solution of alkene **2.230** in DCM was added $NaHCO_3$ (52.2 mg, 0.621 mmol) followed by *m*CPBA (53.6 mg, 0.310 mmol). The reaction mixture was stirred for 2h before it was quenched with sodium sulfite and extracted with DCM (3X), The combined organic layers were washed with $NaHCO_3$ and washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (100% hexanes) to provide **2.231** (24.0 mg, 59%) as a colorless oil. NMR analysis indicated a 2:1 mixture of epimers. Only major product was characterized: IR (neat, cm^{-1}) 2959 (m), 2923 (s), 2851 (s), 1651 (m), 1463 (m), 1371 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.24-2.16 (m, 1H), 2.08-1.99 (m, 1H), 1.92-1.81 (m, 2H), 1.77-1.09 (m, 16 H), 1.33 (s, 3H), 1.02 (d, *J*=7.3 Hz, 3H), 0.89 (d, 6.3 Hz, 3H), 0.78 (d, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0 (C_{quat}), 133.7 (C_{quat}), 125.5 (C_{quat}), 119.5 (CH), 55.2 (CH), 44.5 (CH), 38.9 (CH), 35.7 (CH), 32.9 (CH_2), 30.7 (CH), 30.1 (CH_2), 29.3 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 19.6 (CH_3), 19.6 (CH_2), 17.9 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{32}O$ $(M)^+$ 276.2453, found $(M)^+$ 258.2362.

(±)-(5*S*,6*R*,9*R*,10*S*,14*R*)-9-Isopropyl-2,6-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-1-ene (2.230). To a solution of epoxide **2.231** (5.0 mg, 0.018 mmol) in freshly distilled ether (0.5 mL) was added LiAlH$_4$ (2.1 mg, 0.054 mmol). The solution was stirred at room temperature for 3 hours then 11.6 mg of LiAlH$_4$ was added and the mixture was refluxed another 3 hours. The mixture was cooled to room temperature and quenched with a saturated solution of ammonium chloride. The mixture was extracted 3x with diethyl ether. The combined organic layers were washed with NaHCO$_3$ and washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (0% to 5% ethyl acetate in hexanes) to provide **2.230** (2.7 mg, 54%) and recovered starting material (2.2 mg) as a colorless oil. The NMR was compared to **2.230** for identification.



(±)-(5*S*,9*R*,10*S*)-9-Isopropyl-2,6-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-1,13-diene (2.233). To a -78 °C solution of epoxide **2.231** (4.1 mg, 0.015 mmol) in distilled (over LiAlH$_4$) ether (0.50 mL) was added Dibal-H (0.074 mL, 0.074 mmol) dropwise. The reaction was warmed up to room temperature and was let to stir overnight. The reaction mixture was quenched with a saturated solution of sodium tartrate, extracted with EtOAc (3x) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (100% hexanes) to provide **2.233** (2.6 mg, 100% according to recovered starting material) as a colorless oil. IR (neat, cm^{-1}) 2917 (s), 2949 (s), 1462 (m), 1376 (w); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.44-5.39 (m, 1H), 3.21-3.12 (m, 1H), 2.17-2.10 (m, 1H), 2.09-1.75 (m, 6H), 1.71-1.63 (m, 2H), 1.45-1.07 (m, 7H), 1.73 (s, 3H), 0.96 (d, *J*=7.0 Hz, 3H), 0.94 (d, *J*=6.5 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 140.0 (C$_{quat}$), 133.7 (C$_{quat}$), 125.5 (C$_{quat}$), 119.5 (CH), 55.2 (CH), 44.5 (CH), 38.9 (CH), 35.7 (CH), 32.9 (CH$_2$), 30.7 (CH), 30.1 (CH$_2$), 29.3

(CH_2), 23.7 (CH_2), 22.6 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 19.6 (CH_3), 19.6 (CH_2), 17.9 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{30}$ (M^+) 258.2348, found $(M)^+$ 258.2352.



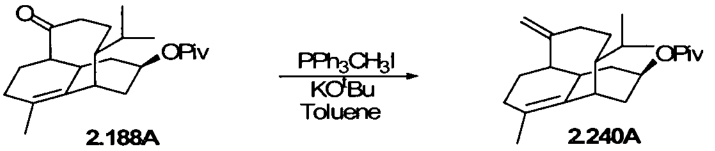
2.218 [3:1]

2.237 [3:1]

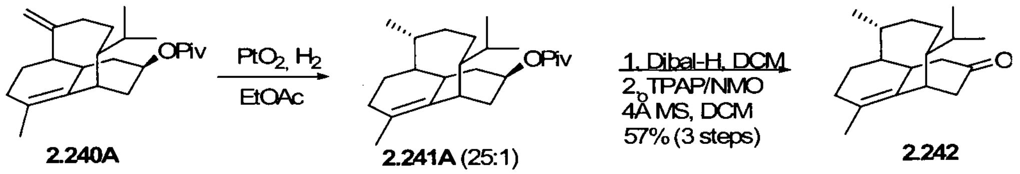
(±)-(5*S*,6*R*,9*R*,10*S*,13*R*)-2,2-Dimethyl-propionic acid 13-hydroxy-6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-1-en-3-yl ester (2.237). Based on the reference by Paquette.[249] To a solution of alkene **2.218** (13.6 mg, 0.038 mmol) in methanol (0.2 mL) and dichloromethane (1.8 mL) was added rose bengal (0.2 mg). The solution was cooled to -10 °C and oxygen was bubbled into the mixture. A 300 W lamp was installed and the light was shone onto the mixture for 40 minutes. At that point, $P(OMe)_3$ (0.046 mL, 0.381 mmol) was added to the mixture and the resulting solution was stirred for 1 hour at room temperature. Another 30 equivalents of $P(OMe)_3$ was then added. After 2.5 hours, the solvent was evaporated. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide **2.237** (4.1 mg, 29%) as a colorless oil. IR (neat, cm^{-1}) 3055 (s), 2961 (s), 2874 (m), 1712 (s), 1266 (s), 1163 (m), 739 (s); ^1H NMR (500 MHz, C_6D_6) δ 5.94 (s, 1H), 5.89-5.87 (m, 1H), 5.77-5.76 (m, 1H), 2.55-2.49 (m, 2H), 2.32-2.28 (m, 2H), 1.88-1.34 (m, 12H), 1.30 (s, 3H), 1.23 (s, 9H), 0.97 (d, J=7.0 Hz, 3H), 0.93 (d, J=6.5 Hz, 3H), 0.82 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.1 (C_{quat}), 139.4 (C_{quat}), 125.4 (CH), 68.1 (CH), 61.2 (C_{quat}), 50.8 (CH), 42.3 (CH), 38.4 (C_{quat}), 35.5 (CH), 34.7 (CH), 34.1 (CH_2), 29.6 (CH), 27.5 (CH_2), 27.0 (CH_3x3), 27.0 (CH_2), 27.0 (CH), 26.5 (CH_2), 21.4 (CH_3), 21.2 (CH_3), 20.5 (CH_3), 20.1 (CH_3), 19.5 (CH_3); HRMS (EI) m/z calcd for $C_{24}H_{38}O$ [$(M-H_2)^+$] 374.2821, found 374.2818.

This structure was identified based on the following:

1. The methyl at C8 had a chemical shift of 1.30 consistent with a non-allylic methyl.
2. A quaternary center had a chemical shift of 61.2 indicating that it was substituted with an oxygen.
3. The trisubstituted alkene coupled with H_a or H_b



(±)-(1*S*,3*S*,5*S*,6*R*,10*R*)- 2,2-Dimethyl-propionic acid 6-isopropyl-13-methyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.240A). To a flask containing CH_3PPh_3I (1.01 g, 2.50 mmol) was added dropwise KO^{t}Bu (1.0 M in THF, 2.75 mL, 2.75 mmol) and the resulting yellow solution was stirred for 20 minutes. A solution of ketone **2.188A** (301 mg, 0.834 mmol) in toluene (1.5 mL) was added via cannula. The mixture was stirred at reflux for 2 h, cooled to r.t. and quenched with a saturated solution of ammonium chloride. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (2% ethyl acetate in hexanes-dry pack) to provide **2.240A** (213.4 mg, 72%) as a colorless oil. IR (neat, cm^{-1}) 2924 (s), 1726 (s), 1438 (m), 1283 (w), 1163 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80-4.72 (m, 1H), 4.63-4.60 (m, 2H), 3.36-3.32 (m, 1H), 2.65-2.60 (m, 1H), 2.36-2.25 (m, 2H), 2.03-1.85 (m, 5H), 1.73 (s, 3H), 1.73-1.68 (m, 1H), 1.65-1.55 (m, 1H), 1.32-1.22 (m, 6H), 1.17 (s, 9H), 0.92 (d, *J*=6.1 Hz, 3H), 0.89 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C_{quat}), 155.5 (C_{quat}), 131.7 (C_{quat}), 128.5 (C_{quat}), 113.5 (CH_2), 71.8 (CH), 54.0 (CH), 47.2 (CH), 38.7 (C_{quat}), 38.4 (CH), 34.1 (CH), 32.9 (CH_2), 32.2 (CH_2), 30.4 (CH), 30.4 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 27.3 (CH_3x3), 26.0(CH_2), 21.7 (CH_3), 21.3 (CH_3), 18.9 (CH_3); HRMS (EI) m/z calcd for $C_{24}H_{38}O_2$ [M^+] 358.2872, found 358.2856.



(±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-one (2.242). Platinum oxide (2.4 mg, 0.011 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.240A** (75.9 mg, 0.213 mmol) in ethyl acetate (2.1 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. NMR analysis indicated only one isomer.

The crude mixture was dissolved in dichloromethane (2.5 mL) and cooled to -78 °C. Dibal-H (1.0 M in toluene, 0.752 mL, 0.752 mmol) was then added dropwise. The reaction was stirred for 2 hours before being quenched with a 1 M sodium tartrate solution. The solution was stirred for 0.5 hours. The mixture was extracted with dichloromethane (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

A mixture of crude alcohol in dichloromethane (2.5 mL) was cannulated to a flask containing flame-dried molecular sieves (4 Å, 394 mg). NMO (58.8 mg, 0.502 mmol) was added, followed by TPAP (4.4 mg, 0.013 mmol). The reaction was stirred for 2 hrs, then filtered through a silica gel pad (ethyl acetate) and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 39.3 mg of **2.242** (57% over 3 steps, > 25:1) as a colorless oil. *Please note that this ketone is sensitive and should be kept in the fridge or used immediately.*

IR (neat, cm^{-1}) 2928 (s), 2871 (s), 1711 (s), 1458 (m), 1382 (w);

^{1}H NMR (500 MHz, CDCl$_3$)

H	Chemical shift (δ)	COSY	HMQC	NOESY	HMBC
A	3.47-3.45 (m, 1H)	E(w), F,J	38.1	E,F,H,J,LM	-
B	2.89 (ddd, *J*=16.8, 6.2, 1.5 Hz, 1H)	C,D	41.8 (with D)	C(w),D,G(w),K	214, 44,38
C	2.81-2.76 (m, 1H)	B,D, G(w), H	38.1	D,G	-
D	2.55 (ddd, *J*=17.0, 10.8, 1.5 Hz, 1H)	B,C	41.8 (with B)	B,C(w)	214, 130, 38
E	2.44 (ddd, *J*=16.0, 1.9, 1.9 Hz, 1H)	A,F	39.5 (with F)	A,F,I, LM	214, 130, 38
F	2.32 (ddd, *J*=16.0, 8.3, 1.3 Hz, 1H)	A,E	39.5 (with E)	A,E	214, 38
G	2.04-1.90 (m, 4H)	C,G	44.2 + 3 in 30-29 region	B,C,H,I,K	130,44,30
H	1.75 (d, *J*=1.1 Hz, 3H)	C	18.2	A,G.J	130, 30
I	1.63-1.33 (m, 6H)	J,LM,K	30-29 region, 21.4	G,J,K, LM, E	38, 21, 18
J	1.22-1.12 (m, 2H)	I	52.7, 21.4	A,B.H,I,LM	21
K	1.08 (d, *J*=7.4 Hz, 3H)	I	21.6	B,G,I	44,39,29.9 or 29.6
L	0.92 (d, *J*=6.4 Hz, 3H)	I	21.6	I	52, 30, 21
M	0.90 (d, *J*=6.5 Hz, 3H)	I	20.9	A,E,I	52, 30, 21

(w)=weak interaction

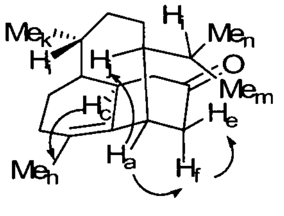
^{13}C NMR (125 MHz, CDCl$_3$)

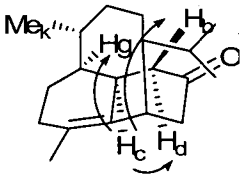
δ 214.7 (C$_{quat}$), 130.3 (C$_{quat}$), 129.4 (C$_{quat}$), 52.7 (CH), 44.2 (CH), 41.8 (CH$_2$), 39.6 (CH), 39.5 (CH$_2$), 38.1 (CH), 37.9 (CH), 30.4 (CH), 30.4 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 21.4

(CH$_3$), 21.4 (CH$_2$), 21.4 (CH$_3$), 20.8 (CH$_3$), 18.2 (CH$_3$); HRMS (EI) m/z calcd for $C_{19}H_{30}O$ [M$^+$] 274.2294, found 274.2286.

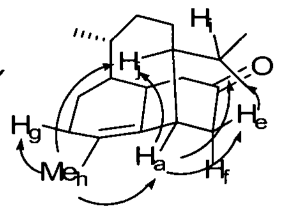
Summary of important interactions:

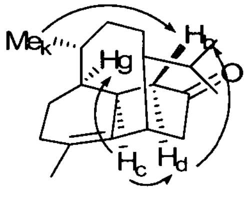
COSY

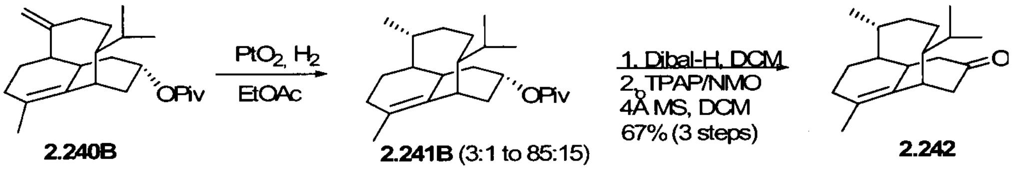




NOESY





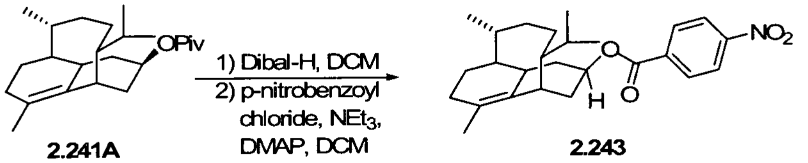


(±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-one (2.242). Platinum oxide (1.4 mg, 0.006 mmol) was weighed directly into a flame-dried flask filled with argon. A solution of alkene **2.240B** (44.0 mg, 0.123 mmol) in ethyl acetate (1.3 mL) was cannulated into the reaction flask. The reaction flask was put under vacuum and filled with argon three times. Then, the reaction flask was put under vacuum and filled with hydrogen three times. The reaction was stirred overnight under an atmosphere of hydrogen with vigorous stirring. In the morning, the atmosphere of hydrogen was changed to argon. Then, careful filtration through celite with ethyl acetate was done followed by concentration *in vacuo*. The ratio of isomers varied from 85:15 to 75:25.

The crude mixture was dissolved in dichloromethane (1.2 mL) and cooled to -78 °C. Dibal-H (1.0 M in toluene, 0.369 mL, 0.369 mmol) was then added dropwise. The reaction was stirred for 2 hours before being quenched with a 1 M sodium tartrate solution. The solution was stirred for 0.5 hours. The mixture was extracted with dichloromethane (3x) and the organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

The crude alcohol in dichloromethane (1.2 mL) was cannulated to a flask containing flame-dried molecular sieves (4 Å, 193 mg). NMO (28.8 mg, 0.246 mmol) was added, followed by TPAP (2.2 mg, 0.006 mmol). The reaction was stirred for 2 hrs, then filtered through a silica gel pad (ethyl acetate) and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 22.4 mg of **2.242** and **epi-2.242** (67% over 3 steps; ratio of 85:15) as a colorless oil. *Please note that this ketone is sensitive and should be kept in the fridge or used immediately.*

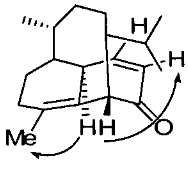
By NMR (^{1}H and ^{13}C), the major product obtained corresponded to **2.242**. The minor product was assigned as **epi-2.242:** (characterized as mixture with **2.242**) IR (neat, cm^{-1}) 2928 (s), 2871 (s), 1711 (s), 1458 (m), 1382 (w); ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.47-3.45 (m, 1H), 2.89 (ddd, J=16.8, 6.2, 1.5 Hz, 1H), 2.81-2.76 (m, 1H), 2.55 (ddd, J=17.0, 10.8, 1.5 Hz, 1H), 2.44 (ddd, J=16.0, 1.9, 1.9 Hz, 1H), 2.32 (ddd, J=16.0, 8.3, 1.3 Hz, 1H), 2.04-1.90 (m, 4H), 1.75 (d, J=1.1 Hz, 3H), 1.63-1.33 (m, 6H), 1.22-1.12 (m, 2H), 0.88 (d, J=6.4 Hz, 3H), 0.88 (d, J=7.5 Hz, 3H), 0.73 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 214.7 (C$_{\text{quat}}$), 130.7 (C$_{\text{quat}}$), 129.8 (C$_{\text{quat}}$), 53.5 (CH), 43.2 (CH), 40.4 (CH$_2$), 39.5 (CH$_2$), 38.2 (CH), 37.6 (CH), 35.6 (CH), 31.4 (CH$_2$), 30.6 (CH), 29.9 (CH$_2$), 29.6 (CH$_2$), 22.6 (CH$_3$), 21.4 (CH$_3$), 21.1 (CH$_2$), 21.1 (CH$_3$), 18.4 (CH$_3$); HRMS (EI) m/z calcd for $C_{19}H_{30}O$ [M$^+$] 274.2294, found 274.2286.



(±)-(1*S*,3*S*,5*S*,6*R*,9*R*,10*R*)-4-Nitro-benzoic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.243). To a solution of crude alcohol (0.431 mmol) in dichloromethane (4.3 mL) was added triethylamine (0.299 mL, 2.16 mmol), p-nitrobenzoylchloride (160 mg, 0.862 mmol) and DMAP (1 crystal) sequentially. The reaction was stirred at room temperature until complete disappearance of the starting material (3 hours). The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5% ethyl acetate in hexanes-dry pack) to provide **2.243** (143.2 mg, 56% over 3 steps) as a yellow solid. Recrystallization from petroleum ether gave crystals valid for X-ray analysis. IR (neat, cm^{-1}) 2975 (s), 2871 (m), 1716 (s), 1532 (s), 1268 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24 (d, *J*=8.9 Hz, 2H), 8.19 (d, *J*=11.6 Hz, 2H), 4.94-4.86 (m, 1 H), 3.41-3.36 (m, 1H), 2.45-2.41 (m, 1H), 2.22-2.13 (m, 2H), 2.07-1.98 (m, 3H), 1.89-1.88 (m, 2H), 1.72 (d, *J*=1.8 Hz, 3 H), 1.62-1.40 (m, 7H), 1.32-1.19 (m, 2H), 1.16 (d, *J*=7.8 Hz, 3H), 0.93 (d, *J*=6.4 Hz, 3H), 0.92 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.3 (C$_{quat}$), 150.5 (C$_{quat}$), 136.4 (C$_{quat}$), 131.7 (C$_{quat}$), 130.8 (CHx2), 129.0 (C$_{quat}$), 123.5 (CHx2), 74.9 (CH), 54.6 (CH), 42.5 (CH), 41.1 (CH), 39.4 (CH), 34.7 (CH), 33.5 (CH$_2$), 30.8 (CH), 30.7 (CH$_2$), 30.6 (CH$_2$), 29.7 (CH$_2$), 29.1 (CH$_2$), 21.8 (CH$_3$), 21.8 (CH$_3$), 21.2 (CH$_3$), 20.6 (CH$_2$), 18.4 (CH$_3$); HRMS (EI) m/z calcd for $C_{26}H_{35}NO_4$ [M$^+$] 425.2566, found 425.2563. MP= 78.2-80.5 °C.

2.242 2.250

(±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-2,13-dien-4-one (2.250). To a -78 °C solution of ketone **2.242** (23.5 mg, 0.086 mmol) in THF (0.5 mL) was added a solution of KHMDS (42.9 mg, 0.215 mmol) in THF (0.5 mL). The resulting solution was stirred for one hour before adding triethylamine (0.072 mL, 0.516 mmol) and TBSCl (62.2 mg, 0.430 mmol in 0.5 mL THF) sequentially. The solution was stirred for 15 minutes and quenched with a saturated solution of sodium bicarbonate. The mixture was warmed to room temperature and extracted 3x with hexanes. The combined organic portions were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude silyl enol ether was dissolved in acetonitrile (0.8 mL) and water was added (0.2 mL). To this mixture, NMO (15.1 mg, 0.129 mmol) was added followed by OsO$_4$ (4% in H$_2$O, 0.026 mL, 0.004 mmol). The solution was stirred at room temperature for 2 hours before quenching with a saturated solution of sodium sulfite. The solution was stirred for 15 minutes before extracting the aqueous layer 3x with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (15% ethyl acetate in hexanes) gave 3.5 mg of dienone **2.250** as a yellow oil (15% yield). IR (neat, cm^{-1}) 2956 (s), 2929 (s), 1799(s), 1463 (m), 838 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 (dd, *J*=7.2, 4.7 Hz, 1H), 5.09 (dd, *J*=5.9, 4.8 Hz, 1H), 3.80-3.79 (m, 1H), 3.17-3.16 (m, 1H), 2.19-2.12 (m, 1H), 2.08-2.01 (m, 2H), 1.96-1.91 (m, 1H), 1.71 (s, 3H), 1.68-1.63 (m, 3H), 1.56-1.45 (m, 5H), 1.00 (d, *J*=7.8 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1 (C_{quat}), 130.7 (C_{quat}), 128.4 (C_{quat}), 103.1 (CH), 98.5 (CH), 48.9 (CHx2), 43.2 (CH), 40.9 (CH), 39.3 (CH), 31.9 (CH), 31.5 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 21.7 (CH_2), 21.5 (CH_3x2), 19.5 (CH_3), 19.0 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{28}O$ [M$^+$] 272.2140, found 272.2169.



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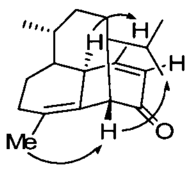

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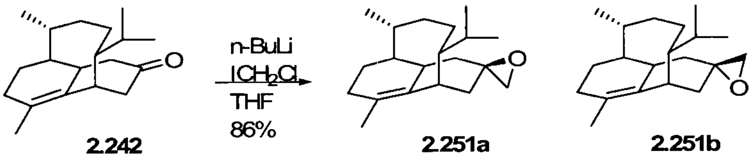
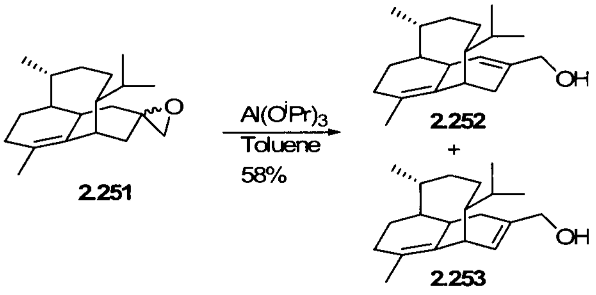


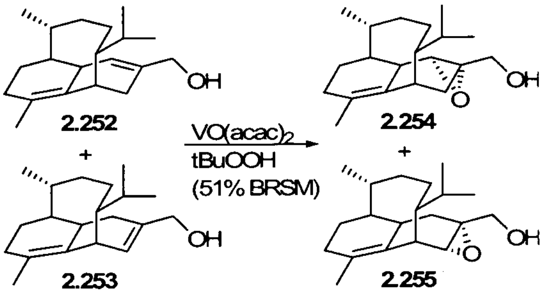
(±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-ene-3-spiro-1'-oxirane (2.251). To a -78 °C solution of ketone **2.242** (78.3 mg, 0.285 mmol) in THF (2.9 mL) was added chloroiodomethane (0.108 mL, 1.484 mmol) and *n*-BuLi (0.833 mL, 1.425 mmol) sequentially. The reaction was left warming up overnight. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to provide **2.251** (70.9 mg, 86%) as a colorless oil. Major: IR (neat, cm^{-1}) 2927 (s), 2871 (m), 1463 (m), 1379 (w); ^{1}H NMR (500 MHz, C_6D_6) δ 3.57-3.53 (m, 1H), 2.83-2.79 (m, 1H), 2.54 (d, *J*=5.0 Hz, 1H), 2.48 (d, *J*=5.0 Hz, 1H), 2.39 (dd, *J*=12.9, 12.9 Hz, 1H), 2.11-1.92 (m, 2H), 1.91-1.85 (m, 3H), 1.81 (d, *J*=1.9 Hz, 3H), 1.79-1.41 (m, 4H), 1.40-1.14 (m, 6H), 1.24 (d, *J*=7.7 Hz, 3H), 1.04 (d, *J*=6.3 Hz, 3H), 0.96 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 133.5 (C_{quat}), 127.9 (C_{quat}), 58.4 (C_{quat}), 54.9 (CH), 52.6 (CH_2), 42.7 (CH), 41.5 (CH), 37.7 (CH), 34.0 (CH), 33.4 (CH_2), 31.4 (CH_2), 30.9 (CH), 30.8 (CH_2), 30.6 (CH_2), 30.2 (CH_2), 22.1 (CH_3), 21.9 (CH_3), 21.3 (CH_2), 21.2 (CH_3), 18.5 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{32}O$ [M^+] 288.2453, found 288.2434.

Minor: IR (neat, cm^{-1}) 2926 (s), 2870 (m), 1454 (m), 1379 (w); ^1H NMR (500 MHz, C_6D_6) δ 3.44-3.38 (m, 1H), 2.59 (dd,J=11.9, 11.9 Hz, 1H), 2.45-2.32 (m, 3H), 2.08-1.75 (m, 6H), 1.69 (d, J=1.8 Hz, 3H), 1.67-1.13 (m, 9H), 1.14 (d, J=7.8 Hz, 3H), 0.90 (d, J=6.0 Hz, 3H), 0.86 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 133.8 (C_{quat}), 127.9 (C_{quat}), 59.1 (C_{quat}), 55.0 (CH), 54.0 (CH_2), 42.9 (CH), 41.5 (CH), 40.2 (CH), 35.6 (CH), 35.1 (CH_2), 31.2 (CH_2), 31.0 (CH_2), 30.9 (CH_2), 30.8 (CH), 30.1 (CH_2), 22.0 (CH_3), 21.9 (CH_3), 21.3 (CH_3), 21.0 (CH_2), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{32}O$ [M^+] 288.2453, found 288.2430.

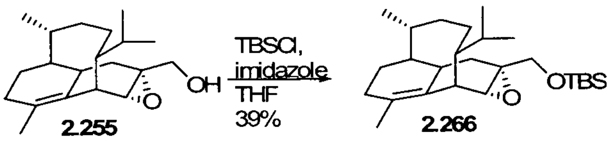


(±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-(6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-2,13-dien-3-yl)-methanol (2.252) and (±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-(6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-3,13-dien-3-yl)-methanol (2.253). Aluminum triisopropoxide (80.7 mg, 0.395 mmol) was added to a flame-dried seal tube. Then, a solution of epoxide **2.251** (38.0 mg, 0.132 mmol) in toluene (1.3 mL) was cannulated and the tube was sealed. The reaction was stirred for 18 hours at 80 °C. The reaction was diluted with ether and quenched with 1M sodium tartrate. The solution was stirred for 1 hour before the layers were separated. 1M NaOH was then added to the aqueous phase and the resulting mixture was extracted 3x with ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to provide **2.252** and **2.253** as an inseparable yellow oil (21.9 mg, 58%, approx. 2:1 ratio). Each isomer is one. IR (neat, cm^{-1}) 3384 (br), 2925 (s), 2970 (s), 1637 (m), 1463 (m), 1379 (w), 1036 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 5.70-5.65 (m, 2H), 3.96 (s, 4H), 3.56-3.42 (m, 2H), 3.39-3.29 (m, 6H), 2.55-1.70 (m, 14H), 1.62 (s, 3H), 1.60 (s, 3H), 1.50-1.22 (m, 12H), 1.01 (d, J=7.5 Hz, 3H), 1.01 (d,

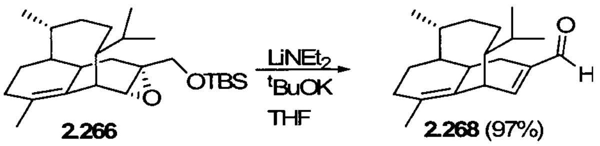
J=7.7 Hz, 3H), 0.89 (d, J=6.0 Hz, 3H), 0.83 (d, J=6.7 Hz, 3H), 0.79 (d, J=6.3 Hz, 3H), 0.76 (d, J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.8 (C_{quat}x2), 134.5 (C_{quat}), 132.8 (C_{quat}), 128.0 (C_{quat}), 126.9 (C_{quat}), 123.2 (CH), 120.2 (CH), 68.9 (CH_2), 67.8 (CH_2), 54.8 (CH), 54.5 (CH), 43.6 (CH), 42.7 (CH), 41.3 (CH), 40.8 (CH), 38.7 (CH), 37.7 (CH), 35.9 (CH), 34.2 (CH), 31.4 (CH_2), 31.3 (CH), 31.1 (CH_2), 30.7 (CH), 30.7 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.0 (CH_2), 27.0 (CH_2), 21.9 (CH_3x2), 21.6 (CH_3x2), 21.5 (CH_3), 21.4 (CH_3), 21.1 (CH_2), 20.5 (CH_2), 18.5 (CH_3), 18.4 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{32}O$ [M^+] 288.2453, found 288.2437.



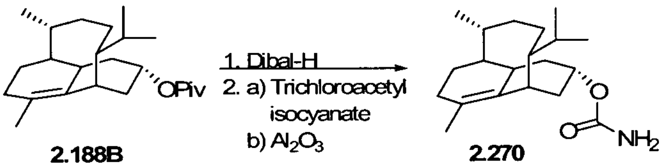
(±)-(1*R*,2*S*,3*R*,5*S*,6*R*,9*R*,10*S*)-(6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]- 2-oxa-cyclopa[d]tetradeca-13-en-3-yl)-methanol (2.254) and (±)-(1*R*,3*R*,4*R*,5*S*,6*R*,9*R*,10*S*)-(6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]-3-oxa-cyclopa[d]tetradeca-13-en-3-yl)-methanol (2.255). To a solution of allylic alcohols **2.252** and **2.253** (33.5 mg, 0.116 mmol) in dichloromethane (2 mL) was added VO(acac)$_2$ (1.5 mg, 0.006 mmol-made dilution in dichloromethane and added as a solution) then *t*-BuOOH (5-6 M in decane, 0.032 mL, 0.162 mmol). The resulting red solution was stirred for 1 hour before adding another portion of each reagent. After 30 minutes, there was no change by TLC and the reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine, dried with magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in hexanes) to provide **2.254** (4.4 mg) and **2.255** (10.5 mg) in a 42% combined yield as yellow oils. The allylic alcohols were immediately protected in the next step.



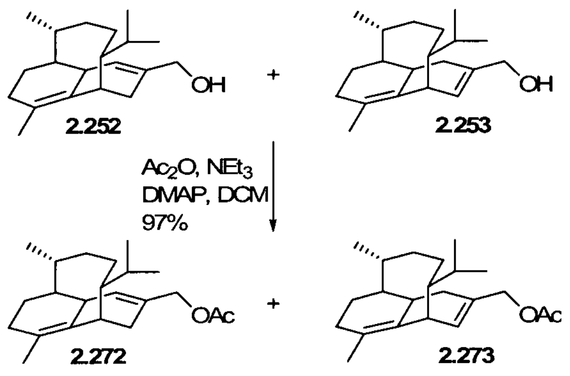
(±)-(1*R*,3*R*,4*R*,5*S*,6*R*,9*R*,10*S*)-*tert*-Butyl-dimethyl-[(6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]-3-oxa-cyclopa[d]tetradeca-13-en-3-yl)-methanoxy]-silane (2.266). To a solution of alcohol **2.255** (10.5 mg, 0.034 mmol) in THF (0.2 mL) was added imidazole (14.0 mg, 0.206 mmol) and TBSCl (15.4 mg, 0.102 mmol). The mixture was stirred overnight before quenching with water. The mixture was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine, dried with magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide **2.266** (7.2 mg, 39% yield) as a yellow oil. IR (neat, cm^{-1}) 2955 (s), 2928 (s), 1473 (m), 1255 (m), 837 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (d, *J*=10.8 Hz, 1H), 3.78-3.70 (m, 1H), 3.66 (d, *J*=10.7Hz, 1H), 3.24 (d, *J*=2.5 Hz, 1H), 2.72 (dd, *J*=15.3, 9.4 Hz, 1H), 2.55-2.42 (m, 1H), 2.27-2.22 (m, 1H), 2.17-2.01 (m, 1H), 1.97-1.84 (m, 4H), 1.74 (s, 3H), 1.73-1.33 (m, 7H), 1.29 (d, *J*=7.6 Hz, 3H), 1.08 (s, 9H), 1.05 (d, *J*=6.6 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.9 (C_{quat}), 128.2 (C_{quat}), 68.7 (CH), 59.8 (CH), 59.0 (C_{quat}), 56.8 (CH), 51.4 (CH), 43.1 (CH), 38.4 (CH), 33.6 (CH), 31.4 (CH), 31.3 (CH_2), 31.0 (CH_2), 30.2 (CH_2), 27.3 (CH_2), 26.6 (CH_3x3), 23.3 (CH_3), 21.7 (CH_3), 21.6 (CH_2), 21.4 (CH_3), 18.5 (C_{quat}), 18.2 (CH_3), -5.2 (CH_3), -5.3 (CH_3); HRMS (EI) m/z calcd for $C_{23}H_{36}O_2Si$ [M-(C_3H_{10})] 372.2485, found 372.2571.



