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The Attempted Synthesis of Teucrolivin A via the Oxy-Cope/Claisen/Ene Reaction; Diastereoselective Formation of Quaternary Centers Directed By Macrocyclic Conformation and its Application to the Formal Synthesis of (-)-Mesembrine

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by

Steve Arns

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies

In partial fulfillment of the requirements for the

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Abstract

This thesis is the account of a journey through the world of total synthesis. It is a story of our attempts to tackle some of the persistent challenges faced by the synthetic chemist, showcasing our solutions through total synthesis. These issues include the rapid generation of complex molecules with high selectivity, and the stereoselective generation of quaternary centers.

Out initial efforts were focused on the application of the oxy-Cope/Claisen/ene reaction towards the total synthesis of the natural product teucrolivin A. A route was developed to give access to advanced intermediates required for its synthesis. However the existing methodology did not fully accommodate the complete core structure of the target.

This prompted an in-depth examination of the oxy-Cope/Claisen/ene reaction with a new class of substrate. From this study were able to gain insight into the use of this tandem reaction with sterically demanding substrates and we were able to assess the applicability of these substrates for use in the synthesis of teucrolivin A.

Shifting gears, we developed an anionic oxy-Cope/alkylation sequence by which to generate all-carbon quaternary centers. This methodology exhibited high diastereoselectivity, where the selectivity was governed by the conformational preferences of a macrocycle in which an enolate generated from the anionic oxy-Cope rearrangement was embedded.

Finally we applied this new procedure for the generation of quaternary carbon centers to the formal synthesis of the alkaloid natural product (-)-mesembrine.

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First and foremost, I have to thank Louis for his guidance as my supervisor throughout my time in grad school. His enthusiasm, patience, and his willingness to teach and share have helped me flourish as a scientist. These past few years have been nothing but enjoyable, and of course have been a fantastic educational experience.

It also goes without say that my Ph.D. experience would not have been the same without my labmates. I leave with great memories of times had both in and out of the lab, and I wish them great success in whatever path in life they choose to take. As well, this work wouldn't have been possible without the support of the chemistry department as a whole; other labs, faculty members and support staff alike. Thanks guys!

I'd like to thank my parents Keith and Lynda and my brother Mike. While they didn't offer much support when it came to figuring out what was going on in my fumehood, their support and enrouragement have made me who I am today and I am forever grateful for all the opportunities they have provided me. Also, I have to thank my wonderful girlfriend Toni for her love and support, and for letting me monopolize our computer while I wrote this thesis!

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1

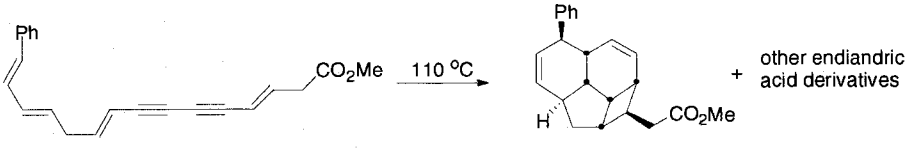
Natural Product Synthesis

Introduction

From its inception as a fledgling science in the nineteenth century to its evolution today as a powerful tool for assembling complex molecules, natural product synthesis is arguably the flagship discipline of organic chemistry.[1] The last fifty years have seen a rapid increase in both the complexity and size of the targets which have succumbed to total synthesis, and often these syntheses serve as a showcase for new methodologies which have been specifically developed to construct a natural product.

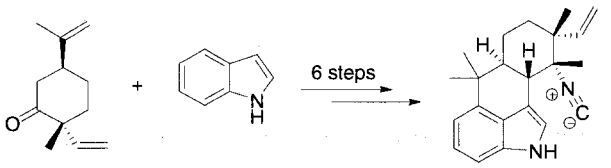
Current trends in natural products synthesis lean towards the rapid construction of these molecules using a minimum number of simple steps. Transformations which can imbue significant molecular complexity into a target in a single step also demonstrate particular utility in this respect. Nicolaou's synthetic approach[2] to the endiandric acid methyl esters[3] using cascading pericyclic reactions is a classic example of the latter concept, while the former is well represented in Baran's synthesis[4] of the complex alkaloid ambiguine H (**1.5**) without the use of protecting groups in only 10 steps.

Scheme 1.1: Nicolaou's approach to endiandric acid A methyl ester



1.1 1.2

Scheme 1.2: A short illustration of Baran's approach to ambiguine H



1.3 **1.4** **1.5**

Despite the wondrous achievements attainted to date by the synthetic community, there are still many weaknesses in the arsenal of transformations available to construct a natural product. The stereoselective installation of quaternary carbon centers into the carbon skeleton of a target is one of these challenges.[5] Also, the execution of a key step with high levels of diastereoselectivity and selectivity for a single product is much desired but often difficult to obtain.[6]

Knowing these challenges, we now begin a story describing how these problems facing synthesis can be partially resolved. Herein is described an attempt at the total synthesis of the natural product teucrolivin A using the highly selective oxy-Cope/Claisen/ene reaction, and the power of a conceptually unique quaternary carbon forming alkylation reaction is exemplified by completing a formal synthesis of the alkaloid (-)-mesembrine.

Natural Products

Natural products can be defined as any chemical that is produced by a living system. Taking into account the vast number of organisms known and the seemingly endless possibilities by which they can connect and arrange atoms, the potential number of natural products is in essence infinite.[7]

Despite this, natural products can be broadly classified into just two groups; primary and secondary metabolites. Surprisingly, there are a limited number of manifolds by which these compounds are synthesized. Primary metabolites are the essential building blocks

of life and include amino acids, carbohydrates, fats and proteins. These molecules arise from fundamental processes like photosynthesis, the primary metabolic pathways, or they exist as products of the environment.

It is the secondary metabolites however that have captured the minds of chemists and inspired them to undertake great synthetic endeavors. Structurally diverse and virtually innumerable, many of these compounds serve no apparent purpose other than that they are relics of the evolutionary process, while others act as essential compounds to ensure survival.[8]

It is this biological activity, among other things, either in the organism that creates it or in another living system that often drives us to create natural products synthetically. Whereas the secondary metabolites in Nature arise from only three major secondary metabolic pathways and a handful of precursors, the methods available to chemists are much more diverse. Despite this, we still cannot replicate the elegant simplicity and efficiency of Nature in building such complex molecules, which is ultimately one of the key goals of total synthesis.

Terpenes: Teucrolivin A

Secondary metabolites are classified according to their structure, which is directly related to the method by which they are biosynthesized. Terpenes are one such broad class of metabolite and are characterized as consisting of small 5-carbon sub-units called isoprenes (**1.6**). Initially this pattern was recognized in a series of low molecular weight terpenes such a menthol (**1.7**), but has since been acknowledged in thousands of compounds that are now classed as terpenes.[9]

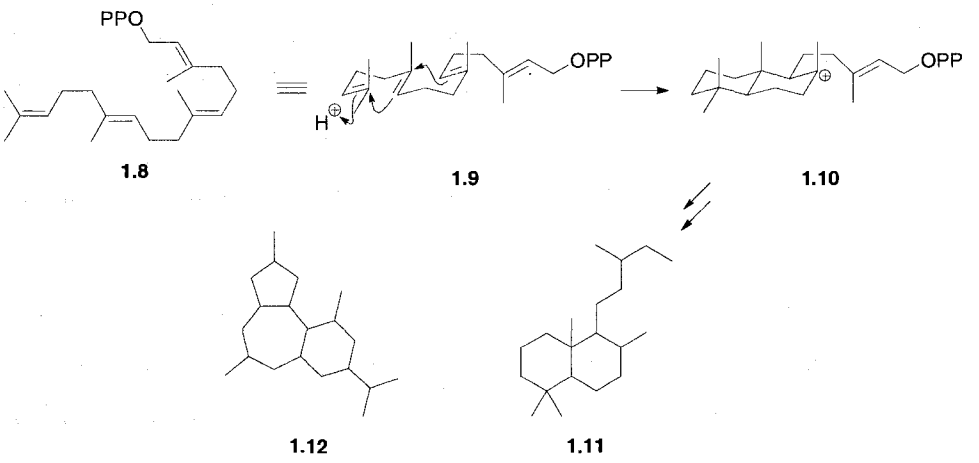
Figure 1.1: The isoprene unit and menthol

1.6 **1.7**

Terpenes are further differentiated by the number of isoprene units in their structure. Those with one through four isoprenes are classified as hemiterpenes, monoterpenes, sesquiterpenes and diterpenes. Diterpenes, particularly those with dense oxygen functionalization, are interesting in that they quite often exhibit pronounced biological activity, and their structures can be quite complex and compact, therefore offering challenging synthetic targets.[10]

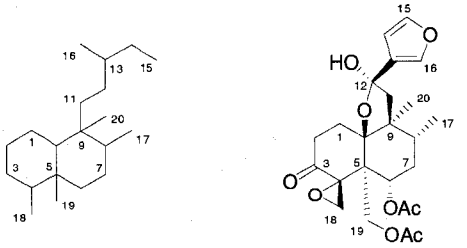
Virtually all diterpenes arise from biogenetic precursor **1.8**, geranylgeranylpyrophosphate. Different series of cyclizations and sigmatropic shifts result in the generation of the various sub-classes of the diterpenes. For example, the simple cyclization of *trans-trans*-geranylgeranylpyrophosphate **1.9** gives carbocation **1.10**, which corresponds to the labdane diterpene carbon skeleton **1.11**. Of course, more elaborate diterpenes can also be generated along the same lines. For example, the daphnane diterpenes whose carbon skeleton is represented as **1.12** arises from the same biogenetic precursor as **1.11**.[9]

Scheme 1.3: Diterpenes from geranylgeranylpyrophosphate



Our interest lays with the clerodane diterpene teucrolivin A (**1.14**).[11] The clerodane diterpenes, whose skeletons are represented by structure **1.13**, are directly related to and arise from the labdane series of natural products. This compact, highly oxygenated natural product has not previously been synthesized, and represents to us a formidable synthetic challenge, in part due to the high concentration of stereogenic centers on the decalin skeleton. In addition, we wished to apply a methodology developed in our laboratory to its synthesis which is extremely efficient in constructing *trans*-decalin ring systems similar to that seen in **1.14** and other diterpenes.

Figure 1.2: The clerodane skeleton and teucrolivin A



1.13 1.14

Origins and Biological Activity

Clerodane diterpenes are widespread in several species of plants, particularly those of the genus *Teucrium* and *Salvia*. Teucrolivin A (**1.14**), one of several teucrolivins, was first isolated in 1991 from the aerial parts of *Teucrium oliverianum*, a Saudi Arabian plant used in traditional medicine as a treatment for diabetes.

All of the clerodanes including teucrolivin A are insect antifeedants. Teucrolivin A is the most potent of the teucrolivins as an antifeedant, with an FI_{50} of 3-70 ppm[11] against the final stage Lepidopteran larvae *S. littoralis*, *S. frugiperda* and *H. armegira*.[12]

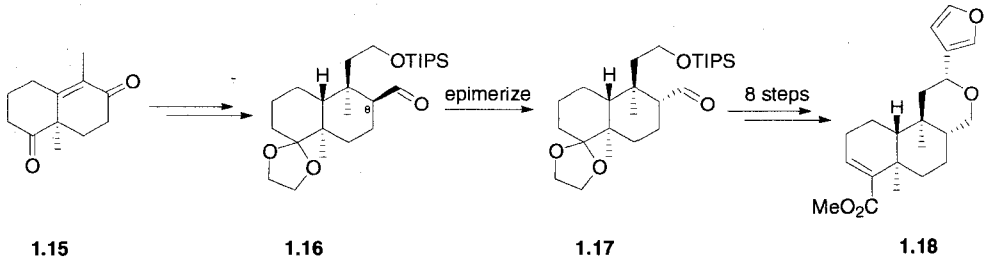
Clerodanes are also known to exhibit a wide spectrum of biological activities for which tecurolivin A has never been tested, hence a total synthesis would allow for the preparation of quantities of this substance for further biological studies.

Synthetic Approaches to the Clerodanes

Whilst a synthesis of teucrolivin A itself has yet to be reported, clerodanes as a class of diterpene have received some attention from the synthetic community owing to their structural diversity and biological activities. Accordingly, there are numerous approaches that can be used when trying to construct one of these natural products. The key issue in their construction is forming the characteristic decalin ring system with appropriate stereochemical control, for which no general approach exists.[13]

Circumventing the need to form the decalin by using a modified Wieland-Miescher ketone (**1.15**) as starting material, Hagiwara and co-workers were able to generate the clerodane (-)-methyl barbascoate[14] **1.18** using the intrinsic stereochemical preferences of **1.15** to direct the final stereochemical outcome.[15] Elaboration of **1.15** to **1.16** followed by an epimerization at C8 afforded the decalin skeleton with the correct absolute stereochemistry. A final series of reactions achieved the total synthesis of **1.18** in 12 overall steps from previously reported compounds.

Scheme 1.4: Hagiwara's synthesis of (-)-methyl barbascoate

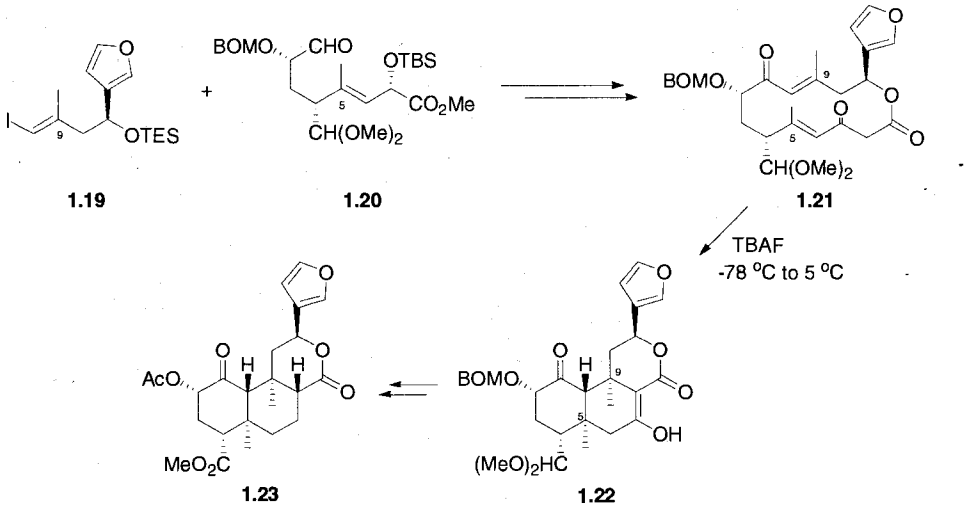


1.15 **1.16** **1.17** **1.18**

The Evans group also undertook the synthesis of a clerodane diterpene in an approach that established the decalin system using a transannular bis-Michael addition.[16] The synthesis of salvinorin A[17] (**1.23**), a more complex relative of methyl barbascoate **1.18**, began from fragments **1.19** and **1.20**. Coupling of these two fragments was accomplished by a chelate-controlled Grignard addition and a Shiina macrolactonization,[18] ultimately giving macrocycle **1.21**.

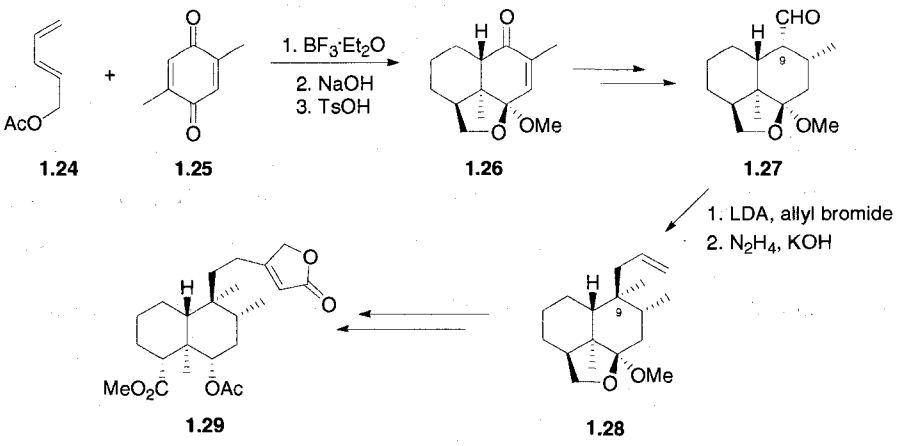
The pivotal bis-Michael addition occurred with relative ease simply by treating **1.21** with TBAF, which gave compound **1.22**. This step is quite remarkable in that it established three of the remaining stereocenters, including the two quaternary carbons at C5 and C9 with the methyl substituents arranged in a 1,3-diaxial fashion. Simple functional group interconversions completed the synthesis of **1.23** in 33 overall steps.

Scheme 1.5: Evans' synthesis of salvinorin A



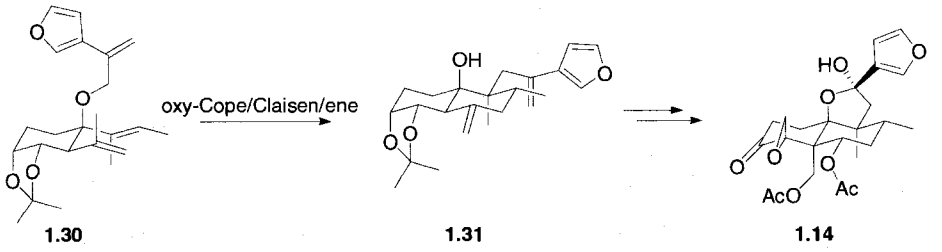
Another obvious approach to these diterpenes is through the use of the Diels-Alder reaction, which Goldsmith and co-workers applied to the synthesis[19] of the clerodane ajugarin IV (**1.29**).[20] The *trans*-decalin ring structure arose from a Diels-Alder reaction between diene **1.24** and benzoquinone **1.25** followed by several functional group interconversions. The four remaining stereocenters were installed in a stepwise fashion where the diastereoselectivity was driven by the stereochemical bias of the newly formed decalin. The quaternary carbon not installed during the Diels-Alder reaction at C9 was put in place using a simple alkylation of an enolate generated from LDA, as seen in the conversion of **1.27** to **1.28**. In the end, the synthesis was completed in 28 steps from the Diels-Alder reaction.

Scheme 1.6: Goldsmith's synthesis of ajugarin IV



Each of the above mentioned syntheses represent novel entries to the clerodane skeleton, and are just several illustrations of the various methods that have been conceived to do so.[13] Undoubtedly there is still much room for improvement in the methods by which they can be synthesized, particularly with respect to the controlled formation of the stereocenters about the decalin core. Our approach to these challenging targets uses the powerful oxy-Cope/Claisen/ene reaction[21] to establish the core decalin structure **1.31** of teucrolivin A with exceptional selectivity and efficiency, which will be discussed in due course.

Scheme 1.7: Our approach to the clerodane diterpene teucrolivin A



Quaternary Carbons

One of the enduring problems faced in synthesis is the stereocontrolled construction of all-carbon quaternary centers. Rightfully so, general methods for their construction are highly sought after. One only needs to look at a handful of natural products to realize that they are a ubiquitous structural feature throughout the whole spectrum of known compounds, and methods to construct them are a necessary requirement to engage in total synthesis.

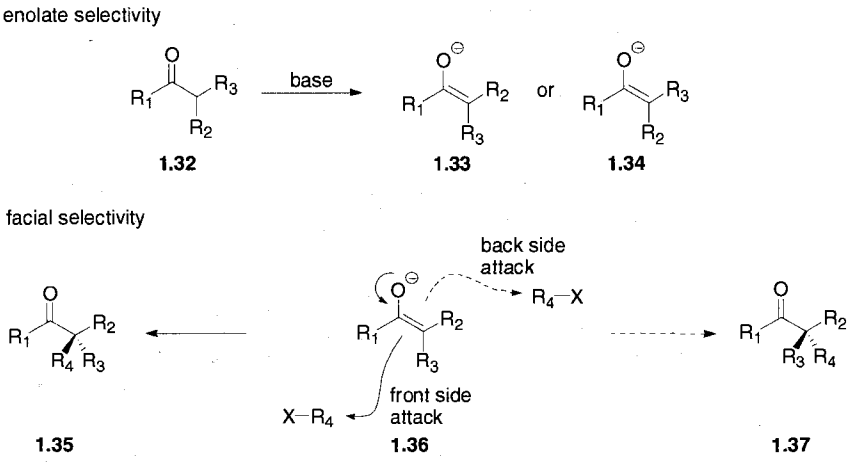
Methods which can accomplish this desired transformation are almost as varied as the quaternary centers themselves. Virtually all classes of reactions have been applied to some extent in solving this problem, from cycloadditions to transition metal catalyzed couplings to simple alkylations. The current trend in this field is directed towards stereo and enantioselective processes, particularly those mediated by transition metals.

Quaternary Centers by Direct Alkylation of an Enolate

The direct alkylation of an enolate represents a conceptually simple yet fundamental mode of reactivity by which to access quaternary carbon centers.[5] This manifold of reactivity is attractive in that the potential starting materials used to generate the appropriate α,α-disubstituted enolates for forming quaternary centers are widespread, as are the electrophilic coupling partners.[22]

At first glance such a procedure could be deemed routine. It is however anything but routine as in order to observe selectivity it is necessary to control both the geometry of the enolate generated and to create a facial bias for electrophilic attack on the enolate. The ultimate goal is to exert control over both of these factors in tandem as both are intrinsically linked to the stereochemical outcome of the reaction.

Scheme 1.8: E/Z and facial selectivity in enolate alkylation



Of the two issues, E/Z selectivity in enolate generation is the most problematic. While easily addressed through the use of cyclic substrates, no general solution has been presented to solve the problem with their acyclic counterparts. The issue of facial selectivity is better resolved, with the use of chiral auxiliaries or the inherent steric bias of a substrate to shield one face of an enolate as perhaps the most common solutions. With these concepts in mind, some notable methods by which to achieve the formation of quaternary centers via enolate alkylation are discussed below.

