Formal Synthesis of Vinigrol and Efforts towards the Total Synthesis of Digitoxigenin

by

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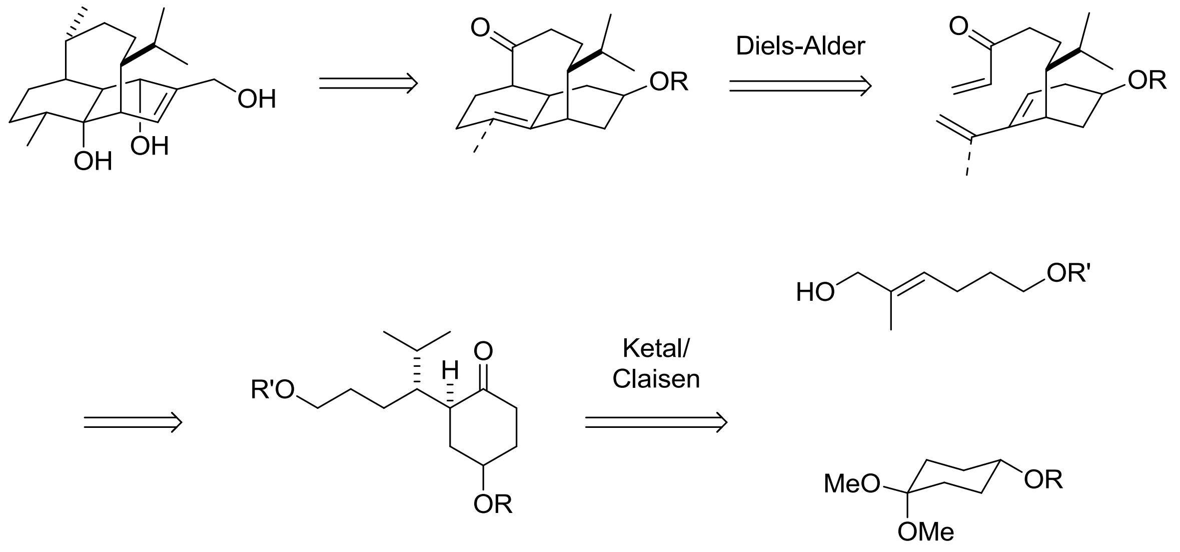
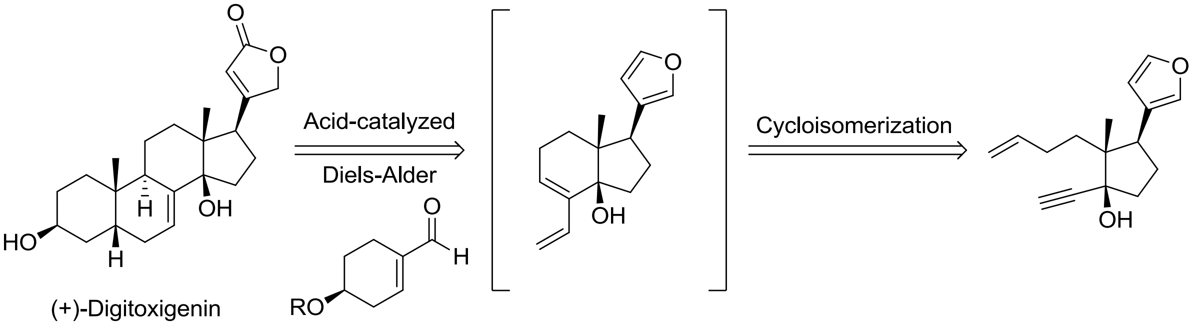
Abstract

Vinigrol was isolated in 1987 from the fungal strain *Virgaria nigra* F-5408 by Hashimoto and co-workers. This compound was identified as having antihypertensive and platelet aggregation properties as well as being recognized as a tumor necrosis factor inhibitor. Aside from its interesting biological activities, vinigrol also possesses a unique structural motif consisting in a decahydro-1,5-butanonaphthalene core decorated with 8 contiguous stereocenters. Despite synthetic efforts by many research groups since its isolation, it wasn't until 2009 that the first total synthesis of vinigrol was reported by Baran and co-workers. Herein is presented a formal synthesis of this highly compact molecule which relies upon a highly diastereoselective ketal Claisen rearrangement as the stereodefining step and an intramolecular Diels-Alder reaction to access the tricyclic structure of the molecule.



(+)-Digitoxigenin is a cardiac glycoside used in the treatment of many ailments such as congestive heart failure. It is a member of the cardenolides, a sub-type of steroid

containing certain structural differences such as cis A/B and C/D ring junctions, a tertiary hydroxyl group at C14 and a butenolide substituent at C17. Although a few syntheses of this class of compounds have been reported, general strategies to access their framework is scarce. Herein we report our studies towards the total synthesis of digitoxigenin which rely upon a cascading gold-catalyzed cycloisomerization (or enyne metathesis)/Diels-Alder reaction.



Acknowledgements

Such an endeavour would not have been possible without the much appreciated help and support of the people surrounding me. First and foremost, I would like to thank Prof. Louis Barriault for allowing me to conduct cutting edge research as a part of his laboratory. His guidance and mentorship were an integral part of my studies and the independence which he grants his students fully promotes the development of autonomy and personal scientific thought.

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There are some members from other labs that also had an impact on me, such as Isabelle from the Beauchemin lab. She has always been a great friend, ever since undergrad and I'm sad to see that our paths have now diverged. I would also like to thank Dave and David from the Fagnou group for lending out chemicals and helpful discussions. I wish all of them lots of happiness throughout their lives.

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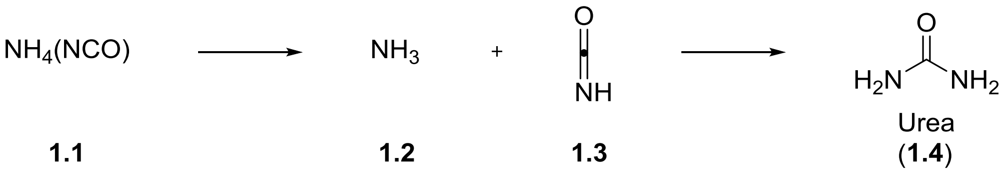
Chapter 1

Introduction

Total Synthesis

With the widespread advancements in the fields of inorganic and organic chemistry throughout the 18th and 19th centuries, organic chemists began turning their attention from strictly investigating novel chemical reactions to applying them towards the synthesis of natural products. Friedrich Wohler is credited with the first of these syntheses when he discovered the formation of urea (**1.4**) from ammonium isocyanate (**1.1**) in 1828 (***Scheme 1.1***).[1]

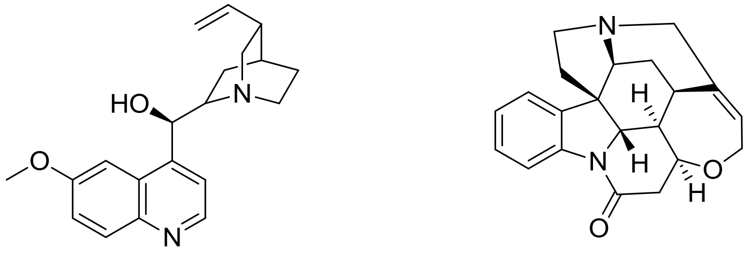
Scheme 1.1 *– Conversion of ammonium cyanate to urea*



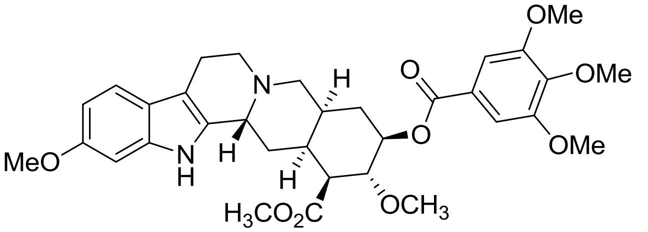
1.1 **1.2** **1.3** (**1.4**)

From that point to the beginning of the 20th century, organic chemists tackled a wide variety of natural product targets with gradually increasing structural complexity. However, throughout the 1940's began a quantum leap in molecular complexity with the research conducted by Prof. Robert Woodward's group at Harvard. Well-planned routes coupled with persistence allowed the group to synthesize targets that, until then, chemists believed unattainable. Such targets included quinine (**1.5**),[2] strychnine (**1.6**)[3] and reserpine (**1.7**)[4] (***Figure 1.1***).

Figure 1.1 *– Complex natural products synthesized by the Woodward group*

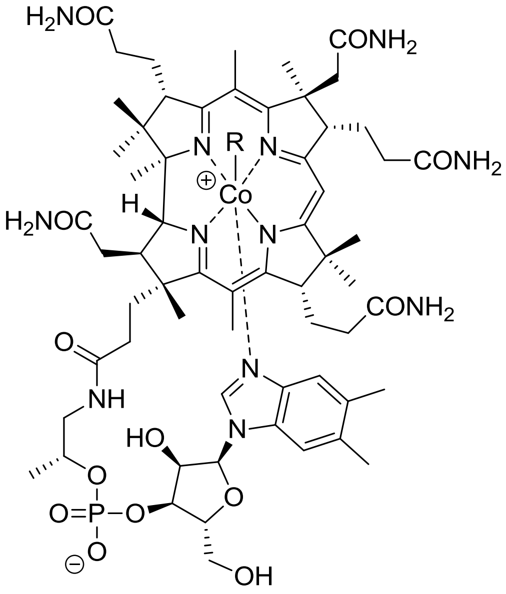

Quinine
(**1.5**)

Strychnine
(**1.6**)


Reserpine
(**1.7**)

Finally, in 1973, in collaboration with the Eschenmoser group, Woodward et al. reported the total synthesis of vitamin B_{12} **(1.8)** in almost 100 steps from commercially available materials (***Figure 1.2***).[5] Although this feat required contributions from nearly 100 students and post-docs, it established that given enough time and resources, any naturally occurring compound could succumb to chemical synthesis. Woodward eventually received the Nobel Prize for his contributions in 1965.

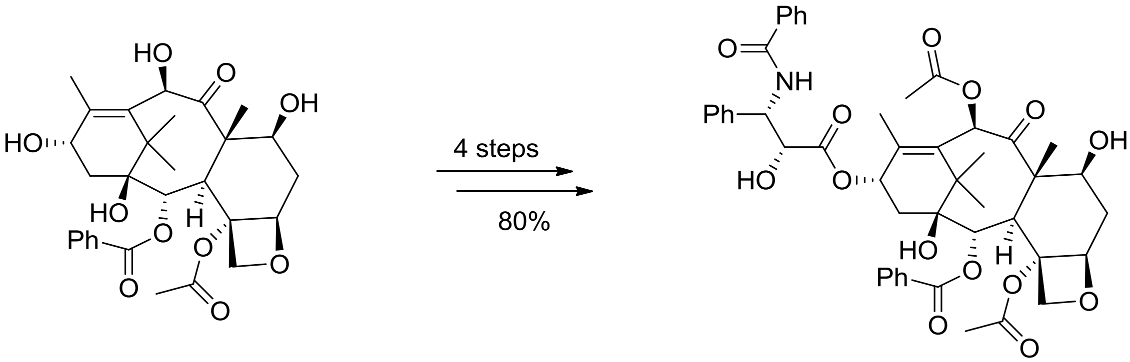
Figure 1.2 *– Structure of vitamin B_{12}*



Vitamin B_{12} (**1.8**)
R = CN

Since then, organic chemistry has continued to evolve, especially through the development of enantioselective reactions and their application to the total synthesis of natural products. Although total synthesis has often been used to validate the structure and stereochemistry of newly isolated natural products, it can also lead to applications in medicine for the treatment of a variety of diseases, such as cancer. A demonstration of both the synthesis of a difficult target and its application in medicine is the example of taxol (**1.10**) (***Scheme 1.2***). Although syntheses of this target have been accomplished from simple building blocks,[6] **1.10** is now prepared industrially in 80% yield through a 4-step semi-synthetic route from 10-deacetylbaccatin III (**1.9**), which is isolated from the needles of the Pacific Yew tree.[7]

***Scheme 1.2** – Industrial preparation of taxol from 10-deacetylbaccatin III*



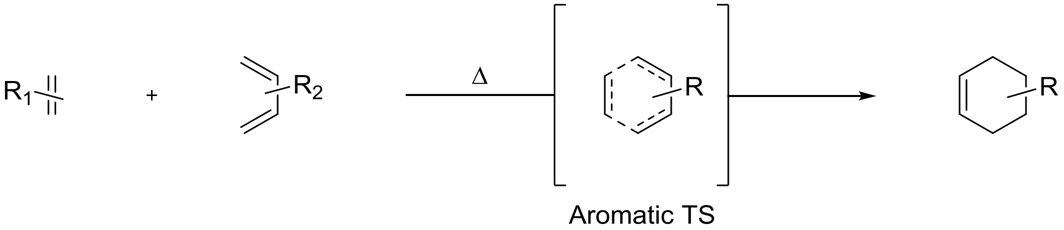
10-Deacetylbaccatin III
(**1.9**)

Taxol
(**1.10**)

The Diels-Alder Reaction

Organic chemistry and total synthesis would not have evolved into such impressive fields without the advent of key chemical reactions throughout their history. One notable example of this is the Diels-Alder reaction, which allows the formation of cyclohexene rings (**1.14**) from the combination of a conjugated diene (**1.12**) and an alkene (**1.11**), also referred to as the dienophile (***Scheme 1.3***). The relative ease with which the reaction takes place can be attributed to a highly stabilized aromatic transition state (**1.13**), in which all six π electrons are delocalized. Otto Diels and Kurt Alder performed extensive studies on the reaction starting in 1928 for which they received the Nobel Prize in 1950.[8,9]

Scheme 1.3 *– The Diels-Alder reaction*

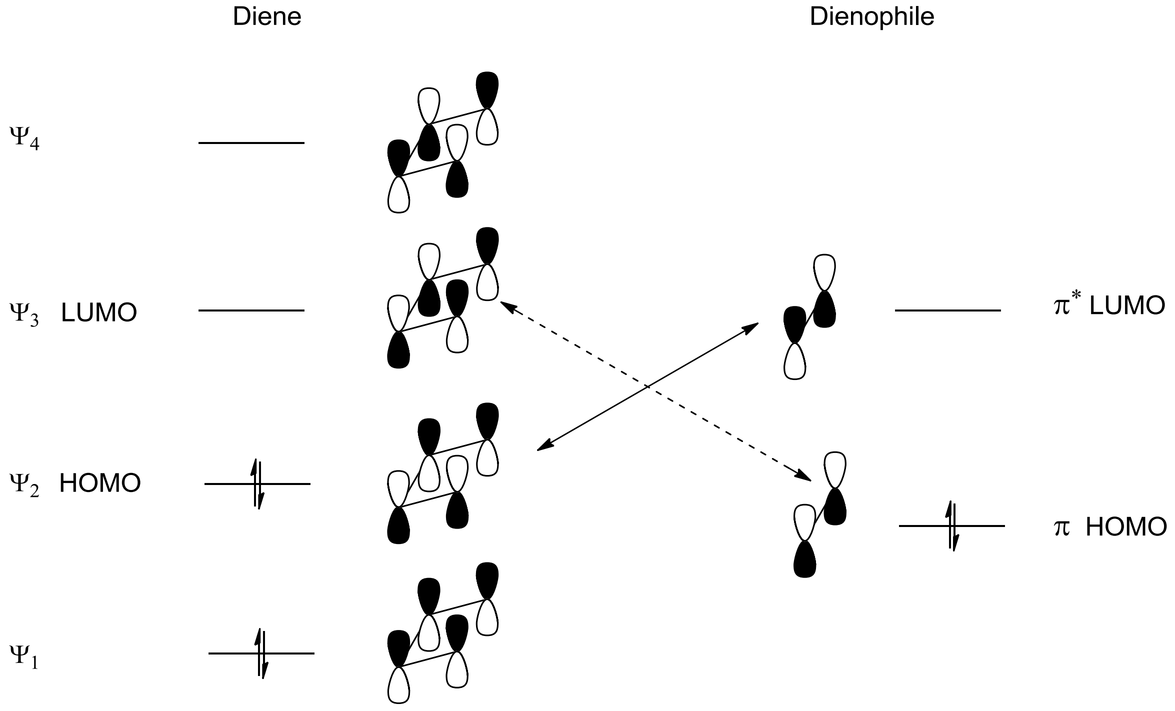


1.11 **1.12** **1.13** **1.14**

Molecular Orbital Analysis

A molecular orbital analysis of the 6π-electron process demonstrates that the reaction is indeed thermally allowed, provided there is a favorable overlap between the HOMO of the diene and the LUMO of the dienophile (***Figure 1.3***).[10] This is the case for normal electron demand Diels-Alder reactions in which an electron-rich diene reacts with an electron-deficient alkene. However, in some instances, the energy barrier will be lower between the LUMO of the diene and the HOMO of the dienophile. These inverse-demand Diels-Alder reactions are mostly obtained upon reaction of an electron-rich dienophile with an electron-poor diene.

***Figure 1.3** – Molecular orbital analysis of the Diels-Alder reaction*



Regiochemical Outcome

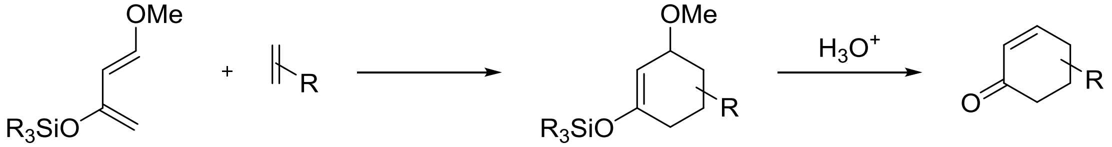
Substituents on both reaction partners will create an imbalance in molecular orbital coefficients which will affect the reaction's regiochemical outcome. The electronics of the system can therefore be tweaked to allow optimal orbital overlap and enhance desired product formation. ***Scheme 1.4*** depicts some substitution patterns often encountered in normal-demand Diels-Alder reactions and their effects on orbital distribution. Indeed, dienes **1.15** and **1.16**, containing electron-donating groups (EDG), will react with dienophiles **1.17**, containing electron-withdrawing groups (EWG), to produce 1,4- (**1.18**) and 1,2- (**1.19**) disubstituted cyclohexene rings respectively.

***Scheme 1.4** – Example of substitution effects on molecular orbital coefficients and regiochemical outcome*

1.15 **1.16** **1.17** **1.18** **1.19**

In 1974, the Danishefsky group exploited this concept to create a very electron-rich diene, now known as the Danishefsky diene (**1.20**) (***Scheme 1.5***).[11] By placing two electron-donating groups in the 1 and 3 positions of the diene, reaction times were significantly shortened and regioselectivity was highly enhanced. Diels-Alder reactions with diene **1.20** give rise to enol ethers **1.22**, which can then be used as synthetic handles to further derivatize the product. For example, when **1.22** is treated under acidic conditions, enones **1.23** are obtained.

***Scheme 1.5** – Danishefsky's diene*

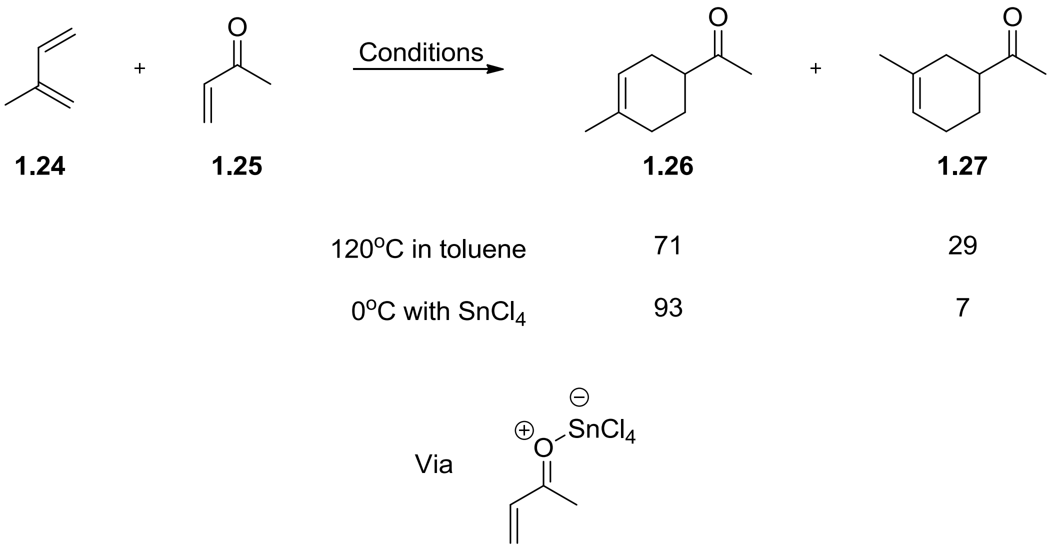


1.20 **1.21** **1.22** **1.23**
R = Alkyl

Lewis Acid Catalysis

Another way of promoting the Diels-Alder reaction, without permanently modifying the diene or dienophile, involves the use of Lewis acids as complexing agents to lower the LUMO of the dienophile. In 1960, the Yates group was the first to report this application by using a stoichiometric amount of $AlCl_3$ to accelerate the cycloaddition.[12] Since then, much research has been conducted to develop milder conditions using catalytic versions of the reaction and by developing a wide array of novel acids. This method has become very attractive as it leads to decreased reaction temperatures and times while increasing yields and regio- and diastereoselectivities. A comparison between a catalyzed and non-catalyzed reaction is depicted in ***Scheme 1.6***. Indeed, the addition of $SnCl_4$ to the reaction mixture allows the reaction between **1.24** and **1.25** to occur at 0 °C rather than 120 °C to yield a mixture of cyclohexenes **1.26** and **1.27**. The regioselectivity of the reaction was also increased from 71 : 29 to 93 : 7 under these conditions.[13]

Scheme 1.6 *– Effect of $SnCl_4$ on the Diels-Alder reaction of **1.24** and **1.25***



1.24 **1.25** **1.26** **1.27**

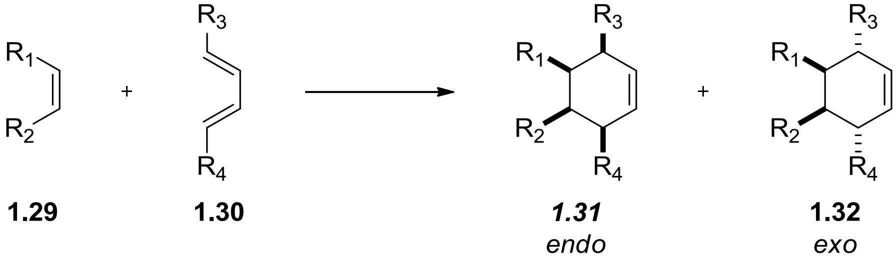
	1.26	1.27
120°C in toluene	71	29
0°C with $SnCl_4$	93	7

1.28

Stereoselectivity

The Diels-Alder reaction has become very widely used in organic synthesis because it allows the incorporation of much molecular complexity in a single step from simple starting materials with excellent stereocontrol. Since the reaction proceeds through a concerted reaction mechanism, the stereochemistry of the alkenes is reflected in that of the final product (***Scheme 1.7***). For example, the *cis* relationship between R_1 and R_2 in alkene **1.29** translates to a *syn* relationship in cyclohexenes **1.31** and **1.32**. However, the relative stereochemistry between the centers stemming from alkene **1.29** and those from diene **1.30** arises from the approach of both compounds in the transition state. This may give rise to *endo* (**1.31**) or *exo* (**1.32**) products. *Endo* products are favoured by extended conjugation in the alkene due to increased secondary orbital overlap with the diene, whereas the presence of strong steric interactions generally favours the *exo* product.

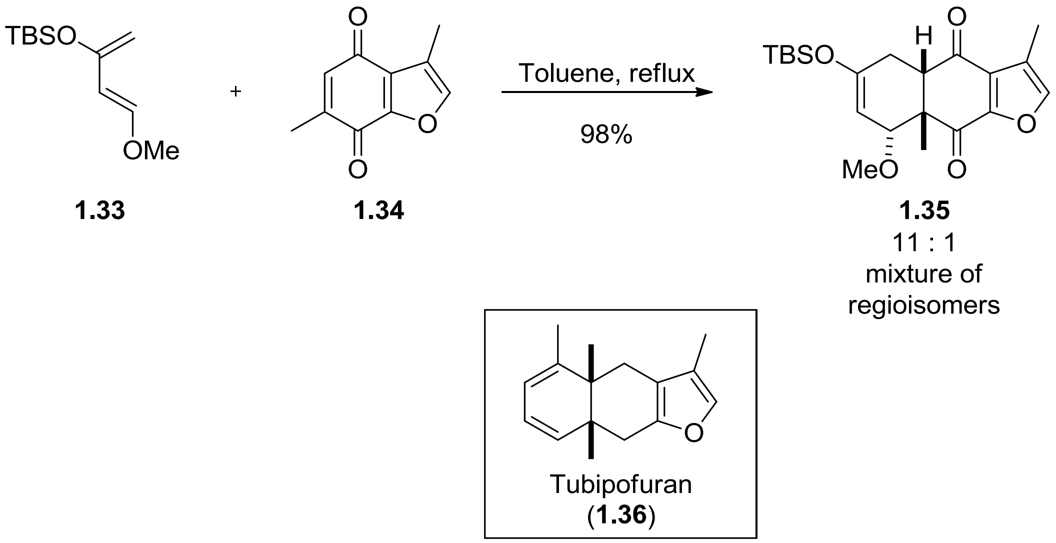
Scheme 1.7 *– Stereoselectivity in the Diels-Alder reaction*



Recent Applications in Total Synthesis

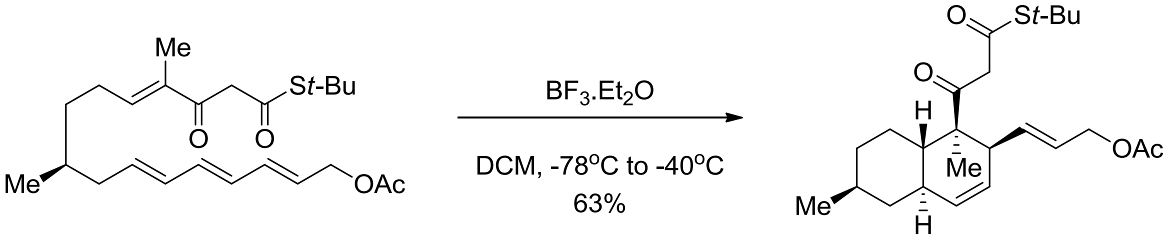
Studies conducted on the Diels-Alder reaction by various research groups has allowed its reliable use in total synthesis to predictably create up to four stereocenters and different ring systems in organic scaffolds.[14] There are three different types of Diels-Alder reactions depending on the relative position of the dienophile to the diene: intermolecular, intramolecular and transannular reactions. Intermolecular reactions occur between two distinct molecules resulting in the formation of a single ring. An example is depicted in ***Scheme 1.8***, which illustrates the key step from the Kanematsu group's total synthesis of tubipofuran (**1.36**). Indeed, the use of Danishefsky's diene (**1.33**) led to an excellent yield and regioselectivity to form tricyclic core **1.35**.[15]

Scheme 1.8 *– Kanematsu's application of an intermolecular Diels-Alder reaction in the total synthesis of tubipofuran*



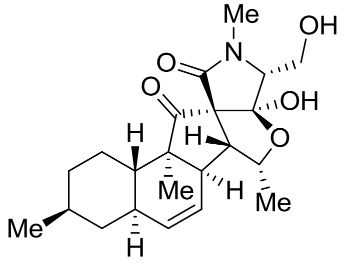
Intramolecular reactions are observed when the diene and dienophile are both part of the same molecule, which results in the formation of two new rings. In 2011, the Li group exploited this type of Diels-Alder reaction in their synthesis of (-)-fusarisetin A (**1.39**) (***Scheme 1.9***).[16] Their key step allowed the formation of the molecule's decalin system while setting the configuration of four stereocenters.

Scheme 1.9 *– Application of an intramolecular Diels-Alder reaction in Li's total synthesis of (-)-fusarisetin A*



1.37

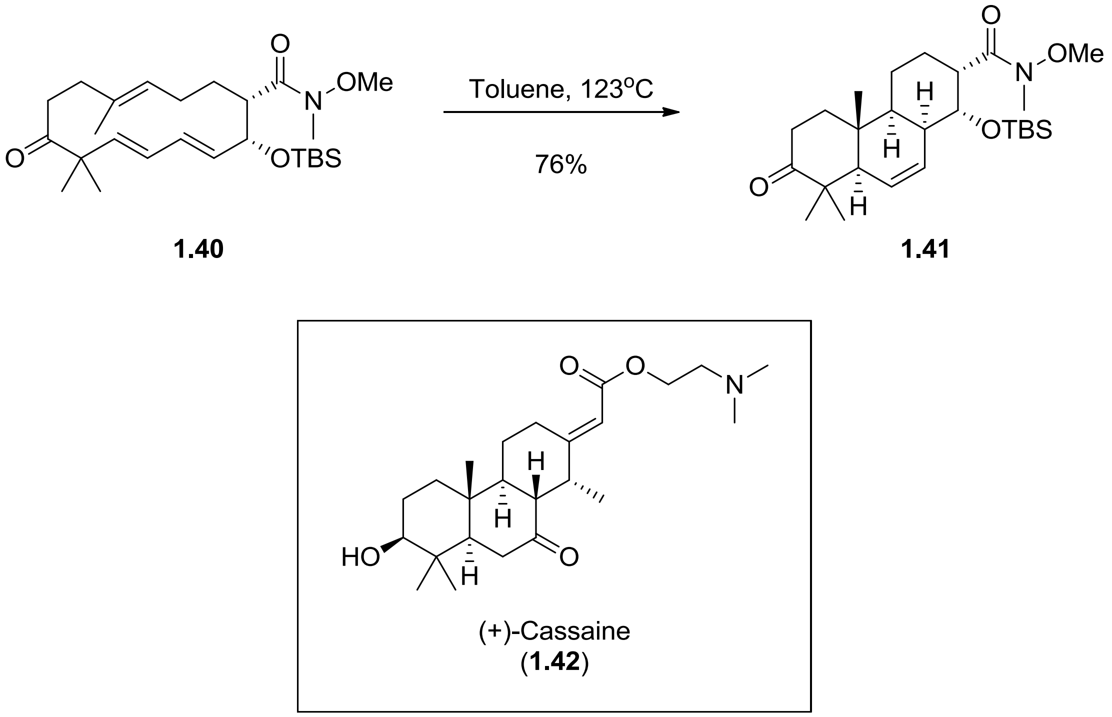
1.38



(-)-Fusarisetin A
(**1.39**)

Finally, the less frequently encountered transannular Diels-Alder reactions occur when the diene and dienophile are present within a preformed ring system. The reaction therefore gives rise to three new rings in the final product. The Deslongchamps group performed much pioneering work on this variant and successfully applied it towards the total synthesis of various natural products. One such example is demonstrated in their synthesis of (+)-cassaine (**1.42**), in which the key reaction efficiently installs four new stereocenters and generates the tricyclic core found in the natural product (***Scheme 1.10***).[17]

***Scheme 1.10** – Application of a transannular Diels-Alder reaction in Deslongchamps' total synthesis of (+)-cassaine*



1.40

1.41

(+)-Cassaine
(**1.42**)

Although the Diels-Alder reaction was discovered over 80 years ago, it is still highly studied and exploited to this day. The following work illustrates two more applications of this reaction in the field of natural product synthesis.

Chapter 2

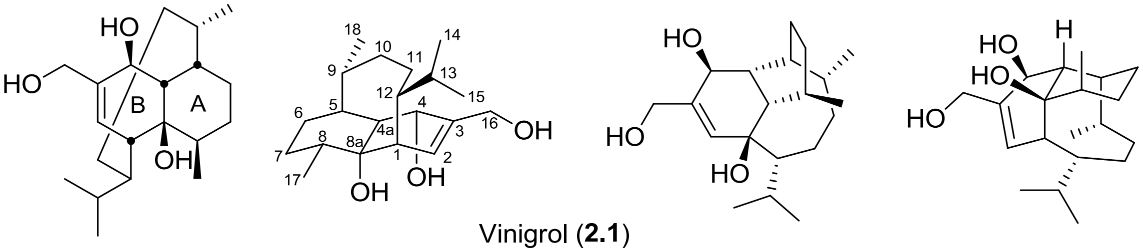
The Quest for Vinigrol

Introduction

In 1987, Hashimoto and co-workers isolated a novel diterpene from *Virgaria nigra* F-5408, a fungal strain found at the foot of Mount Aso in Japan.[18] They named the compound vinigrol (**2.1**) and it was not only found to possess a variety of biological activities, but also featured a novel structure in natural products (***Figure 2.1***). Indeed, these characteristics have sparked interest from many scientists around the world to the point that there have been 8 patents filed, 20 studies towards and 10 Ph.D. theses, but only 1 total synthesis reported over the past 25 years.[19]

From a chemical point of view, its structure presents a formidable challenge, especially stemming from its compact tricyclic core (***Figure 2.1***). This core is composed of an unprecedented decahydro-1,5-butanonaphthalene structure, consisting of a *cis*-fused decalin system (rings A and B) bridged by a 4 carbon chain at positions 1 and 5. The structure also possesses 8 contiguous stereocenters, featuring a C8 methyl group and a C8a tertiary alcohol in a *syn* orientation. Finally, the compound is also comprised of a primary allylic and a secondary alcohol.

***Figure 2.1** – Different perspectives of vinigrol*

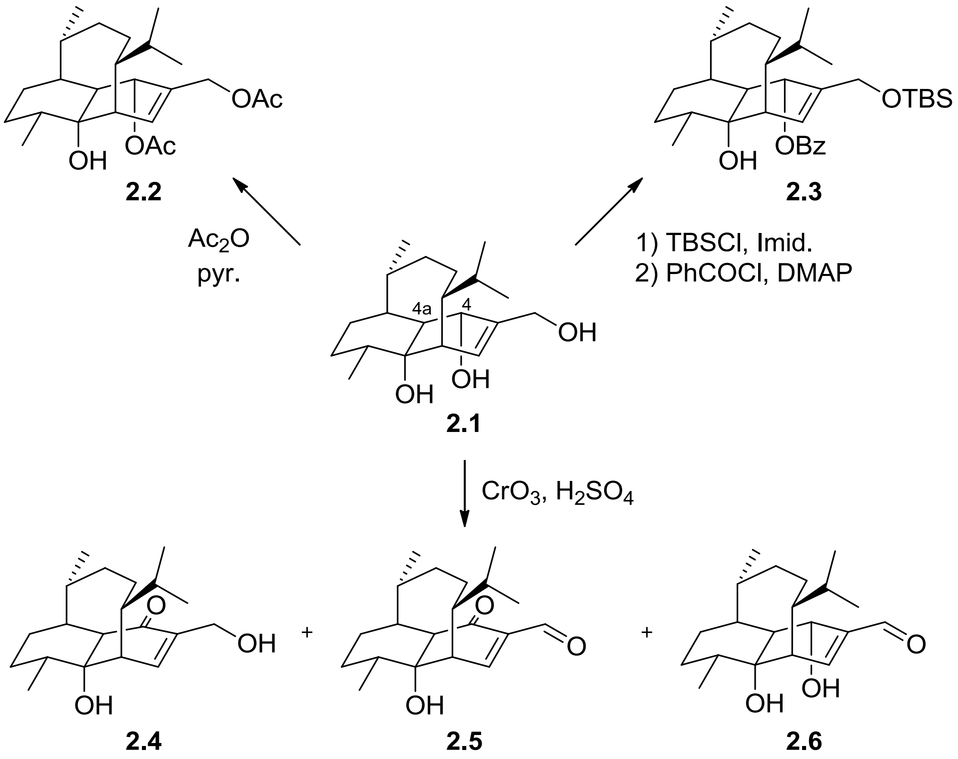


Vinigrol (**2.1**)

Isolation and Structure Elucidation

Vinigrol (**2.1**) was first isolated from cultured mycelium using solvent extractions, followed by many silica gel chromatographies.[18] Although it was obtained pure as colorless prisms, it was impossible to confidently assign its structure using conventional structure elucidation techniques (^{1}H and ^{13}C NMR, IR, MS and X-ray crystallography). A variety of synthetic analogs were therefore prepared (***Scheme 2.1***) and it was found that crystals of compound **2.5** were amenable to X-ray crystallographic analysis. This allowed the determination of the relative configuration of most stereocenters, except for the one at C4, which was destroyed in the oxidation process. To this end, Hashimoto and coworkers analyzed the C4/C4a coupling constant from the ^{1}H NMR spectrum of **2.1** and found its value to be near 0. This value corresponds to a dihedral angle approaching 90^{o} according to the Karplus Curve. This work therefore established all of the natural product's stereocenters.

***Scheme 2.1** – Structure elucidation through derivitization*



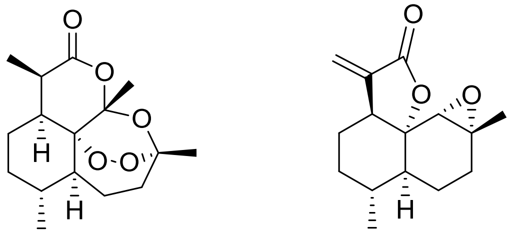
Biological Effects

Much of the interest in this molecule stems from its wide range of reported biological activities. Shortly after vinigrol (**2.1**) was isolated, Ando and co-workers found that the natural product exhibited antihypertensive and platelet aggregation inhibition properties.[20,21] Three years later, Norris and co-workers filed a patent describing vinigrol's ability to act as a tumor necrosis factor (TNF) antagonist. It was also suggested that the molecule possessed many other interesting activities such as its use in the treatment of inflammation and in preventing the conversion of the AIDS-related complex into AIDS.[22] Finally, in 1995, Fujisawa Pharmaceutical Company Limited filed a patent suggesting that HIV infectious diseases could be treated with the natural product.[23]

Biosynthesis

Before describing the synthetic efforts towards the target molecule, it is interesting to consider how nature builds this complex natural product. To this end, Corey and Goodman proposed a biosynthesis of vinigrol (**2.1**) based on studies of the structurally related artemisinin (**2.7**) and arteannuin (**2.8**) (***Figure 2.2***).[24]

Figure 2.2 *– Related structures*

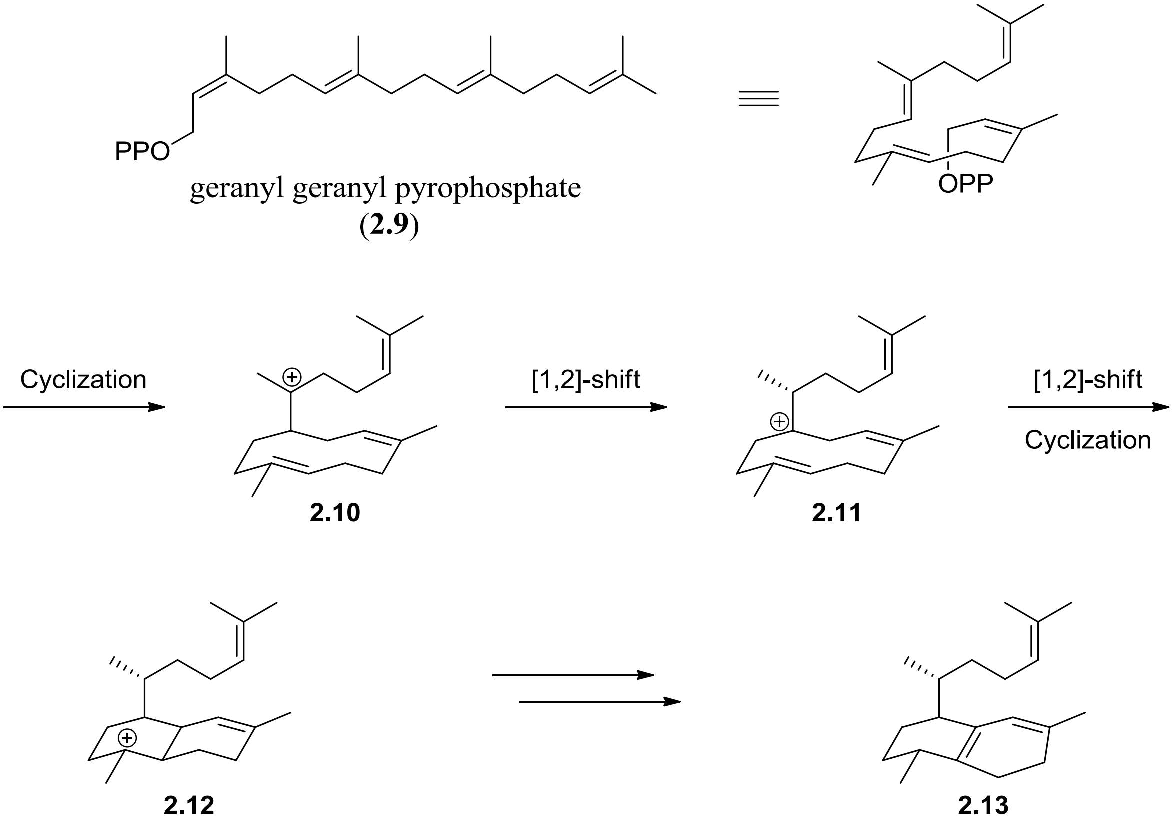


artemisinin
(**2.7**)

arteannuin
(**2.8**)

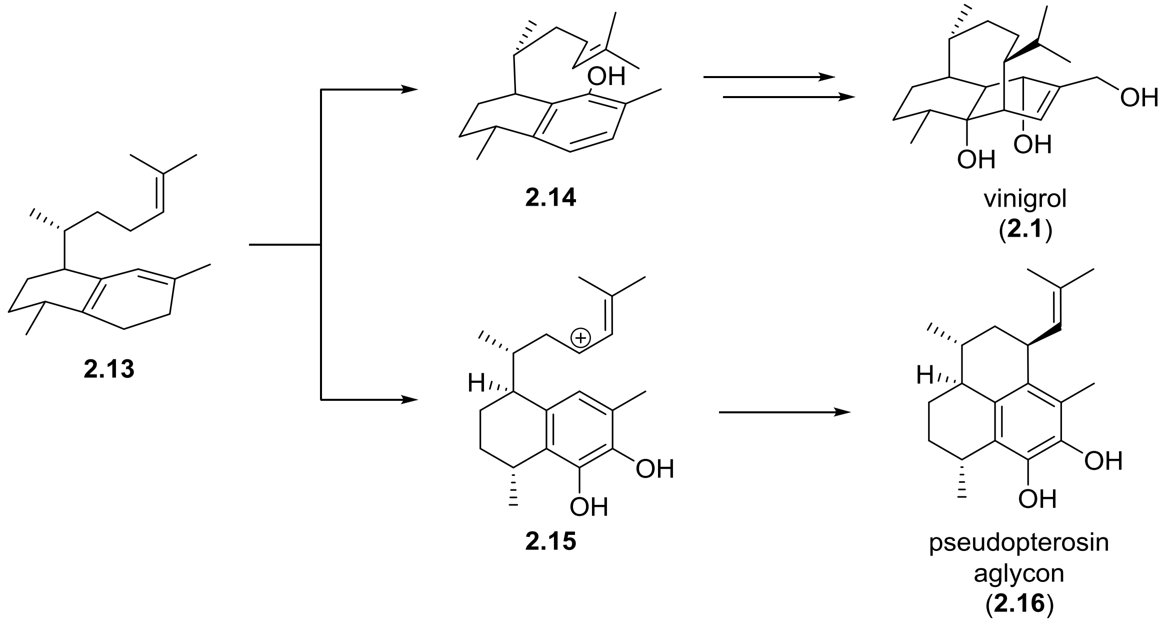
The proposed sequence begins with an enzymatically-induced cyclization reaction of geranyl geranyl pyrophosphate (**2.9**) to form macrocycle **2.10** (***Scheme 2.2***). Intermediate **2.10** then undergoes a series of [1,2]-hydride shifts, eliminations and a cyclization to form compound **2.13**, which contains two of the three required cycles, but none of the oxygen atoms found in **2.1**.

Scheme 2.2** - Proposed biosynthesis of intermediate **2.15



Intermediate **2.13** is then oxidized to phenol **2.14** which is poised to react through a phenolic coupling reaction to form the 8-membered *ansa* belt. Further oxidations install the final hydroxyl groups to obtain the natural product (**2.1**) (***Scheme 2.3***). Their proposal is further supported by the biosynthetic studies performed on pseudopterosin (**2.16**) which possesses a similar framework and stereochemistry.

Scheme 2.3 *- Common intermediate to pseudopterosin and vinigrol biosyntheses*



2.13

2.14

vinigrol (**2.1**)

2.15

pseudopterosin aglycon (**2.16**)

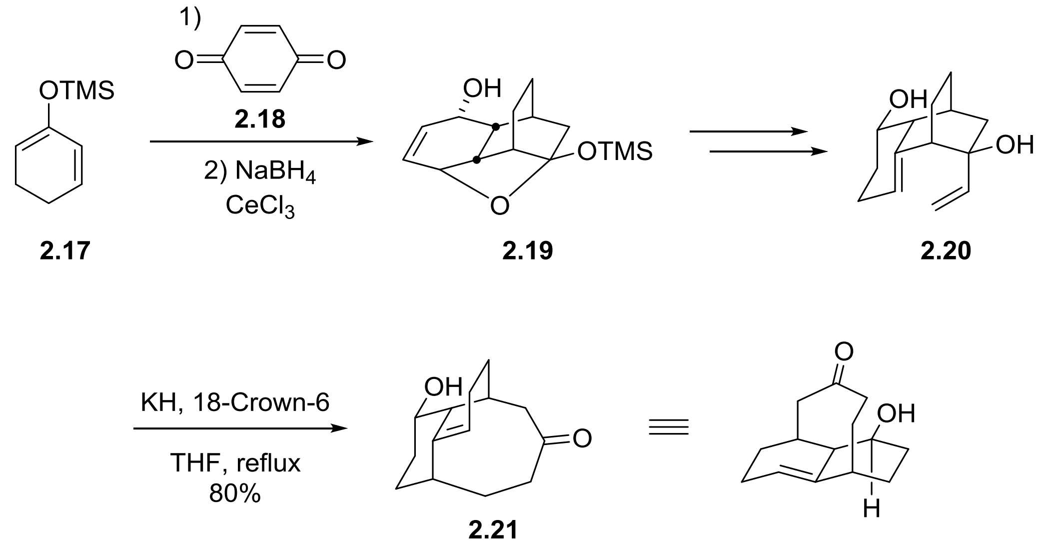
Synthetic Efforts

Over the past 25 years, many renowned research groups have focused much energy towards the total synthesis of vinigrol (**2.1**). The following groups have faced many pitfalls and have contributed to the rich history of the molecule: Hanna, Paquette, Corey, Matsuda, Mehta, Barriault, Fallis, Njadarson and Baran. This section discusses the advancements made by each group in chronological order of their first reported efforts and shows the progress made in each case.[19]

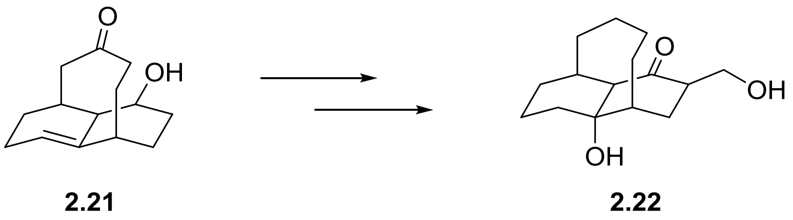
Hanna's Work

The Hanna group was the first to report an approach towards the total synthesis of vinigrol (**2.1**). The sequence elegantly relies on different pericyclic reactions to assemble the tricyclic core of the natural product. In the group's first approach, the synthesis began with an intermolecular Diels-Alder reaction on diene **2.17**.[25] The intermediate was treated under Luche conditions[26] to yield tetracycle **2.19** which was then converted to diene **2.20** in a few steps (***Scheme 2.4***). Hanna envisioned that submitting **2.20** to anionic oxy-Cope conditions would furnish the tricyclic system of the molecule with the appropriate stereochemistry. Indeed, upon heating **2.20** with KH in the presence of a crown ether, tricycle **2.21** was formed in 80% yield. This work constituted the first successful synthesis of the tricyclic core of vinigrol (**2.1**) in 10 steps. In a subsequent report, the group also managed to install all required oxygen atoms found in the final product, although some oxidation states would require adjustments (***Scheme 2.5***).[27]

***Scheme 2.4** - Hanna's initial synthesis of the tricyclic core*

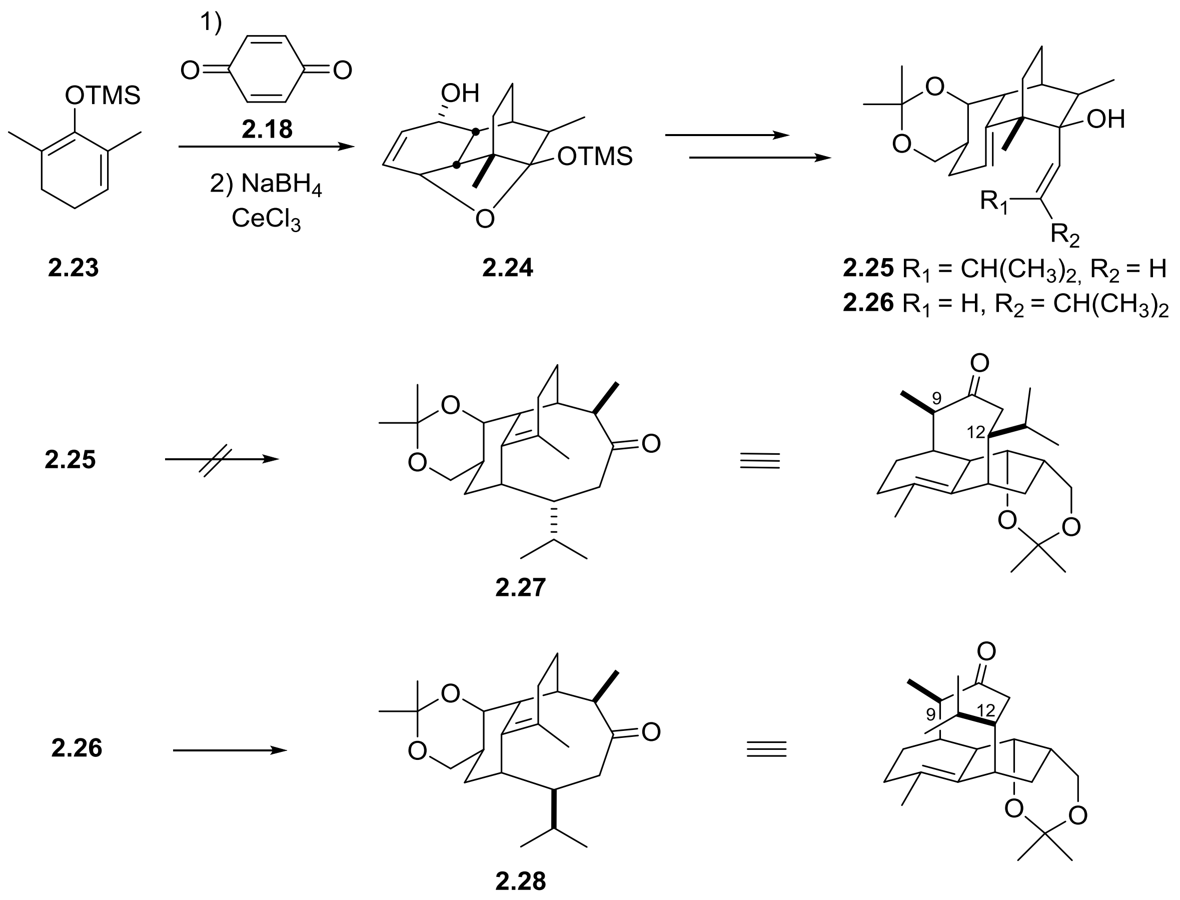


***Scheme 2.5** – Installation of all oxygen atoms of vinigrol*



Although their initial work was a milestone, compound **2.22** lacked synthetic handles enabling the completion of the synthesis. In a subsequent effort, the group attempted to incorporate more functional groups prior to the oxy-Cope rearrangement.[28] Indeed, following a similar initial sequence, they obtained tetracycle **2.24** containing two methyl groups (***Scheme 2.6***). After some manipulation, the group managed to synthesize an analog of **2.20**, but containing an isopropyl group attached to the mono-substituted alkene. To be thorough, the group synthesized both geometries of the alkene (*i.e. E* and *Z*) and submitted them to their previously developed conditions. To their disappointment, only compound **2.26** underwent the cyclization to give the incorrect stereochemistry of the isopropyl group. Although the methyl group at C9 could potentially be epimerized, this was not the case at C12.

Scheme 2.6 *– Hanna's more functionalized approach*



2.23

2.24

2.25 $R_1 = CH(CH_3)_2$, $R_2 = H$
2.26 $R_1 = H$, $R_2 = CH(CH_3)_2$

2.25

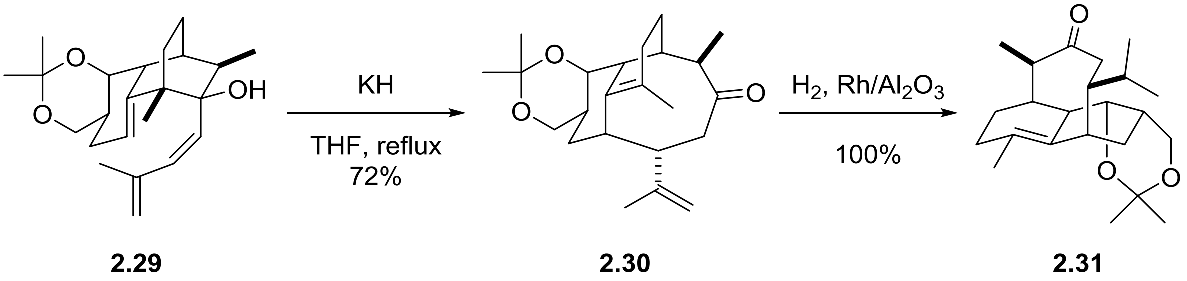
2.27

2.26

2.28

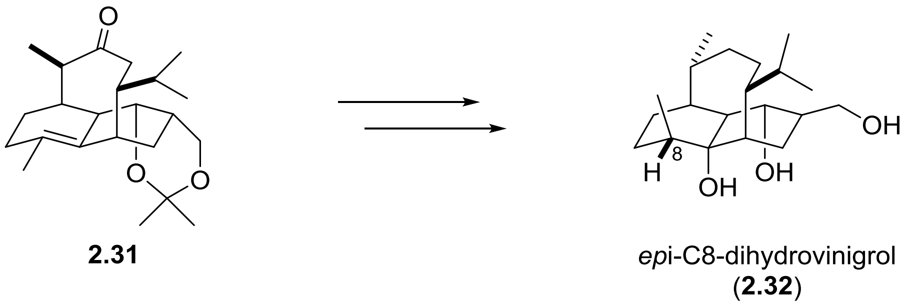
It was believed that the reason that the anionic oxy-Cope rearrangement did not work with the *Z*-geometry was strong steric interactions generated between the endocyclic alkene and the isopropyl substituent at the transition state. To address this, the group substituted the isopropyl for an isopropene group which offers a more stabilized transition state, through decreased steric interactions and extended conjugation (***Scheme 2.7***). Indeed, submitting compound **2.29** to the anionic oxy-Cope rearrangement successfully led to the entire carbocyclic skeleton structure of vinigrol (**2.30**) possessing many of the stereocenters found in the natural product.

Scheme 2.7 – *Successful anionic Oxy-Cope with an isopropene group*



Ultimately, the Hanna group's efforts culminated with their last report in 2009 with the synthesis of *epi*-C8-dihydrovinigrol (**2.32**) (***Scheme 2.8***).[29] Despite the fact that the group never completed the synthesis, they contributed largely to establish a solid foundation of knowledge on which other groups could build.

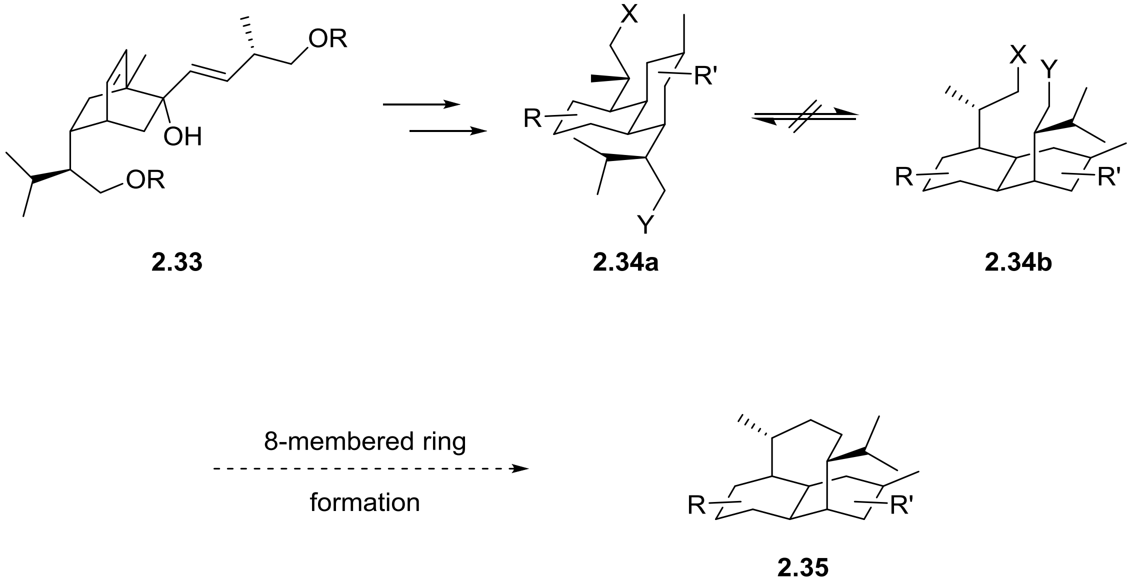
Scheme 2.8 – *Synthesis of epi-C8-dihydrovinigrol*



Paquette's Approach

In the mid-2000's, the Paquette group published a series of papers on their attempts towards the synthesis of **2.1**.[30] Their enantioselective approach was based on an oxy-Cope rearrangement to furnish the decalin system of the molecule. Although their approach was successful at forming decalin framework **2.34**, all attempts at the formation of the 8-membered ring to yield compound **2.35** failed (***Scheme 2.9***). Many different strategies were envisioned such as Grubbs' ring closing metathesis, Dieckmann cyclization, S_N2 and ring contraction reactions. Different ring and chain substitution patterns were attempted without success. It was later calculated that the energy required to bring the two side chains in an axial orientation and in close proximity to enable a reaction (*i.e.* the energy barrier between **2.34a** and **2.34b**), was far too demanding. The Paquette group's work did, however, demonstrate that the formation of the octalin ring in the final stages of the synthesis was not a viable pathway.