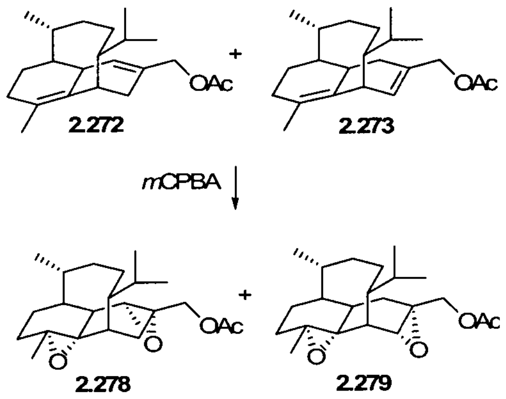
(±)-(1*R*,5*R*,6*R*,9*R*,10*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-3,13-diene-3-carbaldehyde (2.268). To a solution of dry potassium *tert*-butoxide (21.9 mg, 0.195 mmol) in THF (0.2 mL) was added freshly distilled (over CaH_2) diethylamine (0.020 mL, 0.195 mmol). The solution was cooled to -78 °C and *n*-BuLi (0.127 mL, 0.195 mmol) was added dropwise. The orange-brown solution was stirred 15 minutes before the addition of epoxide **2.263** (7.1 mg, 0.013 mmol) in THF (0.5 mL) via a cannula. The solution was warmed to 0 °C by transferring the flask into an ice bath. The red solution did not have any starting material left. The reaction was quenched with water and extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to provide **2.268** (3.6 mg, 97% yield) as a yellow oil. IR (neat, cm^{-1}) 2927 (s), 2874 (m), 1685 (s), 1463 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 6.46-6.44 (m, 1H), 3.58-3.55 (m, 1H), 2.94 (dd, *J*=19.0, 10.0 Hz, 1H), 2.60-2.57 (m, 1H), 2.27-2.18 (m, 1H), 1.87-1.65 (m, 4H), 1.64 (d, *J*=2.0 Hz, 3H), 1.45-1.30 (m, 8H), 1.02 (d, *J*=7.8 Hz, 3H), 0.89 (d, *J*=6.7 Hz, 3H), 0.82 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9 (C_{quat}), 150.3 (CH), 143.0 (C_{quat}), 128.2 (C_{quat}), 127.2 (C_{quat}), 54.9 (CH), 40.9 (CH), 39.2 (CH), 34.8 (CH), 34.0 (CH), 31.3 (CH), 31.1 (CH_2), 30.4 (CH_2), 30.0 (CH_2), 23.2 (CH_2), 22.2 (CH_3), 21.3 (CH_2), 21.1 (CH_3x2), 18.0 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{30}O$ [M^+] 286.2297, found 286.2267.



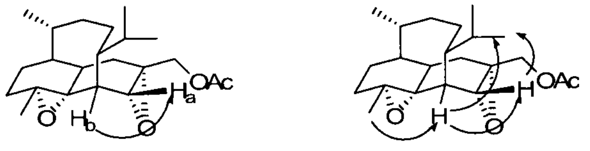
(±)-(1*S*,3*R*,5*S*,6*R*,10*R*)-Carbamic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (2.270). To a 0 °C of the crude alcohol (23.5 mg, 0.085 mmol) in dichloromethane (1 mL) was added trichloroacetylisocyanate (0.015 mL, 0.128 mmol). The mixture was stirred at room temperature for 1 hour until disappearance of the starting material. Aluminum oxide (850 mg) was added with dichloromethane (1 mL). The solution was stirred at room temperature for 1 hour. The solvent was removed *in vacuo*. The residue was purified by flash chromatography (30% ethyl acetate in hexanes) to provide **2.270** (30.2 mg, 99% yield) as a yellow solid. IR (neat, cm^{-1}) 3357 (br), 2924 (s), 2873 (m), 1707 (s), 1402 (w), 1330 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 5.07-5.06 (m, 1H), 4.51-4.49 (m, 2H), 3.20-3.18 (m, 1H), 2.36-2.29 (m, 1H), 2.09-1.80 (m, 7H), 1.71 (s, 3H), 1.63-1.16 (m, 9H), 1.11 (d, *J*=7.8 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (C_{quat}), 132.7 (C_{quat}), 126.7 (C_{quat}), 71.2 (CH), 54.2 (CH), 42.0 (CH), 41.0 (CH), 34.1 (CH), 31.2 (CH), 30.6 (CH_2), 30.5 (CH), 30.4 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 21.0 (CH_2), 20.6 (CH_3), 18.3 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{30}$ [M-(CH_3NO_2)] 258.2348, found 258.2362. MP=83.2-85.0 °C.



(±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-Acetic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-2,13-dien-3-ylmethyl ester (2.272) and (±)-(1*R*,5*S*,6*R*,9*R*,10*S*)-Acetic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-3,13-dien-3-ylmethyl ester (2.273). To a solution of alcohols **2.252** and **2.253** (10.8 mg, 0.037 mmol) in dichloromethane (1 mL) was added triethylamine (0.031 mL, 0.222 mmol) then acetic anhydride (0.016 mL, 0.172 mmol). A crystal of DMAP was added and the solution was stirred for 2 hours. The reaction was quenched with a saturated solution of ammonium chloride followed by extraction with ethyl acetate (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide **2.272** and **2.273** as an inseparable yellow oil (11.9 mg, 97%). Each isomer is one. IR (neat, cm^{-1}) 2926 (s), 2869 (m), 1743 (s), 1455 (w), 1385 (m), 1241 (s), 1035 (m); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.85-5.81 (m, 2H), 4.51 (d, *J*=4.3 Hz, 4H), 4.08-4.00 (m, 1H), 3.91-3.88 (m, 2H), 3.87-3.82 (m, 1H), 3.51-3.49 (m, 2H), 3.27-3.11 (m, 2H), 2.60-2.47 (m, 4H), 2.27-2.22 (m, 2H), 2.18-2.06 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.00-1.85 (m, 8H), 1.72 (d, *J*=1.5 Hz, 3H), 1.70 (s, 3H), 1.66-1.23 (m, 8H), 1.12 (d, *J*=7.5 Hz, 3H), 0.99 (d, *J*=6.3 Hz, 3H), 0.93 (d, *J*=6.1 Hz, 3H), 0.93 (d, *J*=7.2 Hz, 3H), 0.89 (d, *J*=6.4 Hz, 3H), 0.89 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.2 (C$_{quat}$), 179.9 (C$_{quat}$), 134.6 (C$_{quat}$x2), 131.9 (C$_{quat}$x2), 127.9 (C$_{quat}$), 126.8 (C$_{quat}$), 126.5 (CH), 119.5 (CH), 69.5 (CH$_2$), 68.8 (CH$_2$), 54.4 (CH), 54.1 (CH), 43.9 (CH), 43.2 (CH), 42.3 (CH), 40.8 (CH), 40.3 (CH), 37.5 (CH), 35.3 (CH), 34.9 (CH), 31.2 (CH$_2$), 31.1 (CH$_3$x2), 30.9 (CH$_2$), 30.4 (CH$_2$x2), 30.3 (CH), 30.0 (CH), 29.6 (CH$_2$), 28.6 (CH$_2$), 27.9 (CH$_2$), 26.9 (CH$_2$), 22.3 (CH$_3$), 21.6 (CH$_3$), 21.3 (CH$_3$), 21.1 (CH$_3$x2), 20.9 (CH$_3$), 20.7 (CH$_2$), 20.1 (CH$_2$), 18.8 (CH$_3$), 18.2 (CH$_3$); HRMS (EI) m/z calcd for C$_{22}$H$_{34}$O$_2$ [M$^+$] 330.2559, found 330.2536.

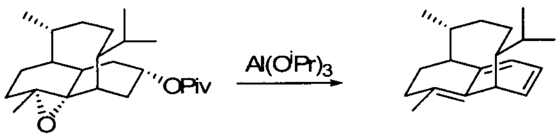


(±)-(1*S*,2*S*,3*S*,5*S*,6*R*,9*R*,10*S*,13*R*,14*S*)-Acetic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]-2,13-di-oxa-cyclopa[d]tetradecanylmethyl ester (2.278) and (±)-(1*R*,3*R*,4*R*,5*R*,6*R*,9*R*,10*S*,13*R*,14*R*)-Acetic acid 6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]-3,13-di-oxa-cyclopa[d]tetradecanylmethyl ester (2.279). To a 0 °C solution of alkene **2.272** and **2.273** (11.9 mg, 0.036 mmol) in dichloromethane (1.5 mL) was added $NaHCO_3$ (6.7 mg, 0.079 mmol) and *m*CPBA (8.9 mg, 0.040 mmol) sequentially. The solution was stirred for 30 minutes and quenched with a saturated solution of sodium sulfite. The mixture was extracted with dichloromethane (3x) and the organic layers were washed with a saturated solution of sodium bicarbonate, then, brine and finally, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 20 to 50% ethyl acetate in hexanes) afforded 3.4 mg of **2.278** and **2.279** (26%) as a colorless oil. Only the major isomer (**2.279**) was characterized. IR (neat, cm^{-1}) 2956 (s), 1743 (s), 1455 (m), 1379 (m), 1233 (s), 1036 (m); ^1H NMR (500 MHz, C_6D_6) δ 4.26 (d, *J*=11.8 Hz, 1H), 3.97 (d, *J*=11.8Hz, 1H), 3.02 (d, *J*=3.4 Hz, 1H), 2.48 (dd, *J*=3.8 Hz, 3.8 Hz, 1H), 2.11-2.08 (m, 3H), 2.02-1.74 (m, 4H), 1.67 (s, 3H), 1.54-1.25 (m, 8H), 1.19 (s, 3H), 0.91 (d, *J*=7.0 Hz, 3H), 0.77 (d, *J*=6.5 Hz, 3H), 0.72 (d, *J*=6.7Hz, 3H); ^{13}C NMR (125 MHz, C_6D_{63}) δ 169.5 (C_{quat}), 67.6 (CH_2), 61.4 (C_{quat}), 58.1 (C_{quat}), 57.0 (C_{quat}), 55.9 (CH), 45.4 (CH), 41.1 (CH), 40.2 (CH), 39.6 (CH), 33.5 (CH_2), 33.0 (CH), 31.3 (CH), 30.5 (CH_2), 28.1 (CH_2), 27.0 (CH_2), 23.9 (CH_3), 21.5 (CH_3), 21.3 (CH_3), 21.1 (CH_2), 20.9 (CH_3), 19.9 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{30}O_2$ $[(M-C_2H_4O_2)^+]$ 302.2246, found 302.2259.



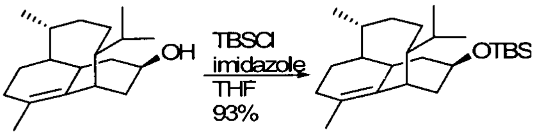
COSY 2.279 NOESY

-H$_a$ is d at 3.02 while H$_b$ is dd at 2.48. The methyl adjacent to the epoxide was at 1.19 ppm while the acetate methyl was at 1.67. The important interactions are shown above.



2.219 [3:1] **2.292**

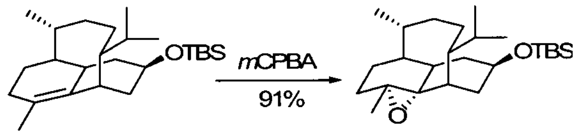
(±)-(5*R*,6*R*,9*R*,10*S*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-1,3,13-triene (2.292). A solution of epoxide **2.219** (6.0 mg, 0.016 mmol) in toluene was cannulated to a seal tube containing aluminum isopropoxide (9.8 mg, 0.048 mmol). The tube was sealed and heated at 80 °C for 18 hours. Another portion of aluminum isopropoxide was added and the solution was heated to 110 °C for 5 hours. The reaction was diluted with ether and quenched with 1M sodium tartrate. The solution was stirred for 1 hour before the layers were separated. 1M NaOH was then added to the aqueous phase and the resulting mixture was extracted 3x with ether. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide **2.292** (3.1 mg, 76%) as a yellow oil. IR (neat, cm^{-1}) 2926 (s), 2849 (m), 1459 (w), 1374 (w); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.02-5.99 (m, 1H), 5.76-5.73 (m, 1H), 5.39-5.38 (m, 1H), 3.44-3.42 (m, 1H), 2.13-1.98 (m, 4H), 1.79-1.77 (m, 2H), 1.75 (s, 3H), 1.58-1.17 (m, 6H), 0.97 (d, *J*=7.1 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 137.2 (C$_{quat}$), 131.7 (C$_{quat}$), 130.9 (C$_{quat}$), 127.5 (CH), 125.9 (CH), 115.6 (CH), 54.0 (CH), 44.1 (CH), 40.3 (CH), 37.6 (CH), 33.2 (CH$_2$), 29.8 (CH$_2$), 29.8 (CH), 27.9 (CH$_2$), 21.5 (CH$_3$), 21.3 (CH$_3$), 20.5 (CH$_2$), 19.4 (CH$_3$), 17.6 (CH$_3$); HRMS (EI) m/z calcd for $C_{19}H_{28}$ [M$^+$] 256.2191, found 256.2170.



2.293 **2.294**

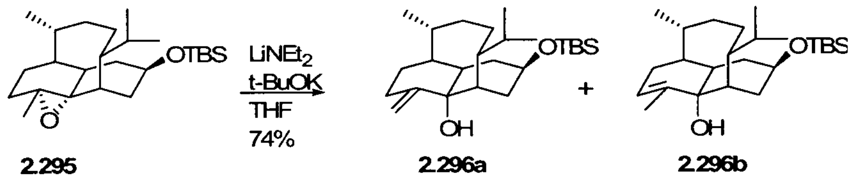
(±)-(1*S*,3*S*,5*S*,6*R*,9*R*,10*S*)-*tert*-Butyl-(6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yloxy)-dimethyl-silane (2.294). To a solution of alcohol **2.293** (13.0 mg, 0.047 mmol) in tetrahydrofuran (0.16 mL) was added imidazole

(32.0 mg, 0.470 mmol) and TBSCl (35.4 mg, 0.235 mmol) sequentially. The reaction was stirred at room temperature until complete disappearance of the starting material (18 hours). The reaction was quenched with water. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5% ethyl acetate in hexanes-dry pack) to provide **2.294** (17.1 mg, 93%) as a colorless oil. IR (neat, cm^{-1}) 2928 (s), 2858 (m), 1472 (w), 1256 (w), 1096 (m), 1075 (m); ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.55-3.49 (m, 1H), 3.26-3.21 (m, 1H), 2.27-2.22 (m, 1H), 2.02-1.84 (m, 6H), 1.77-1.72 (m, 1H), 1.69 (s, 3H), 1.62-1.26 (m, 9H), 1.15 (d, *J*=7.7Hz, 3H), 0.92 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=10.0 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 133.3 (C$_{\text{quat}}$), 127.7 (C$_{\text{quat}}$), 70.9 (CH), 54.7 (CH), 42.5 (CH), 41.2 (CH), 39.7 (CH), 37.5 (CH$_2$), 34.8 (CH), 33.3 (CH$_2$), 30.7 (CH$_2$), 30.6 (CH$_2$), 30.5 (CH), 29.8 (CH$_2$), 26.0 (CH$_3$x3), 21.7 (CH$_3$x2), 21.2 (CH$_3$), 20.4 (CH$_2$), 18.4 (C$_{\text{quat}}$), 18.3 (CH$_3$), -4.6 (CH$_3$), -4.7 (CH$_3$); HRMS (EI) m/z calcd for $C_{25}H_{46}OSi$ [M$^+$] 390.3318, found 390.3314.



2.294 **2.295**

(±)-(1*S*,3*S*,5*S*,6*R*,9*R*,10*S*,13*R*,14*R*)-*tert*-Butyl-(6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}] -13-oxa-cyclopa[d]tetradec-13-en-3-yloxy)-dimethyl-silane (2.295). To a 0 °C solution of alkene **2.294** (33.8 mg, 0.087 mmol) in dichloromethane (2 mL) was added NaHCO$_3$ (30.7 mg, 0.365 mmol) and *m*CPBA (40.7 mg, 0.183 mmol) sequentially. The reaction was stirred for 1 hour until disappearance of the starting material. The reaction was quenched with a saturated solution of sodium sulfite. The mixture was stirred 20 minutes and extracted with ethyl acetate (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide **2.295** (32.4 mg, 91%) as a yellow oil. IR (neat, cm^{-1}) 2954 (s), 2928 (s), 1472 (m), 1462 (m), 1250 (m), 1114 (m); ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 4.22-4.17 (m, 1H), 2.25-2.19 (m, 2H), 2.17-2.12 (m, 1H), 2.03 (dd, *J*=24.8, 12.4 Hz, 1H), 1.92-1.87 (m, 1H), 1.81-1.76 (m, 1H), 1.69-1.26 (m, 10H), 1.22 (s, 3H), 1.20-1.12 (m, 2H), 0.97 (s, 9H), 0.95 (d, *J*=7.2 Hz, 3H), 0.79 (d, *J*=7.2 Hz, 3H), 0.71 (d, *J*=7.2 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, C$_6$D$_6$) δ 68.5 (CH), 63.9 (C_{quat}), 60.1 (C_{quat}), 49.9 (CH), 45.8 (CH), 40.3 (CH), 38.1 (CH), 37.7 (CH_2), 35.2 (CH), 32.7 (CH_2x2), 31.5 (CH_2), 30.9 (CH), 28.1 (CH_2), 25.8 (CH_3x3), 23.2 (CH_3), 21.9 (CH_3), 21.4 (CH_3), 21.4 (CH_2), 20.9 (CH_3), 18.4 (C_{quat}), -4.7 (CH_3), -4.8 (CH_3); HRMS (EI) m/z calcd for $C_{25}H_{46}O_2Si$ [M^+] 406.3267, found 406.3281.



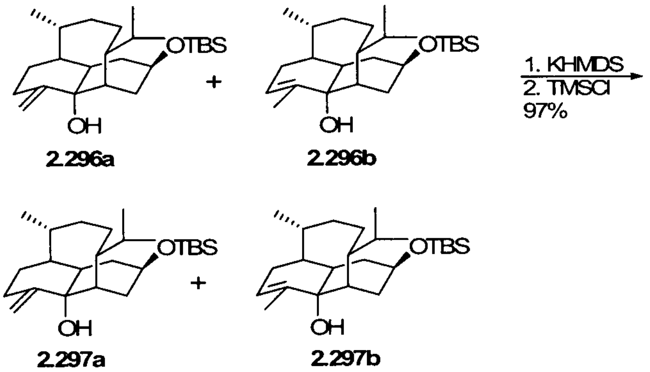
(±)- (1*R*,5*S*,6*R*,9*R*,10*S*,12*S*,14*R*)-12-(*tert*-Butyl-dimethyl-silanyloxy)-9-isopropyl-6-methyl-2-methylene-tricyclo[8.4.0.0^{5,14}]tetradecan-1-ol (2.296a) and (±)-(1*R*,5*S*,6*R*,9*R*,10*S*,12*S*,14*R*)-12-(*tert*-Butyl-dimethyl-silanyloxy)-9-isopropyl-2,6-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-2-en-1-ol (2.296b). To a solution of dry potassium *tert*-butoxide (48.0 mg, 0.452 mmol) in 0.7 mL tetrahydrofuran was added freshly distilled diethylamine (0.044 mL, 0.452 mmol). The solution was cooled to -78 °C and n-BuLi was added dropwise. The yellow solution was stirred 30 minutes before cannulating the epoxide (23.1 mg, 0.057 mmol) in tetrahydrofuran (0.5 mL). The flask was transferred to an ice bath and the solution was stirred for 30 minutes. The reaction mixture turned red. After complete disappearance of the starting material, the reaction was quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with diethyl ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to provide **2.296a** and **2.296b** (17.0 mg, 74%) as a colorless oil (ratio 1:1).

IR (neat, cm^{-1}) 3442 (br), 2960 (s), 2928 (s), 1466 (m), 1252 (m), 1071 (s);

(2.296a) ^1H NMR (500 MHz, C_6D_6) δ 4.99 (s, 1H), 4.80 (d, *J*=2.0 Hz, 1H), 2.47-2.41 (m, 1H), 2.27-2.13 (m, 3H), 2.09-1.90 (m, 4H), 1.70-1.65 (m, 2H), 1.63-1.23 (m, 10H), 1.08 (s, 9H), 0.89 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=7.3 Hz, 3H), 0.84 (d, *J*=7.1Hz, 3H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 154.1 (C_{quat}), 110.0 (CH_2), 76.8 (C_{quat}), 67.1 (CH), 45.8 (CH), 44.1 (CH), 43.1 (CH), 40.9 (CH), 36.3 (CH_2), 35.7 (CH), 35.7 (CH_2), 34.3 (CH), 32.6 (CH_2), 31.7 (CH_2), 31.2 (CH_2), 26.4 (CH_3x3), 26.2 (CH_3), 25.9 (CH_2), 20.9 (CH_3), 20.6 (CH_3), 18.5 (C_{quat}), -4.1 (CH_3), -4.2 (CH_3);

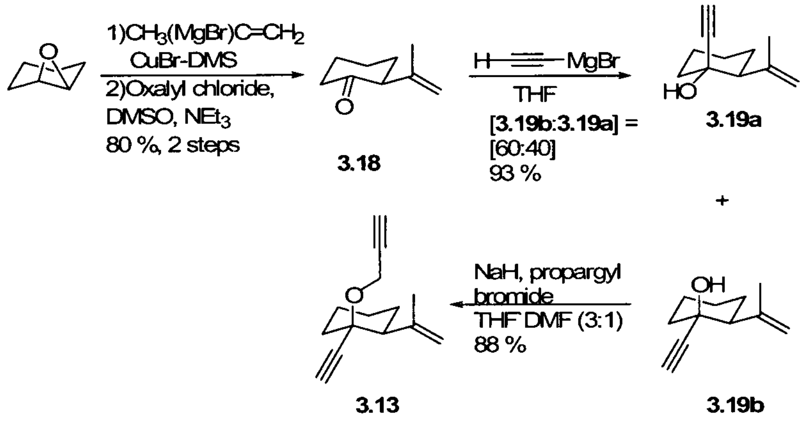
(2.296b) ^1H NMR (500 MHz, C_6D_6) δ 5.24 (d, *J*=6.0Hz, 1H), 4.92-4.85 (m, 1H), 2.21-2.12 (m, 2H), 2.05-1.84 (m, 5H), 1.70 (dd, *J*=17.4, 7.6 Hz, 1H), 1.64-1.59 (m, 1H), 1.60 (s, 3H),

1.63-1.23 (m, 8H), 1.03 (s, 9H), 0.92 (d, J=7.6 Hz, 3H), 0.80 (d, J=6.6 Hz, 3H), 0.78 (d, J=6.6 Hz, 3H), 0.18 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.0 (C_{quat}), 125.0 (CH), 75.6 (C_{quat}), 66.5 (CH), 46.2 (CH), 43.1 (CH), 42.5 (CH), 35.7 (CH), 35.6 (CH_2), 35.3 (CH), 34.8 (CH_2), 33.9 (CH), 31.9 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 25.6 (CH_3x3), 25.0 (CH_3), 21.0 (CH_3), 18.8 (CH_3), 17.8 (C_{quat}), 16.8 (CH_3), -4.1 (CH_3), -4.5 (CH_3);
HRMS (EI) m/z calcd for $C_{21}H_{37}O_2Si$ [$(M-C_4H_9)^+$] 349.2557, found 349.2576.



(±)-(1*R*,5*S*,6*R*,9*R*,10*S*,12*S*,14*R*)- 12-(*tert*-Butyl-dimethyl-silanyloxy)-9-isopropyl-6-methyl-2-methylene-1-trimethylsilanyloxy-tricyclo[8.4.0.0^{5,14}]tetradecane (2.297a) and (1*R*,5*S*,6*R*,9*R*,10*S*,12*S*,14*R*)- 12-(*tert*-Butyl-dimethyl-silanyloxy)-9-isopropyl-2,6-dimethyl-1-trimethylsilanyloxy-tricyclo[8.4.0.0^{5,14}]tetradec-2-ene (2.297b). To a 0 °C solution of KHMDS (53.3 mg, 0.267 mmol) in tetrahydrofuran (0.2 mL) was cannulated the allylic alcohol **2.296** (14.7 mg, 0.036 mmol). The resulting yellow solution was stirred for 30 minutes before adding freshly distilled TMSCl (0.027 mL, 0.217 mmol). The clear solution was stirred 40 minutes. After complete disappearance of the starting material, the reaction was quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with diethyl ether (3X) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was quickly purified by flash chromatography (5% ethyl acetate in hexanes) to provide **2.297** (16.7 mg, 97%) as a colorless oil.

Procedures-Chapter 3



(±)-2-Isopropenyl-cyclohexanone (3.18)

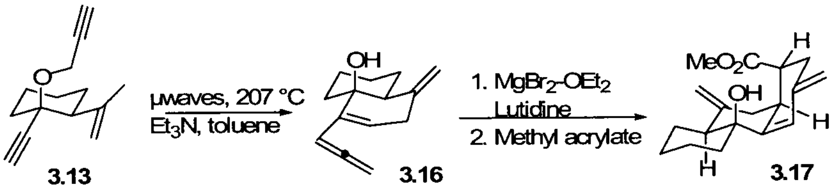
Compound was synthesized by the method reported by Roxanne Clément.[125]

(±)-[1*S*, 2*S*]-1-Ethynyl-2-isopropenyl-cyclohexanol (3.19b)

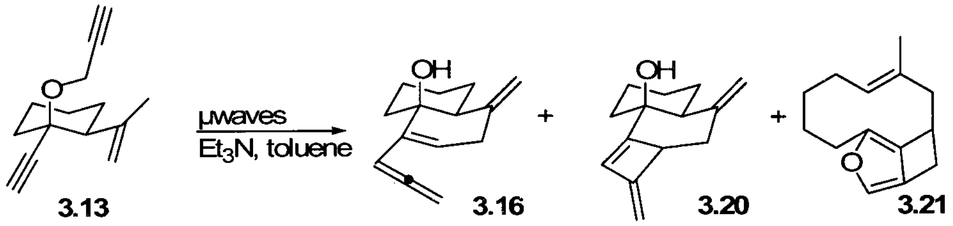
Compound was synthesized by the method reported by Roxanne Clément.[125]

(±)-[1*S*, 2*S*]-1-Ethynyl-2-isopropenyl-1-prop-2-ynyloxy-cyclohexane (3.13)

Compound was synthesized by the method reported by Roxanne Clément.[125]



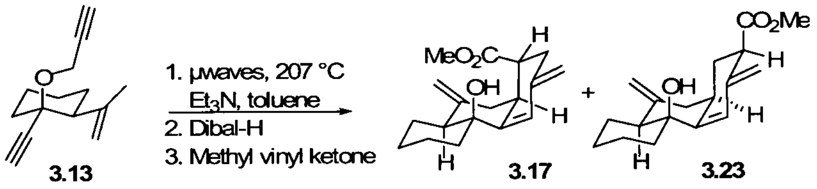
(±)-[1*S*, 4b*S*, 8a*S*,10a*S*]-4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene-1-carboxylic acid methyl ester (3.17). To a solution of **3.13** (39.9 mg, 0.197 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.28 mL, 1.97 mmol). The solution was degassed with argon (30 minutes) and subsequently heated with microwaves at 207 °C for 60 minutes. The solution was concentrated and the resulting residue was re-dissolved in DCM (2 mL). In a separate flask, a solution of $MgBr_2{\cdot}OEt_2$ (0.102 g, 0.394 mmol) in DCM (4 mL) was stirred for 20 minutes. Then, lutidine (0.09 mL, 0.788 mmol) was added to the solution. After 30 minutes of stirring, the crude material (**3.16**) was cannulated into the flask. The solution was stirred 2 hours at room temperature and methyl acrylate (0.177 mL, 1.97 mmol) was added. The solution was stirred overnight and quenched with NH_4Cl (sat. aq.). The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (15% ethyl acetate in hexanes) afforded **3.17** (23.5 mg, 42%) as a yellow oil. The NMR data corresponded to the previously reported characterization.[125]



To a solution of **3.13** (51.5 mg, 0.255 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.355 mL, 2.55 mmol). The solution was degassed with argon (30 minutes) and subsequently heated with microwaves at 200 °C for 35 minutes. The solution was concentrated and once it was cooled to room temperature, it was put under the pump (very important as the compound is somewhat volatile). Purification by flash chromatography (5% ethyl acetate/ 95% hexanes) gave allene product **3.16** (yield not calculated since it is unstable on silica gel) along with the tricyclic compound **3.21** (13.9 mg, 27% yield) and tricyclic compound **3.20** (2.2 mg, 4% yield) as yellow oils.

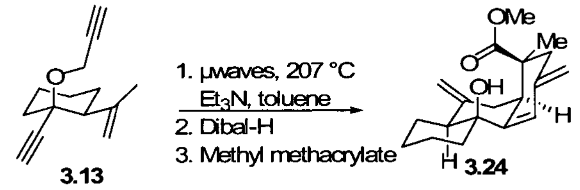
(±)-2,4-Dimethylene-2a,3,4,4a,5,6,7,8-octahydro-2H-cyclobuta[a]naphthalen-8a-ol (3.20). IR (neat, cm^{-1}) 3462 (br), 3079 (w), 2932 (s), 2854 (m), 1718 (w), 1667 (w), 1446 (w), 1276 (w), 890 (w); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.93 (s, 1H), 5.00 (d, J=1.6 Hz, 1H), 4.75 (d, J=1.0Hz, 1H), 4.60 (d, J=1.2 Hz, 1H), 4.50 (s, 1H), 3.12 (dd, J=10.4, 6.7 Hz, 1H), 2.68 (dd, J=12.4, 6.8 Hz, 1H), 2.05-1.96 (m, 4H), 1.83-1.79 (m, 1H), 1.71-1.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.3 (C_{quat}), 150.3 (C_{quat}), 147.6 (C_{quat}), 123.3 (CH), 110.9 (CH_2), 97.2 (CH_2), 70.1 (C_{quat}), 51.3 (CH), 46.3 (CH), 41.3 (CH_2), 31.2 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 20.6 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{18}O$ $(M)^+$ 202.1358, found 202.1358.

(±)-7-Methyl-13-oxa-tricyclo[7.4.1.0^{11,14}]tetradeca-1(14),6,11-triene (3.21). IR (neat, cm^{-1}) 2928 (s), 2856 (m), 1570 (w), 1436 (m), 1222 (w), 976 (w), 727 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (s, 1H), 4.99 (t, *J*=7.5 Hz, 1H), 3.72-3.66 (m, 1H), 3.25 (ddd, *J*=13.7, 5.7, 1.2 Hz, 1H), 2.66 (ddd, *J*=13.7, 3.1, 1.1 Hz, 1H), 2.62-2.49 (m, 3H), 2.03-1.87 (m, 4H), 1.82-1.73 (m, 1H), 1.69 (s, 3H), 1.41-1.32 (m, 1H), 1.11-1.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7 (C_{quat}), 133.9 (C_{quat}), 129.6 (CH), 128.7 (CH), 124.8 (C_{quat}), 124.5 (C_{quat}), 45.0 (CH_2), 41.2 (CH), 32.1 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 26.7 (CH_2), 22.6 (CH_2), 16.3 (CH_3); HRMS (EI) m/z calcd for $C_{14}H_{17}O$ $(M-H)^+$ 201.1274, found 201.1275.

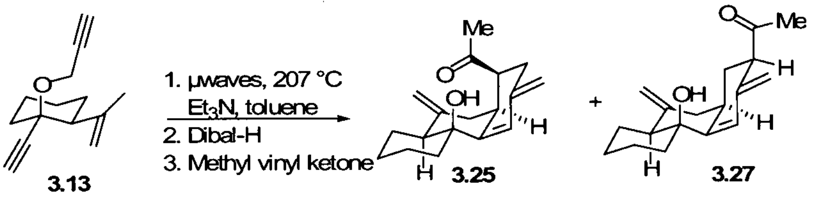


(±)-[1*S*, 4b*S*, 8a*S*,10a*S*]-4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene-1-carboxylic acid methyl ester (3.17). To a solution of **3.13** (38.8 mg, 0.192 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.27 mL, 1.92 mmol). The solution was degassed with argon (30 minutes) and subsequently heated with microwaves at 200 °C for 35 minutes. The solution was concentrated and the resulting residue was re-dissolved in DCM (2 mL) and cooled to -78 °C. Dibal-H (1.5 M in toluene, 0.166 mL, 0.250 mmol) was added dropwise and stirred 2 hours at that temperature and 30 minutes at 0 °C. Methyl acrylate was added and the solution was stirred over the weekend. The reaction was quenched with sodium tartrate (1M solution) and stirred for 1 hour. The aqueous layer was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (15% ethyl acetate in hexanes with triethylamine) afforded **3.17** and **3.23** (21.9 mg, 40%, [**3.17**:**3.23**]=[8:1]) as a yellow oils. The NMR data of **3.17** corresponded to the previously reported characterization.[125]

(±)-[2*R*, 4b*S*, 8a*S*,10a*S*]-4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene-2-carboxylic acid methyl ester (3.23). IR (neat, cm^{-1}) 3451(br), 2932 (s), 2857 (m), 1735 (s), 1439 (s), 735 (w); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.38 (d, *J*=2.1 Hz, 1H), 4.98 (s, 1H), 4.90 (s, 2H), 4.82 (s, 1H), 4.78 (s, 1H), 3.73 (s, 3H), 3.28-3.25 (m, 1H), 2.62 (dd, *J*=14.1, 5.0 Hz, 1H), 2.56-2.48 (m, 1H), 2.31-2.26 (m, 1H), 2.20-2.10 (m, 3H), 2.08-2.02 (m, 4H), 1.80-1.68 (m, 3H), 1.65-1.48 (td, *J*=13.6, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0 (C_{quat}), 148.9 (C_{quat}), 146.3 (C_{quat}), 140.8 (C_{quat}), 124.7 (CH), 112.0 (CH_2), 109.2 (CH_2), 70.7 (C_{quat}), 51.7 (CH_3), 45.2 (CH), 44.3 (CH), 37.7 (CH_2), 36.7 (CH_2), 33.5 (CH_2), 31.7 (CH), 25.2 (CH_2), 23.9 (CH_2), 21.5 (CH_2); HRMS (EI) m/z calcd for $C_{17}H_{21}O_3$ $(M-CH_3)^+$ 273.1485, found 273.1491.