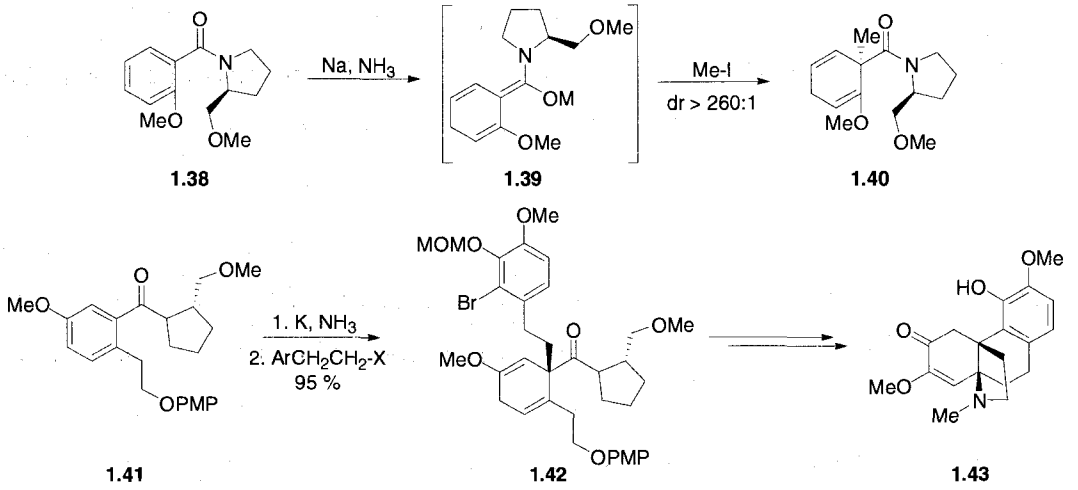
Methods for Quaternary Center Formation by Enolate Alkylation

Recent technologies designed to access quaternary centers via enolate alkylation often do not rely upon the simple deprotonation of an aldehyde or ketone in order to generate the enolate. Arthur Schultz has done just this by developing a methodology where the enolate is generated by the Birch reduction of a benzoic acid derivative and the facial selectivity is controlled by a prolinol-derived chiral auxiliary.[23]

A typical reaction is illustrated in the conversion of **1.38** to **1.40** where an initial Birch reduction of **1.38** gives enolate **1.39** which is alkylated with iodomethane to form the quaternary center with exceptional diastereoselectivity. While the generation of the

enolate and the alkylation occur with high levels of selectivity, the sense of induction in the newly formed quaternary center is highly substrate dependant. This methodology is particularly useful for the stereocontrolled formation of six-membered rings (see Scheme 1.9), and as such has successfully been applied to numerous total syntheses, including that of the hasubanan alkaloid (+)-cepharamine (**1.43**).[24]

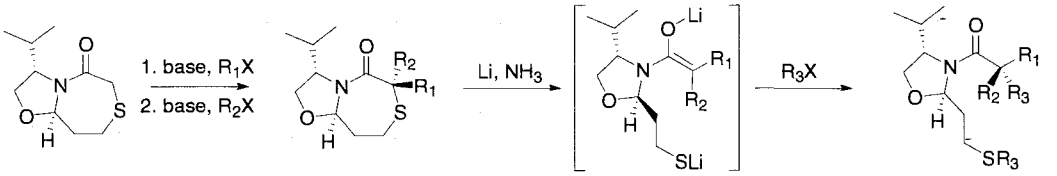
Scheme 1.9: Schultz' approach to enolate alkylation



Gleason and co-workers have taken a slightly different approach to selectively generating quaternary centers by using chiral bicyclic thioglycolate lactams as chiral auxiliaries. These auxiliaries serve a dual purpose by generating a stereodefined acyclic enolate equivalent in addition to governing the facial selectivity of the alkylation.[25]

This methodology begins with a double alkylation of lactam **1.44** to generate an α,α-disubstituted enolate precursor **1.45** where addition occurs on the convex face of the lactam. A dissolving-metal reduction of **1.45** generates the desired stereodefined enolate that can be alkylated to selectively form a quaternary center. Removal of the chiral auxiliary is straightforward, easily giving both primary alcohols and carboxylic acids. This process creates opposite stereoisomers simply by changing the order of addition of the electrophiles.

Scheme 1.10: Gleason's approach to generating quaternary centers

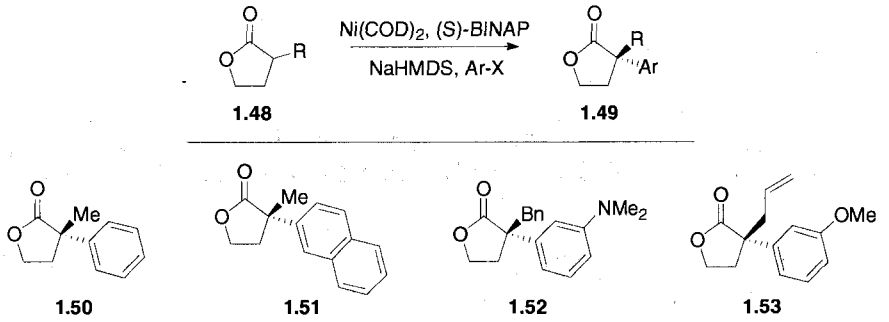


The generation of all-carbon quaternary centers has also been accomplished through metal-catalyzed enantioselective reactions of enolate intermediates. While still a relatively young field with much room for growth and improvement, some notable achievements have been made.

In a representative example, Buchwald and Spielvogel recently described a Ni-BINAP catalytic system capable of building quaternary centers from enolates generated from α-substituted γ-butryolactones.[26] Compound **1.48** forms an enolate after treatment with a strong base, which transmetallates to give a nickel enolate. Under the influence of a chiral BINAP ligand, an enantioselective cross-coupling occurs to give chiral products of type **1.49**.

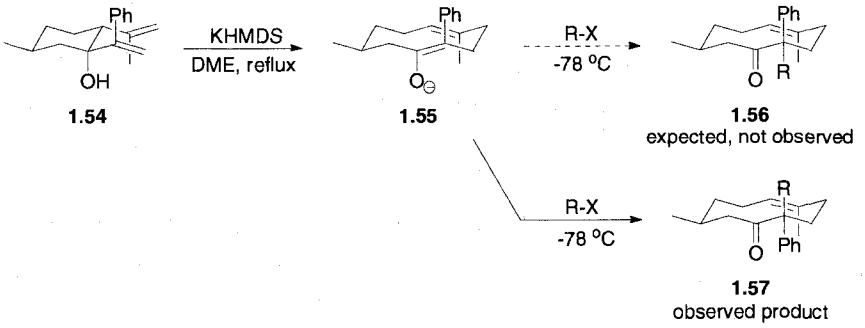
While not strictly an enolate alkylation by virtue of the fact that the enolate and electrophile undergo a coupling mediated by nickel, it is significant in that it opens the door to a vast series of non-classic electrophiles, and it points towards the inevitable future for many chemical transformations. This methodology cannot yet offer control over the geometry of the enolate, hence the use of cyclic substrates.

Scheme 1.11: Buchwald's approach to generating quaternary carbons



Drawing inspiration from the seminal work of W. C. Still,[27] we sought to utilize the preferential conformation of macrocyclic enolates to construct quaternary carbon centers. Using an anionic oxy-Cope rearrangement we stereoselectively generate a tetrasubstituted macrocyclic enolate (**1.55**) which can then be alkylated with a variety of electrophiles. The facial selectivity is governed by the conformational preferences of the macrocycle in which the enolate is embedded, which through a novel manifold gives the opposite diastereoselectivity then what was predicted.

Scheme 1.12: Our approach to generating quaternary centers



2

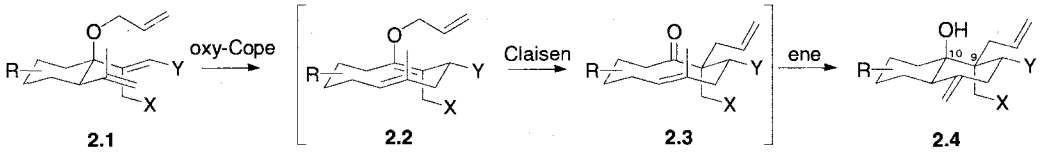
An Oxy-Cope/Claisen/Ene Approach to Teucrolivin A

The Oxy-Cope/Claisen/Ene Reaction

The Barriault lab has long been interested in cascading pericyclic reactions that impart significant molecular complexity in a single step.[28] Several processes that have been thoroughly investigated include the oxy-Cope/ene reaction[29] and the oxy-Cope/ene/Claisen reaction.[30] Both have been applied to various total synthesis, with the oxy-Cope/ene cascade being used as a key step in the construction of (-)-arteannuin M.[31] The oxy-Cope/ene/Claisen reaction served as the foundation for an attempt at the synthesis of the antibiotic tetrodecamycin.[32]

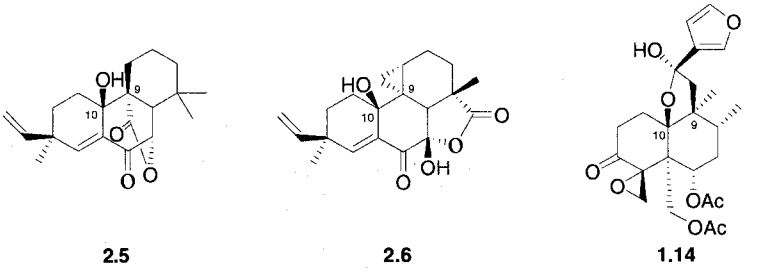
The oxy-Cope/Claisen/ene reaction was developed to address several challenging synthetic issues, including the stereoselective formation of quaternary carbon centers in a congested structure, at the same time moving from a relatively simple starting material to a complex product.[21] This reaction cascade is summarized in Scheme 2.1. It was found that heating allylic ethers typified by general structure **2.1** in a microwave reactor induced an oxy-Cope reaction to give enol **2.2**, which then underwent a second [3,3]-shift, giving **2.3**. This intermediate is situated to undergo a transannular ene reaction, which ultimately affords the final product in the sequence, *trans*-decalin **2.4**. Reaction yields are good to excellent, and excellent diastereoselectivity is often obtained.

Scheme 2.1: Overview of the oxy-Cope/Claisen/ene cascade



Of note is that this reaction generates a quaternary center at C9 adjacent to a tertiary alcohol at C10, if we follow diterpene nomenclature. This structural sub-element is present in a variety of terpenes, including LL-S491β[33] (**2.5**), myrocin C (**2.6**)[34] and the previously discussed clerodane diterpene teucrolivin A (**1.14**). As such, the oxy-Cope/Claisen/ene cascade represents a potentially powerful, and general, approach to these types of natural products and has been used in several attempted total synthesis.[35]

Figure 2.1: LS-491β, myrocin C and teucrolivin A



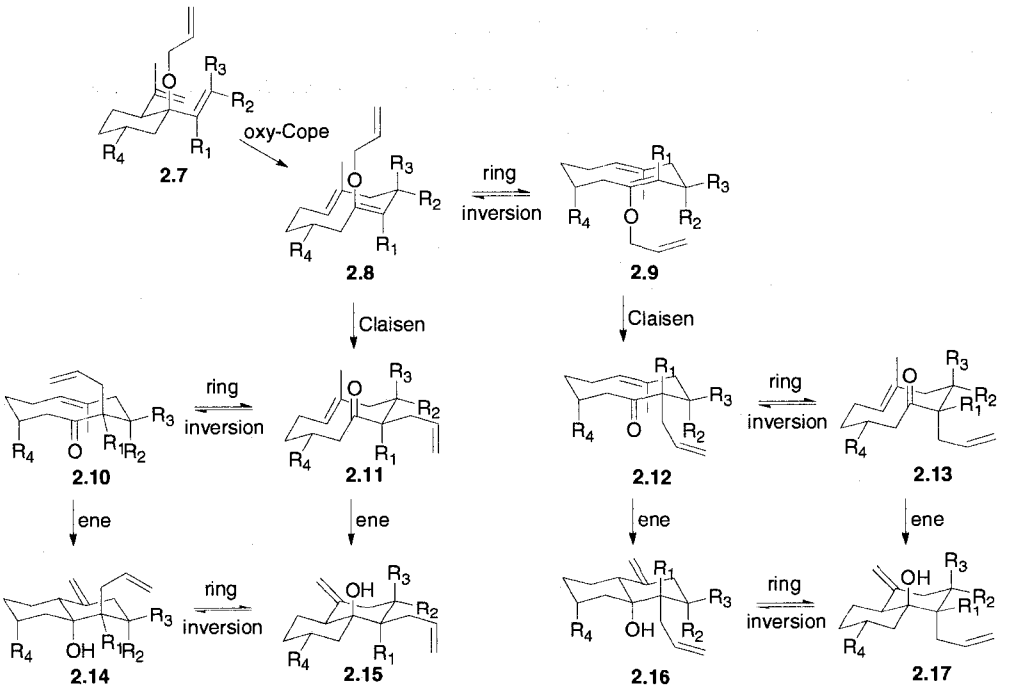
The most remarkable aspect of this pericyclic cascade is the high level of diastereoselectivity that is observed. For compounds of type **2.7**, there are four possible diastereomeric products. The excellent diastereoselectivity of this process can be explained by taking a closer look at the reaction mechanism, where we find that the diastereoselection is ultimately dictated by the conformational preferences of macrocyclic intermediates **2.8** and **2.11**.

The initial oxy-Cope reaction proceeds through a chair-like transition state, affording intermediate **2.8**. From this macrocycle two reaction manifolds are possible: a ring inversion to give diastereomeric macrocycle **2.9**, or a Claisen rearrangement to give

intermediate **2.11**. Experimental and theoretical evidence both point towards the energy barrier for the Claisen rearrangement being much lower then that for the ring inversion, hence the ring inversion is not observed and there is no occurrence of products **2.16** and **2.17**.[36]

From **2.11** we can obtain ene product **2.15** directly, or **2.11** can again undergo a ring inversion to **2.10**, which gives ene product **2.14**. For this phase of the reaction, the ring inversion is fast and the ratio of products **2.14**:**2.15** is governed by the Curtin-Hammett principle, meaning the product ratio is a direct reflection of the transition state energy difference for the two ene reactions. For the majority of our substrates, we observe compounds structurally related to **2.15** as the major product of the reaction, although there are exceptions.

Scheme 2.2: Detailed mechanism of the oxy-Cope/Claisen/ene reaction



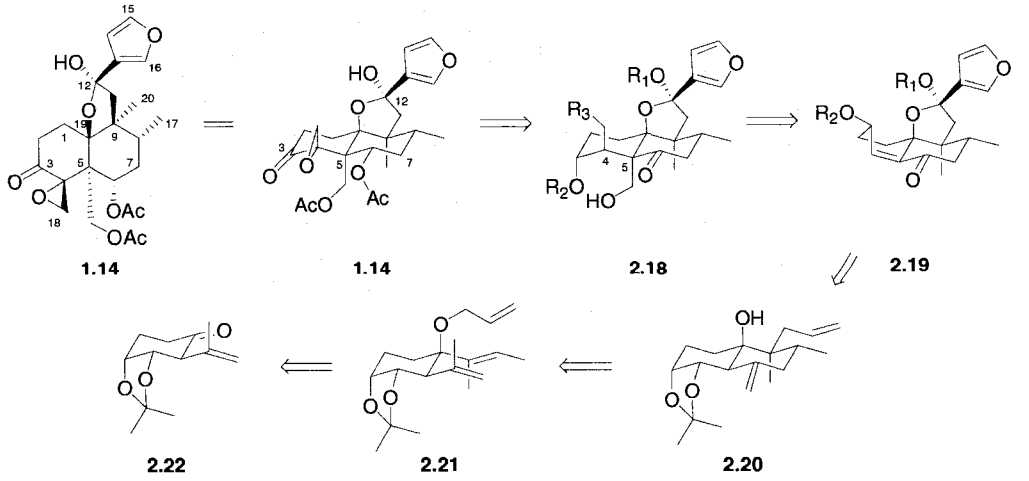
With a thorough understanding of the oxy-Cope/Claisen/ene reaction in hand, we now look towards its application to the total synthesis of teucrolivin A.

Initial Retrosynthetic Analysis

A closer inspection of teucrolivin A (**1.14**) unveils several significant challenges when considering a synthesis. It was proposed that the decalin core could be established with the oxy-Cope/Claisen/ene cascade. Hand in hand with this comes the issue of establishing the stereogenic centers not controlled by the pericyclic cascade, namely those at C4, C6 and C12. Attention must also be paid to the high level of oxygenation; adequate functionality must be present to introduce this oxygenation. Finally, the tandem process does not generate the quaternary center at C5.

Teucrolivin A (**1.14**) can ultimately be derived from intermediate **2.18** through a series of functional group interconversions. The quaternary carbon at C5, not installed by the tandem reaction, can arise from a 1,4-addition/enolate alkylation sequence performed upon **2.19**, whose parent compound is **2.20**. This *trans*-decalin is the product of an oxy-Cope/Claisen/ene reaction, revealing **2.21** as a key intermediate, which should be easily accessible from ketone **2.22**, a compound that has been applied to previous total synthesis in our lab.

Scheme 2.3: Initial retrosynthetic analysis of teucrolivin A



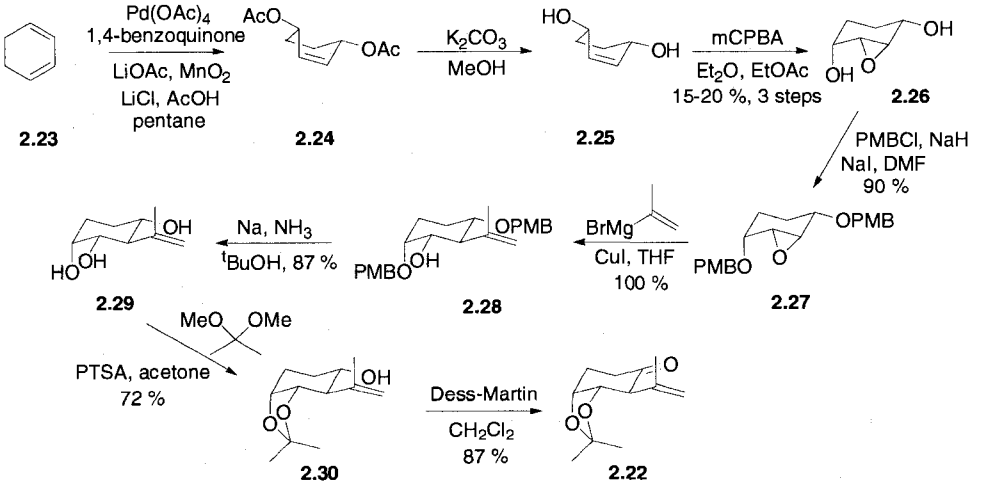
Synthesis of the Cyclohexanone

A Previously Developed Route to **2.22**

Cyclohexanone **2.22** was initially developed in a bid to synthesize the natural product vinigrol using an oxy-Cope/Claisen/ene reaction.[35a] Having met failure using this approach, this ketone was subsequently abandoned. However, it reemerged as a viable synthetic intermediate en route to teucrolivin A.

Starting from 1,3-cyclohexadiene, diol **2.26** is readily available in 3 steps according to the procedure of Simpkins and co-workers.[37] Protection of the alcohols proceeds smoothly, and a copper (I) mediated epoxide opening affords intermediate **2.28** in excellent yields. Deprotection using a Birch protocol and subsequent 1,2-diol selective protection of triol **2.29** gives cyclohexanol **2.30**, which is easily oxidized with Dess-Martin periodinane[38] to cyclohexanone **2.22**.

Scheme 2.4: Known approach to cyclohexanone ***2.22***

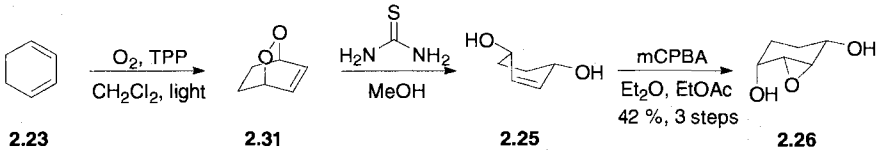


A Revised Approach

While the approach described is an acceptable route to cyclohexanone **2.22**, it suffers from several limitations, particularly when these reactions are performed on a large scale. With a palladium catalyst loading for the oxidation of 1,3-cyclohexadiene of 5 %, it creates a cost limitation when done using large quantities. Also, while the Birch deprotection of the PMB ethers is quite facile, it is difficult to conduct on scale up.

Searching for alternative oxidation protocols, it was discovered that an analogous transformation of **2.23** to **2.25** can be accomplished by using a [4+2] cycloaddition of 1,3-cyclohexadiene with singlet oxygen, followed by cleavage of the peroxide bond.[39] After scanning several reactions it was determined that irradiating of a solution of 1,3-cyclohexadiene bubbled with oxygen in the presence of TPP (5,10,15,20-tetraphenyl-21H,23H-porphine) as a photosensitizer were the optimal conditions.[39a] The resulting endo-peroxide was readily cleaved using thiourea, giving **2.25**.[39a] As an added bonus, a two-fold increase in the overall yield of **2.26** was observed.

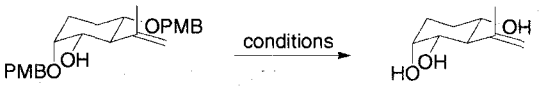
Scheme 2.5: A new synthesis of diol ***2.26***



2.23 **2.31** **2.25** **2.26**

The cleavage of PMB ethers is most often accomplished using catalytic hydrogenation. This however is not possible with compound **2.28** due to the presence of olefin functionality, hence the use of Birch conditions in the original route. As a result, a series of alternative protocols were investigated that are chemoselective for PMB ether cleavage, and are summarized in Table 2.1. In the end, the Birch conditions were replaced by treating the bis-PMB ether **2.28** with iodine in refluxing MeOH,[40] affording **2.29**.

Table 2.1: Conditions for the deprotection of PMB ethers



2.28 **2.29**

Conditions	Yield
Na, NH_3, -78 °C to room temperature	87 %
H_2, NH_4CO_2[41]	no reaction
$NaCNBH_3$, $BF_3{\cdot}Et_2O$[42]	55 %
I_2, MeOH, reflux	85 %

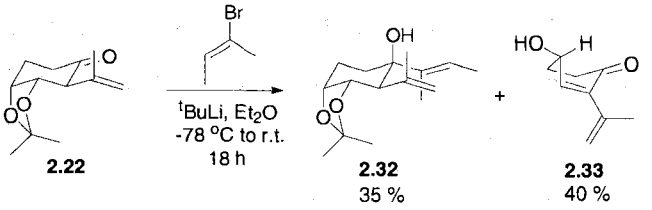
An attempt was also made to go directly from **2.26** to **2.29** using the cuprate conditions developed for converting **2.27** to **2.28**. This could be accomplished by using a large excess of reagents, or by an initial deprotonation of **2.26** with a sacrificial Grignard reagent, phenylmagnesium bromide. Surprisingly the reaction was successful, albeit with a low yield of 28 %, which in the end was not useful.

Alkylation of the Cyclohexanone

Summary of Conditions

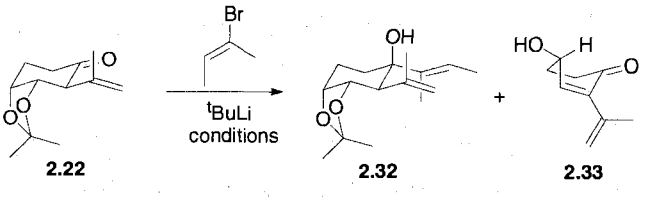
The alkylation of ketone **2.22** with a nucleophile derived from E-2-bromo-2-butene[43] proved to be a surprisingly difficult transformation. In fact, after extensive testing the best yield that could be obtained was only 35 % of the desired product **2.32** along with the generation of unwanted side product **2.33** arising from a deprotonation/elimination. A summary of conditions employed in an attempt to improve this yield are found in Table 2.2.

Scheme 2.6: Alkylation of cyclohexanone ***2.22***



2.22 | **2.32** 35 % | **2.33** 40 %

Table 2.2: Conditions for the alkylation of cyclohexanone ***2.22***



2.22 | **2.32** | **2.33**

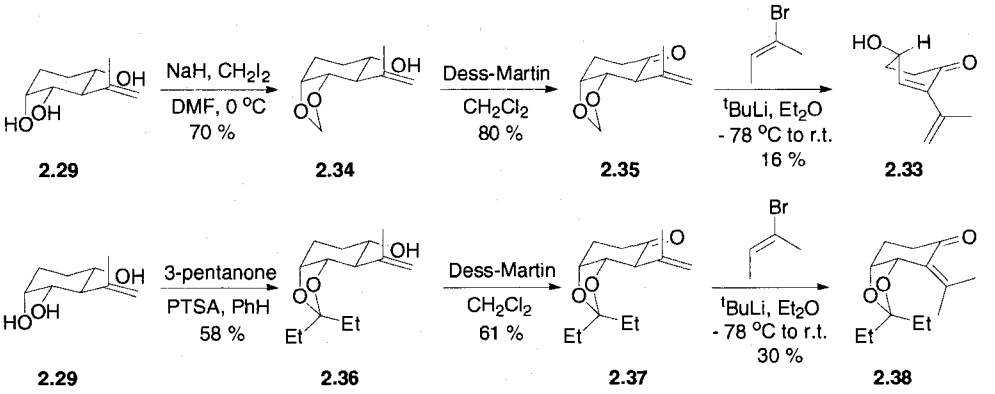
Conditions	Yield (%)			Comments
	2.22	**2.32**	**2.33**	
Et_2O, -78 °C, 4 h	62	10	-	**2.33** observed, not isolated
Et_2O, -78 °C to rt, 18 h	-	35	40	-
Et_2O, -78 °C to rt, 18 h	-	35	38	$NaHCO_3$ quench/workup
THF, -78 °C to rt, 18 h	89	-	-	-
dioxane, -40 °C to rt, 18 h	-	-	-	decomposition
DME, -78 °C to rt, 18 h	-	28	53	-
Et_2O, $CeCl_3$, -78 °C to rt, 18 h	50	22	9	-
THF, $CeCl_3$, -78 °C to rt, 18 h	-	-	-	decomposition
Et_2O, $MgBr_2 \cdot Et_2O$, -78 °C to rt, 18 h[44]	96	-	-	$MgBr_2 \cdot Et_2O$ added after Li-halogen exchange
Et_2O, HMPA, -78 °C to rt, 18 h	-	12	-	extensive decomposition
Et_2O, $LiClO_4$, -78 °C to rt, 18 h[45]	-	-	-	decomposition
Et_2O, $^nBu_4NBr$, -78 °C to rt, 18 h[45]	-	31	40	-
Et_2O, TMEDA, -78 °C to rt, 18 h	-	29	46	-

Unfortunately, it was not possible to suppress the decomposition pathways in this transformation. Et_2O was found to be the only acceptable solvent, although the use of DME did allow for the formation of **2.32** in slightly diminished yield. Lithium anions were the only nucleophiles with sufficient reactivity to give 1,2-addition, and the use of any additives was generally found to be deleterious.