***Scheme 2.9** – Paquette's attempts at closing the 8-membered ring*



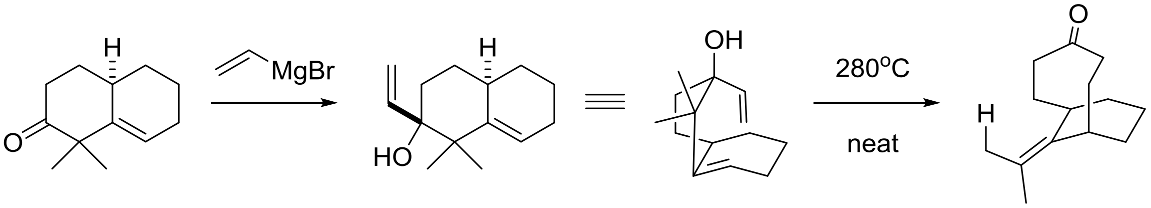
2.33 **2.34a** **2.34b**

2.35

Mehta's Approach

The Mehta group published another application of the oxy-Cope rearrangement towards the synthesis of vinigrol (**2.1**) (***Scheme 2.10***).[31] Treatment of readily available decalin **2.36** with vinylmagnesium bromide furnished desired oxy-Cope precursor **2.37**. When **2.37** was heated at 280 °C in a sealed tube, it underwent the rearrangement to furnish bicyclo[5.3.1]undecane **2.38**. This bicyclic structure corresponds to a fragment that is embedded in the vinigrol skeleton and possesses two correct stereocenters. The approach once again demonstrated the usefulness of the sigmatropic rearrangement in the generation of the 8-membered ring. Although short, very few synthetic handles remained to pursue the synthesis. This was the only report by the group towards the synthesis of the natural product.

***Scheme 2.10** – Mehta's synthesis of bicycle[5.3.1]undecanes*



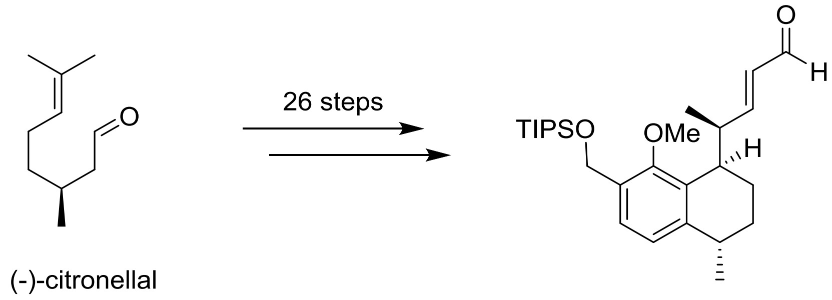
2.36 **2.37** **2.38**

Corey's Work

Electrophilic Aromatic Condensation

The Corey group also performed studies to synthesize this challenging molecule, inspired by their proposed biosynthesis.[24] Their enantiospecific sequence began with commercially available (-)-citronellal (**2.39**) which was converted to protected phenol **2.40** in 26 steps (***Scheme 2.11***).

***Scheme 2.11** – Preperation of precursor*

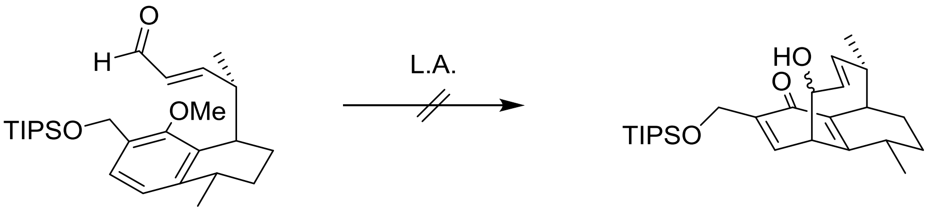


(-)-citronellal
(**2.39**)

2.40

However, when **2.40** was treated with a variety of Lewis acids, the anisole ring failed to condense on the aldehyde to form compound **2.41** (***Scheme 2.12***). Attempts at rendering the carbonyl more electrophilic by using an acyl chloride to push the electrophilic aromatic condensation were only met with disappointment. It was postulated that perhaps the presence of both a tetrasubstituted alkene and especially a disubstituted *E*-alkene inside the 8-membered ring contributed to increased ring strain which prevented cyclization. Despite many attempts, this route was eventually abandoned.

***Scheme 2.12** – Attempted formation of the 8-membered ring*



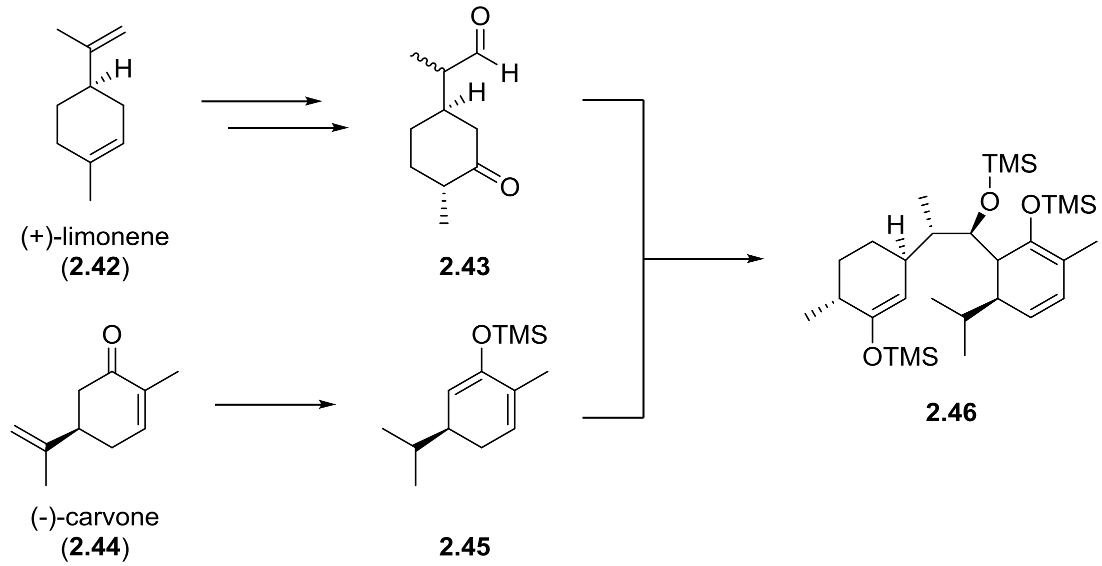
2.40

2.41

Intramolecular Diels-Alder / Grob Fragmentation

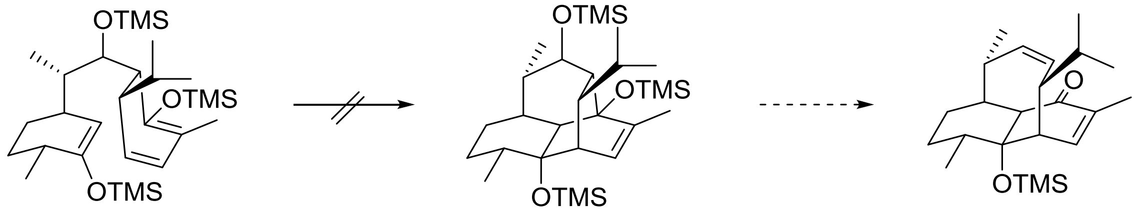
In the Corey group's second approach, it was envisioned that the tricyclic core of **2.1** could come from an intramolecular Diels-Alder reaction followed by a Grob fragmentation. To test this hypothesis, the group synthesized diene **2.46** in a few synthetic steps starting from commercially available enantiopure (+)-limonene (**2.42**) and (-)-carvone (**2.44**) (***Scheme 2.13***).

Scheme 2.13 *– Preparation of intramolecular Diels-Alder precursor*



Unfortunately, all attempts at performing the Diels-Alder reaction failed to give tetracycle **2.47** (***Scheme 2.14***). The lack of success was attributed to an unfavorable electronic pairing between an electron rich dienophile and an electron rich diene. Steric hindrance also likely contributed to the difficulties in this approach; the molecule most likely preferring to adopt a less congested conformation of the linear chain. With the Diels-Alder reaction not working, the theorized subsequent Grob fragmentation could not be validated to yield compound **2.48**.

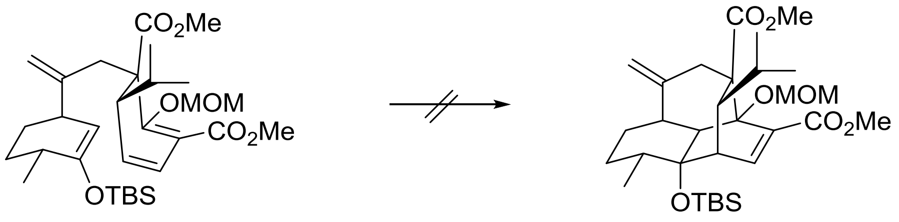
***Scheme 2.14** – Key intramolecular Diels-Alder attempts*



2.46 **2.47** **2.48**

In attempts to circumvent the drawbacks with the Diels-Alder reaction, the diene was made more electron-deficient by adding an ester group and capping the enol ether with a MOM group in lieu of the silyl moiety to give compound **2.49** (***Scheme 2.15***). This would better align the electronics and an inverse electron Diels-Alder reaction would be expected to take place. Once again, the Corey group was never successful in getting the reaction to work and tetracycle **2.50** was never synthesized. These studies were part of the Goodman Ph.D. thesis[24] and the results were never published.

***Scheme 2.15** – Modified intramolecular Diels-Alder precursor*

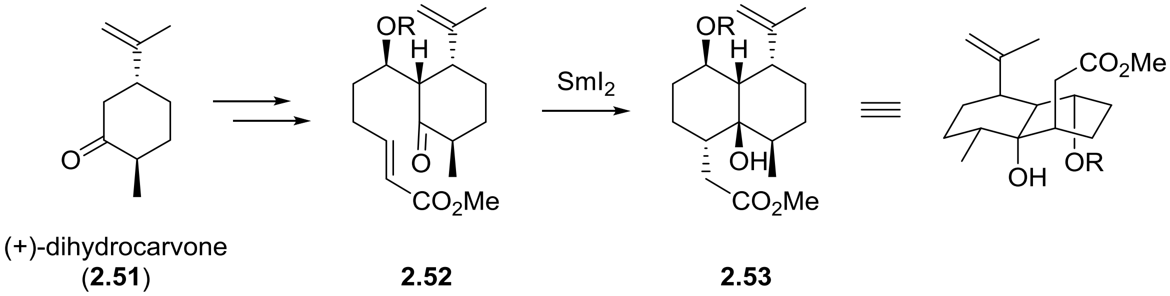


2.49 **2.50**

Matsuda's Approach

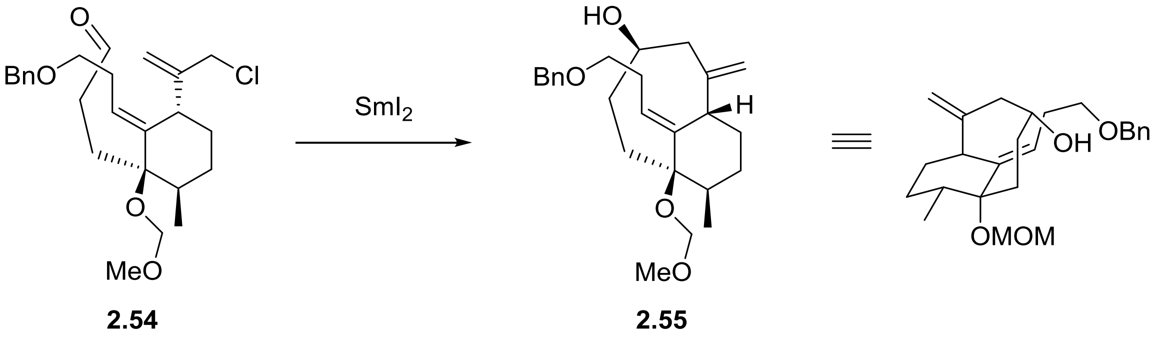
In 1996, Matsuda reported the use of a SmI_2-induced Barbier coupling to synthesize the *cis*-decalin framework of vinigrol (**2.1**).[32] The sequence began with (+)-dihydrocarvone (**2.51**) which was converted to precursor **2.52** through a cross-aldol reaction and a few more transformations (***Scheme 2.16***). Subsequent treatment of **2.52** with SmI_2 afforded decalin **2.53** with the correct stereochemistry. This constituted a very short and efficient synthesis of the decalin framework, containing 6 of the 8 stereocenters contained in the final product, but there were no further reports on the subsequent formation of the octalin ring with compound **2.53**.

Scheme 2.16 *– SmI_2 mediated reductive coupling*



Although the group did not report the formation of the *ansa* belt from decalin **2.53**, they did report the construction of the bicyclo[5.3.1]undecene portion of vinigrol (**2.1**) using a similar approach as above. Indeed, cyclization precursor **2.54** was readily synthesized and treated with SmI_2 to afford bicyclic core **2.55** (***Scheme 2.17***). Though only 4 stereocenters found in the natural product were formed, this approach allowed the synthesis of the more challenging 8-membered ring. However, the group never disclosed the preparation of the tricyclic core of the molecule nor the installation of the elusive isopropyl group.

Scheme 2.17 *– Application of reductive coupling to octalin ring formation*



Barriault's Work

Oxy-Cope/Claisen/Ene Cascade

Over the past decade, the Barriault group has published a series of pericyclic approaches towards the total synthesis of vinigrol (**2.1**). The group's first approach consisted in an oxy-Cope/Claisen/Ene cascade[33] of allyl ether **2.57** which was synthesized in a few synthetic steps from readily available epoxide **2.56** (***Scheme 2.18***).[34] Precursor **2.57** smoothly underwent the desired rearrangements, when subjected to microwave irradiation at 180 °C, to furnish decalin **2.58** with high diastereocontrol. Upon heating, **2.57** is predisposed to undergo an oxy-Cope rearrangement to give ring expanded allene **2.59**. This compound is then poised to perform a Claisen rearrangement furnishing ketone **2.60**, which finally undergoes an ene reaction to provide **2.58**.

Scheme 2.18 *– Synthesis of vinigrol's decalin system through an oxy-Cope/Claisen/Ene cascade*

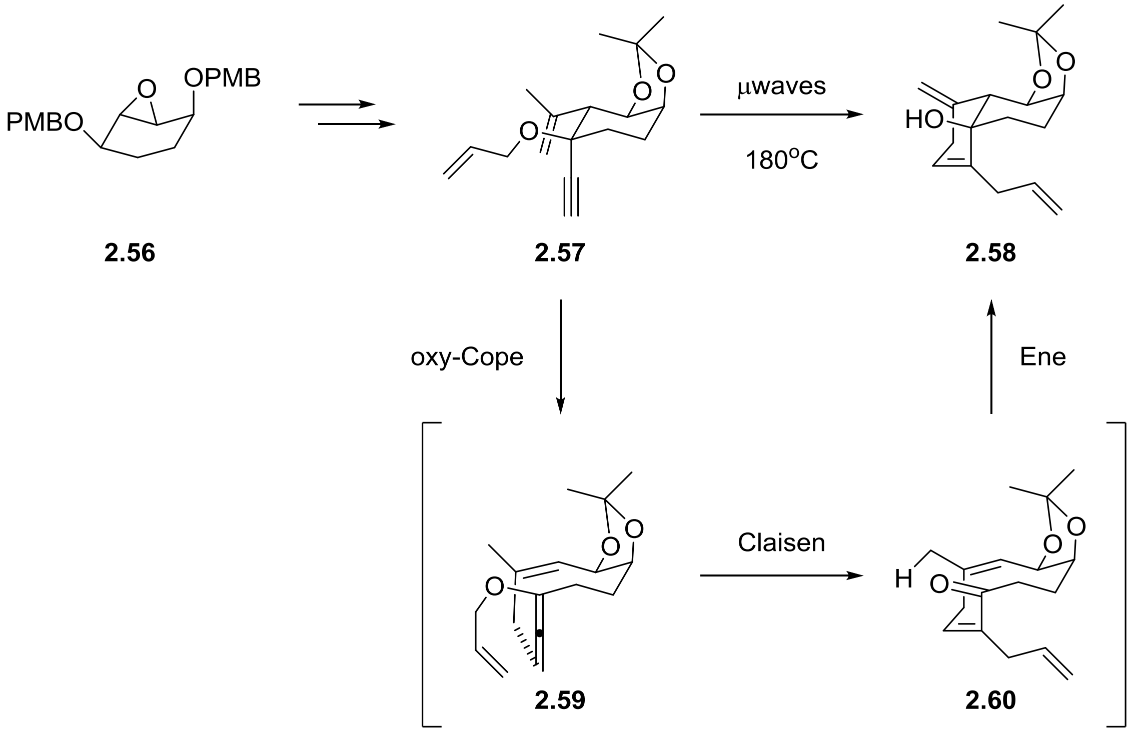
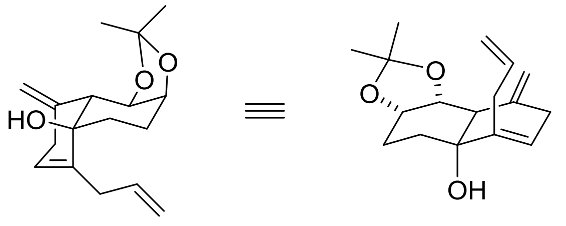


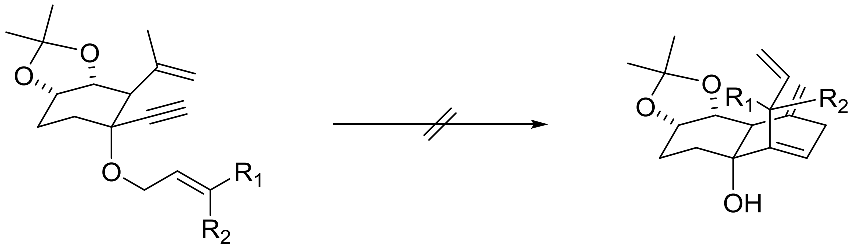
Figure 2.3** – Different perspectives of **2.58



2.58

With this result in hand, the group attempted to incorporate the isopropyl moiety into precursor **2.57**. To this end, compounds **2.61** and **2.63** were synthesized (***Scheme 2.19***). Unfortunately, both *E*- and *Z*- alkenes failed to undergo the desired rearrangement and this route was abandoned because it would not be viable to stereoselectively incorporate the isopropyl group at a later stage in the synthesis using compound **2.58**.

***Scheme 2.19** – Application of the cascade to a more substituted precursor*



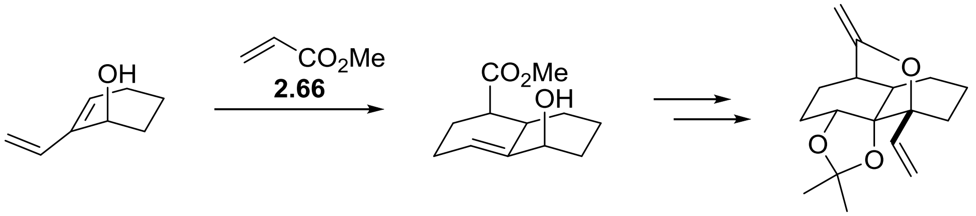
2.61, $R_1 = CH(CH_3)_2$
$R_2 = H$
2.63, $R_1 = H$
$R_2 = CH(CH_3)_2$

2.62, $R_1 = CH(CH_3)_2$
$R_2 = H$
2.64, $R_1 = H$
$R_2 = CH(CH_3)_2$

1st Generation Hydroxy-Directed Diels-Alder (HDDA)/Claisen sequence

At this stage, the group decided to investigate another approach which consisted in a hydroxy-directed Diels-Alder reaction between diene **2.65** and methyl acrylate (**2.66**) to furnish decalin **2.67** (***Scheme 2.20***).[35] Through some transformations, **2.67** was converted to vinyl allyl ether **2.68** to set up the subsequent Claisen rearrangement.

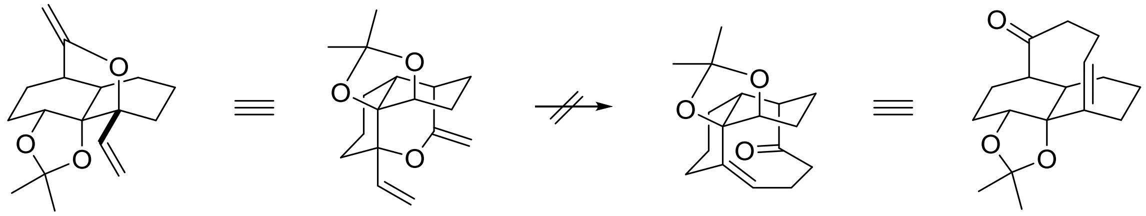
Scheme 2.20 *– Hydroxy-directed Diels-Alder approach to the decalin system*



2.65 **2.67** **2.68**

The group then attempted the envisioned Claisen reaction which would afford the 8-membered ring and, at the same time, unveil the tricyclic core of the natural product. Unfortunately, submission of **2.68** to a variety of conditions (thermal and acid catalyzed conditions) only led to degradation of the starting material (***Scheme 2.21***).

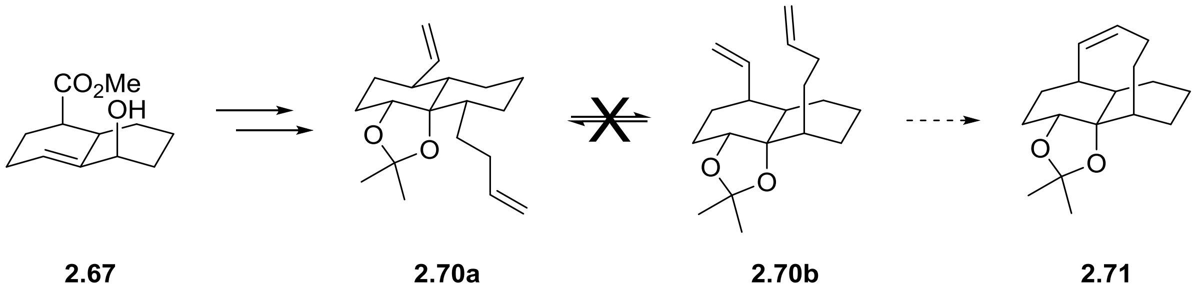
Scheme 2.21 *– Attempts at synthesizing the tricyclic core through a Claisen rearrangement*



2.68 **2.69**

The group then turned their attention to a similar approach, utilizing HDDA adduct **2.67** (***Scheme 2.22***). They hoped that the octalin belt could come from the ring closing metathesis (RCM) of diene **2.70**. At this time, Paquette's approach had not been published, but the Barriault group observed the same result: the *ansa* bridge could not be synthesized via a RCM reaction of a decalin system.

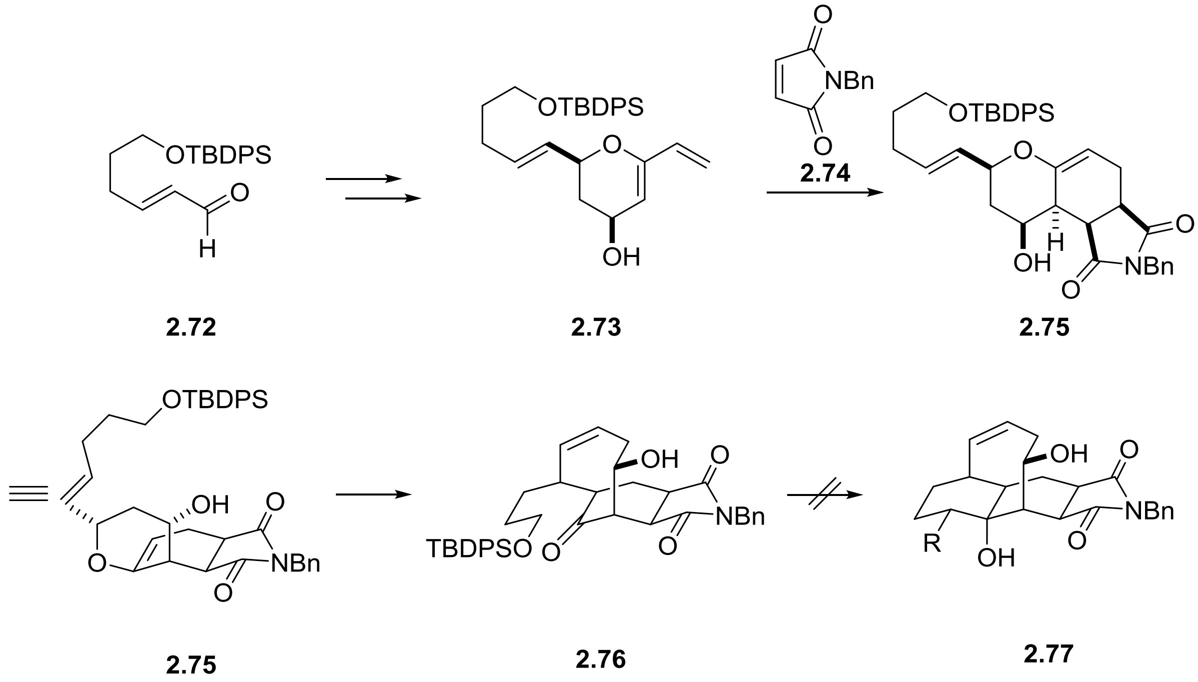
***Scheme 2.22** – Attempted formation of 8-membered ring through ring closing metathesis*



2nd Generation HDDA/Claisen sequence

In the same report, the Barriault group reported another approach based on a hydroxy-directed Diels-Alder and a subsequent Claisen rearrangement.[35,36] In this iteration, a sequence in which the octalin belt would be formed before the decalin system was envisioned. The synthesis began with known enone **2.72**, which was transformed into diene **2.73** in 7 steps (***Scheme 2.23***). With the Diels-Alder precursor in hand, they performed the first key reaction using *N*-benzylmaleimide (**2.74**) as dienophile, yielding tricyclic structure **2.75** as sole diastereomer. Exposing **2.75** to microwave irradiation allowed the Claisen rearrangement to take place, furnishing compound **2.76** having the 8-membered ring in place. However, all attempts at closing the final cyclohexane ring by nucleophilic addition to the ketone left the group in despair. A variety of conditions were attempted with different structural variations to both the nucleophile and the ring system, but without success. The low reactivity of the ketone was attributed to a highly congested environment and this approach was abandoned.

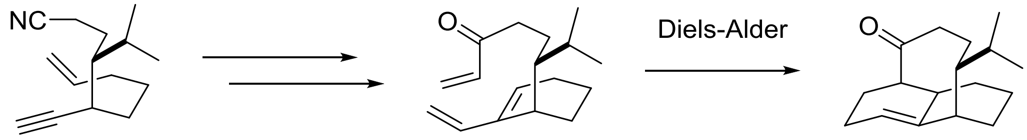
***Scheme 2.23** – Intermolecular Diels-Alder/Claisen approach towards vinigrol*



Intramolecular Diels-Alder Reaction

In 2007, the Barriault group published a report on a new approach toward the synthesis of the tricyclic core of vinigrol (**2.1**).[37] With all the data available from their research and from the literature, it became apparent that the secret to the synthesis of the tricyclic core is that the two final assembled rings in the molecule should be synthesized in a single step. The Barriault group therefore imagined a substrate in which an intramolecular Diels-Alder reaction would form both the octalin belt and the second cyclohexane ring simultaneously. To test this hypothesis, enyne **2.78** was synthesized and converted to precursor **2.79** in 4 steps via an enyne metathesis and subsequent redox and alkylation processes (***Scheme 2.24***). To their delight, upon treatment of **2.79** with Lewis acids, the tricyclic core of vinigrol (**2.80**) was formed as a single isomer.

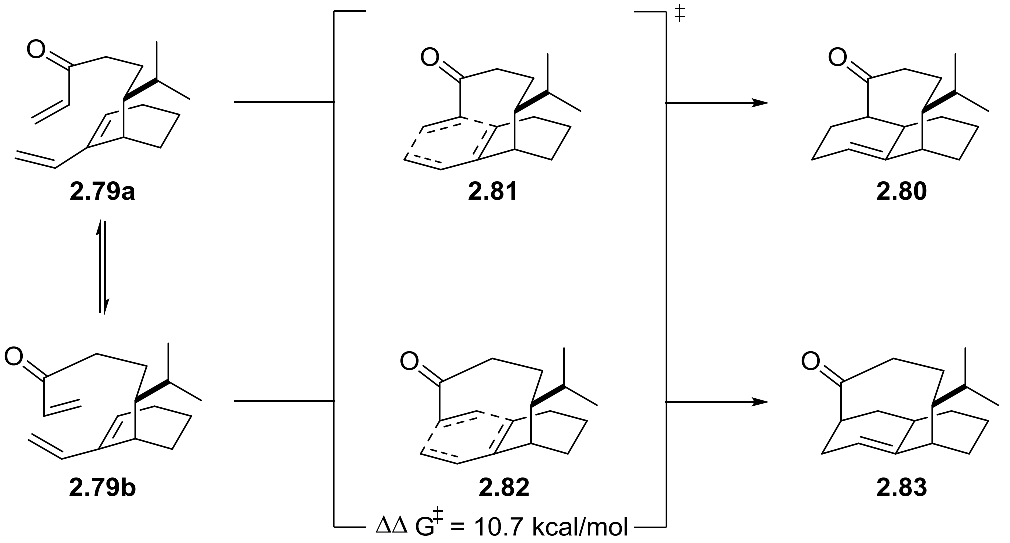
***Scheme 2.24** – Intramolecular Diels-Alder approach towards vinigrol*



2.78 **2.79** **2.80**

The Barriault group had not set out blindly on this venture and had performed DFT calculations to ensure that the correct isomer would indeed be observed. It was found that there was a 10.7 kcal/mol energy difference between transitions states **2.81** and **2.82**, favouring the formation of the desired 8-membered ring product **2.80** (***Figure 2.4***).

***Figure 2.4** – Diels-Alder transition state calculations*

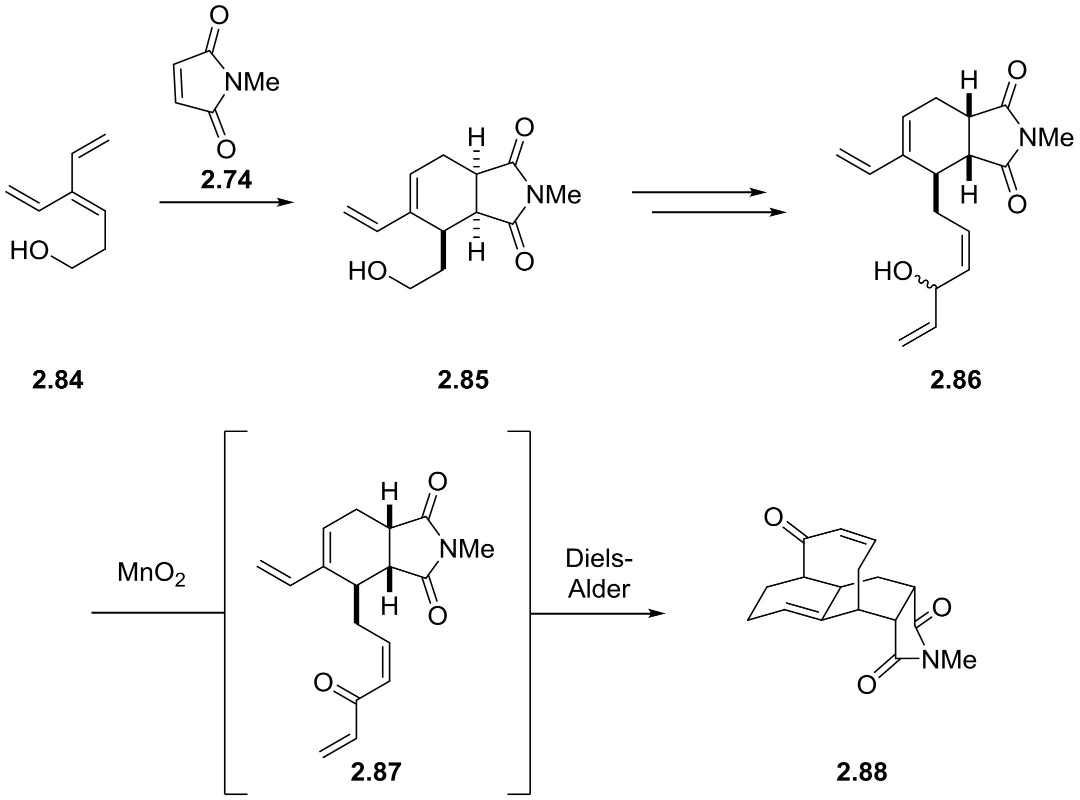


The group therefore became the second to synthesize the core of **2.1**. However, this approach turned out to be quite lengthy (20 steps to **2.80**) and the substrate had insufficient handles to allow the completion of the synthesis. A new substrate would therefore have to be designed to allow more flexibility.

Fallis' Approach

In late 2007, the Fallis group reported their synthesis of the tricyclic core of vinigrol (**2.1**) based on a diene transmissive Diels-Alder approach.[38] Triene **2.84** was treated with *N*-methylmaleimide (**2.74**) and successfully underwent a monocycloaddition to afford diene **2.85** which was converted to allylic alcohol **2.86** in a few steps (***Scheme 2.25***). Oxidation of **2.86** with MnO_2 furnished intermediate enone **2.87** which underwent an intramolecular Diels-Alder reaction to afford the tricyclic core of the natural product. No subsequent attempts at the completion of the synthesis have been reported by the group.

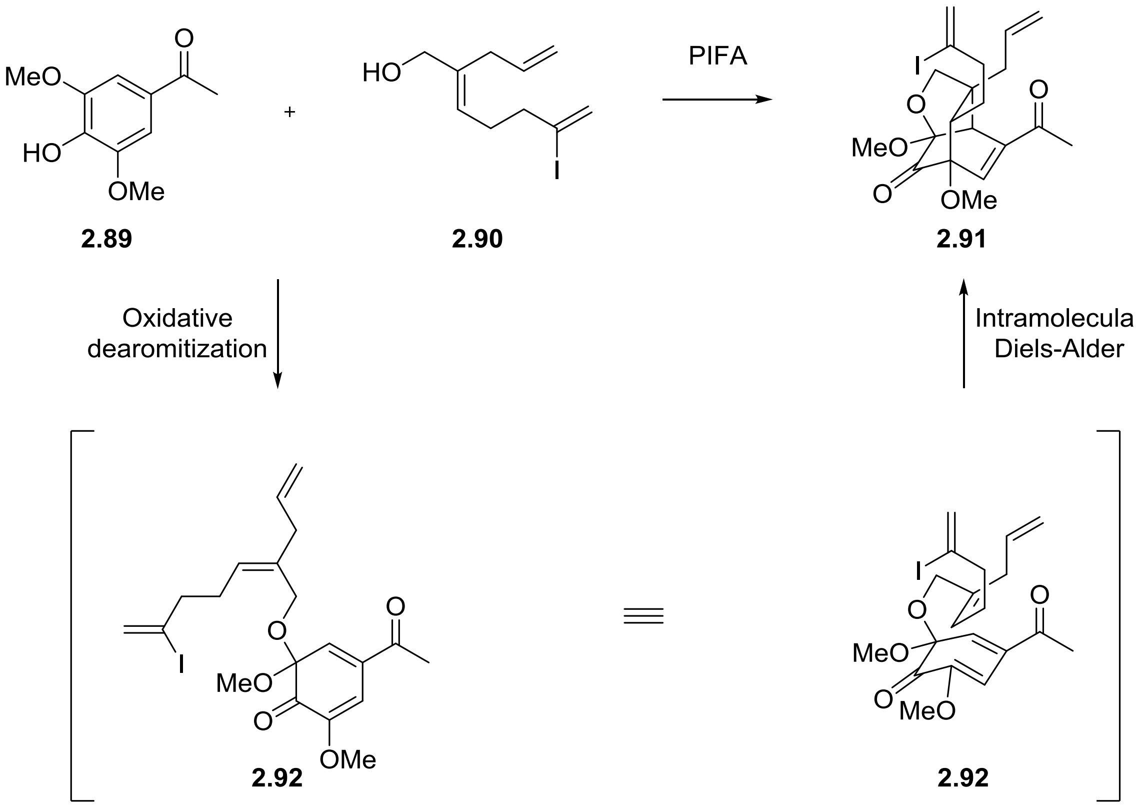
***Scheme 2.25** – Diene transmissive Diels-Alder approach to the tricyclic core*



Njardarson's Approach

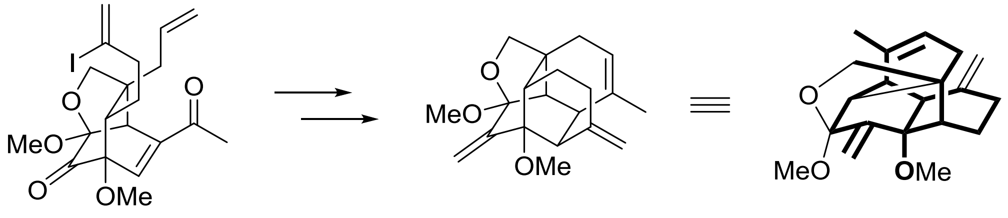
In 2009, the Njardarson group published their approach towards synthesizing the natural product.[39] In their short approach, the group utilized a hypervalent iodine promoted oxidative coupling of phenol **2.89** with allylic alcohol **2.90** (***Scheme 2.26***). They designed the phenol to be symmetrical as to avoid regiochemical issues and the reaction proceeded to form intermediate **2.92**, which was predisposed to undergo an intramolecular Diels-Alder reaction yielding tricyclic structure **2.91**.

***Scheme 2.26** – Oxidative dearomatization/Diels-Alder cascade*



A radical-based reaction was then used to cyclize the vinyl iodide and a ring-closing metathesis was used to form the final ring in compound **2.93** (***Scheme 2.27***). This approach led to the synthesis of the 3 rings present in the final product with the correct stereochemistry, but fragmentation reactions will be necessary to cleave the extra bonds in **2.93**. The underlying tricyclic core corresponding to vinigrol (**2.1**) is highlighted in bold bonds. No further reports on the progress of their total synthesis have been reported to date.

Scheme 2.27 *– Synthesis of the tricyclic core*



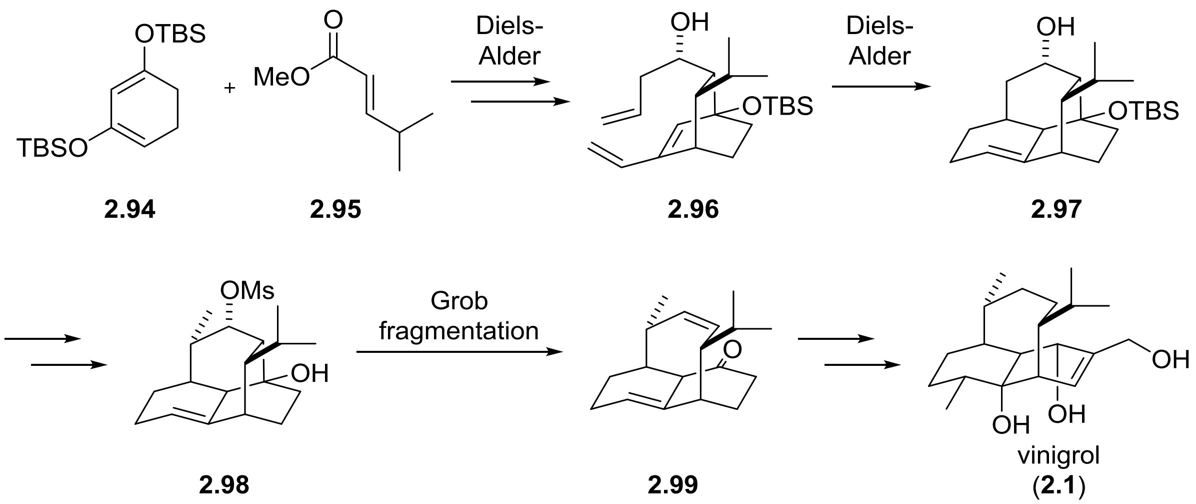
2.91

2.93

Baran's Total Synthesis

In 2008, the Baran group reported their approach to the core of vinigrol (**2.1**).[40] It consisted in an intramolecular Diels-Alder reaction followed by a Grob fragmentation at a later point in the synthesis. Their efforts culminated in the report of the first total synthesis of vinigrol (**2.1**) in late 2009.[41] The sequence began with an intermolecular Diels-Alder reaction between cyclohexadiene **2.94** and dienophile **2.95** to form a bicyclic structure which was then converted to precursor **2.96** in a few steps (***Scheme 2.28***). Diene **2.96** underwent an intramolecular Diels-Alder reaction when exposed to heat to generate tetracycle **2.97** which was converted to **2.98** in a short sequence. Compound **2.98** then underwent a Grob fragmentation when exposed to strongly basic conditions to reveal the tricyclic core of the natural product. Finally, all that was left was to install the remaining functional groups with the correct stereochemistry. Ultimately, the group finished the first total synthesis of vinigrol (**2.1**) in 25 steps from commercially available materials. Although the approach is somewhat reminiscent of a combination between Barriault's latest approach and one of Corey's approaches, the Baran group's work constitutes a milestone in the field of total synthesis.

Scheme 2.28 *– Baran's total synthesis of vinigrol*



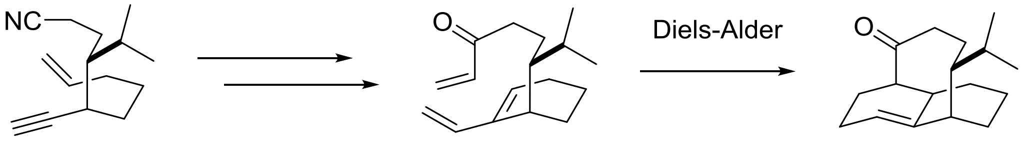
Chapter 3

Towards the Total Synthesis of Vinigrol

Novel Retrosynthetic analysis

In 2007, our group published an intramolecular Diels-Alder approach towards the synthesis of the tricyclic core of vinigrol (**2.80**).[37] Unfortunately, the substrate utilized in this report was not sufficiently functionalized to allow the total synthesis to be accomplished, but still demonstrated the feasibility of the approach (***Scheme 3.1***).

Scheme 3.1 *– Barriault's synthesis of the tricyclic core*

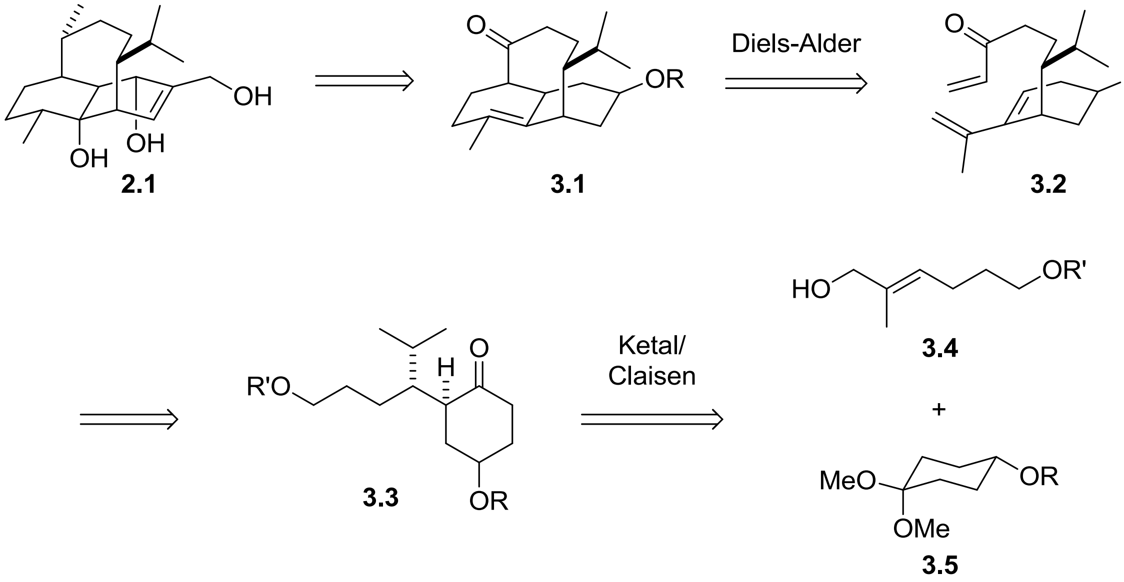


2.78 **2.79** **2.80**

Compound **2.80** not only lacked sufficient functionality, but the designed sequence was quite lengthy (20 steps) and not amenable to large scale synthesis. To circumvent these problems, a new substrate for the intramolecular Diels-Alder approach was designed by Prof.

Barriault and Dr. Christiane Grisé-Bard. The novel route was initially undertaken by Dr. Grisé-Bard, who was able to complete the synthesis of the tricyclic core and perform some preliminary investigations on further functionalization.[42] The selected route highlighted a diastereoselective ketal/Claisen rearrangement as the stereodefining step. The retrosynthetic analysis of this approach is presented in ***Scheme 3.2***.

Scheme 3.2 *- Novel retrosynthetic analysis*



Synthesis of Diels-Alder Precursor

The sequence began with the synthesis of both precursors for the ketal/Claisen rearrangement. Allylic alcohol **3.11** was prepared by treating an excess of 1,4-butanediol (**3.6**) with TBDPSCl and DIPEA to furnish mono-protected alcohol **3.7** in quantitative yield (***Scheme 3.3***). In the initial sequence, **3.7** was then oxidized under Swern conditions to the corresponding aldehyde which was used crude in a Horner-Emmons-Wadsworth olefination reaction with phosphonopropionate **3.9**.[43] This two-step procedure yielded ester **3.8** in 88% as an 87/13 mixture of *E*/*Z* products. Reduction of the mixture with DIBAL-H gave allylic alcohol **3.11** in 81% yield (***Scheme 3.4***), but separation of the two isomers required many flash chromatographies resulting in a very time-consuming purification process. It was later found[44] that the olefination could be performed *in situ* with phosphonium bromide **3.10** to yield 82% of a 94/6 *E*/*Z* mixture of compound **3.8** (***Table 3.1***).[45] Although the overall yield of both processes is similar, this procedure was simpler, less time consuming, used a cheaper phosphorus-based reagent, required less silica for purification and removed one synthetic step from the sequence.

Scheme 3.3 *– Synthesis of ester* ***3.8***

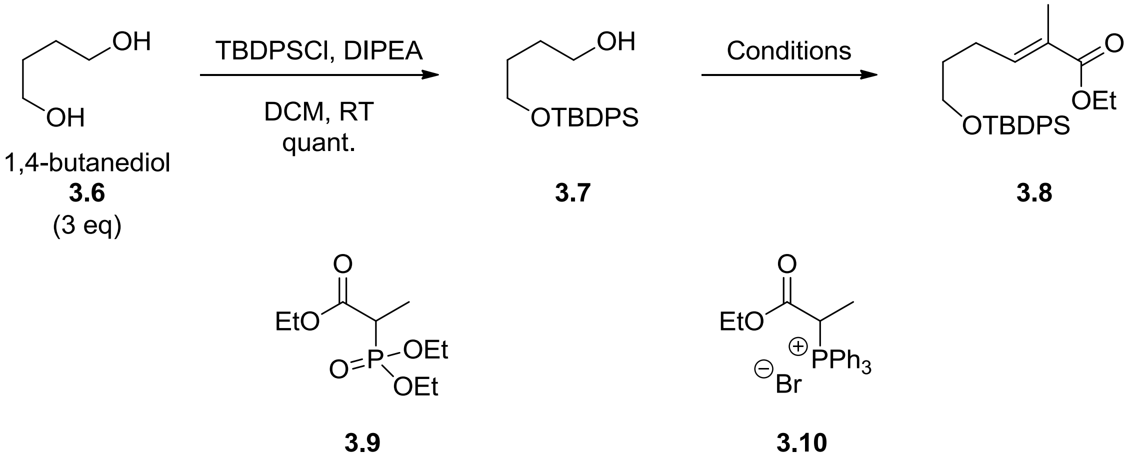
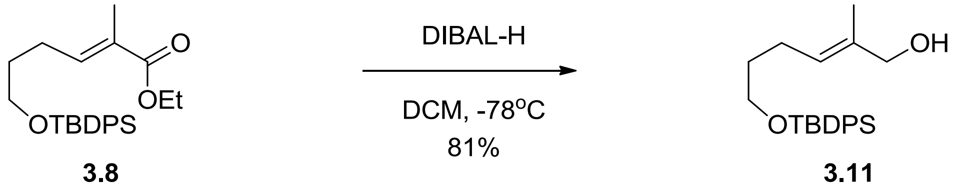


Table 3.1 *- Comparison of conditions to synthesize compound* ***3.8***

Entry	Conditions	Yield (%)	*E*/*Z* ratio
1	1) Swern 2) NaH, **3.9**	88 over 2 steps	87/13
2	Swern, then **3.10**	82	94/6

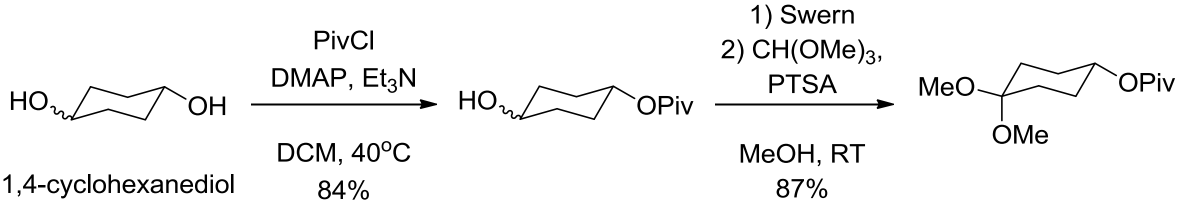
Scheme 3.4** – Preparation of allylic alcohol **3.11



3.8 **3.11**

The synthesis of dimethyl ketal **3.14** was investigated next (***Scheme 3.5***). The sequence began with the mono-protection of 1,4-cyclohexanediol (**3.12**), as a mixture of isomers, with PivCl to yield alcohol **3.13** in 84% yield. The mixture of isomers was of no consequence as the next step consisted in a Swern oxidation followed by treatment of the resulting crude ketone with $CH(OMe)_3$ to yield 87% dimethyl ketal **3.14** over 2 steps.

Scheme 3.5** – Preparation of dimethyl ketal **3.14

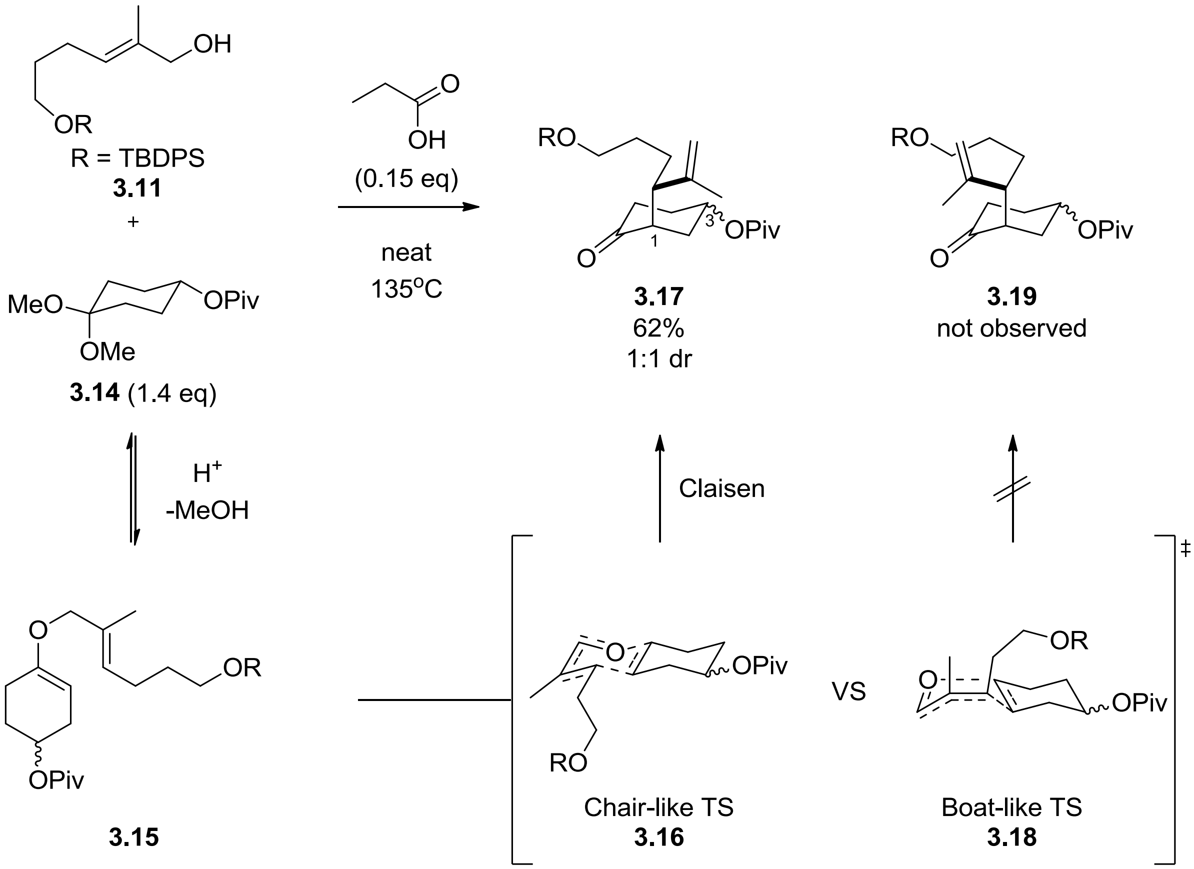


1,4-cyclohexanediol
3.12 **3.13** **3.14**

With both precursors in hand, the diastereoselective ketal/Claisen rearrangement could be investigated. The reaction allowed the installation of the isopropyl group with the correct stereochemistry, which is a particularly difficult chiral center to install, especially at a late stage in the synthesis.[46] After much optimization, it was found that heating precursors **3.11** and 1.4 equivalents of **3.14** in the presence of propionic acid at 135°C, as a neat solution, furnished ketone **3.17** in 62% yield.[6] The reaction proceeded with perfect control of the isopropyl chiral center, but as a 1 to 1 mixture of diastereomers at the pivaloate position (C3) (***Scheme 3.6***). This was of no concern, since it was imagined that this stereocenter would be destroyed by oxidation at a later stage of the synthesis.

The reaction proceeds through a transketalization reaction to form enol ether **3.15** and the equilibrium is pushed by removal of the generated MeOH, by distillation. The molecule was then poised to undergo the desired Claisen rearrangement which could proceed through two possible transition states, **3.16** and **3.18**. The selectivity is rationalized on the basis that chair-like transition state **3.16** is lower in energy than boat-like transition state **3.18** and therefore favours the formation of desired product **3.17**. It was found that ketal **3.14** co-eluted with the final product rendering purification somewhat difficult. This issue was addressed by mild hydrolysis of the excess reagent with oxalic acid in a mixture of THF and H_2O. This method selectively hydrolyzed compound **3.14** without affecting the stereochemical integrity of C1, which was found to be prone to epimerization under certain conditions.