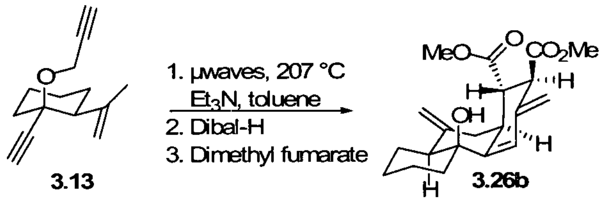


(±)-[1*S*, 4b*S*, 8a*S*,10a*R*]-4b-Hydroxy-1-methyl-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene-1-carboxylic acid methyl ester (3.24). Using the same method described above for the oxy-Cope/Claisen/ene/HDDA with Dibal-H. With methyl methacrylate as the dienophile, compound **3.24** (18.0 mg, 31% yield, > 25:1) was obtained. The NMR data corresponded to the previously reported characterization.[125]



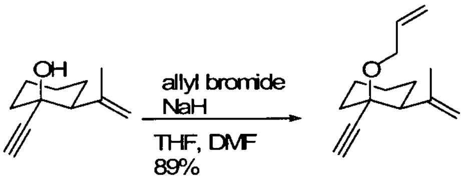
(±)-[1*S*, 4b*S*, 8a*S*,10a*S*]-1-(4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthren-1-yl)-ethanone (3.25). Using the same method described above for the oxy-Cope/Claisen/ene/HDDA with Dibal-H. With methyl vinyl ketone as the dienophile, compounds **3.25** and **3.27** (13.4 mg, 26% yield, [3.25:3.27]=[2:1]) were obtained. The NMR data for **3.25** corresponded to the previously reported characterization.[125]

(±)-[2*R*, 4b*S*, 8a*S*,10a*S*]-1-(4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthren-2-yl)-ethanone (3.27). IR (neat, cm^{-1}) 3431 (br), 2921 (s), 2854 (m), 1702 (s), 1440 (m), 1351 (m), 891 (w); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.38 (d, J=2.1 Hz, 1H), 4.98 (s, 1H), 4.91 (s, 1H), 4.83 (s, 1H), 4.65 (s, 1H), 3.25 (d, J=13.3 Hz, 1H), 2.62 (dd, J=16.7, 6.6 Hz, 1H), 2.57-2.53 (m, 1H), 2.24-2.20 (m, 2H), 2.17 (s, 3H), 2.12 (d, J=13.4 Hz, 2H), 1.98 (ddd, J= 12.7, 4.2, 4.2 Hz, 1H), 1.80-1.72 (m, 3H), 1.63-1.40 (m, 4H), 1.37-1.30 (m 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.4 (C_{quat}), 149.1 (C_{quat}), 146.2 (C_{quat}), 141.0 (C_{quat}), 124.9 (CH), 112.6 (CH_2), 109.4 (CH_2), 70.7 (C_{quat}), 54.4 (CH), 44.2 (CH), 37.5 (CH_2), 36.7 (CH_2), 33.3 (CH_2), 31.8 (CH), 27.4 (CH_3), 25.2 (CH_2), 23.9 (CH_2), 21.5 (CH_2); HRMS (EI) m/z calcd for $C_{18}H_{22}O$ $(M-H_2O)^+$ 254.1660, found 254.1682.



3.13 3.26b

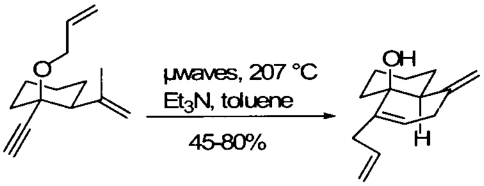
(±)-[1*S*,2*R*, 4b*S*, 8a*S*,10a*S*]-4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene-1,2-dicarboxylic acid dimethyl ester (3.26b). Using the same method described above for the oxy-Cope/Claisen/ene/HDDA with Dibal-H. With dimethyl fumarate as the dienophile, compound **3.26b** (21.5 mg, 32% yield, > 25:1) was obtained. The NMR data corresponded to the previously reported characterization.[125]



3.19b 3.28

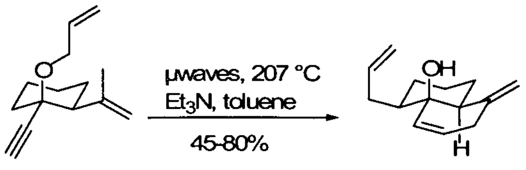
(±)-(1*S*,2*S*)-1-Allyloxy-1-ethynyl-2-isopropenyl-cyclohexane (3.28). To a 0 °C solution of alcohol **3.19b** (142.8 mg, 0.870 mmol) in THF (3 mL) and DMF (1 mL) was added allyl bromide (0.221 mL, 2.61 mmol) and sodium hydride (104 mg, 2.61 mmol). The solution was stirred overnight at room temperature before being quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with ethyl acetate (3x) then the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the residue on silica gel (elution with 5% ethyl acetate in hexanes) afforded 158.3 mg of **3.28** (89%) as a yellow oil. IR (neat, cm^{-1})

2924 (s), 2854 (m), 1462 (w), 1261 (w), 1174 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02-5.87 (m, 1H), 5.28 (dddd, *J*=17.2, 1.8, 1.8, 1.8 Hz, 1H), 5.08 (dddd, *J*=10.5, 1.8, 1.8, 1.8 Hz, 1H), 4.85-4.84 (m, 2H), 4.16-4.11 (m, 1H), 3.94-3.89 (m, 1H), 2.44 (s, 1H), 2.25-2.23 (m, 1H), 2.20 (dd, *J*=12.8, 3.5 Hz, 1H), 1.90 (dddd, *J*=13.0, 13.0, 13.0, 3.8 Hz, 1H), 1.82 (dd, *J*=0.9, 0.9 Hz, 3H), 1.75-1.67 (m, 1H), 1.47-1.43 (m, 4H), 1.27-1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.1 (C_{quat}), 135.6 (CH), 115.3 (CH_2), 113.3 (CH_2), 85.3 (C_{quat}), 74.8 (C_{quat}), 74.0 (CH), 64.3 (CH_2), 54.7 (CH), 35.7 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 22.5 (CH_3), 20.7 (CH_2); HRMS (EI) m/z calcd for $C_{11}H_{15}^+$ ($(M-C_3H_5O)^+$) 147.1168, found 147.1174.



3.28 **3.29**

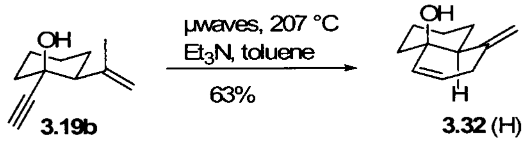
(±)-(4a*S*,8a*S*)-5-Allyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.29). To a solution of allyl ether **3.28** (13.0 mg, 0.066 mmol) in toluene (3 mL) was added triethylamine (0.088 mL, 0.636 mmol) in a microwave cell. The solution was degassed for 20 minutes and heated in the microwave for 60 minutes at 207 °C. The solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 5.8 mg of **3.29** (45%) as a yellow oil. IR (neat, cm^{-1}) 3566 (br), 2933 (s), 2855 (s), 1651 (m), 1446 (m), 1282 (m), 1083 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88-5.78 (m, 1H), 5.43 (br s, 1H), 5.05-5.00 (m, 2H), 4.91 (d, *J*=1.2 Hz, 1H), 4.72 (d, *J*=1.7 Hz, 1H), 2.91-2.67 (m, 4H), 2.19 (dd, *J*=12.2, 1.4 Hz, 1H), 2.08 (d, *J*=13.4 Hz, 1H), 1.81-1.51 (m, 5H), 1.32-1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7 (C_{quat}), 142.4 (C_{quat}), 137.5 (CH), 124.1 (CH), 115.6 (CH_2), 108.2 (CH_2), 72.4 (C_{quat}), 48.8 (CH), 36.2 (CH_2), 35.4 (CH_2), 34.3 (CH_2), 25.8 (CH_2), 23.5 (CH_2), 21.3 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{20}O$ (M^+) 204.1514, found 204.1529.



3.28

3.30

(±)-(4*R*,4a*R*,8a*S*)-4-Allyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.30). To a solution of allyl ether **3.28** (44.7 mg, 0.219 mmol) in toluene (3 mL) was added triethylamine (0.303 mL, 2.186 mmol) in a microwave cell. The solution was degassed for 20 minutes and heated in the microwave for 60 minutes at 207 °C. The solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 22.3 mg of **3.30** (50%) as a yellow oil. IR (neat, cm^{-1}) 3460 (br), 2938 (s), 2861 (s), 1695 (m), 1649 (m), 1442 (m), 1111 (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.09-6.05 (m, 1H), 5.85-5.72 (m, 2H), 5.05-4.94 (m, 3H), 4.76 (d, *J*=1.7Hz, 1H), 2.89-2.65 (m, 2H), 2.58-2.50 (m, 1H), 2.21-1.90 (m, 2H), 1.83-1.21 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.4 (C_{quat}), 138.6 (CH), 131.6 (CH), 129.3 (CH), 115.6 (CH_2), 109.1 (CH_2), 72.0 (C_{quat}), 49.4 (CH), 44.4 (CH), 36.2 (CH_2), 34.3 (CH_2), 27.1 (CH_2), 25.6 (CH_2), 23.3 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{20}O$ (M^+) 204.1514, found 204.1530.

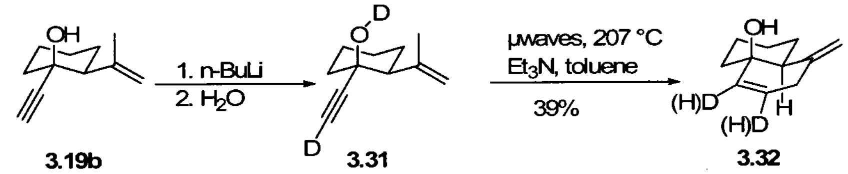


3.19b

3.32 (H)

(±)-(4a*R*,8a*S*)-8-Methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.32(H)). To a solution of alcohol **3.19b** (44.5 mg, 0.271 mmol) in toluene (3 mL) was added triethylamine (0.376 mL, 2.711 mmol) in a microwave cell. The solution was degassed for 20 minutes and heated in the microwave for 60 minutes at 207 °C. The solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 28.2 mg of **3.32** (H) (63%) as a colorless oil. IR (neat, cm^{-1}) 3466 (br), 2932 (s), 2852 (s), 1648 (m), 1295 (w), 1085 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74-5.69 (m, 1H), 5.65-5.61 (m, 1H), 4.93 (d, *J*=1.5 Hz, 1H), 4.73 (d, *J*=1.9 Hz, 1H), 2.87 (d, J_{AB}=19.5 Hz, 1H), 2.72 (dd, *J*=19.5, 4.1 Hz, 1H), 2.15 (dd, *J*=12.2, 1.4 Hz, 1H), 1.84-1.79 (m, 2H), 1.71-1.59 (m, 2H), 1.54-1.49 (m, 2H), 1.42-1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.3 (C_{quat}), 135.2 (CH), 128.0 (CH), 108.8 (CH_2), 69.9 (C_{quat}), 48.5 (CH), 37.0 (CH_2), 36.1 (CH_2), 26.0

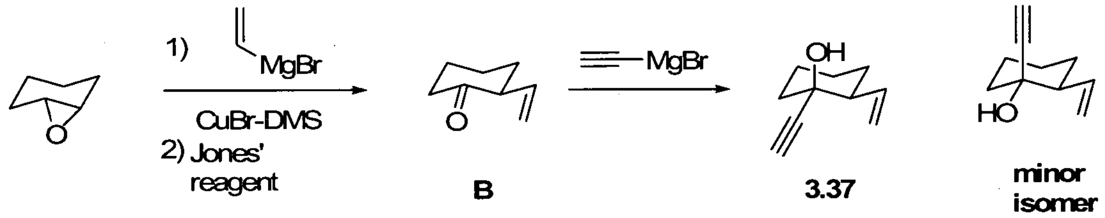
(CH$_2$), 23.1 (CH$_2$), 21.0 (CH$_2$); HRMS (EI) m/z calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1215.



(±)-(4a*R*,8a*S*)-8-Methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.32). To a -78 °C solution of alcohol **3.19b** (39.7 mg, 0.242 mmol) in THF (2.4 mL) was added *n*-BuLi (0.553 mL, 0.968 mmol). The solution was stirred 30 at the same temperature and 10 min. at 0 °C. The solution was cooled back to -78 °C and quenched with D_2O. The mixture was left to warm up to room temperature and the aqueous layer was extracted 3x with diethyl ether. The combined organic fractions were dried with over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. A crude NMR and MS indicated that the product was deuterated and could be used in the next step.

To a crude solution of deuterated alcohol **3.31** in toluene (3 mL) was added triethylamine (0.336 mL, 2.42 mmol) in a microwave cell. The solution was degassed for 20 minutes and heated in the microwave for 60 minutes at 207 °C. The solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 15% ethyl acetate in hexanes) afforded 15.8 mg of **3.32** (39%) as a colorless oil. (Not fully deuterated) IR (neat, cm^{-1}) 3466 (br), 2932 (s), 2852 (s), 1648 (m), 1295 (w), 1085 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.74-5.69 (m, 0.7H), 5.65-5.61 (m, 0.7H), 4.93 (d, *J*=1.5 Hz, 1H), 4.73 (d, *J*=1.9 Hz, 1H), 2.87 (d, J_{AB}=19.5 Hz, 1H), 2.72 (dd, *J*=19.5, 4.1 Hz, 1H), 2.15 (dd, *J*=12.2, 1.4 Hz, 1H), 1.84-1.79 (m, 2H), 1.71-1.59 (m, 2H), 1.54-1.49 (m, 2H), 1.42-1.23 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 146.3 (C_{quat}), 135.2 (CH), 128.0 (CH), 108.8 (CH$_2$), 69.9 (C_{quat}), 48.5 (CH), 37.0 (CH$_2$), 36.1 (CH$_2$), 26.0 (CH$_2$), 23.1 (CH$_2$), 21.0 (CH$_2$); HRMS (EI) m/z calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1215.

Preparation of substrate 3.37:

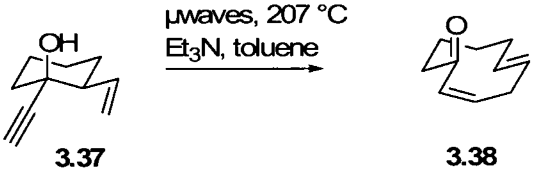


(±)-2-Vinyl-cyclohexanone (B). A dry round bottom flask was charged with CuBr·DMS (1.256 g, 6.11 mmol) and THF (150 mL). The solution was cooled to -30 °C, followed by the addition of vinylmagnesium bromide (99.3 mL, 79.4 mmol). The mixture was stirred for 20 minutes, at which point cyclohexene oxide (6.18 mL, 61.1 mmoles) was added and the solution was stirred to room temperature. The reaction was followed by TLC and quenched with NH$_4$Cl (sat. aq.) upon completion. The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated. The residue was re-dissolved in diethyl ether (100 mL) and Jones' reagent (70.5 mL, 91.7 mmol) was slowly added at 0 °C. The reaction was allowed to reach room temperature. Upon completion, as observed by TLC analysis, the reaction was quenched with NH$_4$Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Flash chromatography (15% ethyl acetate in hexanes) afforded **B** (3.210 g, 42%) as a yellow oil. Characterization data is available through the literature.[250]

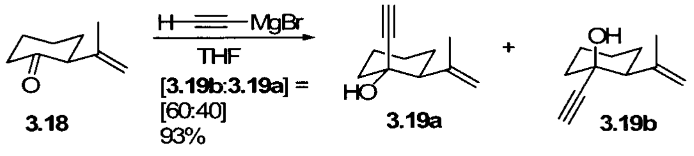
(±)-[1*S*,2*S*]-1-Ethynyl-2-vinyl-cyclohexanol (3.37). To a solution of ketone **B** (0.312 g, 2.52 mmol) in THF (10 mL) at 0 °C was added dropwise ethynylmagnesium bromide (10.1 mL, 5.04 mmol). The reaction was warmed to room temperature and followed to completion by TLC, at which point it was quenched with NH$_4$Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded both diastereoisomers (60:*40*) as yellow oils (163.5 mg, 43%). IR (neat, cm^{-1}) 3464(br), 3303 (m), 2935 (s), 2861 (m), 1730 (w), 1640(w), 1445 (m), 1082 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.16 (ddd, *J*=17.3, 10.7, 6.5 Hz, 1H), 5.22 (ddd, *J*=10.6, 1.6, 1.3 Hz, 1H), 5.15 (ddd, *J*=17.4, 1.6, 1.6 Hz, 1H), 2.43 (s, 1H), 2.34-2.29 (m, 1H), 2.15-1.99 (m, 2H), 1.84 (d, *J*=1.1 Hz, 1H), 1.73-1.49 (m, 4H), 1.42 (s, 1H), 1.34-1.19 (m, 1H); ^{13}C NMR (CDCl$_3$, 100

MHz) δ 138.7 (CH), 118.4 (CH_2), 88.2 (C_{quat}), 71.8 (CH), 68.3 (C_{quat}), 49.1 (CH), 38.8 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 21.0 (CH_2); HRMS (EI) m/z calcd for $C_{10}H_{14}O$ [M^+] 150.1045, found 150.1032.

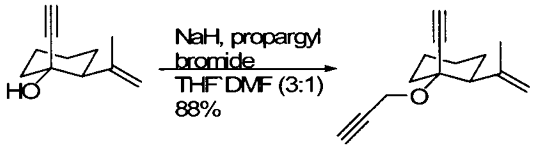
Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3441 (br), 3302 (m), 3080 (w), 2935 (s), 2859 (m), 2106 (w), 1640 (w), 1447 (m), 1051 (m), 642 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.90-5.81 (m, 1H), 5.20-5.14 (m, 2H), 2.48 (s, 1H), 2.45 (s, 1H), 2.08-2.00 (m, 2H), 1.75-1.42 (m, 6H), 1.28-1.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3 (CH), 117.4 (CH_2), 85.1 (C_{quat}), 74.2 (CH), 71.0 (C_{quat}), 53.7 (CH), 39.4 (CH_2), 30.2 (CH_2), 25.4 (CH_2), 24.0 (CH_2); HRMS (EI) m/z calcd for C_8H_{11} [$M-C_2H_3O^+$] 107.0855, found 107.0801.



(±)-(2*Z*,5*E*)-Cyclodeca-2,5-dienone (3.38). To a solution of alcohol **3.37** (11.2 mg, 0.075 mmol) in toluene (3 mL) was added triethylamine (0.103 mL, 0.745 mmol) in a microwave cell. The solution was degassed for 20 minutes and heated in the microwave for 60 minutes at 207 °C. The solvent was evaporated *in vacuo*. Purification of the residue on silica gel (elution with 15% ether in petroleum ether) afforded 8.0 mg of **3.38** (71%) as a colorless oil. IR (neat, cm^{-1}) 2941 (s), 2860 (m), 1688 (s), 1447 (m), 1262 (s), 976 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.88 (ddd, J=12.1, 2.3, 2.3 Hz, 1H), 5.65 (ddd, J=12.2, 3.9, 3.9 Hz, 1H), 5.59-5.47 (m, 2H), 2.81-2.72 (m, 2H), 2.70-2.20 (m, 2H), 2.19-0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.2 (C_{quat}), 135.9 (CH), 132.6 (CH), 132.4 (CH), 130.3 (CH), 44.9 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 33.0 (CH_2), 28.2 (CH_2); HRMS (EI) m/z calcd for $C_{10}H_{14}O$ (M^+) 150.1045, found 150.1042.



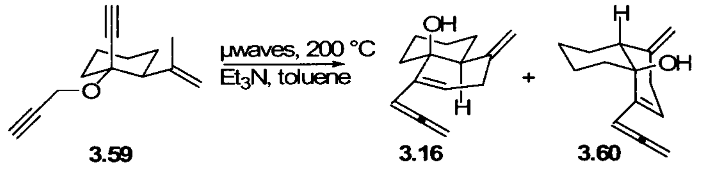
(±)-[1*R*,2*S*]-1-Ethynyl-2-isopropenyl-cyclohexanol (3.19a). To a solution of 2-isopropenyl-cyclohexanone **3.18** (7.56 g, 55 mmol) in THF (12 mL) at 0 °C was added dropwise ethynylmagnesium bromide (273.5 mL, 137 mmol). The solution was warmed to room temperature and stirred 3 hours. The mixture was cooled to 0 °C and quenched with NH_4Cl (sat. aq.). The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5% hexane in benzene to 10% ethyl acetate in hexanes) afforded alcohol **3.19** as mixture of diastereoisomer (b:a = *60:40*) as a yellow oil (8.36 g, 93%). **3.19a**: IR (neat, cm^{-1}) 3450 (br), 3305 (s), 2935 (s), 2859 (m), 1634 (w), 1448 (m), 1063, (m), 1015 (m); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.97 (s, 1H), 4.90 (s, 1H), 2.72 (s, 1H), 2,45 (s, 1H), 2.13-2.07 (m, 2H), 1.86 (s, 3H), 1.74-1.69 (m, 2H), 1.68-1.63 (m, 3H), 1.47 (dt, J = 3.9 Hz, J=12.9 Hz, 1H), 1.29-1.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.7 (C_{quat}), 115.5 (CH_2), 86.3 (C_{quat}), 74.8 (CH), 70.1 (C_{quat}), 56.3 (CH), 40.8 (CH_2), 28.7 (CH_2), 25.9 (CH_2), 24.1 (CH_2), 21.2 (CH_3); HRMS (EI) m/z calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1205. **Major (±)-[1*S*,2*S*] (3.19b):** IR (neat, cm^{-1}) 3548 (m), 3468 (br), 3307 (s), 3079 (w), 2938 (s), 2856 (s), 1639 (m), 1447 (m), 1071 (m), 972 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.95 (s, 1H), 4.79 (s, 1H), 2.37 (s, 1H), 2.23 (s, 1H), 2.18-2.08 (m, 2 H), 1.92 (s, 3H), 1.72-1.37 (m, 6H), 1.28-1.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4 (C_{quat}), 112.8 (CH_2), 89.0 (C_{quat}), 71.7 (CH), 67.4 (C_{quat}), 52.8 (CH), 40.1 (CH_2), 27.0 (CH_2), 26.1 (CH_3), 26.1 (CH_2), 20.8 (CH_2); HRMS (EI) m/z calcd for $C_{11}H_{14}$ [$(M-H_2O)^+$] 146.1095, found 146.1095.



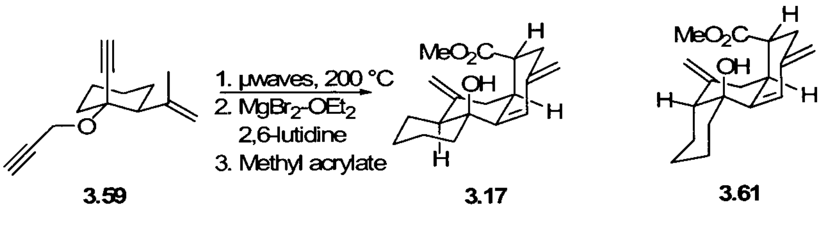
3.19a 3.59

(±)-[1*R*,2*S*]-1-Ethynyl-2-isopropenyl-1-prop-2-ynyloxy-cyclohexane (3.59). To a solution of **3.19a** (586.8 mg, 3.58 mmol) and freshly distilled propargyl bromide (1.98 mL, 17.88 mmol) in THF/DMF (8: 2.7 mL) was added sodium hydride in oil (712 mg, 17.88 mmol) slowly at 0 °C. When exothermic reaction was complete, the reaction was warmed to room temperature and left stirring 3 hours. The reaction was quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography (2% ethyl acetate in hexanes to 5% ethyl acetate in hexanes) afforded **3.59** (0.636 g, 88%) as a yellow oil. IR (neat, cm^{-1}) 3301 (s), 2936 (s), 2861 (m), 1641 (m), 1447 (m), 1081 (s); ^1H

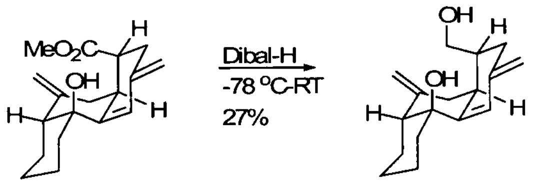
NMR ($CDCl_3$, 500 MHz) δ 4.87 (d, *J*=1.2 Hz, 2H), 4.30 (d, *J*=2.4 Hz, 2H), 2.59 (s, 1H), 2.35 (t, *J*=2.4 Hz, 1H), 2.24-2.16 (m, 2H), 1.86 (t, *J* = 1.2 Hz, 3H), 1.74-1.51 (m, 5H), 1.50-1.45 (dt, *J* = 3.5 Hz, *J* = 11.5 Hz, 1H), 1.27-1.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 146.5 (C_{quat}), 112.46 (CH_2), 81.6 (C_{quat}), 81.2 (C_{quat}), 79.3 (C_{quat}), 78.0 (CH), 73.1 (CH), 53.6 (CH), 52.2 (CH_2), 38.6 (CH_2), 29.8 (CH_2), 25.6 (CH_2), 24.0 (CH_3), 23.5 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{17}O$ [$(M-H)^+$] 201.1279, found 201.1266.



(±)-[4a*S*,8a*R*]-8-Methylene-5-propa-1,2-dienyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.60). To a solution of **3.59** (103.9 mg, 0.514 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.713 mL, 5.14 mmol). The solution was degassed with argon for 30 minutes and subsequently heated with microwaves at 200 °C for 1 hour. The solution was concentrated and flash chromatography of the residue (5% ethyl acetate in benzene) afforded **3.60** (6.1 mg, 6%) as a yellow oil. (Note that **3.16** was detected by proton NMR and compared to the characterization done previously[125]). IR (neat, cm^{-1}) 3417 (br), 2934 (s), 2860 (m), 1943 (w), 1681 (m), 1447 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (t, *J*=3.7 Hz, 1H), 5.77 (t, *J*= 6.9 Hz, 1H), 4.92-4.87 (m, 4H), 2.95 (d, *J*=20.5 Hz, 1H), 2.76 (dd, *J*=20.8, 4.2 Hz, 1H), 2.31-2.23 (m, 2H), 1,84 (s, 1H), 1.67-1.57 (m, 3H), 1.53 (s, 1H), 1.52-1.41 (m, 1H), 1.36 (dt, *J*=2.7 Hz, *J*=13.1Hz, 1H), 1.29-1.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 209.4 (C_{quat}), 145.0 (C_{quat}), 134.5 (C_{quat}), 127.1 (CH), 110.8 (CH_2), 90.0 (CH), 76.7 (CH_2), 72.8 (C_{quat}), 52.7 (CH), 34.9 (CH_2), 32.1 (CH_2), 28.1 (CH_2), 24.6 (CH_2), 22.8 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{18}O$ $(M)^+$ 202.1358, found 202.1382.

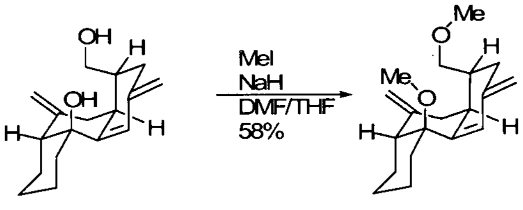


(±)-[1*S*, 4b*S*, 8a*R*,10a*S*]-4b-Hydroxy-3,9-dimethylene-1,2,3,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene-1-carboxylic acid methyl ester (3.61). To a solution of **3.59** (212.8 mg, 1.05 mmol) in acetonitrile (15 mL) in a microwave cell was added Et_3N (1.46 mL, 10.5 mmol). The solution was degassed with argon (30 minutes) and subsequently heated with microwaves at 200 °C for 90 minutes. The solution was concentrated and the resulting residue was re-dissolved in DCM (10 mL). In a separate flask, a suspension of $MgBr_2{\cdot}OEt_2$ (0.543 g, 2.1 mmol) in DCM (20 mL) was stirred for 20 minutes. Then, lutidine (0.489 mL, 4.2 mmol) was added to the solution. After 30 minutes of stirring, the crude material was cannulated into the flask. The solution was stirred 2 hours at room temperature and methyl acrylate (0.945 mL, 10.5 mmol) was added. The solution was stirred overnight and quenched with NH_4Cl (sat. aq.). The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (15% ethyl acetate in hexanes with triethylamine) afforded **3.61** (24.4 mg, 8%) and **3.17** (50.0 mg, 17%) as a yellow oils. **3.61**: IR (neat, cm^{-1}) 3462 (br), 2934 (s), 2857 (m), 1737 (s), 1442 (w); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.38 (s, 1H), 4.93-4.85 (m, 5H), 3.71 (s, 3H), 2.84-2.80 (m, 1H), 2.71-2.66 (m, 1H), 2.47 (d, *J*= 7.1 Hz, 2H), 2.17 (t, *J*=13.5 Hz, 1H), 2.11-2.07 (m, 2H), 1.99-1.90 (m, 2H), 1.88-1.82 (m, 2H), 1,80-1.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 174.6 (C_{quat}), 148.2 (C_{quat}), 145.6 (C_{quat}), 141.6 (C_{quat}), 120.6 (CH), 112.7 (CH_2), 111.5 (CH_2), 75.3 (C_{quat}), 52.0(CH_3), 49.9 (CH), 43.6 (CH), 38.9 (CH_2), 36.3 (CH), 33.4 (CH_2), 29.0 (CH_2), 24.5 (CH_2), 22.3 (CH_2), 21.1 (CH_2); HRMS (EI) m/z calcd for $C_{18}H_{24}O_3$ $(M)^+$ 288.1725, found 288.1726.



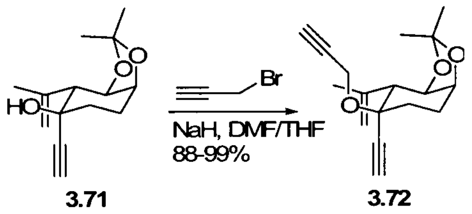
3.61 3.62

(±)-[4a*S*, 8a*S*, 8*S*, 10a*R*]-8-Hydroxymethyl-6,10-dimethylene-1,3,4,6,7,8,8a,9,10,10a-decahydro-2H-phenanthren-4a-ol (3.62). To a solution of **3.61** (23.2 mg, 0.080 mmol) in THF (1.6 mL) at -78 °C was added Dibal-H (1.5 M solution in toluene, 0.268 mL, 0.402 mmol) dropwise. The solution was warmed up to room temperature slowly. After 3 hours, no more starting material was visible. The mixture was quenched with 1 M sodium tartrate solution and stirred overnight. The mixture was extracted 3 X with ethyl acetate and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (40% ethyl acetate in hexanes with triethylamine) afforded **3.62** as a colorless oil (5.6 mg, 27%). IR (neat, cm^{-1}) 3406 (br), 2930 (s), 2860 (m), 1717 (m), 1637 (m), 1443 (m); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.38(s, 1H), 4.96 (d, *J*=1.7Hz, 1H), 4.88-4.87(m, 2H), 4.81(s,1H), 3.69-3.57(m, 2H), 2.52(td, *J*=13.7Hz, *J*=4.1Hz, 1H), 2.32 (dd, *J*=12.5Hz, *J*=4.0 Hz, 1H), 2.25 (dd, *J*=14.4 Hz, *J*=3.8 Hz, 1H), 2.20-1.20 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0 (C_{quat}), 142.2 (C_{quat}), 124.6 (C_{quat}), 120.3 (CH), 111.4 (CH_2), 110.4 (CH_2), 76.6 (CH_2), 74.9 (C_{quat}), 63.9 (CH_2), 29.4(CH), 39.2 (CH), 37.1 (CH_2), 35.9 (CH), 33.3 (CH_2), 30.0(CH_2), 21.8 (CH_2), 20.6 (CH_2); HRMS (EI) m/z calcd for $C_{17}H_{22}O$ $[M-(H_2O)]^+$ 242.1671, found 242.1644.