Modification of the Ketal

It was thought that steric congestion about the carbonyl function of **2.22** might be playing a part in the low recovered yields of **2.32**. As expected, the nucleophile attacks *anti* to the isopropenyl side chain (see Figure 2.2), but it may be that the acetonide protecting group for the 1,2-diol may be partially shielding one face of the ketone, diverting some of the starting material into the enolization pathways. To evaluate this idea we replaced the acetonide with ketals that were both more and less bulky then an acetonide, as illustrated in Scheme 2.7.

Scheme 2.7: Modification of the ketal protecting group



Surprisingly, exchanging the acetonide protecting group for either a methylidene or 3-pentylidene protecting group[46] and subsequent exposure to the optimized alkylation procedure did not yield the alkylation product. Ketone **2.35** extensively decomposed, with the only isolable product being the deprotonation/elimination product **2.33**, while

ketone **2.37** afforded isomerization product **2.38**, also arising from an initial deprotonation.

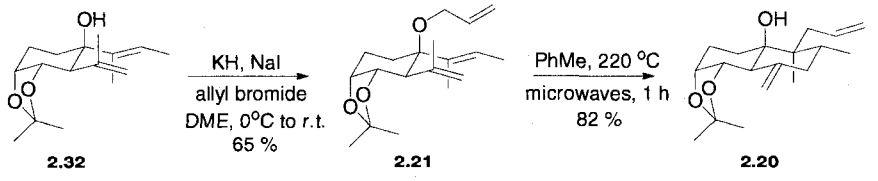
While the methylidene acetal would facilitate alkylation, it also would make the acidic proton leading to an enolate more accessible. If the deprotonation becomes even faster relative to alkylation, the decomposition pathways will become even more prominent. The 3-pentylidene acetal may be bulky enough to stop all approach of the nucleophile on the ketone, but still allows for deprotonation to occur. With a poorer leaving group this leads to a conjugated product rather then elimination. It seems the acetonide protecting group is uniquely suitable for allowing the alkylation of **2.22** to occur.

First Approach Towards Teucrolivin A

Applying the Oxy-Cope/Claisen/Ene Cascade

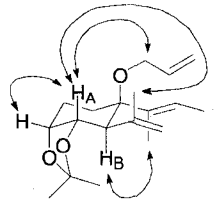
The simple allylation of tertiary alcohol **2.32** produced the starting material **2.21** for the pivotal oxy-Cope/Claisen/ene cascade. As we expected, the microwave-assisted thermal pericyclic cascade gave the desired *trans*-decalin **2.20** in good yield as a single diastereomer. The relative stereochemistry of both **2.21** and **2.20** was proven by 1D and 2D NMR experiments.

Scheme 2.8: The oxy-Cope/Claisen/ene reaction of ***2.21***

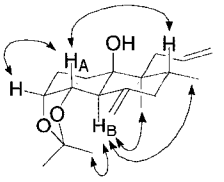


2.32 **2.21** **2.20**

Figure 2.2: Key NOESY correlations for ***2.21*** *and* ***2.20***



J_{A-B} = 9.8 Hz, trans coupling
2.21



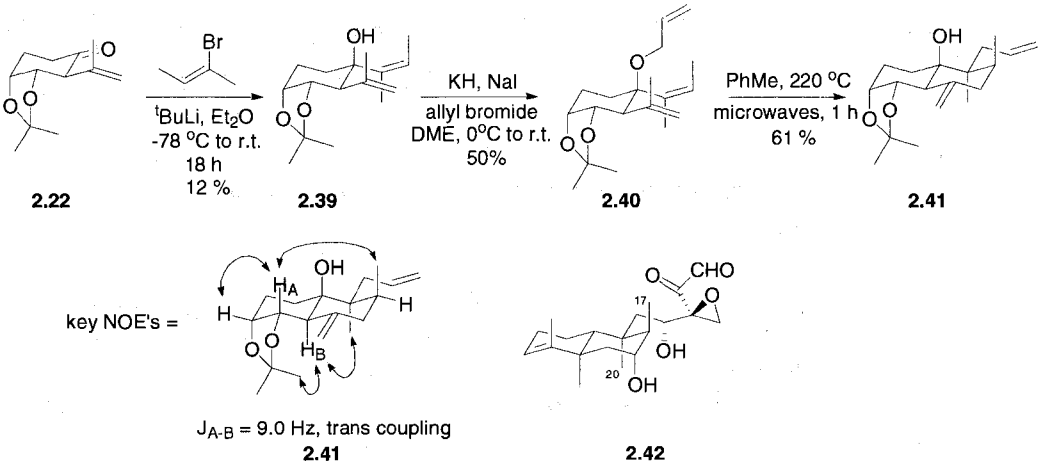
J_{A-B} = 9.0 Hz, trans coupling
2.20

An Additional Oxy-Cope/Claisen/Ene Cascade

During the course of our studies we also had an opportunity to alkylate ketone **2.22** with Z-2-bromo-2-butene to determine whether or not the pericyclic cascade could be used to construct the clerodane skeleton with an *anti* arrangement between C17 and C20. This is exemplified in the clerodane diterpene terpentecin[47] (**2.42**), and represents a much rarer structural orientation compared to those with a *syn* relationship between C17 and C20.

Using the optimized conditions described above, the alkylation with Z-2-bromo-2-butene does proceed, but in poor yield, probably due to the increased steric demands of the nucleophile. Allylation of tertiary alcohol **2.39** proceeds smoothly, as does the pericyclic cascade, giving decalin **2.41** in moderate yields, successfully accessing those systems with an *anti* C17-C20 relationship. It should be noted that yields for these transformations have not been optimized.

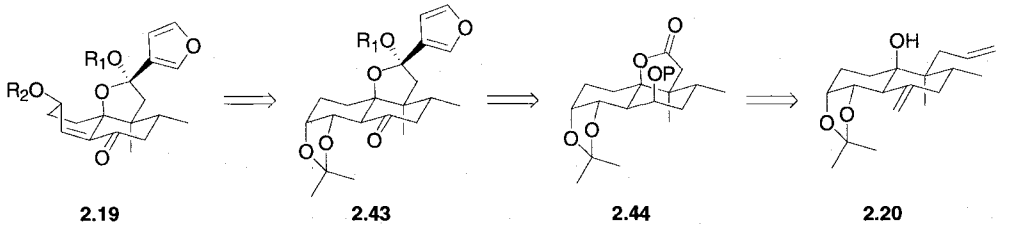
Scheme 2.9: Constructing an anti C17-C20 relationship



Attempted Installation of the Furanyl Hemiacetal

Having successfully executed the crucial *trans*-decalin forming transformation, we could begin to think about introducing the more advanced functionalities seen in teucrolivin A. It was thought that an intermediate needed for late-stage functional group installation (**2.19**) could be formed from **2.43**, which in turn arises from an alkylation of lactone **2.44**.

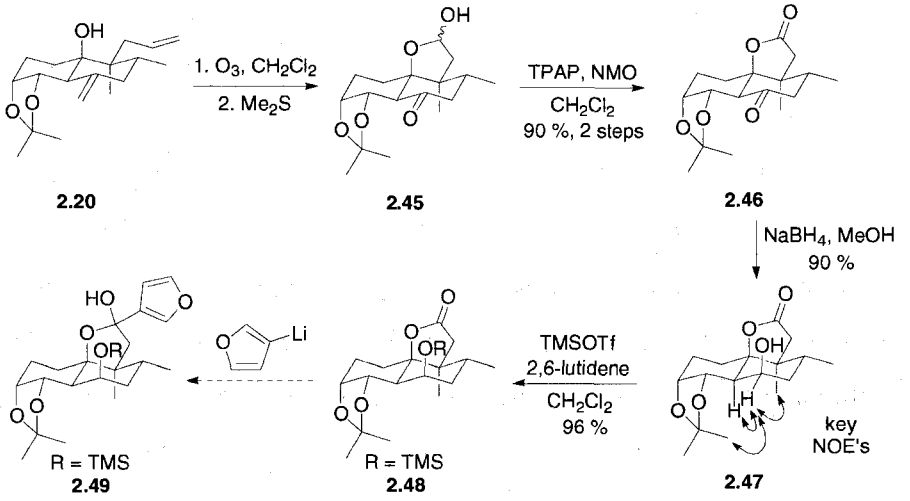
Scheme 2.10: Retrosynthetic approach to installing the 3-furanyl moiety



Decalin **2.20** was treated with ozone, and the resulting crude lactol was immediately oxidized with TPAP and NMO, affording lactone **2.46**. Selective reduction of the ketone functionality using $NaBH_4$ and protection of the resulting axial secondary alcohol gave trimethylsilyl ether **2.48**. Much to our dismay, we were met with failure when we attempted to alkylate lactone **2.48** using nucleophiles derived from 3-bromofuran.[48] This

could be due to competing enolization of the lactone, or it may be a result of the congested steric environment of the lactone. In fact, attempts to protect secondary alcohol **2.47** using larger protecting groups, or using less reactive reagents was also not successful, pointing towards a crowded steric environment.

Scheme 2.11: Towards installing the furan

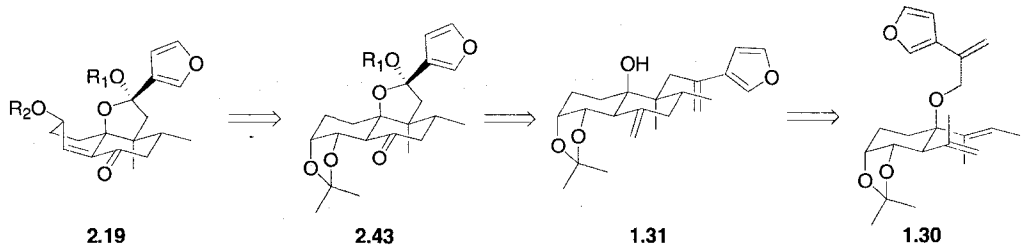


Second Approach Towards Teucrolivin A

Retrosynthetic Analysis

In light of the failure to install the requisite furanyl functionality on to intermediate **2.48**, we needed to devise a new strategy to install this key fragment. Instead of incorporating the furan after the oxy-Cope/Claisen/ene reaction, we postulated that we could overcome this problem by inserting the furan prior to the pericyclic cascade. Proposed intermediate **2.43** could arise from an oxidative olefin cleavage of **1.31**; the resulting ketone such generated should spontaneously cyclize to the lactol **2.43**. In turn, **1.31** arises as the product of the oxy-Cope/Claisen/ene reaction of **1.30**. To access this compound, we simply have to allylate tertiary alcohol **2.32** with a substituted allyl bromide whose structure is highlighted in red.

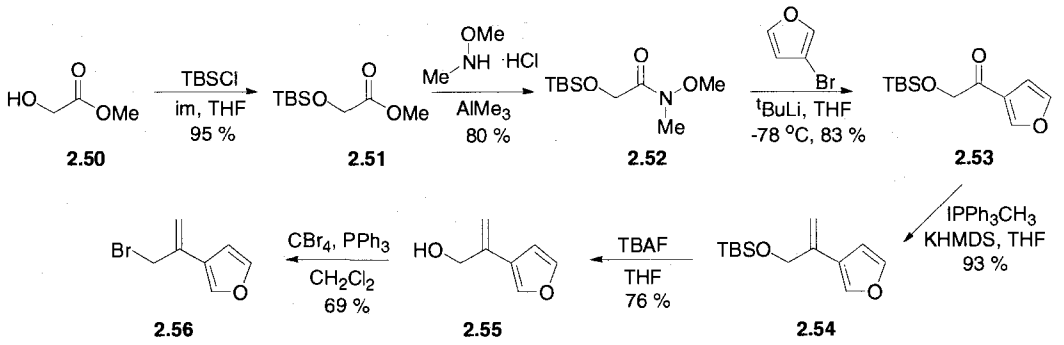
Scheme 2.12: A new retrosynthetic approach to install the furan



Synthesis of a Substituted Allyl Bromide

This substituted allyl bromide is readily prepared from commercially available methyl glycolate in six simple steps. Protection of the primary alcohol as the TBS ether and conversion of the ester to a Weinreb amide (**2.52**) proceeds smoothly. Alkylation with a nucleophile derived from 3-bromofuran and subsequent Wittig olefination are also quite facile, giving **2.54**. Deprotection and bromination ultimately afford the required allyl bromide **2.56**, a surprisingly unstable compound that cannot be stored.

Scheme 2.13: Synthesis of the substituted allyl bromide

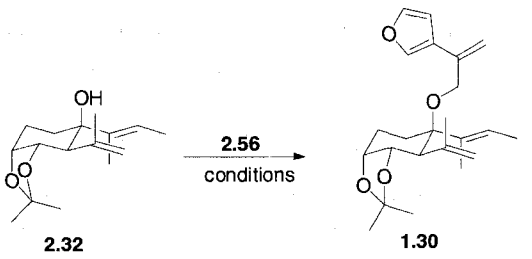


Development of a New Allylation Reaction

Unfortunately, subjecting tertiary alcohol **2.32** to the allylation conditions that work well with allyl bromide were not ideal for use with the substituted allyl bromide **2.56**. While the desired product **1.30** was formed, the yield was generally low and wildly variable. A

variety of different reaction parameters were then investigated to see if we could obtain a reproducible and acceptable yield of **1.30**.

Table 2.3: Conditions screened for allylation with ***2.56***



2.32 **1.30**

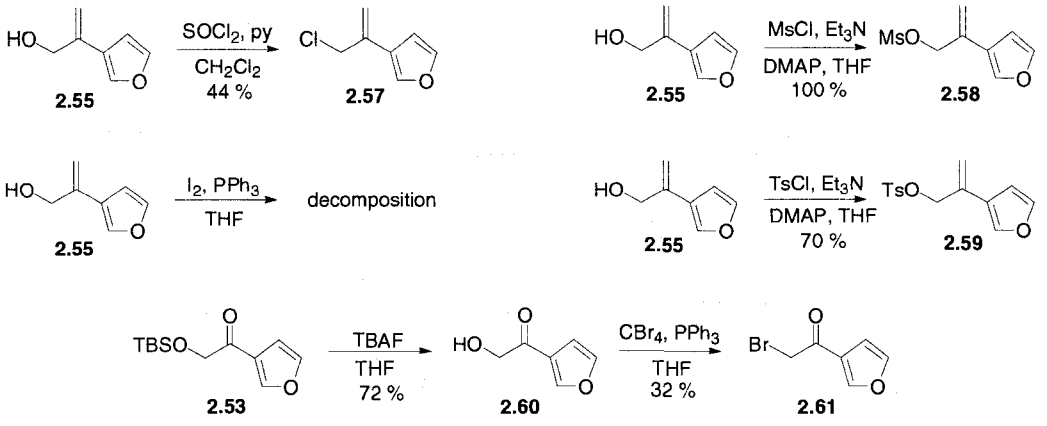
Entry	Conditions[a]	Yield (%)	Comments
1	KH, NaI, DME, 0 °C, 16 h	5-35	
2	KH, DME, 0 °C, 16 h	40	
3	KH, NaI, THF, 0 °C, 16 h	33	
4	KH, THF, 0 °C, 16 h	47	
5	KHMDS, DME, 0 °C, 17 h	12	66 % returned S.M.
6	KHMDS, THF, 0 °C, 16 h	19	57 % returned S.M.
7	NaH, THF, 0 °C, 16 h	-	79 % returned S.M.
8	NaH, DMF, 0 °C, 2 h	-	decomposition

[a]All reactions were allowed to warm to room temperature after approximately 4 hours, with the exception of entry 8

Whereas NaI is a crucial ingredient in the allylation of **2.32** with allyl bromide, it was found to be detrimental to the yield of **1.30**. This reaction proceeds quite slowly, and it is thought that compound **2.56** decomposes before it can react, which is accentuated by the *in situ* formation of the more reactive iodide. As well, prolonged exposure of **2.32** to KH in ethereal solvent results in the observation of anionic oxy-Cope derived side products before it can be allylated. While we did obtain an acceptable yield of **1.30** (entry 4), the self-decomposition of the starting material to some extent cannot be avoided due to the slow rate of reaction.

In another bid to improve the yield of the allylation, we exchanged the bromide for other leaving groups, hoping an electrophile of different stability and reactivity would hasten the allylation of the tertiary alcohol, or would not decompose over the course of the reaction. All of the new electrophiles synthesized, including the mesylate, were stable relative to the bromide. Unfortunately using them in place of the bromide did not improve the yield of the allylation, with yields in all cases being similar to or lower then that of the optimized conditions from Table 2.3.

Scheme 2.14: Synthesis of alternatives to allyl bromide ***2.56***



A New Pericyclic Cascade

With compound **1.30** in hand, regardless of the difficulties in developing an efficient allylation, the stage was set to try the oxy-Cope/Claisen/ene reaction. This represented the first example of such a reaction with functionalization at the 2-position of the allyl fragment.

Delightfully, microwave-accelerated heating of **1.30** did afford the desired compound **1.31**, but much to our surprise we also observed decalin **2.62**, an adduct whose type has not been previously documented in these reactions. Unfortunately this product formed in variable amounts depending on the run, and ultimately detracts from the yield of **1.31**,

from which it must arise. Surmising that trace acid in the reaction medium may be responsible for this undesired cyclization, we solved the problem by adding triethylamine to the reaction, which completely suppressed the occurrence of this side reaction and actually improved the efficiency of the overall transformation. We obtained an X-ray structure of **2.62** which, as it arises from **1.31**, proves the structure of the product of the pericyclic cascade.

Scheme 2.15: Oxy-Cope/Claisen/ene reaction with the substituted allyl fragment

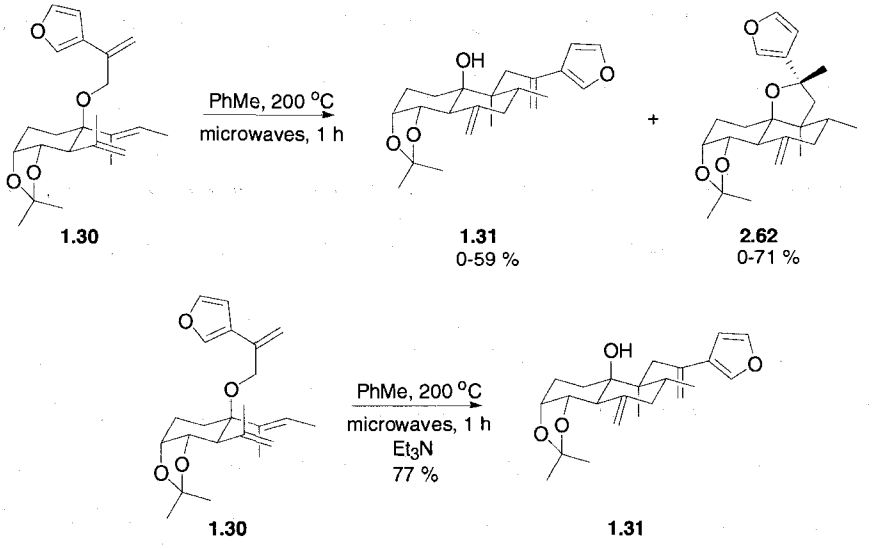
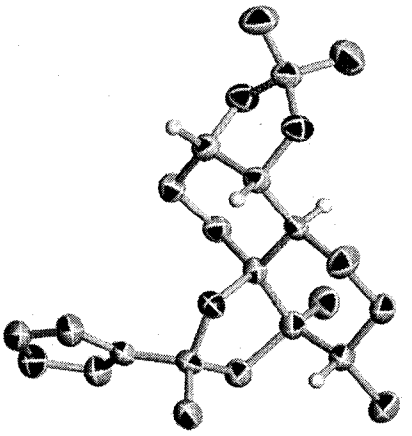


Figure 2.3: X-ray crystallographic structure of ***2.62***



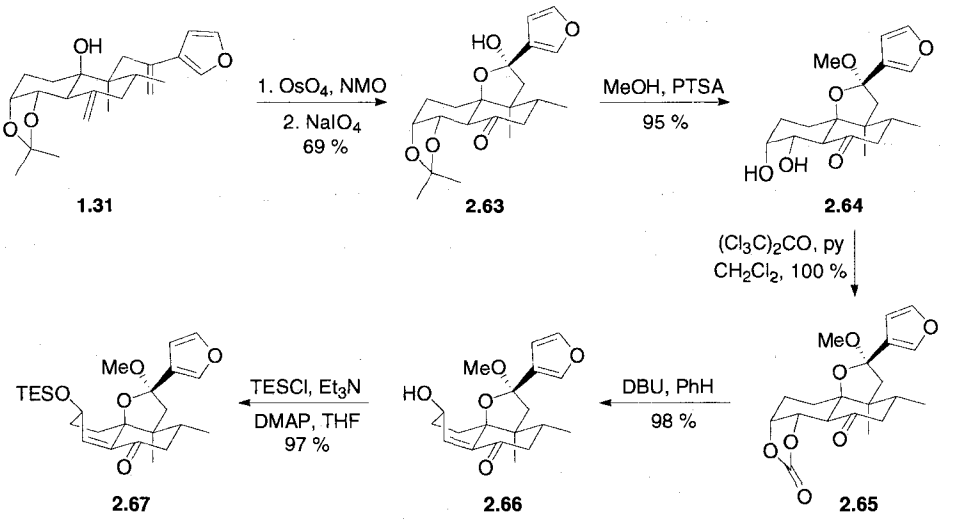
Attempts To Complete the Total Synthesis of Teucrolivin A

Having met success in establishing the core structure of teucrolivin A with the furan moiety now incorporated, we turned our attention to advancing the synthesis towards a compound resembling **2.19**, from which we hoped to install the remaining quaternary center at the ring junction.

Compound **1.31** is easily oxidized by a Lemieux-Johnson protocol giving hemiketal **2.63**. In this case, ozone causes degradation of the compound, presumably through undesired side reaction with the furan. Protection of the hemiketal as a mixed ketal by treatment with PTSA in MeOH also served to remove the acetonide protecting group,[49] which was desirable. At this point the orientation of the anomeric carbon in either **2.63** or **2.64** could not be confirmed by 2D NMR experiments, but as they arose under thermodynamic conditions it was assumed they were the same as that seen in the natural product.

As can be expected, the mixed ketal was extremely unstable in the presence of acid, such that even a mildly acidic workup would cause degradation. Treatment of the diol with triphosgene generated a carbonate[50] which upon exposure to DBU underwent an interesting E1CB elimination to afford the α,β-unsaturated ketone **2.66**. The secondary alcohol concurrently generated was protected as the triethylsilyl ether **2.67**. With this advanced intermediate now in place, the stage was set for installation of the quaternary center at the ring junction.