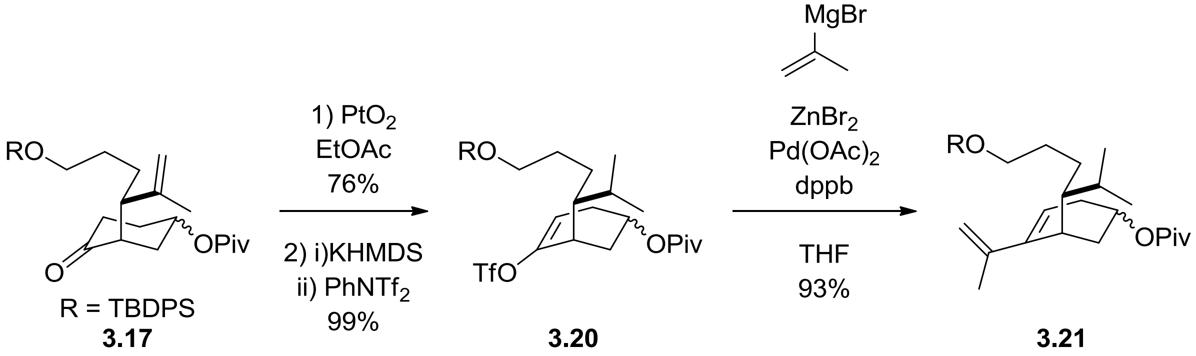
Scheme 3.6 ***-*** *Diastereoselective ketal/Claisen rearrangement*



The next goal was to convert the ketone **3.17** to the required diene for the key intramolecular Diels-Alder reaction. The first step was to hydrogenate the alkene, as previous studies showed that the presence of this alkene had a detrimental effect on the Diels-Alder reaction. Treatment of alkene **3.17** with Adams' catalyst in EtOAc provided the isopropyl group in 76% yield (***Scheme 3.7***).[47] In some instances, this reaction would not go to completion as it seemed that the presence of ketal **3.14** would poison the catalyst while undergoing hydrolysis to the corresponding ketone. Passing the reaction mixture on a silica gel column to remove the ketone and resubmitting **3.17** to the same conditions generally solved the problem. The next step consisted in transforming the ketone moiety to a diene through a coupling reaction by first converting it to enol triflate **3.20**. Formation of the enolate by careful deprotonation with KHMDS at -78 °C in THF followed by treatment with

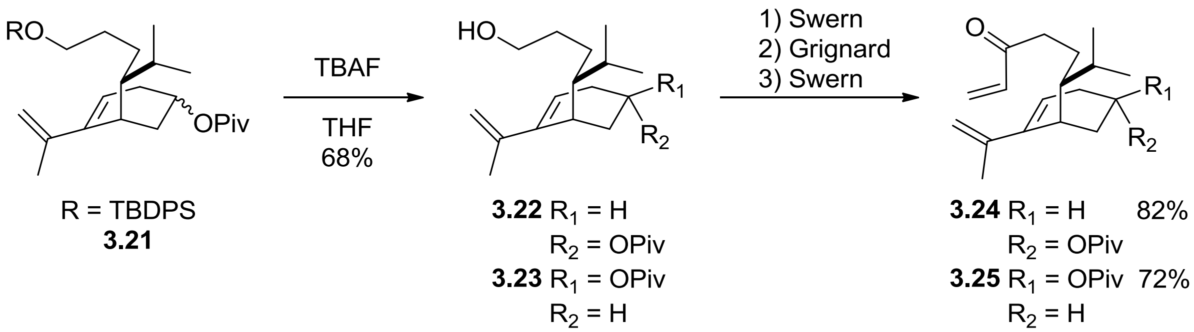
$PhNTf_2$ yielded 99% of coupling partner **3.20**. Subjection of **3.20** to Negishi cross-coupling conditions with isopropenylmagnesium bromide furnished 93% diene **3.21**.[48]

Scheme 3.7** - Synthesis of diene **3.21



With the diene in place, the final challenge before the key Diels-Alder reaction was the formation of the dienophilic portion of the substrate. To this end, TBDPS-protected **3.21** was treated with TBAF in THF to release a separable mixture of primary alcohols **3.22** and **3.23** in 68% yield. Each diastereomer was separately submitted to an oxidation-alkylation-oxidation sequence to form enones **3.24** and **3.25** (***Scheme 3.8***). Oxidation of primary alcohols **3.22** and **3.23** to the corresponding aldehyde under Swern conditions followed by alkylation with vinylmagnesium bromide and reoxidation under Swern conditions led to the formation of Diels-Alder precursors **3.24** and **3.25** in 82% and 72% yields, respectively. It is important to note that each intermediate in the sequence was sensitive to purification and has a tendency to decompose. The intermediates therefore needed to be immediately carried through to the next step without purification.

Scheme 3.8 *- Intramolecular Diels-Alder precursor preparation*



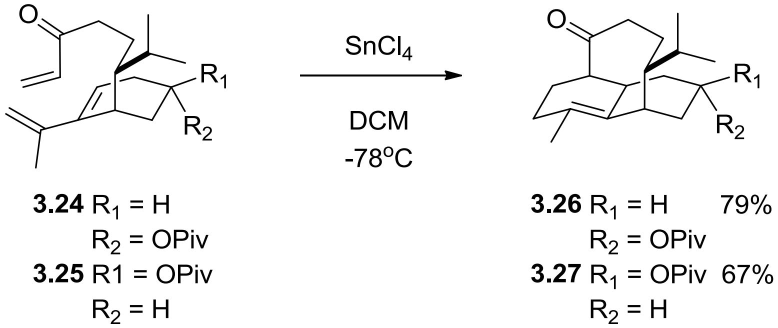
R = TBDPS
3.21

3.22 R_1 = H
R_2 = OPiv
3.23 R_1 = OPiv
R_2 = H

3.24 R_1 = H 82%
R_2 = OPiv
3.25 R_1 = OPiv 72%
R_2 = H

The stage was then set for the key step and after optimization of the Lewis acid, it was found that tin tetrachloride was the optimal reagent and promoted the desired cycloaddition to afford structures **3.26** and **3.27** in 67% and 79% yields (***Scheme 3.9***). This route allowed the formation of the tricyclic core of vinigrol (**2.1**) in 11 steps.

Scheme 3.9 *– Formation of the tricyclic core via an intramolecular Diels-Alder reaction*

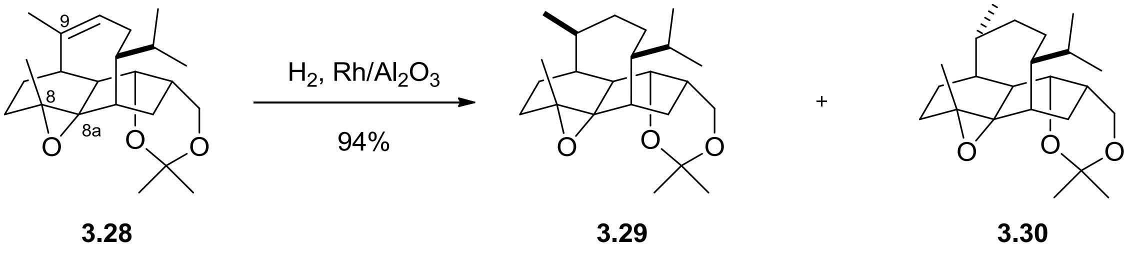


3.24 R_1 = H
R_2 = OPiv
3.25 R1 = OPiv
R_2 = H

3.26 R_1 = H 79%
R_2 = OPiv
3.27 R_1 = OPiv 67%
R_2 = H

With most of the carbocyclic framework of vinigrol (**2.1**) in place, the attention was then focused on the remaining stereogenic centers and functional groups required to complete the synthesis, which began with the installation of the methyl group at C9. It was imagined that this could be accomplished through an olefination/hydrogenation protocol on ketones **3.26** and **3.27**. There was some concern over this sequence, as Hanna and co-workers had a similar approach in installing this stereogenic center, but with disappointing diastereoselectivity.[28] Their attempts at hydrogenating alkene **3.28** led to a 3 to 2 mixture of products **3.29** and **3.30** (***Scheme 3.10***). Nonetheless, our group decided to investigate the effects of having an exocyclic alkene on the diastereoselectivity.

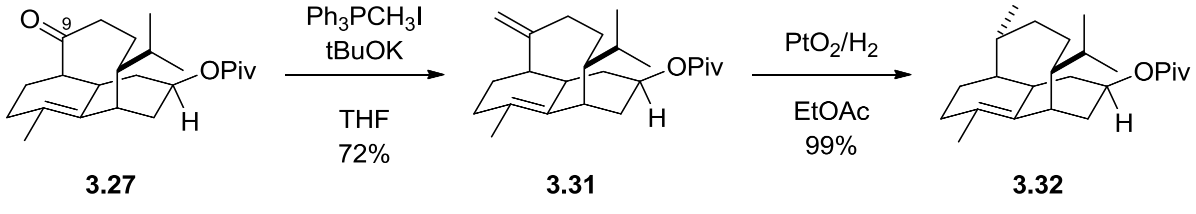
Scheme 3.10 *– Hanna's hydrogenation to generate the C9 chiral center*



dr = 3 : 2

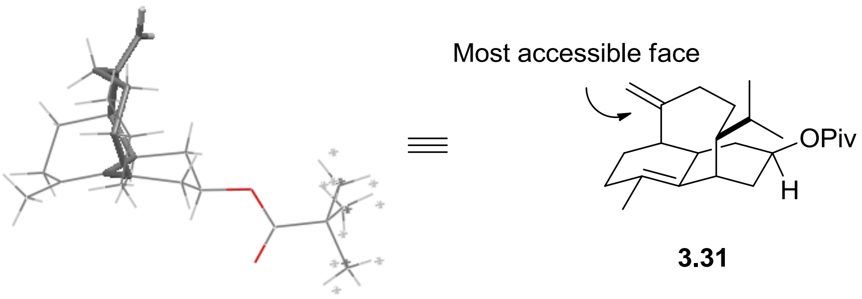
Wittig olefination of ketone **3.27** under Conia conditions,[49] proceeded smoothly to yield alkene **3.31** in 72% (***Scheme 3.11***). To our delight, hydrogenation of **3.31** with PtO_2 in EtOAc led to quantitative conversion to desired diastereomer **3.32** as a single product. The stereochemistry was unambiguously assigned by X-ray crystallographic analysis of the corresponding *para*-nitrobenzoate. The diastereoselectivity was initially attributed to conformational effects, since upon inspection of the X-ray structure of **3.31** (***Figure 3.2***), one could see that the more accessible face of the alkene leads to the desired diastereomer after hydrogenation.[50]

Scheme 3.11 *– Installation of the C9 methyl group*



dr >25 to 1

Figure 3.1** – X-ray structure of **3.31



3.31

It is important to note that there are notable differences between Hanna's system and the latter which are likely the cause for the increased selectivity. The presence of the endocyclic double bond in the *ansa* bridge of compound **3.28** likely adds rigidity to this cycle and pulls the C9 methyl group closer to the cyclohexane ring, increasing sterics on the desired face of the alkene. Furthermore, the presence of the epoxide in compound **3.28** could force the C8 methyl closer to the 8-membered ring, which shields one face of the trisubstituted alkene. Finally, upon inspection of late stage crystal structures from the literature; it was found that the hybridization of C8a appears to have a profound effect on the conformation of the medium-sized ring. Indeed, when C8a is a sp^3 center, the ring seems to adopt a boat/half-chair conformation, whereas a sp^2 carbon seems to induce a crown conformation. Although not entirely conclusive, these differences show the importance of controlling the cyclic conformations to achieve desired selectivities.

Unfortunately, the same outcome was not observed when the above sequence was applied to diastereomer **3.26**. Although, the olefination proceeded in 74% yield, the hydrogenation produced a mixture of diastereomers ranging from 2:1 to 6:1 favouring **3.34** (***Scheme 3.12***). It was impossible to separate both products by column chromatography, even after deprotection to the corresponding free alcohols. It was hypothesized that perhaps the orientation of the pivaloate group was influencing the conformation of the molecule leading to a reduction in facial selectivity. However, this hypothesis was discarded upon inspection of the X-ray structure of the enantiomer of alkene **3.33** (***Figure 3.2***).[50] When the bond angles and distances were compared between **3.31** and **3.33**, no significant differences were observed. It was therefore proposed that steric effects induced by the pivaloate group were responsible for the observed selectivity.

Scheme 3.12 *- Influence of chiral center on hydrogenation*

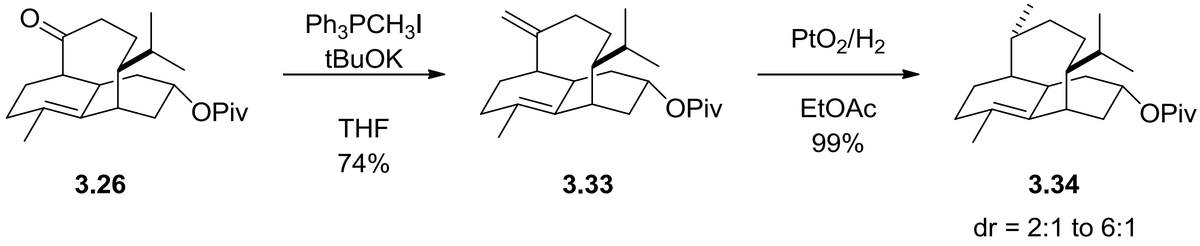
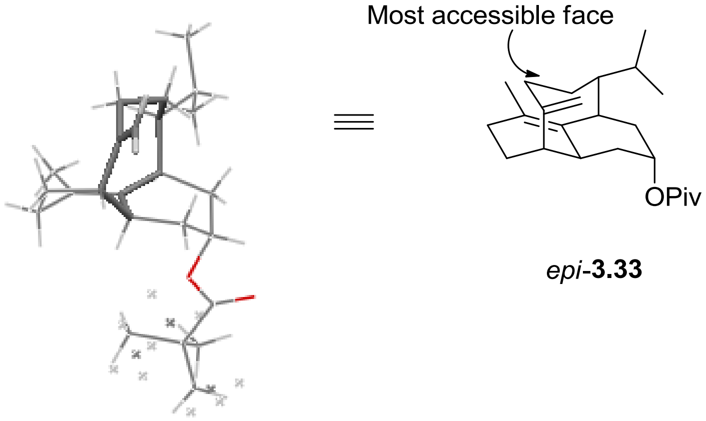


Figure 3.2 *– X-ray structure of epi-**3.33***



To circumvent the diminished stereoselectivity in the hydrogenation of **3.33**, it was anticipated that the stereogenic center could be inverted by an oxidation-reduction process. Deprotection of the hydroxyl group in **3.33** with DIBAL-H, followed by oxidation under Ley's conditions,[51] gave ketone **3.35** in 82% yield over 2 steps (***Scheme 3.13***). Unfortunately, reduction of **3.35** under different conditions gave inseparable mixtures of secondary alcohols **3.36** and **3.37**, always favouring undesired compound **3.37**. ***Table 3.2*** depicts different reducing agents employed and the ratios of diastereomers obtained. The boron based hydride sources (entries 1 and 3) led to lower yields than the aluminum based DIBAL-H (**3.39**). Also, smaller reducing agents were more successful at forming the desired isomer.

***Scheme 3.13** – Attempts at chiral center inversion*

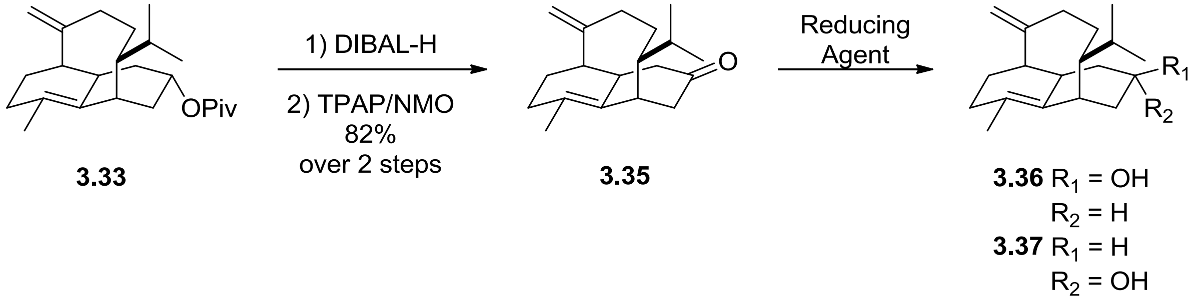


***Table 3.2** – Effect of reducing agent on the **3.36/3.37** ratio*

Entry	Reducing Agent	Yield (%)	3.36/3.37 ratio
1	L-selectride (**3.38**)	34%	1/25
2	DIBAL-H (**3.39**)	91%	1/3
3	$NaBH_4$	29%	1/1.5

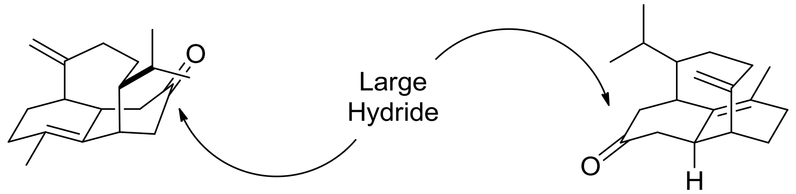
***Figure 3.3** – Structures of L-selectride and DIBAL-H*

L-selectride
3.38

DIBAL-H
3.39

These results suggest that the cyclohexane ring likely adopts boat conformation **3.35b** in preference to half-chair conformation **3.35a** (***Figure 3.4***). Attack of the hydride onto the ketone through the Bürgi-Dunitz angle[52] appears to be more strongly hindered by the cyclohexene ring than by the isopropyl and methylene groups.

Figure 3.4 *– Conformational effects on reduction selectivity*



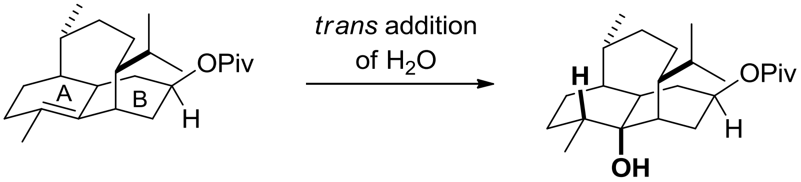
3.35a

3.35b

Attempts at functionalizing the A-ring

The synthesis was carried on with one of the two diastereomers while other options for the hydrogenation step were considered and elaborated. The next challenge in the synthesis was the functionalization of the tetrasubstituted alkene. The overall transformation consisted in a formal *trans* addition of H_2O across the alkene in **3.32** (***Scheme 3.14***), which we believed could be achieved through an epoxidation-ring opening protocol. Unfortunately, this approach proved unfruitful using a variety of hydride sources and radical-promoting Lewis acids on compound **3.41** (***Scheme 3.15***).[42]

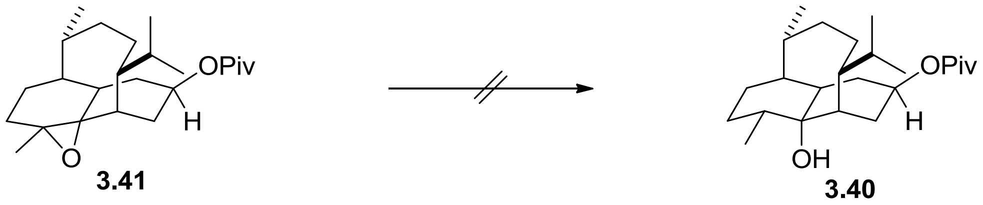
Scheme 3.14 *- Installation of the tertiary alcohol*



3.32

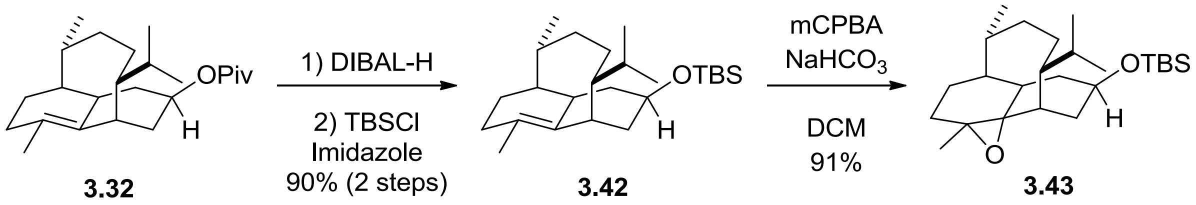
3.40

***Scheme 3.15** – Opening of epoxide*



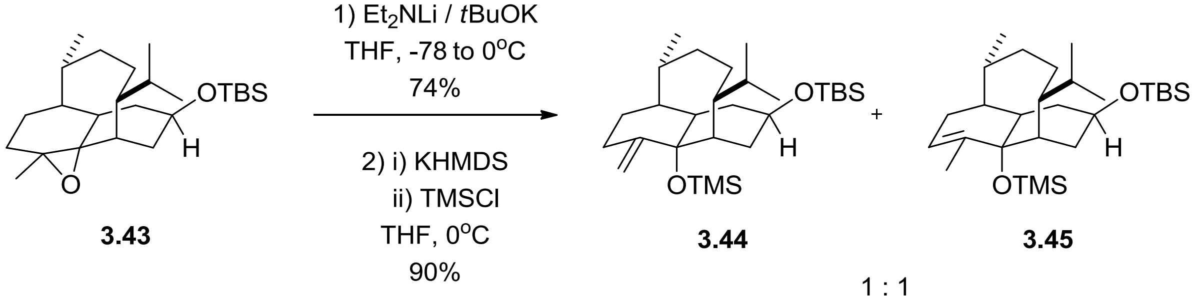
It was then imagined that epoxide **3.41** could be opened with a strong base and the resulting alkene could be hydrogenated. It was found by Dr. Grisé-Bard that a change in protecting group was necessary at this stage, since opening of epoxide **3.41** under basic conditions failed when the pivaloate group was present. Treatment of pivaloate **3.32** with DIBAL-H and treatment of the resulting hydroxyl group with TBSCl and imidazole furnished silyl protected alcohol **3.42** in 90% yield over 2 steps (***Scheme 3.16***). Epoxidation of alkene **3.42** proceeded smoothly with *m*CPBA and $NaHCO_3$ in DCM at 0 ^{o}C giving **3.43** in 91% yield.

Scheme 3.16** – Epoxidation of alkene **3.42



Treatment of **3.42** with potassium diethylamide in THF gave 74% of an inseparable 1:1 mixture of *endo* to *exo*-cyclic allylic alcohols **3.44** and **3.45** (***Scheme 3.17***). The next step in the synthesis was the hydrogenation of the double bond, but steric bulk was needed on the bottom face of the molecule to favour formation of the correct diastereomer at C8. To this end, the tertiary alcohol was protected to furnish a mixture of **3.44** and **3.45** in 90% yield, after deprotonation with KHMDS followed by treatment with TMSCl in THF. With these substrates in hand, hydrogenation of the alkene could be investigated. At this stage of the synthesis, the project was passed on to me, since Dr. Grisé-Bard graduated around this time.

Scheme 3.17** – Preparation of alkenes **3.44** and **3.45



Hydrogenation

A variety of conditions were tried to hydrogenate compounds **3.44** and **3.45** to compound **3.46** (***Scheme 3.18***) as seen in **Table 3.3**. Attempted hydroboration of the alkene and diimide reduction[53] led to recovery or decomposition of the starting material. Treatment under heterogeneous metal hydrogenation at 1 atmosphere of H_2 also led to recovery of the starting material. Finally, the hydrogenation pressures were increased up to 20 atm, but this led to the regeneration of alkene **3.42** in 32% yield, likely through the insertion of the metal into the alkene, followed by elimination of the –OTMS group.

Scheme 3.18** - Hydrogenation of alkenes **3.44** and **3.45

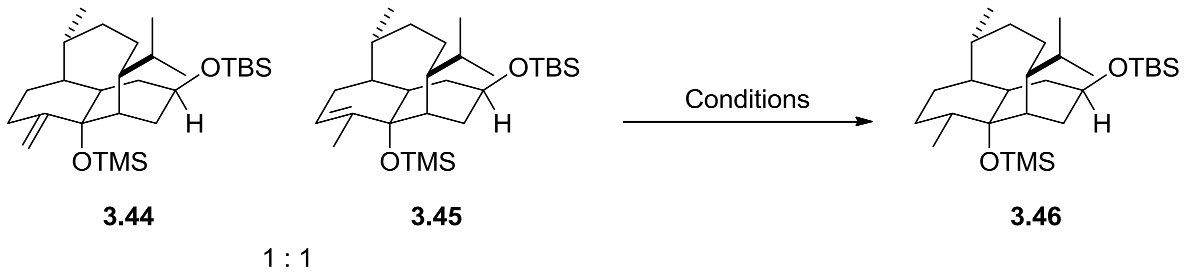


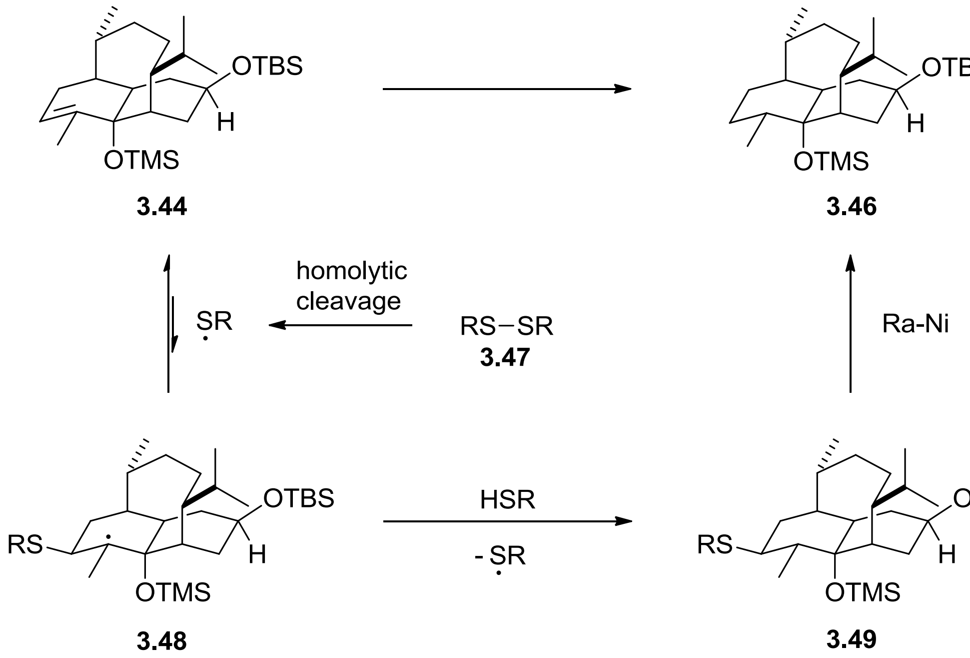
Table 3.3** – Hydrogenation conditions attempted on alkenes **3.44** and **3.45

Entry	Reagent	Temperature (°C)	Pressure (atm)	Result
1	BH_3 or 9-BBN	0 to RT	1	No reaction
2	Diimide	reflux/µwaves	1	Decomposed
3	Pd/C	RT to reflux	1	No reaction
4	$Pd(OH)_2$	RT to reflux	1	No reaction
5	Ra-Ni	RT to reflux	1	No reaction
6	PtO_2	RT to reflux	1	No reaction
7	PtO_2	RT	10	No reaction
8	PtO_2	RT	20	**3.42** (32 %)

Thiol-ene reaction

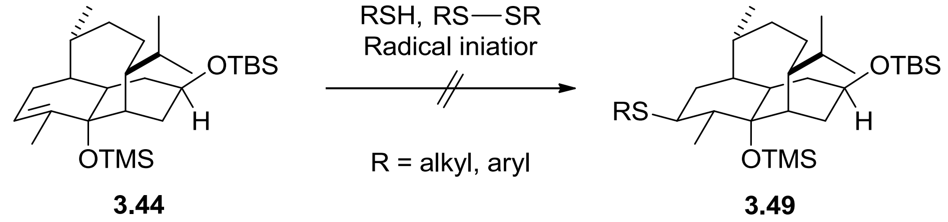
Since the alkene seemed to be too sterically hindered to undergo hydrogenation reactions, we imagined that perhaps a radical process would be more appropriate by functionalizing the less substituted carbon to give a stable tertiary radical. The process is known as the thiol-ene reaction and there are some examples in the literature.[54] We envisioned that a disulfide (**3.47**) would undergo homolytic cleavage when irradiated with light and that the sulfur radicals generated could add to alkene **3.44** to form tertiary radical **3.48**. The radical could then abstract a hydrogen atom from a sulfide present in solution to yield compound **3.49**, regenerate the sulfur radical and propagate the chain (***Scheme 3.19***). Sulfide **3.49** could then be treated with a reducing agent such as Ra-Ni to generate desired product **3.46**.

Scheme 3.19 *– Thiol-ene reaction*



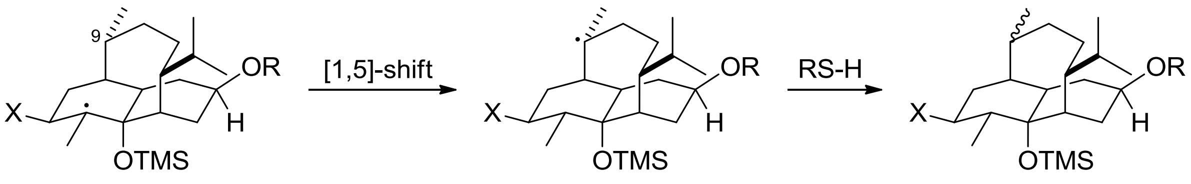
Unfortunately, despite attempting many different combinations of thiols, disulfides, radical initiators and solvents, no reaction was observed (***Scheme 3.20***). These processes are known to be reversible with the rate determining step being the hydrogen atom abstraction and we believe that the regeneration of the sulfide radical may be much faster than hydrogen abstraction, due to steric interactions.

Scheme 3.20 *– Attempted thiol-ene reactions*



Although plausible, the reversibility of the sulfur radical addition may not be the cause for the lack of reactivity, because there is also another possible hydrogen abstraction mechanism. Indeed, upon formation of tertiary radical **3.50**, the compound could be prone to undergo an intramolecular [1,5]-shift to form radical **3.51** (***Scheme 3.21***). This phenomenon could have led to an observed epimerization at C9. Since no epimerization was observed, it is possible that the initial radical addition may not have taken place at all.

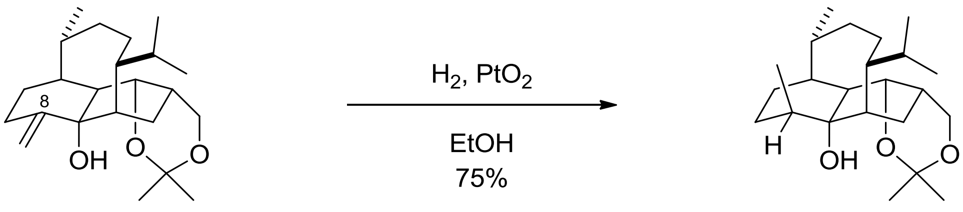
Scheme 3.21 *- Possible epimerization of C9 methyl group*



3.50 **3.51** **3.52**

As we were working on this step, Hanna and co-workers disclosed their final report towards the synthesis of vinigrol.[29] Their efforts culminated with the synthesis of *epi*-C8-dihydrovinigrol through the hydrogenation of an allylic alcohol similar to substrate **3.44**. They were never able to install the methyl group at C8 with the correct stereochemistry through hydrogenation (***Scheme 3.22***). With this result and our own conclusions on this pathway, we sought out a different method to installing the stereogenic center at C8.

Scheme 3.22 *– Hanna's hydrogenation*

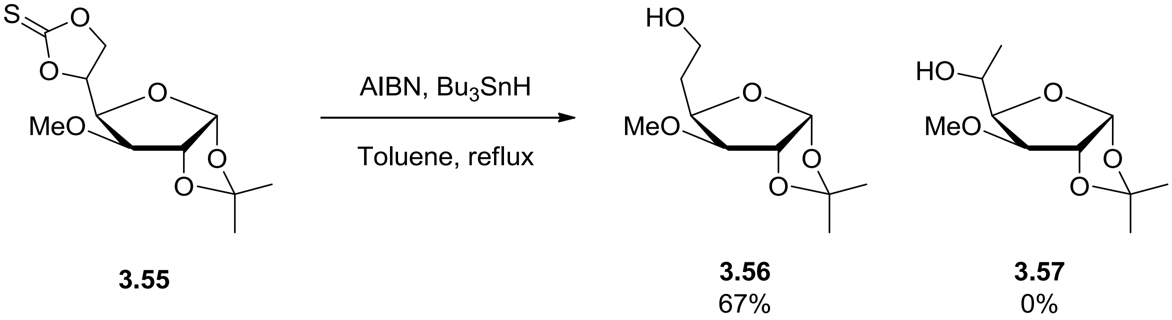


3.53 **3.54**

Dihydroxylation route

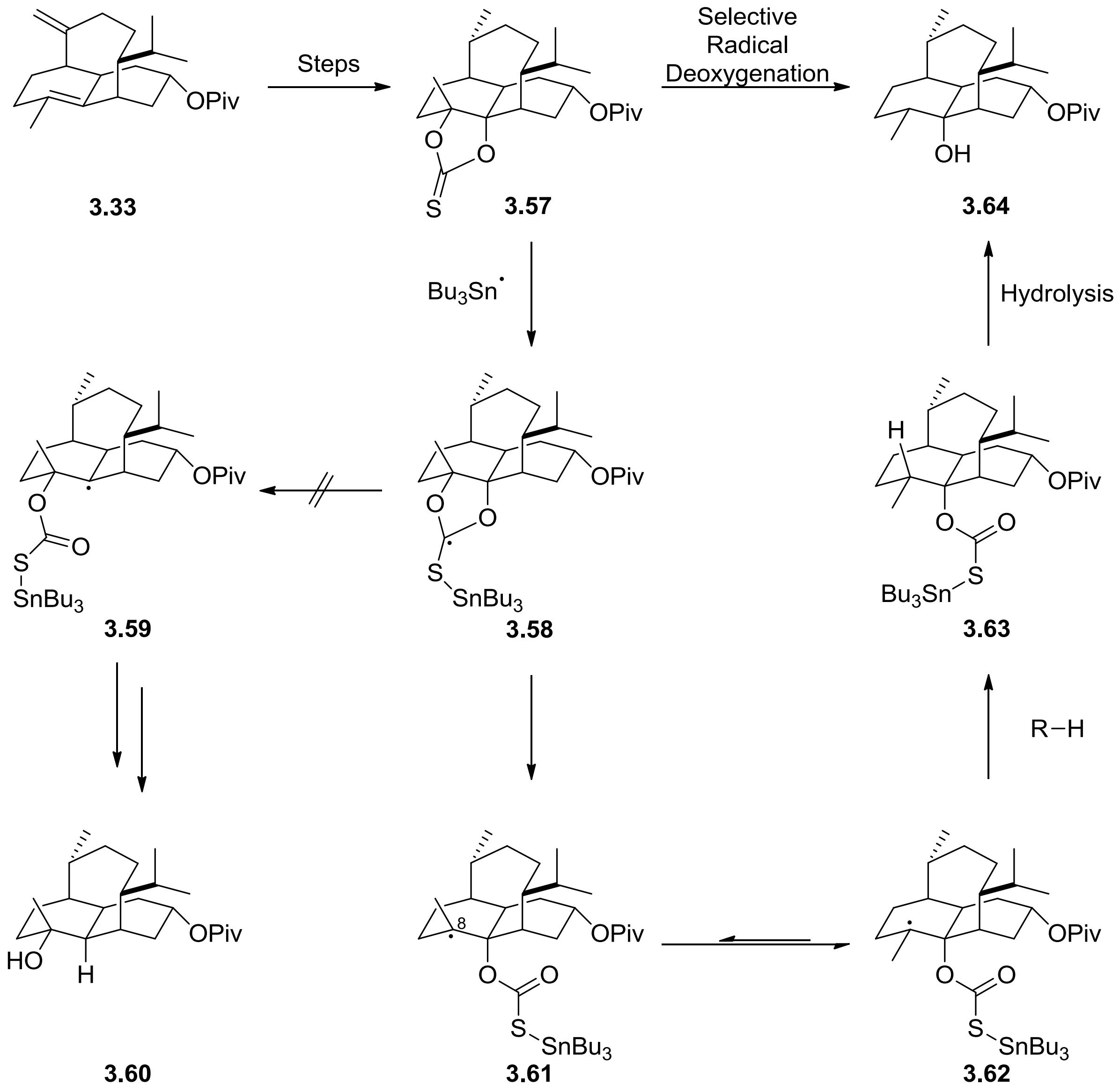
Drawing inspiration from the thiol-ene approach, we envisioned other ways of generating a tertiary radical at C8. The reaction that initially came to mind was a Barton-McCombie deoxygenation reaction. There have been reports in the literature of selective monodeoxygenation reactions of 1,2-diols via a radical reduction of the corresponding thiocarbamate when there is a stability difference between the generated carbon centered radicals. One example is depicted in ***Scheme* 3.23** in which treatment of thiocarbamate **3.55** with AIBN and Bu_3SnH favoured the formation of a secondary radical over a primary radical. This led to the selective formation of monodeoxygenated compound **3.56** in 67% yield.[55]

Scheme 3.23 – Selective reduction of furanose derivative **3.55**



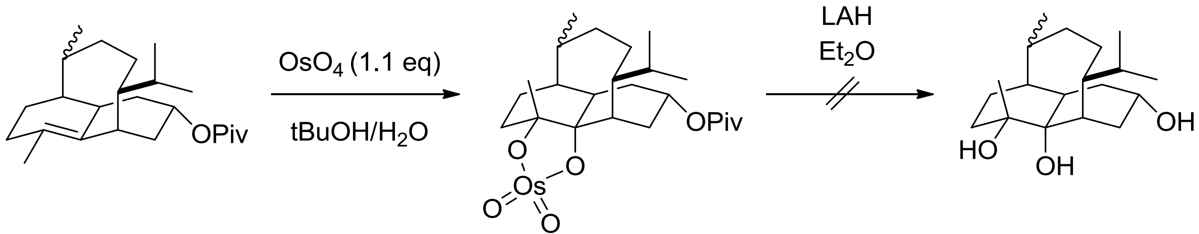
In our case, we believed that alkene **3.33** could be easily converted to thiocarbamate **3.57** through a dihydroxylation/protection sequence. It was then hypothesized that upon treatment of **3.57** under radical conditions, stable radical **3.58** would be generated and poised to fragment via two possible pathways. We thought that fragmentation could favour the formation of the radical at C8 (**3.61**) over C8a (**3.59**), perhaps through an increase in steric decompression (***Scheme 3.24***). This radical could then exist in 2 possible conformations either having the methyl group in an axial (**3.61**) or equatorial orientation (**3.62**). We hoped that **3.62** could then undergo hydrogen abstraction from the top face or undergo a [1,5]-shift in this conformation (similar to the one depicted in ***Scheme 3.21***) to afford desired product **3.64** after hydrolysis.

Scheme 3.24 *- Selective radical reduction of* ***3.57***



To test this hypothesis, alkene **3.34** was treated with osmium tetroxide in the presence of NMO (***Scheme 3.25***). It is well documented that dihydroxylation of tetrasubstituted alkenes have low turnovers,[56] which was demonstrated in this case by the necessity of using a stoichiometric amount of OsO_4 to obtain complete conversion. Due to steric hindrance surrounding the alkene, aqueous hydrolysis of the resulting osmate ester was impossible, concurring with results obtained by Hanna and co-workers.[29] In order to cleave the osmate ester, **3.65** was treated with LAH in Et_2O, but triol **3.66** was never obtained. This method would have had the added advantage of simultaneously cleaving the pivaloate to liberate the secondary alcohol. We believe that triol **3.66** may have bound to aluminum from the LAH and all attempts to hydrolyze the Al-O bonds resulted in decomposition or isolation of starting material. It was also attempted to hydrolyze the osmate ester using methanesulfonamide, a reagent known to significantly accelerate the rate of Sharpless dihydrohydroxylation reactions,[57] but without success. This route was therefore abandoned and another approach was designed.

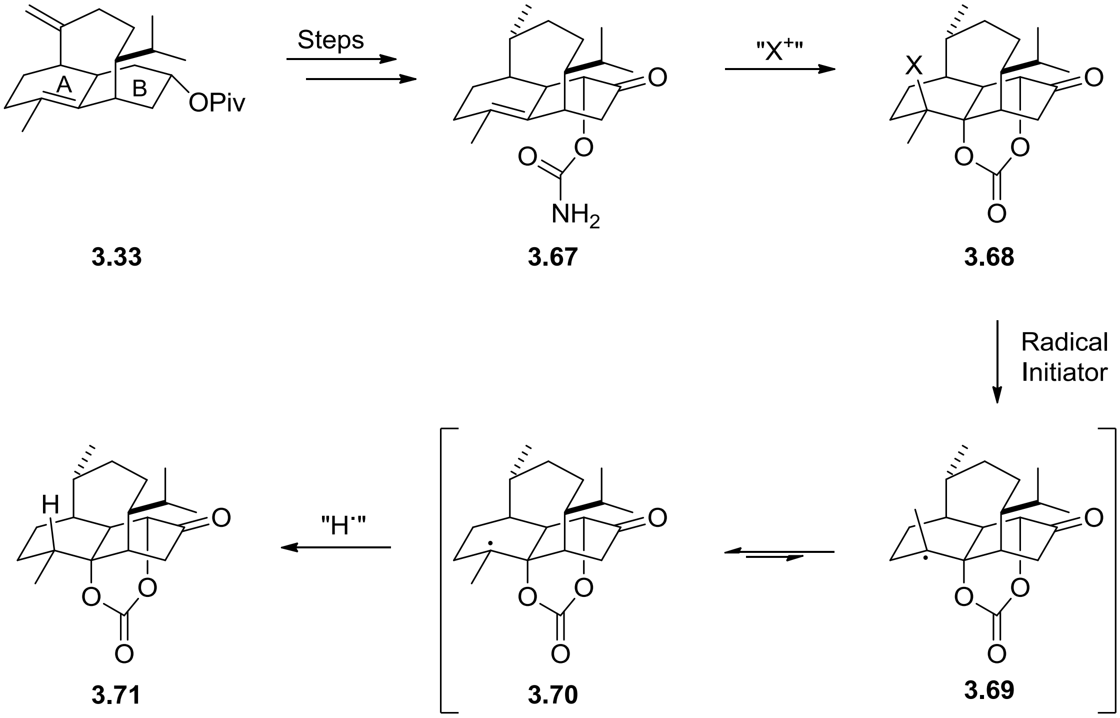
Scheme 3.25 *– Attempted synthesis of triol* ***3.66***



Attempts at functionalizing the B ring

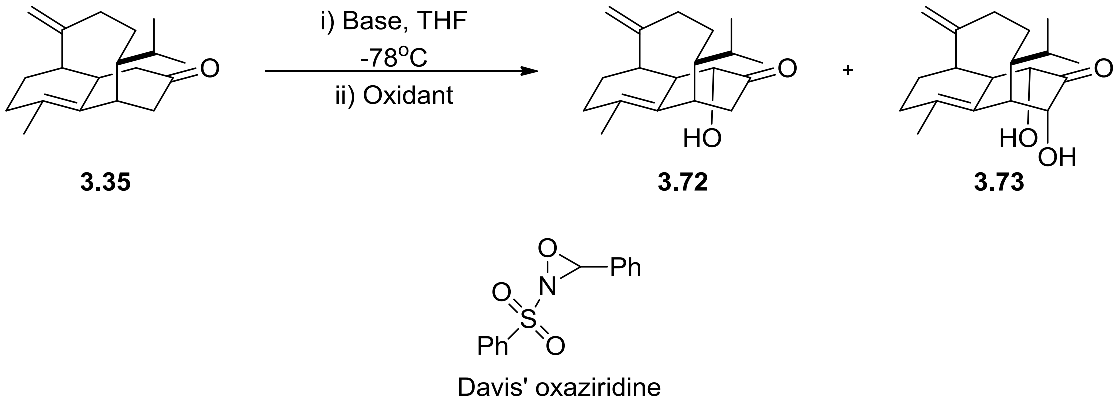
Since the complete functionalization of the A ring was not accomplished due to many drawbacks, we decided to investigate the functionalization of the B ring. We sought to design an approach that would allow the functional groups on the B ring to be used as handles to then react on the A ring. We believed that this could be achieved through the synthesis of carbamate **3.67** from alkene **3.33** (***Scheme 3.26***). Compound **3.67** could then be subjected to halocyclization conditions to install the tertiary hydroxyl group and the halogen could be reduced under radical conditions to yield tetracycle **3.71**. Very few synthetic steps would remain to attain vinigrol (**2.1**).

Scheme 3.26 *- Proposed radical dehalogenation*



The first hurdle to this route was selectively installing the secondary hydroxyl group. We were concerned with this step because the reaction could potentially yield four products, *i.e.* 2 regioisomers both with 2 possible diastereomers. To investigate the reaction ketone **3.35** (***Scheme 3.27***) was treated with different bases and oxidizing agents (***Table 3.4***). KHMDS was found to be the most effective base, whereas its lithium and sodium counterparts led to no reaction or decomposition of the starting material (entries 1-3). Davis' oxaziridine (**3.74**)[58] and MoO_5·Py·HMPA (MoOPH), a reagent developed by Vedejs,[59] were used as oxidants (entries 3 and 4) with the more electrophilic **3.74** giving the best results. Although a single isomer was obtained in 63% yield, the stereochemistry was not established at this point because of purification issues. The reaction was also found to be highly irreproducible and could not be scaled beyond 10 mg. This irreproducibility likely resulted from the scale limitations, purification issues, varying degrees of over oxidation to form product **3.73** and degradation of the starting material. At one point, the problem was also thought to arise from different concentrations of adventitious oxygen, as it is known to oxidize enolates to form α-hydroxy ketones.[60] Although quenching the enolate by bubbling oxygen through the solution and reducing the formed peroxide with $(EtO)_3P$ did produce the desired compound, this method only afforded approximately 5% of **3.72**. Finally, deuterium studies showed that deprotonation of the ketone was efficient and thus reactivity problems were mainly caused by the oxidation process.

Scheme 3.27** – Selective oxygenation of ketone **3.35



3.35 **3.72** **3.73**

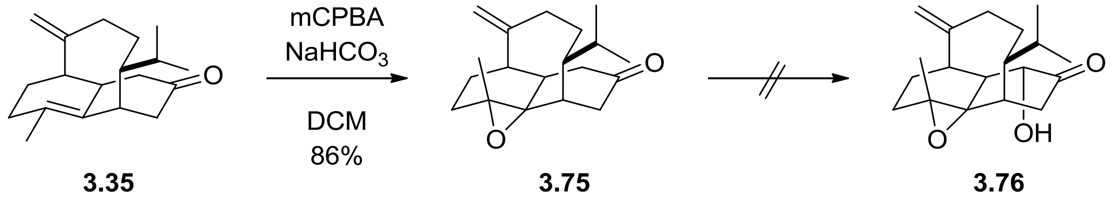
3.74

***Table 3.4** – Oxygenation conditions*

Entry	Base	Oxidant	Yield (%)
1	LiHMDS	Oxaziridine **3.74**	No reaction (-78 °C-0 °C) Decomposition (RT)
2	NaHMDS	Oxaziridine **3.74**	No reaction (-78 °C-0 °C) Decomposition (RT)
3	KHMDS	Oxaziridine **3.74**	63
4	KHMDS	MoO_5.Py.HMPA (MoOPh)	32
5	KHMDS	$O_2/(EtO)_3P$	< 5

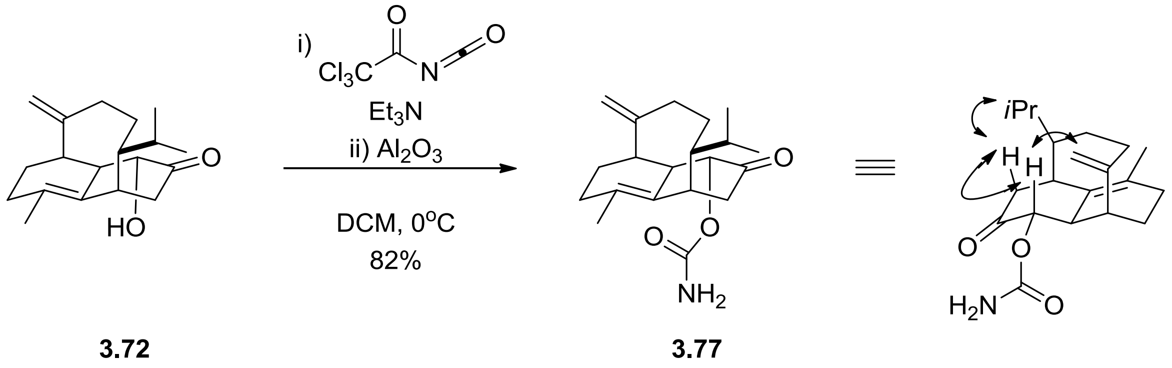
Another hypothesis for the reactivity problem was the possible interference of the tetrasubstituted alkene during the oxidation process.[61] To evaluate this, alkene **3.35** was epoxidized using *m*CPBA to rapidly yield 86% of epoxide **3.75** (***Scheme 3.28***). Unfortunately, all attempts at performing the α-hydroxylation of this compound did not yield desired product **3.76**.

Scheme 3.28** – Epoxidation of alkene **3.35



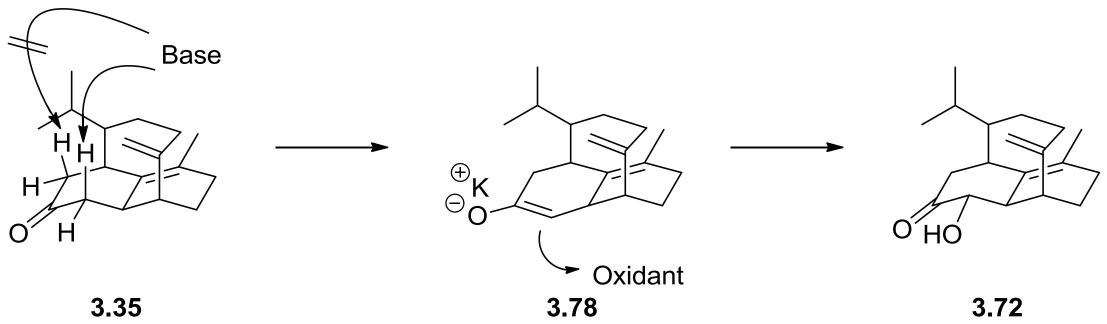
Nevertheless, we decided to proceed with the small quantity of **3.72** obtained and form the carbamate moiety to hopefully assign the stereochemistry of the secondary hydroxyl group. Treatment of alcohol **3.72** with trichloroacetylisocyanate followed by mild hydrolysis of the trichloroacetyl functionality with basic alumina afforded primary carbamate **3.77** in 82% yield (***Scheme 3.29***).[62] At this stage it was possible to obtain the product sufficiently pure to analyze the NOE interactions and determine which product was formed in the previous oxygenation reaction. To our delight, the spectra obtained confirmed the formation of desired product **3.72** with the correct stereochemistry.

Scheme 3.29 *– Synthesis and stereochemical assignment of* ***3.77***



The selectivity of the reaction can be explained by the fact that in its lowest energy conformation (***Scheme 3.30***), the acidic protons α to the ketone are on the top face of the molecule (axial and perpendicular to the π system), which is consistent with the observed reduction ratios in ***Table 3.2***. Upon deprotonation, there are severe interactions between the bulky base and the isopropyl group of the *ansa* bridge, which favour the formation of enolate **3.78**. The oxidant then approaches from the less sterically hindered bottom face to yield desired hydroxy-ketone **3.72**.

Scheme 3.30 *- Explanation of regioselectivity*



The final questions to be addressed through this route were the diastereoselectivity of the disubstituted alkene hydrogenation and the possibility of functionalizing the tetrasubstituted alkene. Hydrogenation of compound **3.77** on PtO_2 yielded 87% of **3.79** as a single product (***Scheme 3.31***). Although the stereochemistry of the product could not be assigned, it is probable that the desired selectivity was obtained based on previous studies. Unfortunately, only a very small quantity of **3.79** was synthesized, which is mainly due to the inefficient oxidation reaction. Nonetheless, a few reaction conditions were still tested for the halolactonization reaction[59,63] but none led to the isolation of desired product **3.68** (***Table 3.5***). This result can be rationalized by the fact that the halonium ion must form on the more sterically hindered face of the molecule, i.e. *anti* to the carbamate moiety, which is likely unfavorable. Also, upon performing a thorough literature search, we found no examples of iodolactonization reactions on tetrasubstituted alkenes. For these reasons, and the fact that the oxidation reaction was not scalable or reproducible, this pathway was discarded and another had to be devised to complete the total synthesis of vinigrol (**2.1**).

Scheme 3.31** – Hydrogenation of alkene **3.77** and attempted halolactonization of **3.79

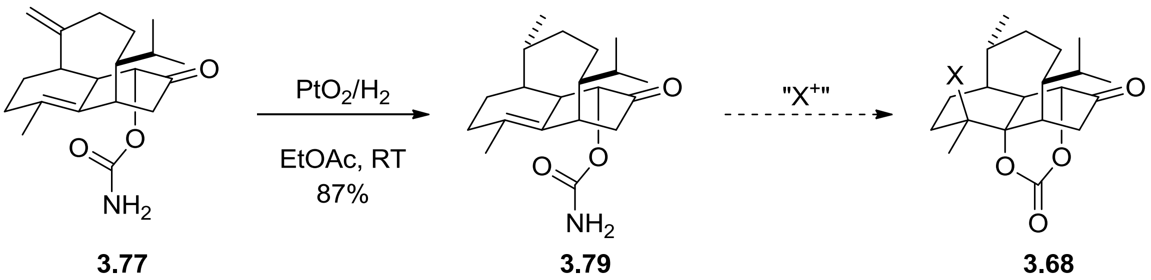


***Table 3.5** – Iodocyclization conditions*

Reagent	Additives	Solvent	Result
I_2	AgOTf	THF/H_2O	No isolated product
I_2	AgOTf/$NaHCO_3$	ACN	Decomposed
IBr	none	DCM	Decomposed

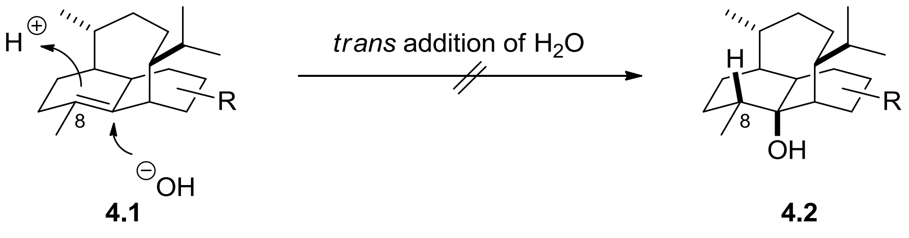
Chapter 4

Formal Synthesis of Vinigrol

Modified retrosynthesis

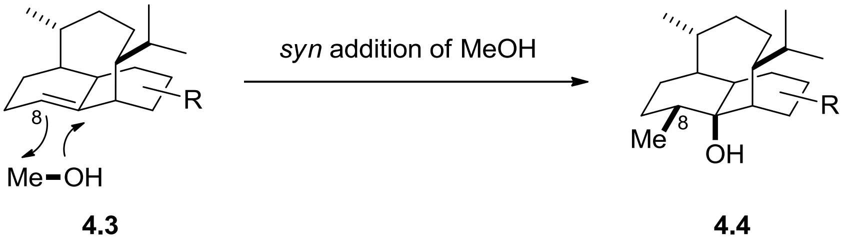
The main challenge from our previous route turned out to be the installation of the C8 methyl group with the correct stereochemistry. Although many different approaches were attempted, none allowed us to accomplish this feat. Indeed, our strategy which consisted in the formal *trans* addition of water across the tetrasubstituted alkene in **4.1** was discarded and we sought to find an alternative (***Scheme 4.1***).

Scheme 4.1 - *Functionalization of alkene* ***4.1***



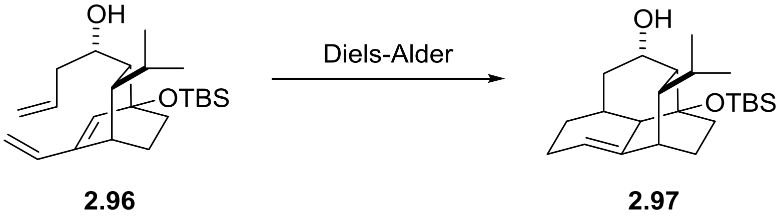
A slightly modified way of tackling the problem would be to remove the methyl group in compound **4.1** to give trisubstituted alkene **4.3** (***Scheme 4.2***). With this approach, the installation of the desired C8 methyl group could be achieved through a formal *syn* addition of methanol. Although there are no direct ways to functionalize an alkene in such a way, we envisioned different multi-step sequences which might allow the desired transformation to take place.

Scheme 4.2 **-** *Functionalization of alkene* ***4.3***



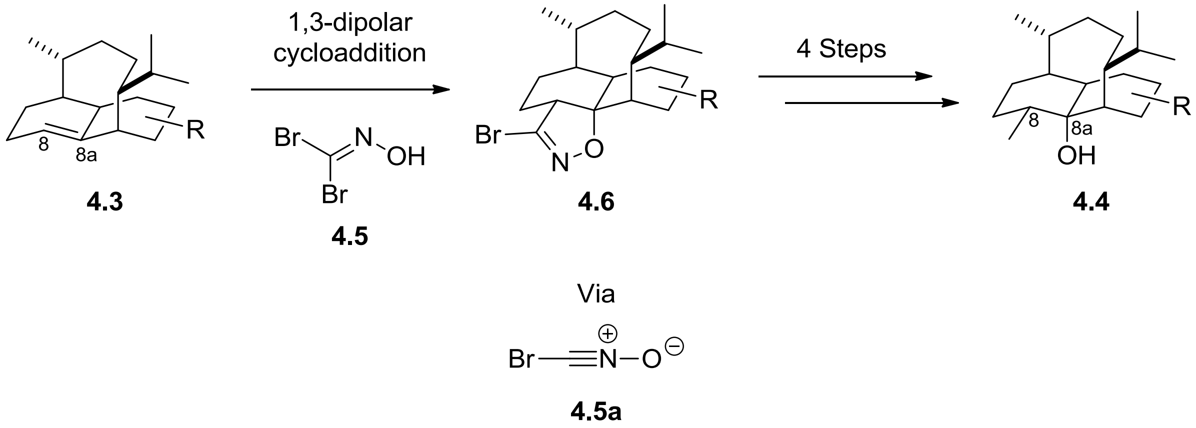
Towards the end of 2009, Baran and co-workers disclosed their report on the total synthesis of vinigrol (**2.1**).[41] Their strategy relied upon an intramolecular Diels-Alder reaction of substrate **2.101** to yield tetracycle **2.102** (***Scheme 4.3***), a product somewhat similar to alkene **4.3**.