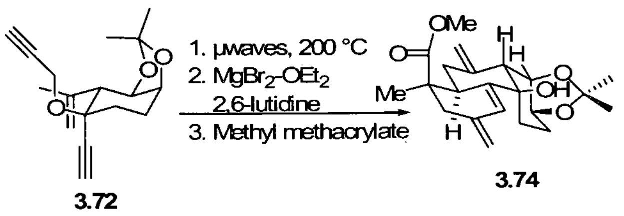


3.62 **3.63**

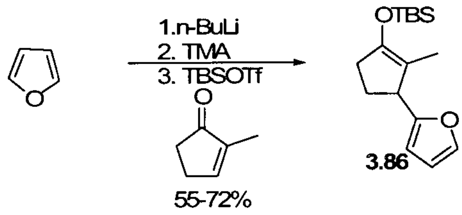
(±)-[4a*S*, 8a*S*, 8*S*, 10a*R*]-4a-Methoxy-8-methoxymethyl-6,10-dimethylene-1,2,3,4,4a,6,7,8,8a,9,10,10a-dodecahydro-phenanthrene (3.63). To a 0 °C solution of diol **3.62** (7.3 mg, 0.028 mmol) in DMF (0.75 mL)/THF (0.25 mL) was added NaH (4.5 mg, 0.112 mmol). The resulting solution was stirred 5 minutes then freshly distilled MeI was added (7 μL, 0.112 mmol). The reaction mixture was stirred for 5 hours at room temperature. At this point, 50% of product was mono-methylated and 50% was the desired product. To prevent decomposition, the solvent was removed *in vacuo* and the crude reaction mixture was purified by flash chromatography (10% ethyl acetate/ 90% hexanes) giving **3.63** (4.3 mg, 50%). The mono-methylated product (4.0 mg, 50%) was resubmitted the same reaction conditions and left overnight. The isolated yield after resubmitting the mono-methylated product was 58%. IR (neat, cm^{-1}) 2927 (s), 2857 (m), 2599 (w), 1443 (s), 1125 (w), 1071 (w); ^1H NMR (C_6D_6, 500 MHz) δ 6.30 (s, 1H), 4.97 (s,2H), 4.92 (s, 1H), 4.89 (s, 1H), 3.25 (dd, *J* = 8.5, 6.4 Hz, 1H), 3.15 (dd, *J*=8.5, 7.3 Hz, 1H), 3.10 (s, 3H), 3.02 (s, 3H), 2.53 (dd, *J*=14.7; 6.0 Hz, 1H); 2.45-2.41 (m, 2H), 2.27-2.23 (m, 2H), 2.16-2.13 (m, 2H), 1.92 (dd, *J*=10.0, 8.8 Hz, 1H), 1.79-1.75 (m, 1H), 1.68-1.66 (m, 1H), 1.59-1.53 (m,2H), 1.27 (m, 3H) ^{13}C NMR (C_6D_6, 125.8 MHz) δ 149.2 (C_{quat}), 142.5 (C_{quat}), 128.8 (C_{quat}), 125.3 (CH), 113.0 (CH_2), 110.6 (CH_2), 79.9 (C_{quat}), 72.8 (CH_2), 59.0 (CH_3), 49.2 (CH_3), 46.7 (CH), 38.0 (CH), 37.7 (CH), 36.9 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 23.0 (CH_2), 22.7 (CH_2); HRMS (EI) m/z calcd for $C_{19}H_{28}O_2$ [M^+] 288.2089, found 288.2037.



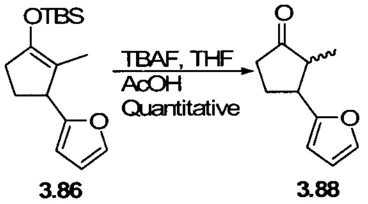
(±)-[1a*S*,4a*S*,4*R*,5*R*]-5-Ethynyl-4-isopropenyl-2,2-dimethyl-5-prop-2-ynyloxy-hexahydro-benzo[1,3]dioxole (3.72). To a solution of alcohol **3.71** (22.0 mg, 0.093 mmol) in THF (0.75 mL) and DMF (0.25 mL) was added propargyl bromide (41 μL, 0.466 mmol). After 5 min., NaH (18.6 mg, 0.466 mmol) was added slowly. The resulting dark mixture was stirred 3 hours and quenched with a saturated solution of ammonium chloride. The mixture was extracted 3x with ether and the combined organic fractions were washed with brine, dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (20% ethyl acetate/80% hexanes) gave propargyl ether **3.72** (26.0 mg, 99%). IR (neat, cm^{-1}) 3283 (s), 2986 (m), 2868 (w), 1647 (m), 1457 (s), 1376 (m), 1242 (m), 1215 (m), 1160 (m), 1055 (s); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (t, *J*=1.3 Hz, 1H), 5.03 (s, 1H), 4.28 (d, *J*=2.4 Hz, 2H), 4.24-4.20 (m, 2H), 2.65 (s, 1H), 2.49-2.40 (m, 1H), 2.37 (t, *J*=2.4 Hz, 1H), 2.22-2.15 (m, 1H), 2.07-2.00 (m, 2H), 1.93 (d, *J*=0.7 Hz, 3H), 1.89-1.80 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 142.3 (C_{quat}),114.7 (CH_2), 108.1 (C_{quat}), 80.8 (CH), 80.2 (CH), 79.2 (C_{quat}); 77.5 (CH); 77.4 (C_{quat}), 73.5 (C_{quat}), 72.3 (CH), 55.1 (CH), 52.4 (CH_2), 32.7 (CH_2), 28.3 (CH_3), 26.2 (CH_3), 24.1 (CH_3), 23.5 (CH_2); HRMS (EI) m/z calcd for $C_{16}H_{19}O_3$ $(M-CH_3)^+$ 259.1334, found 259.1340.



(±)-[4*R*,5*S*,8*R*,9*R*,13*S*,14*R*]-9-Hydroxy-4,16,16-trimethyl-2,7-dimethylene-2,3,4,5,6,7,8,9,11,12,13,14-dodecahydro-15,17-dioxa-cyclopenta[a]phenanthrene-4-carboxylic acid methyl ester (3.74). To a solution of **3.72** (19.3 mg, 0.070 mmol) in toluene (12 mL) in a microwave cell was added Et_3N (0.098 mL, 0.703 mmol). The solution was degassed with argon (30 minutes) and subsequently heated with microwaves at 200 °C for 40 minutes. The solvent was removed *in vacuo* and purification by flash chromatography yielded **3.73** (6.1 mg, 32%) that was used directly in the next step. $MgBr_2{\cdot}OEt_2$ (23 mg, 0.089 mmol) was dissolved in DCM (0.6 mL) and stirred 20 minutes before the addition of lutidine (21 μL, 0.178 mmol). After stirring for 30 minutes, allene **3.73** in DCM (0.4 mL) was cannulated. The resulting mixture was stirred 2 hours then methyl methacrylate was added (47 μL, 0.44 mmol). After stirring for 18 hours, there was still starting material. Another 25 μL (0.23 mmol) of methyl methacrylate was added. After stirring another 24 hours, the reaction was quenched with a saturated solution of ammonium chloride, extracted 3x with DCM. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography gave compound **3.74** as a yellow oil (2.4 mg, 43% based on recovered SM). IR (neat, cm^{-1}) 3506 (br), 2923 (s), 2851 (m), 1731 (s), 1450 (w), 1374 (w), 1233 (w), 1213 (w), 1113 (m), 1049 (s); ^1H NMR (C_6D_6, 500 MHz) δ 6.99 (s, 1H), 5.03 (s, 1H), 4.89 (s, 1H), 4.69 (s, 1H), 4.61 (s, 1H, exchange D_2O), 4.38 (dd, *J*=4.9, 1.8 Hz, 1H), 4.35 (s, 1H), 4.08 (m, 1H), 3.35 (s, 3H), 2.81 (d, *J*= 14.9 Hz, 1H), 2.73 (s, 1H), 2.35 (d, *J*=14.5 Hz, 1H), 2.23 (dd, *J*=12.7 Hz, 2.7Hz, 1H), 2.17 (dd, *J*=11.8 Hz, 3.6 Hz, 1H), 2.09-2.02 (m, 2H), 1.72-1.68 (m, 1H), 1.51-1.45 (m, 1H), 1.42 (s, 3H), 1.36-1.28 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (C_6D_6, 126 MHz) δ 176.6 (C_{quat}), 144.9 (C_{quat}), 141.3 (C_{quat}), 127.2 (C_{quat}), 121.8 (CH), 114.2 (CH_2), 111.6 (CH_2), 108.3 (C_{quat}), 76.8 (CH), 73.9 (C_{quat}), 71.7 (CH), 53.1 (CH_3), 51.2 (CH), 45.3 (C_{quat}), 43.7 (CH), 41.9 (CH_2), 35.5 (CH_2), 29.7 (CH_2), 28.5 (CH_3), 26.0 (CH_3), 25.5 (CH_2), 23.1 (CH_3); HRMS (EI) m/z calcd for $C_{22}H_{30}O_6$ $(M)^+$ 374.2093, found 374.2066.



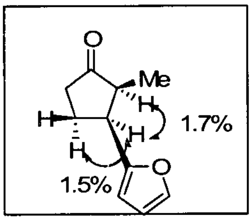
(±)-*tert*-Butyl-(3-furan-2-yl-2-methyl-cyclopent-1-enyloxy)-dimethyl-silane (3.86). To a -78 °C solution of furan (0.3 mL, 4.11 mmol) in THF (18 mL) was added *n*-BuLi (2.088 mL, 4.52 mmol) dropwise. After complete addition, the mixture was stirred at 0 °C for 2 hours (the mixture turned light yellow). The solution was cooled down to -78 °C and cannulated to another flask containing trimethylaluminum (2.0 M solution in hexanes, 2.055 mL, 4.11 mmol) in THF (18 mL). Note that the cannula was wrapped with foil containing dry ice to keep the mixture at -78 °C. After stirring for 45 min., this solution was cannulated to another flask with 2-methylcyclopentenone (0.4 mL, 4.07 mmol) and freshly distilled TBSOTf (1 mL, 4.35 mmol) in THF (18 mL). The resulting mixture was stirred 1 hour before quenching with a saturated solution of potassium carbonate. It was extracted 3x with ether and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (5% ethyl acetate/95% hexanes) gave 815.7 mg of a yellow oil (**3.86**, 72% yield). This compound was known but no characterization was available.[164] IR (neat, cm^{-1}) 2956 (s), 2930 (s), 2857 (s), 1744 (m), 1690 (s), 1331 (m), 1252 (m), 839 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (dd, J=0.8, 1.8 Hz, 1H), 6.27 (dd, J=1.9, 3.1 Hz, 1H), 5.97 (dd, J=0.5, 3.1 Hz, 1H), 3.70 (t, J=5.7 Hz, 1H), 2.46-2.41 (m, 1H), 2.32-2.18 (m, 2H), 1.95-1.88 (m, 1H), 1.48 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5 (C_{quat}), 149.0 (C_{quat}), 141.3 (CH), 113.9 (C_{quat}), 110.3 (CH), 104.7 (CH), 44.9 (CH_2), 32.9 (CH), 27.6 (CH_3), 26.1 (CH_2), 18.5 (C_{quat}), 11.0 (3 x CH_3), -3.6 (CH_3), -3.7 (CH_3); HRMS (EI) m/z calcd for $C_{16}H_{26}O_2Si$ $(M)^+$ 278.1702, found 278.1710.



(±)-3-Furan-2-yl-2-methyl-cyclopentanone (3.88). To a solution of silyl enol ether **3.86** (815.7 mg, 2.93 mmol) in THF (30 mL) was added glacial acetic acid (0.503 mL, 8.79 mmol) followed by TBAF (4.39 mL, 4.39 mmol). The solution was stirred 1 hour and was quenched with water. The aqueous layer was extracted 3x with ether and the combined organic layers were washed with a saturated solution of sodium bicarbonate then brine, dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (30% ether/ 70% pet. ether) yielded **3.88** as a mixture of *cis* and *trans* isomers (yellow oil, 482.4 mg, 100% yield). Note that solvents were carefully removed on the rotavap at 30 °C. These compounds were known but the full characterization was not available (*Bull. Soc. Chim. Belg.* **1984**, *93*, 11, 1019).

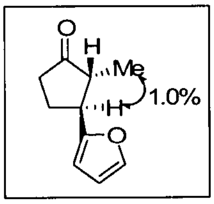
cis: IR (neat, cm^{-1}) 2971 (m), 2935 (m), 2875 (w), 1740 (s), 1149 (m), 1009 (m), 734 (m); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (dd, *J*=1.9, 0.8 Hz, 1H), 6.26 (dd, *J*=3.2, 1.9 Hz, 1H), 6.03 (ddd, *J*=3.2, 0.7, 0.7, 1H), 3.58 (ddd, *J*= 7.3, 7.3, 5.0, 1H), 2.53-2.47 (m, 2H), 2.37-2.30 (m, 1H), 2.27-2.02 (m, 2H), 0.82 (d, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.7 (C_{quat}), 155.5 (C_{quat}), 141.4 (CH), 109.7 (CH), 106.2 (CH), 47.6 (CH), 39.7 (CH), 36.0 (CH_2), 25.4 (CH_2), 10.4 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{12}O_2$ $(M)^+$ 164.0837, found 164.0837.

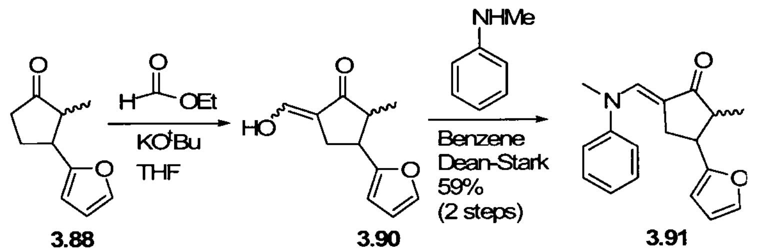
nOe interactions:



trans: IR (neat, cm^{-1}) 2965 (m), 2927 (s), 2853 (m), 1739 (s), 1449 (m); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 1H), 6.31 (dd, *J*=3.2, 1.9Hz, 1H), 6.03 (d, *J*=3.2 Hz, 1H), 2.92 (ddd, *J*= 11.4, 11.4, 6.2 Hz, 1H), 2.48 (dd, *J*= 18.3, 8.3 Hz, 1H), 2.34-2.18 (m, 3H), 2.02-1.96 (m, 1H), 1.12 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.8 (C_{quat}) 156.0 (C_{quat}), 141.4 (CH), 110.0 (CH), 104.8 (CH), 49.3 (CH), 43.6 (CH), 37.1 (CH_2), 26.4 (CH_2), 12.6 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{12}O_2$ $(M)^+$ 164.0837, found 164.0842.

nOe interaction:

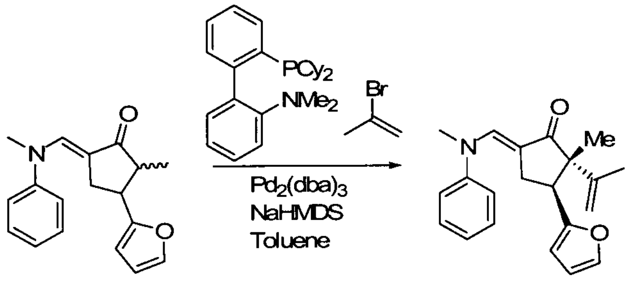




(±)-3-Furan-2-yl-2-methyl-5-[(methyl-phenyl-amino)-methylene]-cyclopentanone (3.91). To a 0 °C solution of KO^{t}Bu (88 mg, 0.785 mmol) in THF (0.6 mL) (1.0M solution of KO^{t}Bu in THF can also be used) was added freshly distilled ethyl formate (238 μL, 2.96 mmol) dropwise (evolution of gas occurred). This solution was cooled to -10 °C and ketone **3.88** (117.2 mg, 0.713 mmol) in ethyl formate (475 μL, 5.91 mmol) was cannulated. The dark orange mixture was stirred 30 minutes at -10 °C then at room temperature overnight. The dark red reaction paste was quenched with water and transferred to a separatory funnel. After diluting the mixture with ether, HCl (1 M) was added until a pH of 1 was obtained. The aqueous layer was extracted 3x with ether. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. This crude material was dissolved in 2 mL of benzene and *N*-methylaniline (100 μL, 0.927 mmol) was added. The reaction was setup with a Dean-Stark apparatus. The reaction was heated to reflux to azeotopically remove water for 5 hours. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. Purification by flash chromatography (30% ethyl acetate/70% hexanes) yielded **3.91** as a mixture of *cis* and *trans* (118.6 mg, 59% for 2 steps).

cis: IR (neat, cm^{-1}) 2961 (w), 2840 (w), 1690 (m), 1607 (m), 1573 (s), 1494 (m), 1195 (m), 935 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 7.34-7.30 (m, 3H), 7.13-7.10 (m, 3H), 6.28 (dd, *J*=3.2, 1.9 Hz, 1H), 6.04 (d, *J*=3.1 Hz, 1H), 3.47 (s, 3H), 2.85-2.79 (m, 2H), 2.66-2.59 (m, 1H), 2.45-2.39 (m,1H) 1.15 (d, *J*=6.9Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.6 (C_{quat}), 156.9 (C_{quat}), 145.9 (C_{quat}), 141.5 (CH), 141.2 (CH), 129.0 (2xCH), 124.7 (CH), 121.2 (2x CH), 109.9 (CH), 107.3 (C_{quat}), 104.6 (CH), 47.6 (CH), 42.3 (CH), 40.2 (CH_3), 32.1 (CH_2), 13.7 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{19}NO_2$ $(M)^+$ 281.1416, found 281.1422. Yellow solid MP = 68.5-70.5 °C.

trans: (Characterized as the minor product in the mixture) IR (neat, cm^{-1}) 2964 (w), 2925 (w), 2871 (w), 1690 (m), 1607 (m), 1574 (s), 1495 (m), 1198 (m), 935 (w); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (s, 1H), 7.35-7.30 (m, 2H), 7.28-7.26 (m, 1H), 7.15-7.10 (m, 3H), 6.24 (dd, *J*=3.1, 1.8 Hz, 1H), 5.97 (d, *J*=3.1 Hz, 1H), 3.50 (s, 3H), 2.86-2.78 (m, 2H), 2.70 (dd, *J*=14.9, 6.5 Hz, 1H), 2.64-2.59 (m, 1H), 0.84 (d, *J*=7.3Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.9 (C_{quat}), 156.3 (C_{quat}), 147.4 (C_{quat}), 141.7 (CH), 141.1 (CH), 129.0 (2xCH), 124.7 (CH), 121.4 (2xCH), 109.7 (CH), 106.7 (C_{quat}), 105.5 (CH), 46.6 (CH), 42.2 (CH), 37.9 (CH_3), 30.7 (CH_2), 11.7 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{19}NO_2$ $(M)^+$ 281.1416, found 281.1424. Yellow oil.

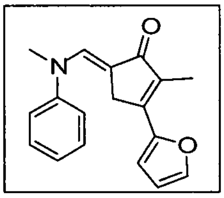


3.91 **3.92**

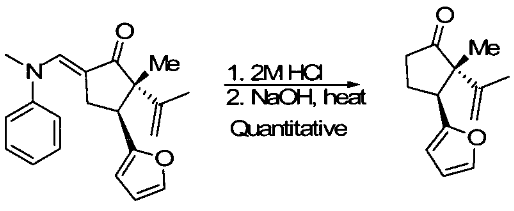
(±)-(2*S*,3*S*)-3-Furan-2-yl-2-isopropenyl-2-methyl-5-[(methyl-phenyl-amino)-methylene]-cyclopentanone (3.92). NaHMDS (245.4 mg, 1.303 mmol) and $Pd_2(dba)_3$ (8.1 mg, 0.008 mmol) were added to an oven-dried Schlenk tube in the glovebox. The ligand 2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)bipenyl) (3.7 mg, 0.009 mmol) was added to a flask containing ketone **3.91** (73.3 mg, 0.261 mmol). The ligand and ketone were dissolved in toluene (0.5 mL) under an atmosphere of argon and cannulated to the Schlenk tube. After rinsing with 0.5 mL of toluene, 2-bromopropene was added to the reaction flask (0.115 mL, 1.303 mmol). Another 0.3 mL of toluene was used to rinse the Schlenk tube. After carefully closing the Schlenk tube, the dark purple solution was stirred for 3 days at 90 °C. The reaction was cooled to room temperature and loaded directly on a column for purification by flash chromatography (40% ethyl acetate/60% hexanes). Compound **3.92** (29.4 mg, 35% yield), recovered starting material (15.0 mg) and enone **3.93** were isolated (27%). IR (neat, cm^{-1}) 2967 (w), 2920 (w), 1688 (m), 1605 (m), 1572 (s), 1494 (m), 1209 (m), 926 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (t, *J*=1.6Hz, 1H), 7.37-7.33 (m, 2H), 7.29 (dd, *J*=1.8, 0.8 Hz, 1H), 7.17-7.13 (m, 3H), 6.26 (dd, *J*=3.2, 1.8 Hz, 1H), 5.99 (d, *J*=3.2 Hz, 1H), 5.04 (t, *J*=1.3 Hz, 1H), 4.79 (s, 1H), 3.53 (s, 3H), 3.51-3.48 (m, 1H), 2.82-2.75 (m, 2H), 1.79 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.4 (C_{quat}), 154.9 (C_{quat}), 145.8 (C_{quat}), 145.6 (C_{quat}), 142.7 (CH), 141.1 (CH), 129.0 (2xCH), 125.0 (CH), 121.7

(2xCH), 113.5 (CH_2), 109.8 (CH), 106.3 (C_{quat}), 106.1 (CH), 58.1 (C_{quat}), 41.4 (CH_3), 40.7 (CH), 29.0 (CH_2), 20.1 (CH_3),16.8 (CH_3); HRMS (EI) m/z calcd for $C_{21}H_{23}NO_2$ $(M)^+$ 321.1729, found 321.1726. Yellow oil.

3-Furan-2-yl-2-methyl-5-[(methyl-phenyl-amino)-methylene]-cyclopent-2-enone (3.93)

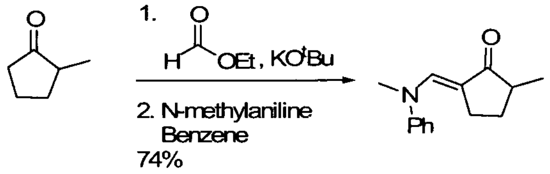


IR (neat, cm^{-1})2922 (w), 2855 (w), 1665 (s), 1572 (s), 1493 (m), 1254 (s), 1153 (w); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 1H), 7.53 (d, *J*=1.5 Hz, 1H), 7.36-7.33 (m, 2H), 7.20-7.12 (m, 3H), 6.65 (d, *J*=3.4, 1H), 6.51 (dd, *J*=3.2, 1.8 Hz, 1H), 3.56 (s, 5H), 2.10 (dd, *J*=4.0, 1.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.1 (C_{quat}), 151.8 (C_{quat}), 146.7 (C_{quat}), 143.5 (CH), 143.3 (C_{quat}), 139.5 (CH), 135.6 (C_{quat}), 129.2 (2xCH), 124.4 (CH), 120.7 (2xCH), 111.9 (CH), 111.5 (CH), 106.7 (C_{quat}), 39.1 (CH_3), 31.9 (CH_2), 10.1 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{17}NO_2$ $(M)^+$ 279.1259, found 279.1259. Yellow oil.



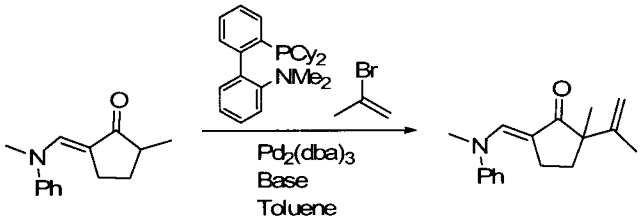
3.92 3.94

(±)-(2*S*,3*S*)-3-Furan-2-yl-2-isopropenyl-2-methyl-cyclopentanone (3.94). Ketone **3.92** (4.1 mg, 0.013 mmol) was dissolved in THF (0.1 mL) and 2M HCl (38 μL, 0.077 mmol) was added. The resulting solution was stirred 1h15 until there was no more starting material. The reaction mixture was quenched with water, extracted 3x with ether, dried with $MgSO_4$, filtered and concentrated. The yellow oil was suspended in 1 mL of 1 M NaOH and heated to 90 °C for 2 hours. The reaction was quenched with HCl (1 M), extracted with ether (3x), dried with $MgSO_4$, filtered and concentrated. Purification by flash chromatography (30% ether / 70% pet. ether) gave **3.92** as a clear oil (3.3 mg, 100% yield). IR (neat, cm^{-1}) 2958 (w), 2918 (s), 2849 (m), 1740 (s); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (dd, *J*=1.9, 0.8 Hz, 1H), 6.29 (dd, J=3.2, 1.9 Hz, 1H), 6.05 (ddd, J=3.2, 0.8, 0.8 Hz, 1H), 5.03 (t, J=1.3 Hz, 1H), 4.79 (s, 1H), 3.63 (dd, J=9.7, 6.1 Hz, 1H), 2.60-2.55 (m, 1H), 2.38-2.26 (m, 2H), 2.20-2.18 (m, 1H), 1.77 (dd, J=1.4, 0.7 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.6 (C_{quat}), 154.4 (C_{quat}), 144.5 (C_{quat}), 141.4 (CH), 113.8 (CH_2), 109.8 (CH), 106.4 (CH), 58.7 (C_{quat}), 43.3 (CH), 37.0 (CH_2), 23.2 (CH_2), 20.0 (CH_3),16.3 (CH_3); HRMS (EI) m/z calcd for $C_{13}H_{16}O_2$ $(M)^+$ 204.1150, found 204.1156.



3.96

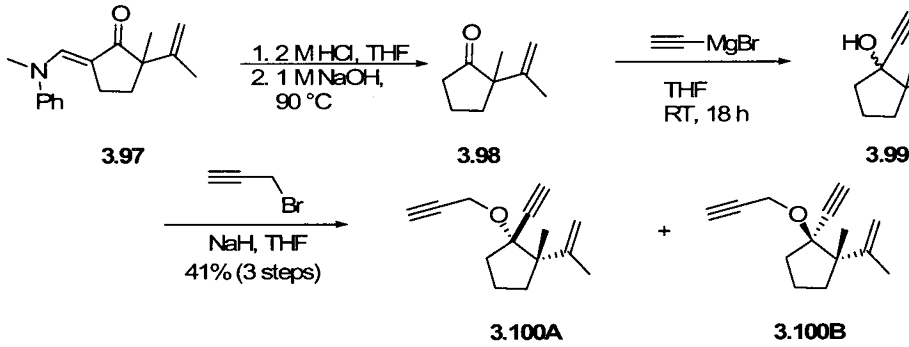
(±)-2-Methyl-5-[(methyl-phenyl-amino)-methylene]-cyclopentanone (3.96). Compound was synthesized by the method reported by Buchwald.[169]



3.96

3.97

(±)-2-Isopropenyl-2-methyl-5-[(methyl-phenyl-amino)-methylene]-cyclopentanone (3.97). NaHMDS (367 mg, 2 mmol) and $Pd_2(dba)_3$ (18.4 mg, 0.02 mmol) were added to an oven-dried Schlenk tube in the glovebox. The ligand 2-(dicyclohexylphosphino)-2'-(N,N-dimethylamino)bipenyl) (19.6 mg, 0.05 mmol) was added to a flask containing ketone **3.96** (210.9 mg, 0.98 mmol). The ligand and ketone were dissolved in toluene (4 mL) under an atmosphere of argon and cannulated to the Schlenk tube. After rinsing with 1 mL of toluene, 2-bromopropene was added to the reaction flask (0.178 mL, 2.0 mmol). Another 1 mL of toluene was used to rinse the Schlenk tube. After carefully closing the Schlenk tube, the dark purple solution was stirred for 1 day at 23 °C. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (40% ethyl acetate/60% hexanes with triethylamine) gave compound **3.97** (203.2 mg, 81% yield). IR (neat, cm^{-1}) 2959 (m), 2925 (m), 1687 (m), 1605 (m), 1574 (s), 1495 (m), 1363 (w), 1212 (s), 922 (m), 756 (m); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.59 (s, 1H), 7.35-7.31 (m, 2H), 7.14-7.10 (m, 3H), 4.85 (t, *J*=1.4 Hz, 1H), 4.83 (s, 1H), 3.48 (s, 3H), 2.42 (dd, *J*=6.4, 6.5 Hz, 2H), 2.11 (ddd, *J*=12.8, 6.4, 6.3 Hz, 1H), 1.73 (d, *J*= 0.6 Hz, 1H), 1.58-1.52 (ddd, *J*=15.4, 6.4, 6.4 Hz, 1H), 1.19 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 208.0 (C$_{quat}$), 147.2 (C$_{quat}$), 146.6 (C$_{quat}$), 142.7 (CH), 129.5 (CHx2), 125.0 (CH), 121.7 (CHx2), 111.6 (CH$_2$), 108.7 (C$_{quat}$), 54.4 (C$_{quat}$), 40.6 (CH$_3$), 34.4 (CH$_2$), 25.3 (CH$_2$), 22.5 (CH$_3$), 20.3 (CH$_3$); HRMS (EI) m/z calcd for $C_{17}H_{21}NO$ (M)$^+$ 255.1623, found 255.1629.



(±)-1-Ethynyl-2-isopropenyl-2-methyl-1-prop-2-ynyloxy-cyclopentane (3.100).

(Step 1) Ketone **3.97** (812.4 mg, 3.18 mmol) was dissolved in THF (16 mL) and 2M HCl (9.6 mL, 4.8 mmol) was added. The resulting solution was stirred 18 hours until there was no more starting material. The reaction mixture was quenched with water, extracted 3x with ether and concentrated. The yellow oil was suspended in 31.8 mL of 1 M NaOH and heated to 90 °C for 11 hours (8 hours then RT overnight then 3 more hours). The reaction was quenched with HCl (1 M), extracted with ether (3x), dried with MgSO$_4$, filtered and concentrated. The resulting ketone **3.98** was used crude in the next step. Purification of an aliquot allowed for the characterization of **3.98.** IR (neat, cm^{-1}) 2959 (s), 2926 (s), 2872 (m), 1735 (s), 1631(w), 1457 (w); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 4.88 (t, *J*=1.3 Hz, 1H), 4.75 (s, 1H), 2.30-2.18 (m, 3H), 1.88-1.82 (m, 2H), 1.71 (dd, *J*=1.4, 07 Hz, 3H), 1.68-1.62 (m, 1H), 1.13 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 206.1 (C$_{quat}$), 145.1 (C$_{quat}$), 112.1 (CH$_2$), 54.5 (C$_{quat}$), 37.4 (CH$_2$), 35.9 (CH$_2$), 21.3 (CH$_3$), 19.3 (CH$_3$), 18.7 (CH$_2$); HRMS (EI) m/z calcd for $C_9H_{14}O$ (M)$^+$ 138.1045, found 138.1017.

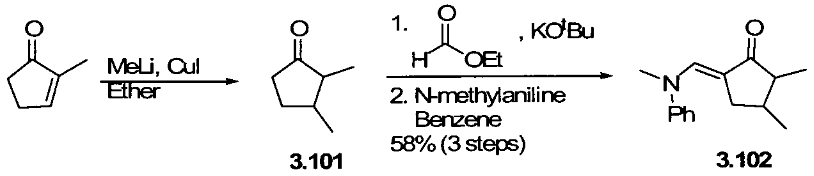
(Step 2) To a 0 °C solution of crude ketone **3.98** in THF (1.4 mL) was added ethynyl magnesium bromide (15.9 mL, 3.182 mmol) dropwise. The solution was stirred at room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. The mixture of alcohols was used crude in the next step.

(Step 3) To a 0 °C solution of crude alcohols (crude, 3.003 mmol) in THF (2.1 mL) and DMF (0.7 mL) was added sodium hydride (132 mg, 3.3 mmol). After stirring for 5 min., freshly distilled propargyl bromide (0.366 mL, 3.3 mmol) was added. The reaction was warmed to room temperature and stirred 2 hours. The reaction was quenched with a saturated solution of ammonium chloride, extracted 3X with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (50% benzene/ 50% hexanes) gave mixture of products **3.100A** and **3.100B** (262.4 mg, 41% yield). Separation of both isomers was done using flash chromatography (25% benzene/75% hexanes) giving **3.100A** ([1R, 2S] 53.4 mg) and **3.100B** ([1S, 2S] 28.9 mg).

3.100A: (2nd spot) IR (neat, cm^{-1}) 3299 (s), 3088 (w), 2969 (s), 2926 (m), 2875 (m), 1637 (m), 1455 (m), 1373 (m), 1115 (m), 1086 (m), 1060 (s), 1044 (s), 893 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.78 (t, J=1.5 Hz, 1H), 4.78 (s, 1H), 4.28 (dd, J_{AB} = 15.9, J_{AX} = 2.5 Hz, 1H), 4.23 (dd, J_{AB}=15.9, J_{BX} = 2.4 Hz, 1H), 2.61 (s, 1H), 2.38 (ddd, J=14.4, 8.8, 4.8 Hz, 1H), 2.34 (dd, J= 2.4, 2.4 Hz, 1H), 2.26-2.19 (m, 1H), 1.99 (ddd, J= 14.7, 10.5, 6.9 Hz, 1H), 1.92 (s, 3H), 1.79-1.67 (m, 2H), 1.65-1.58 (m, 1H), 1.15 (d, J=0.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.3 (C_{quat}), 111.3 (CH_2), 85.7 (C_{quat}), 82.8 (C_{quat}), 81.3 (C_{quat}), 77.2 (CH), 73.2 (CH), 55.5 (C_{quat}), 52.9 (CH_2), 36.4 (CH_2), 35.2 (CH_2), 24.6 (CH_3), 21.4 (CH_3), 19.4 (CH_3); HRMS (EI) m/z calcd for $C_{13}H_{15}O$ $(M-CH_3)^+$ 187.1117, found 187.1153. Yellow oil.

3.100B: (1st spot) IR (neat, cm^{-1}) 3301 (s), 2967 (s), 2925 (s), 1637 (m), 1455 (m), 1438 (m), 1377 (m), 1096 (s), 1056 (s), 892 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.77 (s, 2H), 4.39 (dd, J_{AB} = 15.3, J_{AX} = 2.5 Hz, 1H), 4.18 (dd, J_{AB}=15.3, J_{BX} = 2.4 Hz, 1H), 2.51 (s, 1H), 2.36 (t, J=2.4 Hz, 1H), 2.27-2.20 (m, 1H), 2.13-2.04 (m, 2H), 1.85 (s, 3H), 1.81-1.58 (m, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4 (C_{quat}), 110.4 (CH_2), 84.4 (C_{quat}), 83.8 (C_{quat}), 81.1 (C_{quat}), 75.9 (CH), 73.3 (CH), 54.5 (C_{quat}), 53.6 (CH_2), 36.4 (CH_2), 34.8 (CH_2), 20.9

(CH3), 20.3 (CH3), 18.0 (CH3); HRMS (EI) m/z calcd for $C_{13}H_{15}O$ $(M-CH_3)^+$ 187.1117, found 187.1118. Yellow oil.