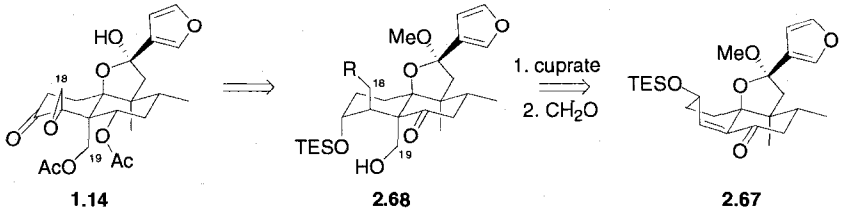
Scheme 2.16: Synthesis of advanced intermediate **2.67**



A 1,4-Addition/Enolate Alkylation Approach

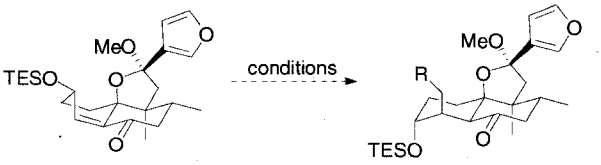
In addition to installing carbon C19 which will form the quaternary center at the ring junction, it is necessary to install the epoxide carbon C18, as seen in teucrolivin A (**1.14**). It was thought we could accomplish both goals from **2.67** by forming **2.68** in one step using a substituted cuprate to introduce functionality that would give a handle in install the C18 epoxide, and quenching with a formaldehyde equivalent to introduce an oxygenated C19.[51] It was proposed the 1,4-addition would occur *anti* to the silyl ether, thus the enolate quench would occur *anti* to this newly formed stereocenter, and the bulky mixed ketal to give **2.68**.

Scheme 2.17: Illustration of the 1,4-addition/enolate alkylation approach



Our initial attempts were directed towards finding conditions to induce the 1,4-addition. Our first bold attempts using a relatively complex procedure to add the hydroxymethyl anion equivalent[52] tributylmethoxymethoxystannane[53] were not successful, with only starting material being recovered in each case. This unfortunate trend continued even when the conditions were simplified to cause a 1,4-addition using a much less complex procedure and a simpler cuprate reagent. Because of the failure to observe the 1,4-addition, we never attempted a quench with a formaldehyde equivalent.

Table 2.4: Attempted conditions to induce the 1,4-addition



2.67 **2.69**

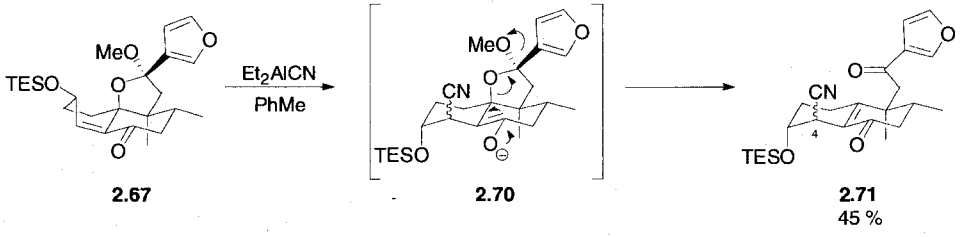
Entry	Nucleophile	Copper Source	Additives/Conditions[a]	Result
1	Bu_3Sn⌒OMOM	CuBr·DMS	^{n}BuLi, ^{i}PrMgCl, TMSCl, THF, 4 h	S.M.
2	Bu_3Sn⌒OMOM	CuBr·DMS	^{n}BuLi, ^{i}PrMgCl, TMSCl, THF, 24 h	S.M.
3	Bu_3Sn⌒OMOM	CuCN	^{n}BuLi, ^{i}PrMgCl, TMSCl, THF, 6 h	S.M.
4	Bu_3Sn⌒OMOM	CuI	^{n}BuLi, ^{i}PrMgCl, TMSCl, THF, 6 h	S.M.
5	BrMg⌒=	CuBr·DMS	TMSCl, THF, 6 h	S.M.
6	BrMg⌒=	CuCN	TMSCl, THF, 6 h	S.M.
7	BrMg⌒=	CuCN	THF, 6 h	S.M.
8	BrMg⌒=	CuI	THF, 6 h	S.M.

[a]All reactions preformed at -78 °C

During the course of this investigation we postulated the 1,4-addition might benefit from activation by a Lewis acid. Despite the potential problem with the mixed ketal, we decided to proceed with the treatment of **2.67** with Et_2AlCN, a reagent known to act as a Lewis acid while providing nucleophilic cyanide.[54] While the 1,4-addition of cyanide was a success, we did not obtain our desired product, instead isolating the fragmentation product **2.71** as an unassigned 1.6:1 mixture of diastereomers at C4. This fragmentation

presumably results from a collapse of the enolate generated (**2.70**) after the 1,4-addition and represents a potentially fatal flaw to any route involving a similar enolate. It is also possible that **2.67** decomposes through an oxonium intermediate generated by reaction of the acetal with the Lewis acidic Et_2AlCN.

*Scheme 2.18: Treatment of **2.67** with Et_2AlCN*

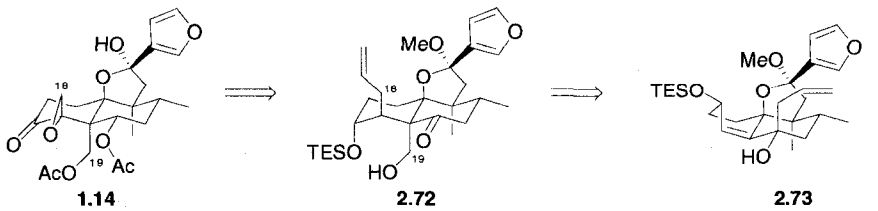


2.67 **2.70** **2.71**
45 %

An Anionic Oxy-Cope/Enolate Alkylation Approach

Concurrent with the development of our first approach to install carbons C18 and C19 we also envisioned that this outcome could be attained by the use of an anionic oxy-Cope/enolate alkylation sequence. This was conceived before the results concerning the treatment of **2.67** with Et_2AlCN discussed above were noted. We thought that **2.73**, available from ketone **2.67**, should upon an oxy-Cope rearrangement generate an enolate that could be trapped by a formaldehyde equivalent to give **2.72** with both C18 and C19 in place.

Scheme 2.19: Illustration of the anionic oxy-Cope/enolate alkylation approach

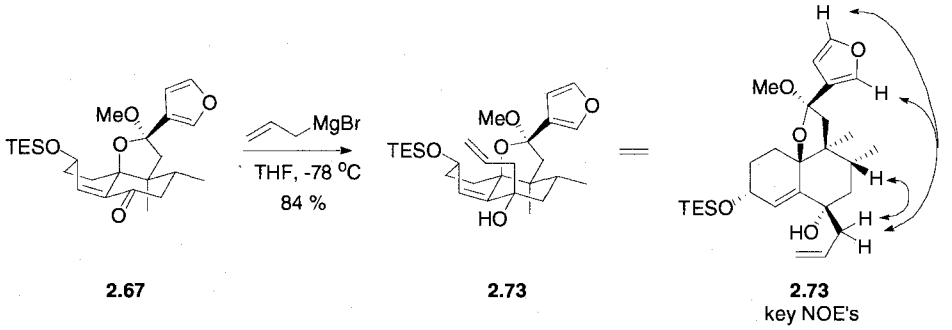


1.14 **2.72** **2.73**

The alkylation of **2.67** with allylmagnesium bromide afforded the desired 1,2-addition product **2.73** in good yield. Both the orientation of the newly formed stereocenter and the

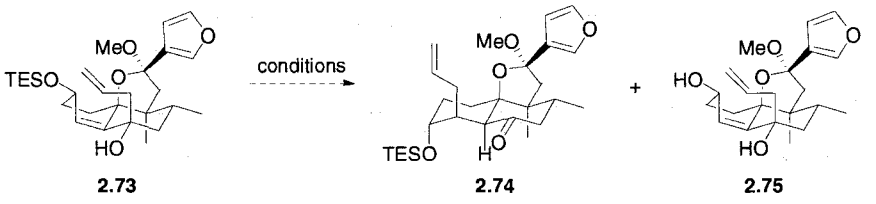
orientation of the anomeric carbon were clearly discernable by NOE analysis, with the alkylation occurring *anti* to the silyl ether and the anomeric carbon having the same configuration as that seen in teucrolivin A (**1.14**). Again, we thought it would be prudent to find conditions that would induce the anionic oxy-Cope rearrangement of **2.73** prior to quenching with a carbon electrophile.

Scheme 2.20: Alkylation and confirmation of stereochemistry



2.67 **2.73** **2.73** key NOE's

*Table 2.5: Attemped anionic oxy-Cope rearrangement of **2.73***



2.73 **2.74** **2.75**

Entry	Conditions	Yield			Comments
		2.73	**2.74**	**2.75**	
1	KHMDS, DME, reflux	-	-	64	-
2	KHMDS, THF, reflux	-	-	48	partial decomposition
3	KH, 18-crown-6, THF, reflux	-	-	-	decomposition
4	KH, THF, reflux	49	-	29	-

It quickly became apparent from the few conditions attempted that the TES protecting group was not robust enough to withstand the relatively harsh anionic oxy-Cope rearrangement conditions, so it was decided to replace it with the more stable TBS

protecting group. This was partly chosen because many standard protocols to install more robust protecting groups were incapable of protecting the secondary alcohol **2.66**, and TBSOTf, which we employed, is both commercially available and readily prepared. Tertiary alcohol **2.77** could then be used to test anionic oxy-Cope conditions to give **2.78**, which should be easily adapted to form the desired compound **2.79**.

Scheme 2.21: Exchange to a TBS protecting group

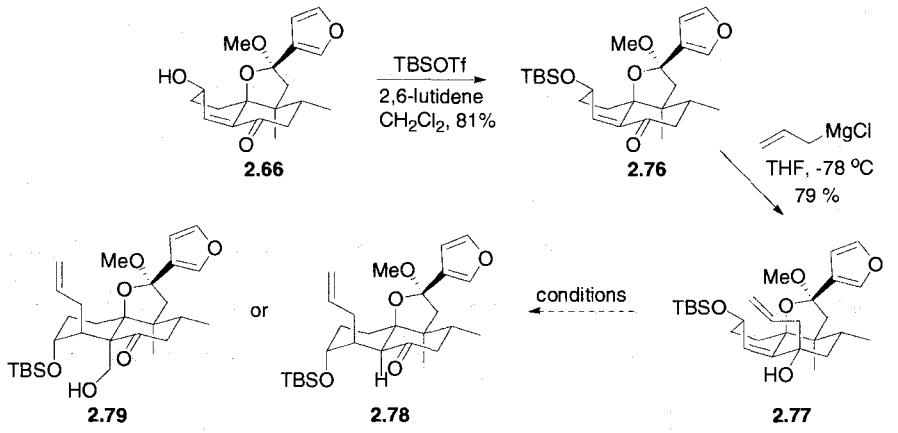


Table 2.6: Attempted anionic oxy-Cope rearrangement of **2.77**

Entry	Conditions	Yield			Comments
		2.77	2.78	2.75	
1	KHMDS, DME, reflux	-	-	62	
2	KHMDS, THF, reflux	88	-	-	
3	KH, 18-crown-6, DME, reflux	-	-	-	decomposition
4	KH, DME, reflux	94	-	-	
5	KH, 18-crown-6, THF, reflux	-	-	-	decomposition
6	KH, reflux	91	-	-	

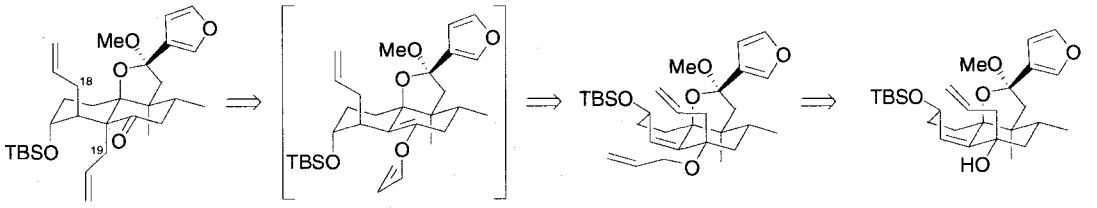
In the end, exchanging the protecting group did not facilitate the occurrence of an anionic oxy-Cope rearrangement. Treatment of **2.77** with typical conditions usually resulted in no reaction or decomposition of the starting material, although one instance of

desilylation was observed (Entry 1). In light of the discovered of enolate degradation in other examples discussed above this, approach was abandoned. It may be however that the decomposition pathways begin by fragmentation of the enolate generated from the anionic oxy-Cope rearrangement.

An Oxy-Cope/Claisen Rearrangement

With reaction pathways invoking an enolate now not considered viable, we turned our attention to other tactics not involving such an intermediate. Keeping true to the theme of cascading pericyclic reactions to construct teucrolivin A, it was thought an oxy-Cope/Claisen reaction would be able to install both C18 and C19. Compound **2.80** would arise from the Claisen rearrangement of **2.81**, which in turn is the product of the [3,3]-shift of **2.82**. Thermally, these two transformations should happen sequentially in the same reaction vessel. While selectivity issues between the two allyl fragments may arise in subsequent steps, it would achieve the goal of constructing the quaternary center at the ring junction.

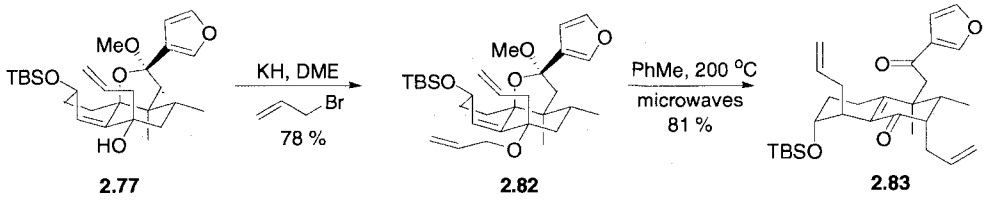
Scheme 2.22: Retrosynthetic analysis for the oxy-Cope/Claisen cascade



2.80 **2.81** **2.82** **2.77**

After a routine allylation of **2.77**, the resulting compound **2.82** was subjected to the same microwave-accelerated thermal conditions used for our other pericyclic cascades. The product **2.83** which was isolated as the exclusive product from the reaction was completely unexpected.

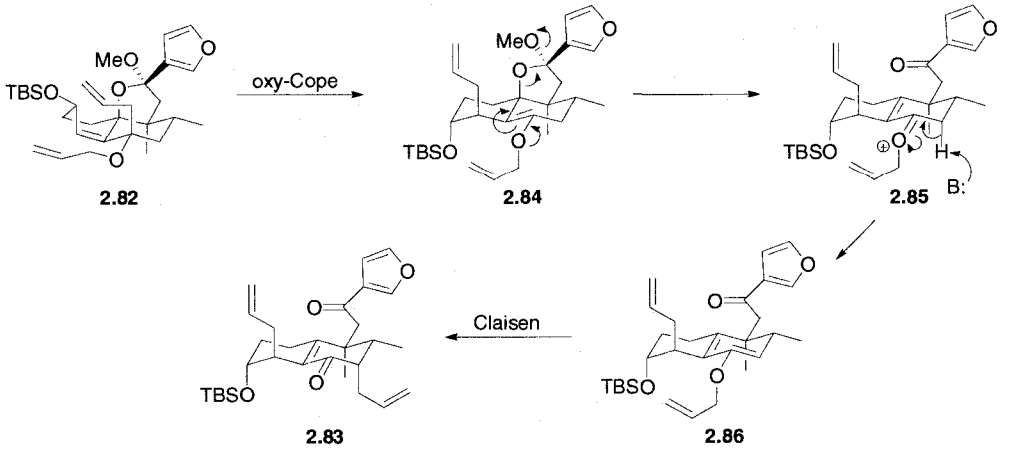
Scheme 2.23: Generation of an unexpected product



2.77 **2.82** **2.83**

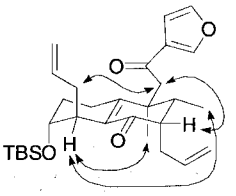
It is proposed that **2.83** arises first from an oxy-Cope rearrangement of **2.82** to give intermediate **2.84**. Rather then undergoing the desired Claisen rearrangement, this intermediate eliminates methoxide by generation of oxonium **2.85**. A proton abstraction generates another intermediate (**2.86**) which is then situated to undergo a different Claisen rearrangement to give the observed product **2.83**. While the results involving an enolate leading to elimination can be rationalized by the combination of a good leaving group departing under the influence of a strong electron push, similar reactivity is not expected when the enolate is replaced by an enol ether. The domination of an unfavorable process like this is most likely the result of a very crowded steric environment at the ring junction were the desired product **2.80** be produced and, anionic fragmentation pathways aside, suggests that the installation of the quaternary center will be very difficult from any of our intermediates originating from the oxy-Cope/Claisen/ene cascade.

*Scheme 2.24: Proposed mechanism for the transformation of **2.82** to **2.83***



2.82 **2.84** **2.85** **2.83** **2.86**

Figure 2.4: Key NOESY correlations proving the structure of ***2.83***



2.83

Conclusions

A route was developed and improved to synthesize a precursor for the oxy-Cope/Claisen/ene cascade in pursuit of the synthesis of teucrolivin A. The pericyclic cascade was a success, but it was shown that the furanyl moiety seen in the natural product is best installed prior to the tandem reaction. Once this goal was accomplished the synthesis was advanced to a point where we could address the installation of a key quaternary center at the decalin ring junction. A variety of approaches were implemented without success due to competing elimination reactions and a crowded steric environment at the decalin ring junction.

3

A Challenging Pericyclic Cascade

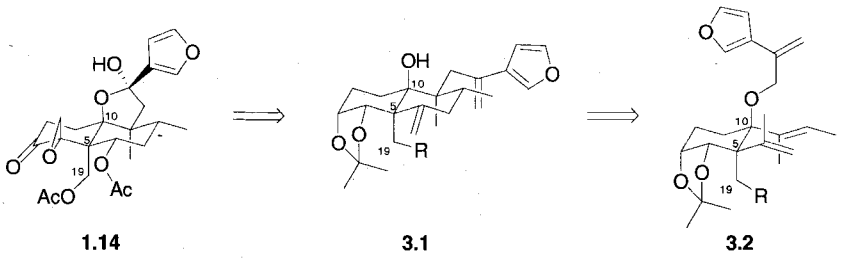
Introduction

As it stood, the chemistry developed en route to the synthesis of teucrolivin A was efficient at constructing the *trans*-decalin core of the natural product, but it was clear that this approach was limited in its capacity to grant access to the quaternary center at the ring junction. Rather then installing this challenging structural motif after the oxy-Cope/Claisen/ene reaction, we turned our attention to its incorporation prior to this key step.

Initial Observations

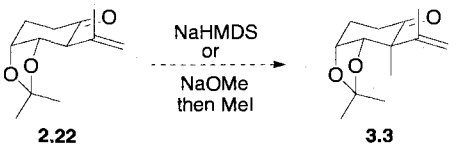
The obvious method to do this would be to simply modify our existing synthesis from the start to include the desired carbon, which ideally would bear some functionalization interchangeable to the acetate at C19 seen in teucrolivin A (**1.14**). The natural product would arise from *trans*-decalin **3.1**, which in turn originates from **3.2** via the oxy-Cope/Claisen/ene reaction. It is in this transformation that we are entering unknown territory as the reaction has never been studied when the substrate bears a quaternary center (C5) adjacent to the tertiary ether (C10).

Scheme 3.1: Retrosynthetic concept for a pre-existing quaternary center



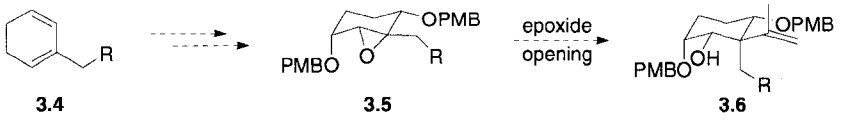
The simplest route by which we could incorporate the desired quaternary center would be via the simple alkylation of **2.22**. Unfortunately, though somewhat expected, a test reaction to convert **2.22** to **3.3** was unsuccessful due to the almost immediate decomposition of the starting material upon treatment with base.

Scheme 3.2: A simple solution to the problem



A closer inspection of our synthetic pathway to compound **2.22** reveals that adapting the chemistry to start with an appropriate 2-substituted 1,3-cyclohexadiene such as **3.4** is not easily accomplished. The first issue arises with the availability of such starting materials, which cannot be readily purchased and are only available through multi-step synthesis in mediocre yields.[55] Secondly, several of the developed transformations are unlikely to yield the same outcome with the inclusion of this new functionality, for example the opening of epoxide **3.5** would not be expected to afford desired compound **3.6**. These issues prompted us to undertake a model study of the oxy-Cope/Claisen/ene reaction of substrates with an existing quaternary center as to evaluate the feasibility of this approach prior to beginning a seemingly complex synthesis of a compound similar to **3.2**.

Scheme 3.3: Difficulties in an adapted synthetic route

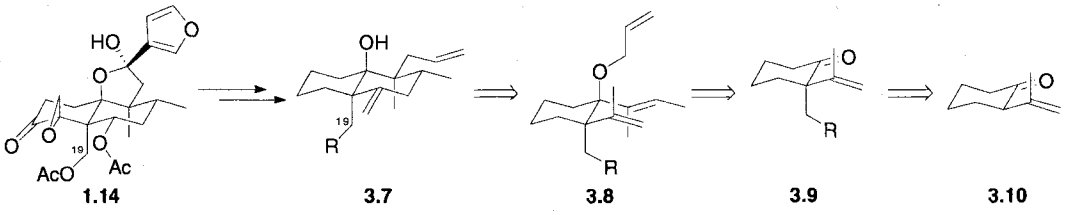


3.4 **3.5** **3.6**

Proposed Model Study

We wished to evaluate the simplest substrates that could be directly transposed onto the core structure of teucrolivin A (**1.14**). Stripping the core of all functionality except for that needed in the tandem reaction, we arrive at compound **3.7**, where R is a functional group interchangeable with the acetate ester at C19 in the natural product. **3.7** is the tandem reaction product of **3.8**, which should be readily available from **3.9** by an alkylation/allylation sequence. Ketone **3.9** will arise from a simple alkylation of **3.10**, a compound easily prepared from cyclohexene oxide.[41]

Scheme 3.4: Retrosynthetic analysis for the model study



1.14 **3.7** **3.8** **3.9** **3.10**

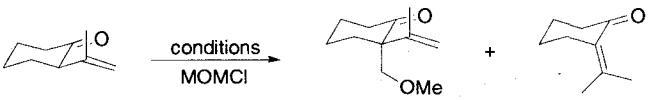
Preparation of Substrates and Initial Oxy-Cope/Claisen/Ene Investigations

A Methoxymethyl Substituted Quaternary Center

With a variety of R groups to choose from in the model study, we decided that selecting a group that mimics the oxygenation at C19 seen in teucrolivin A would be appropriate. To this end we decided to use MOMCl as the electrophile in the alkylation of **3.10**, which gives ketone **3.11**. Regioselectivity aside, the main difficulty with this alkylation is the suppression of a competing conjugation of the olefin with the ketone to give **3.12**, which

arises from the same enolate needed for the alkylation. A survey of the conditions employed trying to achieve this goal is shown in Table 3.1.

*Table 3.1: Alkylation of **3.10** with MOMCl*

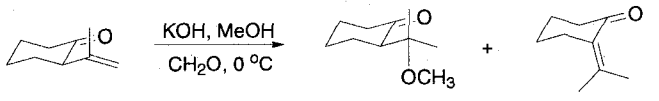


3.10 **3.11** **3.12**

Entry	Conditions	Yield (%)		Comments
		3.11	**3.12**	
1	NaOMe, THF, 0 °C, 4 h	-	59	
2	NaOMe, THF, r.t., 16 h	4	55	
3	NaOMe, THF, reflux, 4 h	-	-	decomposition
4	NaOMe, Et_20, 0 °C, 4 h	-	62	
5	KH, Et_3B, THF, r.t.[56]	-	35	
6	NaHMDS, THF, r.t.	24	24	

An aldol reaction[57] between ketone **3.10** and formaldehyde was attempted, but it also gave mainly the conjugated product **3.12**, along with a product arising from the 1,4-addition of MeOH to **3.12**.