Scheme 4.3 **-** *Baran's intramolecular Diels-Alder reaction*



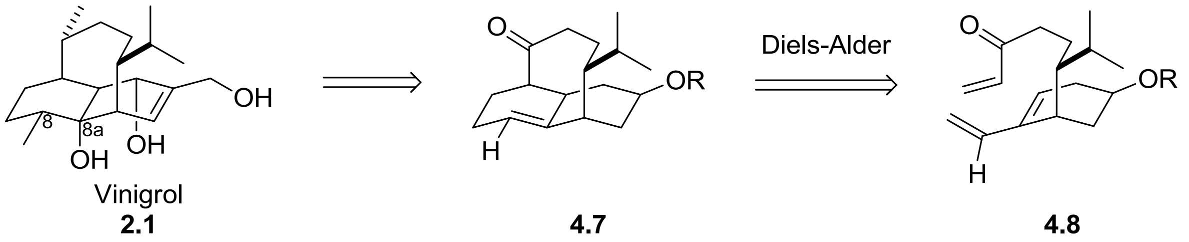
Indeed, this group was able to exploit the presence of the trisubstituted double bond to successfully install both the C8a tertiary hydroxyl and C8 methyl groups contained in the natural product (***Scheme 4.4***). Their multi-step procedure consisted in a 1,3-dipolar cycloaddition with nitrile oxide **4.5a**, generated *in situ* from dibromoformaldoxime **4.5**, to furnish isoxazole **4.6**.[64] A few more transformations allowed the formation of **4.4**, successfully installing the required methyl and hydroxyl groups.

Scheme 4.4 *- Functionalization of alkene* ***4.3***



Based on this report, we believed that we could complete the total synthesis by first synthesizing compound **4.8**, lacking the methyl group on the diene portion, and subjecting it to an intramolecular Diels-Alder reaction (***Scheme 4.5***). With alkene **4.7** we could attempt to develop a novel method for installing the C8 methyl and C8a tertiary alcohol or if all attempts failed, we could still rely on the chemistry developed by the Baran group to perform the task.

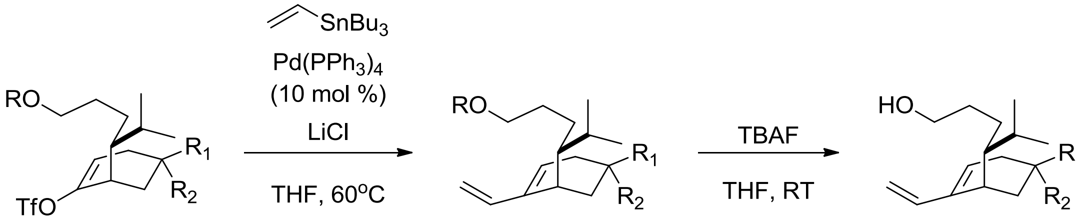
Scheme 4.5 *- Modified retrosynthetic scheme*



Synthesis of the tricyclic core

To test this hypothesis, we devised a new synthetic scheme which began with the same route, as depicted in ***Schemes 3.3*** to ***3.7,*** to form enol triflates **4.9** and **4.10** (***Scheme 4.6***). However, in this case, the diene-forming Negishi coupling was replaced by a Stille reaction using tributylvinyltin as coupling partner.[41,65] Indeed heating each diastereomer of the triflate (**4.9** and **4.10**) separately in the presence of tributylvinyltin and 10 mol% of $Pd(PPh_3)_4$ at 60 °C in THF produced the corresponding dienes. Compound **4.11** was obtained in 80% yield whereas diene **4.12** was highly contaminated with inseparable tin by-products. Treatment of both dienes with TBAF led to the deprotection of the hydroxyl group to afford primary alcohols **4.13** and **4.14** in 84% and 64% (over 2 steps), respectively.

Scheme 4.6 *– Formation of primary alcohols* ***4.13*** *and* ***4.14***



R = TBDPS

4.9 R_1 = OPiv
R_2 = H
4.10 R_1 = H
R_2 = OPiv

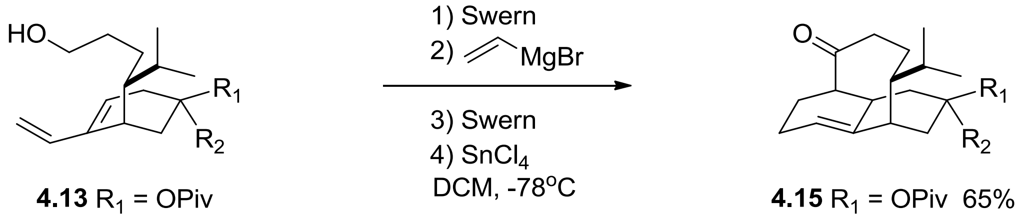
R = TBDPS

4.11 R_1 = OPiv 80%
R_2 = H
4.12 R_1 = H
R_2 = OPiv

4.13 R_1 = OPiv 84%
R_2 = H
4.14 R_1 = H 64% (2 steps)
R_2 = OPiv

Subjecting alcohols **4.13** and **4.14** to identical oxidation/alkylation/oxidation/Diels-Alder sequences furnished the corresponding tricyclic cores **4.15** and **4.16** in 65% and 67% yields over 4 steps (***Scheme 4.7***).

Scheme 4.7** – Formation of tricyclic cores **4.15** and **4.16



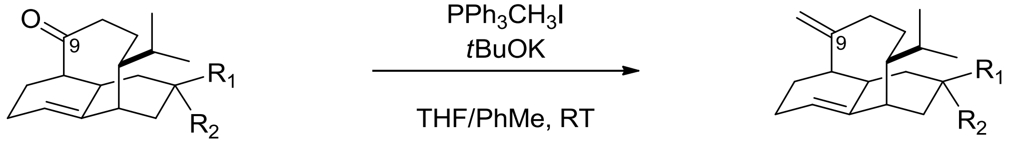
4.13 R_1 = OPiv
R_2 = H
4.14 R_1 = H
R_2 = OPiv

4.15 R_1 = OPiv 65%
R_2 = H
4.16 R_1 = H 67%
R_2 = OPiv

Installation of C9 methyl group

With the core structures in hand, we next turned our attention towards the installation of the C9 methyl group. Treatment of ketones **4.15** and **4.16** under Wittig conditions at room temperature yielded corresponding alkenes **4.17** and **4.18** in 88% and 91% respectively (***Scheme 4.13***).

Scheme 4.8** – Wittig reaction on ketones **4.15** and **4.16



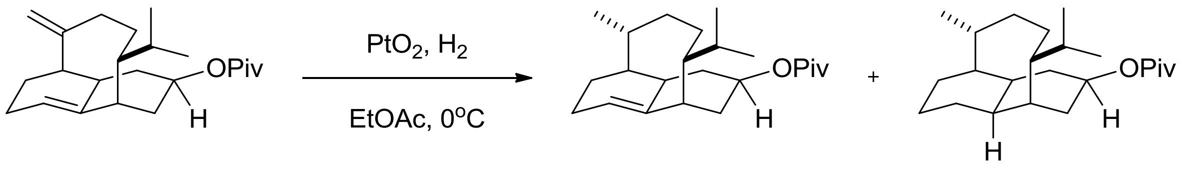
4.15 R_1 = OPiv
R_2 = H
4.16 R_1 = H
R_2 = OPiv

4.17 R_1 = OPiv 88%
R_2 = H
4.18 R_1 = H 91%
R_2 = OPiv

At this stage, we had some concerns over the regioselectivity of the hydrogenation reaction, since trisubstituted alkenes are generally more reactive towards hydrogenation than their tetrasubstituted equivalents. Fortunately, it was possible to obtain some selectivity when treating alkene **4.17** with PtO_2 and hydrogen in EtOAc at 0 °C to provide alkene **4.19**

(***Scheme 4.9***). Unfortunately, variable quantities of over-reduced compound **4.20** were also obtained. The reaction was impossible to monitor by TLC, and ^{1}H NMR or GC analyses were too lengthy to allow appropriate control of reaction time. To our delight, we serendipitously discovered that changing suppliers for the platinum catalyst allowed for full selectivity in the hydrogenation process (***Table 4.1***). Indeed, when changing from the Alfa Aesar catalyst to the Sigma-Aldrich equivalent (same mesh size and water content) excellent results were obtained in each reaction conducted that may be attributed to the presence of an impurity which poisons the catalyst. It is noteworthy that this reaction was reproduced with various bottles and batches of Sigma-Aldrich's product and identical results were obtained in each case.

Scheme 4.9** – Selective hydrogenation of alkene **4.17



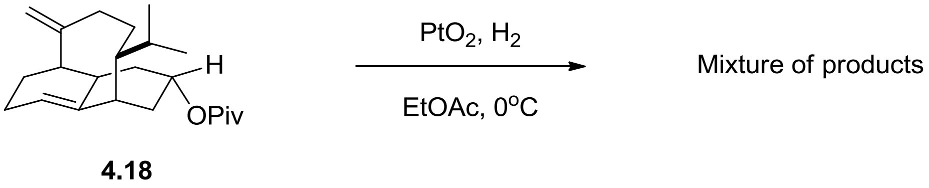
4.17 **4.19** **4.20**

Table 4.1** – Hydrogenation conditions for alkene **4.17

Entry	Source of PtO_2	Temperature	Yield (%)	4.19/4.20 Ratio
1	Alfa Aesar	RT	98%	10/90
2	Alfa Aesar	0 °C	99%	30/70
3	Sigma-Aldrich	0 °C	99%	100/0

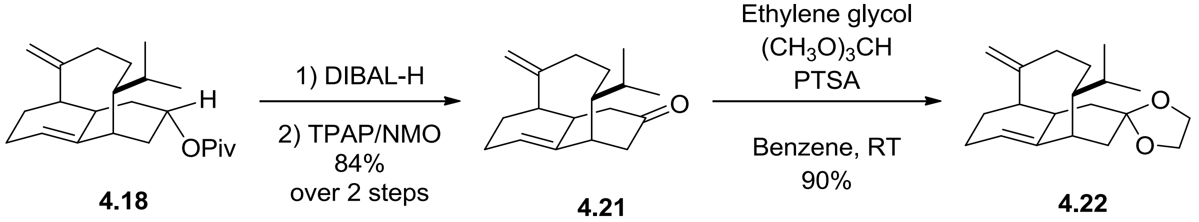
When the same reaction conditions were applied to alkene **4.18**, a mixture of products ensued from the unselective C9 reduction, reminiscent of the hydrogenation of alkene **3.33** (***Chapter 3***), and problems in regioselectivity (***Scheme 4.10***).

Scheme 4.10** – Attempted selective hydrogenation of alkene **4.18



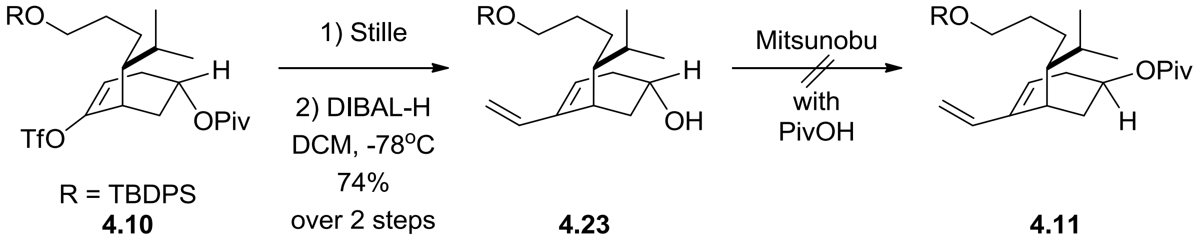
In an attempt to add steric hindrance to the top face of the molecule, ketal **4.22** was synthesized. Indeed, treatment of pivaloate **4.18** with DIBAL-H followed by oxidation under Ley conditions[48] furnished ketone **4.21** in 84% over 2 steps. Subsequent treatment of the ketone with ethylene glycol, $(CH_3O)_3CH$ and a catalytic amount of PTSA at RT yielded ketal **4.22** in 90% (***Scheme 4.11***). Unfortunately, this method did not increase the selectivity of the hydrogenation reaction and an alternative method for converging both diastereomeric routes was sought.

Scheme 4.11** – Synthesis of ketal **4.22



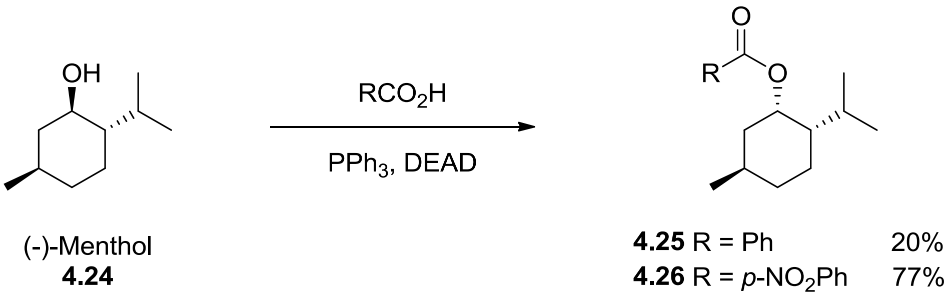
To this end, we decided to attempt to convert diastereomer **4.12** into diene **4.11** via a Mitsunobu inversion of hydroxyl **4.23** (***Scheme 4.12***).[66] This would allow the streamlining of both diastereomeric routes, thereby reducing synthetic manipulations. To test the reaction, enol triflate **4.10** was treated under Stille conditions and the resulting diene was deprotected with DIBAL-H in DCM to produce secondary alcohol **4.23** 74% yield over 2 steps. Unfortunately, all attempts at producing desired diastereomer **4.11** through a Mitsunobu reaction with pivalic acid (PivOH) failed to deliver the desired product.

Scheme 4.12** – Attempted Mitsunobu inversion of alcohol **4.23



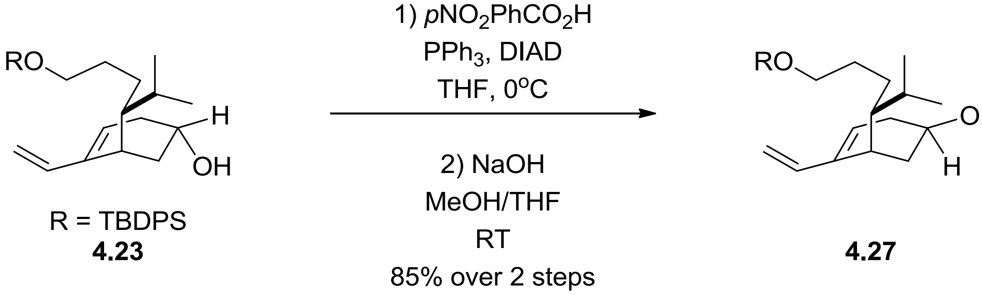
It is well documented that sterically hindered secondary alcohols do not undergo facile Mitsunobu inversions with aliphatic carboxylic acids as nucleophiles.[67] In 1994, Dodge et al. published a study on the rates and yields of Mitsunobu reactions on (-)-menthol (**4.24**) (***Scheme 4.13***).[68] In the report, they found that increased rates and yields were obtained with increasing acidity of the incoming nucleophile. Indeed, benzoic acid is generally more effective as a nucleophile than aliphatic counterparts; however in cases where benzoic acid is not effective, it was found that the more acidic *para*-nitrobenzoic acid is a valuable alternative. In their studied case, inverted product **4.26** was obtained in 77% when using the latter compared to a 20% yield of **4.25** when using benzoic acid.

***Scheme 4.13** – Dodge's study on the Mitsunobu inversion of (-)-menthol*



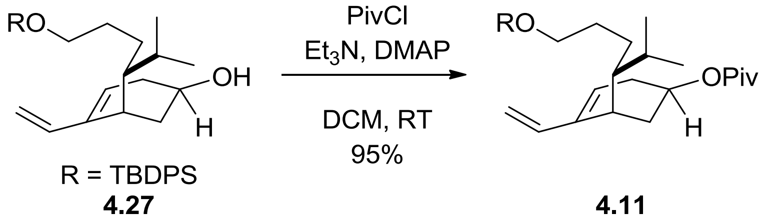
Although alcohol **4.23** may not seem particularly hindered, it is possible that the sidechain is sufficiently bulky to slow the reaction. Another drawback is that the formed phosphonium intermediate may undergo faster elimination than inversion to form a conjugated triene. Some elimination products were indeed observed in initial attempts at the Mitsunobu reaction. Drawing inspiration from the Dodge et al. study, the reaction with *para*-nitrobenzoic acid proved fruitful yielding the corresponding inverted product which was hydrolyzed with NaOH in 85% yield over two steps to furnish secondary hydroxyl **4.27** (***Scheme 4.14***).

***Scheme 4.14** – Mitsunobu inversion of alcohol **4.23** with para-nitrobenzoic acid*



Finally reprotection of alcohol **4.27** with a pivaloate group in 95% yield completed the conversion of **4.12** to desired diastereomer **4.11** (***Scheme 4.11***).

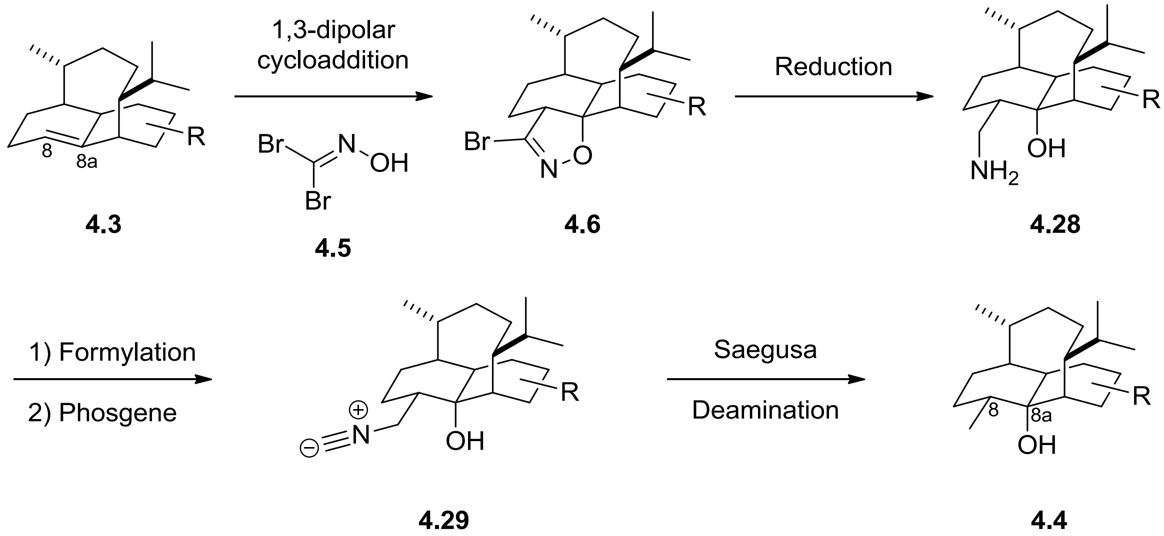
Scheme 4.15 – Successful synthesis of desired diastereomer 4.11



Installation of the C8 methyl and C8a hydroxyl groups

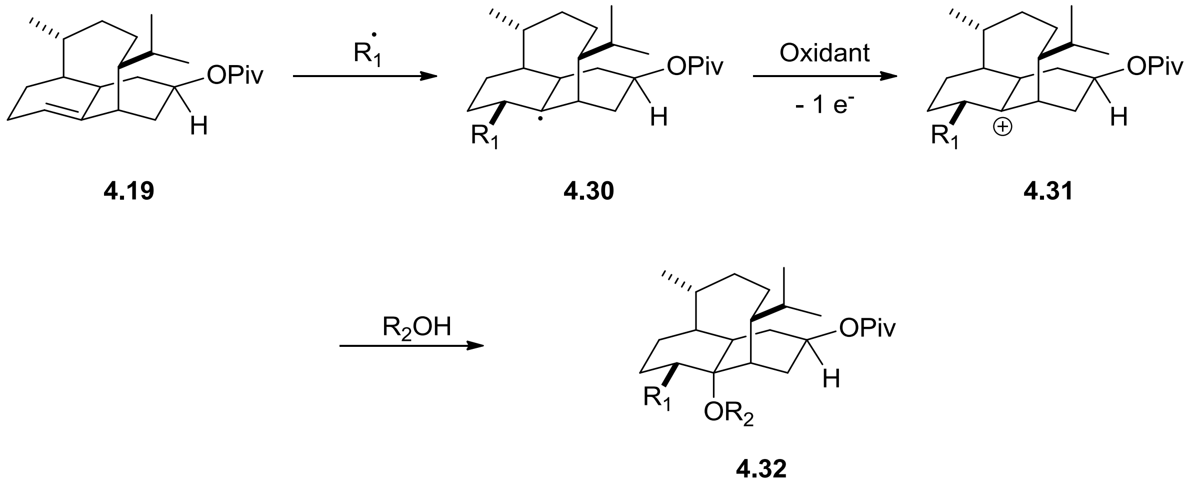
The next challenge to tackle was the installation of the elusive C8 methyl and C8a hydroxyl groups. We wanted to develop a novel strategy for the installation of these groups that would be shorter than the 5-step sequence reported in Baran's total synthesis which relies on a 1,3-dipolar cycloaddition (***Scheme 4.16***).

Scheme 4.16 *- Baran's 5-step sequence to install C8 methyl and C8a hydroxyl groups*



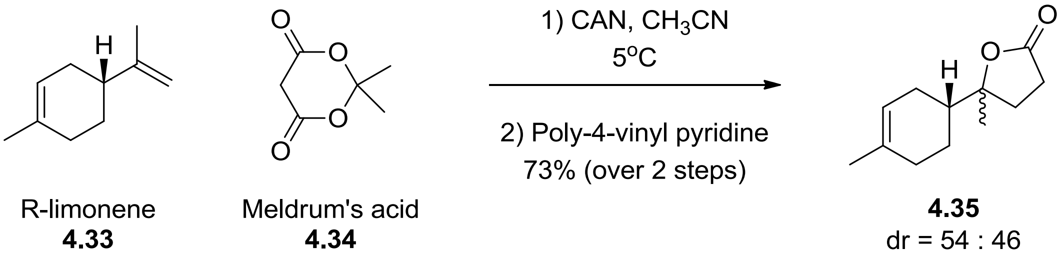
In the Baran sequence, many steps are required to remove the undesired nitrogen atom introduced through the cycloaddition reaction. We wanted to minimize synthetic steps through the investigation of radical chemistry to perform the desired transformation. We thought that this could be accomplished through a radical oxidation sequence (***Scheme 4.17)***. Treatment of alkene **4.19** with an alkyl radical $(R_1^{\cdot})$ could furnish tertiary radical **4.30**. A compatible oxidant could then remove an electron, yielding carbocation **4.31**, which may then react with a nucleophile such as a molecule of solvent (water or alcohol) to form the desired C-O bond. The bottom face of the molecule should be the most accessible for both nucleophilic attacks due to steric interactions with the *ansa* bridge, which would give the desired *syn* stereochemistry in product **4.32**.

Scheme 4.17 *- Oxidative radical addition to alkene **4.19** hypothesis*



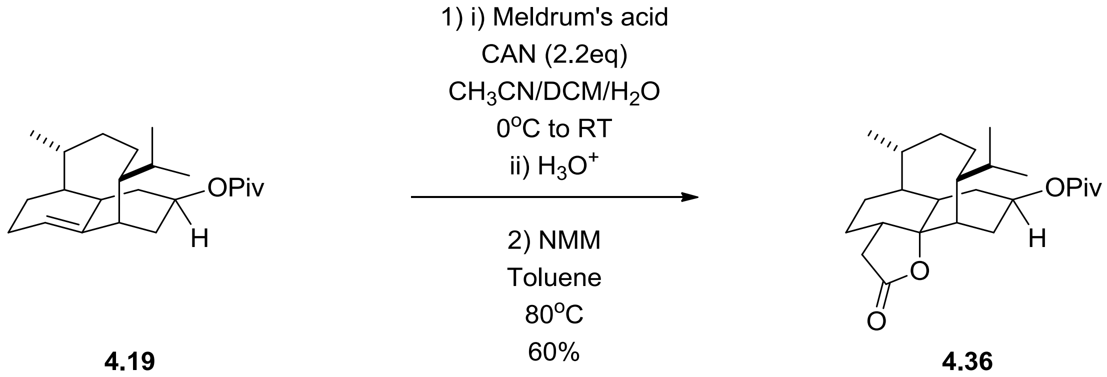
In practice, this reaction could be difficult to develop, because the oxidant must selectively react with the tertiary radical and not the necessary protic solvent present. Fortunately, by scavenging the literature for examples of similar reactivity, we came across a relatively unexploited reaction reported by Mane et al., which allows the direct synthesis of lactones from alkenes (***Scheme 4.18***).[69] They reported that treatment of *R*-limonene (**4.33**) with Meldrum's acid (**4.34**) and cerium ammonium nitrate (CAN) followed by decarboxylation of the generated carboxylic acid, yielded 73% of lactone **4.35** with a diastereomeric ratio of 54 : 46.

Scheme 4.18 *- Direct synthesis of lactones from alkenes*



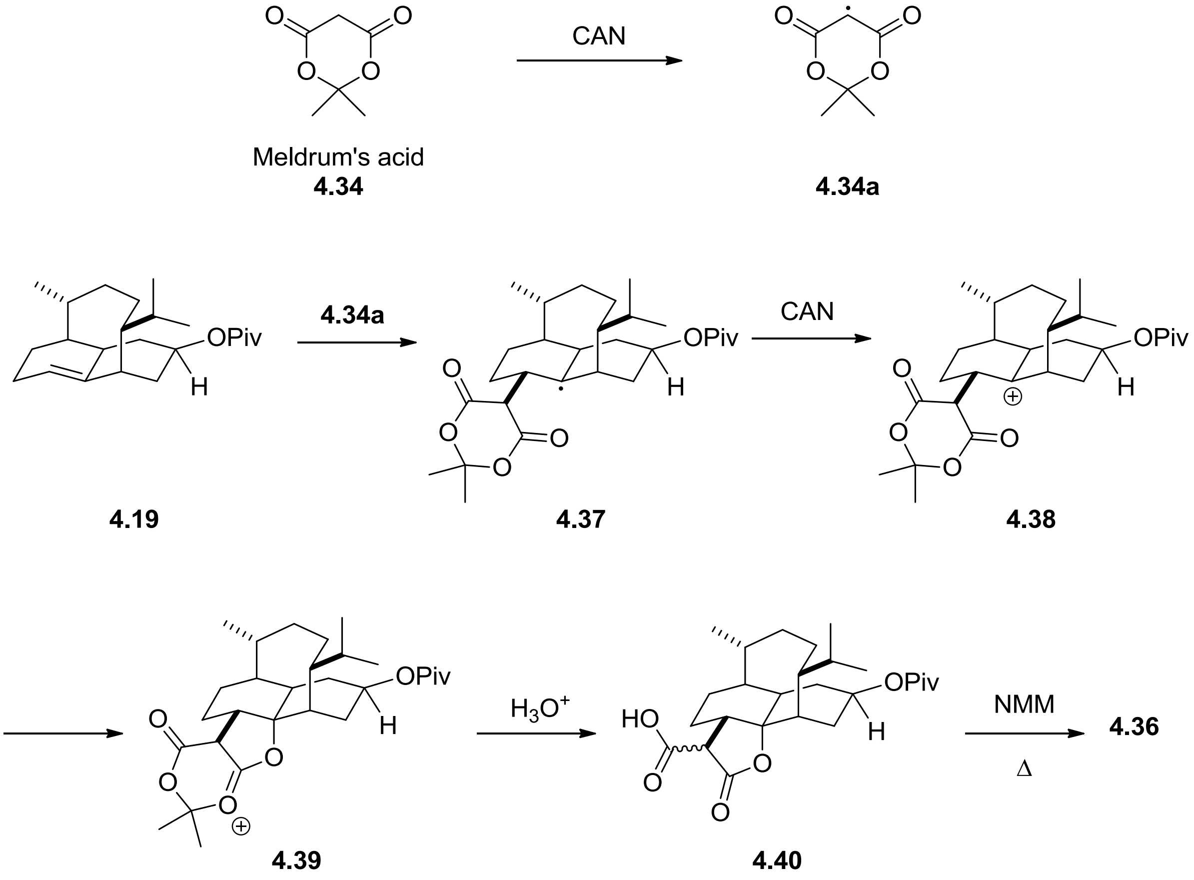
Although the reaction conditions in ***Scheme 4.18*** were selective for disubstituted over trisubstituted alkenes, Szumny et al. reported the use of this reaction on trisubstituted cyclic alkenes.[70] We therefore subjected alkene **4.19** to similar reaction conditions and were delighted when lactone **4.36** was obtained with complete control of diastereo- and regioselectivity (***Scheme 4.19***). In our case, it was found that *N*-methylmorpholine (NMM) was more effective at performing the decarboxylation than poly-4-vinyl pyridine.

Scheme 4.19** – Synthesis of lactone **4.36



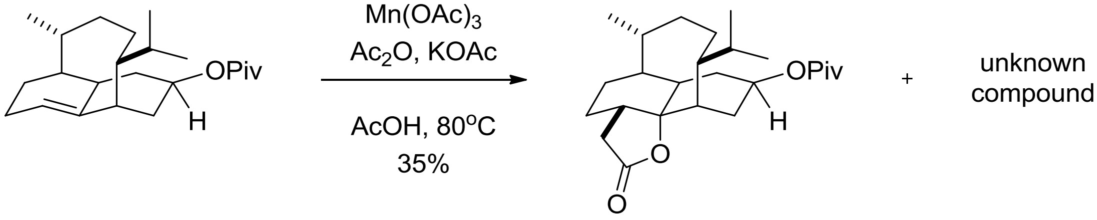
The reaction proceeds through a mechanism similar to that proposed in ***Scheme 4.17***. Indeed, under the reaction conditions, Meldrum's acid (**4.34**) is oxidized by the first equivalent of CAN to form radical **4.34a** which adds to alkene **4.19** yielding tertiary radical **4.37** (***Scheme 4.20***). This compound is then oxidized by a second equivalent of CAN to form carbocation **4.38** which is trapped by a carbonyl group to form oxonium **4.39** containing the required carbon-oxygen bond. The reaction mixture is then treated with an acidic aqueous solution to breakdown intermediate **4.39** and yield carboxylic acid **4.40**. Decarboxylation with NMM in toluene at 80 °C then furnishes desired lactone **4.36**.

Scheme 4.20 *- Mechanism for the formation of lactone* ***4.36***



Alternatively, the same transformation was attempted in a 1 step procedure that was reported by Mukherjee et al. using $Mn(OAc)_3$.[71] Treatment of alkene **4.19** with this reagent in the presence of Ac_2O and KOAc in AcOH at 80 °C yielded lactone **4.36** in 35% as an inseparable mixture with an unknown compound (***Scheme 4.21***). Although shorter, this sequence was lower yielding and gave a mixture of compounds and was therefore discarded.

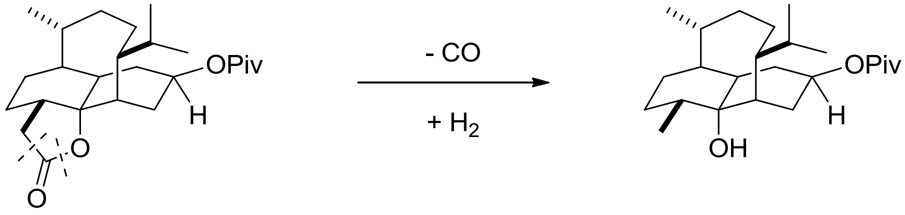
Scheme 4.21 *– Other conditions for the formation of lactone **4.33***



4.19 **4.36**

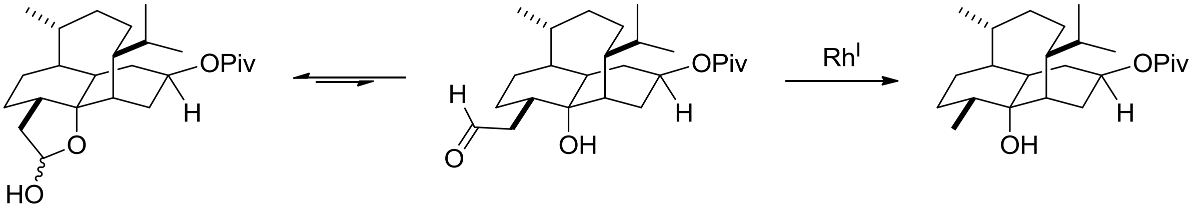
The next challenge was the formal reductive removal of carbon monoxide from lactone **4.36** (***Scheme 4.22***). The first reaction that came to mind to achieve this transformation was a rhodium-catalyzed decarbonylation reaction of corresponding lactol **4.42** (***Scheme 4.23***).[72,73,74] Indeed, lactol **4.42** should exist as an equilibrium between its cyclic (**4.42**) and hydroxy-aldehyde (**4.43**) forms and we believed that the equilibrium could be pushed towards product **4.41** formation in the presence of a rhodium (I) complex.

Scheme 4.22 *- Theoretical conversion of lactone **4.36** to alcohol **4.41***



4.36 **4.41**

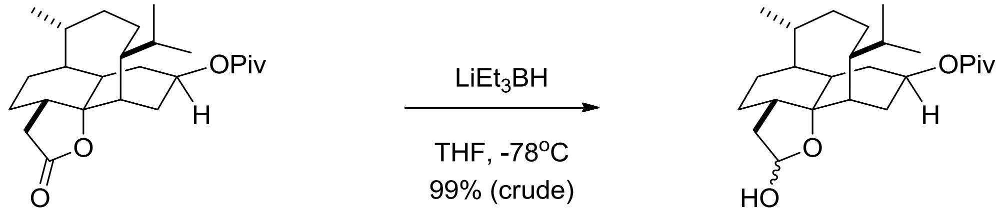
Scheme 4.23 *- Proposed decarbonylation of lactol **4.42***



4.42 **4.43** **4.41**

To minimize possible interactions between the secondary hydroxyl group and the metal complex, we sought to find a chemoselective reduction which would allow partial reduction of lactone **4.36** to lactol **4.42**, without removing the pivaloate group. We believed that this selectivity would be achievable based on the increased electrophilicity of lactones compared to esters and due to the fact that the carbonyl in the lactone should be more accessible. After many attempts it was found that while L-Selectride seemed too sterically hindered to offer sufficient reactivity and selectivity at low temperatures, the less bulky super-hydride ($LiEt_3BH$) allowed complete reduction of the lactone without deprotecting the hydroxyl group (***Scheme 4.24***). Unfortunately, compound **4.42** could not be obtained analytically pure due to instability during the purification process and was used crude. Nevertheless, lactol **4.42** was subjected to standard decarbonylation conditions, but no desired product was observed in any case.

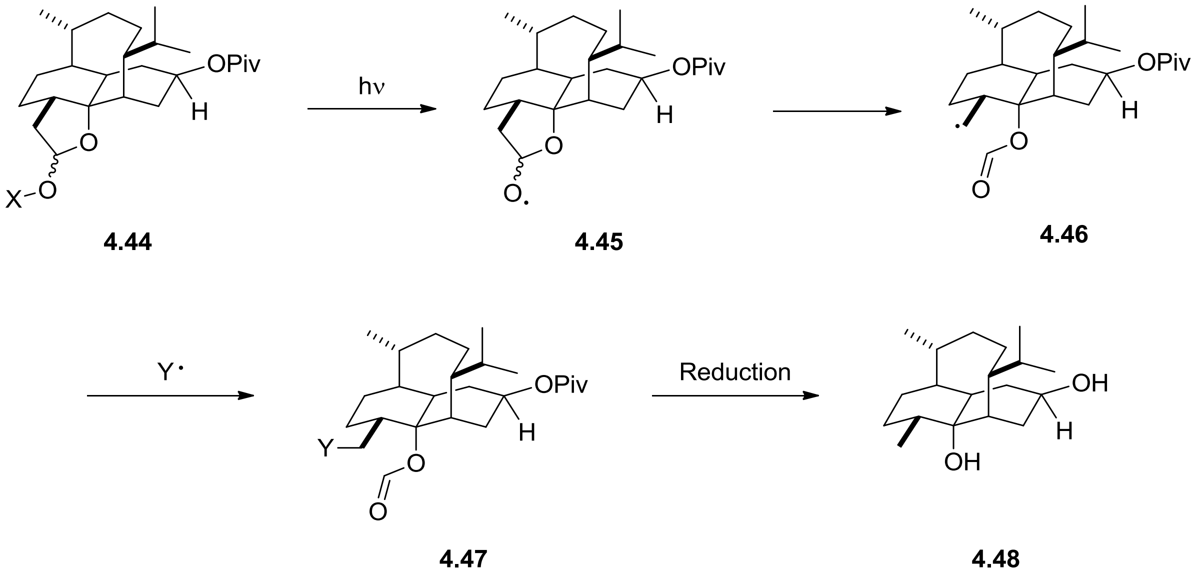
Scheme 4.24 *– Selective reduction of lactone* ***4.36***



4.36 **4.42**

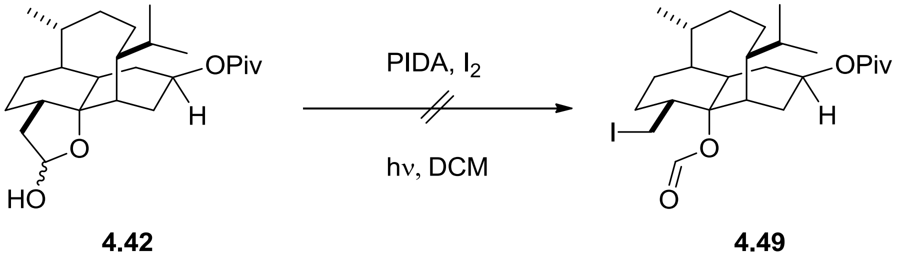
After much research, it was found that the carbon-carbon bond between the alkyl and carbonyl groups in lactols can be cleaved through a radical process (***Scheme 4.25***). If a sufficiently weak bond could be generated between the hydroxyl group and a heteroatom, it should be able to be cleaved homolytically, either through heat or under photo irradiation, to generate unstable hydroxyl radical **4.45**. This radical could then undergo β-fragmentation to generate alkyl radical **4.46** which can be trapped with another reagent to give formate ester **4.47**. Full reduction of **4.47** could then generate desired diol **4.48**.

Scheme 4.25** - Proposed radical fragmentation approach to diol **4.48



These reaction types were a main focus of the Suginome and Suarez groups' research and are well documented.[75,76,77] Indeed a variety of different reagents have been demonstrated to promote these fragmentation reactions on a variety of substrates: HgO, $Pb(OAc)_4$ and PIDA which are generally used in conjunction with I_2 as a trapping reagent. Unfortunately, no desired product was obtained after trying different combinations of these reagents. A typical unfruitful reaction is depicted in ***Scheme 4.26***.

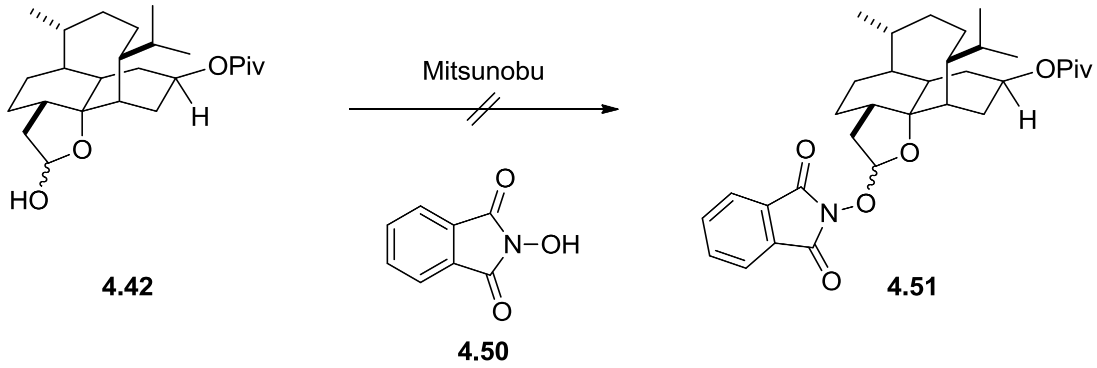
Scheme 4.26** – Attempted Suarez fragmentation of lactol **4.42



Another reaction that came to our attention was disclosed by the Suarez group in 1999.[78] In this report, lactols are subjected to a Mitsunobu reaction with *N*-

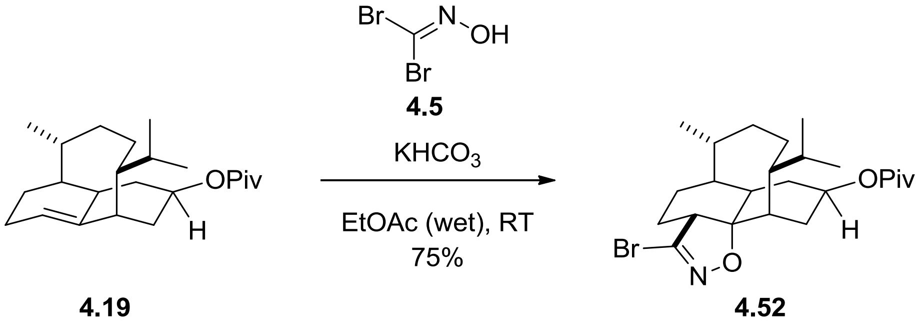
hydroxyphthalimide (**4.50**) to yield compounds such as **4.51**. These compounds contain a particularly weak N-O bond which can be exploited to undergo the radical fragmentation depicted in ***Scheme 4.25***. This reaction has the added advantage of using Bu_3SnH as trapping reagent affording the desired methyl group directly. In Suarez' report, however, yields are generally quite low and the pthalimides (**4.51**) have a tendency of being difficult to synthesize and isolate. Indeed, all attempts at forming compound **4.51** led to decomposition of the starting material (***Scheme 4.27***).

Scheme 4.27** - Attempted synthesis of phthalimide **4.48



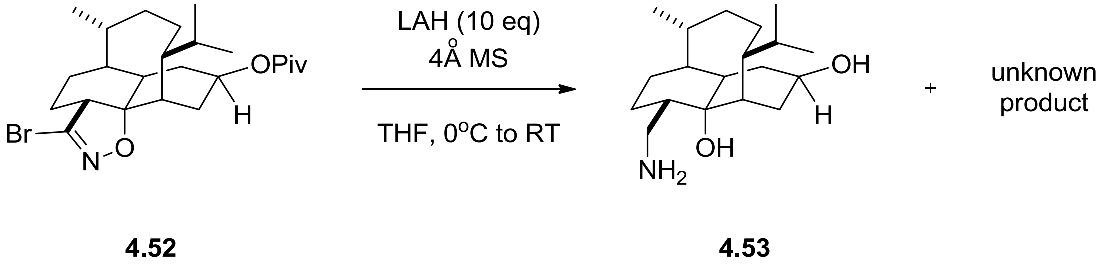
At this stage we decided to abandon this route and focus our attention at finishing the synthesis. We therefore employed the Baran group's chemistry to install the required methyl and tertiary hydroxyl groups. Treatment of alkene **4.19** with dibromoformaldoxime (**4.5**) in the presence of $KHCO_3$ in wet EtOAc yielded 75% of cyclic adduct **4.52**, with complete regioselectivity (***Scheme 4.28***). The presence of water in the solvent was found to be crucial for higher yields as the biphasic system helps to solubilise the inorganic base and increase interactions between reagents throughout the reaction.

Scheme 4.28 *- 3+2 cycloaddition on alkene **4.19***



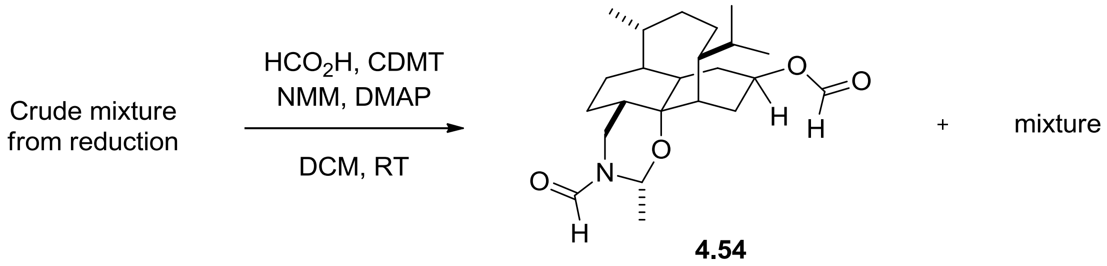
The reduction of bromoisoxazole **4.52** proved to be more challenging than anticipated, as repeating the Baran group's procedure led to irreproducible results. Indeed, inconsistent product mixtures and yields were obtained until it was found that the addition of 4Å molecular sieves to the reaction media had a beneficial effect (***Scheme 4.29***). This allowed reaction yields to be more consistent and the product mixtures obtained were less complex. However, there was always the presence of an unknown impurity formed in the reaction.

Scheme 4.29 *- Reduction of isoxazole **4.52***



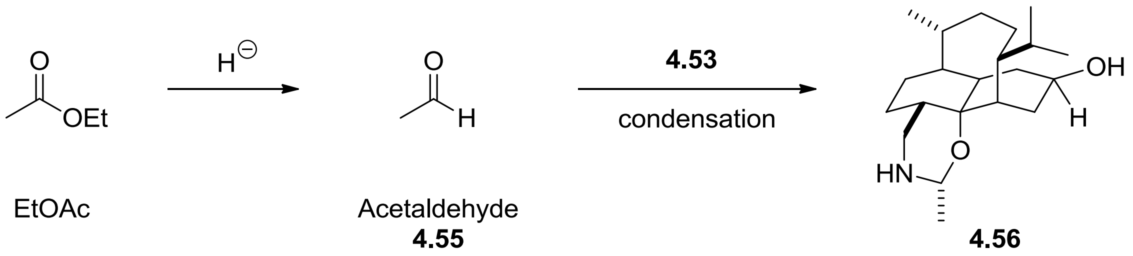
The reaction mixture obtained from the reduction of isoxazole **4.52** was treated under formylation conditions to attempt to identify the main impurity (***Scheme 4.30***). From this reaction, it was possible to isolate and characterize aminal **4.54**.

Scheme 4.30 - *Structure elucidation of impurity by formylation of mixture*



The formation of the aminal can be explained by the fact that during the quench of excess LAH from the isoxazole reduction step, aqueous HCl was added followed by DCM and the thick paste was stirred for 10 minutes. EtOAc was then added for extraction purposes. It is possible that the reducing agent was not fully neutralized and may have reduced EtOAc to acetaldehyde (**4.55**) which then condensed with aminoalcohol **4.53** to form aminal **4.56** as the main impurity (***Scheme 4.31***). This drawback was easily remediated by using only DCM during the extraction phase.

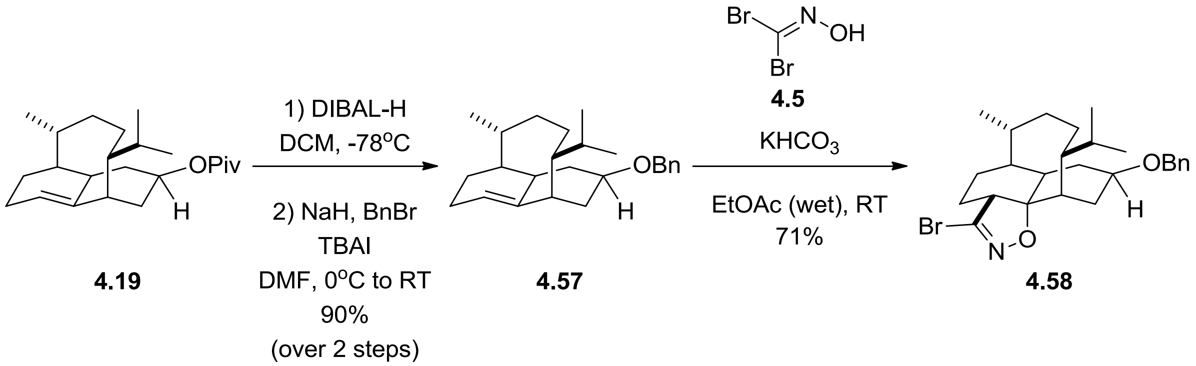
Scheme 4.31 - *Possible formation of aminal* ***4.56***



Unfortunately, we could not develop selective conditions for the formylation of the amine in **4.53** because of the interference with the secondary alcohol. To solve the problem, a different protecting group was sought that would be easy to install, withstand harsh reducing conditions, *i.e.* treatment of the substrate with a large excess of LAH at RT, but would still be easily cleaved. We initially considered the Bn and TBS groups for the task at hand, although there had been previous reports of both reagents being unstable under the required reaction conditions.[79]

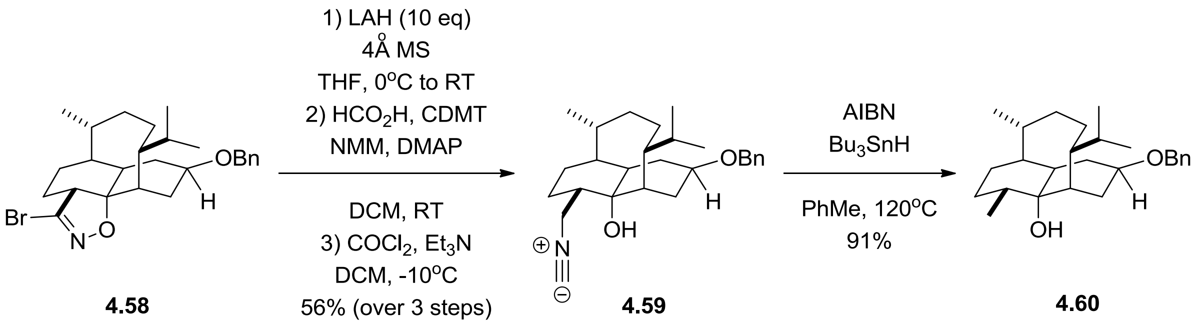
We decided to first investigate the stability of the Bn group in our endeavour. Pivaloate **4.19** was deprotected with DIBAL-H and the crude product was reprotected using NaH and BnBr in the presence of TBAI as an additive to afford benzyl ether **4.57** in 90% yield over 2 steps (***Scheme 4.32***). The 1,3-dipolar cycloaddition proceeded smoothly under identical reaction conditions as in ***Scheme 4.28*** to yield 71% of isoxazole **4.58**.

Scheme 4.32 *- Cycloaddition on alkene* ***4.19***



To our delight, when bromoisoxazole **4.58** was subjected to the LAH reduction, not only was the product reduced effectively, but the protecting group withstood the reaction conditions (***Scheme 4.33***). Treatment of the resulting amino-alcohol under formylating conditions followed by treatment with phosgene yielded isonitrile **4.59** in 56% over 3 steps. Finally, Saegusa deamination[80] of compound **4.59** afforded desired compound **4.60** in 91% yield.

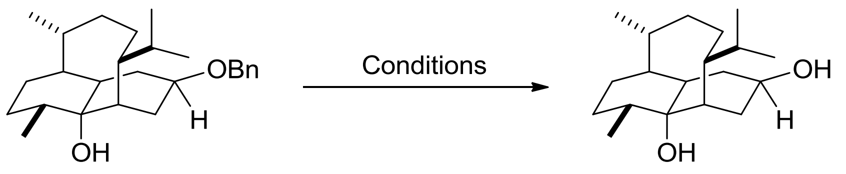
Scheme 4.33 *- Deamination sequence for isoxazole* ***4.58***



Completion of the formal synthesis

Surprisingly, when we attempted to remove the benzyl group under typical hydrogenation conditions, only starting material **4.60** was recovered (***Scheme 4.34***). ***Table 4.2*** describes different conditions that were tried. Varying the heterogeneous catalyst from Pd/C to the more reactive $Pd(OH)_2$ and PtO_2 had no effect on the reaction nor did varying solvents or temperatures. We had to turn to a radical transfer reaction to effectively remove the benzyl group. The addition of a lithium naphthalenide solution[81] directly to neat alcohol **4.60** at 0 °C resulted in the formation of compound **4.48** in 83% yield.

Scheme 4.34** - Deprotection of benzyl ether **4.60



4.60

4.48

Table 4.2** – Deprotection conditions for benzyl ether **4.60

Entry	Reagent	Solvent	Temperature	Result
1	Pd/C	EtOAc	RT to reflux	No reaction
2	Pd/C	EtOH	RT to reflux	No reaction
3	$Pd(OH)_2$	EtOH	RT to reflux	No reaction
4	PtO_2	EtOH	RT to reflux	No reaction
5	Li/Naphthalene	THF	0 °C	83%

At this stage, only two oxidation steps were potentially required to complete a formal synthesis of vinigrol (**2.1**). Oxidation of the secondary alcohol of compound **4.48** was accomplished using TEMPO to afford ketone **4.61** in 94% yield (***Scheme 4.35***).[82] The final step in the sequence consisted in an alpha-oxidation reaction of the ketone. ***Table 4.3*** lists various conditions tried to accomplish the desired transformation. We initially sought to utilize a Rubottom oxidation,[83] because of the difficulties encountered with the previous substrate **3.35** (***Chapter 3***), when attempting to oxidize the corresponding enolate with Davis' oxaziridine. In each case attempted with different bases and silylating reagents, inseparable mixtures of different silylated compounds were obtained. Finally, it was found that applying the conditions from ***Scheme 3.27***, *i.e.* deprotonation with KHMDS and oxidation with Davis' oxaziridine, selectively furnished α-hydroxyketone **4.62** in 40% yield or 65% based on recovered starting material (brsm). The reaction was not pushed to completion out of fear of overoxidation.

Scheme 4.35 *- Completion of the formal synthesis of vinigrol*

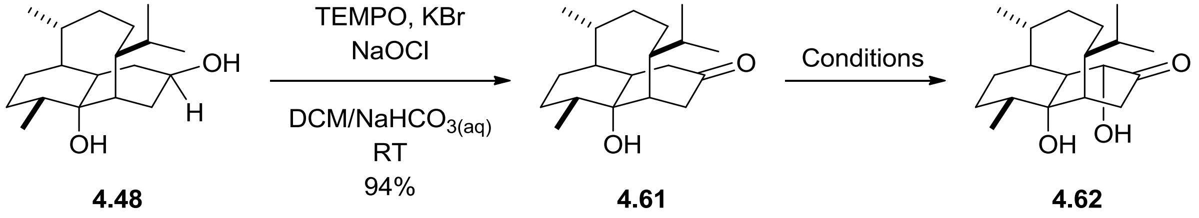
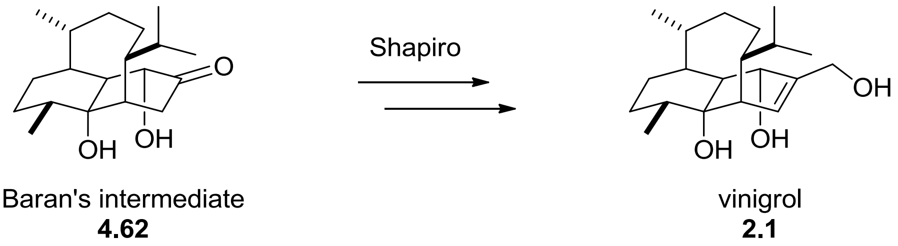


Table 4.3 *– α-oxygenation of ketone* ***4.61***

Entry	Base	Reagent	Temperature (^{o}C)	Yield (%)
1	Et_3N	TMSCl	0	Complex mixture
2	*i*PrNEt	TMSCl	0	Complex mixture
3	Et_3N	TESCl	0 to RT	Complex mixture
4	Et_3N	TBSOTf	0 to RT	No reaction
5	KHMDS	TBSOTf	0 to RT	No reaction
6	KHMDS	Davis oxaziridine	-78 to 0	40 (65 brsm)

With the preparation of compound **4.62**, we intercepted an advanced intermediate in the Baran synthesis for which the ^{1}H and ^{13}C NMR spectra matched those for the Baran group's intermediate.[41] In their report, the 2 final steps consist of the formation of the corresponding hydrazone followed by a Shapiro reaction to install the alkene and allylic alcohol to complete the synthesis (***Scheme 4.36***).

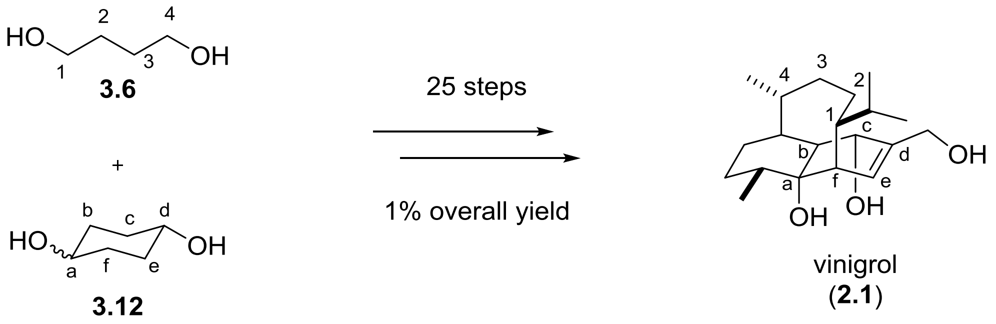
Scheme 4.36 - *Synthesis of vinigrol from Baran's intermediate*



Synthesis overview

Our research ultimately allowed us to accomplish a formal synthesis of vinigrol (**2.1**) in 25 steps for the longest linear sequence (28 total steps) from 1,4-butanediol (**3.6**) and 1,4-cyclohexanediol (**3.12**) in a 1% overall yield (***Scheme 4.37***).[84] These results compare to the length and efficacy of the Baran synthesis (25 steps with a 3% overall yield).