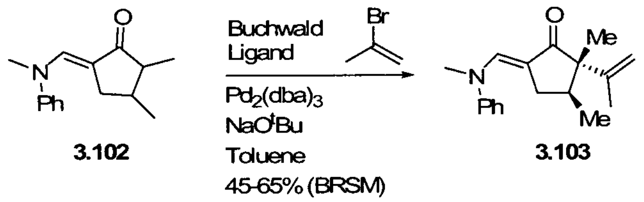


(±)-2,3-Dimethyl-5-[(methyl-phenyl-amino)-methylene]-cyclopentanone (3.102). (Step 1) To a -20 °C suspension of CuI (1.96g, 10.27 mmol) in ether (12.8 mL) was added MeLi (13 mL) dropwise. The solution became bright yellow then clear. After stirring for 15 min., 2-methylcyclopentenone (649.6 mg, 6.76 mmol) in ether (12.8 mL) was cannulated. The reaction mixture immediately turned bright orange. After 30 min. at -20 °C, the reaction was quenched with a saturated solution of ammonium chloride. The mixture was stirred 30 min. before being extracted 3X with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated very carefully.

(Step 2) To a 0 °C solution of KO^{t}Bu in THF (1.0 M, 7.44 mL, 7.44 mmol) was added ethyl formate (2.2 mL, 27.4 mmol) dropwise (evolution of gas occurred). This solution was cooled to -10 °C and crude ketone **3.101** in ethyl formate (4.5 mL, 56 mmol) was cannulated. The dark orange mixture was stirred 30 minutes at -10 °C then at room temperature overnight. The dark red reaction paste was quenched with water and transferred to a separatory funnel. After diluting the mixture with ether, HCl (1 M) was added until a pH of 1 was obtained. The aqueous layer was extracted 3x with ether. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. This crude material was dissolved in 21.6 mL of benzene and *N*-methylaniline (952 μL, 8.79 mmol) was added. The reaction was setup with a Dean-Stark apparatus. The reaction was heated to reflux to azeotopically remove water for 4 hours. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The excess *N*-methylaniline was removed by distillation. The resulting solid was recrystallized by dissolving the solid in hot hexanes giving 586.5 mg of pure *trans* product. The mother liquors were evaporated and purified by flash chromatography (30% ethyl acetate/70% hexanes with triethylamine) to give 320.4 mg of a *cis* and *trans* mixture. The total yield was 58%.

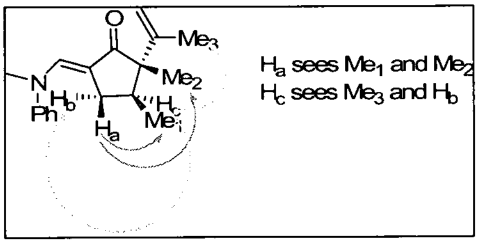
Trans: IR (neat, cm^{-1}) 2955 (w), 2926 (w), 2869 (w), 1739 (w), 1692 (m), 1607 (m), 1576 (s), 1495 (m), 1190 (m), 936 (m); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.54 (s, 1H), 7.34-7.30 (m, 2H), 7.18-7.09 (m, 3H), 3.46 (s, 3H), 2.64 (dd, J=14.7, 7.3 Hz, 1H), 2.06 (ddd, J=14.7, 9.7, 1.6 Hz, 1H), 1.80-1.74 (m, 1H), 1.64-1.56 (m, 1H), 1.10-1.07 (m, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 207.8 (C$_{quat}$), 146.1 (C$_{quat}$), 140.4 (CH), 129.0 (2xCH), 124.2 (CH), 120.8 (2xCH), 109.1 (C$_{quat}$), 50.3 (CH$_3$), 39.7 (CH), 38.0 (CH), 35.1 (CH$_2$), 19.1 (CH$_3$), 13.1 (CH$_3$); HRMS (EI) m/z calcd for $C_{15}H_{19}NO$ (M)$^+$ 229.1467, found 229.1461. Brown solid. MP = 71.9-75.5 °C.

Cis (characterized as a mixture with the *trans* product): IR (neat, cm^{-1}) 2957 (m), 2926 (m), 2869 (w), 1725 (w), 1694 (m), 1608 (m), 1578 (s), 1495 (m), 1191 (m), 936 (w); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.58 (t, J=1.6 Hz, 1H), 7.34-7.30 (m, 2H), 7.12-7.09 (m, 3H), 3.46 (s, 3H), 2.68 (dd, J=14.7, 6.8 Hz, 1H), 2.35-2.29 (m, 2H), 2.20 (ddd, J=14.9, 4.2, 1.4 Hz, 1H), 0.95 (d, J=6.9 Hz, 3H), 0.80 (d, J=6.7 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 208.3 (C$_{quat}$), 146.1 (C$_{quat}$), 141.4 (CH), 129.6 (2xCH), 126.4 (CH), 122.3 (2xCH), 108.1 (C$_{quat}$), 46.8 (CH$_3$), 38.1 (CH), 32.8 (CH$_2$), 32.0 (CH), 16.5 (CH$_3$), 10.4 (CH$_3$); HRMS (EI) m/z calcd for $C_{15}H_{19}NO$ (M)$^+$ 229.1467, found 229.1477. Yellow solid. MP = 56.6-65.6 °C. (Stereochemistry of both isomers could be determined using NOESY experiments.)

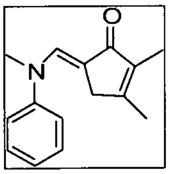


(±)-(2*S*,3*S*)-2-Isopropenyl-2,3-dimethyl-5-[(methyl-phenyl-amino)-methylene]-cyclopentanone (3.103). NaO^{t}Bu (239 mg, 2.49 mmol) and Pd$_2$(dba)$_3$ (22.8 mg, 0.025 mmol) were added to an oven-dried Schlenk tube in the glovebox. The ligand 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)bipenyl) (24.5 mg, 0.062 mmol) was added to a flask containing ketone **3.102** (285.2 mg, 1.24 mmol). The ligand and ketone were dissolved in toluene (4 mL) under an atmosphere of argon and cannulated to the Schlenk tube. After rinsing with 1 mL of toluene, 2-bromopropene was added to the reaction flask (0.221 mL, 2.49 mmol). Another 2.6 mL of toluene was used to rinse the Schlenk tube. After carefully closing the Schlenk tube, the dark purple solution was stirred for 1 day at 50 °C. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (40% ethyl acetate/60% hexanes with triethylamine) gave compound **3.103** (102.4 mg, 45% BRSM) and (±)-2,3-Dimethyl-5-[(methyl-phenyl-amino)-methylene]-cyclopent-2-enone (**3.103A**) (38 mg, 9%). IR (neat, cm^{-1}) 3085 (w), 2963 (s), 2928 (m), 1686 (s), 1607 (s), 1576 (s), 1495 (s), 1361 (m), 1259 (m), 1223 (s), 925 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (t, *J*=1.5 Hz, 1H), 7.35-7.31 (m, 2H), 7.14-7.11 (m, 3H), 4.99 (t, *J*=1.3 Hz, 1H), 4.85 (s, 1H), 3.48 (s, 3H), 2.60 (dd, *J*=14.7, 7.4 Hz, 1H), 2.28-2.19 (m, 1H), 2.12-2.06 (m, 1H), 1.69 (s, 3H), 1.00 (s, 3H), 0.86 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.5 (C_{quat}), 146.4 (C_{quat}), 146.2 (C_{quat}), 142.0 (CH), 129.1 (2xCH), 124.6 (CH), 121.3 (2xCH), 113.1 (CH_2), 108.2 (C_{quat}), 57.4 (C_{quat}), 40.2 (CH_3), 35.9 (CH), 33.5 (CH_2), 20.2 (CH_3), 15.2 (CH_3), 14.1 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{23}NO$ $(M)^+$ 269.1780, found 269.1773.

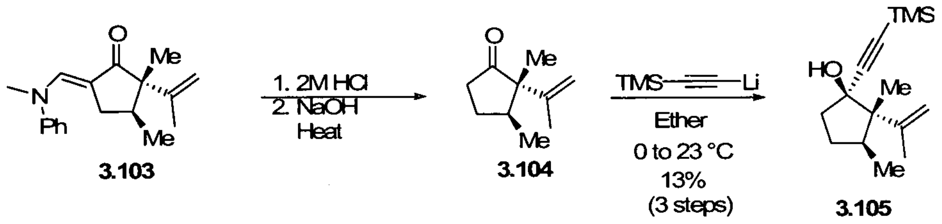
Stereochemistry was determined by NOESY (all connectivity was as predicted). The major interactions are shown below:



(±)-2,3-Dimethyl-5-[(methyl-phenyl-amino)-methylene]-cyclopent-2-enone (3.103A)

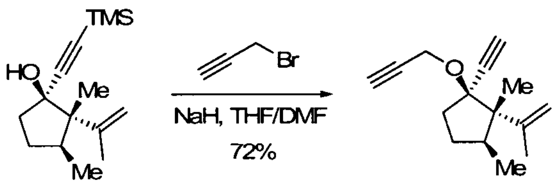


IR (neat, cm^{-1}) 2916 (w), 1677 (m), 1607 (m), 1577 (s), 1494 (m), 1324 (w), 1254 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (s, 1H), 7.34-7.29 (m, 2H), 7.15-7.07 (m, 3H), 3.46 (s, 3H), 3.13 (s, 2H), 1.99 (s, 3H), 1.75 (d, *J*=0.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.4 (C_{quat}), 157.1 (C_{quat}), 146.9 (C_{quat}), 138.2 (CH), 137.2 (C_{quat}), 129.3 (CHx2), 124.2 (CH), 120.6 (CHx2), 107.7 (C_{quat}), 39.0 (CH_3), 37.1 (CH_2), 16.1 (CH_3), 8.5 (CH_3); HRMS (EI) m/z calcd for $C_{15}H_{17}NO$ $(M)^+$ 227.1310, found 227.1285.



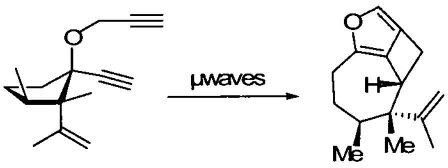
(±)-(1*S*,2*S*,3*S*)-2-Isopropenyl-2,3-dimethyl-1-trimethylsilanylethynyl-cyclopentanol (3.105). (Step 1) Ketone **3.103** (148.2 mg, 0.550 mmol) was dissolved in THF (2.75 mL) and 2M HCl (1.66 mL, 3.3 mmol) was added. The resulting solution was stirred 18 hours until there was no more starting material. The reaction mixture was quenched with water, extracted 3x with ether and concentrated. The yellow oil was suspended in 5.5 mL of 1 M NaOH and heated to 90 °C for 18 hours. The reaction was quenched with HCl (1 M), extracted with ether (3x), dried with $MgSO_4$, filtered and concentrated very carefully. The resulting ketone **3.104** was used crude in the next step.

(Step 2) To a -78 °C solution of trimethylsilylacetylene (0.233 mL, 1.65 mmol) in ether (4 mL) was added *n*-BuLi (0.611 mL, 1.54 mmol) dropwise. The resulting solution was stirred 20 min. at the same temperature. Then, ketone **3.104** (crude mixture, 0.550 mmol) in ether (2 mL) was cannulated into the reaction mixture. The solution was slowly warmed to room temperature and was stirred 18 hours. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (15% ether/ 85% petroleum ether) gave compound **3.105** (17.7 mg, 13%). IR (neat, cm^{-1}) 3481 (br), 2959 (s), 2874 (w), 2164 (w), 1930 (w), 1639 (w), 1458 (w), 1381 (w), 1251 (s), 840 (s); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.90 (t, J=1.5 Hz, 1H), 4.73 (s, 1H), 2.52-2.47 (m, 1H), 2.16-2.11 (m, 1H), 1.95 (s, 1H), 1.90-1.83 (m, 1H), 1.86 (t, J=0.6 Hz, 3H), 1.69-1.61 (m, 1H), 1.29-1.18 (m, 1H), 0.93 (s, 3H), 0.89 (d, J=6.8 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.0 (C_{quat}), 112.1 (CH_2), 109.9 (C_{quat}), 89.0 (C_{quat}), 79.8 (C_{quat}), 55.5 (C_{quat}), 38.0 (CH_2), 36.9 (CH), 27.6 (CH_2), 22.0 (CH_3), 15.9 (CH_3), 13.7 (CH_3), -0.1 (CH_3 x 3); HRMS (EI) m/z calcd for $C_{14}H_{23}OSi$ $(M-CH_3)^+$ 235.1513, found 235.1523.



3.105 **3.106**

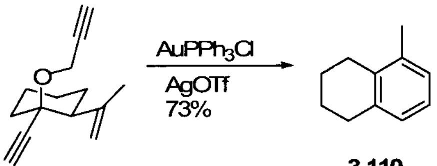
(±)-(1*S*,2*S*,3*S*)-1-Ethynyl-2-isopropenyl-2,3-dimethyl-1-prop-2-ynyloxy-cyclopentane (3.106). To a 0 °C solution of alcohol **3.105** (21.6 mg, 0.086 mmol) in THF (0.2 mL) and DMF (0.065 mL) was added propargyl bromide (0.050 mL, 0.431 mmol) then NaH (17.2 mg, 0.431 mmol). The resulting solution was stirred at room temperature for 5 hours. The reaction mixture was quenched with NH_4Cl, extracted 3x with ether, washed with brine, filtered and concentrated. Purification by flash chromatography (10% ether / 90% petroleum ether) gave propargyl ether **3.106** (13.4 mg, 72%) as a yellow oil. IR (neat, cm^{-1}) 3310 (m), 2955 (s), 2924 (s), 2854 (s), 1637 (w), 1460 (m), 1377 (m), 1105 (m), 1066 (m); ^{1}H NMR (C_6D_6, 300 MHz) δ 5.04 (t, *J*=1.4 Hz, 1H), 4.87 (s, 1H), 4.37 (dd, J_{AB}=15.2, 2.5 Hz, 1H), 4.06 (dd, J_{AB}=15.2, J_{BX}=2.4 Hz, 1H), 2.58-2.50 (m, 1H), 2.11-2.00 (m, 3H), 2.01 (t, *J*=1.2 Hz, 3H), 1.91-1.66 (m, 2H), 1.23-1.07 (m, 1H), 1.03 (s, 3H), 0.85 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 148.2 (C_{quat}), 111.7 (CH_2), 86.4 (C_{quat}), 84.0 (C_{quat}), 81.2 (C_{quat}), 76.3 (CH), 73.7 (CH), 56.1 (C_{quat}), 53.8 (CH_2), 36.6 (CH), 35.4 (CH_2), 27.9 (CH_2), 21.6 (CH_3), 15.3 (CH_3), 13.1 (CH_3); HRMS (EI) m/z calcd for $C_{14}H_{17}O$ $(M-CH_3)^+$ 201.1274, found 201.1295.



3.106 **3.109**

(±)-(6*S*,7*R*,7a*R*)-7-Isopropenyl-6,7-dimethyl-1,4,5,6,7,7a-hexahydro-3-oxa-cyclobuta[cd]azulene(3.109). To a solution of propargyl ether **3.106** (6.6 mg, 0.031 mmol) in toluene (14 mL) in a microwave cell was added Et_3N (0.043 mL, 0.31 mmol). The solution was degassed with argon for 30 minutes and subsequently heated with microwaves at 200 °C for 35 minutes. The solution was concentrated and flash chromatography of the residue (10% ethyl acetate in hexanes) afforded **3.109** (2.2 mg, 33%) as a yellow oil. IR (neat, cm^{-1}) 2955 (s), 2927 (s), 2859 (m), 1715 (w), 1665 (w), 1447 (w), 1379 (w); ^{1}H NMR

($CDCl_3$, 500 MHz) δ 6.76 (s, 1H), 5.02 (s, 1H), 4.97 (s, 1H), 3.73 (d, J=8.6 Hz, 1H), 3.07 (dd, J=7.7, 5.6 Hz, 1H), 2.92-2.85 (m, 1H), 2.62 (ddd, J=12.6, 12.6, 2.4 Hz, 1H), 2.22-2.17 (m, 2H), 1.95 (d, J=12.2 Hz, 1H), 1.70-1.65 (m, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 0.94 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.1 (C_{quat}), 149.8 (C_{quat}), 138.5 (CH), 133.6 (C_{quat}), 131.0 (C_{quat}), 104.6 (CH_2), 50.1 (CH), 40.8 (CH_2), 37.7 (CH), 35.8 (CH_2), 32.0 (CH_2), 29.9 (C_{quat}), 22.3 (CH_3), 20.3 (CH_3), 12.1 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{11}O$ $[(M-C_3H_9)^+]$ 171.0804, found 171.0728.



3.13

3.110

5-Methyl-1,2,3,4-tetrahydro-naphthalene (3.110)

To a solution of propargyl ether **3.13** (39.2 mg, 0.194 mmol) in DCM (0.3 mL) was added $AuPPh_3Cl$ (9.6 mg, 0.019 mmol). To the clear solution was added AgOTf (4.6 mg, 0.019 mmol). The resulting dark purple solution was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and purification was done by flash chromatography (10% ethyl acetate in hexanes). Tetrahydronaphthalene **3.110** was obtained in 73% yield (20.6 mg) as a yellow oil. Characterization was available through the literature.[251]

Procedures-Chapter 4

General information:

Silver trifluoromethanesulfonate (AgOTf) was obtained from Aldrich Chemical Company. Silver tetrafluoroborate ($AgBF_4$), silver hexafluoroantimonate ($AgSbF_6$), gold (III) chloride, gold (I) chloride were purchased from Strem Chemicals. Triphenylphosphinegold(I)chloride ($Au(PPh_3)Cl$) was obtained from Aldrich and Strem.

General procedures

A) Sonogashira coupling[252]

$PdCl_2(PPh_3)_2$ (5 mol%) and CuI (5 mol%) were weighed in the glovebox. A solution of the alkyne (1.0 eq.) in acetonitrile (0.07 M) was cannulated. Following the addition of the appropriate coupling partner (1.1 eq.), the resulting solution was degassed with argon for 10 min. Then, freshly distilled diisopropylethylamine (5.0 eq) was added and the mixture was stirred at room temperature. Upon completion by TLC, the reaction mixture was concentrated and loaded directly onto a silica gel column for purification.

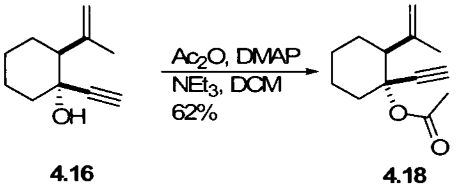
B) Gold(I)-catalyzed benzannulation (Type I: AgOTf and Au(PPh_3)Cl)

AgOTf (2.5 mol%) and Au(PPh_3)Cl (2.5 mol%) were weighed in the glovebox and transferred to a flame-dried flask with a magnetic stirrer. Then, a solution of the substrate in dichloromethane (0.1 M based on the alcohol) was cannulated. The resulting dark solution was stirred for 15-18 hours until completion by TLC. The reaction mixture was filtered through celite and evaporated *in vacuo*. Purification by flash chromatography yielded the desired benzannulated products.

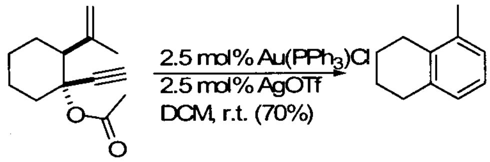
C) Gold(I)-catalyzed benzannulation (Type II: TfOH and Au(PPh_3)Cl)

Au(PPh_3)Cl (1.0 mol%) was weighed in the glovebox and dissolved by a portion of the DCE. Then, a solution of TfOH (1.0 mol%) (0.01 M in ether) was added. Subsequently, the substrate in dichloroethane (0.1 M based on the alcohol) was cannulated. The resulting dark solution was refluxed for 15-18 hours until completion by TLC. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$. The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography yielded the desired benzannulated products.

Detailed experimental



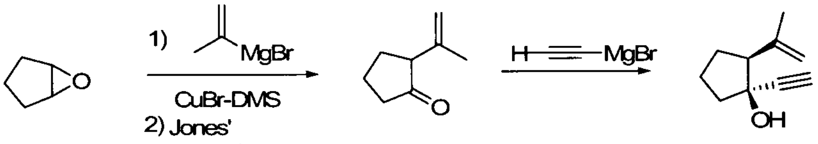
Acetic acid 1-ethynyl-2-isopropenyl-cyclohexyl ester (4.18). To a solution of (±)-[1S,2R]-1-Ethynyl-2-isopropenyl-cyclohexanol **4.16** (or **3.19b** see Procedures-Chapter 3) (0.600 g , 3.66 mmol) in DCM (45.0 mL) was added 4-DMAP (223 mg , 1.83 mmol) followed by triethylamine (0.713 mL, 5.12 mmol) and acetic anhydride (0.420 mL, 4.39 mmol). The following solution was stirred at room temperature for 3 hours. The solution was quenched with water. The mixture was extracted with DCM (3X). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (5% ethyl acetate in hexanes) afforded ester **4.18** (465 mg, 62%) as a colorless oil. IR (neat, cm^{-1}) 2934 (s), 2115 (m), 1733 (m), 1240 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.88 (s, 1H), 4.87 (s, 1H), 2.73-2.69 (m, 1H), 2.65 (s, 1H), 2.43-2.38 (dd, *J*=12.5Hz, *J*=9.5Hz, 1H), 1.98 (s, 3H), 1.85 (s, 3H), 1.78-1.61 (m, 6H), 1.27-1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 169.1(C_{quat}), 145.3(C_{quat}), 113.6(CH_2), 81.1(C_{quat}), 79.8(C_{quat}), 77.3(CH), 52.7(CH), 37.4(CH_2), 29.3(CH_2), 25.6(CH_2), 23.5(CH_2), 23.5(CH_3), 22.1(CH_3); HRMS (EI) m/z calcd for $C_{11}H_{14}$ ($M-C_2H_4O_2^+$) 146.1096, found 146.1107.



4.18 **4.17**

5-Methyl-1,2,3,4-tetrahydro-naphthalene (4.17)

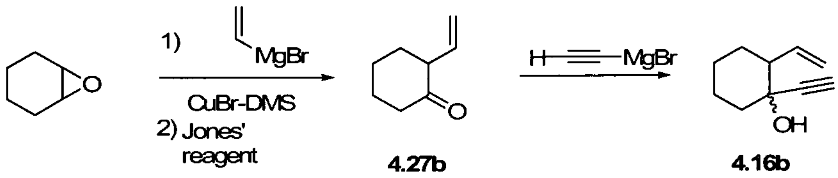
To a solution of acetate **4.18** (43.0 mg, 0.208 mmol) in DCM (1.5 mL) was added $AuPPh_3Cl$ (1.3 mg, 0.005 mmol). To the clear solution was added AgOTf (2.6 mg, 0.005 mmol). The resulting dark purple solution was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo* and purification was done by flash chromatography (10% ethyl acetate in hexanes). Tetrahydronaphthalene **4.17** was obtained in 70% yield (21.3 mg) as a yellow oil. Characterization was available through the literature.[251]



4.27a **4.16a**

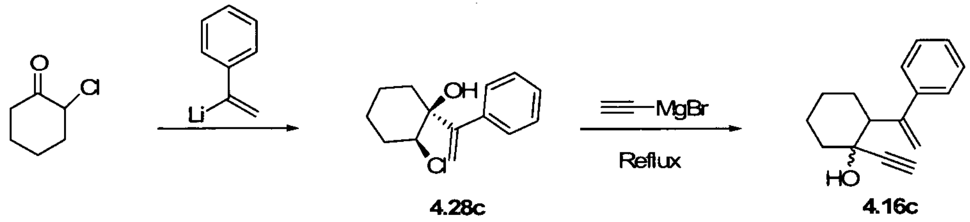
(±)-(1*S*,2*S*)-1-Ethylnyl-2isopropenyl-1-prop-2-ynyloxy-cyclopentane (4.16a)

Compound was synthesized by the method reported by Roxanne Clément.[125]



(±)-1-Ethynyl-2-vinyl-cyclohexanol (4.16b).

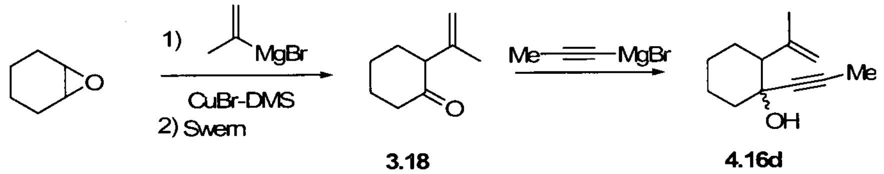
Compound was synthesized as described previously for compound **3.37**. (See Procedures-Chapter 3)



(±)-(1*S*, 2*S*)-2-Chloro-1-(1-phenyl-vinyl)-cyclohexanol (4.28c). To a -90 °C solution of α-bromostyrene (1.27 mL, 8.76 mmol) in ether (36 mL) was added *t*-BuLi (8.24 mL, 14.02 mmol) dropwise. The solution was protected from light and stirred for 75 min. at -90 to -100 °C. After cannulation of 2-chlorocyclohexanone (0.500 mL, 4.38 mmol) in ether (8 mL), the mixture was slowly warmed to -60 °C and followed to completion by TLC. The reaction mixture was cooled to -90 °C and quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes) afforded **4.28c** as a yellow oil (867.6 mg, 84%). IR (neat, cm^{-1}) 3555 (br), 3080 (w), 3054 (w), 2940 (s), 2862 (m), 1191 (m), 1445 (m), 1285 (m), 1069 (s), 986 (s), 701 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (s, 5H), 5.57 (d, *J*=1.5 Hz, 1H), 5.02 (d, *J*=1.5 Hz, 1H), 4.02 (dd, *J*=11.2, 5.8 Hz, 1H), 2.27 (d, *J*=2.3 Hz, 1H), 2.03-1.93 (m, 3H), 1.72-1.64 (m, 3H), 1.47-1.42 (m, 1H), 1.26-1.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2 (C_{quat}), 140.8 (C_{quat}), 129.2 (CHx2), 128.0 (CHx2), 127.4 (CH), 115.2 (CH_2), 76.5 (C_{quat}), 66.2 (CH), 36.9 (CH_2), 32.5 (CH_2), 25.9 (CH_2), 20.6 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{17}ClO$ [M^+] 236.0968, found 236.0950.

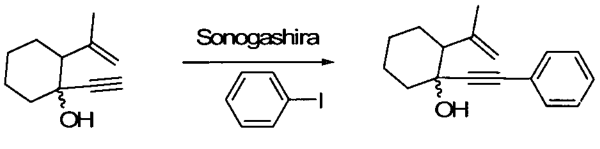
1-Ethynyl-2-(1-phenyl-vinyl)-cyclohexanol (4.16c). To a solution of ketone **4.28c** (0.223 g, 0.943 mmol) in THF (3.7 mL) was added dropwise ethynylmagnesium bromide (5.7 mL, 2.83 mmol). The reaction was heated to reflux and stirred until completion by TLC (5 hours), at which point it was cooled to room temperature and quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded both diastereoisomer (*54:46*) of **4.16c** as yellow oils (134.0 mg, 63%). **Major (±)-[1*S*,2*S*]**: IR (neat, cm^{-1}) 3553 (br), 3292 (m), 2936 (s), 2857 (m), 1493 (m), 1444 (m), 1143 (w), 1067 (m), 971 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.38 (m, 2H), 7.31-7.21 (m, 3H), 5.40 (d, *J*=0.8 Hz, 1H), 5.28 (s, 1H), 2.87 (dd, *J*=12.4, 3.5 Hz, 1H), 2.20 (d, *J*=1.6 Hz, 1H), 2.15-2.11 (m, 1H), 2.07 (s, 1H), 1.87-1.59 (m, 6H), 1.40-1.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.6 (C_{quat}), 144.4 (C_{quat}), 128.2 (CHx2), 127.3 (CH), 127.1 (CHx2), 115.4 (CH_2), 88.1(C_{quat}), 72.1 (CH), 67.4 (C_{quat}), 51.0 (CH), 40.0 (CH_2), 28.0 (CH_2), 26.0 (CH_2), 20.6 (CH_2); HRMS (EI) m/z calcd for $C_{16}H_{18}O$ [M^+] 226.1358, found 226.1351.

Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3566 (br), 3443 (br), 3297 (m), 2935 (s), 2859 (m), 1622 (w), 1444 (m), 1321 (w), 1059 (s), 998 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44-7.43 (m, 2H), 7.35-7.21 (m, 3H), 5.56 (s, 1H), 5.47 (d, *J*=0.5 Hz, 1H), 2.70 (dd, *J*=12.4, 2.9 Hz, 1H), 2.59 (s, 1H), 2.22 (s, 1H), 2.16-2.10 (m, 1H), 1.92-1.63 (m, 6H), 1.44-1.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.3 (C_{quat}), 144.2 (C_{quat}), 128.5 (CHx2), 127.5 (CH), 126.9 (CHx2), 115.8 (CH_2), 85.3 (C_{quat}), 75.3 (CH), 73.5 (C_{quat}), 52.8 (CH), 41.2 (CH_2), 30.9 (CH_2), 26.1 (CH_2), 24.0 (CH_2); HRMS (EI) m/z calcd for $C_{16}H_{18}O$ [M^+] 226.1358, found 226.1353.



2-Isopropenyl-1-prop-1-ynyl-cyclohexanol (4.16d). To a solution of 2-isopropenyl-cyclohexanone **3.18**[125] (0.608 g, 4.40 mmol) in THF (7.8 mL) at 0 °C was added dropwise 1-propynylmagnesium bromide (17.6 mL, 8.81 mmol). The reaction was warmed to room temperature and stirred until completion by TLC, at which point it was quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% hexanes in benzene) afforded both diastereoisomers (*71:29*) of **4.16d** as yellow oils (0.486 g, 62%). **Major (±)-[1*S*,2*S*]:** IR (neat, cm^{-1}) 3549 (br), 3079 (w), 2936 (s), 2855 (s), 1639 (m), 1447 (m), 1370 (m), 1286 (m), 969 (s), 893 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.89 (s, 1H), 4.73 (s, 1H), 2.11 (s, 1H), 2.10-1.99 (m, 2H), 1.88 (s, 3H), 1.71 (s, 3H), 1.66-1.21 (m, 6H), 1.22-1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.5 (C_{quat}), 111.9 (CH_2), 84.2 (C_{quat}), 78.7 (C_{quat}), 66.8 (C_{quat}), 52.6 (CH), 39.8 (CH_2), 26.5 (CH_2), 25.6 (CH_2), 25.6 (CH_3), 20.4 (CH_2), 3.1 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1361

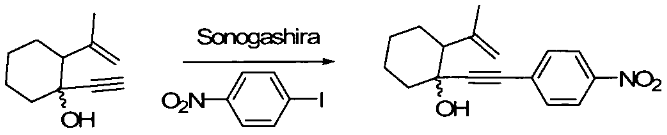
Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3450 (br), 2933 (s), 2857 (m), 2236 (w), 1639 (w), 1446 (m), 1373 (m), 1061 (m), 1012 (m); ^1H NMR ($CDCl_3$, 500 MHz) 4.96-4.95 (m, 1H), 4.88 (d, *J*=1.7Hz, 1H), 2.63 (s, 1H), 2.10-1.98 (m, 2H), 1.84-1.83 (m, 6H), 1.73-1.59 (m, 5H), 1.47-1.42 (m, 1H), 1.27-1.18 (m, 1H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.8 (C_{quat}), 114.7 (CH_2), 81.9 (C_{quat}), 81.0 (C_{quat}), 69.7 (C_{quat}), 56.2 (CH), 40.6 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 23.9 (CH_2), 20.7 (CH_3), 3.5 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{17}$ [$(M-OH)^+$] 161.1325, found 161.1328.



4.16 4.16e

2-Isopropenyl-1-phenylethynyl-cyclohexanol (4.16e). Using the general procedure A for Sonogashira, alcohol **4.16** (128.1 mg, 0.781 mmol) was coupled with iodobenzene (0.096 mL, 0.859 mmol). Purification by flash chromatography (10% ethyl acetate/90% hexanes) gave compounds **4.16e** as yellow oils (113.5 mg, 61%). **Major (±)-[1*S*,2*S*]:** IR (neat, cm^{-1}) 3550 (br), 3463 (br), 3079 (m), 2936 (s), 2855 (s), 2226 (w), 1638 (m), 1490 (s), 1444 (s), 1287 (m), 969 (s), 756 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.36 (m, 2H), 7.28-7.26 (m, 3H), 5.02 (dd, *J*=1.5, 1.5 Hz, 1H), 4.88 (s, 1H), 2.32-2.28 (m, 2H), 2.25-2.20 (m, 1H), 2.04 (s, 3H), 1.79-1.59 (m, 4H), 1.55-1.47 (m, 2H), 1.34-1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.4 (C_{quat}), 131.6 (CHx2), 128.2 (CHx2), 128.1 (CH), 123.0 (C_{quat}), 112.4 (CH_2), 94.1 (C_{quat}), 83.1 (C_{quat}), 67.4 (C_{quat}), 52.7 (CH), 39.7 (CH_2), 26.8 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 20.7 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{20}O$ [M^+] 240.1514, found 240.1535.

Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3537 (br), 3448 (br), 3079 (w), 2933 (s), 2857 (m), 1636 (w), 1597 (w), 1490 (m), 1443 (m), 1063 (m), 1013 (m), 756 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.38 (m, 2H), 7.30-7.26 (m, 3H), 5.00 (dd, *J*=1.5, 1.5 Hz, 1H), 4.96 (s, 1H), 2.78 (s, 1H), 2.23-2.15 (m, 2H), 1.92 (s, 3H), 1.78-1.66 (m, 5H), 1.60-1.52 (m, 1H), 1.34-1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.7 (C_{quat}), 131.6 (CHx2), 128.4 (CHx2), 128.3 (CH), 123.1 (C_{quat}), 115.3 (CH_2), 91.4 (C_{quat}), 86.4 (C_{quat}), 70.4 (C_{quat}), 56.7 (CH), 40.7 (CH_2), 28.8 (CH_2), 25.8 (CH_2), 24.2 (CH_2), 20.9 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{20}O$ [M^+] 240.1514, found 240.1507.