Scheme 3.5: An attempted aldol reaction

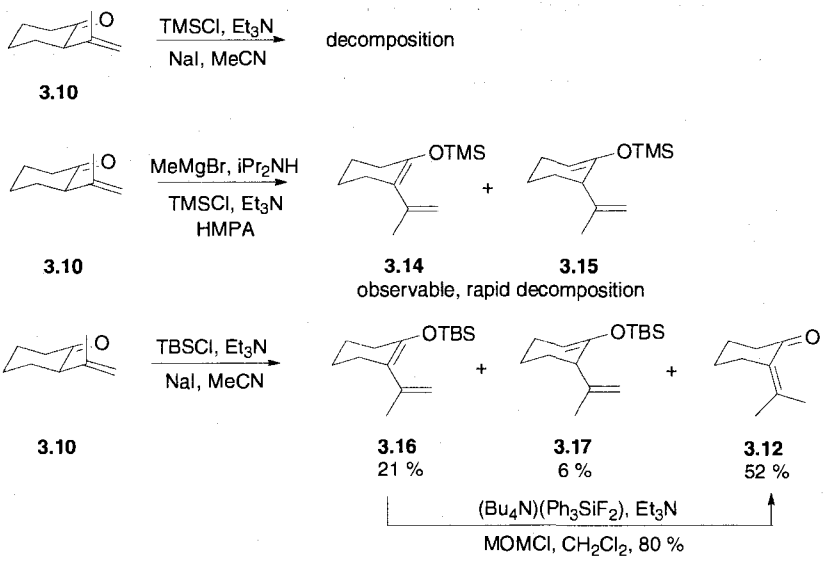


3.10 **3.13** 17 % **3.12** 37 %

These dismal results for the formation of **3.11** led us to investigate whether or not it would be possible to pre-form the desired enolate masked as a silyl enol ether, which could then be activated towards electrophilic attack by MOMCl. Again regioselectivity issues might be problem, but this approach may help suppress the formation of **3.12**. The

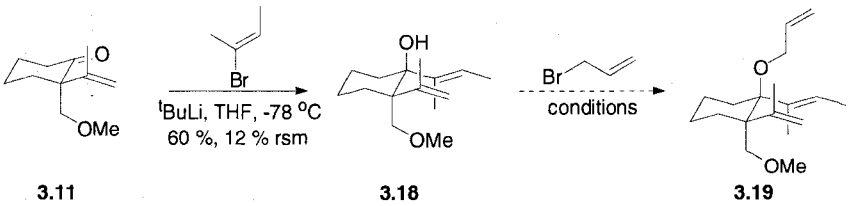
TMS enol ether[58] was not accessible; however, generation of the TBS enol ether was possible, albeit as a regioisomeric mixture of **3.16** and **3.17**, along with the conjugated product **3.12**. Unfortunately, the treatment of **3.16** with a dry fluoride ion source to activate the silyl enol ether in the presence of MOMCl once again gave only the conjugated product **3.12**.

Scheme 3.6: Generation of a silyl enol ether



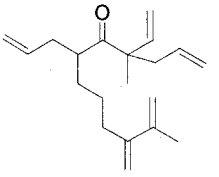
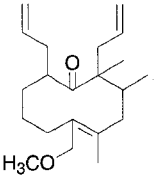
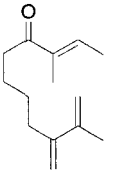
Despite these difficulties, we proceeded towards the tandem reaction precursor. Unlike previous alkylations using E-2-bromo-2-butene as a nucleophile, the transformation of **3.11** to **3.18** was quite facile. The desired allylation of this tertiary alcohol did not fare as well; the reaction was plagued with difficulties, as seen in Table 3.2. Upon generation of the alkoxide after treatment with base, it seems to favor fragmentation pathways, or even anionic oxy-Cope rearrangement, rather then allylation. Compound **3.22** is the direct product of fragmentation. Compound **3.20** arises from the double alkylation of **3.22** and **3.21** is the result of a rather unexpected anionic oxy-Cope/double alkylation sequence. Even the use of trichloroacetimidate, known as an effective allylation reagent with molecules that are base-sensitive resulted in fragmentation.

Scheme 3.7: Alkylation and attempted allylation



3.11 3.18 3.19

Table 3.2: Conditions for the attempted allylation

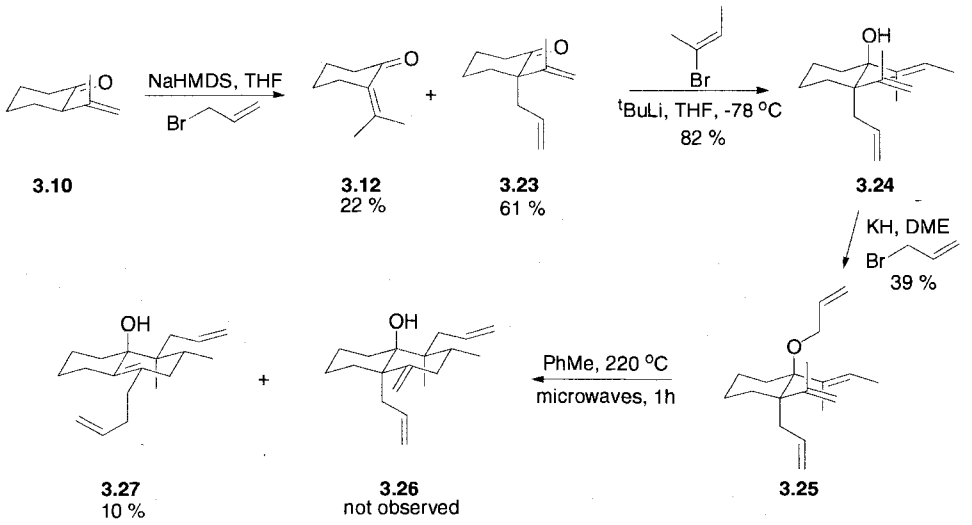
Entry	Conditions	Yield (%)			Structure of Other
		3.18	3.19	Other	
1	KH, THF, 0 °C, 4 h	89	-	-	-
2	KH, DME, 0 °C, 1 h	29	-	39	 **3.20**
3	KH, DME, reflux, 1 h	-	-	19	 **3.21** **3.20** isolated in 42 %
4	KHMDS, THF, 0 °C, 1 h	18	-	44	 **3.22**
5	KHMDS, DME, 0 °C, 1 h	-	-	53	**3.20**
6	NaH, DME, 0 °C to rt, 18 h	98	-	-	-
7	NaH, DMF, 0 °C to rt, 16 h	92	-	-	-
8	^{n}BuLi, THF, 0 °C to rt, 16 h	96	-	-	-
9	LiHMDS, DME, 0 °C to rt, 17 h	94	-	-	-
10	allyl tricholoroacetimidate, TfOH (no allyl Br)	-	-	33	**3.22**

An Allyl Substituted Quaternary Center

The results presented above suggest that it will not be possible to replace the methoxy functionality in **3.18** with any other group that can act as a leaving group, as the same fate will be met upon attempted allylation. Therefore, in the initial quaternary center generating reaction is was decided to replace the MOMCl electrophile with allyl bromide, which would yield an allyl substituted quaternary center. This functionality can be transformed, albeit with a little more effort, into the C19 –OAc seen in teucrolivin A, and will not be an issue during the allylation step.

The overall sequence proceeded a little more smoothly then the analogous transformation using the methoxymethyl substrate. The alkylation of **3.10** using allyl bromide in combination with the optimized conditions previously developed gave **3.23** in a reasonable yield along with some conjugated product **3.12**. The alkylation to give **3.24** also proceeded in good yield and as expected, the allylation of the tertiary alcohol was a success. With the pericyclic cascade precursor in hand, it was submitted to our typical reaction conditions. Amid a very complex mixture, the only isolable product was that of a different pericyclic cascade, compound **3.27**. The desired *trans*-decalin **3.26** was not observed.

Scheme 3.8: Oxy-Cope/Claisen/ene attempt using an allyl substituted quaternary center



Decalin **3.27** must arise from an oxy-Cope/Claisen/ene/Cope rearrangement. **3.26**, the desired product in this scenario, is set to undergo a Cope rearrangement after it has formed. We did recognize this possibility at the outset, but thought that the cascade may stop at the desired product. Despite this, the observation of **3.27** strongly suggests that the oxy-Cope/Claisen/ene reaction is feasible with a pre-formed quaternary center in place were we to use an alternative to the allyl fragment as the desired product **3.26** is an intermediate in the formation of **3.27**.

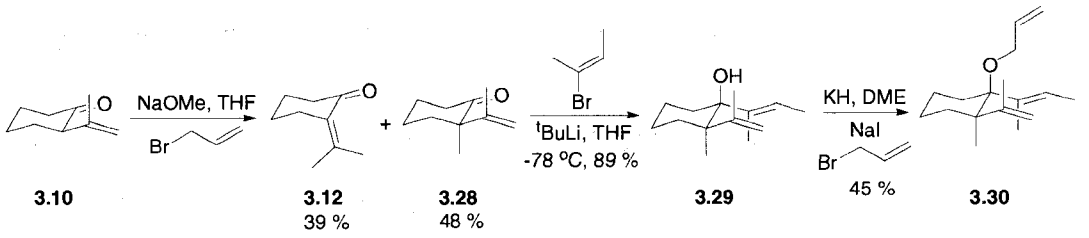
A Methyl Substituted Allyl Fragment

In order to continue our evaluation of this particular oxy-Cope/Claisen/ene reaction, it was decided to simplify the study even more by using only a methyl substituted quaternary center. This still allows for an assessment of the effect of the quaternary center in the pericyclic cascade while eliminating the possibility of any undesired side reactions like those observed above.

The synthesis of ketone **3.28** was previously described by Clément and Barriault.[59] The alkylation with an E-2-bromo-2-butene derived nucleophile was once again facile, and

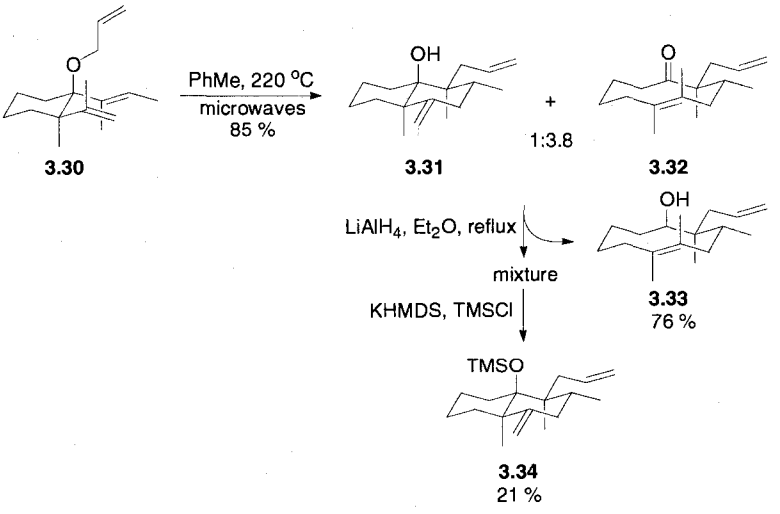
allylation using standard conditions afforded the desired tandem reaction precursor **3.30** in a moderate yield of 45 %.

Scheme 3.9: Synthesis of the oxy-Cope/Claisen/ene precursor



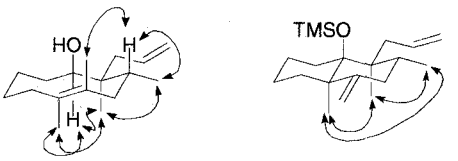
Subjection of **3.30** to microwave-accelerated tandem reaction conditions did afford the desired *trans*-decalin product **3.31**, however it was isolated as an inseparable 1 to 3.8 mixture with macrocyclic ketone **3.32**. This surprising outcome is significant in that it is the first time we have isolated one of the intermediate products from an oxy-Cope/Claisen/ene reaction. In this case, **3.32** results from only the oxy-Cope/Claisen portion of the pericyclic cascade.

Scheme 3.10: Oxy-Cope/Claisen/ene reaction with the methyl quaternary center



The structures of the two inseparable products from the pericyclic cascade were confirmed by chemical separation. Ketone **3.32** was reduced to secondary alcohol **3.33**, and as the reaction did not go to completion the remaining impure *trans*-decalin was separated by protection of the tertiary alcohol as its TMS ether, giving **3.34**. The characterization data was consistent with the proposed structures, and the relative stereochemistries were unambiguously proven by 2D NMR analysis.

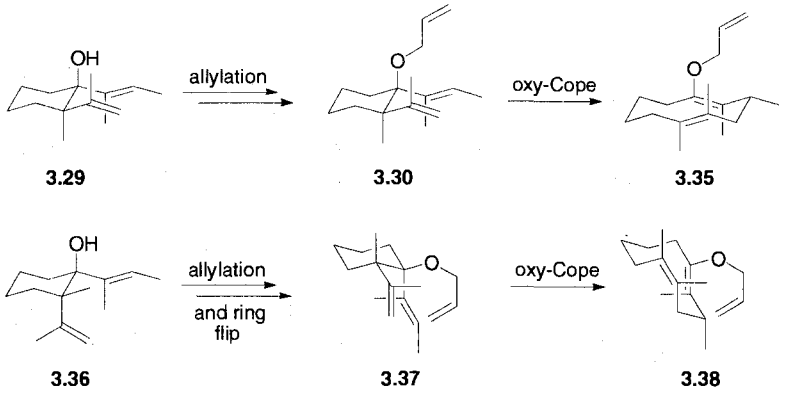
*Figure 3.1: Key NOESY correlations for compounds **3.33** and **3.34***



3.33 **3.34**

Furthermore, the proof of structure for **3.33** provides direct evidence as to the relative stereochemistry of tertiary alcohol **3.29**, which was previously impossible to prove. The oxy-Cope reaction, which generates the macrocyclic olefin, undoubtedly occurs via a chair-like transition state. Were the quaternary methyl to be *syn* with the ether as in compound **3.37**, the oxy-Cope rearrangement would yield a macrocyclic olefin (**3.38**) that was Z with respect to the macrocycle. In contrast, the E olefin with respect to the macrocycle (**3.35**) arises from a precursor (**3.30**) with the quaternary methyl *anti* to the allyl ether. As we observe an E olefin as the oxy-Cope/Claisen product (**3.32/3.33**), it must be that the initial alkylation occurs to give **3.29** with the methyl *anti* to the tertiary alcohol.

Scheme 3.11: Proof of relative stereochemistry for compound ***3.29***

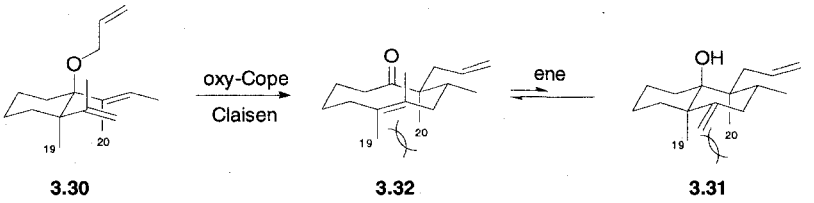


Investigating the Oxy-Cope/Claisen Reaction

We propose the incomplete tandem reaction results from steric interactions that are not present in previous substrates that have been tested in the oxy-Cope/Claisen/ene reaction. In both the macrocyclic product of the oxy-Cope/Claisen reaction **3.32** and the desired *trans*-decalin **3.31** there exists a significant 1,3-diaxial interaction between C19 and C20, which has never been present in previous investigations.

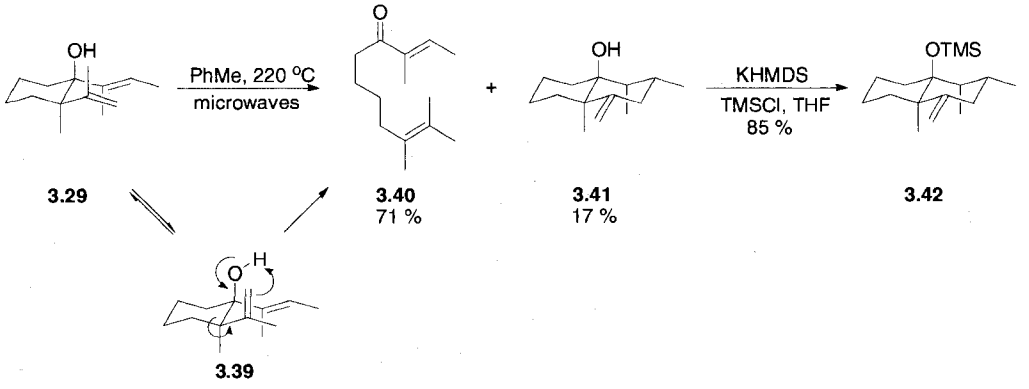
If these two products are in a thermodynamic equilibrium, one can propose that **3.32** is favored over **3.31**. While there is a 1,3-diaxial interaction in both products, carbons C19 and C20 are locked in place in compound **3.31** by virtue of the rigid decalin framework. Macrocycle **3.32** on the other hand has the flexibility to adopt a conformation where this 1,3-diaxial interaction is minimized, hence a ground state conformation of **3.32** would be favored over **3.31**. It could also be said that the 1,3-diaxial interaction twists the olefin such that **3.32** does not readily adopt a conformation that allows reaction through the ene manifold by creating a high energy transition state. In this case, longer reaction times would ultimately produce more of the *trans*-decalin **3.31**. However, resubjection of the mixture of **3.31** and **3.32** to the reaction conditions affords no change in the product ratio, supporting the argument that these products exist in a thermodynamic equilibrium. This is direct contradiction to examples without the methyl quaternary center where the ene reaction is known to be irreversible.[36]

Scheme 3.12: Steric effects in the oxy-Cope/Claisen/ene reaction



Further evidence of this steric interaction playing a deleterious role in the ene reaction of this substrate comes from performing an oxy-Cope/ene reaction on compound **3.29**. Upon heating tertiary alcohol **3.29**, we observe mainly the retro-ene product **3.40**, along with a small amount of the oxy-Cope/ene product **3.41**. Reactions performed on similar substrates without a methyl quaternary center always prefer the oxy-Cope/ene product, except when the allylic alcohol olefin contains electron donating substituents. As this is not the case with **3.29**, the retro-ene product **3.40** must be favored as a result of steric decompression favoring fragmentation of the 6-membered ring rather then forming a product (**3.41**) with a severe 1,3-diaxial interaction.

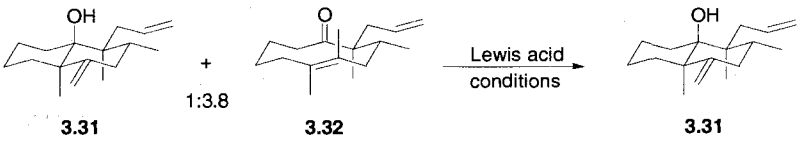
Scheme 3.13: An oxy-Cope/ene reaction



In order to force the reaction towards the desired product, we thought that treatment of the mixture of **3.31** and **3.32** with a Lewis acid might render the ene reaction irreversible while generating the desired product **3.31**. These results are summarized in Table 3.3.

Unfortunately, all examples either led to a return of the starting mixture with no change in the ratio of **3.31** to **3.32**, or the substrates decomposed.

*Table 3.3: Attempted Lewis acid-catalyzed ene reaction of mixture **3.31/3.32***

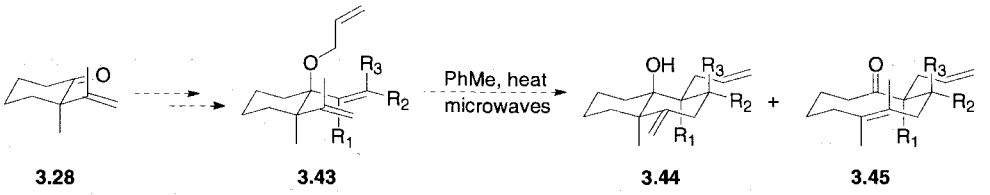


Entry	Lewis Acid	Conditions	Outcome
1	$SnCl_4$	CH_2Cl_2, -78 °C, 1 h	decomposition
2	$BF_3{\cdot}Et_2O$	THF, -78 °C, 7 h	starting material
3	$AlCl_3$	CH_2Cl_2, -78 °C, 0.25 h	decomposition
4	Et_2AlCl	CH_2Cl_2, -78 °C, 4 h	starting material
5	$TiCl_4$	CH_2Cl_2, -78 °C, 1 h	decomposition
6	TMSOTf	CH_2Cl_2, -78 °C, 0.5 h	decomposition
7	TMSOTf	DTBMP, -78 °C, 6 h	starting material
8	TfOH	CH_2Cl_2, -78 °C, 0.5 h	decomposition
9	$AuCl_3$	DCE, reflux, 8 h	starting material

Detailed Study of the Oxy-Cope/Claisen/Ene Reaction

Having established that the oxy-Cope/Claisen/ene reaction does not tolerate our substrate with a methyl quaternary center adjacent to the tertiary ether, we wondered what, if any, other structural features were playing a part in the reaction not being a success. To evaluate this idea, it was necessary to construct a series of compounds typified by general structure **3.43**. Each of R_1, R_2 and R_3 can be easily varied simply by using different nucleophiles in the initial alkylation of **3.28**.

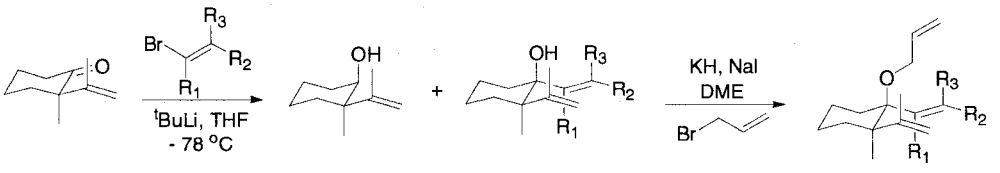
Scheme 3.14: General approach for evaluating the oxy-Cope/Claisen/ene reaction



Synthesis of Starting Materials

Synthesis of compounds **3.43** began with an alkylation of ketone **3.28**, usually with an organolithium derived from the appropriate vinyl bromide. The allylation was achieved using standard allylation conditions with potassium hydride, allyl bromide and catalytic sodium iodide. The majority of the yields described in Table 3.4 are not optimized.

Table 3.4: Synthesis of oxy-Cope/Claisene/ene starting materials

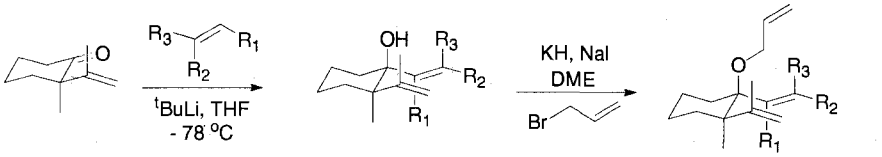


Entry	Substituents			Alkylation Yield (%)			Allylation Yield (%)	Comments
	R_1	R_2	R_3	3.28	3.46	3.47		
a	H	H	H	28	35	20	36	vinyl-MgBr gives only **3.46**
b	Me	H	H	-	-	48	28 (50 rsm)	-
c	H	Me	H	-	-	74	51	-
d	H	H	Me	29	-	51	43	-
e	Me	Me	H	-	-	89	45	our initial investigation
f	H	Me	Me	36	-	30	90	-
g	Me	H	Me	94	-	-	-	no alkylation

h	Me	Me	Me	95	-	-	-	no alkylation
i	Ph	H	H	-	-	72	-	decomposition on allylation

Also generated were a series of compounds where R_1 was a heteroatom substituent. Deprotonation of either ethyl vinyl ether or ethyl vinyl sulfide with a strong base and subsequent alkylation of **3.28** in the end afforded tandem reaction precursors **3.43j** and **3.43k** with R_1 as OEt and SEt respectively.