Scheme 4.37 - *Synthesis summary*



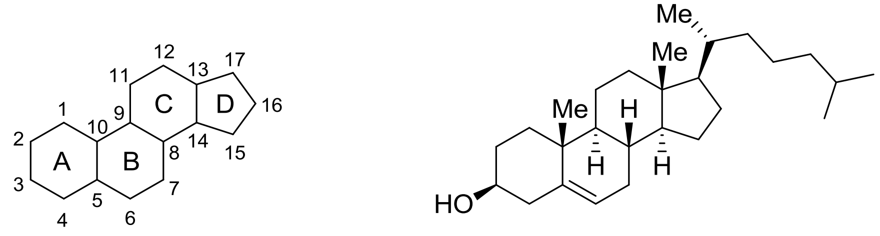
Chapter 5

Towards the Total Synthesis of (+)-Digitoxigenin

Introduction

Steroids constitute a family of natural products that play a vital role in the regulation of many bodily functions, from anti-inflammatory processes to sexual behaviour patterns.[85] They are ubiquitous in nature and several hundred different structures have been identified in plants, animals and fungi. From a chemical point of view, these compounds contain a common framework consisting of four rings (three 6-membered rings and one 5-membered ring) conventionally named A-D (***Figure 5.1***). Structure **5.1** illustrates this ring nomenclature as well as the carbon numbering used for identification, whereas cholesterol **5.2** is an illustrative example which shows the relative stereochemistry and substitution patterns often encountered in steroids.

Figure 5.1 *– Steroidal frameworks*

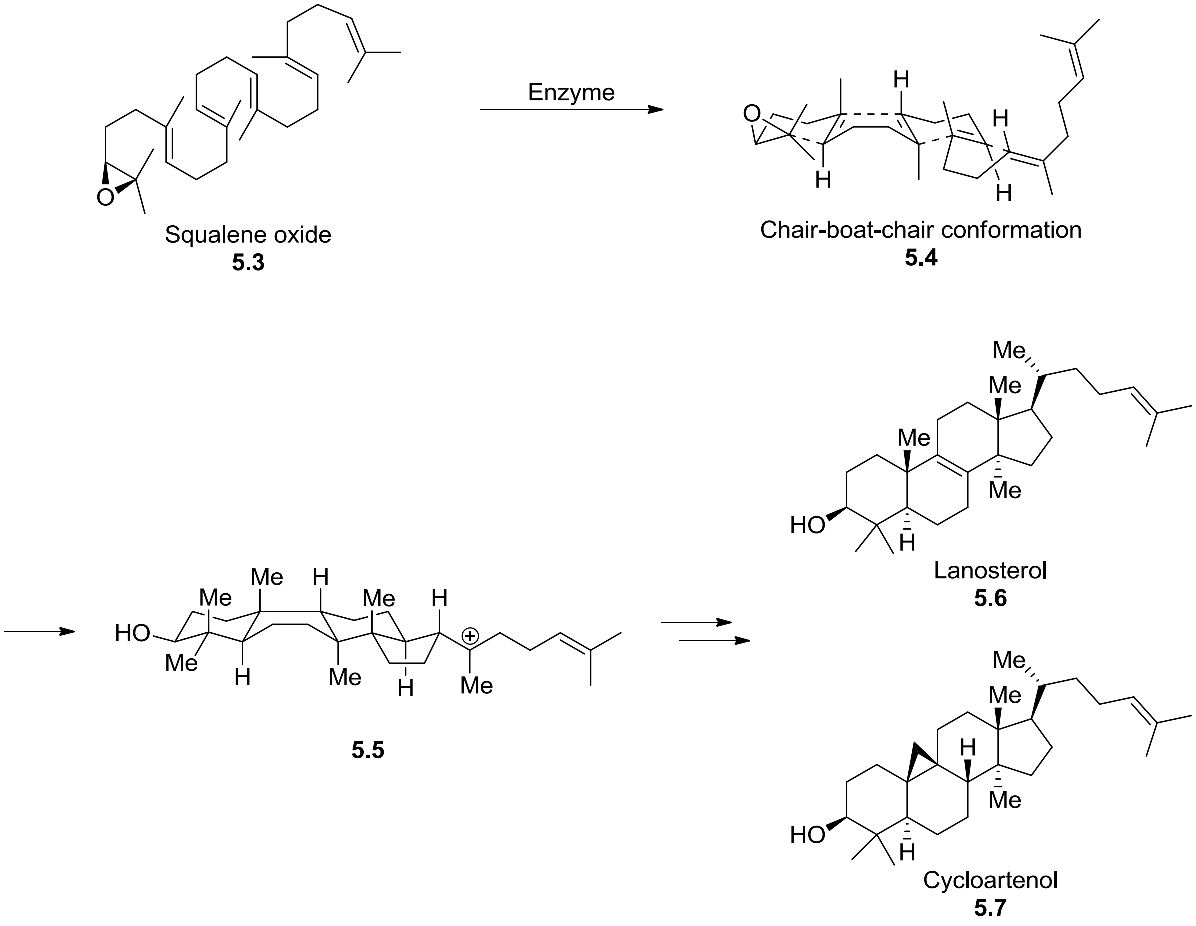


5.1

Cholesterol
5.2

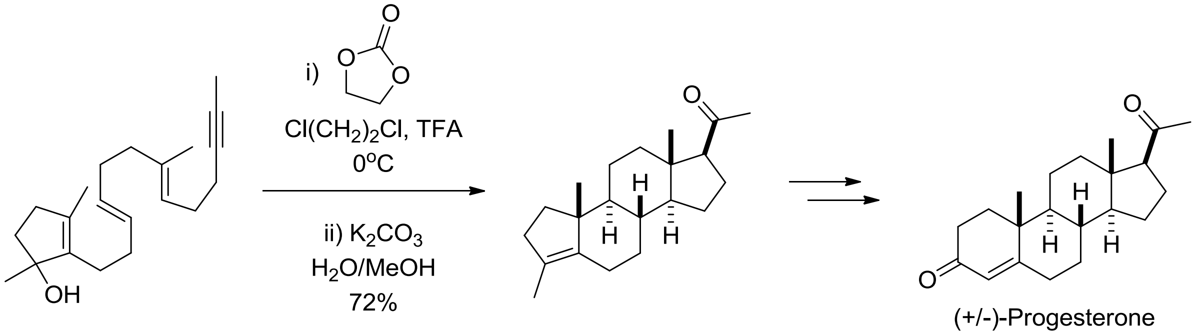
The generally accepted hypothesis for the formation of the steroidal framework in nature stems from a one-step polycyclization of squalene oxide (**5.3**) as shown in the example below (***Scheme 5.1***).[86] Indeed, upon enzymatic activation of the epoxide to partially generate a tertiary carbocation, the chain cyclizes through a chair-boat-chair conformation (**5.4**) to give rise to the steroidal polycyclic core. At this stage, carbocation **5.5** undergoes various transformations to form lanosterol (**5.6**) and cycloartenol (**5.7**) from which steroids are derived.

Scheme 5.1 *- Biosynthesis of lanosterol and cycloartenol*



This concept has been proven and exploited by various groups in the total synthesis of natural products.[87] One of the pioneering examples was the Johnson group's synthesis of progesterone (**5.10**) in 1971 (***Scheme 5.2***).[88] Indeed, treatment of alcohol **5.8** under acidic conditions formed a tertiary carbocation thereby provoking the cationic polycyclization to take place. This reaction formed the core structure of the natural product (**5.9**) in 72% yield with all of the stereocenters in place. Only a few more synthetic steps were necessary to complete the total synthesis.

Scheme 5.2 *- Johnson's total synthesis of progesterone*

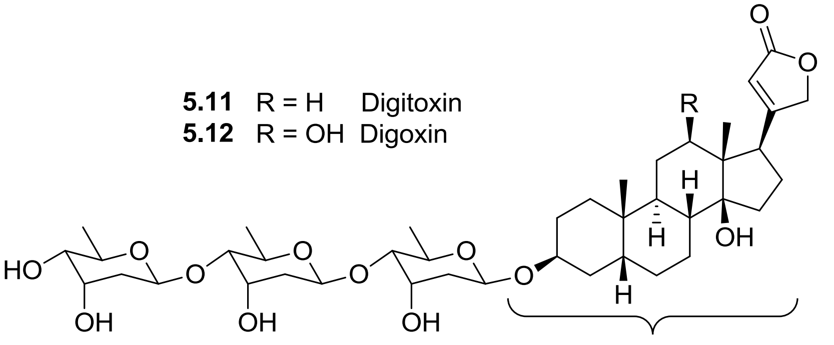


(+/-)-Progesterone

5.8 **5.9** **5.10**

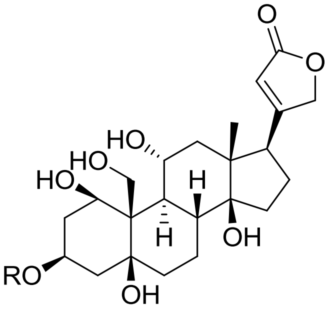
Cardenolides are a subtype of steroid that have been isolated from *Digitalis* extracts and have been widely used in medicine for various treatments, notably for congestive heart failure.[89] They have a very specific framework, derived from the general steroidal core, consisting of the following characteristics: *cis* A/B and C/D ring junctions, a tertiary hydroxyl group at C14 and a butenolide substituent at C17. Their biosynthesis derives from cycloartenol (**5.7**) which undergoes a range of enzymatic processes to incorporate the stereocenters and oxygen atoms found in cardenolides. Members of the cardenolide family are depicted in ***Figure 5.2***, with the simplest in structure being digitoxin (**5.11**). These natural products often have a saccharide moiety appended to the C3 hydroxyl group (**5.11**, **5.12** and **5.15**), but synthetic organic chemists generally focus on the aglycon counterparts for total synthesis projects (**5.13**, **5.14** and **5.16**). To date, there have been only two total syntheses of digitoxigenin, none of digoxigenin and one of ouabagenin, although many semi-syntheses starting from other steroids have been reported.[90]

Figure 5.2 – *Examples of cardenolides*



5.11 R = H Digitoxin
5.12 R = OH Digoxin

5.13 R = H Digitoxigenin
5.14 R = OH Digoxigenin



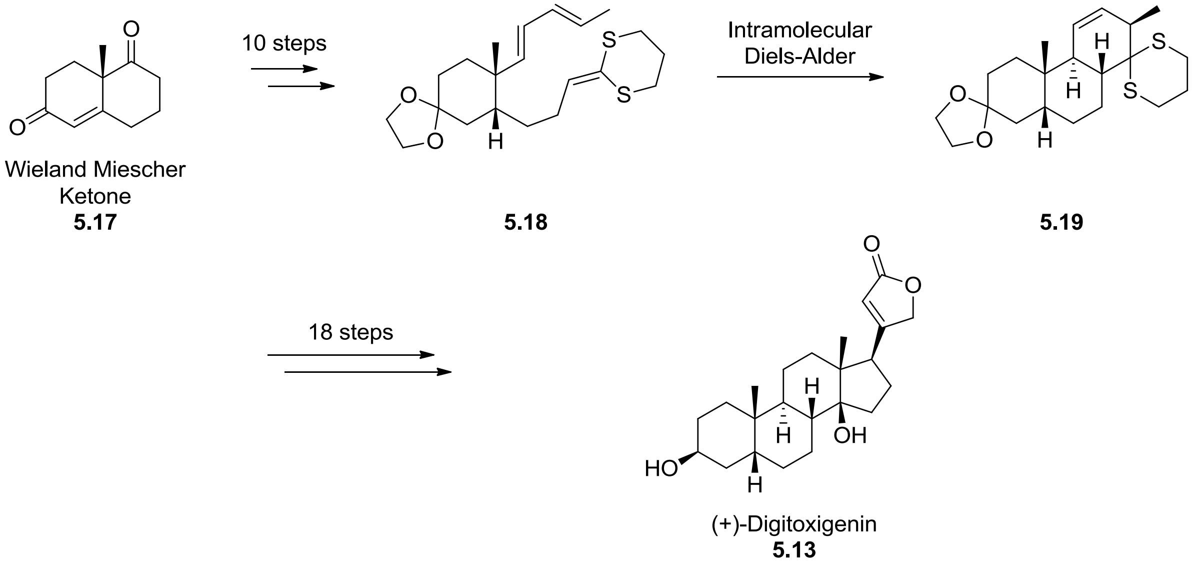
5.15 R = L-rhamnose Ouabain
5.16 R = H Ouabagenin

Synthetic Efforts

Stork's Total Synthesis of Digitoxigenin

The first total synthesis of (+)-digitoxigenin (**5.13**) was reported by Stork et al. in 1994 (***Scheme 5.3***).[91] Their approach began with the Wieland-Miescher ketone (**5.17**) being converted to triene **5.18** in 10 steps which was then poised to undergo a key intramolecular Diels-Alder reaction yielding pentacycle **5.19**. This step allowed the formation of the three cyclohexane rings found in the natural product with the correct stereochemistry. Finally, 18 more steps were required to attain the target compound for a total of 29 steps from commercially available materials.

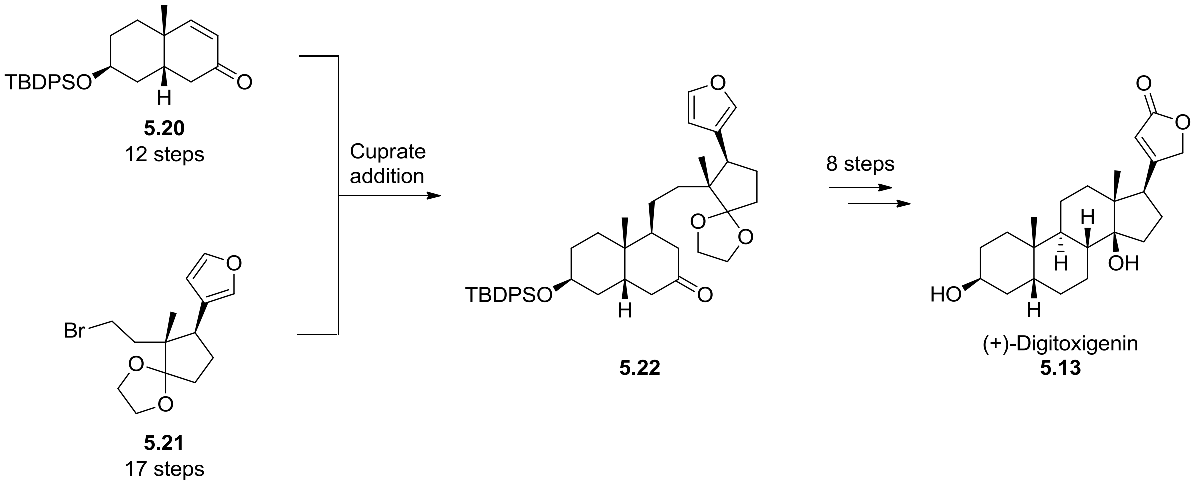
Scheme 5.3 **-** *Stork's total synthesis of (+)-digitoxigenin*



Nakada's Total Synthesis of Digitoxigenin

In 2007, Nakada et al. published their total synthesis of **5.13** (***Scheme*** ***5.4***).[92] Their key step involved merging two enantiomerically pure fragments (**5.20** and **5.21**) via a cuprate addition to afford intermediate **5.22**. The route required 8 more steps to complete the total synthesis. Although this approach was convergent and required 26 steps for the longest linear sequence, the route consisted in a total of 38 synthetic manipulations.

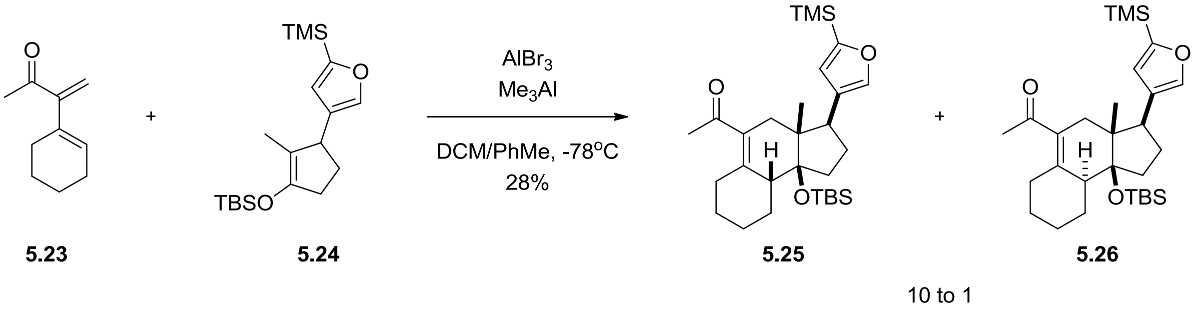
Scheme 5.4 *- Nakada's total synthesis of (+)-digitoxigenin*



Jung's Approach to Ouabain

Much research has also been conducted by various groups to achieve the total syntheses of ouabagenin (**5.16**) and ouabain (**5.15**), the most biologically active members of the cardenolides. In 2002, the Jung group published a general approach towards the synthesis of the BCD ring portion of the molecule based on a highly substituted intermolecular Diels-Alder reaction (***Scheme*** *5.5*).[93] Indeed, treatment of diene **5.23** and dienophile **5.24** with $AlBr_3$ and Me_3Al resulted in an inverse demand Diels-Alder which furnished desired fragment **5.25** in 28% with a diastereomeric ratio of 10 to 1 effectively generating three stereocenters, two of them quaternary. Despite this result, the Jung group has not reported further progress in their attempts at synthesizing ouabain (**5.15**).

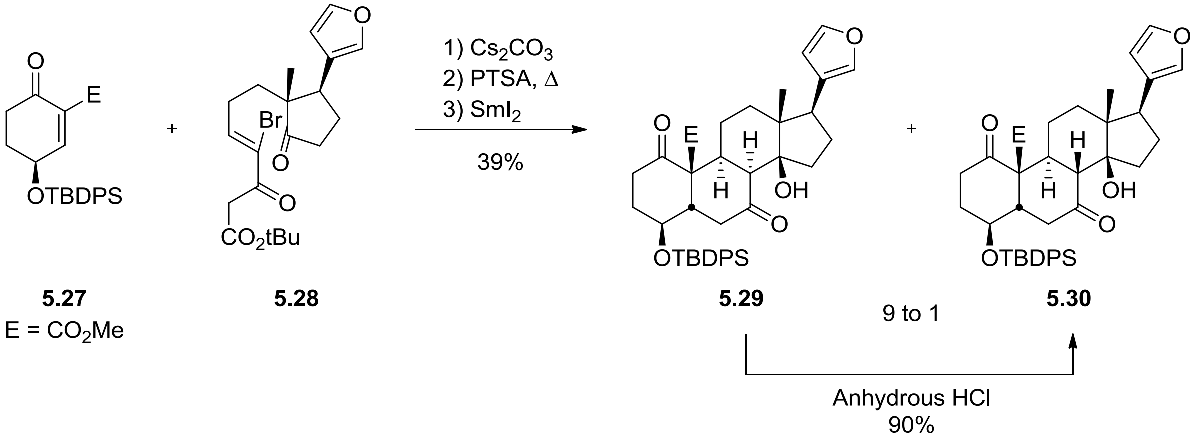
***Scheme 5.5** - Jung's approach to BCD fragment of ouabain*



Deslongchamps' Approach to Cardenolides and Total Synthesis of Ouabain

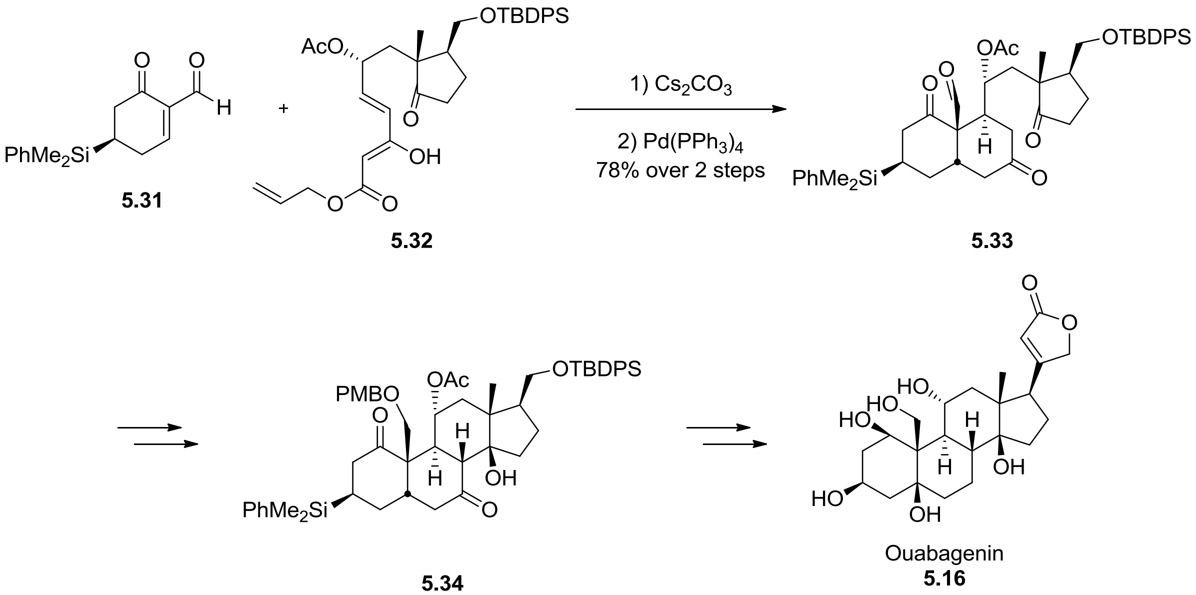
The Deslongchamps group has long been focused on the development of general strategies to synthesize steroidal frameworks. In 2002, this group reported an approach to the synthesis of cardenolides which was based on a double-Michael reaction between diketoesters **5.27** and **5.28** (***Scheme 5.6***).[94] A three-step process allowed the formation of tetracycles **5.29** and **5.30** in 39% yield, but favouring the incorrect diastereomer at C8. This center could however be epimerized under acidic conditions to afford the desired cardenolide core (**5.30**) in 90% yield.

***Scheme 5.6** - Deslongchamps' double Michael approach to the cardenolide core*



In 2008, the Deslongchamps group successfully applied this strategy to the total syntheses of ouabagenin (**5.16**) and ouabain (**5.15**) (***Scheme 5.7***).[95,96] The preparation of **5.16** required 41 steps, as the longest linear sequence, with 6 additional steps to convert this compound into ouabain (**5.15**).

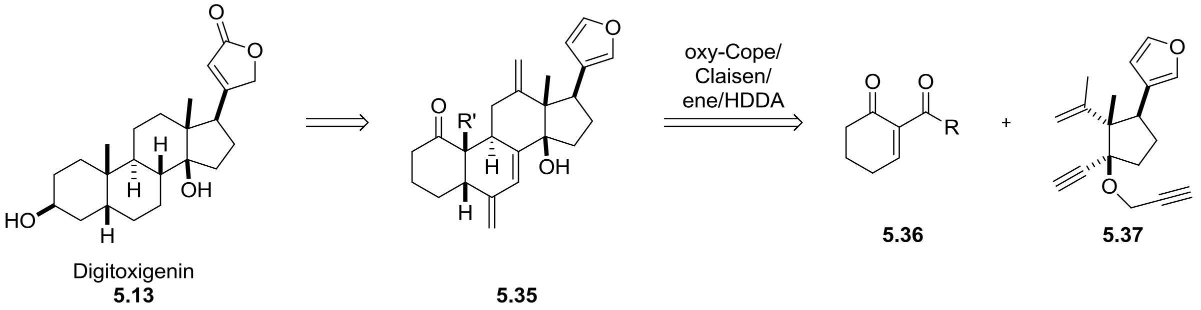
***Scheme 5.7** - Deslongchamps' total syntheses of oubagenin and ouabain*



Barriault's Approach to Digitoxigenin

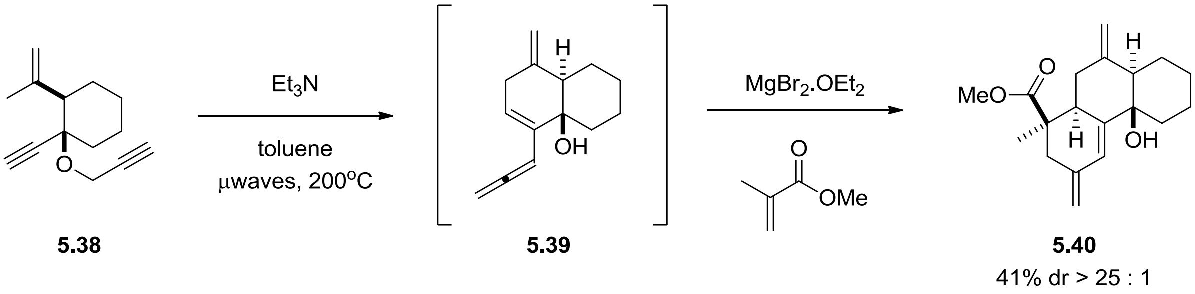
The cardenolides' interesting structure combined with a lack of efficient strategies to access them and their widespread use in medicine prompted us to develop a rapid approach towards the synthesis of the cardenolide core. In our group Dr. Christiane Grisé-Bard has studied the application of an oxy-Cope/Claisen/ene/hydroxy-directed Diels-Alder cascade to the total synthesis of digitoxigenin (**5.13**) (***Scheme 5.8***).[42] It was believed that the natural product could be obtained from compound **5.35** which in turn, could be the result of the cascade between substrate **5.37** and dienophile **5.36**.

Scheme 5.8 **-** *Barriault and Grisé-Bard's approach to digitoxigenin*



The approach was based on a methodology reported by our laboratory which shows that heating precursor **5.38** to 200 °C under microwave irradiation in the presence of Et_3N leads to decalin **5.39** (***Scheme 5.9***).[97] This compound then undergoes a hydroxy-directed Diels-Alder reaction, when treated *in situ* with $MgBr_2.OEt_2$ as a complexing agent, to afford tricyclic system **5.40** in 41% as a single diastereomer.

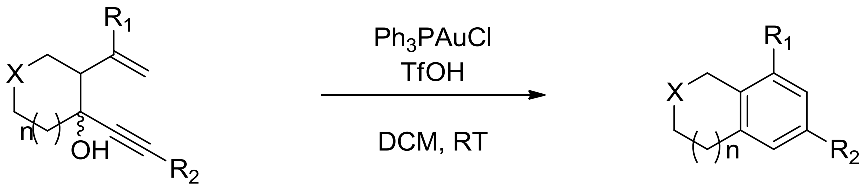
Scheme 5.9 - O*xy-Cope/Claisen/ene/hydroxy-directed Diels-Alder cascade precedent*



Background on Gold(I)-Catalyzed Reactions

Unfortunately, the methodology was not applicable to the formation of the required *cis* C/D ring junction found in digitoxigenin (**5.13**). However, during her investigations, Dr. Grisé-Bard discovered an interesting gold(I)-catalyzed benzannulation reaction (***Scheme 5.10***).[98] Indeed, treatment of enynes **5.41** with Ph_3PAuCl and TfOH at room temperature afforded aromatic compounds **5.42** in poor to very good yields.

Scheme 5.10 - *Gold(I)-catalyzed benzannulation*



5.41

5.42
10-86%

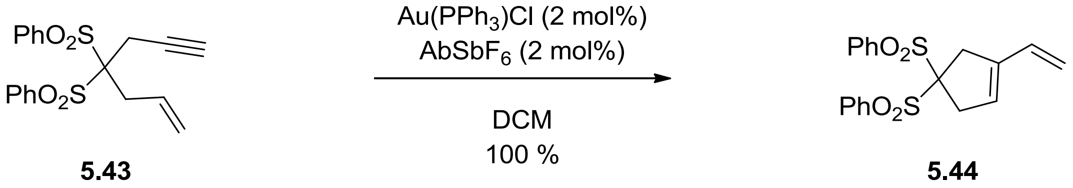
The reaction not only had a synthetic purpose, demonstrated in our laboratory's synthesis of isofregenedol,[99] but implied a more significant impact by demonstrating the use of a protic acid to activate the gold chloride catalyst. Indeed, until Dr. Grisé-Bard's report, activation of gold(I) chloride species was accomplished through abstraction of the chlorine atom with a silver salt (***Equation 5.1***).

Equation 5.1 *– Activation of gold(I) catalysts by silver salts*

$$Ph_3PAuCl \quad + \quad AgOTf \longrightarrow Ph_3PAu^{\oplus}\,{}^{\ominus}OTf \quad + \quad AgCl$$

With this discovery, we were intrigued as to its application to other gold(I)-catalyzed processes such as the cycloisomerization of enynes to form dienes reported by Echavarren in 2004.[100] One example was the reaction of enyne **5.43** to yield diene **5.44** in 100% yield (***Scheme 5.11***).

Scheme 5.11 - *Echavarren's gold(I)-catalyzed cycloisomerization of 1,6-enynes*

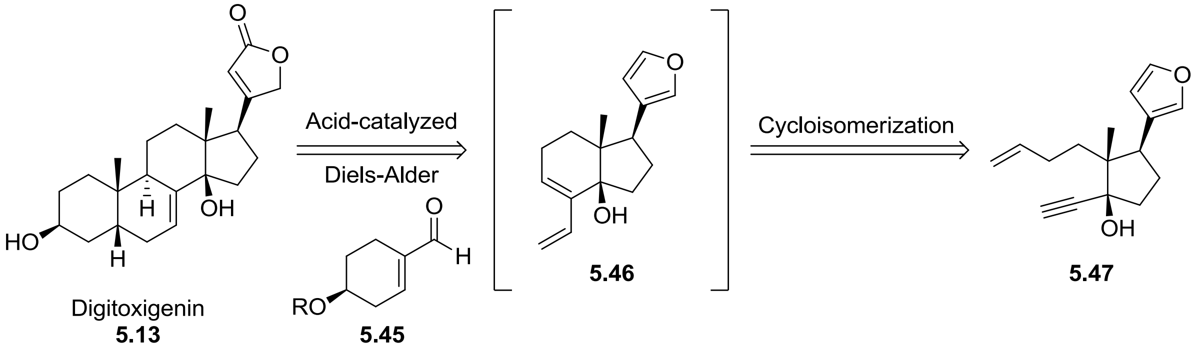


Novel Approach to Digitoxigenin

Retrosynthetic Analysis

Since this reaction leads to the formation of dienes, we envisioned coupling it with a Diels-Alder reaction. The ultimate goal of the project was therefore to develop a gold(I)-catalyzed cycloisomerization/Diels-Alder cascade in which an acid would act as both the gold catalyst activator and the Diels-Alder promoter (***Scheme 5.12***). This would hopefully allow the formation of the tetracyclic core of the natural product in a single step from enyne **5.47**. This retrosynthesis was somewhat an evolution of Dr. Grisé-Bard's work and would constitute a rapid and convergent approach that would generate much molecular complexity, forming three bonds, two cycles and three stereocenters, in a single step.

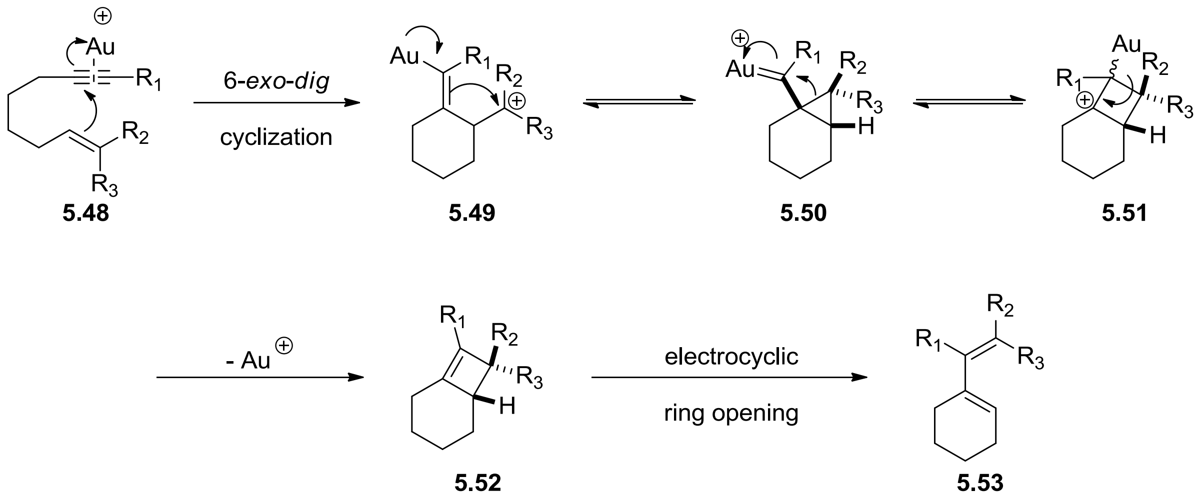
Scheme 5.12 - *Barriault's novel retrosynthesis*



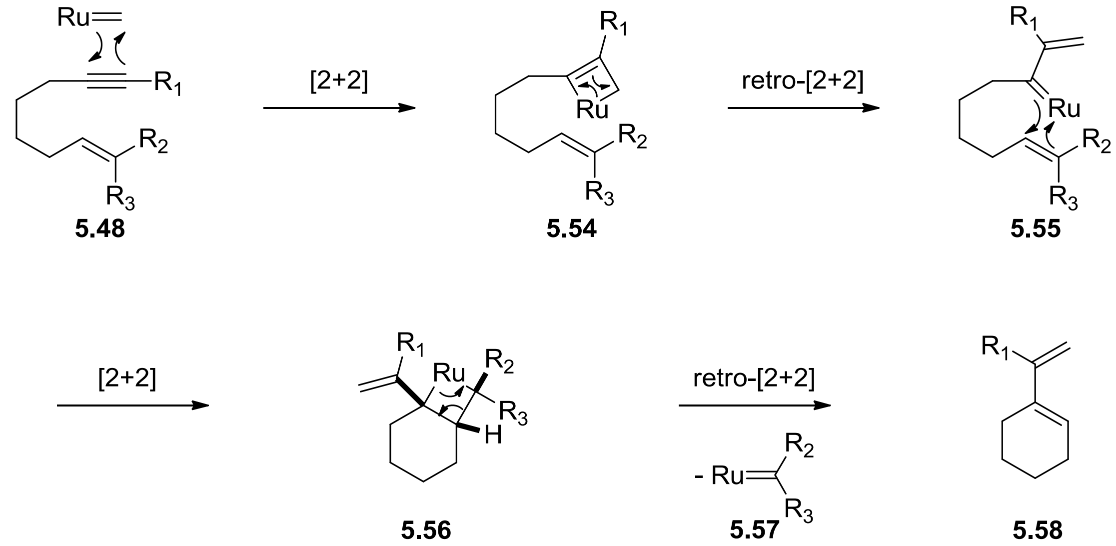
We were confident that this route would be possible for different reasons. If the gold(I)-catalyzed cycloisomerization reaction was unsuccessful, we could always rely on an enyne metathesis using one of the Grubbs catalysts. However, there was a strong desire to use the former for various reasons: lower catalyst loadings are generally required and a broader scope of substitution patterns and functional groups are tolerated compared to the Grubbs catalysts. Finally, when the project was started in 2007, there had not been reports of gold(I)-catalyzed reactions used in natural product synthesis.

Although the retrosynthesis in ***Scheme 5.12*** is shown for digitoxigenin (**5.13**), we desired to develop a general approach to the cardenolides which would also allow the synthesis of many derivatives. ***Schemes 5.13*** and ***5.14*** show the mechanisms for the gold(I)-catalyzed cycloisomerization and the enyne metathesis respectively. In ***Scheme 5.13*** all atoms from the starting material (**5.48**) are maintained in the diene product (**5.53**) compared to ***Scheme 5.14*** in which the terminal carbon of the alkene moiety in **5.48** is replaced by a methylene atom which leads to a loss of substitution at that position. Despite this inconvenience, enyne metatheses have a proven track record in organic synthesis.[101]

Scheme 5.13 - *Mechanism of the gold(I)-catalyzed cycloisomerization of enynes*

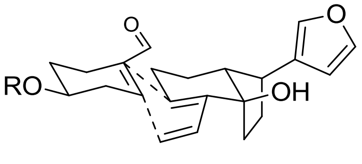


***Scheme 5.14** - Mechanism of the Grubbs' catalyzed enyne metathesis*



We were also confident in regards to the regio- and stereochemical outcome of the Diels-Alder reaction based on a few factors. The concave shape of the diene should shield its bottom face and a large R group on the secondary hydroxyl of the dienophile should shield its top face from reacting. Finally, an endo approach of the dienophile should be favoured leading to the formation of the desired compound (***Figure 5.3***). If necessary, an additive could also be used to link the aldehyde and tertiary hydroxyl moieties to undergo a hydroxy-directed Diels-Alder similar to that in ***Scheme 5.9***.

***Figure 5.3** – Proposed Diels-Alder approach*

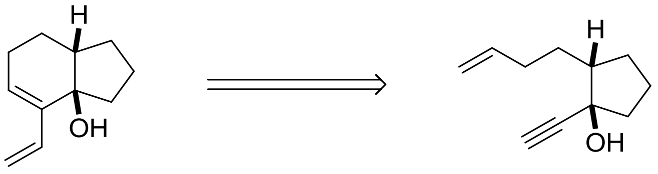


5.59

Model Study

Before undertaking the actual synthesis, we set out to conduct studies on a model substrate to evaluate the feasibility and limitations of the cycloisomerization reaction. To this end, we decided to focus on the synthesis of diene **5.60** which would include the *cis* C/D ring junction and the tertiary hydroxyl group, but would lack all other functionalities found in the natural product (***Scheme 5.15***). The cycloisomerization precursor would therefore be enyne **5.61** which we set out to synthesize.

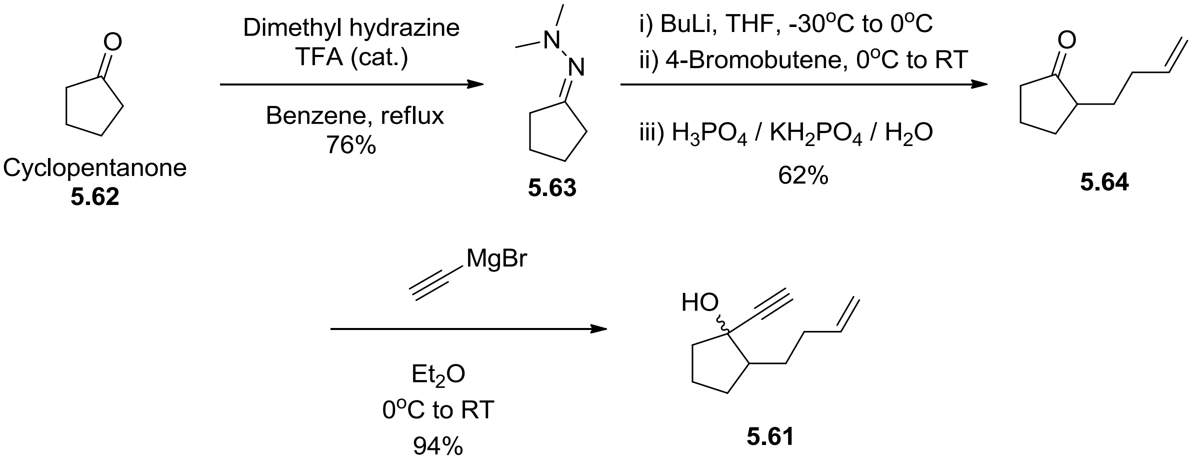
Scheme 5.15 *– Retrosynthesis of proposed model substrate*



5.60 **5.61**

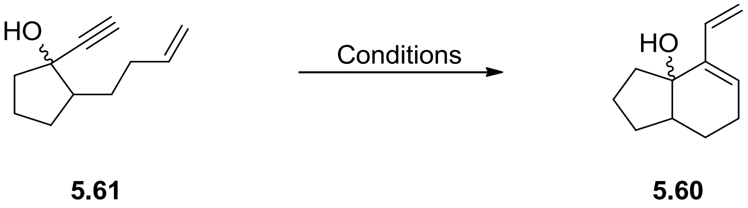
Ketone **5.64** was prepared following a procedure by Blanco et al. which consisted in the mono-alkylation of cyclopentanone (**5.62**) with 4-bromobutene via corresponding dimethylhydrazone **5.63** (***Scheme 5.16***).[102] Addition of ethynyl magnesium bromide to ketone **5.64** yielded alcohol **5.61** in 94% as an inseperable 2 to 3 mixture of diastereomers. The use of Et_2O rather than THF was crucial in this reaction to avoid the formation of various impurities.

Scheme 5.16** – Synthesis of enyne **5.61



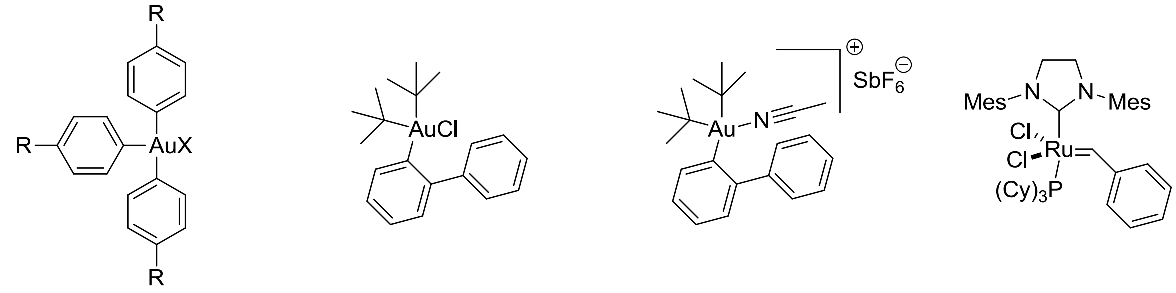
With precursor **5.61** in hand, we began investigating the desired gold(I)-catalyzed cycloisomerization reaction. We subjected enyne **5.61** to various reaction conditions to screen the effect of the ligand, additive and solvent on the reaction (***Table 5.1***). Unfortunately, no desired diene (**5.60**) was obtained; **5.61** being either unreactive or decomposing under typical gold catalyst activation conditions (entries 1-7). In 2007, Echavarren et al. reported the preparation of stable cationic gold catalyst **5.69**, which was shown to promote the cycloisomerization of 1,7-enynes.[103,104] The use of this catalyst on substrate **5.61** only led to no reaction at low temperature, but decomposition upon heating (entries 8-10). Finally, attempting an enyne metathesis using Grubbs' 2nd generation catalyst gave no reaction upon heating in DCM or benzene (entries 11-13), but appeared to give trace amounts of **5.60** after refluxing the reaction mixture in DCM in the presence of ethylene. This reaction could not be further optimized by changing the ruthenium catalyst, solvent or temperature. This result wasn't entirely surprising as free hydroxyl groups are often found to be detrimental to these reactions by binding to the metal catalyst and inhibiting its action.[98]

Table 5.1** – Conditions for the formation of diene **5.60



Entry	Catalyst/Additive	Solvent	Temperature	Result
1	**5.65**/AgOTf	DCM	RT	No reaction
2	**5.65**/$AgSbF_6$	DCM	RT	No reaction
3	**5.65**/$AgNO_3$	DCM	RT	No reaction
4	**5.65**/TfOH	DCM	RT	Decomposition
5	**5.66**	DCM	RT to reflux	Decomposition
6	**5.67**/AgOTf	DCM	RT to reflux	Decomposition
7	**5.68**/AgOTf	DCM	RT to reflux	Decomposition
8	**5.69**	DCM	0 ^{o}C	No reaction
9	**5.69**	DCM	RT to reflux	Decomposition
10	**5.69**	Benzene	RT to reflux	Decomposition
11	**5.70**	DCM	RT to reflux	No reaction
12	**5.70**	Benzene	RT to reflux	No reaction
13	**5.70**/ethylene	DCM	reflux	Traces of **5.60**

***Figure 5.4** – Gold(I) and ruthenium catalysts*



5.65 R = H, X = Cl
5.66 R = H, X = NTf$_2$
5.67 R = CF$_3$, X = Cl

5.68

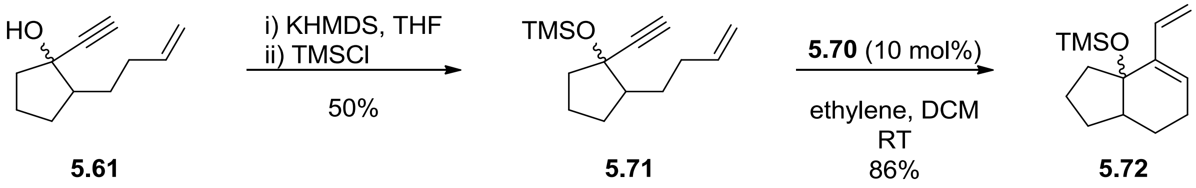
5.69

5.70

Effect of hydroxyl group on the cyclization

We therefore set out to investigate two factors affecting the cyclization reactions: the effect of the free hydroxyl group and the length of the alkyl chain separating the ene and yne functionalities (*i.e.* 1,6-enyne vs 1,7-enyne). We decided to first protect the hydroxyl in **5.61** with a silyl group by deprotonating with KHMDS and quenching the alkoxide with TMSCl to yield 50% of enyne **5.71** (***Scheme 5.17***). Although desired diene **5.72** was not observed under various reaction conditions with gold catalysts, the enyne metathesis reaction proceeded in 86% yield, confirming the detrimental effect of the hydroxyl group on this reaction.

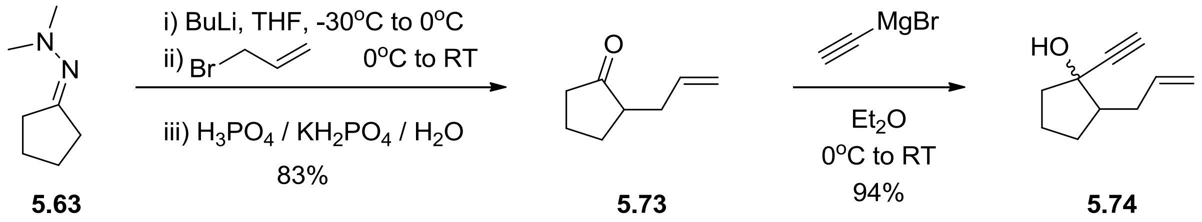
Scheme 5.17** - Synthesis of diene **5.72



Effect of chain length on cyclization

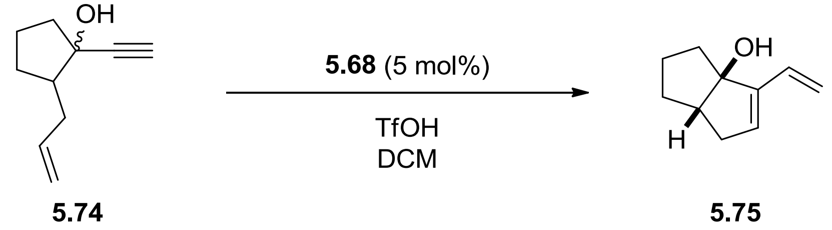
At this stage, we had found a set of conditions that would allow us to form the desired diene (**5.60**), despite the necessity for protecting the alcohol in the precursor. We still decided to investigate the effect of chain length on the cycloisomerization reaction. We therefore synthesized 1,6-enyne **5.74** in the same manner as enyne **5.61**, but alkylating with allyl bromide to yield ketone **5.73** in 83% (***Scheme 5.18***). Once again, the corresponding enyne (**5.74**) was obtained as an inseparable mixture of diastereomers in 94% yield upon alkylation with ethynylmagnesium bromide.

Scheme 5.18** - Synthesis of enyne **5.74



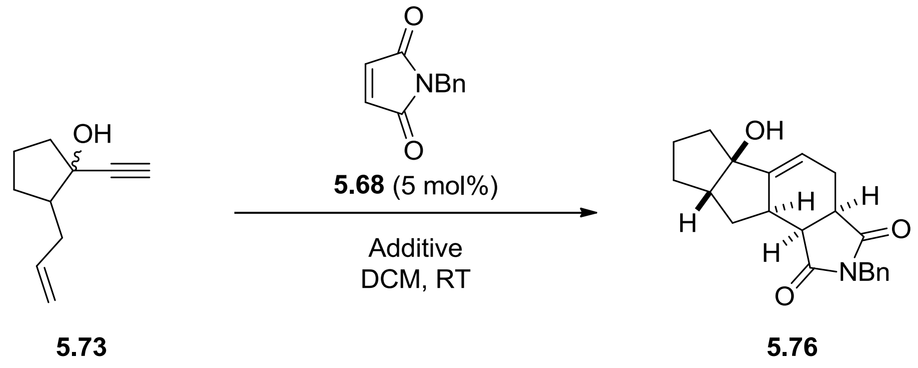
Upon treatment of enyne **5.74** with gold catalysts in dichloromethane at room temperature, what appeared to be corresponding diene **5.75** could be seen in the crude NMR (***Scheme 5.19***). Unfortunately, the reaction was not very clean and **5.75** could not be isolated to confirm the structure.

Scheme 5.19** - Attempted synthesis of diene **5.75



Since diene **5.75** could not be isolated, we decided to attempt the cycloisomerization/Diels-Alder cascade to trap it *in situ*. Indeed, having *N*-benzylmaleimide, a strongly activated dienophile, present in the reaction mixture enabled us to obtain the desired product in 40% yield (***Table 5.2***). Unfortunately, varying the number of equivalents of additive, catalyst and dienophile had no effect on the yield of the reaction. The same effect was observed for the variation of concentration and temperature, and it was also found that dichloromethane was the optimal solvent after a thorough solvent screening. We also attempted to subject enynes **5.61** and **5.71** to these conditions in a final hope to synthesize diene **5.60**, but without success.

Table 5.2 *– In situ trapping of diene* ***5.75*** *with N-benzylmaleimide*



Entry	Additive	Yield (%)
1	AgOTf	50
2	TfOH	32
3	TMSOTf	40

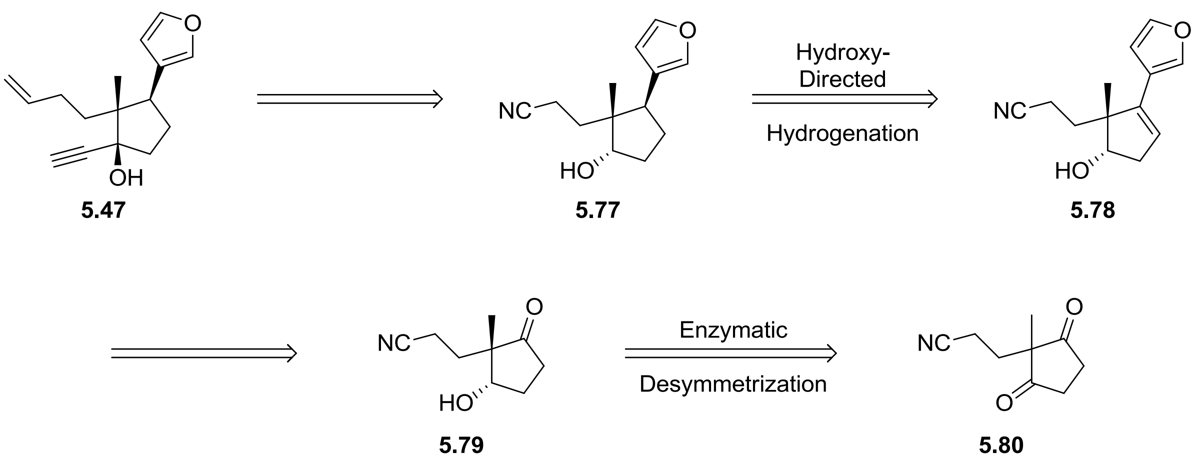
We rationalized the fact that enyne **5.73** underwent the desired cycloisomerization reaction due to a more facile 5-exo-dig cyclization compared to the initial 6-exo-dig cyclization required for enyne **5.61**. With these results, we decided to discard the cycloisomerization and focus on the enyne metathesis route to synthesize digitoxigenin (**5.13**).

Application of the Methodology towards the Total Synthesis of Digitoxigenin

Initial route

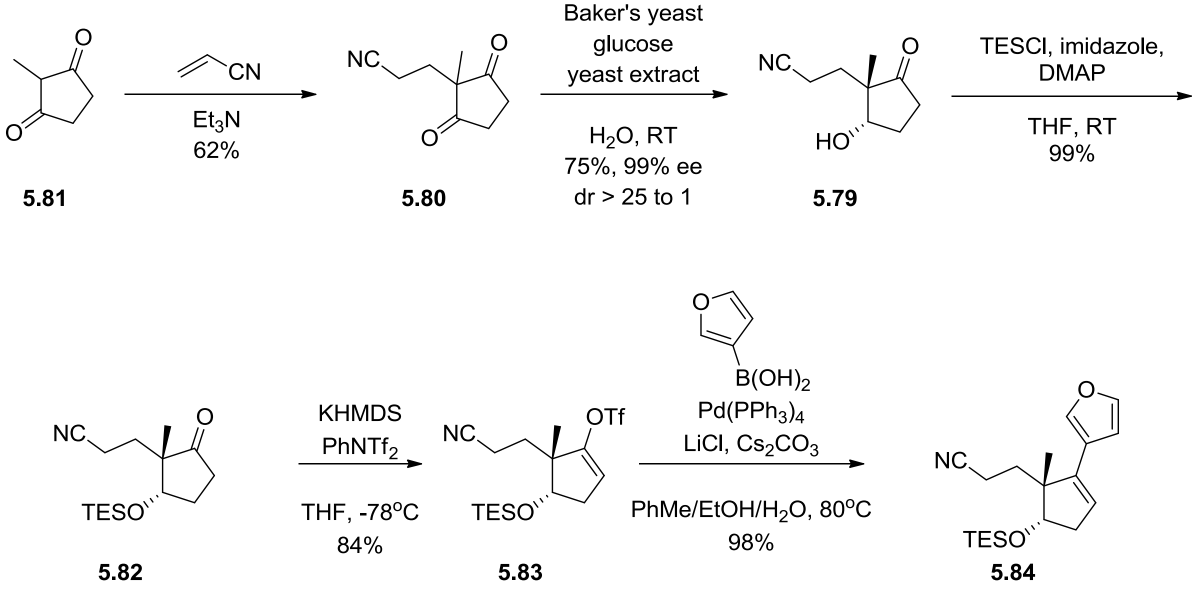
We next decided to tackle the synthesis of enyne **5.47** which we believed could come from alcohol **5.77** (***Scheme 5.20)***. The furan chiral center could result from a hydroxy-directed hydrogenation on substrate **5.78**, which in turn, could be prepared via a coupling reaction of **5.79**. Finally, compound **5.79** was known in the literature and can be accessed from an enzymatic desymmetrization of diketone **5.80**.[105]

Scheme 5.20 - *Retrosynthetic analysis of 1st route towards enyne **5.47***



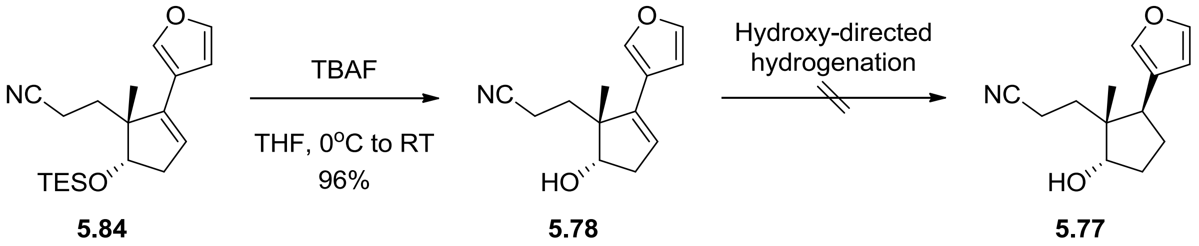
The synthesis began with dione **5.81** which could be alkylated with acrylonitrile in triethylamine at reflux to give **5.80** in 62% and then enzymatically reduced using Baker's yeast, glucose and yeast extract in water to yield keto-alcohol **5.79** in 75% yield (>99% ee and >25 to 1 dr) (***Scheme 5.21***). Although the enantioselectivity and yields were good, this reaction was not very practical and could not be scaled efficiently beyond 1 gram of substrate. The main difficulties were the high dilutions required and the high aqueous solubility of alcohol **5.79** which made these manipulations very time-consuming. Indeed, a continuous organic extractor had to be used for over 48h with 1L of EtOAc to recover less than 1 gram of product. Nevertheless, the synthesis was continued in order to test the validity of our strategy. The hydroxyl group in **5.79** was protected by treatment with TESCl, DMAP and imidazole in THF to yield 99% of silyl ether **5.82**. Formation of enol triflate **5.83** was accomplished in 84% yield by deprotonating with KHMDS followed by reaction with $PhNTf_2$. Finally, a Suzuki coupling with 3-furylboronic acid was employed to install the furan moiety, yielding **5.84** in 98% yield.[106]

Scheme 5.21 *- Preparation of compound* ***5.84***



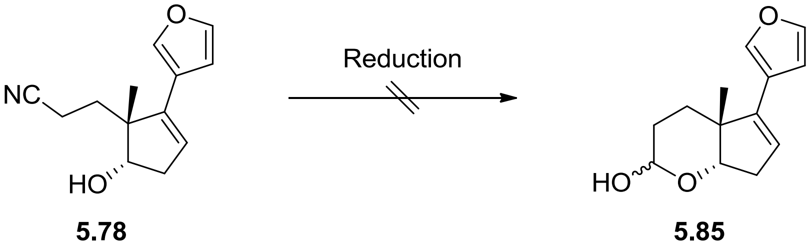
The next step in the synthesis called for a hydroxy-directed hydrogenation. Silyl ether **5.84** was cleaved using TBAF to yield secondary alcohol **5.78** in 96% yield (***Scheme 5.22***). Unfortunately, treatment of **5.78** with Crabtree's catalyst in DCM under an atmosphere of hydrogen,[107] led to no conversion to desired reduced compound **5.77**.