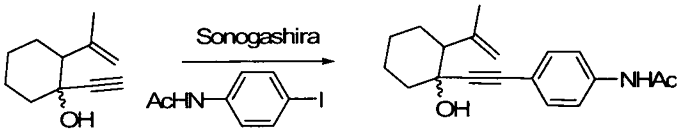


4.16 4.16f

2-Isopropenyl-1-(4-nitro-phenylethynyl)-cyclohexanol (4.16f). Using the general procedure A for Sonogashira, alcohol **4.16** (101.1 mg, 0.616 mmol) was coupled with 1-iodo-4-nitrobenzene (172 mg, 0.678 mmol). Purification by flash chromatography (10% ethyl acetate/90% hexanes to 20% ethyl acetate/80% hexanes) gave compounds **4.16f** as yellow oils (135.9 mg, 77%). **Major (±)-[1*S*,2*S*]:** IR (neat, cm^{-1}) 3542 (br), 3079 (w), 2937 (s), 2856 (m), 2226 (w), 1638 (w), 1594 (s), 1530 (s), 1345 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, *J*=9.0 Hz, 2H), 7.49 (d, *J*=9.0 Hz, 2H), 5.03 (dd, *J*=1.5, 1.5 Hz, 1H), 4.88 (s, 1H), 2.33-2.28 (m, 2H), 2.23-2.19 (m, 1H), 1.99 (dd, *J*=1.2, 0.8 Hz, 3H), 1.79-1.59 (m, 4H), 1.57-1.49 (m, 2H), 1.34-1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.1 (C_{quat}), 147.1 (C_{quat}), 132.3 (CHx2), 130.1 (C_{quat}), 123.7 (CHx2), 112.8 (CH_2), 99.7 (C_{quat}), 81.8 (C_{quat}), 67.8 (C_{quat}), 52.7 (CH), 39.4 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 20.5 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{19}NO_3$ [M^+] 285.1365, found 285.1364.

Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3533 (br), 3441 (br), 3078 (m), 2934 (s), 2858 (m), 2223 (w), 1594 (s), 1519 (s), 1345 (s), 855 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, *J*=8.9 Hz, 2H), 7.52 (d, *J*=8.9 Hz, 2H), 5.02 (dd, *J*=1.5, 1.5 Hz, 1H), 4.95 (s, 1H), 2.83 (s, 1H), 2.24-2.16 (m, 2H), 1.89 (s, 3H), 1.82-1.54 (m, 6H), 1.36-1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100

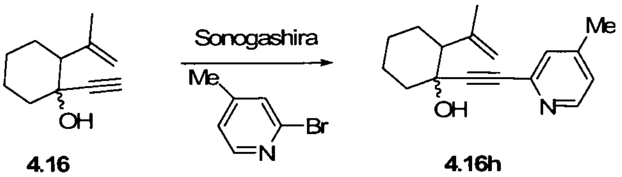
MHz) δ 147.3 (C_{quat}), 145.1 (C_{quat}), 132.4 (CHx2), 130.0 (C_{quat}), 123.7 (CHx2), 115.7 (CH_2), 97.1 (C_{quat}), 84.6 (C_{quat}), 70.5 (C_{quat}), 56.6 (CH), 40.6 (CH_2), 28.8 (CH_2), 25.8 (CH_2), 24.2 (CH_2), 21.0 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{19}NO_3$ [M^+] 285.1365, found 285.1370.



4.16 4.16g

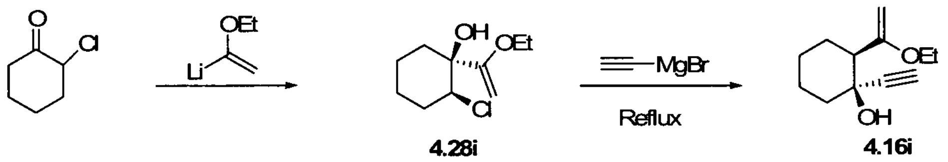
N-[4-(1-Hydroxy-2-isopropenyl-cyclohexylethynyl)-phenyl]-acetamide (4.16g). Using the general procedure A for Sonogashira, alcohol **4.16** (116.0 mg, 0.707 mmol) was coupled with *N*-(4-Iodo-phenyl)-acetamide[253] (203.0 mg, 0.778 mmol). Purification by flash chromatography (10% ethyl acetate/90% dichloromethane) gave compounds **4.16g** as yellow foams (182.1 mg, 87%). **Major (±)-[1*S*,2*S*]:** IR (neat, cm^{-1}) 3305 (br), 3102 (w), 2934 (s), 2856 (w), 1671 (s), 1597 (s), 1530 (s),, 1512 (s), 1316 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44-7.42 (m, 3H), 7.31-7.29 (m, 2H), 5.01 (dd, *J*=1.5, 1.5 Hz, 1H), 4.86 (s, 1H), 2.31-2.26 (m, 2H), 2.22-2.17 (m, 1H), 2.15-2.14 (m, 3H), 2.01 (s, 3H), 1.91 (s, 1H), 1.76-1.46 (m, 5H), 1.29-1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4 (C_{quat}), 148.5 (C_{quat}), 138.0 (C_{quat}), 132.5 (CHx2), 129.2 (C_{quat}), 119.5 (CHx2), 112.6 (CH_2), 94.0 (C_{quat}), 83.1 (C_{quat}), 67.6 (C_{quat}), 52.9 (CH), 40.0 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 25.9 (CH_2), 24.8 (CH_3), 20.7 (CH_2); HRMS (EI) m/z calcd for $C_{19}H_{23}NO_2$ [M^+] 297.1729, found 297.1721.

Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3305 (br), 2934 (s), 2857 (m), 1672 (s), 1595 (s), 1530 (s), 1512 (s), 1315 (s), 839 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.43 (m, 2H), 7.35-7.33 (m, 3H), 5.00 (s, 1H), 4.94 (s, 1H), 2.79 (s, 1H), 2.22-2.16 (m, 5H), 1.91(s, 3H), 1.77-1.52 (m, 6H), 1.31-1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4 (C_{quat}), 145.7 (C_{quat}), 138.1 (C_{quat}), 132.4 (CHx2), 119.5 (CHx2), 118.8 (C_{quat}), 115.3 (CH_2), 91.0 (C_{quat}), 86.1 (C_{quat}), 70.4 (C_{quat}), 56.8 (CH), 40.7 (CH_2), 28.8 (CH_2), 25.9 (CH_2), 24.9 (CH_3), 24.2 (CH_2), 21.1 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{23}NO_2$ [M^+] 297.1729, found 297.1738.



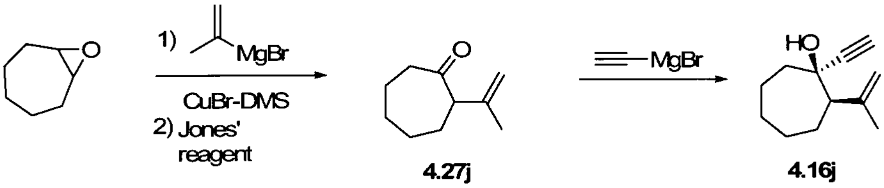
4.16 4.16h

2-Isopropenyl-1-(5-methyl-pyridin-2-ylethynyl)-cyclohexanol (4.16h). Using the general procedure A for Sonogashira, alcohol **4.16** (108.2 mg, 0.659 mmol) was coupled with 2-bromo-5-methylpyridine (127.2 mg, 0.725 mmol). Purification by flash chromatography (30% ethyl acetate/70% hexanes) gave compounds **4.16h** as yellow solids (120.5 mg, 72%). **Major (±)-[1*S*,2*S*]:** IR (neat, cm^{-1}) 3244 (br), 2928 (s), 2855 (m), 2223 (w), 1642 (m), 1559 (m), 1482 (s), 1141 (m), 977 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (s, 1H), 7.39 (d, *J*=8.9 Hz, 1H), 7.25 (d, *J*=7.2 Hz, 1H), 4.99 (dd, *J*=1.6, 1.6 Hz, 1H), 4.87 (s, 1H), 2.39 (d, *J*=1.3 Hz, 1H), 2.33-2.29 (m, 1H), 2.32 (s, 3H), 2.25-2.20 (m, 1H), 2.00 (s, 3H), 1.81-1.45 (m, 6H), 1.32-1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5 (CH), 148.3 (C_{quat}), 140.4 (C_{quat}), 136.7 (CH), 132.8 (C_{quat}), 126.9 (CH), 112.7 (CH_2), 93.3 (C_{quat}), 82.9 (C_{quat}), 67.5 (C_{quat}), 53.0 (CH), 39.4 (CH_2), 26.8 (CH_2), 25.9(CH_2), 25.9 (CH_3), 20.6 (CH_2), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{21}NO$ [M^+] 255.1623, found 255.1596; mp = 123.9-128.8 °C.
Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3290 (br), 2932 (s), 2857 (m), 2223 (w), 1642 (m), 1595 (m), 1561 (m), 1478 (s), 1067 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 7.41 (dd, *J*=8.0, 2.5 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 4.99 (dd, *J*=1.6, 1.6 Hz, 1H), 4.95 (s, 1H), 2.88 (s, 1H), 2.30 (s, 3H), 2.22-2.18 (m, 2H), 1.92 (s, 3H), 1.78-1.74 (m, 5H), 1.61-1.52 (m, 1H), 1.27-1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.7 (CH), 145.7 (C_{quat}), 140.5 (C_{quat}), 136.8 (CH), 132.8 (C_{quat}), 126.7 (CH), 115.3 (CH_2), 90.9 (C_{quat}), 85.9 (C_{quat}), 70.5 (C_{quat}), 56.6 (CH), 40.6 (CH_2), 28.7 (CH_2), 25.8 (CH_2), 24.1 (CH_2), 21.1 (CH_3), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{21}NO$ [M^+] 255.1623, found 255.1603; mp = 102.6-106.1 °C.



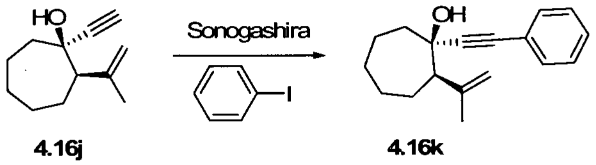
(±)-[1*S*,2*S*]-2-Chloro-1-(1-ethoxy-vinyl)-cyclohexanol (4.28i). To a -78 °C solution of ethyl vinyl ether (3 mL, 31.5 mmol) in THF (1.5 mL) was added *t*-BuLi (5.50 mL, 8.76 mmol) dropwise. The solution was protected from light and stirred for 30 min. at -78 °C. The resulting black solution was warmed to 0 °C for 10 min. then cooled back to -78 °C. After cannulation of 2-chlorocyclohexanone (0.250 mL, 2.19 mmol) in THF (15 mL), the mixture was stirred at -78 °C and followed to completion by TLC (45 min.). The reaction mixture was quenched with isopropanol followed by water. The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes with triethylamine) afforded **4.28i** as a yellow oil (370.4 mg, 83%). IR (neat, cm^{-1}) 3561 (br), 2978 (m), 2940 (s), 2863 (w), 1623 (m), 1446 (m), 1286 (m), 1248 (s), 1139 (s), 1074 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.41-4.35 (m, 2H), 3.96 (d, J=2.4 Hz, 1H), 3.71 (q, J=7.0 Hz, 2H), 2.31 (s, 1H), 1.99-1.83 (m, 2H), 1.76-1.53 (m, 4H), 1.46-1.31 (m, 2H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7 (C_{quat}), 80.3 (CH_2), 75.1 (C_{quat}), 65.0 (CH), 63.4 (CH_2), 35.9 (CH_2), 32.0 (CH_2), 26.1 (CH_2), 20.4 (CH_2), 14.5 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{17}O_2Cl$ [M^+] 204.0917, MS was unavailable because of compound volatility.

(±)-[1*S*,2*S*]-2-(1-Ethoxy-vinyl)-1-ethynyl-cyclohexanol (4.16i). To a solution of ketone **4.28i** (0.370 g, 1.81 mmol) in THF (7.1 mL) was added dropwise ethynylmagnesium bromide (10.9 mL, 5.43 mmol). The reaction was heated to reflux and stirred until completion by TLC (5 hours), at which point it was cooled to room temperature and quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes with triethylamine) afforded **4.16i** as a yellow oil (145.1 mg, 41%). IR (neat, cm^{-1}) 3531 (s), 3292 (m), 2940 (s), 2856 (m), 1659 (m), 1617 (m), 1292 (s), 1072 (s), 973 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 2H), 3.86 (d, J=2.2 Hz, 1H), 3.82-3.65 (m, 2H), 2.35 (s, 1H), 2.25 (dd, J=12.8, 3.5 Hz, 1H), 2.08-1.99 (m, 1H), 1.94-1.79 (m, 1H), 1.74-1.38 (m, 6H), 1.26 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9 (C_{quat}), 88.2 (C_{quat}), 84.0 (CH_2), 70.6 (CH), 68.5 (C_{quat}), 63.4 (CH_2), 52.1 (CH), 38.8 (CH_2), 26.1 (CH_2), 25.4 (CH_3), 20.3 (CH_2), 14.5 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{18}O_2$ [M^+] 194.1307, found 194.1282.

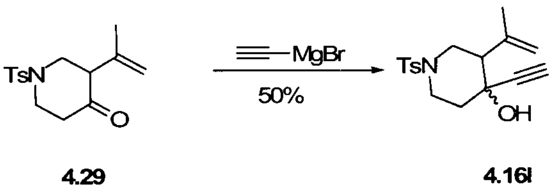


2-Isopropenyl-cycloheptanone (4.27j). A dry round bottom flask was charged with CuBr·DMS (0.428 g, 2.08 mmol) and THF (54 mL). The solution was cooled to -30 °C, followed by the addition of isopropenylmagnesium bromide (54.1 mL, 27.0 mmol). The mixture was stirred for 20 minutes, at which point cycloheptene oxide[254] (2.33 g, 20.8 mmol) was added and the solution was stirred to room temperature. The reaction was followed by TLC and quenched with NH_4Cl (sat. aq.) upon completion. The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was re-dissolved in diethyl ether (30 mL) and Jones' reagent (11.7 mL, 31.2 mmol) was slowly added at 0 °C. The reaction was allowed to reach room temperature. Upon completion, as observed by TLC analysis, the reaction was quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded **4.27j** (1.14 g, 36%) as a yellow oil. IR (neat, cm^{-1}) 3084 (w), 2930 (s), 2856 (m), 1703 (s), 1642 (m), 1454 (m), 889 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.83 (dd, *J*=1.4, 1.4 Hz, 1H), 4.72 (s, 1H), 3.00 (dd, *J*=11.4, 3.5 Hz, 1H), 2.60-2.51 (m, 1H), 2.41-2.33 (m, 1H), 1.93-1.83 (m, 4H), 1.68 (s, 3H), 1.65-1.57 (m, 1H), 1.54-1.38 (m, 1H), 1.37-1.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.1 (C_{quat}), 144.5 (C_{quat}), 112.1 (CH_2), 60.4 (CH), 42.4 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 28.4 (CH_2), 25.5 (CH_2), 21.9 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found 152.1188.

(±)-[1*S*,2*S*]-1-Ethynyl-2-isopropenyl-cycloheptanol (4.16j). To a solution of ketone **4.27j** (0.565 g, 3.71 mmol) in THF (6 mL) at 0 °C was added dropwise ethynylmagnesium bromide (18.6 mL, 9.28 mmol). The reaction was warmed to room temperature and stirred until completion by TLC, at which point it was quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes) afforded the alcohol **4.16j** as a yellow oil (0.524 g, 79%). IR (neat, cm^{-1}) 3533 (br), 3307 (m), 3073 (w), 2931(s), 2862 (m), 1641 (w), 1444 (m), 1065 (w); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.00 (dd, *J*=1.5, 1.5 Hz, 1H), 4.78 (s, 1H), 2.42-2.37 (m, 3H), 2.19 (dd, *J*=14.5, 9.5 Hz, 1H), 1.95 (t, *J*=0.5 Hz, 3H), 1.89-1.69 (m, 5H), 1.52-1.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.7 (C_{quat}), 113.9 (CH_2), 90.0 (C_{quat}), 70.7 (CH), 70.0 (C_{quat}), 56.8 (CH), 42.1 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 25.5 (CH_3), 21.5 (CH_2); HRMS (EI) m/z calcd for $C_{12}H_{18}O$ [M^+] 178.1358, found 178.1349.



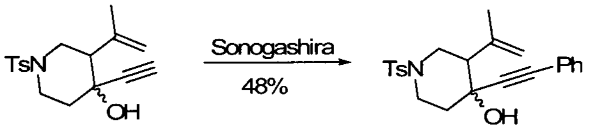
(±)-[1*S*,2*S*]-2-Isopropenyl-1-phenylethynyl-cycloheptanol (4.16k). Using the general procedure A for Sonogashira, alcohol **4.16j** (109.2 mg, 0.613 mmol) was coupled with iodobenzene (0.075 mL, 0.674 mmol). Purification by flash chromatography (5% ethyl acetate/95% hexanes) gave compound **4.16k** as a yellow oil (120.5 mg, 77%). IR (neat, cm^{-1}) 3526 (br), 3077 (w), 2927 (s), 2857 (m), 1638 (w), 1490 (m), 1443 (m), 755 (s), 691 (m); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.39-7.36 (m, 2H), 7.28-7.26 (m, 3H), 5.05 (s, 1H), 4.84 (s, 1H), 2.52 (d, *J*=10.5 Hz, 1H), 2.51 (s, 1H), 2.30 (dd, *J*=14.3, 9.8 Hz, 1H), 2.03 (s, 3H), 1.99-1.72 (m, 5H), 1.58-1.37 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 149.9 (C$_{quat}$), 131.6 (CHx2), 128.3 (CHx2), 128.2 (CH), 123.1 (C$_{quat}$), 113.9 (CH$_2$), 95.4 (C$_{quat}$), 82.6 (C$_{quat}$), 70.4 (C$_{quat}$), 57.1 (CH), 42.1 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 28.8 (CH$_2$), 25.6 (CH$_3$), 21.7 (CH$_2$); HRMS (EI) m/z calcd for $C_{18}H_{22}O$ [M$^+$] 254.1671; found 254.1686.



4-ethynyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol (**4.16l**). To a solution of 3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-one **4.29**[204] (0.910 g, 3.10 mmol) in THF (2 mL) at 0 °C was added dropwise ethynylmagnesium bromide (15.4 mL, 7.72 mmol). The solution was warmed to room temperature and stirred 3 hours. The mixture was cooled to 0 °C and quenched with NH$_4$Cl (sat. aq.). The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate in hexane) afforded compound **4.16l** as a mixture of diastereoisomers as a beige solid (0.497 g, 50%). **Major (±)-[3*S*,4*S*]**: IR (neat, cm^{-1}) 3495 (br), 3279 (br), 2926 (w), 2867 (w), 1340 (m), 1168 (s); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.62 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 5.03 (s, 1H), 4.68 (s, 1H), 3.63-3.58 (m, 1H), 3.55-3.51 (ddd, *J*= 10.9, 2.0, 3.3 Hz, 1H), 2.59-2.38 (m, 4H), 2.44 (s, 1H), 2.42 (s, 3H), 2.41 (bs, 1H), 2.09 (dd, *J*=3.1, 3.1 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 144.2

(C$_{quat}$), 143.7 (C$_{quat}$), 133.2 (C$_{quat}$), 129.8 (2xCH), 127.6 (2xCH), 113.8 (CH$_2$), 86.2 (C$_{quat}$), 72.6 (CH), 64.6 (C$_{quat}$), 50.4 (CH), 45.2 (CH$_2$), 41.1 (CH$_2$), 37.9 (CH$_2$), 26.3 (CH$_3$), 21.6 (CH$_3$); HRMS (EI) m/z calcd for $C_{17}H_{21}NO_3S$ (M^+) 319.1242, found 319.1234; mp = 143.0-148.5 °C.

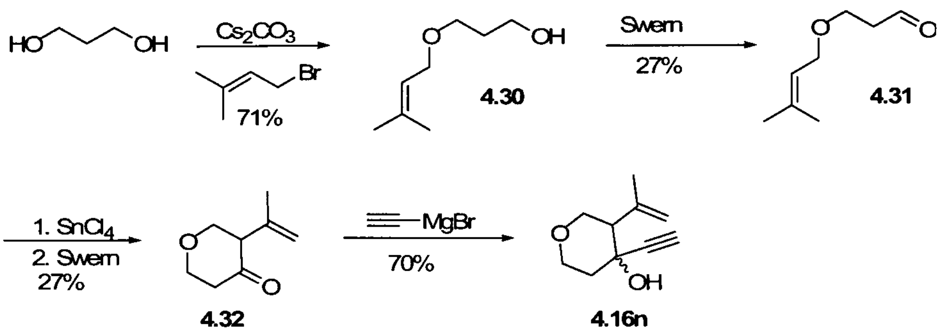
Minor (±)-[3*S*,4*R*]: IR (neat, cm^{-1}) 3490 (br), 3274 (s), 2926 (m), 2866 (w), 1340 (s), 1167 (s); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.65 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 5.04 (t, *J*=1.5 Hz, 1H), 4.95 (s, 1H), 3.86-3.80 (m, 1H), 3.78-3.74 (m, 1H), 2.71 (ddd, *J*=12.5, 12.5, 2.6 Hz, 1H), 2.63 (dd, *J*=11.9, 11.9 Hz, 1H), 2.58 (br, 1H), 2.42 (s, 3H), 2.39 (dd, *J*=11.8, 3.7 Hz, 2H), 2.04-1.99 (m, 1H), 1.83 (dd, *J*=12.7, 4.4 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ143.6 (C$_{quat}$), 141.3 (C$_{quat}$), 134.0 (C$_{quat}$), 129.8 (2xCH), 127.5 (2xCH), 116.6 (CH$_2$), 83.5 (C$_{quat}$), 76.3 (CH), 68.9 (C$_{quat}$), 53.2 (CH), 47.2 (CH$_2$), 44.0 (CH$_2$), 39.0 (CH$_2$), 22.1 (CH$_3$), 21.6 (CH$_3$); HRMS (EI) m/z calcd for $C_{17}H_{21}NO_3S$ (M^+) 319.1242, found 319.1240; mp = 116.0-126.0 °C.



4.16l **4.16m**

3-Isopropenyl-4-phenylethynyl-1-(toluene-4-sulfonyl)-piperidin-4-ol (4.16m). Using the general procedure A for Sonogashira, alcohol [3S,4S]-**4.16l** (0.280 g, 1.00 mmol) was coupled with iodobenzene (0.108 g, 1.11 mmol). Purification by flash chromatography (10% ethyl acetate/90% hexanes) gave compound **4.16m** as a yellow solid (181.0 mg, 48%).

(±)-[3*S*,4*S*]: IR (neat, cm^{-1}) 3496(br), 2932(m), 2870(m), 1595(w), 1345(s), 1210(s); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.58(d, *J*=8.3Hz, 2H), 7.29-7.26(m, 2H), 7.24-7.23 (m, 5H), 4.99(s, 1H), 4.67(s, 1H), 3.59-3.56(m, 1H), 3.53-3.49(m, 1H), 2.57-2.49(m, 3H), 2.36(s, 3H), 2.20-2.06(m, 3H), 1.96(s, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 144.3(C$_{quat}$), 143.6(C$_{quat}$), 133.3(C$_{quat}$), 131.6(2xCH), 129.8(CHx2), 128.7(CH), 128.4(2xCH), 127.7(2xCH), 122.2(C$_{quat}$), 113.8(CH$_2$), 91.5(C$_{quat}$), 84.3(C$_{quat}$), 65.1(C$_{quat}$), 50.8(CH), 45.4(CH$_2$), 41.3(CH$_2$), 38.0(CH$_2$), 26.3(CH$_3$), 21.6(CH$_3$); HRMS (EI) m/z calcd for $C_{23}H_{25}NO_3S$ (M^+) 395.1555, found 395.1575; mp = 155.8-156.7 °C.



3-(3-Methyl-but-2-enyloxy)-propan-1-ol (4.30). 1,3-propanediol (0.110 g, 1.43 mmol) was dissolved in DMF (2 mL) and the mixture was stirred at 0 °C for 15 minutes. At that point, NaH (30.0 mg, 1.24 mmol) was added and the resulting solution was stirred 15 minutes before 1-bromo-3-methyl-but-2-ene (0.070 mL, 0.590 mmol) was added. The solution was stirred until the reaction was complete by TLC. The reaction was quenched with NH_4Cl, extracted 3X with Et_2O, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (30-60% ethyl acetate in hexanes) gave **4.30** (60.0 mg, 71%) as a colorless oil. IR (neat, cm^{-1}) 3402(s), 2930(s), 2867(s), 1085(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.33-5.29(m, 1H), 3.94(d, *J*=6.9Hz, 2H), 3.75(t, *J*=5.7Hz, 2H), 3.59(t, *J*=5.8Hz, 2H), 2.14(br, 1H), 1.81(dddd, *J*=5.8, 5.8, 5.8, 5.8Hz, 2H), 1.72(s, 3H), 1.65(s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 137.2(C_{quat}), 120.9(CH), 69.4(CH_2), 67.6(CH_2), 62.3(CH_2), 32.1(CH_2), 25.8(CH_3), 18.0(CH_3); HRMS (EI) m/z calcd for $C_8H_{16}O_2$ (M^+) 144.1150, found 144.1151.

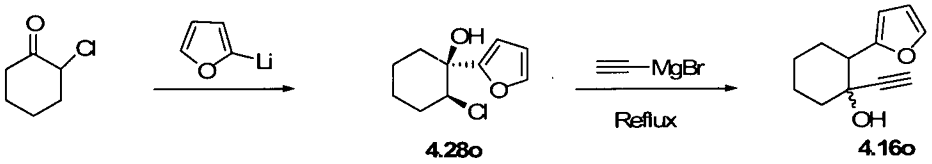
3-(3-Methyl-but-2-enyloxy)-propionaldehyde (4.31). DMSO (1.94 mL, 27.3 mmol) was slowly added to a solution of oxalyl chloride (1.19 mL, 13.7 mmol) in DCM (34 mL) at -78°C. After stirring for 20 minutes, **4.30** in DCM (16 mL) was added and the mixture was stirred for another 90 minutes. Triethylamine (7.90 mL, 56.9 mmol) was added and the solution was again stirred at 0°C for another hour before being quenched with NH_4Cl (sat. aq.). The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (30% ethyl acetate in hexane) gave **4.31** (0.820 g, 51%) as a yellow oil. IR (neat, cm^{-1}) 2863(s), 1725(s), 1085(m); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74(s, 1H), 5.30-5.26(m, 1H), 3.93(d, *J*=6.9Hz, 2H), 3.71(t, *J*=6.1Hz,*J*=6.1Hz, 2H), 2.62(td, *J*=1.7Hz, *J*=6.2Hz, 2H), 1.70(s, 3H), 1.63(s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 201.3(CH), 137.5(C_{quat}), 120.7(CH), 67.6(CH_2), 63.6(CH_2), 44.0(CH_2), 25.8(CH_3), 18.0(CH_3); HRMS (EI) m/z calcd for $C_7H_{11}O_2$ $(M\text{-}Me)^+$ 127.0754, found 127.0761.

3-Isopropenyl-tetrahydro-pyran-4-one (4.32). To a suspension of molecular sieves (0.41 g) in DCM (8.1 mL) was added **4.31** (0.580 g, 4.23 mmol). The mixture was cooled to -78 °C and tin tetrachloride (0.410 mL, 0.423 mmol) was added dropwise. The solution was stirred at -60 °C for 1 hour before it was quenched with NH_4Cl. The solution was allowed to stir overnight at room temperature. The mixture was filtered through celite and the resulting solution was extracted with DCM 3X. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated.

DMSO (0.430 mL, 6.13 mmol) was slowly added to a solution of oxalyl chloride (0.270 mL, 3.06 mmol) in DCM (8.0 mL) at -78°C. After stirring for 20 minutes, the alcohol in DCM (4.0 mL) was added and the mixture was stirred for another 90 minutes. Triethylamine (1.78 mL, 12.8 mmol) was added and the solution was again stirred at 0°C for another hour before being quenched with NH_4Cl (sat. aq.). The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (25% ethyl acetate in hexanes) gave **4.32** (0.100 g, 27%) as a colorless liquid. IR (neat, cm^{-1}) 2968(s), 2856(s), 1718(m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.99 (s, 1H), 4.85 (s, 1H), 4.10-4.06 (m, 2H), 3.87-3.79 (m, 2H), 3.13 (dd, J= 8.5, 6.0 Hz, 1H), 2.53-2.49 (m, 2H), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 206.1(C_{quat}), 139.9(C_{quat}), 114.8(CH_2), 71.4(CH_2), 68.3(CH_2), 58.8(CH), 41.9(CH_2), 22.0(CH_3); HRMS (EI) m/z calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0840.

4-Ethynyl-3-isopropenyl-tetrahydro-pyran-4-ol (4.16n). To a solution of **4.32** (0.100 g, 0.703 mmol) in THF (7 mL) at 0 °C was added dropwise ethynylmagnesium bromide (3.50 mL, 1.76 mmol). The solution was warmed to room temperature and stirred 3 hours. The mixture was cooled to 0 °C and quenched with NH_4Cl (sat. aq.). The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (20% ethyl acetate in hexanes) afforded compound **4.16n** as a mixture of diastereoisomers as colorless oils (0.822 g, 70%). **Major (±)-[3*S*,4*S*]**: IR (neat, cm^{-1}) 3351(br), 3231(s), 2961(m), 2864 (m), 1113(s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.04-5.03(t, J=1.4Hz, 1H), 4.75(s, 1H), 3.73-3.70(m, 2H), 3.61-3.56(m, 2H), 2.52-2.48(dd, J=9.8, 6.1Hz, 1H), 2.44(s, 1H), 2.35(br, 1H), 2.04-1.93(m, 2H), 1.96(dd, *J*=1.4Hz, *J*=1.0Hz, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 143.8(C$_{quat}$), 113.7(CH$_2$), 87.0(C$_{quat}$), 71.9(CH), 66.2(CH$_2$), 64.7(C$_{quat}$), 62.7(CH$_2$), 51.1(CH), 38.6(CH$_2$), 26.5(CH$_3$); HRMS (EI) m/z calcd for $C_{10}H_{13}O_2$ $(M-H)^+$ 165.0921, found 165.0919.

Minor (±)-[3*S*,4*R*]: IR (neat, cm^{-1}) 3381(br), 2962(s), 2869 (m), 1640(w), 1107(s); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.03-5.02(t, *J*=1.6Hz, 1H), 4.96(s, 1H), 3.99-3.94(m, 1H), 3.85(dd, *J*=11.5, 4.0Hz, 1H), 3.75-3.69(ddd, *J*=7.6Hz, 7.6Hz, 2.3Hz, 1H), 3.64-3.58(dd, *J*=11.5Hz, 1H), 2.61(br, 1H), 2.56(s, 1H), 2.40-2.36(dd, *J*=11.5, 4.0Hz, 1H), 1.99-1.94(m, 1H), 1.87 (dd, *J*=12.4, 4.6 Hz, 1H), 1.84(s, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 141.3(C$_{quat}$), 115.9(CH$_2$), 84.5(C$_{quat}$), 75.6(CH), 68.9(C$_{quat}$), 68.6(CH$_2$), 65.8(CH$_2$), 54.6(CH), 40.6(CH$_2$), 22.5(CH$_3$); HRMS (EI) m/z calcd for $C_{10}H_{13}O_2$ $(M-H)^+$ 165.0921, found 165.0919.

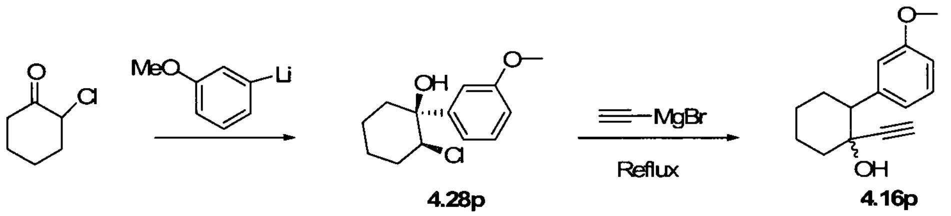


(±)-[1*S*,2*S*]-2-Chloro-1-furan-2-yl-cyclohexanol (4.28o). To a 0 °C solution of furan (0.287 mL, 3.95 mmol) in THF (17 mL) was added *n*-BuLi (2.63 mL, 4.21 mmol) dropwise. The solution was stirred for 90 min. then cooled to -78 °C. After cannulation of 2-chlorocyclohexanone (0.300 mL, 2.63 mmol) in THF (5 mL), the mixture was stirred at -78 °C and followed to completion by TLC (45 min.). The reaction mixture was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded **4.28o** as a yellow oil (439.8 mg, 83%). IR (neat, cm^{-1}) 3545 (br), 2941 (s), 2863 (m), 1505 (m), 1447 (m), 1347 (w), 1293 (m), 1155 (s), 986 (s), 739 (s); ^{1}H NMR (CDCl$_3$, 300 MHz) 7.33 (dd, *J*=0.9, 0.8 Hz, 1H), 6.32-6.28 (m, 2H), 4.46 (dd, *J*=8.0, 6.2 Hz, 1H), 2.65-2.61 (m, 1H), 2.07-2.00 (m, 3H), 1.86-1.64 (m, 3H), 1.52-1.31 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 158.5 (C$_{quat}$), 141.6 (CH), 110.3 (CH), 105.6 (CH), 73.4 (C$_{quat}$), 66.7 (CH), 37.2 (CH$_2$), 32.2 (CH$_2$), 25.6 (CH$_2$), 20.6 (CH$_2$); HRMS (EI) m/z calcd for $C_{10}H_{13}O_2Cl$ $[M^+]$ 200.0604, found 200.0607.