Scheme 3.15: Synthesis of some additional substrates



3.28

3.47j
R_1 = OEt, R_2, R_3 = H, 74 %
3.47k
R_1 = SEt, R_2, R_3 = H, 95 %

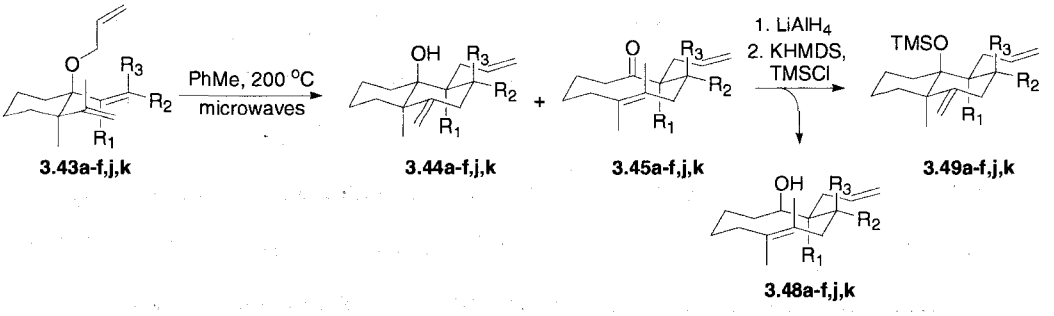
3.43j
R_1 = OEt, R_2, R_3 = H, 67 %
3.43k
R_1 = SEt, R_2, R_3 = H, 45 %

Oxy-Cope/Claiene/Ene Reaction

With a series of compounds containing the methyl quaternary center and variable functionality on adjacent fragments of the molecule now in hand, a survey of the scope and limitations of this reaction with these particular steric environments was initiated.

Each of the allyl ethers **3.43a-f**, **3.43j**, and **3.43k** were submitted to a set of standardized microwave-accelerated reaction conditions. In most cases after the pericyclic cascade there was a mixture of products that needed to be chemically separated in order for the products to be accurately characterized. **3.48** was isolated by the reduction of ketone **3.45** from the mixture of **3.44** and **3.45**. **3.49** was isolated by capping the teriary alcohol found in the remaining mixture of **3.44** and **3.45** from the initial reduction step. The results of this study are found in Table 3.5.

Table 3.5: A study of the oxy-Cope/Claisen/ene reaction



Entry	Substituents			Oxy-Cope/Claisen/Ene		Chemical Separation	
	R_1	R_2	R_3	Yield (%)	Ratio 3.44:3.45	Yield 3.48 (%)	Yield 3.49 (%)[1]
a	H	H	H	82	1.0 : 0.0	-	-
b	Me	H	H	94	1.0 : 4.3	65	13 (79)
c	H	Me	H	92	1.0 : 0.0	-	-
d	H	H	Me	84	1.0 : 1.0	34	44 (10)
e	Me	Me	H	85	1.0 : 3.8	76	8 (21)
f	H	Me	Me	complex mixture		-	-
j	OEt	H	H	94	1.0 : 1.4	40	30 (87)
k	SEt	H	H	91	1.0 : 7.0	70	8[2]

[1]First yield is that of the crude tertiary alcohol recovered as the byproduct of the reduction. The yield quoted in brackets is that of the TMS ether isolated from this crude mixture

[2]Separable as the tertiary alcohol from **3.48** – not protected as the TMS ether

These results suggest that the presence or absence of functionality at R_1 plays a significant role in determining the outcome of the oxy-Cope/Claisen/ene reaction. When there is no functionalization of the allylic ether olefin (**3.43a**, R_1, R_2, R_3 = H), or when we remove the R_1 methyl from our initially investigated substrate (**3.43c**, R_1, R_3 = H, R_2 = Me) we observe only the desired product of the pericyclic cascade. This result with **3.43c** also illustrates that the R_2 methyl has no bearing on the obtained product ratio as when it is the only substituent present the reaction goes to completion.

The role of the R_1 methyl is confirmed when the reaction was performed on a substrate with only substitution at R_1 (**3.43b**, R_1 = Me, R_2, R_3 = H). In this case we once again

obtain a mixture of **3.44b** and **3.45b**, with the macrocyclic product **3.45b** being obtained as the major product. It is the 1,3-diaxial interaction between the quaternary center methyl and the functionality at R_1 which are responsible for the observation of the oxy-Cope/Claisen product along with the desired product.

Suprisingly, when only R_3 is functionalized ($R_3 \neq H$), as in **3.43d,** we obtain a mixture of **3.44d** and **3.45d** (1 : 1). In this case, the observation of the macrocycle **3.45d** can be rationalized by the axial positioning of the methyl group in the decalin product. If the ene reation is under thermodynamic control, this unfavorable orientation must make it such that the stability of the *trans*-decalin **3.44d** is similar to that of the macrocycle **3.45d.** It could also be that for this substrate the reaction is kinetically controlled and the axial methyl group creates a high energy transition state that slows the rate of reaction. The mixture of **3.44d** and **3.45d** was not resubjected to the reaction conditions to prove either manifold.

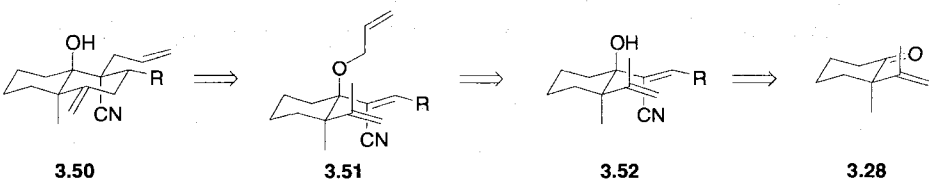
Finally, the results concerning the heteroatom substitution of R_1 deserve note. When R_1 is OEt, the ratio of **3.44** to **3.45** is almost 1 to 1, whereas the macrocycle **3.45** is favored when R_1 is equal to Me. One might propose that this is due to an acceleration of the ene reaction due to the presence of an electron-withdrawing substituent α to the enophile, hence promoting the ene portion of the cascade. This phenomenon however should have no bearing on the reaction outcome as it is assumed to be thermodynamically controlled. It is more likely a result of the smaller size of the ethyl ether (A-value = 0.9 kcal/mol) versus the methyl (A-value = 1.7 kcal/mol), giving a reduced 1,3-diaxial interaction. This is confirmed by exchanging the OEt for SEt. The larger A-value of the SEt functionality gives a corresponding increase in the amount of **3.45** relative to **3.44**.

The Next Generation of Substrate

The findings discussed above suggest that our pericyclic cascade can be persuaded to generate the oxy-Cope/Claisen/ene product rather then the intermediate macrocycle by reducing the size of the R_1 group. R_1 however must still be some functionality that can

be converted to a methyl group after the fact. Satisfying both of these requirements is the nitrile functionality; its conversion to a methyl is relatively straightforward, and its small size (A-value = 0.17 kcal/mol) relative to a methyl should encourage the formation of the *trans*-decalin over the macrocyclic ketone.

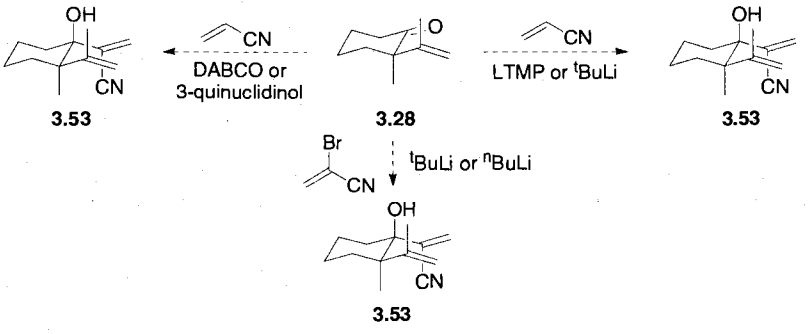
Scheme 3.16: Inclusion of the nitrile functionality



3.50 **3.51** **3.52** **3.28**

Unfortunately, nucleophiles that are appropriate for the conversion of **3.28** to compounds of structure **3.52** are not well known in the literature. In an effort to both test the feasibility of the use of a nitrile and to devise a route to compounds of type **3.52** we attempted to form **3.53** through various transformations. Simple deprotonation of acrylonitirle and alkylation of **3.28**, while known for acrylonitrile derivatives,[60] was unsuccessful. As expected, the transmetalation of 2-bromoacrylonitrile simply resulted in decomposition of the alkylating reagent, and the difficult Baylis-Hillman reaction[61] of acrylonitrile with ketone **3.28** was also met with failure.

Scheme 3.17: Attempted synthesis of tertiary alcohol ***3.52***



3.53 **3.28** **3.53** **3.53**

In a more roundabout fashion, we sought to apply a known procedure that converts hydroxyacetylenes into olefin dinitriles,[62] as per the conversion of **3.54** to **3.57**. The synthesis of tertiary alcohol **3.58**[59] has been previously described, and its halogenation[63] proceedes smoothly to give **3.59** in moderate yields. This route however was quickly terminated once the conditions[64] to convert **3.55** to **3.56** were not successful when applied to our substrates.

Scheme 3.18: Second attempt at inclusion of a nitrile functionality

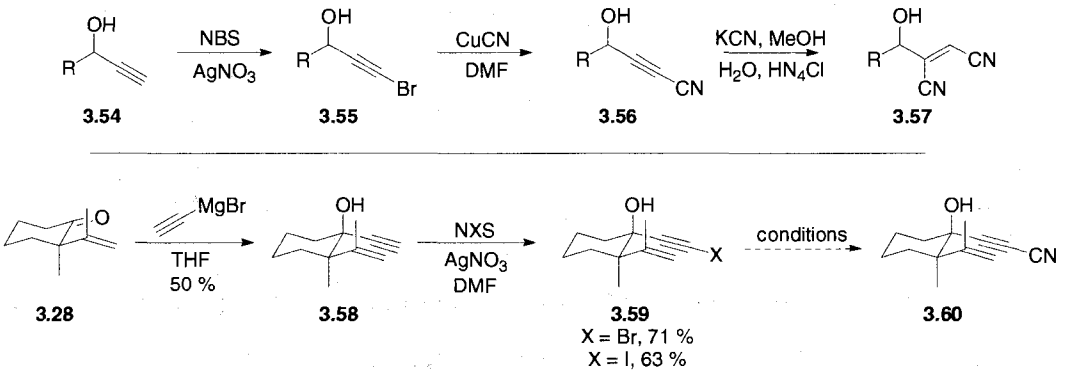


*Table 3.6: Conditions attempted for the conversion of **3.59** to **3.60***

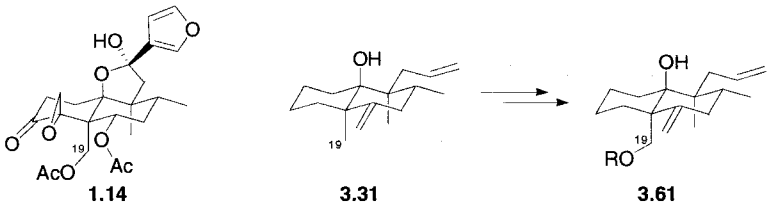
Entry	X	Conditions	Outcome
1	Br	CuCN, DMF, 50 °C	no reaction
2	Br	CuCN, DMF, H_2O, 50 °C	no reaction
3	Br	CuCN, $NH_2OH{\cdot}HCl$, DMF, 50 °C	no reaction
4	I	CuCN, DMF, 50 °C	no reaction
5	I	CuCN, DMF, H_2O, 50 °C	no reaction
6	I	CuCN, $NH_2OH{\cdot}HCl$, DMF, 50 °C	no reaction

Oxidation of the Quaternary Methyl Group

While we were not successful in incorporating the nitrile group in place of the methyl for our study of the oxy-Cope/Claisen/ene cascade, we were still interested in applying this

new class of substrate to the synthesis of teucrolivin A. In light of the difficulties encountered when trying to include any functionality at C19, we became interested in protocols which can oxidize methyl groups at decalin ring junctions. A survey of the literature shows that this type of reactivity, while rare, is known in steroid chemistry, and is typically accomplished by a transition metal-catalyzed oxidation of a C-H bond of the methyl group.[65] The desired outcome is illustrated in the conversion of **3.31** to **3.61**.

Scheme 3.19: Concept of methyl group oxidation



1.14 **3.31** **3.61**

This oxidation cannot be performed on the product of the tandem cascade directly; **3.31** must be adequately functionalized for such a reaction to occur. The preparation of the oxidation precursor is detailed in Scheme 3.20. Preparation of the precursor (**3.64**) occurs in a four step sequence through routine chemistry. Much to our dismay, the oxidation step was not a success. The overall oxidation protocol or **3.64** is itself a four step process,[66] but the first step, a palladium C-H insertion, failed hence subsequent steps were not attempted. Despite this failure, it does not signal the end of this approach as there are several other oxidation protocols that can be investigated. Incidentally, an X-ray crystal structure of **3.63** was obtained, providing further confirmation of the structure of the oxy-Cope/Claisen/ene reaction cascade product.

Scheme 3.20: Attempted oxidation of the quaternary methyl group

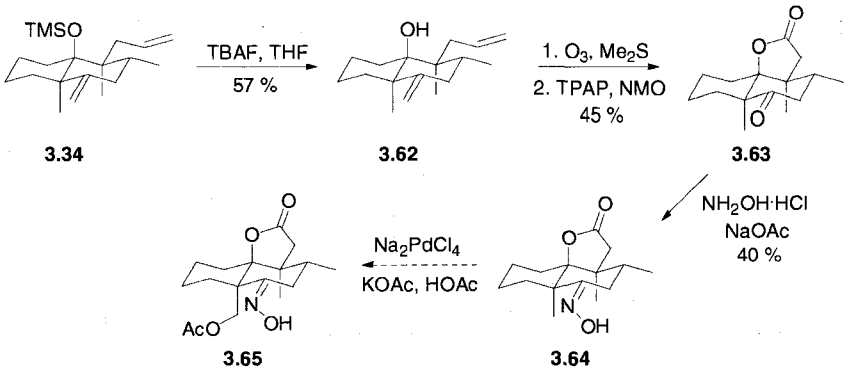
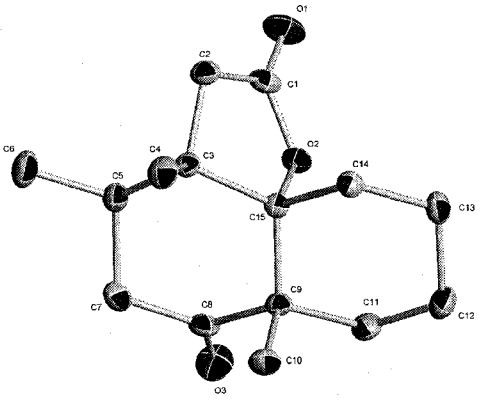


Figure 3.2: X-ray crystallographic structure of ***3.63***



Conclusions

A series of model compounds were synthesized in order to evaluate whether or not the oxy-Cope/Claisen/ene reaction will tolerate the formation of a quaternary center at the decalin ring junction. A starting material was constructed which would introduce a methyl quaternary center at the ring junction, and it was found the oxy-Cope/Claisen/ene reaction does not go to completion in this case, with the reaction actually favoring the oxy-Cope/Claisen product.

A detailed study of what steric effects are giving rise to this phenomenon was undertaken, and a variety of approaches were not successful in forcing this challenging pericyclic cascade to favor the desired decalin product.

4

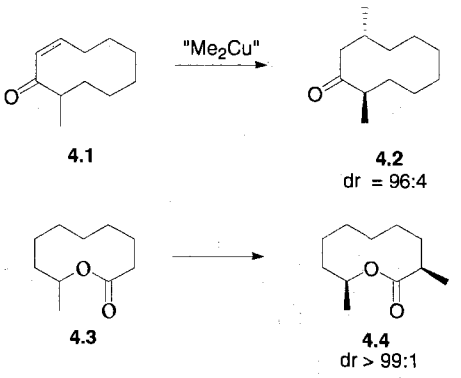
Diastereoselective Alkylation Directed By Macrocyclic Conformation

Introduction

The Barriault lab has had a long standing interest in those chemical transformations whose stereochemical outcome is mediated by the conformation of macrocyclic intermediates. One only has to look in the preceding chapters to see that our particular interest is centered on how the conformational preferences of macrocyclic intermediates in cascading pericyclic reactions leads to the formation of complex products with excellent diastereoselectivity.

The idea of macrocyclic conformation controlling reaction diastereoselection has been previously noted. Its first recognition was by Still and co-workers in a series of reactions preformed on 8- to 12-membered rings, as seen in Scheme 4.1.[27] They proposed the stereoselectivity arose from the transformations occurring on a favored macrocyclic conformation dictated by the pre-existing functionality on the ring. Since then this concept has been applied to other simple reactions occurring on medium to large sized rings.

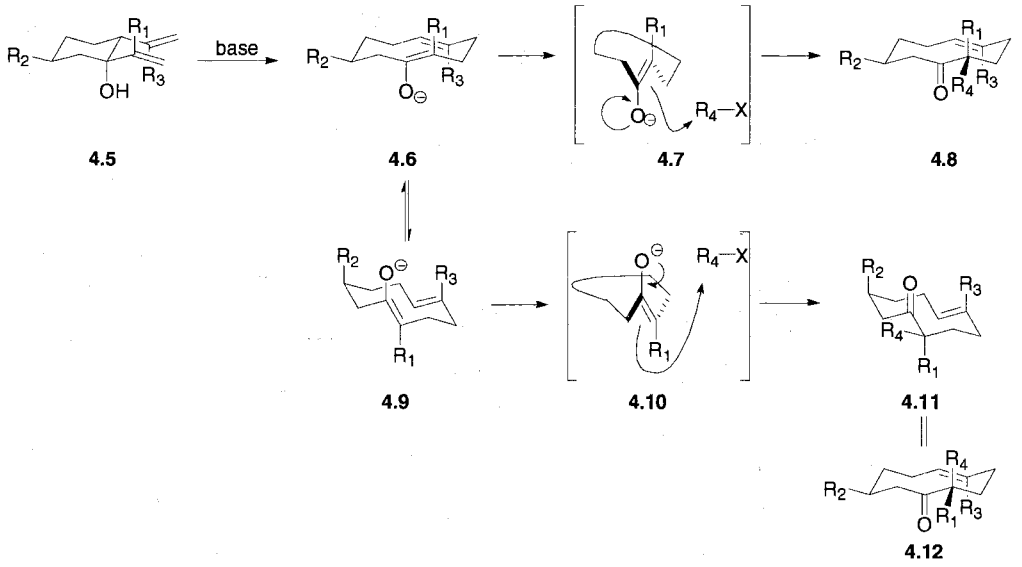
Scheme 4.1: Still's observation of macrocyclic control



In a departure from the theme of tandem pericyclic reactions, but with the effects of macrocyclic conformation on reaction selectivity still in mind, we looked to apply this concept to other transformations. In light of the discussions above about the ongoing need for new methods by which to construct all-carbon quaternary centers, we wondered whether or not macrocyclic conformation could be used to control the facial selectivity in the alkylation of tetrasubstituted enolates.

To this end, we proposed the use of an anionic oxy-Cope/alkylation sequence to accomplish this goal. The anionic oxy-Cope rearrangement[67] of *trans*-1,2-divinylcyclohexanols such as **4.5** serves multiple purposes. As the sigmatropic rearrangement preferentially occurs via a chair-like transition state, it should stereoselectively generate only an E olefin with respect to the ring (see **4.6**). In addition, it also serves as the manifold by which to generate both the tetrasubstituted enolate and the macrocycle in which it is embedded.

Scheme 4.2: Proposed anionic oxy-Cope/alkylation sequence



The facial selectivity in the alkylation phase of the reaction should be governed by the conformational preferences of macrocyclic enolate **4.6**. Enolate **4.6** has the option to undergo ring inversion to **4.9**. However, assuming this process is under thermodynamic control it should be that **4.6** is favored over **4.9** by virtue of R_2 occupying an equatorial position. As in each conformation only one face of the enolate is available for electrophilic attack (the other being shielded by the macrocycle), there are only two possible diastereomeric products (**4.8** and **4.12**). Because macrocyclic enolate **4.6** is expected to be a more energetically favored conformation, compounds related to **4.8** with the incoming electrophile R_4 *anti* with R_2 should be the major products upon alkylation.

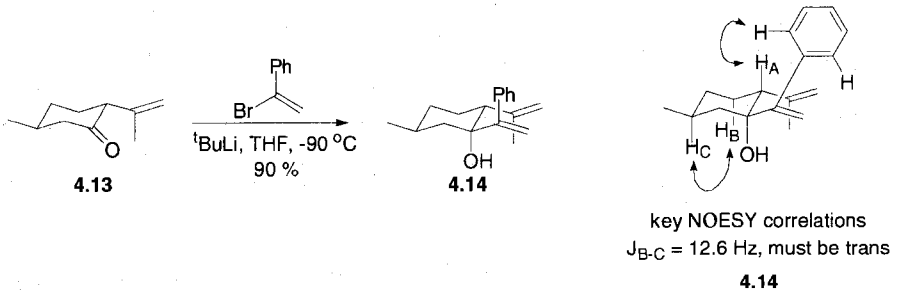
The Anionic Oxy-Cope/Alkylation Reaction

Preparation of Starting Materials

We selected isopulegone **4.13** as the starting material for our investigation. It is an attractive starting material for several reasons, including its inclusion of all functionality necessary for our study, and its availability as a racemic mixture and as both enantiomers. The synthesis of the prerequisite 1,2-divinylcyclohexanol **4.14** has been previously

described, and is readily available by treatment of **4.13** with the lithium anion of α-bromostyrene. The relative stereochemistry was proven by the analysis of both 1D and 2D NMR spectra.

Scheme 4.3: Synthesis of the trans-1,2-divinylcyclohexanol



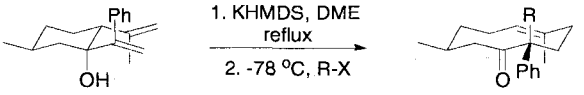
4.13 **4.14** **4.14**

Investigating the Reaction

Considerable effort by Denissova,[68] Grisé[69] and Lebrun[70] was directed towards finding conditions which would allow the anionic oxy-Cope/alkylation to occur. Optimization studies determined that the anionic oxy-Cope rearrangement is most efficient when conducted in refluxing DME in the presence of KHMDS. Upon completion of the rearrangement, the reaction is cooled and treated with an electrophile suitable for alkylation. The enolate itself is quite susceptible to protonation by even the smallest traces of acid, and the resulting ketone products, in the presence of excess electrophilic reagents, tend to undergo further unwanted alkylations.

With a set of optimized conditions developed, we set about testing the reaction with a variety of electrophiles, as summarized in Table 4.1.

Table 4.1: Anionic oxy-Cope/alkylation reaction



4.14 **4.15a-h**

Entry	R-X	R	Yield (%)	Comments
a	H_2O	H	90	-
b	ethyl iodide	Et	48	done by Grisé/Denissova
c	benzyl bromide	Bn	84	done by Lebrun
d	4-methoxybenzyl chloride	PMB	46	-
e	allyl bromide	All	72	-
f	propargyl bromide	Pro	60	-
g	methoxymethyl chloride	MOM	71	done by Lebrun
h	Davis' oxaziridine	OH	88	-
i	benzoyl chloride	Bz	-	recovered **4.15a** Bz enol ether
j	acetyl chloride	Ac	-	recovered **4.15a**
k	acrolein	-	trace	recovered **4.15a**

The anionic oxy-Cope/alkylation reaction worked well with a variety of electrophiles, in each case returning the desired product as a single detectable diastereomer. Yields are generally good to excellent with most electrophiles. Notably we observe diminished yields with the use of unactivated electrophiles such as ethyl iodide, and those which are highly susceptible to generate acids by decomposition typically did not undergo to the desired reaction. We were also able to generate a quaternary α-hydroxyketone (**4.15h**) by treating the intermediate enolate with the Davis' oxaziridine.[71]

The elucidation of the relative stereochemistry of this series of compounds is generally quite challenging for the 10-membered ring ketone products. Fortunately, these compounds are perfectly situated to undergo a transannular ene reaction, which imparting an element of rigidity in the carbon skeleton of the compounds, would make a 2D NMR

study more likely to afford definitive results as to the relative orientation of the newly formed quaternary center with the distal methyl group.