Scheme 5.22 *- Attempted hydrogenation of alkene* ***5.78***



Since it is known that certain functional groups such as amines inhibit Crabtree's catalyst,[104] we believed that the nitrile group was binding irreversibly to the iridium preventing the reaction from taking place. We therefore set out to reduce **5.78** to corresponding lactol **5.85**, which could hopefully be hydrogenated (***Scheme 5.23***). Unfortunately, all attempts at reducing the nitrile with DIBAL-H, under a variety of reaction conditions, led to recovered starting material or complex product mixtures. Concerned of possible interactions between the alcohol and reagents, we attempted similar reaction conditions on compound **5.84**, but with the same results.

Scheme 5.23 *- Attempted reduction of nitrile* ***5.78***

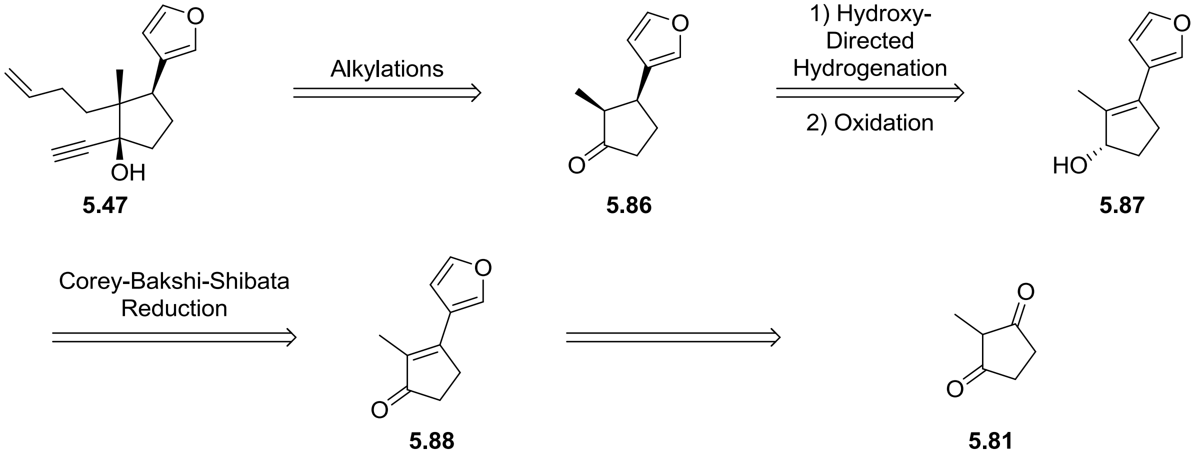


Due to the problematic hydrogenation of alkene **5.78** and the lack of practicality for the yeast mediated desymmetrization reaction, we decided to set this route aside and focus on developing a new route.

Second route

We imagined that enyne **5.47** could stem from alkylations of known ketone **5.86** (***Scheme 5.24***).[91] Although the Deslongchamps group developed a route to **5.86**, it relied on less practical reactions such as a cuprate addition to install the furan ring. We decided to investigate a more rapid and convenient approach. To this end, we thought that both chiral centers in **5.86** could be obtained via a hydroxy-directed hydrogenation of alcohol **5.87**, which we hoped could be obtained from a CBS reduction on enone **5.88**.[108] Finally, we imagined that **5.88** could be synthesized in a few steps from commercially available dione **5.81**.

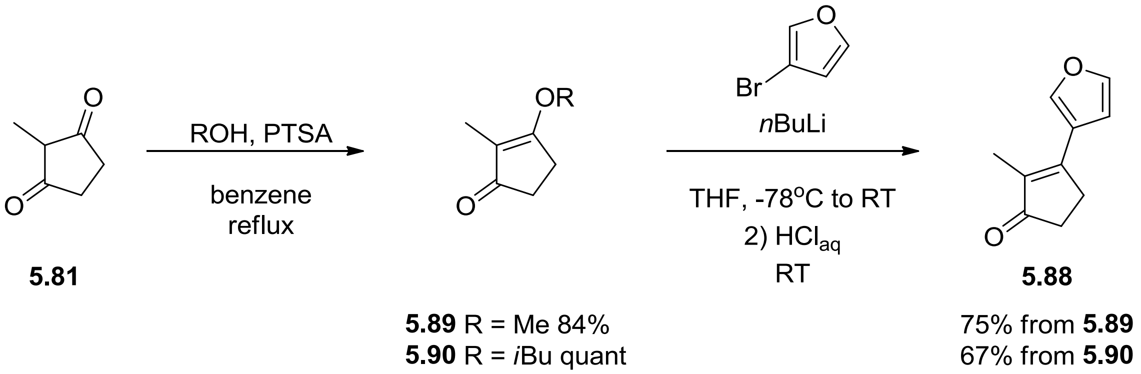
Scheme 5.24 *- Retrosynthetic analysis of 2nd route towards enyne* ***5.47***



Our synthetic endeavour started once again with dione **5.81** which was initially treated with a catalytic amount of sulfuric acid in refluxing methanol to form enol ether **5.89** in 84% yield (***Scheme 5.25***). Treatment of **5.89** with an excess of 3-lithiofuran, generated from the reaction of 3-bromofuran and *n*BuLi at -78 °C, in THF yielded furyl enone **5.88** in 75%. To increase the yield of the first step, *i*BuOH was used rather than MeOH to increase the stability of the corresponding enol ether towards hydrolysis. Indeed, treatment of dione

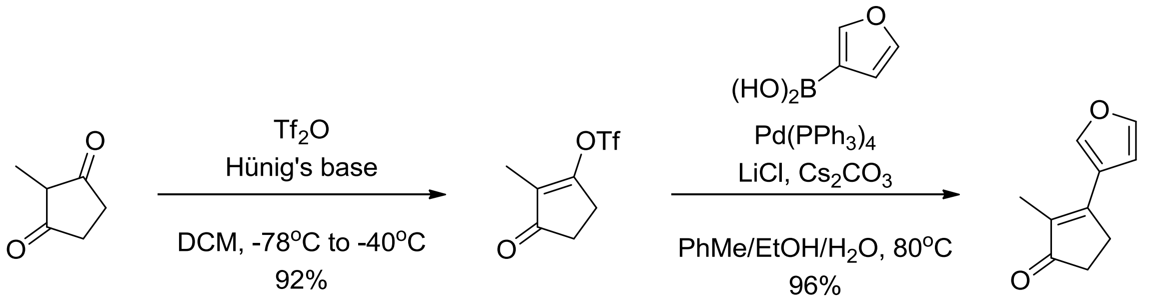
5.81 with PTSA and *i*BuOH in refluxing benzene using a Dean-Stark apparatus led to the isolation of **5.90** in quantitative yield. However, it was found that the subsequent step on this substrate led to a lower yield likely due to the more difficult hydrolysis of the enol ether intermediate. Treatment of **5.90** with 3-lithiofuran in THF followed by acidic cleavage with 4 M HCl yielded **5.88** in 67%. Isolation of the final product often required more than one chromatography followed by many recrystallizations to obtain sufficiently pure product to pursue the synthesis.

Scheme 5.25 - *Introduction of furan moiety*



To address this inconvenience, a more effective and less time-consuming route was found. Treating dione **5.81** with triflic anhydride and Hünig's base at -78 to -40 ^{o}C yielded enol triflate **5.91** in 85% yield (***Scheme 5.26***).[109] Suzuki coupling of **5.91** with 3-furylboronic acid in the presence of 5 mol% Pd(PPh$_3$)$_4$, LiCl and Cs$_2$CO$_3$ in a 3:3:2 mixture of toluene:THF:H$_2$O led to the formation of enone **5.88** in 96% yield after 1 hour. The product of this transformation only required one flash chromatography to obtain a pure product and proved to be much more efficient, requiring only 2 hours of total reaction time compared to 32 hours for the previous method and gave an increased yield of 88% compared to 67% over two steps.

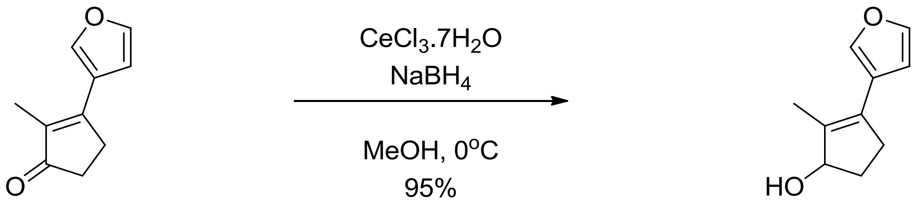
Scheme 5.26 *- Improved synthesis of enone **5.88***



5.81 **5.91** **5.88**

The next challenge consisted in the selective 1,2-reduction of enone **5.88** which was accomplished by treatment under Luche conditions with $CeCl_3$ and $NaBH_4$ in MeOH to give acid sensitive allylic alcohol **5.92** in 95% yield (***Scheme 5.27***).[26] Although this reaction proceeded quite smoothly and in high yield, it was found not to be very reproducible and the work-up process always led to difficult emulsions. The main reason for the poor reproducibility came from the fact that in some cases degradation of the product was obtained, likely from elimination of the hydroxyl group. It is at this point that an enantioselective reduction could be used to allow an asymmetric synthesis of the natural product. However, at this stage, we decided to pursue the racemic route until our key step was validated.

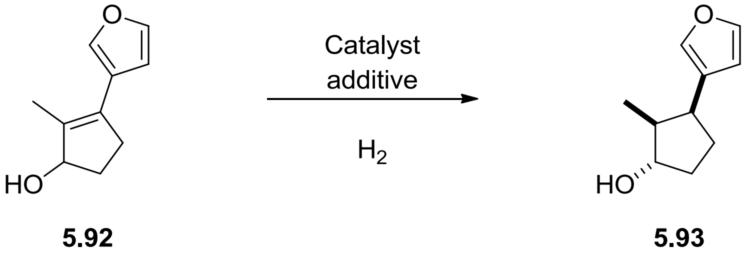
Scheme 5.27 *- Luche reduction of enone **5.88***



5.88 **5.92**

The next step consisted in the transfer of stereogenicity from the hydroxyl group to the neighbouring carbon atoms. To this end, a hydroxy-directed reduction using Crabtree's catalyst was investigated (***Table 5.3***). Unfortunately, it was found that upon treatment of **5.92** with 5 mol% of the iridium catalyst in DCM led to decomposition of the allylic alcohol, likely due to the Lewis acidity of the catalyst (entry 1). The reaction was also tried in the presence of di-*t*Bu-pyridine to buffer the solution, but this led to no conversion to desired product **5.93** (entry 2). Although no decomposition was observed when deprotonating the alcohol with NaH in THF prior to treatment with the catalyst, no conversion was obtained (entry 3). Finally, attempts at hydrogenating **5.92** with heterogeneous Pd catalysts were also unfruitful (entries 4 and 5).

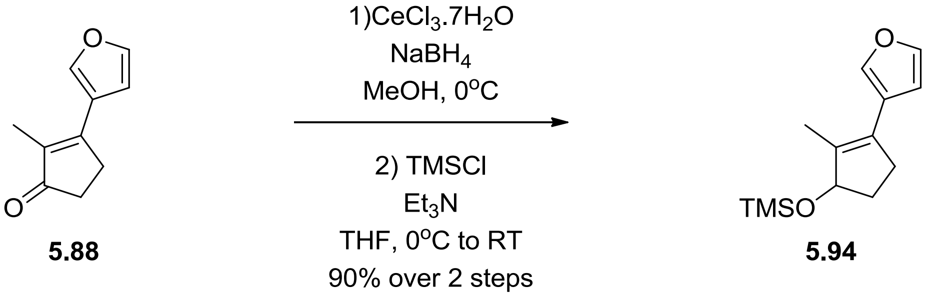
Table 5.3** – Attempted hydrogenation of alkene **5.92



Entry	Metal	Additive	Result
1	Crabtree's catalyst	none	Elimination of hydroxyl group
2	Crabtree's catalyst	di-*t*Bu-pyridine	No reaction
3	Crabtree's catalyst	NaH	No reaction
4	Pd/C	-	No reaction
5	$Pd(OH)_2$	-	No reaction

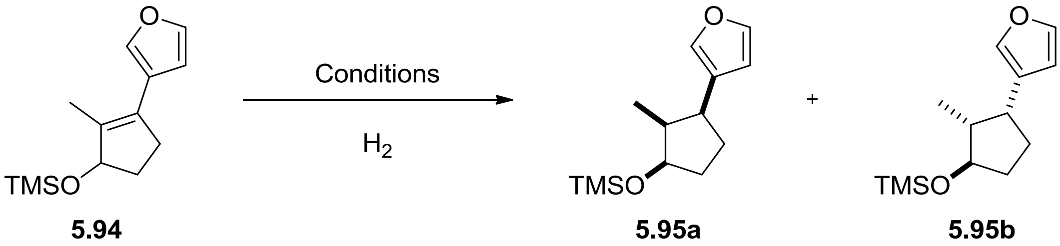
Since the hydroxy-directed hydrogenation was unsuccessful, we envisioned that the desired stereochemistry could be obtained by protecting the alcohol with a silyl group, to increase steric bulk on that face of the molecule, followed by a simple hydrogenation with a Pd catalyst. Treatment of crude product **5.92** with Et_3N and TMSCl in DCM gave silyl ether **5.94** in 90% yield over two steps (***Scheme 5.28)***.

Scheme 5.28 - *Protection of alcohol* ***5.92***



The next step consisted in the hydrogenation of the tetrasubstituted alkene. A variety of palladium catalysts, catalyst loadings, temperatures and reaction times were investigated, as shown in ***Table 5.4***. The reactions were not conducted in typical protic solvents, such as MeOH or EtOH, due to the high lability of the TMS group and sensitivity of the formed allylic alcohol. $Pd(OH)_2$ proved to be too reactive of a catalyst and led to a complex mixture of products, PtO_2 in THF proved to be unreactive (entries 1 and 2). Our first hit came from the use of 10 mol% Pd/C in the presence of Et_3N in EtOAc at room temperature to yield 50% of a 4 : 1 mixture of **5.95a** and **5.95b** (entry 3). By lowering the catalyst loading and reaction temperatures to 1 mol% and 0 °C, it was possible to increase both the yield and diastereoselectivity to 75% with a dr of 16 to 1 (entry 6). This result was satisfactory to continue the total synthesis. Nevertheless, it is interesting to note the trend from entries 4 to 6, in which larger quantities of **5.95b** are generated with higher catalyst loadings. This may be due to an increase in alkene migration at higher loadings followed by hydrogenation of the ensuing trisubstituted alkene.

Table 5.4** – Hydrogenation of silyl ether **5.94

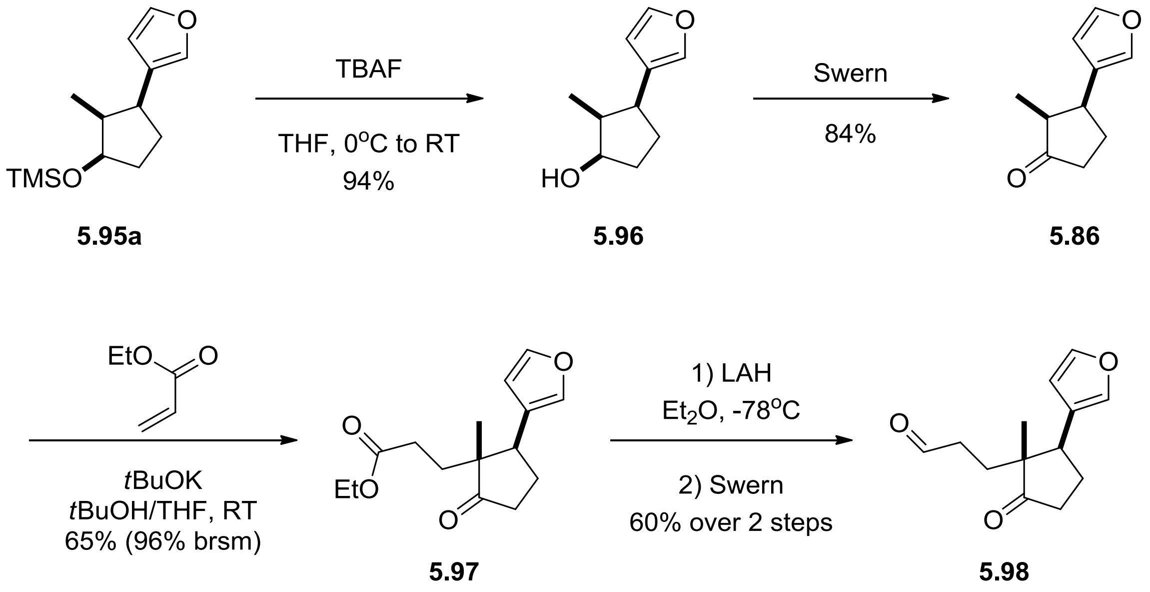


Entry	**Metal**	**Loading** (mol%)	**Solvent**	**Temperature** (°C)	**Yield** **5.95a** : **5.95b**
1	$Pd(OH)_2$	5	EtOAc	RT	Complex mixture
2	PtO_2	5	THF	RT	No reaction
3	Pd/C	10	EtOAc + Et_3N	RT	50% dr = 4 : 1
4	Pd/C	10	EtOAc + Et_3N	0	65% dr = 4 : 1
5	Pd/C	5	EtOAc + Et_3N	0	75% dr = 9 : 1
6	Pd/C	1	EtOAc + Et_3N	0	73% dr = 16 : 1

With the fully reduced cyclopentane moiety in hand, the next challenge was the formation of the quaternary carbon atom through installation of the butene side-chain. To this end, compound **5.95a** was treated with TBAF in THF at 0 °C which furnished alcohol **5.96** in 95% yield which was then oxidized to the corresponding ketone under Swern conditions to give **5.86** in 85% yield (***Scheme 5.29***). Using slightly modified procedures from Deslongchamps' report,[91] ketone **5.86** was converted to keto-aldehyde **5.98** in 3 steps. **5.86** was first reacted in a Michael addition fashion to form the desired quaternary center by treatment with a catalytic amount of *t*BuOK in *t*BuOH and in the presence of ethyl acrylate for 20 minutes which led to the isolation of the corresponding alkylated product **5.97** in 65%

yield (96% brsm). Total reduction of all carbonyl groups present with LAH at 0 ^{o}C in Et_2O and subsequent oxidation under Swern conditions gave keto-aldehyde **5.98** in 60% yield over two steps.

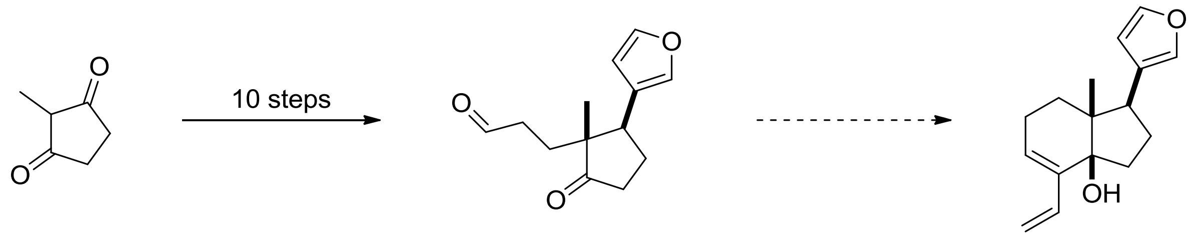
Scheme 5.29 *- Synthesis of keto-aldehyde* ***5.98***



Conclusion and Future Work

In conclusion, our studies have demonstrated that a gold(I)-catalyzed cycloisomerization/Diels-Alder cascade was not likely a viable approach to the synthesis of digitoxigenin (**5.13**), but that an enyne metathesis could be used for the formation of the diene. A ten step synthetic route was developed to synthesize keto-aldehyde **5.98** which can likely be carried through to desired diene **5.46** (***Scheme 5.30***).

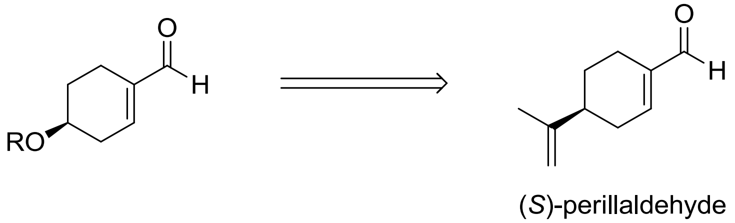
Scheme 5.30 *- Summary of current study*



5.81 **5.98** **5.46**

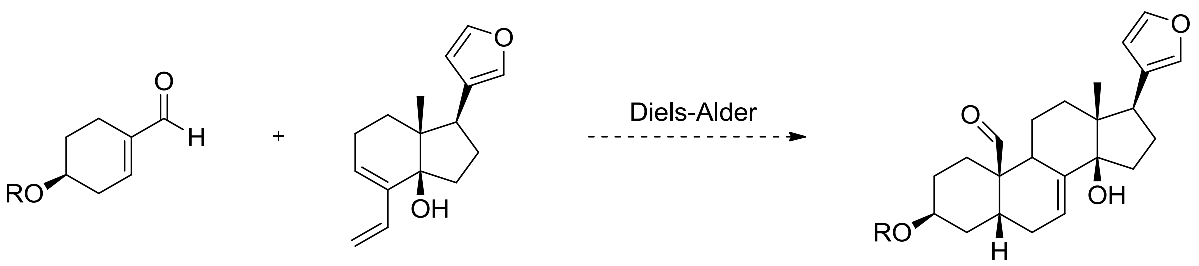
Future work will focus on the synthesis of dienophile **5.45**, which could likely be synthesized from (*S*)-perillaldehyde (**5.99**) in a few steps (***Scheme 5.31***). Once the asymmetric synthesis of **5.46** is completed, studies to combine both enantioenriched fragments in a Diels-Alder reaction could be performed (***Scheme 5.32***).

Scheme 5.31 *- Proposed precursor for dienophile* ***5.45***



5.45 **5.99**

Scheme 5.32 *- Proposed Diels-Alder between* ***5.45*** *and* ***5.46***



5.45 **5.46** **5.100**

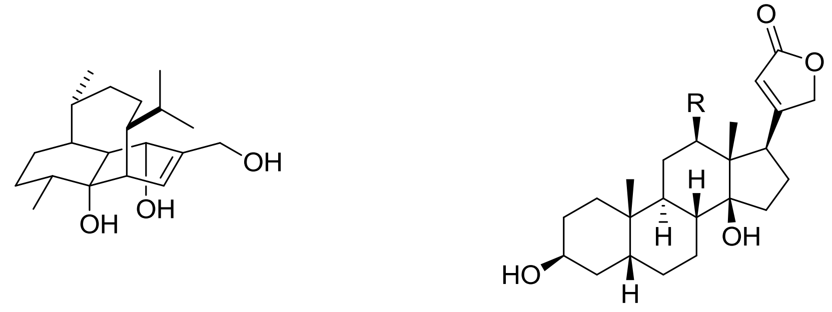
Chapter 6

Summary

Summary of work

The total syntheses of two natural products, vinigrol (**2.1**) and digitoxigenin (**5.13**), have been investigated in this thesis (***Figure 6.1***). The strategy in both cases relied upon a Diels-Alder reaction to build much of the molecules complexity and stereocenters.

***Figure 6.1** – Target natural products*

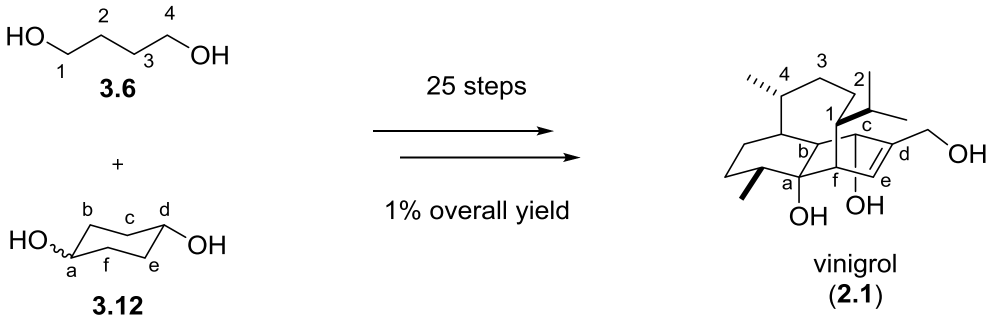


Vinigrol
2.1

Digitoxigenin
5.13

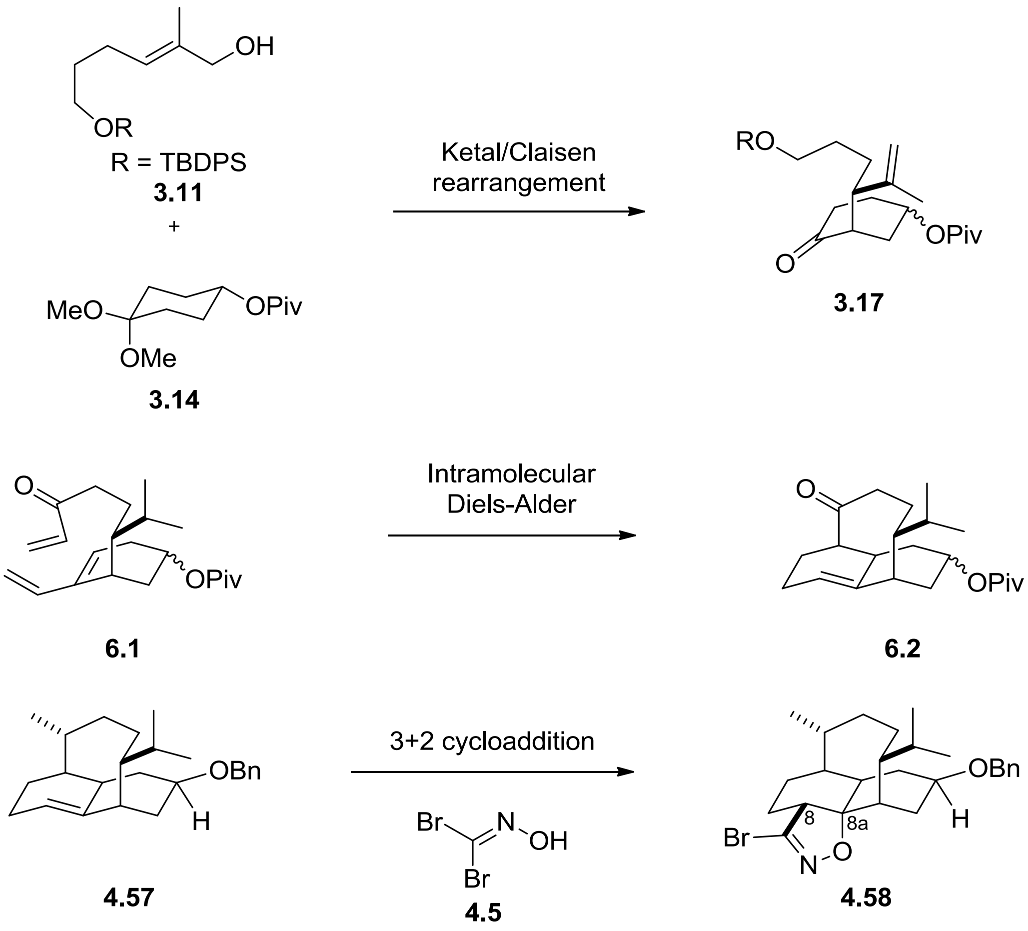
In the case of vinigrol (**2.1**), a formal synthesis was achieved in 25 steps and 1% overall yield from commercially available diol **3.6** (***Figure 6.2***).

***Figure 6.2** – Formal synthesis of vinigrol*



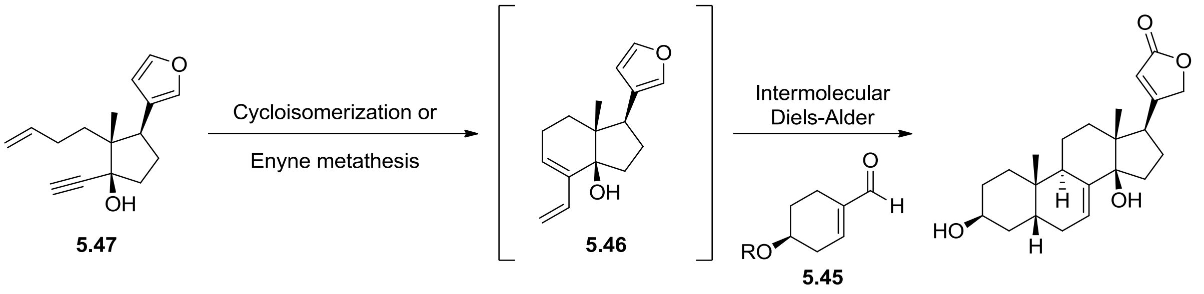
The synthesis demonstrated the use of three pericyclic reactions thoughout the process: a diastereoselective ketal/Claisen rearrangement to install the first stereocenters, an intramolecular Diels-Alder reaction to form the tricyclic core of the molecule and finally a 3 + 2 cycloaddition with a nitrile oxide to allow the installation of the C8 methyl and C8a hydroxyl groups (***Scheme 6.1***). This work led to only the second synthesis of this molecule reported to date.

Scheme 6.1 – Key steps in the formal synthesis of vinigrol



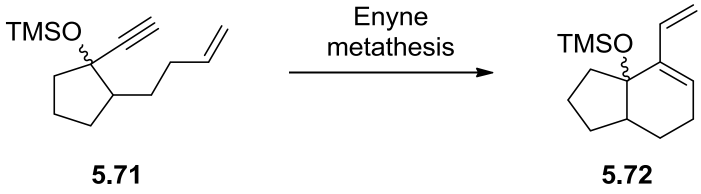
In the case of digitoxigenin (**5.13**), the strategy focused on the use of a gold-catalyzed cycloisomerization or an enyne metathesis of compound **5.47** to form a diene that could be reacted with a dienophile in an intermolecular Diels-Alder reaction to afford the tetracyclic framework of the natural product (***Scheme 6.2***).

***Scheme 6.2** – Proposed route to digitoxigenin*

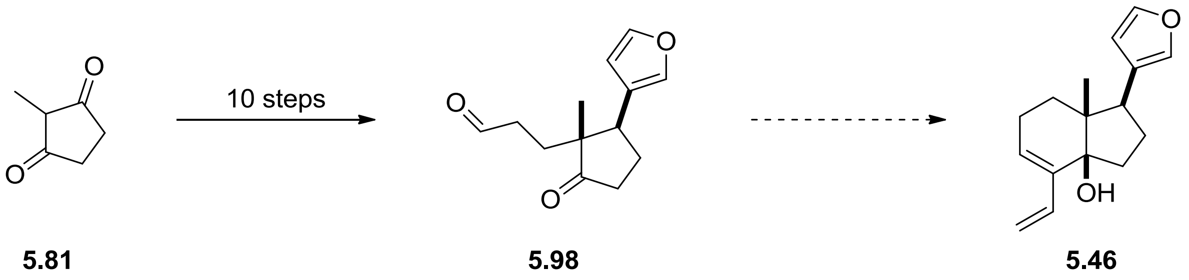


Although the key step of the reaction has not yet been tested, the viability of the enyne metathesis was demonstrated on model substrate **5.71** (***Scheme 6.3***). Finally a route to keto-aldehyde **5.98** was devised in 10 steps from dione **5.81** and only a few more steps are required for the synthesis of diene **5.46** (***Scheme 6.4***).

Scheme 6.3** – Enyne metathesis of model substrate **5.71



Scheme 6.4** – Synthesis of keto-aldehyde **5.98



Claims to original research

1. Exploration of the installation of the C8 methyl and C8a hydroxyl groups of vinigrol on different subtrates.
2. Completion of a formal synthesis of vinigrol.
3. Investigations into the gold-catalyzed cycloisomerization and enyne metathesis reactions and applications towards the total synthesis of digitoxigenin.
4. Exploration of two synthetic routes towards the synthesis of digitoxigenin's tetracyclic core.

Publications from this work

1. Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2111.
2. A complete article on the formal synthesis of vinigrol is in preparation.

Presentations of this work

Oral: "**Formal Syntheis of Vinigrol**", Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, Montreal, Canada, November 2011.

Poster: "**Formal Synthesis of Vinigrol**", Natural Products Gordon Conference, Bryant University, Rhode Island, July 2011.

Oral: "**Towards the Total Synthesis of Vinigrol**", CSC 2011, Montreal, Canada, May 2011.

Poster: “**Towards the Total Synthesis of Vinigrol**”, Pacifichem, Honolulu, United States, December 2010.

Poster: “**Towards the Total Synthesis of Vinigrol**”, Québec-Ontario Minisymposium in Synthetic and Bioorganic chemistry, Ste-Catharines, Canada, November 2010.

Poster: “**Towards the Total Synthesis of Vinigrol**”, Astra Zeneca Student Symposium, Dorval, Canada, September 2010.

Oral: “**Towards the Total Synthesis of Vinigrol**”, CSC 2010, Toronto, Canada, May 2010.

Poster: “**Towards the Total Synthesis of Vinigrol**”, KFOS 2010, Ottawa, Canada, May 2010.

Poster: “**Towards the Total Synthesis of Digitoxigenin**”, University of Ottawa Synthesis Day, Ottawa, Canada, May 2008.

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

Chapter 7

Experimental

General Experimental

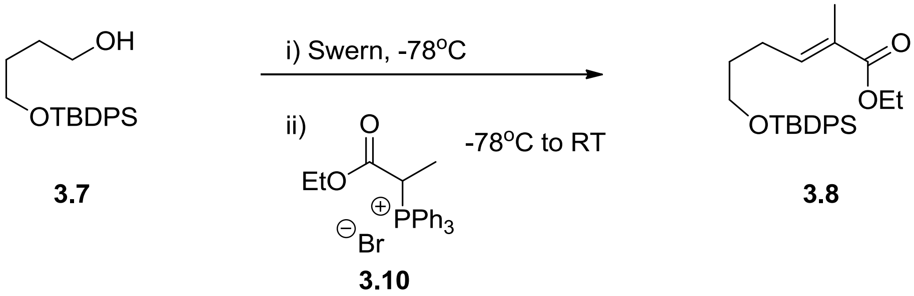
All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All solvents were freshly distilled prior to use; diethyl ether and THF over sodium and benzophenone; toluene, triethylamine, and DCM over calcium hydride. All other commercial reagents were used without purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or *p*-anisaldehyde staining solution. Column chromatographies were carried out with silica gel 60 (230-400 mesh, Merck). ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents, on Bruker AMX 300 MHz, Bruker AMX 500 MHz and Bruker AMX 400 MHz spectrometers. IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer.

HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

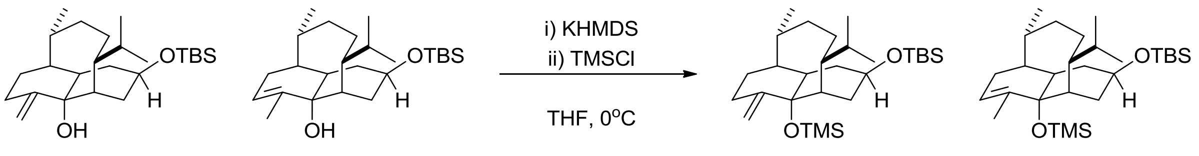
Detailed Experimental Procedures

Procedures for Chapter 3

Experimental procedures and full characterization for compounds **3.7** to **3.43** are available in Christiane Grisé-Bard's thesis.[42]



(*E*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-2-methyl-hex-2-enoic acid ethyl ester (3.8). To a solution of oxalyl chloride (80 µL, 0.95 mmol, 1.5 eq) in DCM (5.5 mL) was added DMSO (75 µL, 1.1 mmol, 1.6 eq) dropwise at -78 °C and stirred 30 minutes. To this solution was cannulated alcohol **3.7** (213 mg, 0.65 mmol, 1.0 eq) in DCM (1 mL) and stirred for 45 minutes. Et_3N (0.32 mL, 2.2 mmol, 3.5 eq) was added and the solution was stirred 10 min at -78 °C. 1-Ethoxycarbonyl-ethyl-triphenylphosphonium bromide (547.5 mg, 1.24 mmol, 1.9 eq) in DCM (1 mL) was added at -78 °C, the solution was warmed to RT and stirred 30 minutes. Et_2O was added followed by H_2O and the layers were separated. The organic phase was washed with H_2O, then brine, dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (5-10% EtOAc/Hexanes) to yield 218.9 mg of alkene **3.8** as a colorless oil (82%, *E*/*Z* = 94/6).



3.44 **3.45**

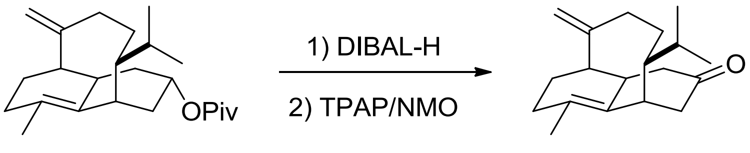
(±)-(1*S*,3*R*,5*S*,6*R*,10*R*, 13*R*, 14*R*)-6-Isopropyl-9-methyl-13-methylene-14-trimethylsilyloxy-3-*tert*butyldimethylsilyloxy-tricyclo[8.4.0.0^{5,14}]tetradecane (3.44) and (±)-(1*S*,3*R*,5*S*,6*R*,10*R*, 13*R*, 14*R*)-6-Isopropyl-9,13-dimethyl-14-trimethylsilyloxy-3-*tert*butyldimethylsilyloxy-tricyclo[8.4.0.0^{5,14}]tetradec-12-ene (3.45)

To a 0 ºC solution of KHMDS (53.3 mg, 0.267 mmol, 7.4 eq) in tetrahydrofuran (0.2 mL) was cannulated allylic alcohol (14.7 mg, 0.0361 mmol, 1.0 eq). The resulting yellow solution was stirred for 30 minutes before adding freshly distilled TMSCl (0.027 mL, 0.22 mmol, 6.0 eq). The clear solution was stirred for 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 16.7 mg of a 2:3 mixture of **3.44** and **3.45** as a colorless oil (16.7 mg, 97%).

Characterized as a mixture of isomers: IR (neat, cm^{-1}) 2955, 2927, 1090; **3.45** (Major): ^{1}H NMR (C_6D_6, 400 MHz) δ 5.30 (br d, *J* = 5.8 Hz, 1H), 4.90-4.82 (m, 1H), 2.50-2.20 (m, 2H), 2.16-1.99 (m, 3H), 1.96-1.89 (m, 1H), 1.80 (dd, *J* = 17.1, 6.3 Hz, 1H), 1.73-1.65 (m, 1H), 1.70 (s, 3H), 1.59-1.28 (m, 8H), 1.07 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.25 (s, 3H), 0.25 (s, 3H), 0.23 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz) δ 137.9 (C), 127.3 (CH), 80.8 (C), 67.2 (CH), 46.1 (CH), 45.7 (CH), 44.7 (CH), 36.1 (CH_2), 35.9 (CH), 34.4 (CH), 33.3 (CH), 32.8 (CH_2), 30.2 (2 CH_2), 28.9 (CH_2), 26.4 (3 CH_3), 26.1 (CH_3), 22.1 (CH_3), 20.9 (CH_3), 18.6 (C), 18.4 (CH_3), 2.3 (3 CH_3), -4.0 (CH_3), -4.0 (CH_3).

3.44 (Minor): ^{1}H NMR (C_6D_6, 400 MHz) δ 5.01 (s, 1H), 4.85 (s, 1H), 4.82-4.73 (m, 1H), 2.63 (d, *J* = 9.3 Hz, 1H), 2.50-2.26 (m, 3H), 2.16-1.99 (m, 3H), 1.85-1.75 (m, 1H), 1.73-1.65

(m, 2H), 1.59-1.28 (m, 8H), 1.08 (s, 9H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.4$ Hz, 3H), 0.24 (s, 3H), 0.24 (s, 3H), 0.22 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz) δ 149.8 (C), 111.7 (CH_2), 80.1 (C), 67.2 (CH), 46.9 (CH), 42.6 (CH), 41.9 (CH), 40.7 (CH), 37.1 (CH), 36.9 (CH), 35.6 (CH_2), 35.5 (CH_2), 32.8 (CH_2), 30.6 (CH_2), 26.4 (3 CH_3), 25.3 (CH_2), 24.6 (CH_2), 22.8 (CH_3), 21.7 (CH_3), 18.5 (CH_3), 18.4 (C), 2.2 (3 CH_3), -4.0 (CH_3), -4.1 (CH_3); HRMS (EI) m/z calcd for $C_{28}H_{54}O_2Si_2$ [M^+] 478.3662, found 478.3622.



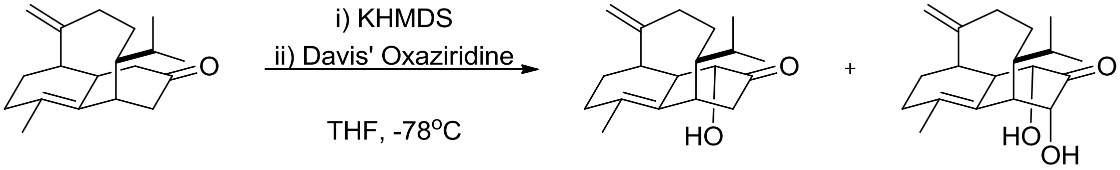
3.33 **3.35**

(±)-(1*R*,5*S*,6*R*,10*S*)-6-Isopropyl-13-methyl-9-methylenetricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-one (3.35)

To a solution of pivalate **16a** (222.0 mg, 0.619 mmol, 1.0 eq) in DCM (7.0 mL) was added 1.0 M DIBAL-H in toluene (2.20 mL, 2.20 mmol, 3.5 eq) dropwise at -78 °C and stirred at that temperature for 2 h. The mixture was then quenched by the addition of a saturated aqueous solution of sodium tartrate at -78 °C and allowed to warm to RT and stirred for 30 min. The layers were separated and the aqueous phase was extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. The product was used crude in the next step.

To a flask containing flame dried 4 Å molecular sieves (950 mg) was cannulated a solution of the alcohol from the previous step in DCM (6.2 mL) at RT. NMO (160.0 mg, 1.37 mmol, 2.2 eq) was then added in one portion followed by TPAP (22.0 mg, 0.0626 mmol, 0.1 eq) and the solution was stirred for 2h. The mixture was filtered through a pad of SiO_2 eluting with EtOAc and concentrated. Purification by flash chromatography (15% EtOAc/Hexanes) yielded 138.6 mg of ketone **24** as a clear oil (82% over 2 steps).

IR (neat, cm^{-1}) 2939, 2874, 1709; ^{1}H NMR (C_6D_6, 400 MHz) δ 4.69 (d, *J* = 2.7 Hz, 1H), 4.64 (dd, *J* = 2.6, 0.7 Hz, 1H), 3.25-3.23 (m, 1H), 2.70-2.62 (m, 1H), 2.35-2.27 (m, 4H), 2.21 (dd, *J* = 13.7, 12.4 Hz, 1H), 2.11 (ddd, *J* = 16.4, 8.6, 0.8 Hz, 1H), 1.86-1.70 (m, 4H), 1.65 (dd, *J* = 13.3, 6.5 Hz, 1H), 1.59 (br s, 3H), 1.19-1.02 (m, 3H), 0.98-0.90 (m, 1H), 0.80 (d, *J* = 6.1 Hz, 3H), 0.73 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 211.2 (C), 154.2 (C), 130.9 (C), 129.5 (C), 115.1 (CH_2), 53.0 (CH), 48.0 (CH), 40.7 (CH_2), 39.3 (CH_2), 37.3 (CH), 36.4 (CH), 32.6 (CH_2), 30.2 (CH), 30.0 (CH_2), 27.8 (CH_2), 25.8 (CH_2), 21.1 (CH_3), 21.0 (CH_3), 18.2 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{28}O_1$ [M$^+$] 272.2140, found 272.2144.



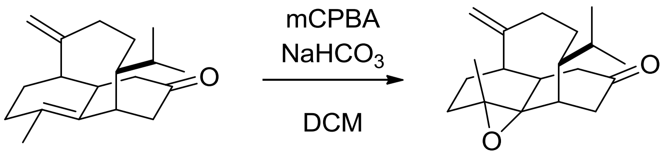
3.35 **3.72** **3.73**

(±)-(1*R*,4*S*,5*S*,6*R*,10*S*)-4-Hydroxy-6-Isopropyl-13-methyl-9-methylenetricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-one (3.72) and (±)-(1*R*,2*R*,4*S*,5*S*,6*R*,10*S*)-2,4-Dihydroxy-6-Isopropyl-13-methyl-9-methylenetricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-one (3.73)

To a suspension of KHMDS (11.4 mg, 0.0571 mmol, 3.0 eq) in THF (0.1 mL) was added ketone **3.35** (5.1 mg, 0.019 mmol, 1.0 eq) as a solution in THF (0.3 mL) at -78 °C. The mixture was stirred for 30 minutes at that temperature and Davis oxaziridine (6.5 mg, 0.025 mmol, 1.3 eq) was added in one portion as a solid. The mixture was warmed to 0 °C and stirred for 30 minutes. The reaction was quenched with saturated NH_4Cl_{aq} and EtOAc was added. The layers were separated and the aqueous layer was extracted with EtOAc (3x) and the combined organic phases were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (25% EtOAc/Hexanes) to yield 3.5 mg of **3.72** as a colorless oil (63%) and 0.8 mg of **3.73** as a colorless oil (14%).

3.72: IR (neat, cm^{-1}) 3405, 2961, 2932, 2905, 1701, 1113; ^{1}H NMR (C_6D_6, 300 MHz) δ 5.03 (d, *J* = 2.7 Hz, 1H), 4.82 (d, *J* = 2.6 Hz, 1H), 4.42 (d, *J* = 9.9 Hz, 1H), 3.74-3.69 (m, 1H), 3.30 (ddd, *J* = 9.5, 4.1, 4.1 Hz, 1H), 3.21 (br d, *J* = 9.9 Hz, 1H), 2.37 (dd, *J* = 17.1, 11.0 Hz, 1H), 2.27 (dd, *J* = 12.6, 12.6 Hz, 1H), 2.22-2.16 (m, 1H), 1.85-1.59 (m, 5H), 1.47 (d, *J* = 2.2, 3H), 1.23 (dd, *J* = 7.0, 7.0 Hz, 1H), 1.11-1.00 (m, 2H), 0.87-0.79 (m, 2H), 0.76 (d, *J* = 5.2 Hz, 3H), 0.62 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 213.3 (C), 154.0 (C), 130.3 (C), 129.6 (C), 116.0 (CH_2), 73.0 (CH), 54.2 (CH), 51.0 (CH), 45.6 (CH), 37.7 (CH), 35.6 (CH_2), 32.8 (CH_2), 30.6 (CH), 30.5 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 21.6 (CH_3), 21.1 (CH_3), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{28}O_2$ [M^+] 288.2089, found 288.2075.

3.73: IR (neat, cm^{-1}) 3413, 2958, 2924, 2885, 1704, 1082; ^{1}H NMR (C_6D_6, 400 MHz) δ 4.97 (dd, *J* = 2.6, 0.9 Hz, 1H), 4.79 (br d, *J* = 2.7 Hz, 1H), 4.34 (br d, *J* = 8.9 Hz, 1H), 3.63 (s, 1H), 3.50 (s, 1H), 3.44 (d, *J* = 1.8 Hz, 1H), 3.17 (ddd, *J* = 9.7, 4.5, 4.5 Hz, 1H), 3.04-3.02 (m, 1H), 2.25 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.08-2.03 (m, 1H), 1.85 (dd, *J* = 14.2, 13.8 Hz, 1H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 3H), 1.45 (d, *J* = 2.2, 3H), 1.42-1.30 (m, 2H), 1.25-1.18 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.05-0.96 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 214.9 (C), 153.7 (C), 130.9 (C), 128.8 (C), 116.2 (CH_2), 72.3 (CH), 71.5 (CH), 54.6 (CH), 52.4 (CH), 51.3 (CH), 45.5 (CH), 33.1 (CH_2), 31.2 (CH), 30.5 (CH_2), 30.4 (CH_2), 25.0 (CH_2), 21.6 (CH_3), 21.3 (CH_3), 18.7 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{28}O_3$ [M^+] 304.2038, found 304.2027.

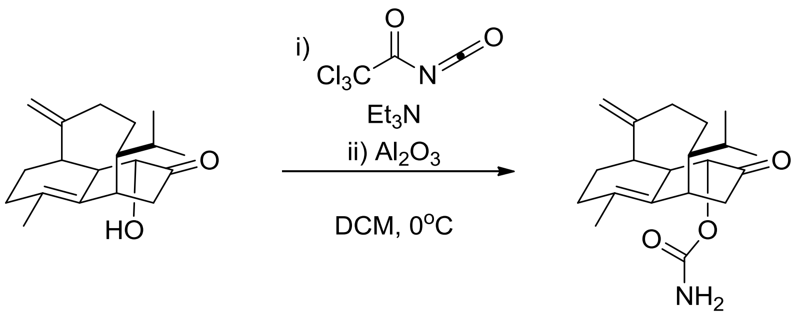


3.35 **3.75**

(±)-(1*R*,5*S*,6*R*,10*S*)-13,14-Epoxy-6-Isopropyl-13-methyl-9-methylenetricyclo[8.4.0.0^{5,14}]tetradecan-3-one (3.75)

To a 0 ºC solution of alkene **3.35** (16.8 mg, 0.0617 mmol, 1.0 eq) in dichloromethane (1 mL) was added $NaHCO_3$ (21.8 mg, 0.259 mmol) and *m*CPBA (28.9 mg, 0.130 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 (10% EtOAc/Hexanes) to provide 15.3 mg of **3.75** as a colorless oil (86%).

IR (neat, cm^{-1}) 2954, 2926, 2874, 1709, 1626, 1454, 1233, 1171, 901; ^{1}H NMR (C_6D_6, 400 MHz) δ 4.73 (d, *J* = 2.6 Hz, 1H), 4.61 (d, *J* = 2.5 Hz, 1H), 2.49-2.48 (m, 2H), 2.45-2.29 (m, 3H), 2.22-2.16 (m, 2H), 1.95 (dd, *J* = 9.7, 4.9 Hz, 1H), 1.75-1.63 (m, 3H), 1.61-1.50 (m, 2H), 1.42-1.34 (m, 1H), 1.29-1.17 (m, 2H), 1.19 (s, 3H), 1.00-0.91 (m, 1H), 0.72 (d, *J* = 6.2 Hz, 3H), 0.62 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 209.7 (C), 151.7 (C), 117.4 (CH_2), 62.8 (C), 62.6 (C), 49.5 (CH), 44.6 (CH), 41.3 (CH), 40.9 (CH_2), 40.2 (CH_2), 39.3 (CH), 34.5 (CH_2), 30.2 (CH), 29.0 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 21.5 (CH_3), 21.0 (CH_3), 21.0 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{28}O_2$ [M^+] 288.2089, found 288.2067.

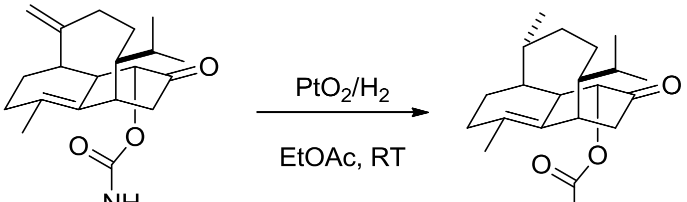


3.72 **3.73**

(±)-(1*R*,4*S*,5*S*,6*R*,10*S*)-4-Hydroxy-6-isopropyl-13-methyl-9-methylen-3-oxotricyclo[8.4.0.0^{5,14}]tetradec-13-en-2-yl carbamate (3.77):

To a solution of hydroxyketone **3.72** (4.0 mg, 0.014 mmol, 1.0 eq) in DCM (1.0 mL) at 0 °C was added trichloroacetylisocyanate (4 µL, 0.03 mmol, 1.6 eq) and the solution was stirred 15 min. To the yellow solution was then added a small scoop of Al_2O_3 and the mixture was stirred for 2 h at RT. The reaction was then filtered on cotton and concentrated. The residue was purified by flash chromatography to yield 4.1 mg of carbamate **3.77** as a colorless oil (82%).

IR (neat, cm^{-1}) 3469, 3368, 3286, 3192, 2929, 1720, 1599, 1392, 1353, 1094; ^1H NMR (C_6D_6, 400 MHz) δ 5.70 (d, *J* = 10.9 Hz, 1H), 4.88 (d, *J* = 2.2 Hz, 1H), 4.86 (d, *J* = 2.2 Hz, 1H), 4.06 (br s, 2H), 3.31-3.24 (m, 1H), 3.05-2.99 (m, 1H), 2.60-2.55 (m, 1H), 2.39 (dd, *J* = 16.4, 11.0 Hz, 1H), 2.28 (t, *J* = 12.8 Hz, 1H), 2.13 (dd, *J* = 16.3, 3.9 Hz, 1H), 1.82-1.69 (m, 2H), 1.62 (dd, *J* = 13.2, 7.3 Hz, 1H), 1.47 (d, *J* = 2.0 Hz, 2H), 1.37-1.27 (m, 3H), 1.20-1.15 (m, 1H), 1.14-1.02 (m, 2H), 0.82-0.75 (m, 1H), 0.73 (d, *J* = 5.6 Hz, 3H), 0.60 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 207.0 (C), 156.0 (C), 153.5 (C), 131.1 (C), 129.4 (C), 116.4 (CH_2), 75.7 (CH), 54.3 (CH), 46.5 (CH), 45.4 (CH), 37.8 (CH), 36.7 (CH_2), 32.7 (CH_2), 30.6 (CH_2), 30.3 (CH), 29.4 (CH_2), 25.1 (CH_2), 21.6 (CH_3), 21.0 (CH_3), 18.7 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{26}O$ [$(M-NH_2CO_2H)^+$] 270.1984, found 270.1965.

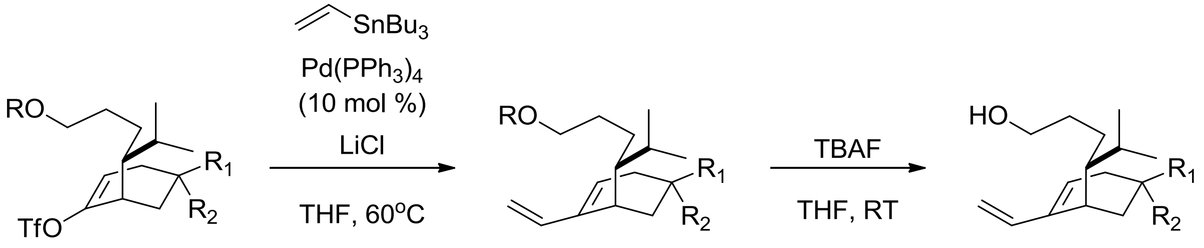


3.77 **3.79**

(±)-(1*R*,4*S*,5*S*,6*R*,10*S*)-4-Hydroxy-6-isopropyl-9,13-dimethyl-3-oxotricyclo[8.4.0.0^{5,14}]tetradec-13-en-2-yl carbamate (3.79):

To a solution of alkene **3.77** (5.2 mg, 0.015 mmol, 1.0 eq) in EtOAc (0.5 mL) was added PtO_2 (0.7 mg, 0.003 mmol, 0.2 eq) at RT and the atmosphere of Ar was changed to an atmosphere of H_2 using a doubled balloon. The mixture was stirred at that temperature for 2h, filtered through celite and concentrated to give 4.5 mg alkene **3.79** as a colorless oil (87%). Used without further purification.

Procedures for Chapter 4



R = TBDPS
4.9 R_1 = OPiv
R_2 = H
4.10 R_1 = H
R_2 = OPiv

R = TBDPS
4.11 R_1 = OPiv
R_2 = H
4.12 R_1 = H
R_2 = OPiv

4.13 R_1 = OPiv
R_2 = H
4.14 R_1 = H
R_2 = OPiv

(±)-(1*R*,5*S*,1'*R*)- 2,2-Dimethyl-propionic acid 5-(4-hydroxy-1-isopropyl-butyl)-4-vinyl-cyclohex-3-enyl ester (4.13) and (±)-(1S,5*S*,1'*R*)-1-[2,2-Dimethyl-propionic acid]–5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-vinyl-cyclohex-3-enyl ester (4.14)

LiCl (1.40 g, 33.0 mmol, 5.0 eq) was flame dried 3x under vacuum. $Pd(PPh_3)_4$ (800.2 mg, 0.692 mmol, 0.1 eq) was added to the flask and a solution of enol triflate **4.9** (4.52 g, 6.59 mmol, 1.0 eq) in THF (70 mL) was added followed by vinyltributyltin (2.70 mL, 9.24 mmol, 1.4 eq). The solution was heated to reflux for 4h, then cooled to RT. Saturated aqueous NH_4Cl and Et_2O were then added and the layers separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were washed with 1M HCl_{aq}, saturated $NaHCO_{3aq}$, dried on $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Hexanes to 5% Et_2O/Hexanes) to afford 2.96 g of **4.11** as a colorless oil (80%).