1-Ethynyl-2-furan-2-yl-cyclohexanol (4.16o). To a solution of ketone **4.28o** (0.439 g, 2.19 mmol) in THF (8.6 mL) was added dropwise ethynylmagnesium bromide (13.1 mL, 6.57

mmol). The reaction was heated to reflux and stirred until completion by TLC (3 hours), at which point it was cooled to room temperature and quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded both diastereoisomers of **4.16o** (54:46) as yellow foams (353.7 mg, 85%). **Major (±)-[1*S*,2*S*]:** IR (neat, cm^{-1}) 3558 (br), 3292 (s), 2938 (s), 2861 (m), 1590 (w), 1503 (m), 1447 (m), 972 (s); ^1H NMR ($CDCl_3$, 300 MHz) 7.35 (s, 1H), 6.33 (s, 1H), 6.18 (d, *J*=3.0Hz, 1H), 2.97 (dd, *J*=12.3, 3.8 Hz, 1H), 2.39 (s, 1H), 2.35 (s, 1H), 2.16-2.09 (m, 1H), 2.02-1.85 (m, 1H), 1.79-1.51 (m, 5H), 1.39-1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0 (C_{quat}), 141.7 (CH), 110.3 (CH), 107.1 (CH), 87.7 (C_{quat}), 71.7 (CH), 68.3 (C_{quat}), 46.6 (CH), 38.8 (CH_2), 26.5 (CH_2), 25.2 (CH_2), 20.5 (CH_2); HRMS (EI) m/z calcd for $C_{12}H_{14}O_2$ [M^+] 190.0994, found 190.0976.

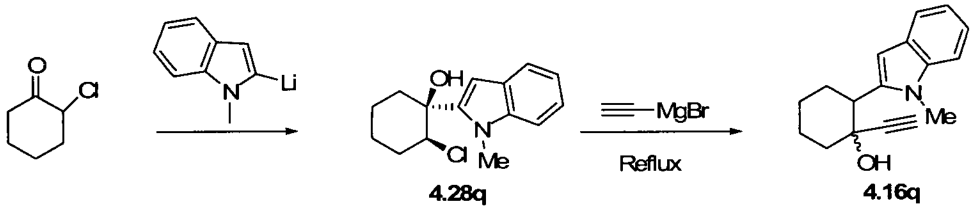
Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3557 (br), 3291 (s), 2937 (s), 2862 (m), 1589 (w), 1503 (m), 1448 (m), 1151 (m), 1058 (s); ^1H NMR ($CDCl_3$, 300 MHz) 7.35 (s, 1H), 6.33 (s, 1H), 6.19 (d, *J*=3.2Hz, 1H), 3.05 (s, 1H), 2.77 (dd, *J*=12.5, 3.6 Hz, 1H), 2.40 (s, 1H), 2.17-2.03 (m, 1H), 1.95-1.84 (m, 1H), 1.80-1.53 (m, 5H), 1.40-1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0 (C_{quat}), 141.7 (CH), 110.3 (CH), 106.6 (CH), 84.6 (C_{quat}), 74.5 (CH), 72.1 (C_{quat}), 48.2 (CH), 39.4 (CH_2), 28.0 (CH_2), 25.3 (CH_2), 23.6 (CH_2); HRMS (EI) m/z calcd for $C_{12}H_{14}O_2$ [M^+] 190.0994, found 190.0981.



(±)-[1*S*,2*S*]-2-Chloro-1-(3-methoxy-phenyl)-cyclohexanol (4.28p). To a -78 °C solution of 3-bromoanisole (0.984 mL, 5.26 mmol) in THF (17 mL) was added *n*-BuLi (2.96 mL, 4.73 mmol) dropwise. The white heterogeneous mixture was stirred for 30 min. After cannulation of 2-chlorocyclohexanone (0.300 mL, 2.63 mmol) in THF (5 mL), the mixture was stirred at -78 °C and followed to completion by TLC (45 min.). The reaction mixture was quenched with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded **4.28p** as a colorless oil (577.8 mg, 91%). IR (neat, cm^{-1}) 3542 (br), 2940 (s), 2861 (m), 1721 (w), 1602 (s), 1584 (s), 1485 (s), 1447 (s), 1433 (s), 1285 (s), 1250 (s), 1165 (m), 1067 (s), 985 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.23 (dd, *J*=7.9, 8.0 Hz, 1H), 7.00 (t, *J*=2.1 Hz, 1H), 6.95 (d, *J*=7.7 Hz, 1H), 6.76 (dd, *J*=8.1, 2.5 Hz, 1H), 4.43 (dd, *J*=10.1, 6.4 Hz, 1H), 3.77 (s, 3H), 2.47 (d, *J*=2.4 Hz, 1H), 2.13-2.05 (m, 2H), 1.99-1.93 (m, 1H), 1.85-1.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7 (C_{quat}), 148.5 (C_{quat}), 129.4 (CH), 116.8 (CH), 112.1 (CH), 111.0 (CH), 75.8 (C_{quat}), 68.0 (CH), 55.3 (CH_3), 40.5 (CH_2), 32.8 (CH_2), 26.3 (CH_2), 21.0 (CH_2); HRMS (EI) m/z calcd for $C_{13}H_{17}O_2Cl$ [M$^+$] 240.0917, found 240.0921.

1-Ethynyl-2-(3-methoxy-phenyl)-cyclohexanol (4.16p). To a solution of ketone **4.28p** (0.414 g, 1.72 mmol) in THF (6.8 mL) was added dropwise ethynylmagnesium bromide (10.3 mL, 5.16 mmol). The reaction was heated to reflux and stirred until completion by TLC (10 hours), at which point it was cooled to room temperature and quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded both diastereoisomers (56:44) of **4.16p** (186.6 mg, 47%). **Major (±)-[1*S*,2*S*]** : (Yellow oil) IR (neat, cm^{-1}) 3471 (br), 3285 (m), 2937 (s), 2858 (m), 1600 (s), 1583 (s), 1487 (m), 1260 (s), 1049 (m), 973 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.24-7.21 (m, 1H), 6.92-6.89 (m, 2H), 6.81 (ddd, *J*=8.2, 2.6, 0.9 Hz, 1H), 3.80 (s, 3H), 2.75 (dd, *J*=13.0, 3.6 Hz, 1H), 2.35 (s, 1H), 2.22-2.17 (m, 1H), 2.03 (dddd, *J*=13.2, 13.2, 13.2, 3.7 Hz, 1H), 1.85-1.52 (m, 6H), 1.44-1.32 (m, 1H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.3 (C_{quat}), 143.1 (C_{quat}), 129.0 (CH), 121.7 (CH), 115.5 (CH), 112.4 (CH), 88.3 (C_{quat}), 72.8 (CH), 68.9 (C_{quat}), 55.3 (CH_3), 52.5 (CH), 39.9 (CH_2), 26.9 (CH_2), 26.0 (CH_2), 20.8 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{18}O$ [M$^+$] 230.1307, found 230.1314. **Minor (±)-[1*S*,2*R*]:** (White solid) IR (neat, cm^{-1}) 3459 (br), 3284 (m), 2934 (s), 1601 (m), 1492 (m), 1257 (m), 1054 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.22 (dd, *J*=7.9, 7.9 Hz, 1H), 6.95-6.93 (m, 2H), 6.81 (ddd, *J*=8.2, 2.5, 1.0Hz, 1H), 3.78 (s, 3H), 2.61 (dd, *J*=13.0, 3.1 Hz, 1H), 2.52 (s, 1H), 2.21 (s, 1H), 2.17-2.13 (m, 1H), 1.97 (dddd, *J*=13.0, 13.0, 13.0, 3.5 Hz, 1H), 1.83-1.59 (m, 5H), 1.39-1.25 (m, 1H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4 (C_{quat}), 141.9 (C_{quat}), 129.1 (CH), 122.1 (CH), 115.2 (CH), 112.7 (CH), 85.1 (C_{quat}), 75.6 (CH), 66.7

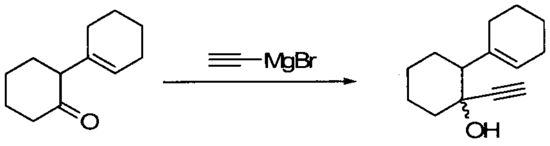
(C_{quat}), 55.3 (CH_3), 54.8 (CH), 40.4 (CH_2), 30.0 (CH_2), 26.1 (CH_2), 24.1 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{18}O$ [M^+] 230.1307, found 230.1324; mp = 123.4-127.2 °C.



(±)-[1*S*,2*S*]-2-Chloro-1-(1-methyl-1*H*-indol-2-yl)-cyclohexanol (4.28q). 1-Methylindole (1.46mL, 11.4mmol) was dissolved in THF (6.8 mL) and the resulting mixture was cooled to 0 °C before *n*-BuLi (7.63 mL, 15.2 mmol) was added. The ice bath was then removed and the solution stirred for 2 hours at room temperature. The mixture was cooled to -78 °C before 2-chloro-cyclohexanone (1.10 mL, 9.50 mmol) dissolved in THF (3.4 mL) was slowly cannulated. The reaction was then stirred at room temperature until completed by TLC. The reaction was quenched with the addition of NH_4Cl, followed by the addition of water to dissolve the precipitate. The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate in hexanes) gave **4.28q** (0.840 g, 33%) as a yellow oil. IR (neat, cm^{-1}) 3530(m), 2940(s), 2861(m), 1720(m), 1467 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, *J*=7.8Hz, 1H), 7.32(d, *J*=8.2Hz, 1H), 7.24-7.20 (m, 1H), 7.12-7.08 (m, 1H), 6.45(s, 1H), 4.73(dd, *J*=6.9, 6.9 Hz, 1H), 4.00(s, 3H), 2.66(br, 1H), 2.47-2.44(m, 1H), 2.19-2.16(m, 2H), 1.87-1.76(m, 2H), 1.64-1.57(m, 2H), 1.46-1.40(m, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ142.5(C_{quat}), 138.4(C_{quat}), 126.9(C_{quat}), 121.7(CH), 120.6(CH), 119.7(CH), 109.1(CH), 99.6(CH), 73.7(C_{quat}), 66.7(CH), 38.5(CH_2), 32.6(CH_2), 32.1(CH_3), 25.7(CH_2), 20.7(CH_2); HRMS (EI) m/z calcd for $C_{17}H_{17}N$ (M^+) 263.1077, found 263.1084.

1-Ethynyl-2-(1-methyl-1*H*-indol-2-yl)-cyclohexanol (4.16q). To a solution of cyclohexanol **4.28q** (46.0 mg, 0.178 mmol) in THF (1 mL) was added dropwise ethynylmagnesium bromide (1.17 mL, 0.582 mmol). The reaction was heated to reflux and stirred until completion by TLC (3 hours), at which point it was cooled to room temperature and quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) gave **4.16q** as a mixture of diastereoisomers (27.3 mg, 61%) as yellow oils. **Major (±)-[1*S*,2*S*]**: IR (neat, cm^{-1}) 3527 (br), 3285 (s), 2938 (s), 2856 (m), 1465 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.67(dt, *J*=7.8, 0.8Hz, 1H), 7.41-7.38 (m, 1H), 7.31-7.26 (m, 1H), 7.20-7.16 (m, 1H), 6.50 (s, 1H), 3.87 (s, 3H), 3.28-3.24 (dd, *J*=12.6, 3.7 Hz, 1H), 3.14 (s, 1H), 2.59 (s, 1H), 2.39-2.33 (m, 1H), 2.33 (s, 1H), 2.17-1.44 (m, 6H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 141.1(C$_{quat}$), 137.5(C$_{quat}$), 127.7(C$_{quat}$), 121.4(CH), 120.2(CH), 119.6(CH), 109.5(CH), 99.6(CH), 88.2(C$_{quat}$), 71.7 (CH), 66.8(C$_{quat}$), 43.7(CH), 38.8(CH$_2$), 30.6(CH$_3$), 27.9(CH$_2$), 25.8(CH$_2$), 20.3(CH$_2$); HRMS (EI) m/z calcd for $C_{17}H_{19}NO$ (M$^+$) 253.1467, found 253.1465.

Minor (±)-[1*R*,2*S*]: IR (neat, cm^{-1}) 3424(m), 3285(m), 2936(s), 2859(m), 1468(m), 1317(m), 1231(w); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.65(d, *J*=7.8Hz, 1H), 7.36(d, *J*=8.2Hz, 1H), 7.24(td, *J*=1.2Hz, *J*=7.0Hz, 7.0Hz, 1H), 7.16-7.12(m, 1H), 6.70(s, 1H), 3.79(s, 3H), 3.01(dd, *J*=3.3Hz, *J*=12.1Hz, 1H), 2.65(s, 1H), 2.44(s, 1H), 2.26-2.22(m, 1H), 2.10-1.73(m, 6H), 1.50-1.38(m, 1H); ^{13}C NMR (CDCl$_3$, 100MHz) δ140.5(C$_{quat}$), 137.2(C$_{quat}$), 127.7(C$_{quat}$), 121.0(CH), 120.3(CH), 119.4(CH), 109.3(CH), 100.3(CH), 84.8(C$_{quat}$), 76.1(CH), 73.6(C$_{quat}$), 46.4(CH), 40.6(CH$_2$), 31.1(CH$_2$), 30.1(CH$_3$), 26.0(CH$_2$), 25.6(CH$_2$); HRMS (EI) m/z calcd for $C_{17}H_{19}NO$ (M$^+$) 253.1467, found 253.1474.



4.16r

2-Ethynyl-bicyclohexyl-1'-en-2-ol (4.16r). To a solution of 2-(1-cyclohexenyl)-cyclohexanone (0.500 g, 2.80 mmol) in THF (4 mL) at 0 °C was added dropwise ethynylmagnesium bromide (14 mL, 7.0 mmol). The reaction was warmed to room temperature and stirred until completion by TLC, at which point it was quenched with NH$_4$Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes) afforded both diastereoisomers (*60:40*) of **4.16r** as white solids (486.3 mg, 85%). **Major (±)-[1*S*,2*S*]**: IR (neat, cm^{-1}) 3439 (br), 3253 (m), 2939 (w), 1642 (m); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.53 (s, 1H), 2.51-2.40 (m, 1H), 2.34 (s, 1H), 2.25 (s, 1H), 2.13-2.06 (m, 1H), 2.04-1.89 (m, 4H), 1.71-1.32 (m, 10H), 1.26-1.11 (m, 1H); ^{13}C

NMR ($CDCl_3$, 75 MHz) 140.8 (C_{quat}), 123.8 (CH), 89.4 (C_{quat}), 71.4 (CH), 67.6 (C_{quat}), 53.0 (CH), 39.9 (CH_2), 32.3 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 22.8 (CH_2), 20.9 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{20}O$ (M^+) 204.1514, found 204.1498; m.p. 77.5-78.3 °C.

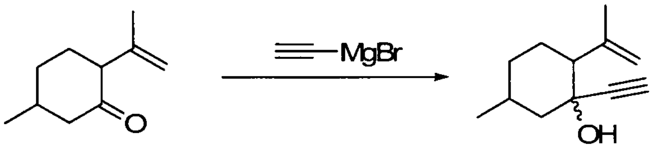
Minor (±)-[1*S*,2*R*]: IR (neat, cm^{-1}) 3305 (br), 3224 (s), 2930 (s), 2863 (s), 2098 (m), 1652 (w), 1446 (s), 1328 (m), 1135 (m), 1064 (s), 1033 (s), 952 (w); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.62 (s, 1H), 2.78 (s, 1H), 2.43-2.36 (m, 2H), 2.09-1.88 (m, 5H), 1.77-1.39 (m, 10H), 1.29-1.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.4 (C_{quat}), 127.0 (CH), 86.5 (C_{quat}), 74.2 (CH), 69.8 (C_{quat}), 57.0 (CH), 40.5 (CH_2), 28.0 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 23.9 (CH_2), 23.0 (CH_2), 22.5 (CH_2); HRMS (EI) m/z calcd for $C_{14}H_{20}O$ [M^+] 204.1514, found 204.1532; mp = 83.0-86.7 °C.

4.16r **4.16s**

2-Phenylethynyl-bicyclohexyl-1'-en-2-ol (4.16s). Using the general procedure A for Sonogashira, alcohol **4.16r** (98.8 mg, 0.484 mmol) was coupled with iodobenzene (0.060 mL, 0.532 mmol). Purification by flash chromatography (5% ethyl acetate/95% hexanes) gave compounds **4.16s** as yellow oils (116.1 mg, 86%). **Major (±)-[1*S*,2*S*]**: IR (neat, cm^{-1}) 3545 (br), 2931 (s), 2855 (w), 1598 (w), 1489 (m), 1443 (m), 1063 (w), 968 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.36-7.34 (m, 2H), 7.28-7.26 (m, 3H), 5.59 (s, 1H), 2.59-2.56 (m, 1H), 2.30 (d, *J*=1.9 Hz, 1H), 2.22-2.18 (m, 1H), 2.13 (dd, *J*=13.0, 3.6 Hz, 1H), 2.07-2.00 (m, 3H), 1.75-1.43 (m, 10H), 1.28-1.24 (m, 1H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.8 (C_{quat}), 131.7 (CHx2), 128.4 (CHx2), 128.2 (CH), 123.5 (CH), 123.3 (C_{quat}), 94.6 (C_{quat}), 83.0 (C_{quat}), 67.9 (C_{quat}), 53.2 (CH), 39.6 (CH_2), 32.1 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 20.8 (CH_2); HRMS (EI) m/z calcd for $C_{20}H_{24}O$ [M^+] 280.1827; found 280.1812.

Minor (±)-[1*S*,2*R*] (characterized as a mixture of *trans* and *cis*): IR (neat, cm^{-1}) 3538 (br), 2931 (s), 2856 (m), 1597 (w), 1489 (m), 1443 (m), 1059 (m), 755 (s), 650 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.38-7.37 (m, 2H), 7.29-7.26 (m, 3H), 5.68 (s, 1H), 2.83 (s, 1H), 2.49-

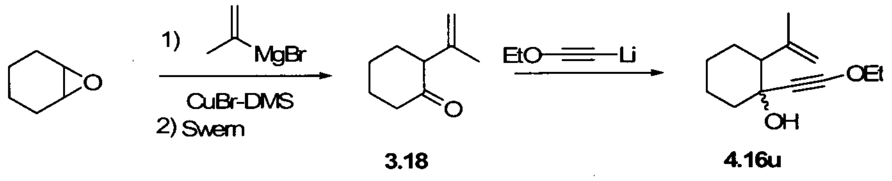
2.46 (m, 1H), 2.29-2.11 (m, 2H), 2.08-1.95 (m, 3H), 1.82-1.43 (m, 10H), 1.30-1.22 (m, 1H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7 (C_{quat}), 131.6 (CHx2), 128.4 (CHx2), 128.1 (CH), 127.0 (CH), 123.3 (C_{quat}), 91.9 (C_{quat}), 86.0 (C_{quat}), 70.4 (C_{quat}), 57.5 (CH), 40.6 (CH_2), 28.3 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 24.2 (CH_2), 23.1 (CH_2), 20.8 (CH_2); HRMS (EI) m/z calcd for $C_{20}H_{24}O$ [M^+] 280.1827, found 280.1807.



4.33 **4.16t**

1-Ethynyl-2-isopropenyl-5-methyl-cyclohexanol (4.16t). To a solution of (±)-isopulegone **4.33**[255] (1.00 g, 6.57 mmol) in THF (1 mL) was added dropwise ethynylmagnesium bromide (1.17 mL, 0.582 mmol). The reaction was stirred until completion by TLC (3 hours) before being quenched with NH_4Cl (sat. aq.). The mixture was extracted with diethyl ether (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes) gave **4.16t** as a mixture of diastereoisomers (0.940 g, 80%) as colorless oils. **Major (±)-[1*S*,2*S*,5*R*]:** IR (neat, cm^{-1}) 3549 (br), 3309 (s), 2951 (s), 1727 (m), 1638 (w), 1455 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.97 (t, J=1.6Hz, 1H), 4.81(s, 1H), 2.37(s, 1H), 2.15-2.08(m, 3H), 1.94(s, 3H), 1.76-1.63(m, 3H), 1.46-1.41(m, 1H), 1.32(dd, J=12.3Hz, J=13.7Hz, 1H), 0.93-0.88(m, 1H), 0.84(d, J=6.6Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 147.9(C_{quat}), 112.4(CH_2), 88.6(C_{quat}), 71.2(CH), 67.4(C_{quat}), 52.2(CH), 48.0(CH_2), 34.5(CH_2), 26.8(CH_2), 26.6(CH), 25.9(CH_3), 21.8(CH_3); HRMS (EI) m/z calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1345.

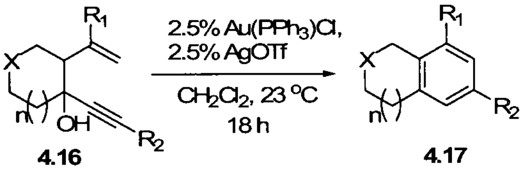
Minor (±)-[1*R*,2*S*,5*R*]: IR (neat, cm^{-1}) 3459 (br), 3307 (s), 2928 (s), 1633 (w), 1455 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ4.95 (t, J=0.7Hz, 1H), 4.88 (s, 1H), 2.43 (s, 1H), 2.10-2.00 (m, 2H), 1.95-1.60 (m, 5H), 1.84 (s, 3H), 1.17 (dd, J=12.3Hz, J=12.3Hz, 1H), 0.92 (d, J=5.2Hz, 3H), 0.95-0.83(m, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ145.4(C_{quat}), 115.2(CH_2), 86.3(C_{quat}), 74.2(CH), 69.6(C_{quat}), 55.7(CH), 48.7(CH_2), 34.4(CH_2), 30.3(CH), 28.0(CH_2), 21.9(CH_3), 21.0(CH_3); HRMS (EI) m/z calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1345.



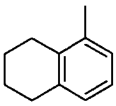
1-Ethoxyethynyl-2-isopropylcyclohexanol (4.16u)

A solution of ethoxyethynyl ether (40% in hexanes, 2.17 mmol, 380 mg) in THF was cooled to -78 °C and *n*-BuLi (1.86 M in hexanes, 1.08 mmol, 0.58 mL). After stirring for 40 minutes, a solution of **3.18**[125] (99.9 mg, 0.72 mmol) in THF (7 mL) was added at -78 °C. After stirring for 5 hours, the reaction quenched with NH_4Cl (sat. aq.). The mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded compound **4.16u** as a mixture of diastereoisomers as colorless oils (78.8 mg, 53%). **Major (±)-[1*S*,2*S*]**: IR (neat, cm^{-1}) 3445 (br), 2931 (s), 2858 (m), 2258 (s), 1603 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.93-4.86(m, 1H), 4.87-4.86 (m, 1H), 4.06 (q, *J*=7 Hz, 2H), 2.54 (s, 1H), 2.09 (dd, *J*=10.7 and 4.2 Hz, 1H), 2.00-1.96 (m, 1H), 1.85 (s, 3H), 1.75-1.58 (m, 5H), 1.45 (ddd, *J*= 12, 12 and 4 Hz, 1H), 1.35 (t, *J*=7 Hz, 3H), 1.22-1.15(m, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 145.1(C_{quat}), 114.3(CH_2), 94.7(C_{quat}), 74.1(C_{quat}), 69.9(C_{quat}), 56.3(CH), 41.2(CH_2), 39.7(CH_2), 28.5(CH_2), 25.6(CH_2), 23.9(CH_2), 21.0(CH_3), 14.3(CH_3); HRMS (EI) m/z calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1475.

There was not enough of the minor compound to characterize it.

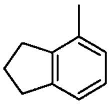


5-Methyl-1,2,3,4-tetrahydro-naphthalene (4.17)



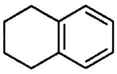
General procedure B was used for the benzannulation of substrate **4.16**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17** (40.2 mg, 84%) as a yellow oil. Characterization is available through the literature.[251]

4-Methyl-indan (4.17a)



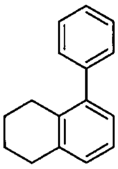
General procedure B was used for the benzannulation of substrate **4.16a**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded indan **4.17a** (11.3 mg, 28%) as a yellow oil. Characterization is available through the literature.[251]

1,2,3,4-Tetrahydro-naphthalene (4.17b)



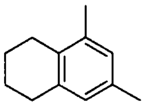
General procedure B was used for the benzannulation of substrate **4.16b**. Purification by flash chromatography (2% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17b** (11.2 mg, 10%) as a yellow oil. Characterization is available through the literature.[256]

5-Phenyl-1,2,3,4-tetrahydro-naphthalene(4.17c)



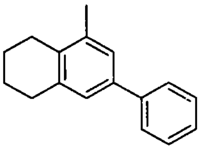
General procedure B was used for the benzannulation of substrate **4.16c**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17c** (46.4mg, 84%) as a yellow oil. Characterization is available through the literature.[256]

5,7-Dimethyl-1,2,3,4-tetrahydro-naphthalene (4.17d)



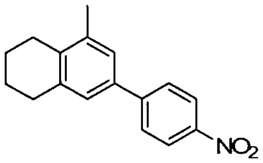
General procedure B was used for the benzannulation of substrate **4.16d**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17d** (48.2 mg, 77%) as a yellow oil. Characterization is available through the literature.[256]

5-Methyl-7-phenyl-1,2,3,4-tetrahydro-naphthalene (4.17e)



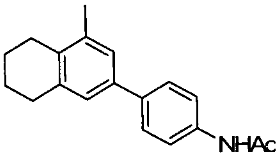
General procedure B was used for the benzannulation of substrate **4.16e**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17e** (28.7 mg, 86%) as a yellow oil.[257] IR (neat, cm^{-1}) 3030 (m), 2927 (s), 1599 (m), 1568 (m), 1473 (s), 1437 (m), 867 (m), 760 (s), 697 (s); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.58-7.55 (m, 2H), 7.42 (d, J=7.3 Hz, 1H), 7.39 (d, J=7.8 Hz, 1H), 7.32-7.17 (m, 3H), 2.83 (dd, J=6.0, 6.0 Hz, 2H), 2.67 (dd, J=6.0, 6.0 Hz, 2H), 2.28 (s, 3H), 1.91-1.76 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 141.5 (C$_{quat}$), 138.2 (C$_{quat}$), 137.6 (C$_{quat}$), 137.2 (C$_{quat}$), 134.9 (C$_{quat}$), 128.7 (CHx2), 127.1 (CHx2), 126.9 (CH), 126.0 (CH), 125.7 (CH), 30.4 (CH$_2$), 26.7 (CH$_2$), 23.5 (CH$_2$), 23.0 (CH$_2$), 19.8 (CH$_3$); HRMS (EI) m/z calcd for $C_{17}H_{18}$ [M$^+$] 222.1409, found 222.1397.

5-Methyl-7-(4-nitro-phenyl)-1,2,3,4-tetrahydro-naphthalene (4.17f)



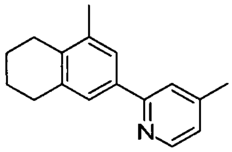
General procedure B was used for the benzannulation of substrate **4.16f**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17f** (29.2 mg, 73%) as a yellow solid. IR (neat, cm^{-1}) 2930 (m), 2858 (w), 1593 (m), 1514 (s), 1341 (s), 1109 (w), 845 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.24 (d, J=8.9 Hz, 2H), 7.70 (d, J=8.9 Hz, 2H), 7.23 (s, 1H), 7.19 (s, 1H), 2.84 (dd, J= 6.2, 6.2 Hz, 2H), 2.66 (dd, J=6.2, 6.2 Hz, 2H), 2.28 (s, 3H), 1.90-1.77 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 148.1 (C$_{quat}$), 146.9 (C$_{quat}$), 138.2 (C$_{quat}$), 137.8 (C$_{quat}$), 137.1 (C$_{quat}$), 135.7 (C$_{quat}$), 127.6 (CHx2), 126.1 (CH), 126.0 (CH), 124.2 (CHx2), 30.4 (CH$_2$), 26.8 (CH$_2$), 23.4 (CH$_2$), 22.9 (CH$_2$), 19.8 (CH$_3$); HRMS (EI) m/z calcd for $C_{17}H_{17}NO_2$ [M$^+$] 267.1259, found 267.1298; mp = 65.7-68.5 °C.

N-[4-(4-Methyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-phenyl]-acetamide (4.17g)



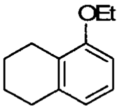
General procedure B was used for the benzannulation of substrate **4.16f**. Purification by flash chromatography (60% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.16g** (31.8 mg, 66%) as a white solid. IR (neat, cm^{-1}) 3251 (m), 2928 (m), 1663 (s), 1605 (m), 1543 (m), 830 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (s, 4H), 7.40 (br, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 2.81 (dd, *J*=5.9, 5.9Hz, 2H), 2.64 (t, *J*=6.1, 6.1 Hz, 2H), 2.25 (s, 3H), 2.18 (s, 3H), 1.85-1.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5 (C_{quat}), 137.7 (C_{quat}), 137.5 (C_{quat}), 137.5 (C_{quat}), 137.2 (C_{quat}), 136.9 (C_{quat}), 134.9 (C_{quat}), 127.5 (CHx2), 125.8 (CH), 125.4 (CH), 120.2 (CHx2), 30.3 (CH_2), 26.6 (CH_2), 24.8 (CH_3), 23.5 (CH_2), 23.0 (CH_2), 19.8 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{21}NO$ [M^+] 279.1623, found 279.1621; mp = 137.7-141.1 °C.

4-Methyl-2-(4-methyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-pyridine(4.17h)



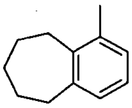
A modified general procedure B was applied in the case of alcohol **4.16h**: To a solution of alcohol **4.16h** (13.5 mg, 0.053 mmol) in dichloromethane (1 mL) was added PTSA (15.1 mg, 0.080 mmol). The mixture was stirred for 2 hours followed by cannulation of a mixture of AgOTf (1.4 mg, 0.0053 mmol) and Au(PPh_3)Cl (2.6 mg, 0.0053 mmol) in dichloromethane (1 mL). The reaction mixture was stirred for 4 days and quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with dichloromethane (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (30% ethyl acetate in hexanes) afforded **4.17h** as white solid (9.4 mg, 75% yield). IR (neat, cm^{-1}) 2926 (s), 2857 (m), 1598 (w), 1561 (w), 1469 (s), 1375 (w), 1027 (w), 828 (m); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (s, 1H), 7.59-7.55 (m, 2H), 7.51-7.49 (m, 2H), 2.83 (dd, *J*=6.3, 6.3 Hz, 2H), 2.64 (t, *J*=6.3, 6.3 Hz, 2H), 2.33 (s,3H), 2.27 (s, 3H), 1.87-1.82 (m, 2H), 1.80-1.74 (m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 155.3 (C$_{quat}$), 150.0 (CH), 137.7 (C$_{quat}$), 137.4 (CH), 137.1 (C$_{quat}$), 136.5 (C$_{quat}$), 136.3 (C$_{quat}$), 131.3 (C$_{quat}$), 125.4 (CH), 125.2 (CH), 120.0 (CH), 30.4 (CH$_2$), 26.9 (CH$_2$), 23.6 (CH$_2$), 23.1 (CH$_2$), 19.8 (CH$_3$), 18.3 (CH$_3$); HRMS (EI) m/z calcd for $C_{17}H_{19}N$ [M$^+$] 237.1517, found 237.1497; mp = 88.6-91.7 °C.

5-Ethoxy-1,2,3,4-tetrahydro-naphthalene(4.17i)



General procedure B was used for the benzannulation of substrate **4.16i**. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17i** (4.2 mg, 12%) as a yellow oil.[258] IR (neat, cm^{-1}) 2928 (s), 1586 (m), 1461 (s), 1335 (w), 1252 (s), 1086 (m); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.02 (dd, *J*=7.9, 7.9 Hz, 1H), 6.65 (d, *J*=7.5 Hz, 1H), 6.61 (d, *J*=7.9 Hz, 1H), 3.99 (q, *J*=7.0 Hz, 2H), 2.73 (dd, *J*=6.2, 6.2 Hz, 2H), 2.64 (dd, *J*=5.9, 5.9 Hz, 2H), 1.79-1.71 (m, 4H), 1.39 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 156.6 (C$_{quat}$), 138.3 (C$_{quat}$), 125.9 (C$_{quat}$), 125.4 (CH), 121.0 (CH), 107.6 (CH), 63.2 (CH$_2$), 29.5 (CH$_2$), 23.0 (CH$_2$), 22.7 (CH$_2$), 22.7 (CH$_2$), 14.8 (CH$_3$); HRMS (EI) m/z calcd for $C_{12}H_{16}O$ [M$^+$] 176.1201, found 176.1208.

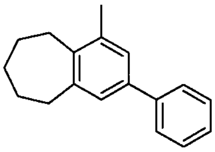
1-Methyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (4.17j)



General procedure B was used for the benzannulation of substrate **4.16j**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded benzannulated product **4.17j** (16.0 mg, 51%) as a yellow oil.[259] IR (neat, cm^{-1}) 3066 (w), 3019 (w), 2920 (s), 2849 (s), 1587 (w), 1466 (m), 1445 (m), 957 (w), 771 (m), 743 (m); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.05-6.85 (m, 3H), 2.80-2.75 (m, 4H), 2.29 (s, 3H), 1.83-1.77 (m, 2H), 1.65-1.53 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 144.0 (C$_{quat}$), 142.0 (C$_{quat}$), 135.1 (C$_{quat}$), 128.2 (CH), 127.1

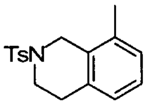
(CH), 125.5 (CH), 36.6 (CH_2), 32.7 (CH_2), 29.9 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 20.8 (CH_3); HRMS (EI) m/z calcd for $C_{12}H_{16}$ [M^+] 160.1252, found 160.1261.

1-Methyl-3-phenyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (4.17k)



General procedure B was used for the benzannulation of substrate **4.16k**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17k** (31.1 mg, 65%) as a yellow oil. IR (neat, cm^{-1}) 2919 (s), 2850 (m), 1603 (w), 1568 (w), 1474 (m), 1443 (m), 875 (m), 757 (s), 694 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60-7.57 (m, 2H), 7.43-7.39 (m, 2H), 7.33-7.28 (m, 1H), 7.24 (s, 1H), 7.21 (s, 1H), 2.89-2.84 (m, 4H), 2.39 (s, 3H), 1.90-1.84 (m, 2H), 1.72-1.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6 (C_{quat}), 141.4 (C_{quat}), 141.1 (C_{quat}), 138.4 (C_{quat}), 135.6 (C_{quat}), 128.7 (CHx2), 127.1 (CHx2), 126.9 (CHx2), 125.9 (CH), 36.8 (CH_2), 32.7 (CH_2), 29.8 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 20.9 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{20}$ [M^+] 236.1565, found 236.1579.