The relative stereochemistry of both compounds **4.15d** and **4.15f** was proven by this method. Transannular ene reaction and methylation of the resultant tertiary alcohols provided perfect vehicles for structural analysis, as shown in Scheme 4.4. In both compounds the newly added electrophiles are *syn* with the distal methyl group. This relative stereochemical relationship was confirmed for this series of compounds by the determination of X-ray crystal structures for both **4.15c** and **4.15g**, confirming and reinforcing the *syn* relationship between the electrophile and distal methyl.

Scheme 4.4: Derivatization to ene reaction products

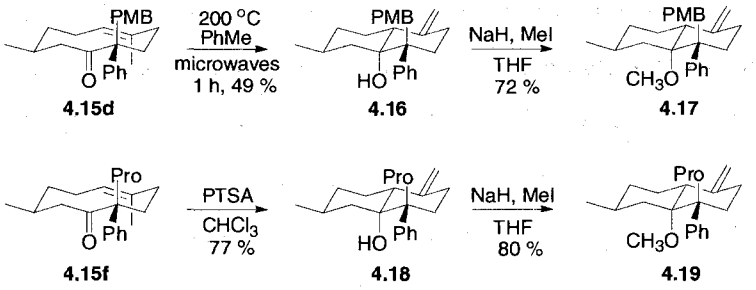


*Figure 4.1: Structural elucidation of compounds **4.17** and **4.19***

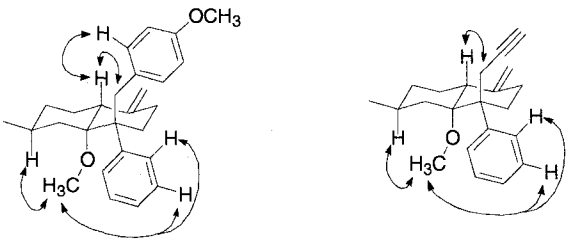
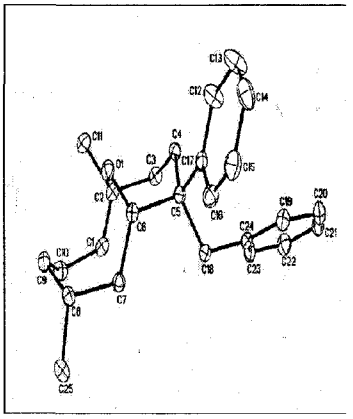
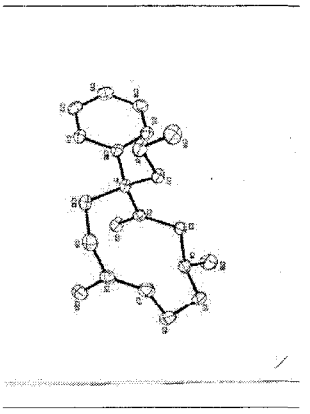


Figure 4.2: X-ray crystallographic structures of ***4.15c*** *and* ***4.15g***

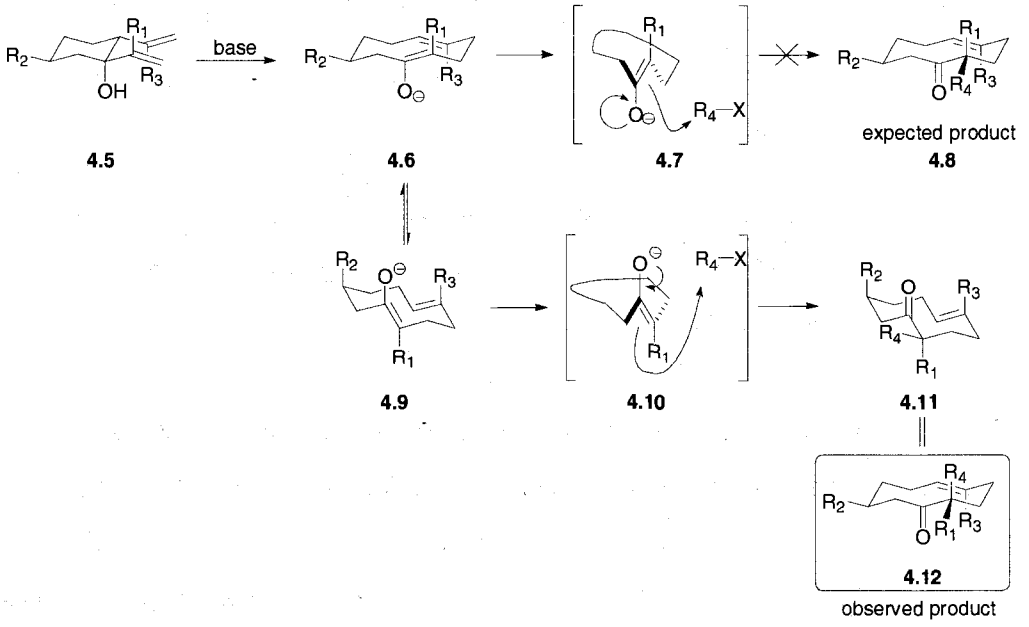




Origins of the Diastereoselectivity

This transformation is remarkable in the observation of only one diastereomeric product for each electrophile tested, validating our proposal that the preferential conformation of macrocyclic enolates can give rise to diastereoselectivity in the generation of quaternary centers. However, in direct contrast to our predictions of stereochemical outcome as outlined in Scheme 4.5 where we expected to see electrophilic addition *anti* to the distal methyl group, we observed in every case addition *syn* with the methyl group.

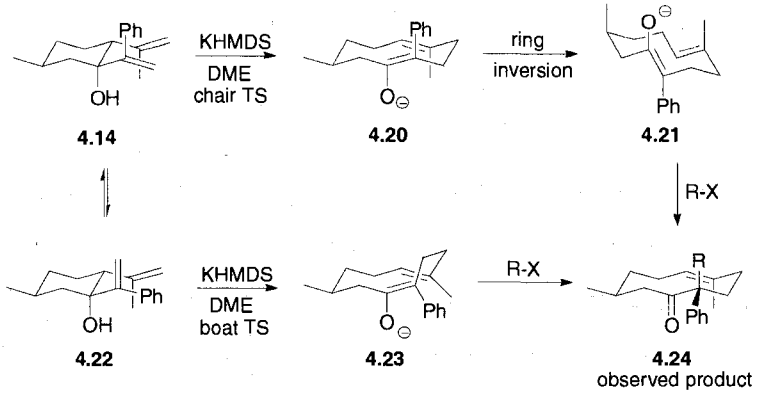
Scheme 4.5: An unexpected outcome



Considering this unexpected outcome, two obvious explainations present themselves. Firstly, was one to assume, as we do, that the anionic oxy-Cope rearrangement proceeds through a chair like transition state, it would afford macrocyclic enolate **4.20**. Whereas the alkylation of enolate **4.20** leads to the expected product, a ring inversion to enolate **4.21** followed by alkylation would give the observed product. It is important to note that both enolates in this case are E with respect to the 10-membered ring, and while we represent **4.20** and **4.21** as chair-chair-chair conformers, there are multiple other possibilities that may be lower in energy then **4.20** which are structurally related to **4.21**, leading to the observed product **4.24**.

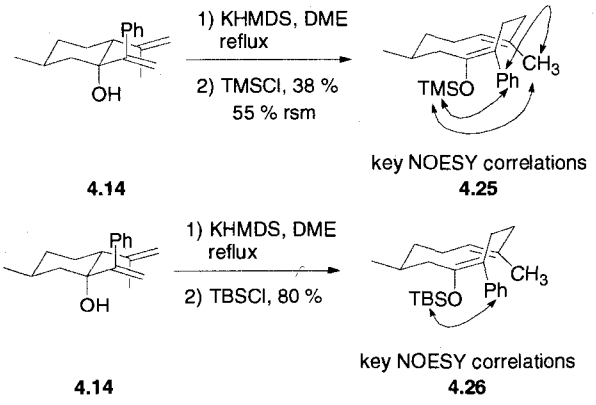
Secondly, it is possible for the anionic oxy-Cope rearrangement to proceed through a boat-like transition state, which would yield macrocyclic enolate **4.23** with the enolate being Z with respect to the 10-membered ring. The direct alkylation of this enolate would lead to the formation of the observed product in this transformation, **4.24**.

Scheme 4.6: Possible mechanistic explanations for the observed diastereoselectivity



The ring inversion pathway to access the observed product **4.24** was discounted by performing a trapping experiment on the intermediate enolate after the anionic oxy-Cope rearrangement. Quenching the reaction with both TMSCl and TBSCl in both instances afforded silyl enol ethers which were Z with respect to the 10-membered ring. As a manifold involving a ring inversion (as in **4.14** to **4.20** to **4.21**) would produce an E enolate with respect to the ring, this cannot be the path leading to the observed diastereoselectivity.

Scheme 4.7: Enolate trapping experiments

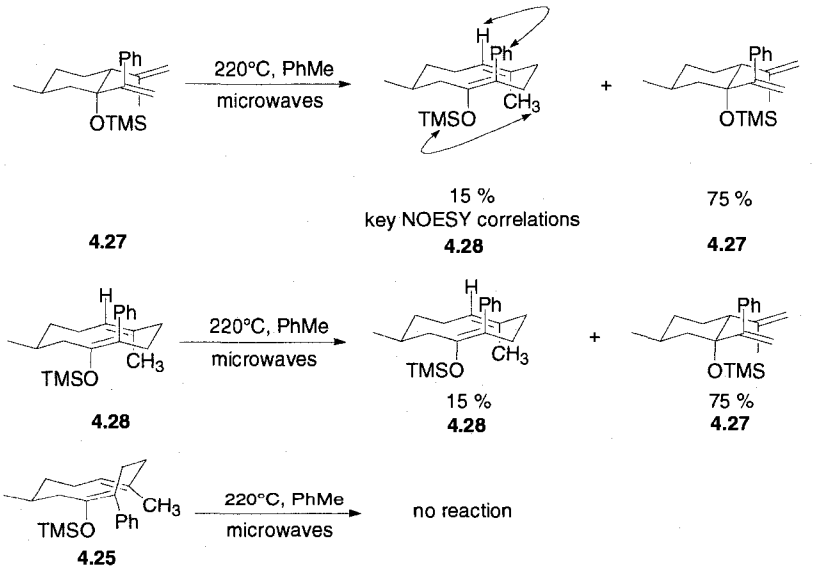


This would suggest that the initial anionic oxy-Cope reaction is indeed going through a boat-like transition state, however strong literature precedent points towards this as being

highly unlikely. Furthermore, heating TMS-protected starting material **4.27** produces the thermal oxy-Cope product **4.28** with the enol ether being *E* with respect to the ring along with returned starting material **4.27**, signifying a chair-like transition state in the thermal reaction.[72]

Compounds **4.27** and **4.28** exist as a thermodynamic mixture. Resubjection of the minor product E silyl enol ether **4.28** results again in a mixture of **4.27** and **4.28**, a telltale sign that the thermal oxy-Cope rearrangement is reversible. This cannot be said for the Z enol ether. Subjection of **4.25** isolated from the enolate quenching experiment to the same thermal conditions resulted in no reaction. This suggests that the activation energy for the retro-oxy-Cope rearrangement of **4.25**, which must go through a boat-like transition state, is very large. Likewise, the forward reaction must also have a correspondingly large energy of activation, hence providing evidence that an analogous anionic reaction would also be an unfavorable process.

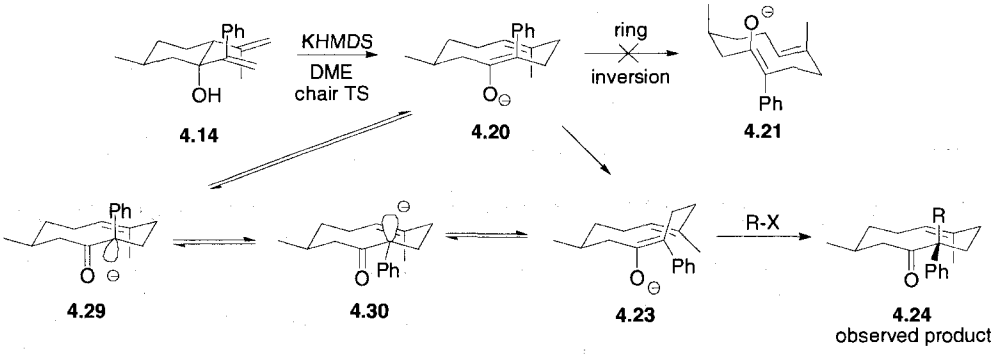
Scheme 4.8: Thermal oxy-Cope rearrangements



Backed by these results, we propose that the initial anionic oxy-Cope rearrangement does indeed go through a chair-like transition state to give intermediate **4.20**, but that this intermediate is thermodynamically unstable. Rather then the enolate undergoing a ring

inversion to **4.21**, a process shown to be highly unfavorable for closely related tetrasubstituted enols embedded in a 10-membered ring, it must undergo an isomerization to give a thermodynamically more stable *Z* enol ether. This inversion may be possible through several manifolds, including but not limited to the enolate existing as a carbon-centered enolate such as **4.29** which undergoes a carbanion inversion or a rotation of the carbonyl-carbanion bond to give **4.30**. If this is the case, it would place the phenyl group in a pseudo-equatorial position and ultimately gives the observed product **4.24**.

Scheme 4.9: Possible manifolds for the enolate isomerization



Conclusions

We have developed a conceptually unique method to generate all-carbon quaternary centers by the alkylation of a tetrasubstitued enolate stereoselectivly formed by an anionic oxy-Cope rearrangement. The facial selectivity, hence the diastereoselectivity, of the process is governed by the conformational preferences of the macrocycle in which the enolate is embedded, and the reaction is general for a wide range of electrophiles. We propose a mechanism involving the complete isomerization of an E enolate to a Z enolate, which explains the unexpected yet excellent diastereoselectivity in the process.

5

The Formal Synthesis of (-)-Mesembrine

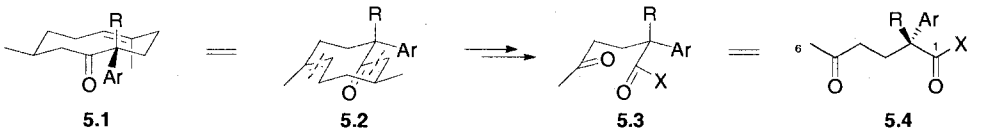
Introduction

In the preceding chapter we illustrated a novel approach to the generation of quaternary carbons through enolate alkylation. In an effort to highlight the utility of our procedure, with particular attention paid to the high level of predictable diastereoselectivity we observed, we decided to enter the arena of total synthesis.

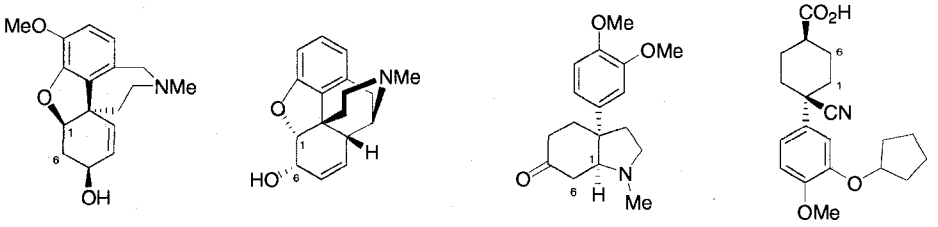
As discussed earlier, quaternary carbons are a universal feature among the myriads of known natural products. The macrocyclic ketone we generate in the anionic oxy-Cope/alkylation reaction unfortunately does not readily map on to the skeletons of a large number of potential targets. However, if one views the alkyl hydrocarbon half of the molecule as one would view a chiral auxiliary - something that can be removed after a key reaction - the synthetic potential of our quaternary center forming process explodes.

The division of the reaction product **5.1/5.2** in half liberates a 1,5-dicarbonyl derivative with an α-quaternary center adjacent to the terminal carbonyl (**5.3/5.4**). One can imagine that the use of a chiral starting material in the alkylation procedure will ultimately afford chiral 1,5-dicarbonyl compounds. This sub-unit of the macrocycle is a ubiquitous structural motif and can serve as a building block for the enantioselective synthesis of many natural products containing a quaternary center.

Scheme 5.1: Revealing the synthetic potential of the reaction



5.1 5.2 5.3 5.4



5.5 5.6 5.7 5.8

The applicability of subunit **5.4** as a foundation for total synthesis can be seen in Scheme 5.1 where it is found embedded in several natural products including galanthamine **5.5**,[73] morphine **5.6**,[74] mesembrine **5.7** and the phosphorodiesterase-4 inhibitor Ariflo **5.8**.[75] In the end we decided on the alkaloid (-)-mesembrine **5.7** as our synthetic target as it is a keystone molecule by which to validate the usefulness of quaternary center generating methodologies.

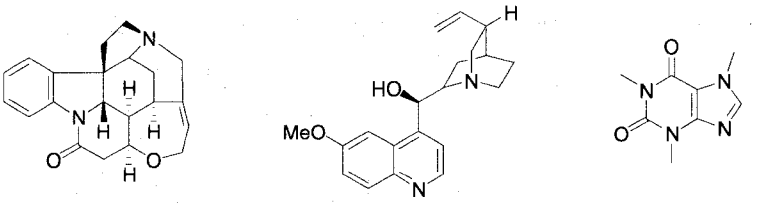
Alkaloids: Mesembrine

Alkaloids can be broadly classified as those secondary metabolites containing a basic nitrogen atom. As one would assume based on this statement, the occurrence of these compounds in Nature is widespread and vast numbers of alkaloids have been isolated and characterized. Alkaloids have arguably been one of the more important classes of natural products throughout time both to chemists and the population at large.

Just a few of the more illustrious members of the alkaloid family include strychnine **5.9**, quinine **5.10**, and caffeine **5.11**. Strychnine is well known amongst those of us that have had issues with rats in our basements; to chemists its first total synthesis represents one of the more monumental moments in organic synthesis. Quinine is equally as recognizable as one of the first malaria prophylactics, with a synthetic history somewhat shrouded in

controversy. Whilst caffeine doesn't share the same synthetic legacy as our previously mentioned alkaloids, it is without a doubt one of the worlds most recognizable.

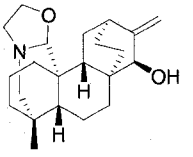
Figure 5.1: Strychnine, quinine and caffeine



5.9 **5.10** **5.11**

The biosynthetic origins of the alkaloids are from simple amino acids. Typically this occurs through the incorporation of an amino acid into one of the three major secondary metabolic pathways. Also possible, but much less common, is the incorporation of nitrogen into another class of metabolites. For example, a terpene can be nitrogenated during or after the formation of the terpene skeleton; this would afford an alkaloid. A typical terpene alkaloid can be seen in Figure 5.2.

Figure 5.2: The diterpene alkaloid (-)-atisine

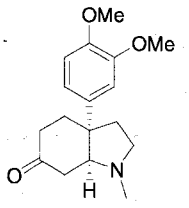


5.12

Alkaloids are classified by the structural motif in which the nitrogen is embedded, which is intrinsically linked to the amino acid nitrogen source. The more typical amino acids involved in the biosynthesis of alkaloids are anthranilic acid, glutamic acid, ornithine, lysine, phenylalanine, tyrosine and tryptophan. Each of these amino acids leads to at least one structural motif that involves nitrogen. For example, tryptophan is normally the nitrogen source for the indole alkaloids whereas orinthine gives pyrrolidine alkaloids.

We are interested in the *Sceletium* alkaloid mesembrine **5.7**,[76] isolated from *Sceletium tortuosum*, a plant known for its use as a stimulant. These *cis*-octahydroindole structures are common among the alkaloids isolated from *Amaryllidaceae* and *Sceletium* species. Mesembrine has recently been shown to be a very potent inhibitor of serotonin re-uptake, with activity being displayed at dosages as small as 100 micrograms.[77] Despite its seemingly small size, mesembrine arises through a surprisingly complex biosynthetic pathway starting from tyrosine and phenylalanine.[8]

Figure 5.3: Mesembrine



5.7

Synthetic Approches to Mesembrine

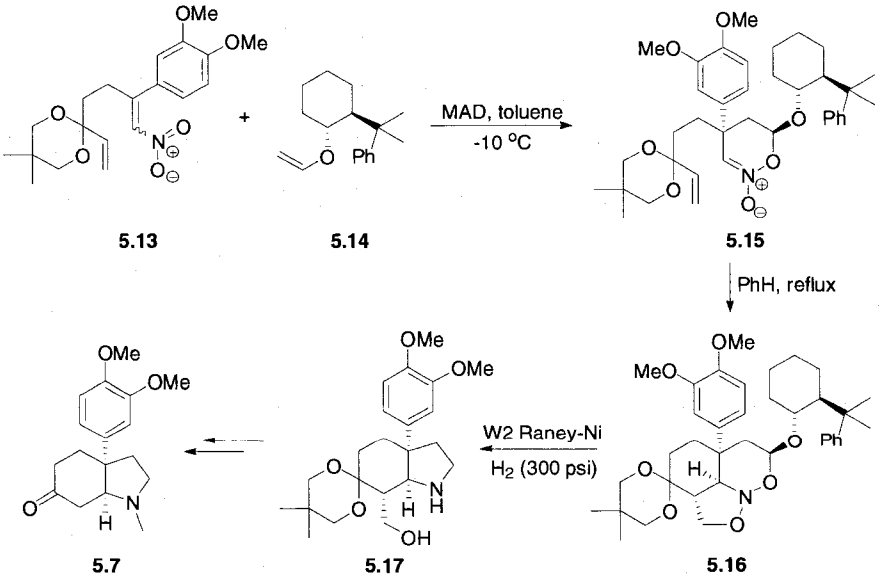
To say that mesembrine is a popular target for total synthesis would be an understatement; there are currently over 40 reports of the total synthesis of natural (-)-mesembrine, its unnatural enantiomer and its racemate.[78,79] Synthetic pursuits of mesembrine are no longer driven by a unique biological activity or a desire to synthesize a new and novel class of natural products. Due to its small size, coupled with the occurrence of a relatively challenging quaternary carbon at its ring junction, mesembrine serves as an excellent banner to display new methodologies aimed at the construction of quaternary centers. It is for this reason that we embarked on a synthetic pursuit of this particular natural product.

The first total synthesis of racemic mesembrine was reported in 1965 by Shamma and Rodriguez,[80] a 20 step synthetic effort that paved the way for further refinements of the approach to this molecule. Various more expedient routes were developed throughout the next 20 years, with the shortest synthesis of the racemic material being just three

steps.[81] It was after these developments that focus shifted from target oriented syntheses of mesembrine to those which served to illustrate emerging new methodologies, several of which are highlighted below.