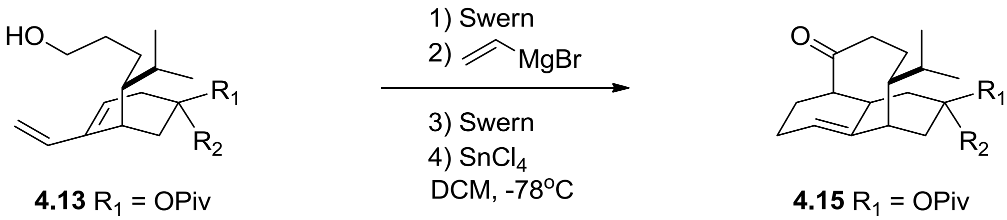
IR (neat, cm^{-1}) 3071, 3050, 2958, 2933, 2861, 1727, 1475, 1161, 1106; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.64 (m, 4H), 7.45-7.34 (m, 6H), 6.12 (dd, *J* = 17.9, 11.2 Hz, 1H), 5.71 (br d, *J* = 6.9 Hz, 1H), 5.08 (d, *J* = 17.6 Hz, 1H), 4.93 (d, *J* = 11.1 Hz, 1H), 4.82-4.71 (m, 1H), 3.62-3.50 (m, 2H), 2.97-2.89 (m, 1H), 2.43-2.33 (m, 1H), 2.10-1.90 (m, 2H), 1.60-1.39 (m, 4H), 1.37-1.31 (m, 1H), 1.28-1.10 (m, 2H), 1.20 (s, 9H), 1.04 (s, 9H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3 (C), 140.4 (C), 138.1 (CH), 135.7 (4 CH), 134.3 (2 C), 129.6 (2 CH), 127.7 (4 CH), 125.2 (CH), 112.7 (CH_2), 70.4 (CH), 64.7 (CH_2), 45.7 (CH), 38.8 (C), 37.7 (CH), 33.9 (CH_2), 31.3 (CH), 31.3 (CH_2), 28.8 (CH_2), 27.3 (3 CH_3), 27.0 (3 CH_3), 25.8 (CH_2), 22.0 (CH_3), 21.4 (CH_3), 19.3 (C); HRMS (EI) m/z calcd for $C_{27}H_{33}OSi[(M-C_4H_9-C_5H_{10}O_2)^+]$ 401.2301, found 401.2279.

To a solution of diene **4.11** (6.04 g, 10.8 mmol, 1.0 eq) in THF (60 mL) was added 1.0M TBAF in THF (30.0 mL, 30.0 mmol, 2.8 eq) and stirred overnight at RT. A saturated aqueous solution of $NaHCO_3$ was added and the layers separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (Hexanes to DCM) to yield 2.91 g of alcohol **4.13** as a colorless oil (84%).

IR (neat, cm^{-1}) 3387, 2961, 2875, 1727, 1478, 1278, 1163; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.18 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.79 (d, *J* = 7.1 Hz, 1H), 5.13 (d, *J* = 17.6 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.81-4.73 (m, 1H), 3.58-3.48 (m, 2H), 2.97 (t, *J* = 8.5 Hz, 1H), 2.44-2.36 (m, 1H), 2.12-2.04 (m, 1H), 2.01-1.94 (m, 1H), 1.63-1.55 (m, 3H), 1.54-1.48 (m, 1H), 1.46-1.32 (m, 2H), 1.25-1.16 (m, 1H), 1.18 (s, 9H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3 (C), 140.4 (C), 138.0 (CH), 125.5 (CH), 112.8 (CH_2), 70.2 (CH), 63.5 (CH_2), 45.5 (CH), 38.8 (C), 37.7 (CH), 33.9 (CH_2), 31.3 (CH_2), 31.3 (CH), 28.9 (CH_2), 27.3 (3 CH_3), 25.4 (CH_2), 22.0 (CH_3), 21.4 (CH_3); HRMS (EI) m/z calcd for $C_{15}H_{24}O$ $[(M-C_5H_{10}O_2)^+]$ 220.1827, found 220.1791.

4.14: Prepared according to the same procedure to yield the desired product in 64% over 2 steps as a colorless oil.

IR (neat, cm^{-1}) 3414, 2965, 2871, 1725, 1474, 1290, 1163; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.22 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.76 (t, *J* = 4.3 Hz, 1H), 5.15-5.10 (m, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 4.97 (d, *J* = 11.2 Hz, 1H), 3.52 (ddd, *J* = 13.2, 6.8, 1.4 Hz, 2H), 2.87 (br s, 1H), 2.43 (d, *J* = 18.0 Hz, 1H), 2.20 (dt, *J* = 18.6, 5.1 Hz, 1H), 1.83-1.69 (m, 2H), 1.68-1.55 (m, 2H), 1.54-1.49 (m, 1H), 1.48-1.40 (m, 1H), 1.28-1.23 (m, 2H), 1.16 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.5 (C), 139.8 (C), 138.6 (CH), 125.5 (CH), 112.1 (CH$_2$), 68.0 (CH), 63.4 (CH$_2$), 45.2 (CH), 38.9 (C), 34.8 (CH), 33.8 (CH$_2$), 31.4 (CH), 30.9 (CH$_2$), 28.0 (CH$_2$), 27.3 (3 CH$_3$), 25.9 (CH$_2$), 22.0 (CH$_3$), 21.4 (CH$_3$); HRMS (EI) m/z calcd for $C_{15}H_{24}O$ [$(M-C_5H_{10}O_2)^+$] 220.1827, found 220.1814.



4.13 R_1 = OPiv
R_2 = H
4.14 R_1 = H
R_2 = OPiv

4.15 R_1 = OPiv
R_2 = H
4.16 R_1 = H
R_2 = OPiv

(±)-(1*S*,3*R*,5*S*,6*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9-oxo-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (4.15) and (±)-(1S,3*S*,5*S*,6*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9-oxo-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (4.16)

To a solution of oxalyl chloride (360 µL, 4.25 mmol, 1.5 eq) in DCM (30 mL) was added DMSO (0.36 mL, 5.0 mmol, 1.8 eq) dropwise at -78 °C and stirred 15 minutes. To this solution was cannulated alcohol **4.13** (900 mg, 2.79 mmol, 1.0 eq) in DCM (30 mL) and stirred for 30 minutes. Et$_3$N (1.36 mL, 9.76 mmol, 3.5 eq) was added and the solution was stirred 15 minutes at -78 °C and warmed to 0 °C and stirred for another 30 minutes. The mixture was quenched at 0 °C by the addition of H$_2$O and the layers were separated. The aqueous phase was extracted with DCM (2x) and once with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and evaporated. To the residue was added a small portion of Et_2O and the flask was placed in the freezer for 20 min to precipitate all remaining salts. The mixture was filtered and concentrated to give a yellow oil which was used crude in the next step (the product was unstable to flash chromatography and had to be used immediately in the next step).

To a solution of aldehyde in toluene at -78 ^oC was added 1.0 M vinylmagnesium bromide in THF (8.40 mL, 8.40 mmol, 3.0 eq) and the solution was stirred at that temperature for 2 h. The reaction was quenched at -78 ^oC by the addition of a satured aqueous solution of NH_4Cl and warmed to RT. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried on $MgSO_4$, filtered and concentrated to yield the allylic alcohol as a yellow oil which was used crude in the next step (the product was unstable to flash chromatography and had to be used immediately in the next step).

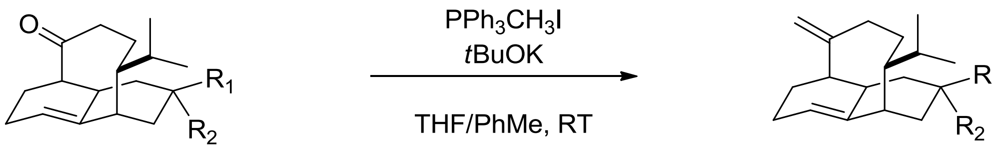
To a solution of oxalyl chloride (360 µL, 4.25 mmol, 1.5 eq) in DCM (30 mL) was added DMSO (0.36 mL, 5.0 mmol, 1.8 eq) dropwise at -78 ^oC and stirred 30 min. To this solution was cannulated the allylic alcohol from the previous step in DCM (30 mL) and stirred for 1h. Et_3N (1.36 mL, 9.76 mmol, 3.5 eq) was added and the solution was stirred 15 min at -78 ^oC and warmed to 0 ^oC and stirred for another 30 min. The mixture was quenched at 0 ^oC by the addition of H_2O and the layers were separated. The aqueous phase was extracted with DCM (2x) and once with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and evaporated. To the residue was added a small portion of Et_2O and the flask was placed in the freezer for 20 min to precipitate all remaining salts. The mixture was filtered and concentrated to give a yellow oil which was used crude in the next step (the product was unstable to flash chromatography and had to be used immediately in the next step).

To a solution of the enone in DCM (50 mL) was added 1.0 M $SnCl_4$ in DCM (4.80 mL, 4.80 mmol, 1.7 eq) at -78 ^oC and stirred for 2h. The reaction was quenched by the addition of Et_3N until the disappearance of the orange color of the solution followed by the addition of a saturated aqueous solution of NH_4Cl. The mixture was warmed to RT and the layers separated. The aqueous phase was extracted with DCM (2x) and once with EtOAc. The combined organic layers were dried on $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (DCM to 15% EtOAc/Hexanes) to yield 634.3 mg of tricyclic core **4.15** as a colorless oil (65% over 4 steps).

IR (neat, cm^{-1}) 2957, 2362, 2334, 1724, 1685, 1478, 1286, 1161; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.89-5.85 (m, 1H), 4.75 (dddd, *J* = 11.9, 4.9, 4.9, 3.3 Hz, 1H), 3.23-3.18 (m, 1H), 2.83-2.80 (m, 1H), 2.67 (dd, *J* = 12.0, 8.4 Hz, 1H), 2.59-2.52 (m, 1H), 2.44-2.37 (m, 1H), 2.14 (t, *J* = 12.6 Hz, 1H), 2.04-1.92 (m, 5H), 1.58-1.43 (m, 2H), 1.38-1.28 (m, 3H), 1.26-1.20 (m, 1H), 1.19 (s, 9H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.0 (C), 178.3 (C), 139.9 (C), 124.9 (CH), 70.7 (CH), 59.2 (CH), 54.4 (CH), 39.7 (CH_2), 38.8 (C), 37.4 (CH), 37.3 (CH), 31.7 (CH_2), 30.3 (CH), 28.0 (CH_2), 27.3 (3 CH_3), 24.2 (CH_2), 22.9 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 21.6 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{24}O$ [$(M-C_5H_{10}O_2)^+$] 244.1827, found 244.1817.

4.16: Prepared following the same 4 step procedure to yield 67% of desired product as a colorless oil.

IR (neat, cm^{-1}) 2957, 2875, 1724, 1689, 1478, 1282, 1163; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.87-5.85 (m, 1H), 5.15-5.11 (m, 1H), 3.10-3.03 (m, 1H), 2.80-2.76 (m, 1H), 2.70 (dd, *J* = 11.6, 8.5 Hz, 1H), 2.54-2.45 (m, 1H), 2.42 (dd, *J* = 14.4, 7.7 Hz, 1H), 2.16-1.88 (m, 6H), 1.57 (dd, *J* = 6.5, 3.2 Hz, 1H), 1.44-1.21 (m, 5H), 1.11 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 217.3 (C), 177.8 (C), 140.7 (C), 123.3 (CH), 69.4 (CH), 58.9 (CH), 54.2 (CH), 39.6 (CH_2), 38.9 (C), 34.2 (CH), 33.8 (CH), 30.3 (CH), 28.7 (CH_2), 27.0 (3 CH_3). 26.6 (CH_2), 24.3 (CH_2), 22.7 (2 CH_2), 21.7 (CH_3), 21.5 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{24}O$ [$(M-C_5H_{10}O_2)^+$] 244.1827, found 244.1793.



4.15 R_1 = OPiv
R_2 = H
4.16 R_1 = H
R_2 = OPiv

4.17 R_1 = OPiv
R_2 = H
4.18 R_1 = H
R_2 = OPiv

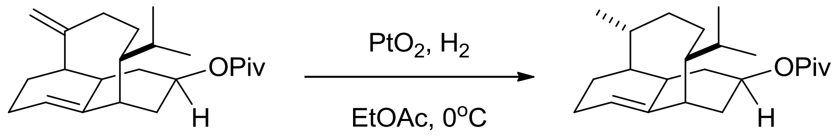
(±)-(1*S*,3*R*,5*S*,6*R*,10*R*, 13*R*, 14*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (4.17) and (±)-(1*S*,3*S*,5*S*,6*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (4.18)

To a suspension of methyltriphenylphosphonium iodide (493.2 mg, 1.22 mmol, 2.8 eq) in toluene (5.0 mL) was added 1.0M t-BuOK in THF (1.22 mL, 1.22 mmol, 2.8 eq) at 0 ^{o}C and stirred for 20 min. A solution of ketone **4.15** (150 mg, 0.433 mmol, 1.0 eq) in THF (4.0 mL) was cannulated to the above mentioned solution at RT and warmed to 65^{o}C for 2h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl at RT and the layers were separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were dried on $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (10% DCM to 50% DCM/Hexanes) yielded 126.9 mg of alkene **4.17** as a colorless oil (84%).

IR (neat, cm^{-1}) 2945, 2879, 2366, 2331, 1724, 1474, 1282, 1161; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74-5.70 (m, 1H), 4.81 (dddd, *J* = 12.3, 5.3, 5.3, 3.3 Hz, 1H), 4.67 (d, *J* = 2.7 Hz, 1H), 4.64 (d, *J* = 2.7 Hz, 1H), 3.13-3.07 (m, 1H), 2.72-2.68 (m, 1H), 2.39-2.32 (m, 1H), 2.30 (t, *J* = 12.6 Hz, 1H), 2.21 (dd, *J* = 14.7, 7.0 Hz, 1H), 1.98-1.89 (m, 5H), 1.78-1.72 (m, 1H), 1.38-1.12 (m, 6H), 1.19 (s, 9H), 0.92 (d, *J* = 5.6 Hz, 3H), 0.90 (d, J = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3 (C), 155.4 (C), 141.4 (C), 123.7 (CH), 114.1 (CH_2), 71.8 (CH), 60.4 (CH), 46.9 (CH), 38.8 (C), 37.8 (CH), 37.6 (CH), 33.2 (CH_2), 31.6 (CH_2), 30.6 (CH), 28.2 (CH_2), 28.1 (CH_2), 27.3 (3 CH_3), 26.4 (CH_2), 23.6 (CH_2), 21.8 (CH_3), 21.6 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{26}$ [$(M-C_5H_{10}O_2)^{+}$] 242.2035, found 242.2046.

4.18: Prepared according to the same procedure to yield the desired product in 91% as a colorless oil.

IR (neat, cm^{-1}) 2938, 2874, 1725, 1163; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.73-5.71 (m, 1H), 5.17-5.14 (m, 1H), 4.65 (d, *J* = 2.7 Hz, 1H), 4.63 (dd, *J* = 2.8, 0.8 Hz, 1H), 3.01-2.95 (m, 1H), 2.66 (ddd, *J* = 8.2, 3.0, 3.0 Hz, 1H), 2.30-2.24 (m, 1H), 2.28 (dd, *J* = 12.7, 12.7 Hz, 1H), 2.21 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.01-1.84 (m, 6H), 1.60 (dd, *J* = 13.5, 13.5 Hz, 1H), 1.40 (ddd, *J* = 15.1, 6.0, 3.3 Hz, 1H), 1.30-1.09 (m, 4H), 1.12 (s, 9H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.2 (C), 155.8 (C), 142.2 (C), 122.3 (CH), 114.1 (CH$_2$), 70.6 (CH), 60.2 (CH), 46.6 (CH), 39.0 (C), 34.6 (CH), 33.6 (CH), 33.1 (CH$_2$), 30.7 (CH), 28.9 (CH$_2$), 28.6 (CH$_2$), 27.1 (3 CH$_3$), 27.1 (CH$_2$), 26.6 (CH$_2$), 23.5 (CH$_2$), 21.9 (CH$_3$), 21.6 (CH$_3$); HRMS (EI) m/z calcd for $C_{18}H_{26}$ [$(M-C_5H_{10}O_2)^+$] 242.2035, found 242.2023.

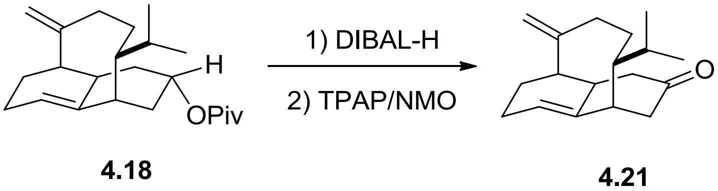


4.17 **4.19**

(±)-(1*S*,3*R*,5*S*,6*R*,9*R*,10*R*)-2,2-Dimethyl-propionic acid 6-isopropyl-9-methyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-yl ester (4.19)

To a solution of alkene **4.17** (177.2 mg, 0.514 mmol, 1.0 eq) in EtOAc (3 mL) was added PtO$_2$ (11.6 mg, 0.0511 mmol, 0.1 eq) at 0 °C and the atmosphere of Ar was changed to an atmosphere of H$_2$. The mixture was stirred at that temperature until the complete consumption of starting material as seen by GC-MS or ^{1}H NMR. The mixture was filtered through celite and concentrated to give 177 mg alkene **4.19** as a colorless oil (99%).

IR (neat, cm^{-1}) 2966, 2933, 2875, 1724, 1284, 1160; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 5.65-5.62 (m, 1H), 4.62 (dddd, *J* = 11.8, 11.8, 5.4, 3.2 Hz, 1H), 3.07-3.01 (m, 1H), 2.42-2.36 (m, 1H), 2.13-1.95 (m, 5H), 1.90-1.83 (m, 1H), 1.81-1.72 (m, 1H), 1.68-1.62 (m, 2H), 1.61-1.50 (m, 3H), 1.48-1.39 (m, 1H), 1.37-1.24 (m, 2H), 1.20-1.13 (m, 1H), 1.19 (s, 9H), 1.18 (d, *J* = 7.8 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3 (C), 142.0 (C), 123.1 (CH), 72.4 (CH), 60.8 (CH), 42.3 (CH), 41.3 (CH), 38.9 (CH), 38.9 (CH), 38.8 (C), 33.0 (CH_2), 31.2 (CH_2), 30.9 (CH), 30.1 (CH_2), 28.6 (CH_2), 27.4 (3 CH_3), 23.8 (CH_2), 22.1 (CH_3), 21.9 (CH_3), 21.5 (CH_3), 20.5 (CH_2); HRMS (EI) m/z calcd for $C_{23}H_{38}O_2$ [M^+] 346.2872, found 346.2873.

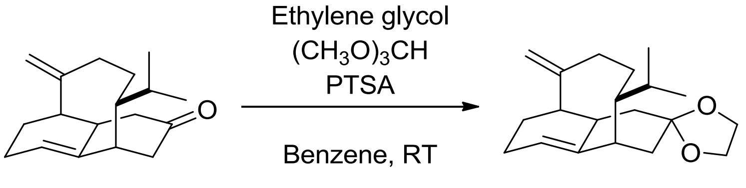


(±)-(1S,5*S*,6*R*,10*R*)-6-Isopropyl-9-methylene-tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3-one (4.21)

To a solution of pivalate **4.18** (115.3 mg, 0.335 mmol, 1.0 eq) in DCM (3.3 mL) was added 1.0M DIBAL-H in toluene (1.20 mL, 1.20 mmol, 3.6 eq) dropwise at -78 °C and stirred at that temperature for 2 h. The mixture was then quenched by the addition of a saturated aqueous solution of sodium tartrate at -78 °C and allowed to warm to RT and stirred for 30 min. The layers were separated and the aqueous phase was extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. The product was used crude in the next step.

To a flask containing flame dried 4 Å molecular sieves (450 mg) was cannulated a solution of the alcohol from the previous step in DCM (3.0 mL) at RT. NMO (90.0 mg, 0.768 mmol, 2.3 eq) was then added in one portion followed by TPAP (12.2 mg, 0.0347 mmol, 0.1 eq) and the solution was stirred for 2 h. The mixture was filtered through a pad of SiO_2 eluting with EtOAc and concentrated. Purification by flash chromatography (15% EtOAc/Hexanes) yielded 71.8 mg of ketone **4.21** as a clear oil (84% over 2 steps).

IR (neat, cm^{-1}) 2945, 2867, 1703; ^{1}H NMR (C_6D_6, 300 MHz) δ 5.58-5.55 (m, 1H), 4.67 (d, *J* = 2.7 Hz, 1H), 4.62 (d, *J* = 2.6 Hz, 1H), 2.92-2.89 (m, 1H), 2.64 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 2.37-2.23 (m, 4H), 2.22-2.05 (m, 2H), 2.03-1.95 (m, 1H), 1.82-1.63 (m, 4H), 1.17-1.03 (m, 3H), 0.96-0.84 (m, 1H), 0.79 (d, *J* = 6.1 Hz, 3H), 0.71 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 210.7 (C), 154.1 (C), 140.4 (C), 124.1 (CH), 115.3 (CH_2), 58.4 (CH), 47.7 (CH), 41.8 (CH), 40.4 (CH_2), 39.6 (CH_2), 35.6 (CH), 33.0 (CH_2), 30.6 (CH), 27.7 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 21.5 (CH_3), 21.3 (CH_3); HRMS (EI) m/z calcd for $C_{18}H_{26}O$ [M^{+}] 258.1954, found 258.1961.

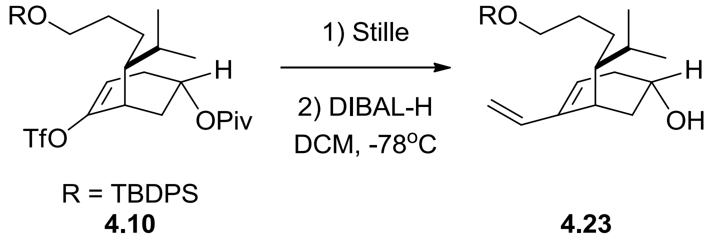


4.21 **4.22**

(±)-(1S,5*S*,6*R*,10*R*)-6-Isopropyl-9-methylene-spiro[tricyclo[8.4.0.0^{5,14}]tetradec-13-en-3,2'-(1,3)-dioxolane] (4.22)

To a solution of ketone **4.21** (35.0 mg, 0.135 mmol, 1.0 eq) in benzene (2.0 mL) were added ethylene glycol (300 µL, 5.38 mmol, 41.4 eq), trimethylorthoformate (60 µL, 0.55 mmol, 4.2 eq) and PTSA (2.5 mg, 0.013 mmol, 0.1 eq) at RT. The mixture was stirred for 2 h, quenched with saturated $NaHCO_{3aq}$ and the layers were separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography eluting with EtOAc/Hexanes (1/9) to yield 35.4 mg of ketal **4.22** as a colorless oil (90%).

IR (neat, cm^{-1}) 2935, 2874, 1123; ^{1}H NMR (C_6D_6, 300 MHz) δ 5.68-5.66 (m, 1H), 4.73 (s, 2H), 3.65-3.55 (m, 4H), 3.26-3.22 (m, 1H), 2.64-2.54 (m, 2H), 2.25 (dd, *J* = 12.9, 12.9 Hz, 1H), 2.10 (ddd, *J* = 14.8, 7.2, 7.2 Hz, 1H), 2.00 (dd, *J* = 12.5 Hz, 1H), 1.96-1.84 (m, 4H), 1.80-1.74 (m, 2H), 1.67 (dd, *J* = 14.3, 6.2 Hz, 1H), 1.25-1.15 (m, 3H), 1.09-1.03 (m, 1H), 0.84 (d, *J* = 5.5 Hz, 3H), 0.82 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) 155.7 (C), 142.2 (C), 122.7 (CH), 114.4 (CH_2), 111.1 (C), 64.5 (CH_2), 64.3 (CH_2), 60.5 (CH), 47.2 (CH), 38.1 (CH), 37.2 (CH), 34.3 (CH_2), 33.4 (CH_2), 32.3 (CH_2), 30.7 (CH), 28.6 (CH_2), 26.8 (CH_2), 23.7 (CH_2), 21.8 (CH_3), 21.5 (CH_3); HRMS (EI) m/z calcd for $C_{20}H_{30}O_2$ [M $^+$] 302.2246, found 302.2260.

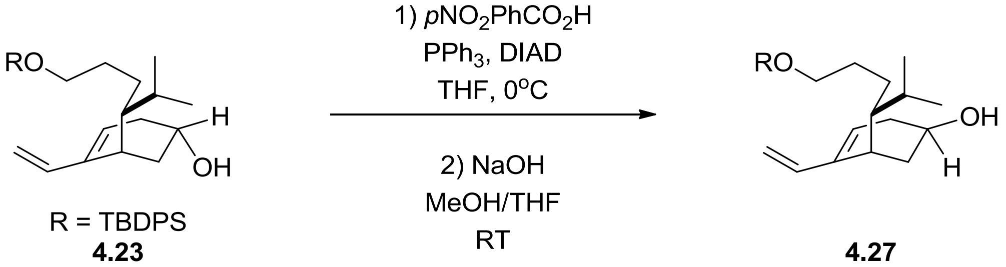


(±)-(1*S*,5*S*,1'*R*)-5-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-vinyl-cyclohex-3-en-1-ol (4.23)

Following the Stille coupling procedure for the preparation of diene **4.11**. To a solution of the resulting diene (2.36 g, 4.21 mmol, 1.0 eq) in DCM (20 mL) at -78 °C was added a 1.0 M solution of DIBAL-H in toluene (8.90 mL, 8.90 mmol, 2.1 eq). The solution was stirred for 30 minutes at that temperature and then quenched with a saturated aqueous sodium tartrate solution. The mixture was warmed to RT and stirred for 30 minutes before the layers were separated. The organic phase was extracted with DCM (3x) and the combined organic phases were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (25% EtOAc/Hexanes) to yield 1.48 g of **4.23** as a colorless oil (74% over 2 steps).

IR (neat, cm^{-1}) 3325, 2952, 2853, 1458, 1422, 1100; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (dd, *J* = 7.8, 1.5 Hz, 4H), 7.44-7.34 (m, 6H), 6.15 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.72 (dd, *J* = 4.1, 4.1 Hz, 1H), 5.10 (d, *J* = 17.6, 1H), 4.94 (d, *J* = 10.9 Hz, 1H), 4.15-4.10 (m, 1H), 3.59-3.49 (m, 2H), 2.88 (br s, 1H), 2.37 (br d, *J* = 18.4 Hz, 1H), 2.13 (dt, *J* = 18.4, 4.9 Hz, 1H), 1.79-1.72 (m, 1H), 1.67-1.37 (m, 6H), 1.30-1.11 (m, 1H), 1.03 (s, 9H), 0.96 (d, *J* = 6.7 Hz, 6H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.9 (2 C), 138.4 (2 CH), 135.6 (4 CH), 134.2 (C), 129.5 (CH), 127.5 (4 CH), 125.5 (CH), 112.1 (CH_2), 65.1 (CH), 64.4 (CH_2), 45.5 (CH), 34.0 (CH_2), 33.8 (CH), 33.7 (CH_2), 31.2 (CH), 31.1 (CH_2), 26.9 (3 CH_3), 26.1 (CH_2), 21.8 (CH_3), 21.3 (CH_3), 19.2 (C); HRMS (EI) m/z calcd for $C_{27}H_{35}O_2Si$ [$(M-C_4H_9)^+$] 419.2406, found 419.2394.

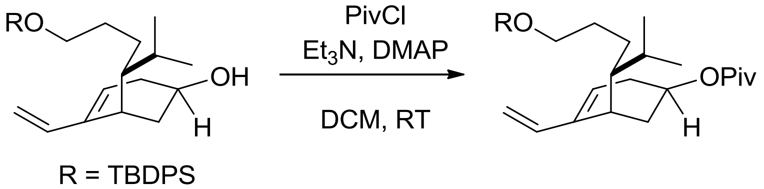


(±)-(1*R*,5*S*,1'*R*)-5-[4-(*tert*-Butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-vinyl-cyclohex-3-en-1-ol (4.27)

To a solution of PPh_3 (3.30 g, 12.6 mmol, 3.0 eq), pNO$_2$-benzoic acid (2.11 g, 12.6 mmol, 3.0 eq) and DIAD (2.43 mL, 12.3 mmol, 2.95 eq) in THF (21 mL) was added a solution of the alcohol **4.23** (2.0 g, 4.2 mmol, 1.0 eq) in THF (21 mmol) dropwise at 0 ^{o}C. The mixture was stirred for 1h and H_2O was added. Et_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O (3x) and the combined organic phases were dried on $MgSO_4$, filtered and concentrated.

The residue was dissolved in a 1:1 mixture of MeOH/THF (42 mL) and NaOH (85.2 mg, 2.13 mmol, 0.5 eq) was added and the mixture was stirred at RT for 3h. H_2O and EtOAc were added, the layers were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic phases were dried on $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (25% EtOAc/Hexanes) to afford 1.70 g of **4.27** as a colorless oil (85% over 2 steps).

IR (neat, cm^{-1}) 3330, 2956, 2932, 2859, 1472, 1428, 1110; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.64 (m, 4H), 7.44-7.35 (m, 6H), 6.12 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.72 (br d, *J* = 6.9 Hz, 1H), 5.08 (d, *J* = 17.6 Hz, 1H), 4.92 (d, *J* = 11.1 Hz, 1H), 3.79-3.71 (m, 1H), 3.60-3.51 (m, 2H), 2.94-2.88 (m, 1H), 2.41-2.33 (m, 1H), 2.04-1.95 (m, 2H), 1.64-1.50 (m, 3H), 1.48-1.37 (m, 2H), 1.33-1.26 (m, 1H), 1.25-1.09 (m, 1H), 1.04 (s, 9H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.3 (C), 138.2 (CH), 135.7 (4 CH), 134.3 (2 C), 129.6 (2 CH), 127.7 (4 CH), 125.8 (CH), 112.4 (CH_2), 68.1 (CH), 64.6 (CH_2), 45.6 (CH), 38.0 (CH), 35.2 (CH_2), 33.9 (CH_2), 33.1 (CH_2), 31.3 (CH), 27.0 (3 CH_3), 25.7 (CH_2), 22.0 (CH_3), 21.3 (CH_3), 19.3 (C); HRMS (EI) m/z calcd for $C_{27}H_{35}O_2Si$ [$(M-C_4H_9)^+$] 419.2406, found 419.2385.

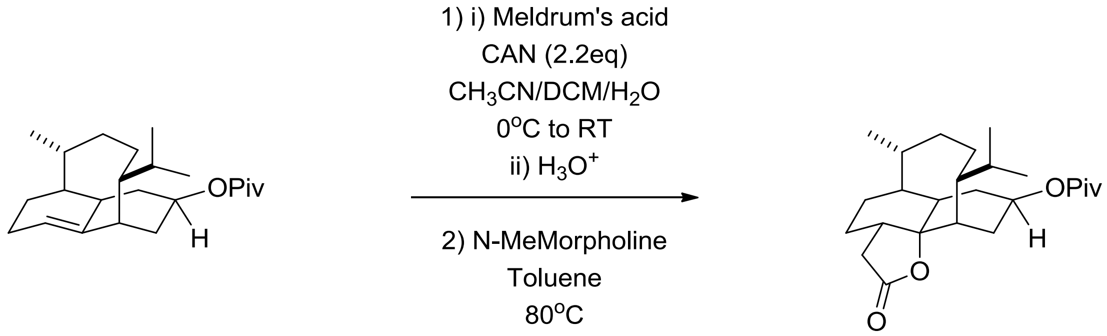


R = TBDPS
4.27

4.11

(±)-(1*R*,5*S*,1'*R*)-1-[2,2-Dimethyl-propionic acid]-5-[4-(*tert*-butyl-diphenyl-silanyloxy)-1-isopropyl-butyl]-4-vinyl-cyclohex-3-enyl ester (4.11)

To a solution of alcohol **4.27** (530.1 mg, 1.11 mmol, 1.0 eq) in DCM (10 mL) were added Et_3N (0.800 mL, 5.74 mmol, 5.2 eq), PivCl (0.400 mL, 3.25 mmol, 2.9 eq) and DMAP (13.6 mg, 0.111 mmol, 0.1 eq) at RT. The solution was stirred overnight and quenched with H_2O. The layers were separated and the aqueous layer was extracted with DCM (3x) and the combined organic phases were washed with 1M HCl_{aq}, dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to afford 591.4 mg of diene **4.11** as a colorless oil (95%).



4.19 **4.36**

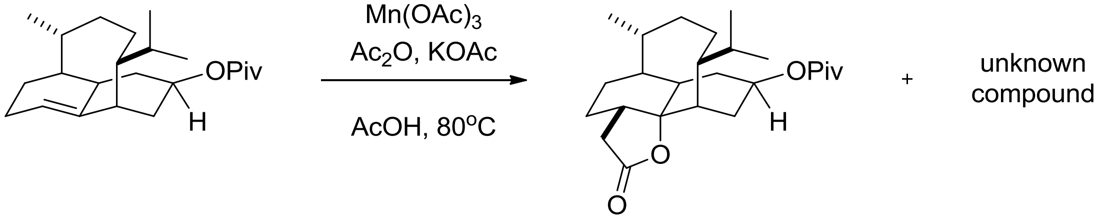
Lactone 4.36

To a solution of alkene **4.19** (139.7 mg, 0.403 mmol, 1.0 eq) in a 4:1 mixture of ACN/DCM (2.5mL) at 0 °C was added Meldrum's acid (63.4 mg, 0.440 mmol, 1.1 eq) followed by CAN (480.3 mg, 0.876 mmol, 2.2 eq) and finally 1 drop of H_2O to ensure solubility. The mixture was stirred until complete disappearance of the orange color (20 minutes), H_2O and EtOAc were added to the reaction mixture and the layers were separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried on Na_2SO_4, filtered and concentrated. The crude product was used without further purification in the next step.

The crude acid was dissolved in toluene (2.0 ml) and NMM (0.130 mL, 1.18 mmol, 3.0 eq) and the solution was heated to 80 °C for 2 h. The solution was cooled to RT, H_2O and EtOAc were added and the layers separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (10% to 30% EtOAc/Hexanes) to yield 97.1 mg of lactone **4.36** as a colorless oil (60% over 2 steps).

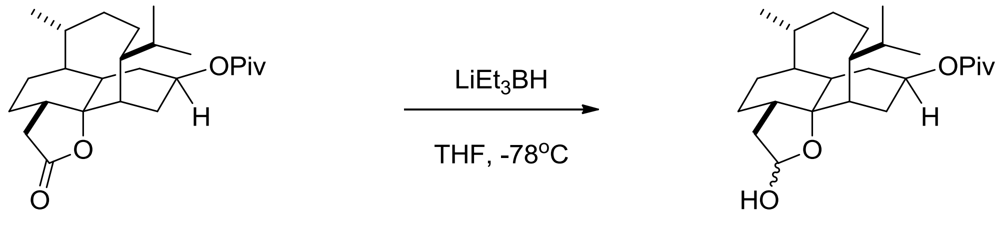
IR (neat, cm^{-1}) 2959, 2915, 2872, 1774, 1724, 1284, 1160; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.37-5.28 (m, 1H), 2.65 (dd, J = 17.3, 8.0 Hz, 1H), 2.55-2.48 (m, 1H), 2.34-2.28 (m, 1H), 2.28 (dd, J = 17.4, 5.1 Hz, 1H), 2.18-2.13 (m, 1H), 2.12-2.03 (m, 1H), 2.00-1.92 (m, 1H), 1.89-1.70 (m, 4H), 1.62-1.44 (m, 10H), 1.17 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9 (C), 175.5 (C), 93.0 (C), 68.9 (CH), 42.5 (CH), 41.2 (CH), 40.6 (CH), 40.1 (CH), 38.7 (C), 36.8 (CH), 35.9

(CH$_2$), 35.7 (CH), 34.9 (CH), 30.0 (CH$_2$), 30.0 (CH$_2$), 28.1 (CH$_2$), 27.4 (3 CH$_3$), 27.2 (CH$_2$), 25.6 (CH$_3$), 25.2 (CH$_2$), 24.6 (CH$_2$), 21.5 (CH$_3$), 20.4 (CH$_3$); HRMS (EI) m/z calcd for $C_{20}H_{30}O_2$ [$(M-C_5H_{10}O_2)^+$] 302.2246, found 302.2251.



4.19 **4.36**

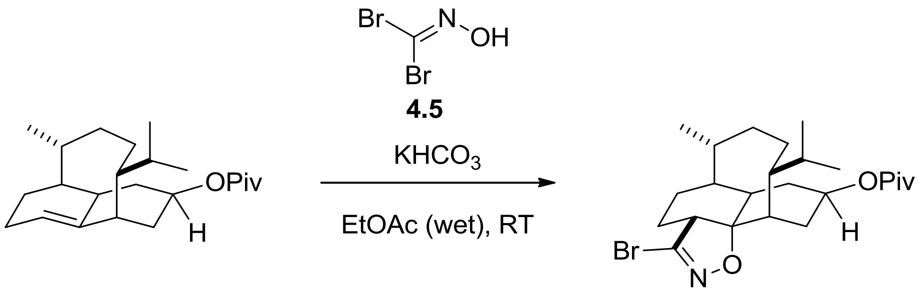
To a solution of **4.19** (13.0 mg, 0.0375 mmol, 1.0 eq) in Ac$_2$O/AcOH (4/1, 0.4 mL) were added KOAc (11.2 mg, 0.114 mmol, 3.0 eq) and Mn(OAc)$_3$.H$_2$O (21.4 mg, 0.0798 mmol, 2.1 eq) at RT. The mixture was heated to 80 ^{o}C, stirred for 2 h and cooled to RT. A saturated solution of NaHCO$_{3aq}$ was added and the layers separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried on MgSO$_4$, filtered and concentrated. The crude product was purified by flash chromatography eluting with EtOAc/Hexanes (1/2) to yield 5.4 mg of colorless oil (35%) containing a mixture of **4.36** and an unknown compound.



4.36 **4.42**

Lactol 4.42

To a solution of lactone **4.36** (20.3 mg, 0.0502 mmol, 1.0 eq) in THF (1.0 mL) at -78 ^{o}C was added a 1.0 M solution of LiEt$_3$BH in THF (0.055 mL, 0.055 mmol, 1.1 eq). The solution was stirred 30 min and quenched by the addition of a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with EtOAc (3x) and the combined organic phases were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes) to yield 20.0 mg of lactol **4.42** as a colorless oil (99%). Compound was unstable to flash chromatography and was used without further purification.



4.5

4.19

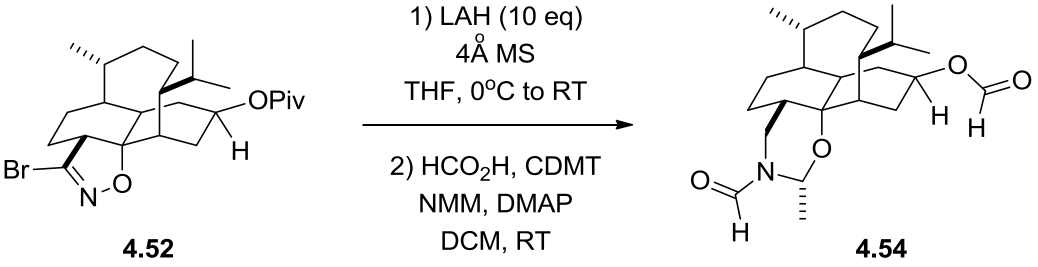
4.52

Isoxazole 4.52

To a solution of alkene **4.19** (126.1 mg, 0.364 mmol, 1.0 eq) in EtOAc (5.0 mL) at RT was added $KHCO_3$ (102.3 mg, 1.02 mmol, 2.8 eq) followed by dibromoformaldoxime (101.4 mg, 0.500 mmol, 1.4 eq) and the mixture was stirred 30 min. Portions of $KHCO_3$ and dibromoformaldoxime were added until the reaction went to completion. A saturated aqueous solution of NH_4Cl was added and the layers separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried on $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (toluene) yielded 127.9 mg of bromoisoxazole **4.52** as a colorless oil (75%).

IR (neat, cm^{-1}) 2961, 2875, 1728, 770; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.44 (dddd, *J* = 11.8, 11.8, 6.5, 6.5 Hz, 1H), 2.98 (dd, *J* = 5.6, 4.4 Hz, 1H), 2.33-2.26 (m, 2H), 2.22-2.07 (m, 3H), 2.03-1.93 (m, 2H), 1.90-1.81 (m, 1H), 1.75-1.66 (m, 1H), 1.63-1.40 (m, 9H), 1.16 (s, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9 (C), 144.8 (C), 93.9 (C), 68.9 (CH), 52.9 (CH), 42.5 (CH), 41.1

(CH), 39.5 (CH), 39.3 (CH), 38.7 (C), 35.0 (CH), 34.7 (CH), 30.5 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 27.3 (3 CH_3), 26.6 (CH_3), 26.4 (CH_2), 21.5 (CH_2), 21.2 (CH_3), 19.8 (CH_3); HRMS (EI) m/z calcd for $C_{24}H_{38}NO_3Br$ [M^+] 467.2035, found 467.2099.

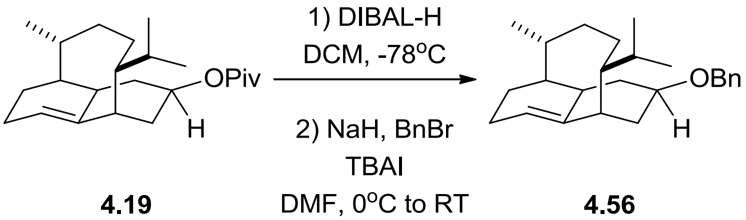


Aminal 4.54

Bromoisoxazole **4.52** was first azeotropically dried 3x with benzene in a vial. Then, to a solution of **4.52** (65.3 mg, 0.139 mmol, 1.0 eq) in THF (2.0 mL) at 0 °C were added grounded 4 Å molecular sieves (475 mg) followed by a 1.0M LAH solution in THF (1.40 mL, 1.40 mmol, 10 eq) dropwise. The mixture was warmed to RT, stirred overnight and quenched by the addition of a few drops of 1M HCl_{aq} at 0^0C followed by saturated $NaHCO_{3aq}$ until a basic pH was reached. EtOAc was added and the mixture was filtered on celite and the layers were separated. The aqueous phase was extracted with EtOAc (4x) and the combined organic phases were dried on Na_2SO_4, filtered and concentrated. The crude product was a colorless foam but contained an unidentifiable mixture of products. The mixture was used in the next step without further purification.

The resulting foam from the previous step was dissolved in DCM (1.1 mL) and formic acid (10 µL, 0.28 mmol, 2.0 eq), CDMT (51.2 mg, 0.292 mmol, 2.1 eq), NMM (35 µL, 0.31 mmol, 2.2 eq) and DMAP (1.7 mg, 0.014 mmol, 0.1 eq) were added in that order at RT. The mixture was stirred for 1h at RT and 1M HCl_{aq} was added and the layers were separated. The aqueous phase was extracted with DCM (3x) and the combined organic phases were washed with 1 M HCl_{aq}, then saturated $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography (50% to 100% EtOAc/Hexanes) to yield 22.9 mg of **4.54** as a colorless foam (42% over 2 steps).

IR (neat, cm^{-1}) 1729,1671; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.36 (s, 1H), 8.03 (s, 1H), 5.47 (dddd, *J* = 11.4, 7.5, 7.5, 7.5 Hz, 1H), 5.01 (q, *J* = 6.0 Hz, 1H), 4.17 (dd, *J* = 13.7, 2.2 Hz, 1H), 2.98 (dd, *J* = 13.6, 3.7 Hz, 1H), 2.85 (app d, *J* = 10.4 Hz, 1H), 2.18-2.01 (m, 4H), 1.96-1.36 (m, 11H), 1.56 (d, *J* = 5.8 Hz, 3H), 1.30-1.25 (m, 1H), 1.08-0.81 (m, 2H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 161.0 (CH), 159.0 (CH), 80.2 (C), 75.9 (C), 70.1 (CH), 42.8 (CH), 41.4 (CH), 40.5 (CH$_2$), 39.7 (CH), 37.9 (CH), 36.0 (CH), 33.4 (CH), 32.0 (CH$_2$), 31.9 (CH), 29.8 (CH$_2$), 28.9 (CH$_2$), 27.5 (CH$_2$), 24.5 (CH$_3$), 24.3 (CH$_2$), 22.1 (CH$_2$), 21.7 (CH$_3$), 20.9 (CH$_3$), 18.8 (CH$_3$); HRMS (EI) m/z calcd for $C_{22}H_{35}NO_2$ [$(M-CH_2O_2)^+$] 345.2668, found 345.2772.



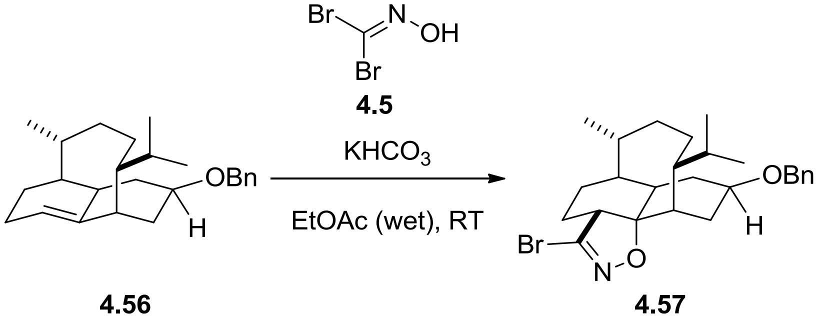
4.19 **4.56**

(±)-(1*S*,3*R*,5*S*,6*R*,9*R*,10*R*)-3-Benzyloxy-6-isopropyl-9-methyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-ene (4.56)

To a solution of pivalate **4.19** (282.0 mg, 0.814 mmol, 1.00 eq) in DCM (6.0 mL) was added a 1.0 M solution of DIBAL-H in toluene (2.80 mL, 2.80 mmol, 3.43 eq) dropwise at -78 °C. The solution was stirred at that temperature for 45 minutes then quenched by the addition of a saturated aqueous solution of sodium tartrate. The mixture was allowed to warm to RT and stirred 30 minutes. The phases were separated and the aqueous layer was extracted with DCM (3x), the organic layer was dried with MgSO$_4$, filtered and concentrated. The crude product obtained as a clear oil was used without purification in the next step.

To a solution of the crude alcohol in DMF (4.0 mL) was added NaH 60% in mineral oil (80.0 mg, 2.00 mmol, 2.45 eq) at 0 °C. The solution was warmed to RT and stirred for 20 minutes. BnBr (0.20 mL, 1.7 mmol, 2.1 eq) was added followed by TBAI (30.0 mg, 0.0812 mmol, 0.1 eq) at that temperature. The mixture was stirred for 2h at RT and quenched by the addition of a saturated aqueous solution of NH_4Cl. Et_2O was then added and the layers were separated. The aqueous phase was extracted with Et_2O (3x) and the combined organic phases were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (5% EtOAC/Hexanes) to yield 258.3 mg of **4.56** as a colorless oil (90% over 2 steps).

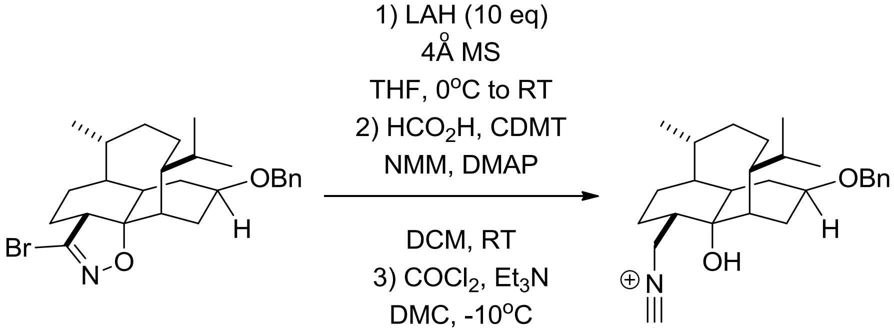
IR (neat, cm^{-1}) 2934, 2871, 1450, 1358, 1092; ^1H NMR (C_6D_6, 300 MHz) δ 7.38-7.34 (m, 2H), 7.21-7.05 (m, 3H), 5.58-5.53 (m, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 3.31-3.20 (m, 1H), 3.01-2.93 (m, 1H), 2.19-1.89 (m, 7H), 1.80-1.25 (m, 8H), 1.23-1.08 (m, 2H), 1.15 (d, *J* = 7.6 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.88 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 143.1 (C), 140.2 (C), 128.5 (2 CH), 127.6 (2 CH), 127.5 (CH), 122.8 (CH), 77.3 (CH), 70.2 (CH_2), 61.1 (CH), 42.7 (CH), 41.7 (CH), 39.4 (2 CH), 33.8 (CH_2), 31.6 (CH_2), 31.0 (CH), 30.3 (CH_2), 30.1 (CH_2), 24.1 (CH_2), 22.2 (CH_3), 22.0 (CH_3), 21.7 (CH_3), 20.7 (CH_2); HRMS (EI) m/z calcd for $C_{18}H_{29}O$ [$(M-C_7H_7)^+$] 261.2218, found 261.2194.



Isoxazole 4.57

To a solution of alkene **4.56** (340.8 mg, 0.964 mmol, 1.0 eq) in EtOAc (5.0 mL) at RT was added $KHCO_3$ (260.3 mg, 2.60 mmol, 2.7 eq) followed by dibromoformaldoxime (260.9 mg, 1.30 mmol, 1.3 eq) and the mixture was stirred 30 min. Portions of $KHCO_3$ and dibromoformaldoxime were added until the reaction went to completion. A saturated aqueous solution of NH_4Cl was added and the layers separated. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were dried on $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (toluene) yielded 323.4 mg of bromoisoxazole **4.57** as a colorless oil (71%).

IR (neat, cm^{-1}) 2961, 2867, 1740, 1457, 1367, 1106, 1071; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.31 (m, 4H), 7.28-7.24 (m, 1H), 4.56 (s, 2H), 4.30-4.22 (m, 1H), 3.00 (dd, J = 6.2, 4.2 Hz, 1H), 2.33-2.16 (m, 5H), 2.06-1.84 (m, 3H), 1.79-1.71 (m, 1H), 1.67-1.62 (m, 1H), 1.59-1.37 (m, 8H), 1.06 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1 (C), 139.3 (C), 128.5 (2 CH), 127.8 (2 CH), 127.6 (CH), 94.8 (C), 73.4 (CH), 71.0 (CH_2), 53.0 (CH), 42.7 (CH), 41.3 (CH), 39.8 (CH), 39.6 (CH), 35.1 (CH), 34.9 (CH), 31.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 26.6 (CH_3), 26.4 (CH_2), 21.6 (CH_2), 21.3 (CH_3), 19.9 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{29}BrNO_2$ [(M-C_7H_7)$^+$] 384.1361, found 384.1362.



4.57 **4.58**

(±)-(1*S*,3*R*,5*S*,6*R*,9*R*,10*R*,13*S*,14*R*)-1-[3-Benzyloxy-14-hydroxy-6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradec-13-yl]-N-methylidynemethanaminium (4.58)

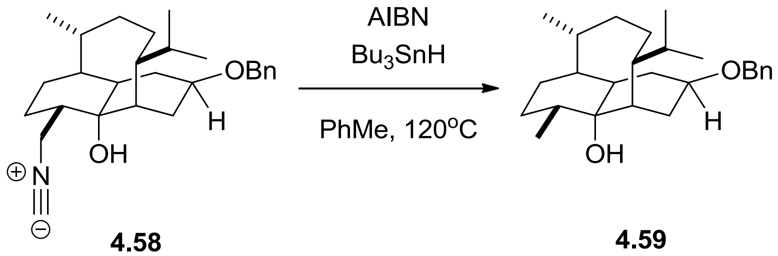
Bromoisoxazole **4.57** was first azeotropically dried 3x with benzene in a vial. Then, to a solution of **4.57** (150.2 mg, 0.316 mmol, 1.0 eq) in THF (4.5 mL) at 0 ^{o}C was added ground 4 Å molecular sieves (1.0g) followed by a 1.0M LAH solution in THF (3.20 mL, 3.20 mmol, 10 eq) dropwise. The mixture was warmed to RT and a plastic cap was placed on the vial and taped in place using electric tape. The mixture was stirred for 18h at RT and quenched by the addition of a few drops of 1 M HCl_{aq} at 0 ^{o}C followed by saturated $NaHCO_{3aq}$ until a basic pH is reached. DCM is added and the mixture is filtered on celite, the layers are separated. The aqueous phase is extracted with DCM (4x) and the combined organic phases are dried on Na_2SO_4, filtered and concentrated. The crude product is obtained as a colorless foam and is used as is for the next step.

The resulting aminoalcohol was dissolved in DCM (2.5 mL) and formic acid (0.05 mL, 0.64 mmol, 2.0 eq), CDMT (118 mg, 0.67 mmol, 2.1 eq), NMM (0.077 mL, 0.70 mmol, 2.2 eq) and DMAP (4 mg, 0.03 mmol, 0.1 eq) were added in that order at RT. The mixture was stirred for 1h at RT and 1M HCl_{aq} was added and the layers were separated. The aqueous phase was extracted with DCM (3x) and the combined organic phases were washed with 1M HCl_{aq}, then saturated $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash chromatography (50% to 100% EtOAc/Hexanes) to yield 114 mg of colorless foam.

The resulting formamide was dissolved in DCM (2.7 mL) and Et_3N (0.56 mL, 4.05 mmol, 15 eq) followed by phosgene (20% wt/toluene, 0.14 mL, 0.28 mmol, 1.05 eq) were added at -10 ^{o}C. The reaction was stirred for 20 minutes and quenched by the addition of saturated $NaHCO_{3aq}$. The layers were separated and the aqueous layer was extracted with DCM (3x) and the combined organic phases were washed with 1 M HCl_{aq} and saturated $NaHCO_{3aq}$. The organic phase was dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes) to yield 78.7 mg of the isonitrile **4.58** as a yellow oil (71%).

IR (neat, cm^{-1}) 2959, 2867, 2146, 1458, 1366, 1091; ^{1}H NMR (C_6D_6, 300 MHz) 7.43-7.39 (m, 2H), 7.25-7.19 (m, 2H), 7.15-7.09 (m, 1H), 4.54 (s, 2H), 4.15-4.03 (m, 1H), 3.16 (dd, $J =$

15.0, 3.3 Hz, 1H), 2.88 (dd, *J* = 15.0, 9.1 Hz, 1H), 2.25-2.04 (m, 2H), 1.92 (d, *J* = 10.2 Hz, 1H), 1.85-1.57 (m, 5H), 1.54-1.07 (m, 11H), 0.82 (d, *J* = 5.9 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 140.3 (C_4), 128.6 (2 CH), 127.7 (2 CH), 127.6 (CH), 75.9 (C_4), 73.2 (CH), 70.4 (CH_2), 45.0 (CH), 43.2 (CH), 42.3 (CH_2), 40.4 (CH), 39.3 (CH), 39.1 (CH), 38.7 (CH), 35.3 (CH), 31.7 (CH_2), 31.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.8 (CH_3), 24.4 (CH_2), 21.9 (CH_3), 20.8 (CH_3), 20.7 (CH_2); HRMS (EI) m/z calcd for $C_{27}H_{37}NO$ [$(M-H_2O)^+$] 391.2875, found 391.2871.

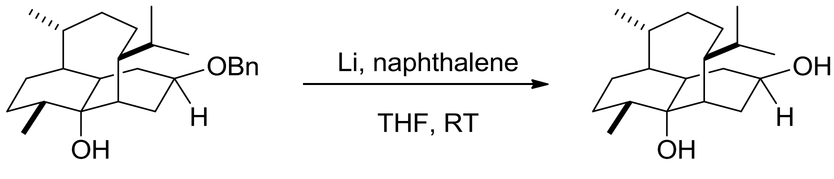


(±)-(1*S*,3*R*,5*S*,6*R*,9*R*,10*R*,13*R*,14*R*)-3-Benzyloxy-6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-14-ol (4.59)

In a sealed tube, isonitrile **4.58** was dissolved in toluene (4.0 mL, degassed 20 min with Ar) and AIBN (0.2 M/toluene, 2.85 mL, 0.57 mmol, 3.0 eq) and Bu_3SnH (0.46 mL, 1.71 mmol, 9.0 eq) were added. The tube was heated to 120 °C for 2 h and then cooled to RT. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (0% to 40% Et_2O/Hexanes) to afford 66.5 mg of alcohol **4.59** as a colorless oil (91%).

IR (neat, cm^{-1}) 3483, 2946, 2867, 1091; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.54-7.52 (m, 2H) 7.32-7.27 (m, 2H), 7.21-7.17 (m, 1H), 4.67 (s, 2H), 4.54-4.46 (m, 1H), 2.32 (dddd, *J* = 13.8, 10.6, 7.5, 1.6 Hz, 1H), 2.11-1.80 (m, 7H), 1.69-1.55 (m, 3H), 1.49-1.37 (m, 4H), 1.35-1.26 (m, 3H), 1.19-1.13 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 140.7(C), 128.5 (2 CH), 127.7 (2 CH), 127.4 (CH), 76.5 (C), 74.0 (CH), 70.5 (CH_2), 43.8 (CH), 43.6 (CH), 40.9 (CH), 40.6 (CH), 39.2 (CH), 35.2 (CH), 32.5 (CH), 32.1 (CH_2), 31.9 (CH_2), 30.4 (CH_2), 29.4

(CH_2), 25.6 (CH_2), 24.9 (CH_3), 24.4 (CH_2), 22.2 (CH_3), 21.2 (CH_3), 14.3 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{31}O$ [$(M-H_2O-C_7H_7)^+$] 275.2375, found 275.2378.