1,2,3,4-Tetrahydro-8-methyl-2-tosylisoquinoline (4.17l)

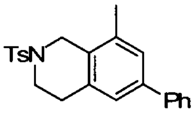


General procedure B was used for the benzannulation of substrate **4.16l**. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded benzannulated product **4.17l** (16.2 mg, 67%) as a white solid.

Mixture of atropoisomers: IR (neat, cm^{-1}) 2922 (w), 2852 (w), 1597 (w), 1461 (w), 1335 (m), 1165 (s), 1094 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, *J*=9.1, 8.4 Hz, 4H), 7.31 (dd, *J*=5.8, 2.1 Hz, 4H), 7.06-6.87 (m, 6H), 4.18 (s, 2H), 4.13 (s, 2H), 3.31 (ddd, *J*=7.1, 5.8, 1.2 Hz, 4H), 2.95-2.83 (m, 4H), 2.41 (s, 6H), 2.25 (s, 2.7 H), 2.16 (s, 3.3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 143.7 (C_{quat}), 143.6 (C_{quat}), 136.3 (C_{quat}), 134.6 (C_{quat}), 133.3 (2x C_{quat}), 133.0 (C_{quat}), 132.9 (C_{quat}), 130.1 (C_{quat}), 129.7 (2xCH), 129.7 (2xCH), 129.3 (CH), 128.6 (C_{quat}), 127.9 (CH), 127.8 (2xCH), 127.7 (2xCH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 126.2 (CH), 47.4 (CH_2), 45.8 (CH_2), 43.8 (CH_2), 43.3 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 21.5

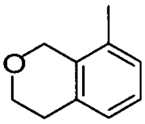
(2xCH_3), 21.0 (CH_3), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{19}NO_2S$ (M^+) 301.1137, found 301.1142; mp = 119.0-123.4 °C.

8-Methyl-6-phenyl-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline (4.17m)



General procedure B was used for the benzannulation of substrate **4.16m**. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17m** (18.2 mg, 67%) as a beige solid. IR (neat, cm^{-1}) 2910(m), 2830(w), 1605(w), 1450(w), 1340(m), 1164(s), 1098(m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75-7.73(m, 2H), 7.52-7.50(m, 2H), 7.41-7.37(m, 2H), 7.33-7.30(m, 3H), 7.21(s, 1H), 7.14(s, 1H), 4.16(s, 2H), 3.35(dd, *J*=5.8, 5.8Hz, 2H), 2.98(dd, *J*=5.7, 5.7Hz, 2H), 2.41(s, 3H), 2.23(s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 143.7(C_{quat}), 140.7(C_{quat}), 139.5(C_{quat}), 135.1(C_{quat}), 133.5(C_{quat}), 133.4(C_{quat}), 129.8(2xCH), 129.3(C_{quat}), 128.7(2xCH), 127.7(2xCH), 127.3(CH), 127.0(2xCH), 126.8(CH), 125.2(CH), 45.7(CH_2), 43.4(CH_2), 29.5(CH_2), 21.5(CH_3), 18.8(CH_3); HRMS (EI) m/z calcd for $C_{23}H_{23}NO_2S$ (M^+) 377.1450, found 377.1442; mp = 52.7-55.1 °C.

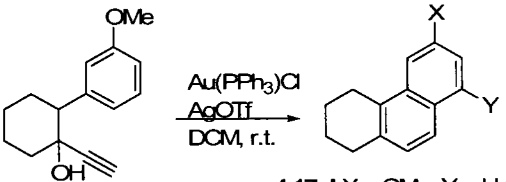
8-Methyl-isochroman (4.17n)



General procedure B was used for the benzannulation of substrate **4.16n**. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17n** (5.0 mg, 51%) as a beige solid. IR (neat, cm^{-1}) 2927 (br), 2855 (m), 1725 (m), 1264 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (dd, *J*=7.5, 7.5 Hz, 1H), 6.98-6.95 (m, 2H), 4.71 (s, 2H), 3.93 (t, *J*=5.6 Hz, 2H), 2.85 (t, *J*=5.6 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 133.5 (C_{quat}), 133.2 (C_{quat}), 133.1 (C_{quat}), 127.6 (CH), 126.6 (CH), 126.1 (CH), 66.5 (CH_2), 64.9 (CH_2), 28.7 (CH_2), 17.8(CH_3); HRMS (EI) m/z calcd for $C_{10}H_{12}O$ (M^+) 148.0888, found 148.0883.

4.16o 4.17o

6,7,8,9-Tetrahydro-naphtho[1,2-b]furan(4.17o). General procedure B was used for the benzannulation of substrate **4.16o**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17o** (18.6 mg, 57%) as an orange oil.[260] IR (neat, cm^{-1}) 2930 (s), 2857 (m), 1492 (m), 1312 (s), 1129 (m), 1031 (m), 803 (s), 733(s); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.55 (d, *J*=2.1 Hz, 1H), 7.31 (d, *J*=7.9 Hz, 1H), 6.96 (d, *J*=7.9Hz, 1H), 6.69 (d, *J*=2.1 Hz, 1H), 2.98 (dd, *J*=11.0, 11.0 Hz, 2H), 2.85 (t, *J*=10.6, 10.6 Hz, 2H), 1.90-1.75 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 153.8 (C$_{quat}$), 144.1 (CH), 133.5 (C$_{quat}$), 124.3 (C$_{quat}$), 124.2 (CH), 121.2 (C$_{quat}$), 117.9 (CH), 106.7 (CH), 29.3 (CH$_2$), 23.4 (CH$_2$), 22.9 (CH$_2$), 22.6 (CH$_2$); HRMS (EI) m/z calcd for C$_{12}$H$_{12}$O [M$^+$] 172.0888, found 172.0887.



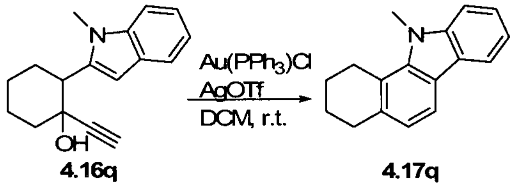
4.16p

4.17pI X = OMe, Y = H (1.5)
4.17pII X = H, Y = OMe (1)

6-Methoxy-1,2,3,4-tetrahydro-phenanthrene (4.17pI) and 8-Methoxy-1,2,3,4-tetrahydro-phenanthrene(4.17pII) General procedure B was used for the benzannulation of substrate **4.16p** however the reaction mixture was heated to reflux for 18 hours in order for the reaction to go to completion. Purification by flash chromatography (2.5% ethyl acetate/hexanes) afforded tetrahydrophenanthrenes **4.17pI** and **4.17pII** (I:II is 1.5:1) as a yellow oil (24.8 mg, 76%).[261] Characterized as a mixture of both isomers:

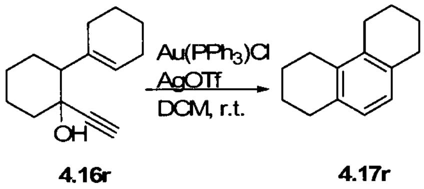
IR (neat, cm^{-1}) 2930 (s), 2857 (m), 1626 (m), 1512 (m), 1391 (m), 1223 (s), 832 (m), 783 (m); **Major (4.17pI):** ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.69 (d, *J*=8.9 Hz, 1H), 7.53 (d, *J*=8.6 Hz, 1H), 7.21 (d, *J*=2.4 Hz, 1H), 7.09 (dd, *J*=8.9, 2.5 Hz, 1H), 7.06 (d, *J*=8.3 Hz, 1H), 3.91 (s, 3H), 3.03 (dd, *J*=6.3, 6.3 Hz, 2H), 2.90 (dd, *J*=6.0, 6.0 Hz, 2H), 1.99-1.83 (m, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 157.9 (C$_{quat}$), 135.1 (C$_{quat}$), 133.8 (C$_{quat}$), 130.4 (C$_{quat}$), 130.0 (CH), 127.5 (C$_{quat}$), 126.1 (CH), 125.5 (CH), 116.8 (CH), 102.1 (CH), 55.4 (CH$_3$), 30.7

(CH_2), 26.0 (CH_2), 23.5 (CH_2), 23.1 (CH_2); **Minor (4.17pII):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, *J*=8.6 Hz, 1H), 7.53 (d, *J*=8.6 Hz, 1H), 7.38 (dd, *J*=8.6, 7.7 Hz, 1H), 7.18 (d, *J*=8.7 Hz, 1H), 6.78 (d, *J*=7.7 Hz, 1H), 3.98 (s, 3H), 3.08 (t, *J*=5.7 Hz, 2H), 2.90 (t, *J*=6.0Hz, 2H), 1.99-1.83 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.0 (C_{quat}), 135.0 (C_{quat}), 133.8 (C_{quat}), 131.4 (C_{quat}), 127.6 (CH), 125.9 (CH), 124.1 (C_{quat}), 119.5 (CH), 115.4 (CH), 103.2 (CH), 55.7 (CH_3), 30.6 (CH_2), 26.2 (CH_2), 23.5 (CH_2), 23.0 (CH_2); HRMS (EI) m/z calcd for $C_{15}H_{16}O$ [M^+] 212.1201, found 212.1198.



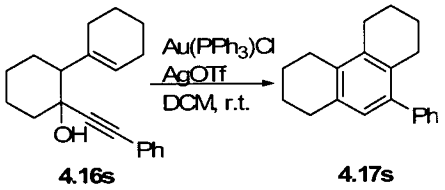
11-Methyl-2,3,4,11-tetrahydro-1*H*-benzo[a]carbazole (4.17q)

General procedure B was used for the benzannulation of substrate **4.16q.** Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17q** (12.2 mg, 81%) as a white solid. IR (neat, cm^{-1}) 2919(m), 2857(w), 1467(s), 1403(s), 745(s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04(d, *J*=7.7Hz, 1H), 7.86(d, *J*=7.9Hz, 1H), 7.48-7.36(m, 2H), 7.22(t, *J*=7.7Hz, 1H), 6.98(t, *J*=8.0Hz, 1H), 4.15(s, 3H), 3.43(t, *J*=5.6Hz, 2H), 3.02(t, *J*=6.1Hz, 2H), 1.99-1.85(m, 4H); ^{13}C NMR ($CDCl_3$, 100MHz) δ141.9(C_{quat}), 140.0(C_{quat}), 135.4(C_{quat}), 124.9(CH), 123.1(C_{quat}), 121.4(CH), 121.3(C_{quat}), 120.6(C_{quat}), 119.5(CH), 118.8(CH), 117.5(CH), 108.6(CH), 33.2(CH_3), 30.7(CH_2), 26.9(CH_2), 23.6(CH_2), 22.8(CH_2); HRMS (EI) m/z calcd for $C_{17}H_{17}N$ (M^+) 235.1361, found 235.1361; mp = 149.3-150.2 °C.

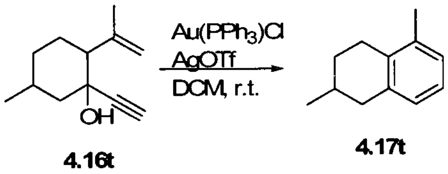


1,2,3,4,5,6,7,8-Octahydro-phenanthrene (4.17r)

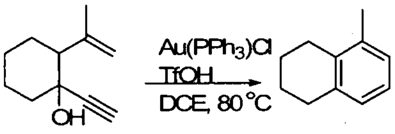
General procedure B was used for the benzannulation of substrate **4.16r**. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17r** (33.3 mg, 70%) as a yellow oil. Characterization is available through the literature.[262]



9-Phenyl-1,2,3,4,5,6,7,8-octahydro-phenanthrene (4.17s). General procedure B was used for the benzannulation of substrate **4.16s.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17s** (37.5 mg, 81%) as a yellow oil.[263] IR (neat, cm^{-1}) 2926 (s), 2857 (m), 1598 (w), 1496 (w), 1441 (w), 695 (m); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.39-7.28 (m, 5H), 6.83 (s, 1H), 2.77 (dd, *J*=6.2, 6.2 Hz, 2H), 2.65-2.55 (m, 6H), 1.87-1.75 (m, 6H), 1.66-1.61 (m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 142.4 (C$_{quat}$), 139.6 (C$_{quat}$), 135.8 (C$_{quat}$), 134.8 (C$_{quat}$), 134.3 (C$_{quat}$), 132.1 (C$_{quat}$), 129.5 (CHx2), 128.1 (CH), 128.0 (CHx2), 126.6 (CH), 30.1 (CH$_2$), 29.0 (CH$_2$), 27.0 (CH$_2$), 26.5 (CH$_2$), 23.7 (CH$_2$), 23.3 (CH$_2$), 23.1 (CH$_2$), 22.9 (CH$_2$); HRMS (EI) m/z calcd for $C_{20}H_{22}$ [M$^+$] 262.1721, found 262.1752.



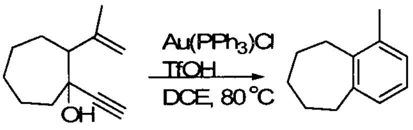
2,5-Dimethyl-1,2,3,4-tetrahydro-naphthalene(4.17t). General procedure B was used for the benzannulation of substrate **4.16t.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17t** (72.6 mg, 74%) as a yellow oil. IR (neat, cm^{-1}) 2917(s), 1587(m), 1455(s), 764 (s); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.04-6.92(m, 3H), 2.83-2.73(m, 2H), 2.63-2.54(m, 1H), 2.43 (dd, *J*=16.3, 10.8 Hz, 1H), 2.22 (s, 3H), 1.98-1.92 (m, 1H), 1.84-1.80 (m, 1H), 1.45-1.35 (m, 1H), 1.05 (d, *J*=6.6Hz, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ136.9(C$_{quat}$), 136.4(C$_{quat}$), 135.2(C$_{quat}$), 127.0(CH), 126.9(CH), 125.2(CH), 38.8(CH$_2$), 31.7(CH$_2$), 28.8(CH), 27.8(CH$_2$), 21.9(CH$_3$), 19.6(CH$_3$); HRMS (EI) m/z calcd for $C_{12}H_{16}$ (M$^+$) 160.1252, found 160.1277.



4.16 **4.17**

5-Methyl-1,2,3,4-tetrahydro-naphthalene (4.17)

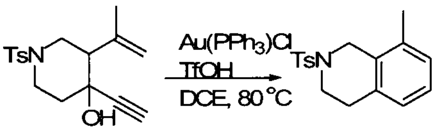
General procedure C was used for the benzannulation of substrate **4.16.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17** (16.9 mg, 48%) as a yellow oil. Characterization already mentioned, see above.



4.16j **4.17j**

1-Methyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (4.17j)

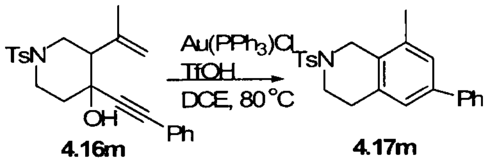
General procedure C was used for the benzannulation of substrate **4.16j.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded benzannulated product **4.17j** (12.0 mg, 68%) as a yellow oil. Characterization already mentioned, see above.



4.16l **4.17l**

1,2,3,4-Tetrahydro-8-methyl-2-tosylisoquinoline (4.17l)

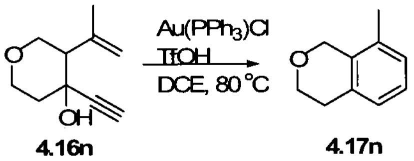
General procedure C was used for the benzannulation of substrate **4.16l.** Purification by flash chromatography (10% ethyl acetate/hexanes) afforded benzannulated product **4.17l** (41.5 mg, 65%) as a white solid. Characterization already mentioned, see above.



4.16m **4.17m**

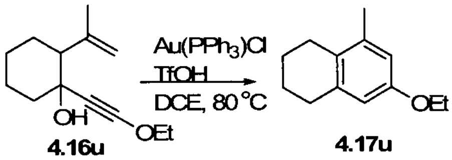
8-Methyl-6-phenyl-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline (4.17m)

General procedure C was used for the benzannulation of substrate **4.16m.** Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17m** (20.0 mg, 56%) as a beige solid. Characterization already mentioned, see above.



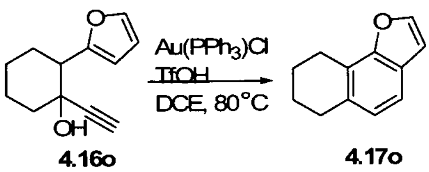
8-Methyl-isochroman (4.17n)

General procedure C was used for the benzannulation of substrate **4.16n.** Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17n** (12.7 mg, 62%) as a beige solid. Characterization already mentioned, see above.



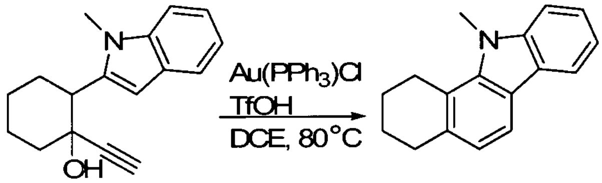
7-Ethoxy-5-methyl-1,2,3,4-tetrahydronaphthalene (4.17u)

General procedure C was used for the benzannulation of substrate **4.16u.** Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17u** (5.7 mg, 51%) as a colorless oil. IR (neat, cm^{-1}) 2925 (br), 2857 (m), 1607 (m), 1477 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.55 (bs, 1H), 6.45 (bs, 1H), 3.97 (q, *J*=7 Hz, 2H), 2.70 (dd, *J*=5.6 Hz, 2H), 2.52 (dd, *J*=5.6 Hz, 2H), 2.15 (s, 3H), 1.83-1.67 (m, 4H), 1.35 (t, *J*=7 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 138.1 (C$_{quat}$), 128.2 (C$_{quat}$), 114.5 (CH), 112.3 (CH), 63.6 (CH$_2$), 30.9 (CH$_2$), 26.4 (CH$_2$), 24.0 (CH$_2$), 23.4 (CH$_2$), 20.1 (CH$_3$), 15.3(CH$_3$); HRMS (EI) m/z calcd for $C_{13}H_{18}O$ (M$^+$) 190.1358, found 190.1353.



6,7,8,9-Tetrahydro-naphtho[1,2-b]furan(4.17o)

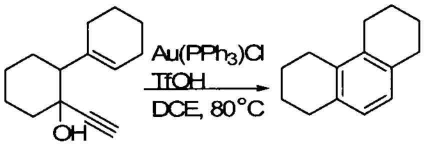
General procedure C was used for the benzannulation of substrate **4.16o.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17o** (15.5 mg, 64%) as an orange oil. Characterization already mentioned, see above.



4.16q **4.17q**

11-Methyl-2,3,4,11-tetrahydro-1*H*-benzo[a]carbazole (4.17q)

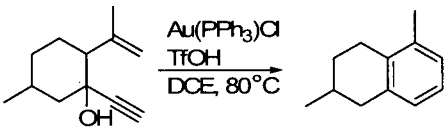
General procedure C was used for the benzannulation of substrate **4.16q.** Purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17q** (21.6 mg, 76%) as a white solid. Characterization already mentioned, see above.



4.16r **4.17r**

1,2,3,4,5,6,7,8-Octahydro-phenanthrene (4.17r)

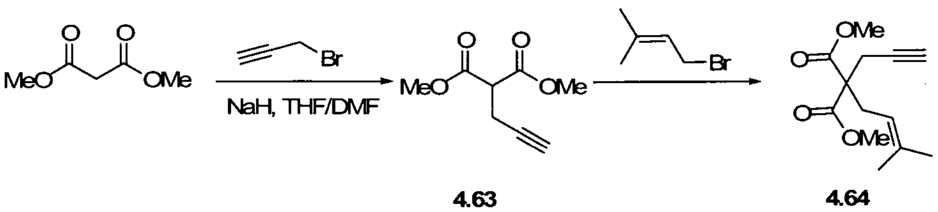
General procedure C was used for the benzannulation of substrate **4.16r.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17r** (16.7 mg, 82%) as a yellow oil. Characterization already mentioned, see above.



4.16t **4.17t**

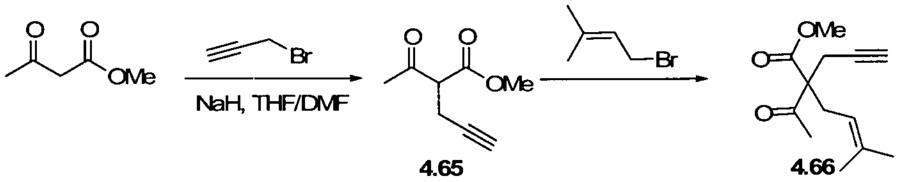
2,5-Dimethyl-1,2,3,4-tetrahydro-naphthalene (4.17t)

General procedure C was used for the benzannulation of substrate **4.16t.** Purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **4.17t** (67.5 mg, 82%) as a yellow oil. Characterization already mentioned, see above.



2-(3-Methyl-but-2-enyl)-2-prop-2-ynyl-malonic acid dimethyl ester (4.64)

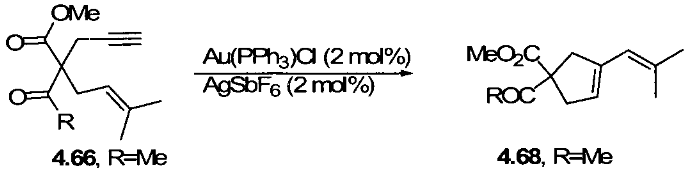
Compound was synthesized by the method reported by Echavarren.[230]



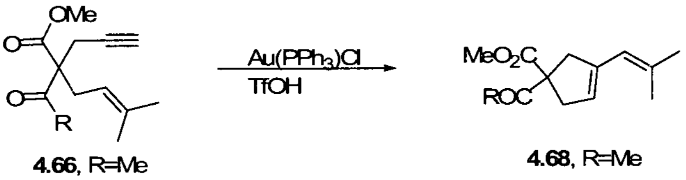
2-Acetyl-5-methyl-2-prop-2-ynyl-hex-4-enoic acid methyl ester (4.66). NaH (0.465g, 11.6 mmol) was added to a flame-dried flask containing 18.5 mL of THF. Once this solution had been cooled to 0°C, methyl acetoacetate (1.20 mL, 11.1 mmol) was added dropwise. The resulting mixture was then stirred at room temperature for an hour before distilled propargyl bromide (1.35 mL, 12.2 mmol) was added. At that point, the resulting solution was stirred at room temperature until completion by TLC. The reaction was quenched with NH_4Cl and the mixture was extracted with ether (3X). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Cs_2CO_3 (5.43 g, 16.6 mmol) was added to a flame-dried flask in the glovebox. A solution of **4.65** (crude) in acetone (42.6 mL) was cannulated into the flask. After stirring the solution for 10 minutes, 3,3-dimethyl-allylbromide (2.56 mL, 22.2 mmol) was added dropwise. The resulting mixture is then stirred until completion by TLC. Once completed, the solution was filtered through celite, then concentrated *in vacuo*. Purification by flash chromatography (6:1 pet ether/ether) afforded **4.66** (539.3 mg, 28%) as a colorless oil.

IR (neat, cm^{-1}) 3286 (s), 2955 (m), 2919 (m), 1746 (s), 1715 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.79-4.75 (dd, *J*=7.6Hz, *J*=7.6Hz, 1H), 3.70 (s, 3H), 2.78-2.64 (m, 2H), 2.68-2.66 (dd, *J*=2.6Hz, 2H), 2.12 (s, 3H), 1.96-1.94 (dd, *J*=2.7Hz, *J*=2.7Hz, 1H), 1.64 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 202.9 (C_{quat}), 171.2 (C_{quat}), 136.9 (C_{quat}), 116.8 (CH), 79.5 (C_{quat}), 71.3 (CH), 63.0 (C_{quat}), 52.7 (CH), 30.1 (CH_2), 26.5 (CH_3), 26.0 (CH_3), 21.6

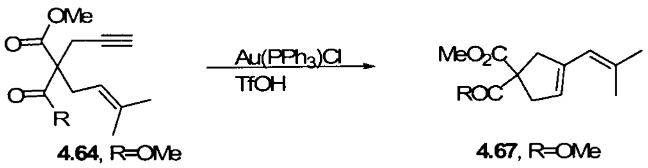
(CH$_2$), 18.0 (CH$_3$); HRMS (EI) m/z calcd for $C_{13}H_{18}O_3$ (H^+-$C_2H_3O_2$) 163.1123, found 163.1125.



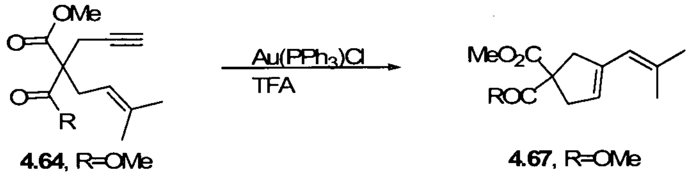
1-Acetyl-3-(2-methyl-propenyl)-cyclopent-3-enecarboxylic acid (4.68). General procedure B was used for the cycloisomerization of **4.66**. Purification by flash chromatography (6:1 pet ether/ether) afforded the cycloisomerized product **4.68** (21.8 mg, 81%) as a colorless liquid. IR (neat, cm^{-1}) 2921 (m), 1743 (s), 1714 (s), 1354 (m); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.68 (s, 1H), 5.33 (s, 1H), 3.72 (s, 3H), 3.07-3.07 (d, J=1.7Hz, 2H), 3.00-2.86 (m, 2H), 2.15 (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 202.9 (C$_{quat}$), 173.4 (C$_{quat}$), 138.7 (C$_{quat}$), 135.8 (C$_{quat}$), 124.3 (CH), 120.6 (CH), 65.8 (C$_{quat}$), 52.8 (CH$_3$), 41.6 (CH$_2$), 38.8 (CH$_2$), 27.3 (CH$_3$), 25.9 (CH$_3$), 19.9 (CH$_3$); HRMS (EI) m/z calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1237.



1-Acetyl-3-(2-methyl-propenyl)-cyclopent-3-enecarboxylic acid (4.68). General procedure C was used for the cycloisomerization of **4.66**. However, the reaction was done at room temperature. Purification by flash chromatography (6:1 pet ether/ether) afforded **4.68** (25.4 mg, 60%) as a colorless liquid. Characterization was reported previously (see above).

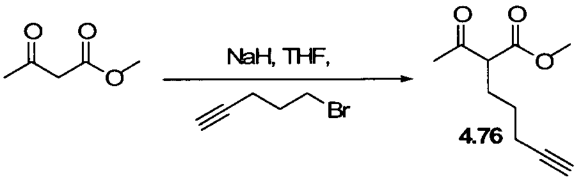


3-(2-Methyl-propenyl)-cyclopent-3-ene-1,1-dicarboxylic acid dimethyl ester (4.67). General procedure C was used for the cycloisomerization of **4.64**. However, the reaction was performed with 2.5 mol% of each, Au(PPh$_3$)Cl and TfOH and the reaction was done at room temperature. Purification by flash chromatography (20% ether/80% petroleum ether) afforded diene **4.67** (22.0 mg, 70%). Characterization was available through the literature.[230]

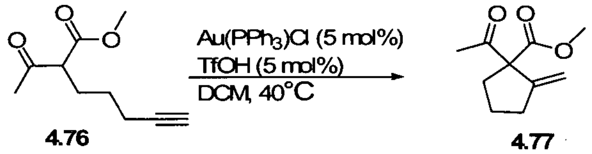


3-(2-Methyl-propenyl)-cyclopent-3-ene-1,1-dicarboxylic acid dimethyl ester (4.67). *washed all glassware in base bath*

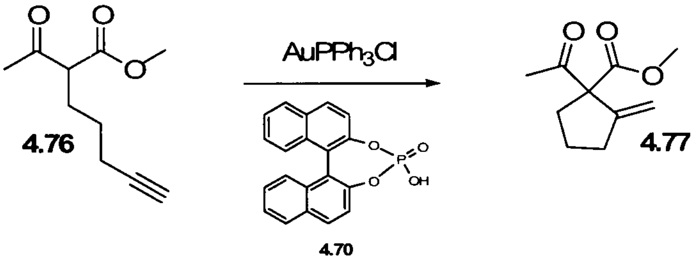
Au(PPh$_3$)Cl (2.0 mg, 0.004 mmol) was weighed in the glovebox in a reaction flask. Then, a solution of **4.64** (20.0 mg, 0.084 mmol) in DCM (1.5 mL) was cannulated to the reaction flask. Trifluoroacetic acid (0.47 mg, 0.004 mmol-made a solution) was then added. The mixture was then cannulated into a sealed tube and stirred overnight at 40 °C. The mixture was cooled to room temperature and quenched with NaHCO$_3$. The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. A crude NMR indicated a 100% conversion. Purification by flash chromatography (5% ether /petroleum ether) afforded the desired compound **4.67** (3.2 mg, 16%). Characterization was available through the literature.[230]



2-Acetyl-hept-6-ynoic acid methyl ester (4.76). THF (7.0mL) was added to a flame-dried flask already containing NaH (0.204 g, 5.10 mmol) and the resulting solution was cooled to -10 °C. After stirring for a few minutes, methyl acetoacetate (0.580 mL, 5.37 mmol) was added dropwise and the new solution was stirred at room temperature for an hour. At that point, bromoalkyne (1.13 g, 5.37 mmol) in THF (2.0 mL) was cannulated into the solution and the mixture was refluxed until completion by TLC. The reaction was quenched with a saturated solution of ammonium chloride at room temperature and the aqueous layer was extracted with ether (3X). The organic layers were combined and washed with brine, dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded the desired compound **4.76** (232.0 mg, 24%). Characterization was available through the literature.[235]



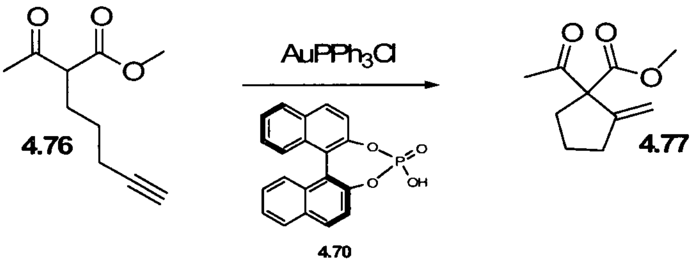
1-Acetyl-2-methylene-cyclopentanecarboxylic acid methyl ester (4.77). Using general procedure C with 2.5 mol% of each catalyst and refluxing in dichloromethane at 40 °C. Purification by flash chromatography (20% ether/80% petroleum ether) afforded **4.77** (20.4 mg, 70%). Characterization was available through the literature.[235]



1-Acetyl-2-methylene-cyclopentanecarboxylic acid methyl ester (4.77).

washed all glassware in base bath

Au(PPh$_3$)Cl (2.7 mg, 0.006 mmol) was weighed in the glovebox in a reaction flask. Then, a solution of **4.76** (20.0 mg, 0.110 mmol) in DCM (2.2 mL) was cannulated to the reaction flask. 1,1'-Binaphthyl-2,2'-diylhydrogenphosphate (1.9 mg, 0.006 mmol) was then added. The mixture was then cannulated into a sealed tube and stirred overnight at 40 °C. The mixture was cooled to room temperature and quenched with NaHCO$_3$. The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded the desired compound **4.77** (5.4 mg, 27%). Characterization was available through the literature.[235]



1-Acetyl-2-methylene-cyclopentanecarboxylic acid methyl ester (4.77).

washed all glassware in base bath

Au(PPh$_3$)Cl (13.5 mg, 0.027 mmol) was weighed in the glovebox in a reaction flask. Then, a solution of **4.76** (100.0 mg, 0.549 mmol) in DCM (2.2 mL) was cannulated to the reaction flask. (S)-1,1'-Binaphthyl-2,2'-diylhydrogenphosphate (9.5 mg, 0.027 mmol) was then added. The mixture was then cannulated into a sealed tube and stirred overnight at 40 °C. The mixture was cooled to room temperature and quenched with NaHCO$_3$. The mixture was extracted with DCM (3X) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (10% ethyl acetate/hexanes) afforded the desired compound **4.77** (30.5 mg, 31%). Characterization was available through the literature.[235]

Glossary of Abbreviations

Ac	acetate
BBN	borabicyclo[3.3.1]nonane
BHT	butylated hydroxytoluene, 2,6-di-*tert*-butyl-4-methylphenol
BRSM	based on recovered starting material
Bn	benzyl
Bu	butyl
BuLi	*n*-butyllithium
c	crown (as 18-crown-6)
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H	diisobutylaluminumhydride
DIPEA	*N,N,N*-diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
DMSO	dimethylsulfoxide
DPPB	1,4-(diphenylphosphino)butane
dr	diastereomeric ratio
DTBMP	2,6-di-*t*-butyl-4-methylpyridine
ent	enantiomer
equiv	equivalents
Et	ethyl
HDDA	hydroxy-directed Diels-Alder

HMBC	heteronuclear multiple bond
HMDS	hexamethyldisilazane or bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectrum
imid.	imidazole
LDA	lithiumdiisopropylamide
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
MOP	1-methyl-1-methoxyethyl ether
mp	melting point
ms	molecular sieves
NMO	*N*-methylmorpholine-*N*-oxide
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
O^tBu	*tert*-butoxide
OTf	trifluoromethylsulfonate
OTs	toluenesulfonate
PCC	pyridiniumchlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PIDA	phenyl iodide diacetate
Piv	pivaloyl $(CH_3)_3C\text{-}CO$
PMB	*para*-methoxybenzyl
PNB	*para*-nitrobenzoyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
py	pyridine
quant.	quantitative yield (i.e. >98%)
RT	room temperature

SM	starting material
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethyl silyl
t-BuLi	*tert*-butyllithium
TES	triethyl silyl
Tf	trifluoromethanesulfonic
TFA	trifluoroacetic acid
TLC	Thin-layer chromatography
TMEDA	tetramethylethylenediamine
THF	tetrahydrofuran
TMA	trimethylaluminum
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Electronic supporting information

1. Proton and Carbon spectra of all new compounds

2. X-ray data

3. Computational data

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