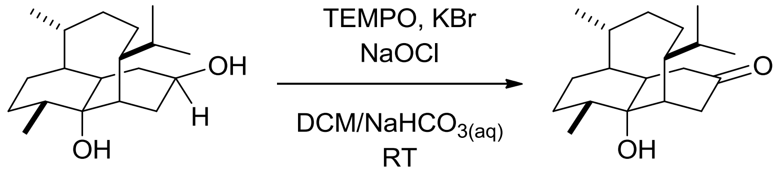


4.59 **4.48**

(±)-(1*S*,3*R*,5*S*,6*R*,9*R*,10*R*,13*R*,14*R*)-6-Isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-3,14-diol (4.48)

To a solution of alcohol **4.59** (65 mg, 0.17 mmol, 1.0 eq) in THF (2.0 mL) at 0 °C was added a 1.0 M solution of Li/Naphthalene in THF (prepared by dissolving 386 mg of naphthalene in 3.0 mL of THF and adding 21 mg of Li and stirring vigorously until a dark green solution is obtained) until the persistence of a green color to the solution for more than 1 minute. The reaction was monitored by TLC and additional portions of Li/naphthalene solution were added until complete consumption of starting material. H_2O and EtOAc were added to the solution and the phases were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (60% EtOAc/Hexanes) to afford 41.6 mg of **4.48** as colorless solid (83%).

IR (neat, cm^{-1}) 3340, 2953, 2871, 1094, 1036; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61-4.52 (m, 1H), 2.23-2.10 (m, 3H), 2.03-1.96 (m, 1H), 1.95-1.88 (m, 1H), 1.87-1.79 (m, 1H), 1.78-1.21 (m, 13H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ hidden by chloroform peak (C), 66.5 (CH), 44.1 (CH), 43.8 (CH), 41.0 (CH), 40.6 (CH), 39.4 (CH), 35.0 (CH_2), 34.8 (CH), 32.6 (CH), 31.7 (CH_2), 31.7 (CH_2), 30.3 (CH_2), 25.4 (CH_2), 24.8 (CH_3), 23.9 (CH_2), 22.1 (CH_3), 21.1 (CH_3), 14.2 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{34}O_2$ (M^+) 294.2559, found 294.2518; m.p. = 163.4-165.6^{o}C.

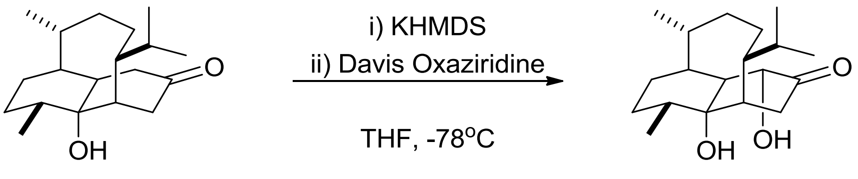


4.48 **4.60**

(±)-(1*S*,5*S*,6*R*,9*R*,10*R*,13*R*,14*R*)-14-Hydroxy-6-isopropyl-9,13-dimethyltricyclo[8.4.0.0^{5,14}]tetradeca-3-one (4.60)

To a mixture of diol **4.48** (27 mg, 0.092 mmol, 1.0 eq) in a 2:5 mixture of saturated $NaHCO_3$/DCM (4 mL) was added TEMPO (1.5 mg, 0.01 mmol, 0.11 eq), KBr (1.2 mg, 0.01 mmol, 0.11 eq) and commercial bleach (6% NaOCl, 0.17 mL, 0.14 mmol, 1.5 eq) at 0 ^{o}C. The mixture was stirred for 1h and saturated $Na_2S_2O_{3aq}$ was added and the mixture was stirred until complete disappearance of color. The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic phases were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (40% EtOAc/Hexanes) to afford 25.3 mg of ketone **4.60** as a colorless oil (94%).

IR (neat, cm^{-1}) 3485, 2961, 2879, 1697, 1333, 1161, 1091; ^{1}H NMR (C_6D_6, 300 MHz) δ 2.80 (dd, *J* = 17.3, 3.8 Hz, 1H), 2.77 (d, *J* = 16.7 Hz, 1H), 2.38-2.30 (m, 2H), 2.07-2.01 (m, 1H), 1.86 (br d, *J* = 7.8 Hz, 1H), 1.82-1.70 (m, 1H), 1.66-1.40 (m, 4H), 1.37-1.13 (m, 5H), 1.11-0.88 (m, 3H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.2 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 210.3 (C), 75.0 (C), 45.2 (CH), 44.4 (CH), 44.1 (CH_2), 43.6 (CH), 40.9 (CH_2), 39.5 (CH_2), 36.5 (CH), 35.2 (CH), 32.8 (CH), 29.9 (CH_2), 29.5 (CH_2), 26.9 (CH_2), 26.6 (CH_2), 24.9 (CH_3), 21.8 (CH_3), 20.9 (CH_3), 14.9 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{32}O_2$ [M^+] 292.2402, found 292.2414.



4.60 **4.61**

(±)-(1*S*,2*R*,5*S*,6*R*,9*R*,10*R*,13*R*,14*R*)-2,14-Hydroxy-6-isopropyl-9,13-dimethyl-tricyclo[8.4.0.0^{5,14}]tetradeca-3-one (4.61)

Ketone **4.60** was azeotropically dried with benzene (3x) prior to submitting it to the reaction conditions. To a suspension of KHMDS (16.4 mg, 0.082 mmol, 6.0 eq) in THF (0.1 mL) was added ketone **4.60** (4.0 mg, 0.014 mmol, 1.0 eq) as a solution in THF (0.3 mL) at -78 °C. The mixture was stirred for 30 minutes at that temperature and Davis oxaziridine (3.7 mg, 0.014 mmol, 1.0 eq) was added in one portion as a solid. The mixture was warmed to 0 °C and stirred for 30 minutes. A second portion of oxaziridine was added (3.7 mg, 0.014 mmol, 1.0 eq) and the mixture stirred for 30 minutes. The reaction was quenched with saturated NH_4Cl_{aq} and EtOAc was added. The layers were separated and the aqueous layer was extracted with EtOAc (3x) and the combined organic phases were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by PTLC (Et_2O) to yield 4.3 mg of **4.61** as a colorless oil (40%, 65% brsm).

IR (neat, cm^{-1}) 3431, 2960, 2929, 2872, 1705, 1086; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.36 (d, J = 6.4 Hz, 1H), 3.86 (br s, 1H), 2.75 (dd, J = 17.8, 9.8 Hz), 1H), 2.44 (d, *J* = 10.3 Hz, 1H), 2.22 (d, *J* = 17.7 Hz, 1H), 2.20-2.12 (m, 1H), 2.00-1.92 (m, 2H), 1.73-1.66 (m, 4H), 1.66-1.60 (m, 2H), 1.57-1.41 (m, 4H), 1.00 (d, *J* = 5.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.5, 76.6 (hidden by solvent peak), 73.3, 58.6, 42.5, 38.8, 37.6, 36.0, 35.4, 31.6, 31.6, 29.0, 25.5, 24.7, 24.0, 21.5, 20.4, 14.2; HRMS (EI) m/z calcd for $C_{19}H_{32}O_3$ [M$^+$] 308.2351, found 308.2345.

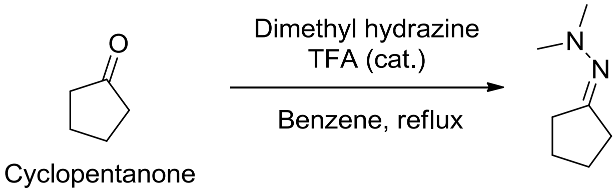
^{1}H NMR data comparison between 4.61 and Baran's intermediate

Our data ^{1}H NMR (CDCl$_3$, 500 MHz) δ in ppm	Baran's data ^{1}H NMR (CDCl$_3$, 600 MHz) δ in ppm
4.36 (d, *J* = 6.4 Hz, 1H)	4.35 (d, *J* = 3.9 Hz, 1H)
3.86 (bs, 1H)	3.86 (bs, 1H)
2.75 (dd, *J* = 17.8, 9.8 Hz, 1H)	2.75 (dd, *J* = 17.7, 9.8 Hz, 1H)
2.44 (d, *J* = 10.3 Hz, 1H)	2.44 (d, *J* = 9.6 Hz, 1H)
2.22 (d, *J* = 17.7 Hz, 1H)	2.22 (d, *J* = 17.8 Hz, 1H)
2.20-2.12 (m, 1H)	2.15 (bs, 1H)
2.00-1.92 (m, 2H)	1.96 (s, 2H)
1.73-1.66 (m, 4H)	1.73-1.66 (m, 4H)
1.66-1.60 (m, 2H)	1.67-1.60 (m, 2H)
1.57-1.41 (m, 4H)	1.57-1.41 (m, 4H)
1.45-1.34 (m, 2H)	1.45-1.34 (m, 2H)
1.00 (d, *J* = 5.7 Hz, 3H)	1.00 (d, *J* = 4.3 Hz, 3H)
0.94 (d, *J* = 6.7 Hz, 3H)	0.94 (d, *J* = 6.4 Hz, 3H)
0.86 (d, *J* = 6.7 Hz, 6H)	0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR data comparison between 4.61 and Baran's intermediate

Our data ^{13}C NMR ($CDCl_3$, 125 MHz) δ in ppm	Baran's data ^{13}C NMR ($CDCl_3$ 150 MHz) δ in ppm
213.5	213.9
Hidden by solvent peak	76.6
73.3	73.4
58.6	58.6
42.5	42.4
40.5	40.5
38.8	38.7
37.6	37.5
36.0	36.1
35.4	35.4
31.6	31.6
31.6	31.5
29.0	29.0
25.5	25.5
24.7	24.7
24.0	24.0
21.5	21.5
20.4	20.4
14.2	14.2

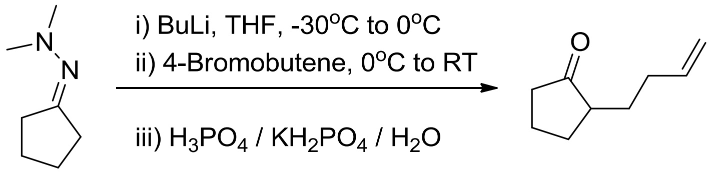
Procedures for Chapter 5



5.62 **5.63**

N'-Cyclopentylidene-*N*,*N*-dimethylhydrazone (5.63)

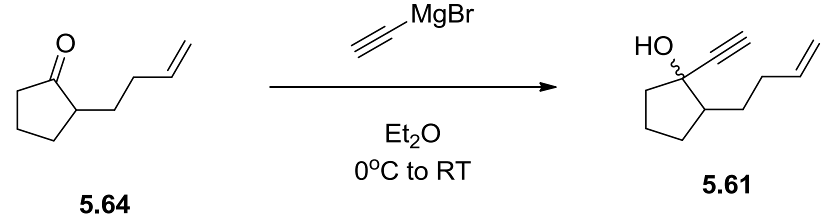
In a flask equipped with a Dean-Stark apparatus and a condenser was refluxed cyclopentanone (**5.62**) (20.0 mL, 226 mmol), dimethylhydrazine (22.4 mL, 294 mmol) and trifluoroacetic anhydride (0.05 mL, 0.67 mmol) in benzene (90 mL) for 3h (6.6 mL of cloudy water isolated). The mixture was allowed to cool to room temperature and diluted with ether (400 mL) and water (100 mL). The layers were separated and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. 18.9 g of **5.63** as a slightly orange oil were obtained (66%). The crude product was used as is for the next step. NMR spectra corresponded to that of the literature.[99]



5.63 **5.64**

2-But-3-enyl-cyclopentanone (5.64)

To a solution of hydrazone **5.63** (5.14 g, 40.7 mmol) in THF (60 mL) was added *n*BuLi 2.0 M in pentane (21.5 mL, 43.0 mmol) at -30 °C and stirred for 45 minutes at 0 °C. 4-bromo-1-butene (4.3 mL, 42.4 mmol) was then added dropwise at 0 °C and the solution was allowed to warm to room temperature and stir at that temperature for 2 hours. H_3PO_4 (20 mL) and water (20 mL) were then added at room temperature and the solution was stirred overnight. The layers were separated and the aqueous phase was extracted with Et_2O (3x). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (20% Et_2O/Hexanes) to afford **5.64** as a yellow oil (3.48 g, 62%). NMR spectra correspond to that of the literature.[99]



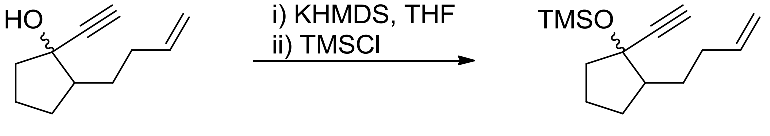
2-But-3-enyl-1-ethynyl-cyclopentanol (5.61)

To a solution of **5.64** (690 mg, 4.99 mmol) in ether (30 mL) was added ethynyl magnesium bromide as 0.5 M solution in THF at 0 °C and allowed to warm to room temperature. The mixture was stirred for 2 hours before the reaction was quenched with a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with ethyl acetate (3x). The organic phase was washed with brine, dried on $MgSO_4$, filtered and concentrated. Flash chromatography (2% to 4% EtOAc/Benzene) afforded **5.61** as a 3:2 mixture of diastereomers as a yellow oil (454 mg, 89%).

Major: IR (neat, cm^{-1}) 3457, 3304, 3074, 2939, 1637, 1442, 995, 911; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.82 (ddt, J =17.2, 10.4, 6.6 Hz, 1H), 5.02 (dddd, J = 17.2, 2.0, 2.0, 1.8 Hz, 1H), 4.94 (ddt, J =10.2, 2.0, 1.2 Hz, 1H), 2.44 (s, 1H), 2.24-2.13 (m, 1H), 2.13-2.03 (m, 1H), 2.03-1.97 (m, 2H), 1.94-1.75 (m, 4H), 1.71 (s, 1H), 1.70-1.60 (m, 1H), 1.46-1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9 (CH), 114.6 (CH_2), 87.2 (C), 75.6 (C), 71.6 (CH), 50.8 (CH), 42.0 (CH_2), 32.4 (CH_2), 28.8 (CH_2), 27.8 (CH_2), 21.4 (CH_2); HRMS (EI) m/z calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found 164.1153.

Minor: IR (neat, cm^{-1}) 3391, 3308, 3076, 2932, 1640, 1451, 1305, 1083, 994, 911; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.81 (ddt, J = 17.2, 10.3, 6.7 Hz, 1H), 5.00 (dddd, J = 17.1, 2.0, 1.9, 1.8

Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H), 2.51 (s, 1H), 2.17 (s, 1H), 2.16-1.98 (m, 2H), 1.98-1.62 (m, 6H), 1.41-1.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0 (CH), 114.6 (CH_2), 85.6 (C), 78.0 (C), 74.2 (CH), 50.3 (CH), 41.8 (CH_2), 32.4 (CH_2), 30.6 (CH_2), 28.9 (CH_2), 20.6 (CH_2); HRMS (EI) m/z calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found 164.1159.



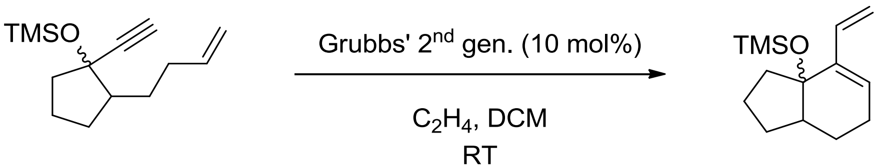
5.61 **5.71**

(2-But-3-enyl-1-ethynyl-cyclopentyloxy)-trimethyl-silane (5.71)

To a solution of **5.61** as a mixture of isomers (1.53 g, 9.32 mmol, 1.0 eq) in THF (50 mL) was added KHMDS (2.19 g, 11.0 mmol, 1.2 eq) at room temperature. The mixture was stirred for 20 minutes and TMSCl (1.30 mL, 10.2 mmol, 1.1 eq) was added. The solution was quenched with a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with ether (3x). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (Hexanes) afforded **5.71** as a mixture of diastereomers (1.25 g, 57%).

Major: IR (neat, cm^{-1}) 3308, 2957, 2871, 1641, 1443, 1250, 1058, 843; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1H), 5.02 (dddd, *J* = 17.2, 2.1, 2.0, 1.8 Hz, 1H), 4.92 (ddt, *J* = 10.1, 2.2, 1.1 Hz, 1H), 2.41 (s, 1H), 2.19-2.00 (m, 2H), 2.00-1.86 (m, 2H), 1.86-1.66 (m, 4H), 1.66-1.55 (m, 1H), 1.42-1.28 (m, 2H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.8 (CH), 114.4 (CH_2), 88.1 (C), 76.4 (C), 72.2 (CH), 52.2 (CH), 43.1 (CH_2), 32.5 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 21.3 (CH_2), 1.6 (3 CH_3); HRMS (EI) m/z calcd for $C_{14}H_{24}OSi$ [M^+] 236.1596, found 236.1579.

Minor: IR (neat, cm^{-1}) 3304, 3077, 2959, 2870, 1449, 1252, 1118, 882, 842; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (ddt, *J* = 17.2, 10.3, 6.7 Hz, 1H), 5.00 (dddd, *J* = 17.1, 2.1, 2.1, 1.8 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H), 2.48 (s, 1H), 2.21-1.97 (m, 3H), 1.90-1.72 (m, 4H), 1.72-1.59 (m, 2H), 1.40-1.20 (m, 2H), 0.16 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 139.3 (CH), 114.1 (CH$_2$), 85.9 (C), 79.1 (C), 75.1 (CH), 51.3 (CH), 42.5 (CH$_2$), 32.6 (CH$_2$), 30.6 (CH$_2$), 27.9 (CH$_2$), 20.4 (CH$_2$), 2.0 (3 CH$_3$); HRMS (EI) m/z calcd for $C_{14}H_{24}OSi$ [M$^+$] 236.1596, found 236.1547.



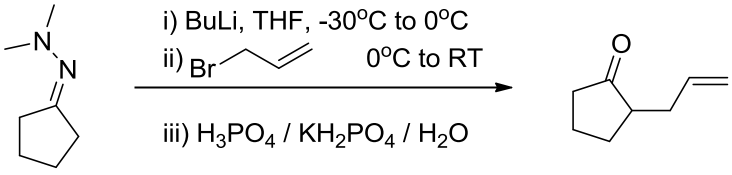
5.71 **5.72**

Trimethyl-(4-vinyl-1,2,3,6,7,7a-hexahydro-inden-3a-yloxy)-silane (5.72)

To a solution of **5.71** (99.9 mg, 0.423 mmol, 1.0 eq) in dichloromethane (15 mL) that was degassed for 30 minutes with argon, was added Grubbs' 2nd generation catalyst (45.3 mg, 0.0534 mmol, 0.13 eq). The argon in the flask was replaced by ethylene gas and the reaction was stirred at room temperature for 90 minutes. The solvent was evaporated and the crude product was purified by flash chromatography (hexanes). **5.72** was obtained as a colorless oil (70.2 mg, 70%).

Major: IR (neat, cm^{-1}) 2954, 2868, 1626, 1446, 1250, 1123, 1045, 839, 752; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.26 (ddd, *J* = 17.7, 11.1, 0.7 Hz, 1H), 5.81 (t, *J* = 3.9 Hz, 1H), 5.34 (d, *J* = 17.7 Hz, 1H), 4.95 (d, *J* = 11.1, 1H), 2.32-2.09 (m, 2H), 2.06-1.94 (m, 1H), 1.85-1.71 (m, 1H), 1.70-1.35 (m, 7H), 0.02 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 140.5 (C), 136.8 (CH), 129.0 (CH), 112.5 (CH$_2$), 79.8 (C), 48.2 (CH), 36.5 (CH$_2$), 27.2 (CH$_2$), 27.1 (CH$_2$), 21.2 (CH$_2$), 20.8 (CH$_2$), 2.1 (3 CH$_3$); HRMS (EI) m/z calcd for $C_{14}H_{24}OSi$ [M$^+$] 236.1496, found 236.1574.

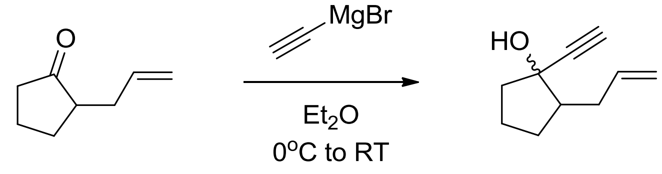
Minor: IR (neat, cm^{-1}) 2955, 2928, 2870, 1630, 1449, 1248, 1116, 1044, 1013, 838; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.20 (ddd, *J* = 17.7, 11.3, 0.6 Hz, 1H), 5.75 (t, *J* = 4.2 Hz, 1H), 5.45 (dd, *J* = 17.7, 1.9 Hz 1H), 5.00 (dd, *J* = 11.3, 1.7 Hz, 1H), 2.20-1.95 (m, 5H), 1.85-1.54 (m, 4H), 1.41-1.27 (m, 2H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.0 (C), 137.1 (CH), 127.2 (CH), 114.2 (CH_2), 84.1 (C), 46.8 (CH), 40.1 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 25.4 (CH_2), 21.9 (CH_2), 2.0 (3 CH_3); HRMS (EI) m/z calcd for $C_{14}H_{24}OSi$ [M^+] 236.1496, found 236.1573.



5.63 **5.73**

(±)-2-Allylcyclopentanone (5.73)

To a solution of hydrazone **5.63** (2.10 g, 16.6 mmol, 1.0 eq) in THF (25 mL) was added *n*BuLi 2.0 M in pentane (8.70 mL, 17.4 mmol, 1.05 eq) at -30 °C and stirred for 45 minutes at 0 °C. Allyl bromide (1.50 mL, 17.4 mmol, 1.05 eq) was then added dropwise at 0 °C and the solution was allowed to warm to room temperature and stirred at that temperature for 2 h. H_3PO_4 (20 mL) and water (20 mL) were then added at room temperature and the solution was stirred overnight. The layers were separated and the aqueous phase was extracted with ether (3x). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (20% Et_2O/Hexanes) to afford **5.73** as a yellow oil (1.71 g, 83%). NMR spectra correspond to that of the literature.[99]



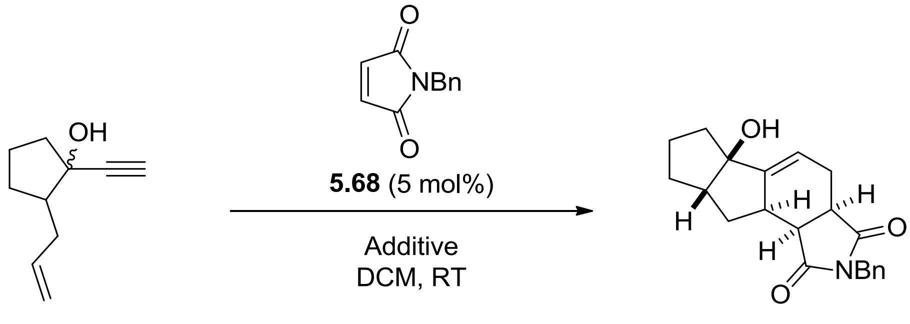
5.73 **5.74**

(±)-2-Allyl-1-ethynylcyclopentanol (5.74)

To a solution of ketone **5.73** (2.59 g, 20.9 mmol, 1.0 eq) in Et_2O (125 mL) was added ethynylmagnesium bromide as a 0.5M solution in THF (125 mL, 62.6 mmol, 3.0 eq) at 0°C and stirred for 2 hours. A saturated aqueous solution of NH_4Cl was added and the layers separated. The aqueous phase was extracted 3 times with Et_2O and the combined organic phases were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography eluting with Hexanes to 10% EtOAc/Hexanes to yield 2.95 g of colorless oil as a 3 : 2 mixture of diastereomers (94%).

IR (neat, cm^{-1}) 3420, 3065; Major: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (m, 1H), 5.07 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 (m, 1H), 2.52-2.44 (m, 1H), 2.46 (s, 1H), 2.12-1.92 (m, 5H), 1.89-1.74 (m, 2H), 1.71-1.60 (m, 1H), 1.50-1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.7 (CH), 115.6 (CH_2), 87.2 (C), 75.4 (C), 71.8 (CH), 51.0 (CH), 42.1 (CH_2), 33.3 (CH_2), 28.8 (CH_2), 21.4 (CH_2);

Minor: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84 (ddd, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.11 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.01 (ddd, *J* = 10.1, 2.1, 1.0 Hz, 1H), 2.56 (s, 1H), 2.51-2.44 (m, 1H), 2.13-2.02 (m, 2H), 1.99-1.87 (m, 3H), 1.78-1.65 (m, 2H), 1.45-1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8 (CH), 116.2 (CH_2), 85.5 (C), 78.0 (C), 74.4 (CH), 50.4 (CH), 41.5 (CH_2), 36.0 (CH_2), 28.8 (CH_2), 20.3 (CH_2); HRMS (EI) m/z calcd for $C_{10}H_{14}O_1$ [M^+] 150.1045, found 150.1002.

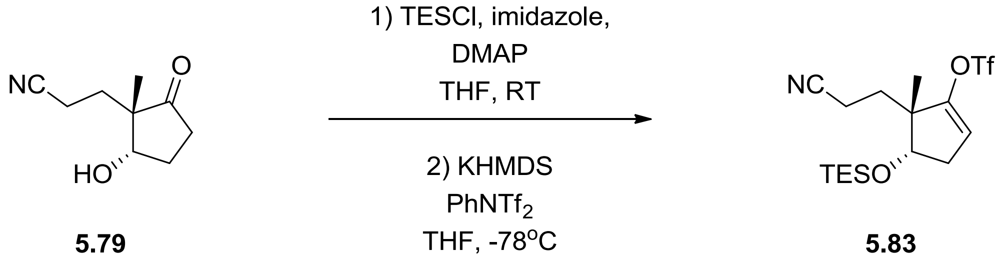


5.74 **5.76**

(±)-(3a*S*,5b*R*,8a*S*,9a*R*,9b*R*)-2-Benzyl-5b-hydroxy-3a,4,5b,6,7,8,8a,9,9a,9b-decahydro-1H-pentaleno[2,1-e]isoindole-1,3(2H)-dione (5.76)

To a suspension of AgOTf (3.2 mg, 6.4 µmol, 0.01 eq) in DCM (0.5 mL) was added gold catalyst (3.4 mg, 6.4 µmol, 0.01 eq) as a solution in DCM (0.5 mL) and stirred for 5 min at RT. A solution of **5.74** (78.5 mg, 0.523 mmol, 1.0 eq) in DCM (1.0 mL) was then cannulated to the mixture and N-benzylmaleimide (240.5 mg, 1.28 mmol, 2.5 eq) was added and the resulting solution was stirred at RT overnight. The solution was concentrated and flashed using EtOAc/Hex (30/70) to yield 48.5 mg of colorless solid (50% based).

IR (neat, cm^{-1}) 3468, 2896, 2871, 1502, 1459, 1367, 1251; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.37-7.34 (m, 2H), 7.33-7.27 (m, 3H), 5.70 (dt, *J* = 7.2, 3.2 Hz, 1H), 4.67 (d, *J* = 13.8 Hz, 1H), 4.50 (d, *J* = 13.8 Hz, 1H), 3.12 (dd, *J* = 16.1, 8.3 Hz, 1H), 3.10 (qd, *J* = 8.4, 1.5 Hz, 1H), 2.84 (ddd, *J* = 15.0, 7.3, 1.6 Hz, 1H), 2.63-2.51 (m, 2H), 2.11-2.04 (m, 1H), 1.89-1.72 (m, 3H), 1.68-1.61 (m, 3H), 1.55-1.47 (m, 1H), 1.43-1.37 (m, 1H), 0.22 (br s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 179.5 (C), 178.2 (C), 153.4 (C), 136.7 (C), 129.1 (2 CH), 128.8 (2 CH), 128.4 (CH), 116.7 (CH), 89.4 (C), 52.7 (CH), 42.5 (CH), 42.3 (CH$_2$), 40.3 (CH), 38.6 (CH$_2$), 37.4 (CH), 30.7 (CH$_2$), 29.8 (CH$_2$), 24.9 (CH$_2$), 24.3 (CH$_2$); HRMS (EI) m/z calcd for $C_{21}H_{23}NO_3$ [M$^+$] 337.1678, found 337.1683.



(+)-(4*S*,5*S*)-5-(2-Cyanoethyl)-5-methyl-4-(triethylsilyloxy)cyclopent-1-enyl trifluoromethanesulfonate (5.83)

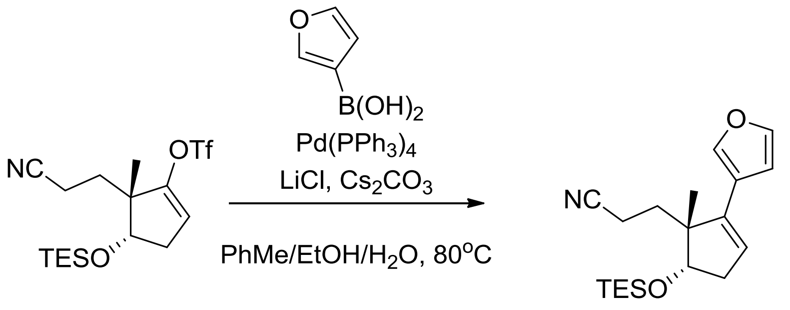
Alcohol **5.79** was prepared according to the literature procedure.[110]

To a solution of alcohol **5.79** (65.2 mg, 0.392 mmol, 1.0 eq) in THF (2.0 mL) were added TESCl (70 µL, 0.43 mmol, 1.1 eq), imidazole (58.3 mg, 0.856 mmol, 2.2 eq) and 1 grain of DMAP. The mixture was stirred for 2 h at RT and quenched with saturated solution of $NaHCO_{3aq}$. The layers were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic phases were dried on $MgSO_4$, filtered and concentrated.

To a solution of the protected alcohol (110.2 mg, 0.392 mmol, 1.0 eq) and N-phenyl-bis(trifluoromethanesulfonimide) (320.8 mg, 0.898 mmol, 2.3 eq) in THF (3.5 mL) was slowly added KHMDS (154.2 mg, 0.773 mmol, 2.0 eq) as a solution in THF (0.5 mL) at -78 °C and stirred for 2 hours. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution at -78 °C and warmed to RT. The mixture was extracted 3 times with EtOAc and the combined organic extracts were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using Hexanes to DCM/Hexanes (40/60) to yield 113.4 mg of colorless oil which corresponded to desired product **5.83**.

IR (neat, cm^{-1}) 2958, 2902, 2255; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.62 (dd, *J* = 3.1, 2.3 Hz, 1H), 4.16 (dd, *J* = 8.0, 7.0 Hz, 1H), 2.65 (ddd, *J* = 16.1, 8.1, 3.2 Hz, 1H), 2.55 (ddd, *J* = 16.6, 11.6, 5.3 Hz, 1H), 2.37 (ddd, *J* = 16.3, 11.4, 4.9 Hz, 1H), 2.17 (ddd, *J* = 16.1, 6.9, 2.2 Hz, 1H), 1.95 (ddd, *J* = 14.0, 11.4, 5.4 Hz, 1H), 1.79 (ddd, *J* = 14.0, 11.6, 4.9 Hz, 1H), 1.15 (s, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.62 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.4 (C), 119.9 (C), 113.2 (CH), 78.1 (CH), 48.9 (C), 37.1 (CH_2), 30.1 (CH_2), 23.2 (CH_3), 13.2

(CH$_2$), 6.9 (3 CH$_3$), 4.9 (3 CH$_2$); HRMS (EI) m/z calcd for $C_{14}H_{21}F_3NO_4SSi$ [$(M-C_2H_5)^+$] 384.0913, found 384.0904; [α_D^{22}] = 39.21° (0.013 M in CHCl$_3$).

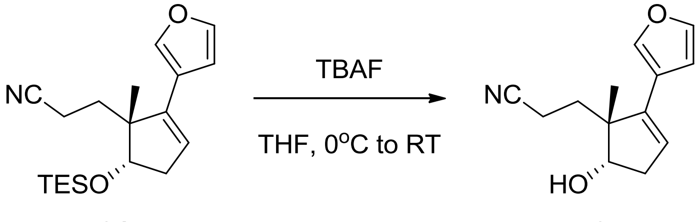


5.83 **5.84**

(-)-3-((1*R*,5*S*)-2-(Furan-3-yl)-1-Methyl-5-(triethylsilyloxy)cyclopent-2-enyl)propanenitrile (5.84)

A solution of **5.83** (55.7 mg, 0.135 mmol, 1.0 eq), 3-furylboronic acid (21.3 mg, 0.190 mmol, 1.5 eq), cesium carbonate (120.8 mg, 0.371 mmol, 2.9 eq) and lithium chloride (18.0 mg, 0.425 mmol, 3.3 eq) in a 2/3/2 mixture of toluene/EtOH/H$_2$O (3.5 mL) was degassed with Ar for 15 min followed by the addition of Pd(PPh$_3$)$_4$ (15.7 mg, 0.0136 mmol, 0.1 eq) and the mixture was refluxed overnight. Water was added to solubilize salts and EtOAc was added. The aqueous phase was extracted 3 times with EtOAc and the combined organic extracts were dried on MgSO$_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography using Hexanes to EtOAc/Hexanes (1/9) to yield 42.3 mg of colorless oil (98%).

IR (neat, cm^{-1}) 2955, 2897, 2257; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.45 (s, 1H), 7.38 (t, *J* = 1.6 Hz, 1H), 6.45 (m, 1H), 5.81 (t, *J* = 2.7 Hz, 1H), 4.17 (t, *J* = 7.7 Hz, 1H), 2.64 (ddd, *J* = 17.1, 8.2, 3.0, 1H), 2.53 (ddd, *J* = 16.6, 11.8, 5.1 Hz, 1H), 2.25 (ddd, *J* = 16.2, 11.6, 4.5, 1H), 2.16 (ddd, *J* = 17.0, 7.5, 2.2 Hz, 1H), 2.05 (ddd, *J* = 13.6, 11.8, 5.1 Hz, 1H), 1.83 (ddd, *J* = 13.6, 12.0, 4.5 Hz, 1H), 1.23 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H) ; ^{13}C NMR (CDCl$_3$, 100 MHz) δ 143.1 (CH), 138.3 (C), 138.1 (CH), 124.5 (CH), 121.0 (C), 120.9 (C), 109.5 (CH), 81.3 (CH), 51.3 (C), 40.5 (CH_2), 31.5 (CH_2), 26.0 (CH_3), 13.5 (CH_2), 7.0 (3 CH_3), 5.0 (3 CH_2); HRMS (EI) m/z calcd for $C_{17}H_{24}NO_2Si$ [$(M-C_2H_5)^+$] 302.1576, found 302.1565; [α_D^{22}] = -25.61° (0.1 M in $CHCl_3$).

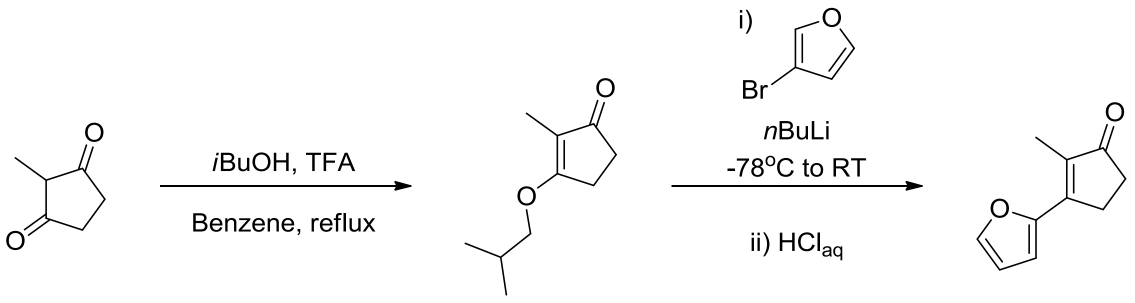


5.84 **5.78**

(-)-3-((1*R*,5*S*)-2-(Furan-3-yl)-5-hydroxy-1-methylcyclopent-2-enyl)propanenitrile (5.78)

To a solution of **5.84** (253.9 mg, 0.766 mmol, 1.0 eq) in THF (3.0 mL) was added a 1.0 M solution of TBAF in THF (1.50 mL, 1.50 mmol, 2.0 eq) at 0°C and stirred for 2 hours. The solvent was evaporated and the crude product purified by flash chromatography using EtOAc/DCM (2/8) to yield 153.2 mg of colorless oil (92%).

IR (neat, cm^{-1}) 3393, 2952, 2904, 2253; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1H), 7.39 (t, *J* = 1.7 Hz, 1H), 6.45 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.81 (t, *J* = 2.6 Hz, 1H), 4.17 (dt, *J* = 7.3, 5.5 Hz, 1H), 2.76 (*J* = 17.4, 7.4, 2.8 Hz, 1H), 2.52 (ddd, *J* = 16.7, 11.2, 5.5 Hz, 1H), 2.36 (ddd, *J* = 16.6, 11.1, 5.4, 1H), 2.25 (ddd, *J* = 17.4, 5.6,2.4 Hz, 1H), 2.07 (ddd, *J* = 13.9, 11.0, 5.5 Hz, 1H), 1.99 (br d, *J* = 5.0 Hz, 1H), 1.94 (ddd, *J* = 13.8, 11.2, 5.0 Hz, 1H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2 (CH), 139.0 (C), 138.1 (CH), 124.3 (CH), 120.9 (C), 120.8 (C), 109.6 (CH), 80.6 (CH), 51.5 (C), 39.8 (CH_2), 30.9 (CH_2), 24.8 (CH_3), 13.6 (CH_2); HRMS (EI) m/z calcd for $C_{13}H_{15}NO_2$ [M^+] 217.1103, found 217.1118; [α_D^{22}] = -24.52° (0.093 M in $CHCl_3$).



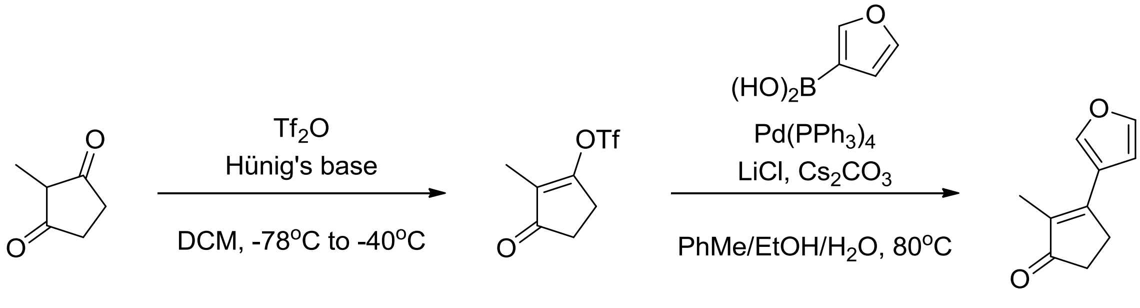
5.81 **5.90** **5.88**

3-(Furan-3-yl)-2-methylcyclopent-2-enone (5.88)

To a solution of 2-methyl-cyclopentane-1,3-dione (**5.81**) (1.10 g, 9.81 mmol, 1.0 eq) in benzene (10 mL) was added isobutanol (3.00 mL, 32.5 mmol, 3.3 eq) and TFA (36 µL, 0.48 mmol, 0.05 eq). The mixture was refluxed overnight in a Dean-Stark apparatus. Et_3N (1 mL) was added and the solvent removed by evaporation. EtOAc and saturated $NaHCO_{3aq}$ were added and the layers separated. The organic layer was washed with $NaHCO_{3aq}$, dried on Na_2SO_4, filtered and concentrated to yield 1.65 g of yellow oil (quantitative) which was used without further purification in the next step.

To a solution of *n*BuLi (1.8 M in pentane, 11.4 mL, 20.6 mmol, 2.1 eq) in THF (75 mL) was added 3-bromofuran (2.96 g, 20.1 mmol, 2.05 eq) at -78 ^{o}C and stirred for 30 min. A solution of **5.90** (1.65 g, 9.81 mmol, 1.0 eq) in THF (25 mL) was then added at -78 ^{o}C and allowed to warm to RT. After stirring for 2 h, 4 M HCl_{aq} (20 mL) were added at 0 ^{o}C and stirred for 30 min. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_{3aq}$, dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (2x) using EtOAC/DCM (1/9) followed by multiple recrystallizations from EtOAc/Hexanes (1/3) to yield 1.07 g of slightly yellow solid (67%).

IR (neat, cm^{-1}) 2957, 2893, 1683; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 7.54 (t, J = 1.7 Hz, 1H), 6.74 (dd, J = 1.9, 0.9 Hz, 1H), 2.84-2.79 (m, 2H), 2.52-2.49 (m, 2H), 1.95 (t, J = 1.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.1 (C), 158.1 (C), 144.1 (CH), 142.7 (CH), 134.8 (C), 123.0 (C), 109.0 (CH), 33.7 (CH_2), 28.1 (CH_2), 9.7 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{10}O_2$ [M^+] 162.0681 , found 162.0699; m.p. = 69-71°C.

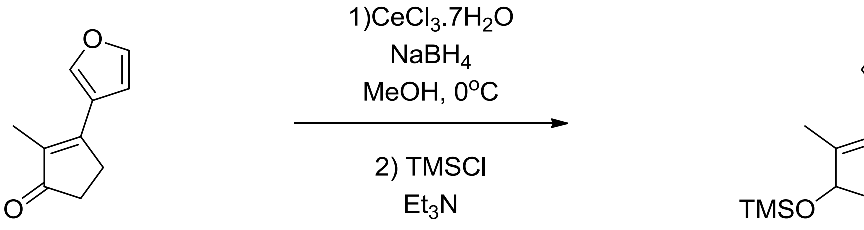


5.81 **5.91** **5.88**

3-(Furan-3-yl)-2-methylcyclopent-2-enone (5.88)

To a solution of 2-methyl-cyclopentane-1,3-dione (**5.81**) (227.8 mg, 2.03 mmol, 1.0 eq) in DCM (13.5 mL) at -78 °C were added *i*Pr_2EtN (820 µL, 4.71 mmol, 2.3 eq) followed by Tf_2O (400 µL, 2.38 mmol, 1.2 eq) dropwise. The solution was warmed to -40 °C and stirred for 1 h after which H_2O and DCM were added. The mixture was warmed to RT and the layers separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (DCM/Hexanes 1/1) to afford 456.0 mg of slightly brown oil (92%). Spectral data concorded to literature values.[106]

A solution of **5.91** (50.3 mg, 0.206 mmol, 1.0 eq), 3-furylboronic acid (29.6 mg, 0.265 mmol, 1.2 eq), cesium carbonate (171.1 mg, 0.525 mmol, 2.5 eq) and lithium chloride (18.0 mg, 0.425 mmol, 2.0 eq) in a 2/3/2 mixture of toluene/EtOH/H_2O (2.7 mL) was degassed with Ar for 15 min followed by the addition of $Pd(PPh_3)_4$ (15.0 mg, 0.0130 mmol, 0.06 eq) and the mixture was refluxed for 2 hours. Water was added to solubilize salts and EtOAc was added. The aqueous phase was extracted 3 times with EtOAc and the combined organic extracts were dried on $MgSO_4$, filtered and concentrated. The resulting crude product was purified by flash chromatography using EtOAc/Hexanes (3/7) to yield 33.3 mg of slightly yellow solid (96%).



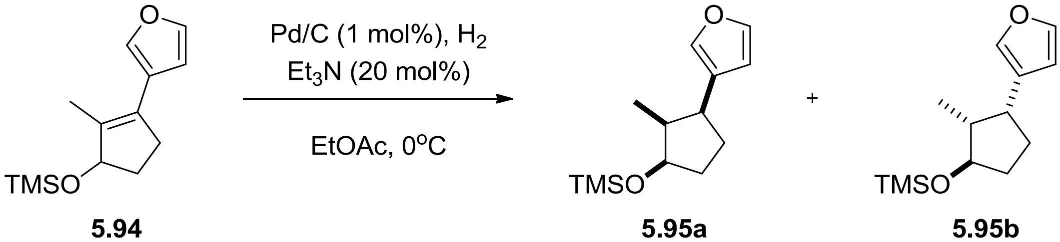
5.88 **5.94**

(±)-(3-(Furan-3-yl)-2-methylcyclopent-2-enyloxy)trimethylsilane (5.94)

To a solution of **5.88** (98.1 mg, 0.605 mmol, 1.0 eq) in MeOH (4.0 mL) was added $CeCl_3.7H_2O$ (275.3 mg, 0.739 mmol, 1.2 eq) at RT and stirred for 10 min. The solution was then cooled to 0 ^oC and $NaBH_4$ (45.0 mg, 1.20 mmol, 2.0 eq) was added portionwise. After 30 min. DCM and H_2O were added and the layers were separated. The aqueous phase was extracted with DCM (3x) and the combined organic layers were dried on Na_2SO_4, filtered and concentrated. The mixture was used in the subsequent step without further purification.

To a solution of the resulting alcohol (0.60 mmol, 1.0 eq) in THF (4.0 mL) was added Et_3N (0.30 mL, 2.2 mmol, 3.7 eq) followed by TMSCl (130 µL, 1.04 mmol, 1.7 eq) at 0°C. The mixture was stirred for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$, the layers were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic phases were dried on $MgSO_4$, filtered and concentrated. The crude product was purified on flash chromatography using hexanes to yield 126.1 mg of colorless oil (90% over 2 steps).

IR (neat, cm^{-1}) 2960, 2857, 2348, 1253, 1090, 748; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (br s, 1H), 7.40 (t, *J* = 1.8 Hz, 1H), 6.56 (dd, *J* = 1.8, 0.9 Hz, 1H), 4.73 (t, *J* = 6.2 Hz, 1H), 2.73-2.64 (m, 1H), 2.50-2.41 (m, 1H), 2.33-2.24 (m, 1H), 1.87-1.85 (m, 3H), 1.76-1.68 (m, 1H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.8 (CH), 140.2 (CH), 135.5 (C), 128.4 (C), 122.8 (C), 109.7 (CH), 81.7 (CH), 33.1 (CH_2), 32.8 (CH_2), 12.9 (CH_3), 0.3 (3 CH_3); HRMS (EI) m/z calcd for $C_{13}H_{20}O_2Si$ [M^+] 236.1233 , found 236.1218.

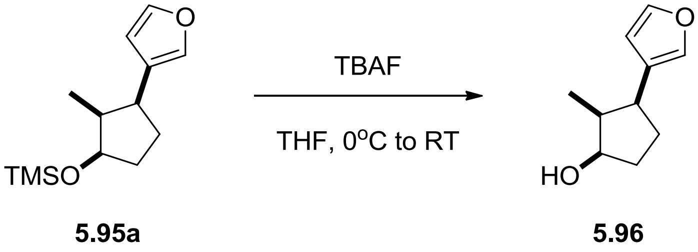


(±)-((1*R*,2*S*,3*S*)-3-(Furan-3-yl)-2-methylcyclopentyloxy)trimethylsilane (5.95a) and (±)-((1*R*,2*R*,3*R*)-3-(Furan-3-yl)-2-methylcyclopentyloxy)trimethylsilane (5.95b)

To a solution of alkene **5.94** (151.8 mg, 0.642 mmol, 1.0 eq) in EtOAc (3.5 mL) at 0 °C was added Et_3N (20 μL, 0.14 mmol, 0.20 eq) followed by 10% Pd/C (6.8 mg, 0.0064 mmol, 0.01 eq). The flask was evacuated and H_2 was bubbled through the solution for 10 min. The mixture was then stirred for 2 h under a H_2 atmosphere and monitored by TLC (DCM/Hexanes 1/9). Argon was bubbled through the solution for 5 min and the mixture was filtered on SiO_2. After evaporation of the solvent, the crude product was purified by flash chromatography (DCM/Hexanes 1/9) to yield 104.8 mg of **5.95a** (69%) and 6.6 mg of **5.95b** (4%) as colorless oils.

5.95a: IR (neat, cm^{-1}) 2948, 2903, 2850, 1506, 1441, 1333; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.18 (t, *J* = 1.6 Hz, 1H), 7.10-7.09 (m, 1H), 6.26 (dd, *J* = 1.7, 0.7 Hz, 1H), 4.03 (ddd, *J* = 6.0, 5.8, 5.2 Hz, 1H), 2.83 (ddd, *J* = 8.7, 8.4, 8.1 Hz, 1H), 2.02-1.93 (m, 1H), 1.83-1.74 (m, 2H), 1.69-1.63 (m, 2H), 0.81 (d, *J* = 7.2 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz) δ 142.8 (CH), 139.7 (CH), 127.4 (C), 111.7 (CH), 76.3 (CH), 42.9 (CH), 37.1 (CH), 33.0 (CH_2), 28.6 (CH_2), 10.0 (CH_3), 0.2 (3 CH_3); HRMS (EI) m/z calcd for $C_{13}H_{22}O_2Si$ [M$^+$] 238.1389, found 238.1370.

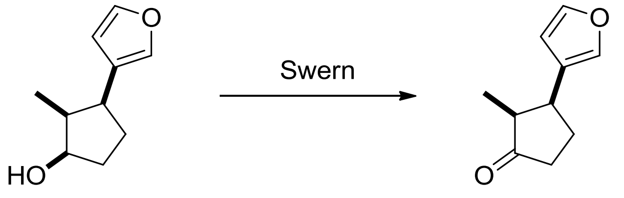
5.95b: IR (neat, cm^{-1}) 2952, 2895, 1502, 1450, 1327; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.13 (t, *J* = 1.6 Hz, 1H), 7.03-7.02 (m, 1H), 6.02 (dd, *J* = 1.6, 0.8 Hz, 1H), 3.86 (ddd, *J* = 5.9, 3.5, 3.5 Hz, 1H), 3.31 (ddd, *J* = 8.2, 8.1, 8.0 Hz, 1H), 2.17-2.08 (m, 1H), 1.99-1.90 (m, 2H), 1.69-1.60 (m, 1H), 1.57-1.47 (m, 1H), 0.66 (d, *J* = 7.2 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (C_6D_6, 100 MHz) δ 142.9 (CH), 139.5 (CH), 126.7 (C), 111.4 (CH), 80.1 (CH), 46.7 (CH), 37.3 (CH), 33.7 (CH_2), 27.8 (CH_2), 13.7 (CH_3), 0.3 (3 CH_3); HRMS (EI) m/z calcd for $C_{13}H_{22}O_2Si$ [M^+] 238.1389, found 238.1373.



(±)-(1*R*,2*S*,3*S*)-3-(Furan-3-yl)-2-methylcyclopentanol (5.96)

To a solution of **5.95a** (24.2 mg, 0.102 mmol, 1.0 eq) in THF (1.0 mL) at 0 °C was added TBAF (1.0 M in THF, 150 µL, 0.150 mmol, 1.5 eq) and the mixture was allowed to warm to RT. The solution was stirred for 2 h and H_2O was added to quench the reaction. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried on $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/Hexanes 1/4) to yield 15.6 mg of **5.96** (94%).

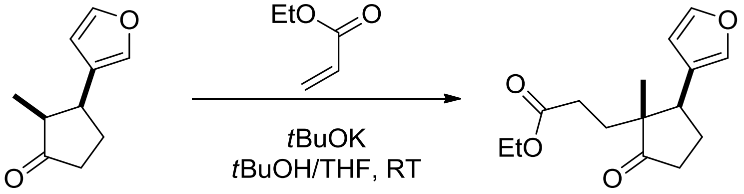
IR (neat, cm^{-1}) 3380, 2967, 2915, 2877, 1502, 1472; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.16 (t, *J* = 1.4 Hz, 1H), 7.08-7.07 (m, 1H), 6.23 (dd, *J* = 1.4, 0.5 Hz, 1H), 3.96 (ddd, *J* = 6.1, 5.6, 5.6 Hz, 1H), 2.78 (ddd, *J* = 8.5, 8.1, 8.0 Hz, 1H), 1.96-1.87 (m, 1H), 1.80-1.68 (m, 3H), 1.62-1.53 (m, 1H), 0.73 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 142.8 (CH), 139.7 (CH), 127.3 (C), 111.7 (CH), 75.7 (CH), 42.5 (CH), 37.5 (CH), 32.7 (CH_2), 28.7 (CH_2), 9.5 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{14}O_2$ [M^+] 166.0994, found 166.0990.



5.96 **5.86**

(±)-(2*S*,3*S*)-3-(Furan-3-yl)-2-methylcyclopentanone (5.86)

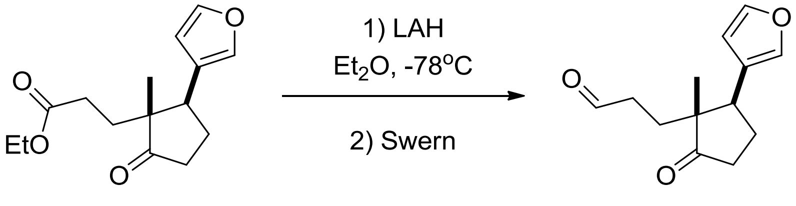
To a solution of oxalyl chloride (250 µL, 2.93 mmol, 1.5 eq) in DCM (20 mL) was added DMSO (0.25 mL, 3.49 mmol, 1.8 eq) dropwise at -78 °C and stirred 15 minutes. To this solution was cannulated alcohol **5.96** (324.3 mg, 1.95 mmol, 1.0 eq) in DCM (20 mL) and stirred for 30 minutes. Et_3N (0.95 mL, 6.84 mmol, 3.5 eq) was added and the solution was stirred 15 minutes at -78 °C and warmed to 0 °C and stirred for another 30 minutes. The mixture was quenched at 0 °C by the addition of H_2O and the layers were separated. The aqueous phase was extracted with DCM (3x). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and evaporated. The crude mixture was purified by flash chromatography (20% Et_2O/Pentane) to yield 268.7 mg of **5.86** as a colorless oil (84%). The spectral data concorded to that of the literature.[91]



5.86 **5.97**

(±)-Ethyl-(2’*S*,3’*R*)-3-[3’-(furan-3-yl)-2’methyl-1’oxocyclopent-2’-yl]-propanoate (5.97)

To a solution of ketone **5.86** (75.0 mg, 0.457 mmol, 1.0 eq) in *t*BuOH (1.8 mL) was added 1.0M *t*BuOK in THF (70 µL, 0.070 mmol, 0.15 eq) followed by ethyl acrylate (80 µL, 0.735 mmol, 1.6 eq) at RT. The mixture was stirred for 20 min and the reaction was quenched with NH_4Cl_{aq}. The layers were separated, the aqueous phase was extracted with Et_2O (3x) and the organic phases were dried on $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (20% to 30% Et_2O/Pentanes) to furnish 78.5 mg of **5.97** as a colorless oil (65%, 96% brsm) and 23.2 mg of **5.86** as a colorless oil (31%). Spectral data for the compound corresponded to literature data.[91]



5.97 **5.98**

(±)-(2’*S*,3’*R*)-3-[3’-(Furan-3-yl)-2’-methyl-1’-oxocyclopent-2’-yl]-propanal (5.98)

To a solution of **5.97** (25.4 mg, 0.0961 mmol, 1.0 eq) in Et_2O (1 mL) was added LAH (8.5 mg, 0.224 mmol, 2.3 eq) at -78 °C and the mixture was stirred for 30 min at that temperature. An aqueous solution of sodium tartrate was added and the mixture allowed to warm to RT and stirred vigorously for 30 min. The layers were separated and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried on $MgSO_4$, filtered and concentrated. The crude product was used without further purification.

To a solution of oxalyl chloride (25 µL, 0.287 mmol, 3.0 eq) in DCM (1 mL) was added DMSO (25 µL, 0.342 mmol, 3.6 eq) dropwise at -78 °C and stirred 15 minutes. To this solution was cannulated the diol from the previous step in DCM (1 mL) and stirred for 30 minutes. Et_3N (90 µL, 0.670 mmol, 7.0 eq) was added and the solution was stirred 15 minutes at -78 °C and warmed to 0 °C and stirred for another 30 minutes. The mixture was quenched at 0 °C by the addition of H_2O and the layers were separated. The aqueous phase was extracted with DCM (3x). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and evaporated. The crude mixture was purified by flash chromatography (30% EtOAc/Hexanes) to yield 12.7 mg of **5.98** as a colorless oil (60% over 2 steps). The spectral data concorded to that of the literature.[91]

Glossary of Abbreviations

Ac	acetate
ACN	Acetonitrile
AIBN	azobisisobutyronitrile
aq	aqueous
BBN	borabicyclo[3.3.1]nonane
brsm	based on recovered starting material
Bn	benzyl
Bu	butyl
CAN	Cerium ammonium nitrate
CBS	Corey-Bakshi-Shibata
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
d	doublet
DCM	dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminumhydride
DIPEA	*N*,*N*,*N*-diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio

e.e.	Enantiomeric excess
eq	equivalents
EDG	Electron-Donating Group
EI	Electrospray Ionization
EWG	Electron-Withdrawing Group
Et	ethyl
HDDA	hydroxy-directed Diels-Alder
HMDS	hexamethyldisilazane or bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HRMS	high resolution mass spectrum
imid.	imidazole
L.A.	Lewis Acid
LAH	Lithium aluminum hydride
LUMO	Lowest Unoccupied Molecular Orbital
m	multiplet
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
Mes	Mesityl
MOM	Methoxymethyl
m.p.	melting point
MS	Mass Spectroscopy
*n*BuLi	*n*-butyllithium

nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OTf	trifluoromethylsulfonate
Ph	phenyl
PIDA	phenyl iodide diacetate
PIFA	Phenyl iodonium bis(trifluoroacetate)
Piv	pivaloyl $(CH_3)_3C$-CO
PMB	*para*-methoxybenzyl
ppm	parts per million
PTSA	*para*-toluenesulfonic acid
Py or pyr.	pyridine
quant.	quantitative yield (i.e. >98%)
Ra-Ni	Raney Nickel
RCM	Ring Closing Metathesis
RT	room temperature
s	singlet
SM	starting material
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenyl silyl
TBS	*tert*-butyldimethyl silyl
TEMPO	2,2,6,6-tetramethylpiperidine

TES	triethyl silyl
Tf	trifluoromethanesulfonic
TFA	trifluoroacetic acid
TLC	Thin-layer chromatography
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Electronic Supporting Information

1. Proton and Carbon spectra of new compounds
2. X-ray data

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