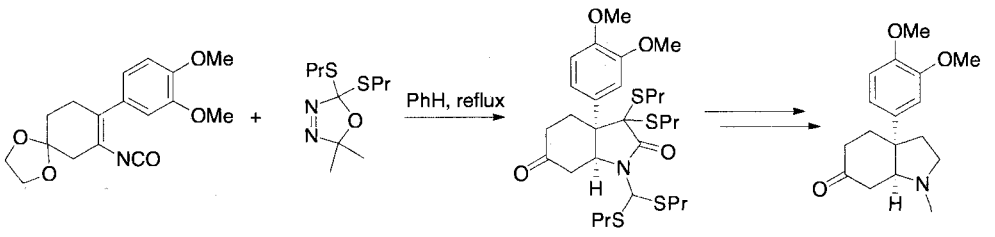
In 1997, Denmark and Marcin reported a total synthesis of (-)-mesembrine using a nitroalkene sequential [4+2]/[3+2] cycloaddition strategy.[82] This method was developed to give access to various nitrogen heterocyclic systems with a quaternary center β to the nitrogen, of which the *cis*-octahydroindole skeleton of mesembrine is an example. A [4+2] cycloaddition catalyzed by MAD (methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide)) between nitroalkene **5.13** and vinyl ether **5.14** gave **5.15**. The vinyl ether **5.14** served a dual purpose in this reaction, also acting as a chiral auxiliary to induce enantioselectivity in the process. Isolating **5.15** and heating in benzene resulted in the second intramolecular cycloaddition, affording complex polycycle **5.16**, which was reduced with W2 Raney-Ni to give **5.17**. This compounds was easily converted into (-)-mesembrine **5.7**, completing the synthesis in 13 steps.

Scheme 5.2: Denmark's nitroalkane [4+2]/[3+2] approach to (-)-mesembrine



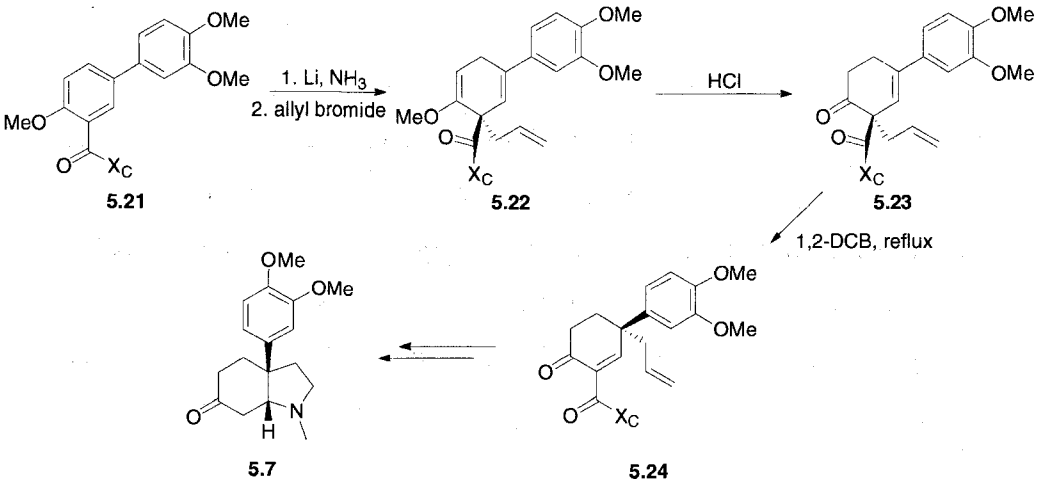
In a somewhat more atom economical approach, Rigby completed a synthesis of racemic mesembrine using a bis(alkylthio)carbene/isocyanate [4+1] cycloaddition strategy, illustrating the utility of nucleophilic carbenes as 1,1-dipole equivalents.[83] Heating **5.19** results in the generation of a bis(alkylthio)carbene upon the expulsion of nitrogen and acetone, which in the presence of **5.18** underwent the desired [4+1] cycloaddition to give **5.20**. Three routine operations then led to mesmebrine **5.7**, completing the synthesis in 9 steps from commercially available materials.

Scheme 5.3: A [4+1] cycloaddition approach to racemic mesembrine



In one of the most recent synthetic reports, Malachowski and co-workers demonstrated the power of an asymmetric Birch reduction/Cope rearrangement in constructing quaternary centers by synthesizing (+)-mesembrine.[84] Their approach starts with an asymmetric Birch reduction of **5.21** directed by a 2-(methoxymethyl)pyrrolidine chiral auxiliary. Followed by a quench with allyl bromide, this gives compound **5.22** which is hydrolyzed to ketone **5.23**. Heating results in a Cope rearrangement, and the establishment of an enantiopure quaternary center corresponding to that seen in (+)-mesembrine, which is readily available from **5.24**, completing the synthesis in 8 overall steps.

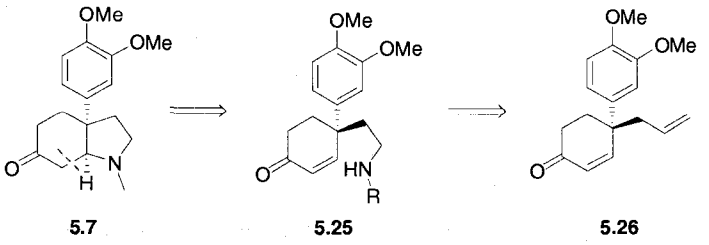
Scheme 5.4: Malachowski's synthesis of (+)-mesembrine



Our Retrosynthetic Analysis

The key reaction in our synthesis of (-)-mesembrine would be the anionic oxy-Cope/alkylation protocol to help establish the challenging quaternary center seen in the natural product. The obvious disconnection to form the pyrrolidine ring is through the intramolecular 1,4-addition of amine **5.25**, which would be expected to occur spontaneously upon its formation. This compound should be easily prepared from **5.26**, perhaps by cleavage of the terminal olefin followed by reductive amination.

Scheme 5.5: Initial retrosynthetic disconnections

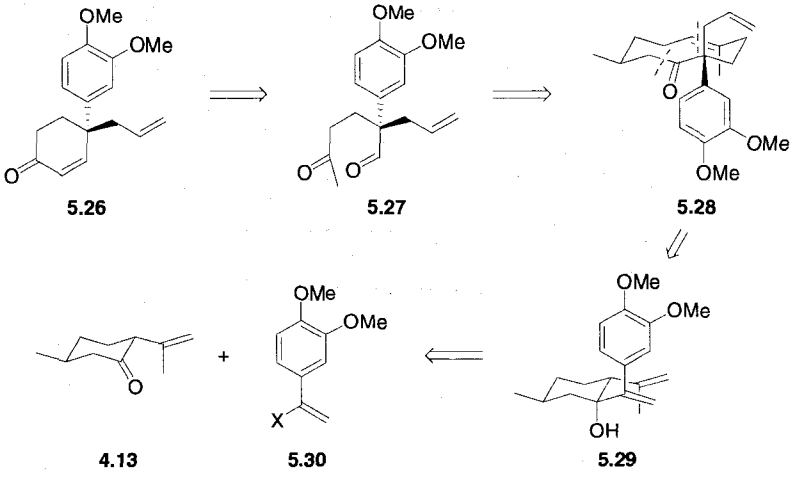


In fact, both the 1,4-addition and compound **5.26** have been previously described in the literature. Because of the intense interest that mesembrine has generated and the number

of syntheses that have been completed, virtually all reasonable end games to access this target have been conceived and implemented. As such, the synthesis of compound **5.26** would represent the formal synthesis of (-)-mesembrine, hence this intermediate en route to (-)-mesembrine became our final target.

5.26 can be generated from the aldol condensation of dicarbonyl **5.27**, which in turn is the product of the cleavage of the two bonds illustrated in decalin **5.28**. This macrocyclic ketone is the product of an anionic oxy-Cope/alkylation using a substituted aryl system in place of what has so far been only a phenyl substituent. Forming **5.28** requires starting from tertiary alcohol **5.29**, which should be available from the alkylation of isopulegone **4.13** with a nucleophile derived from **5.30**.

*Scheme 5.6: Retrosynthetic analysis of compound **5.26***



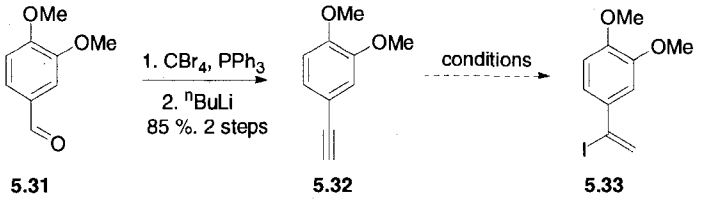
The Synthesis of Mesembrine

Generating a Vinyl Halide

We initially thought the generation of a vinyl halide of structure **5.30** would be a trivial matter, simply by treating known terminal alkyne **5.32**[85] with B-I-9-BBN which would afford the vinyl iodide **5.33**.[86] Unfortunately, a series of standard iodination conditions

were ineffective in generating the desired product. We partially attributed the failure of this reaction to the possible instability of the vinyl iodide product; hence we turned our attention to synthesizing the bromide, which was expected to be more stable.

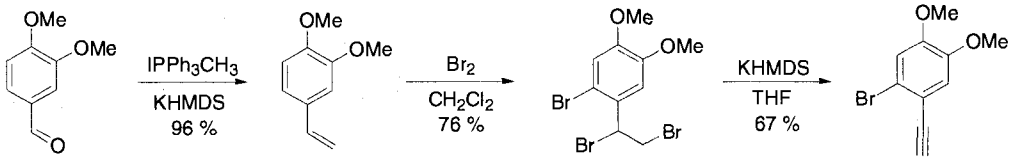
Scheme 5.7: Attempted synthesis of a vinyl iodide



5.31 **5.32** **5.33**

It was envisaged a vinyl bromide would be easily accessible by a bromination/elimination sequence performed on an appropriate aryl olefin. Known compound **5.34** was readily available by the Wittig olefination of aryl aldehyde **5.31** on large scale. Our first attempt at the bromination of this olefin illustrated the reaction was very facile, but in the presence of any excess bromine the electron-rich aromatic ring also was brominated to give unproductive product **5.35**. A test reaction to evaluate whether the elimination of the vinyl bromide was feasible resulted in a double elimination to generate the terminal alkyne **5.36**, signifying accurate control over the amount of base employed would be critical for the successful isolation of the vinyl bromide.

Scheme 5.8: Initial attempt at bromination and elimination

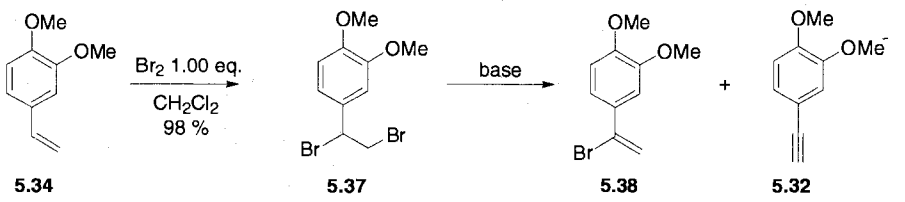


5.31 **5.34** **5.35** **5.36**

As expected, the careful addition of bromine to olefin **5.34** affords the dibromide **5.37** in near-quantitative yield. Of several conditions tested, KHMDS was found to be the ideal base for the elimination reaction to give **5.38**.[87] The observation of alkyne **5.32** was virtually suppressed by using a precise amount of KHMDS in slight excess. While **5.38**

could be purified by silica gel chromatography, it rapidly decomposes on standing such that it must be used immediately upon isolation.

Scheme 5.9: Formation of the vinyl bromide



5.34 **5.37** **5.38** **5.32**

Table 5.1: Attempted conditions in the elimination reaction

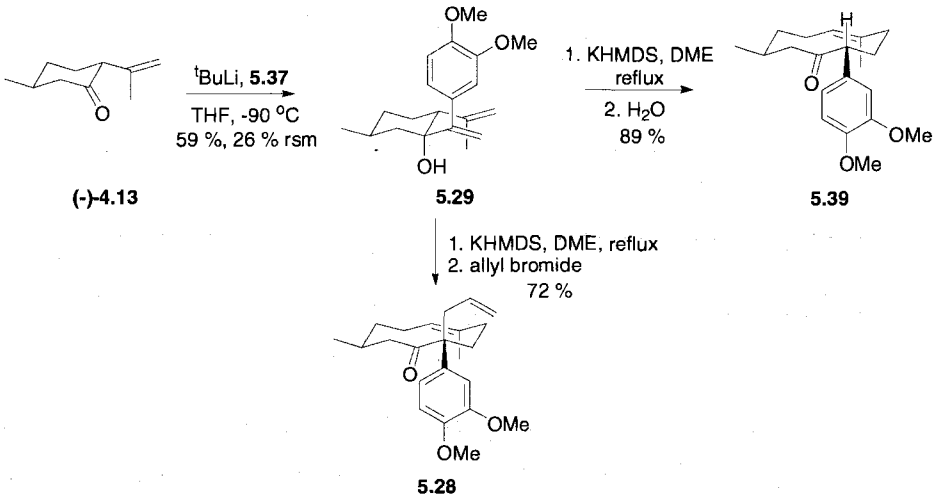
Entry	Conditions	Yield		Comments
		5.38	5.32	
1	Et_3N (1.0 eq), PhH	-	-	no reaction
2	KHMDS (3.0 eq), THF	-	96	-
3	KHMDS (1.20 eq), THF	70	9	-
4	KHMDS (1.05 eq), THF	83	trace	-
5	KHMDS (0.95 eq), THF	75	-	mixture with starting material
6	LiHMDS (1.05 eq), THF	70	-	-
7	DBU (1.05 eq), THF	43	-	-
8	KOH (1.05 eq), MeOH	-	-	decomposition

The Anionic Oxy-Cope/Alkylation Reaction

With the requisite vinyl bromide now in hand, the stage was set to perform the alkylation to give tertiary alcohol **5.28**, which could then be submitted to the pivotal quaternary center generating reaction. The use of (-)-isopulegone **4.13** allowed us to pursue the enantioselective synthesis of mesembrine.

Using previously developed conditions, the alkylation of **4.13** does not go to completion in this case but still affords the tertiary alcohol **5.29** in moderate yield. An initial test of the anionic oxy-Cope rearrangement on substrate **5.29** is a success, generating macrocyclic ketone **5.39** in excellent yield. As expected, the desired anionic oxy-Cope/alkylation reaction is also successful, generating key intermediate **5.28**.

Scheme 5.10: Alkylation and anionic Oxy-Cope/alkylation



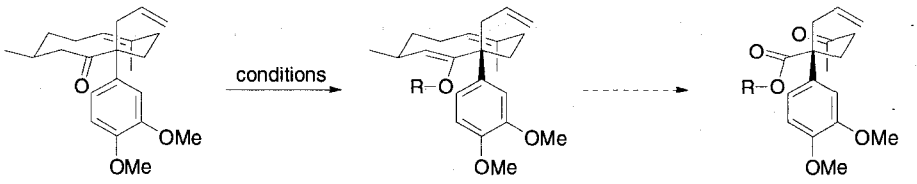
Cleavage of the Macrocycle

Having met success in generating the enantiomerically pure quaternary center required for the synthesis of (-)-mesembrine, we began to focus our efforts on the cleavage to remove the unwanted portion of the macrocycle.

Our initial approach was to form an enol ether **5.40** from the macrocyclic ketone **5.28**, followed by cleavage of both macrocyclic olefins to give **5.41**. At this point we were not concerned with the chemoselectivity of the olefin cleavage (cleavage of the terminal olefin is not desired) as we were more interesting in whether or not the enol ether could be generated and divided. Unfortunately, the generation of the enol ether proved to be the limiting factor in this approach. In a variety of conditions investigated, most gave no reaction, and those that did returned the enol ether in low and highly variable yields. In

addition, preliminary attempts at the cleavage of the enol ether afforded only decomposition products.

Scheme 5.11: First approach to cleavage of the macrocycle



5.28 **5.40** **5.41**

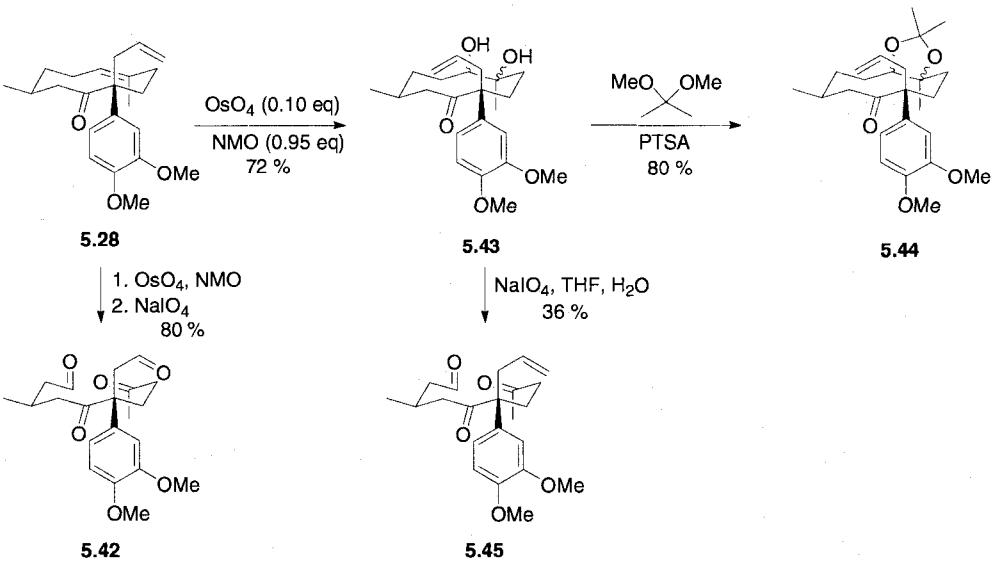
*Table 5.2: Attempted generation of enol ether **5.40***

Entry	R	Conditions	Result
a	Ac	Ac_2O, LHMDS, THF	starting material
b	Ac	Ac_2O, KHMDS, THF	starting material
c	Me	KHMDS (1.25 eq), Me_2SO_4 (1.5 eq)	starting material
d	Me	KHMDS (1.5 eq), Me_2SO_4 (1.5 eq)	starting material
e	Me	KHMDS (10 eq), Me_2SO_4 (1.5 eq)	trace product
f	Me	KHMDS (5 eq), Me_2SO_4 (1.25 eq)	starting material
g	Me	KHMDS (10 eq), Me_2SO_4 (1.25 eq, distilled twice)	0-27%
h	Me	KHMDS (10 eq), Me_2SO_4 (1.25 eq, distilled twice), premixed reagents	starting material
i	Tf	KHMDS (2 eq), $PhN(OTf)_2$ (2 eq)	starting material
j	Tf	KHMDS (10 eq), $PhN(OTf)_2$ (2 eq)	starting material

Having met no success using this route, we turned our attention to the stepwise cleavage of the macrocycle to give the necessary fragment needed for the synthesis. It was readily apparent that the cleavage of the already existing olefins in **5.28** would not be a problem as subjection to Lemieux-Johnson conditions using excess reagents afforded the cleavage product **5.42**.

A more precise application of reagents results in the dihydroxylation of the more electron rich but more substituted macrocyclic olefin to give diol **5.43**. As this product was surprisingly unstable, it was protected as the acetonide **5.44** to confirm the site of dihydroxylation. The relative stereochemistry was not confirmed as it has no bearing on the outcome of the sequence. We also confirmed that diol **5.43** could be cleaved using $NaIO_4$, which gave tricarbonyl **5.45** which was also quite unstable.

Scheme 5.12: Cleavage of the macrocyclic olefin

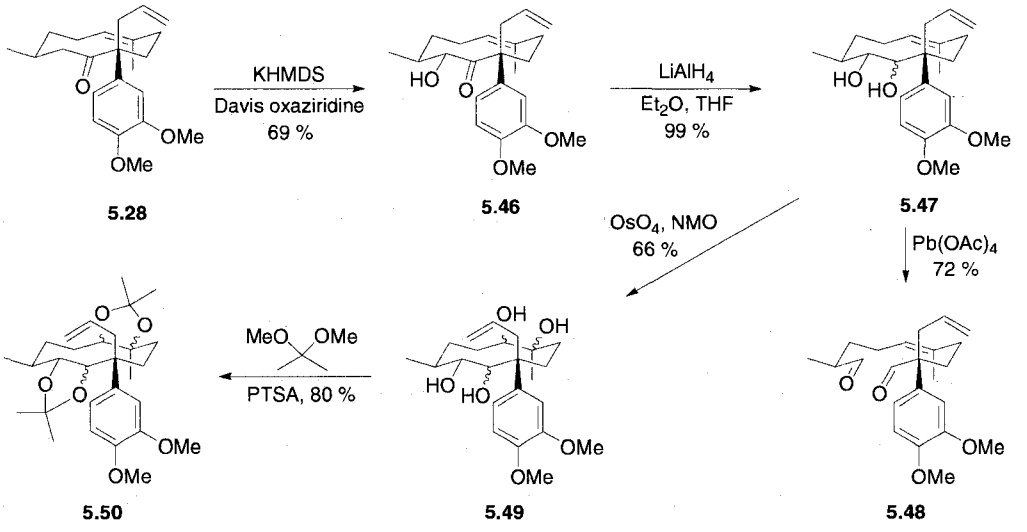


Now needing to address the cleavage of the non-olefinic bond in the macrocycle and knowing the enol cleavage route is not viable, we turned our attention to other methods. Simple α-oxygenation of **5.28** affords α-hydroxyketone **5.46**. It is known that the carbonyl-hydroxy carbon-carbon bond can be cut, but when **5.46** was subjected to several standard sets of conditions, no reaction was observed.

Instead, we opted to reduce ketone **5.46** to **5.47**, whose diol functionality should easily succumb to cleavage. In this case $NaIO_4$ was not an effective reagent for this transformation. Instead, $Pb(OAc)_4$ was used to produce the desired cleavage product **5.48**.

The ideal case by which to generate the fragment needed for the completion of the synthesis would be to perform both bond cleavages simultaneously. We thought that if we could selectively perform a dihydroxylation reaction on **5.47** much like we did for **5.28**, the resulting tetraol could be used to achieve this goal. Delightfully, the careful dihydroxylation of **5.47** was successful in generating **5.49** as a single unassigned diastereomer, and much like its analog **5.43** it was unstable and was protected as the bis-acetonide **5.50** for characterization.

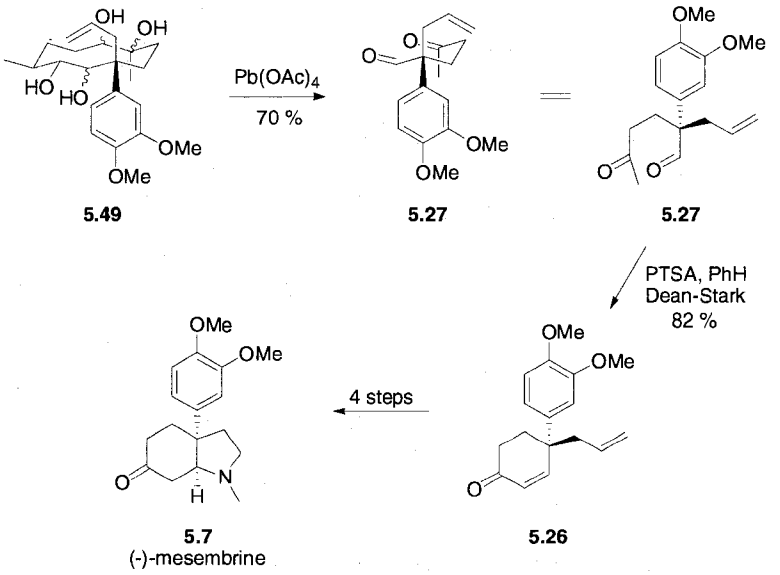
Scheme 5.13: Cleavage of the second macrocyclic bond



Formal Synthesis of (-)-Mesembrine

With the completion of the formal synthesis in sight, we were delighted to find that treatment of **5.49** with $Pb(OAc)_4$ smoothly cut both diol bonds to afford dicarbonyl **5.27**. Perfectly situated to undergo an aldol condensation, treatment with PTSA under Dean-Stark conditions afforded the condensation product **5.26** in good yield.[78b] Compound **5.26** has been implicated in several syntheses of mesembrine,[88] the most recent being Taber's 2005 synthesis,[78a] and as such represents the completion of a formal synthesis of this challenging natural product.

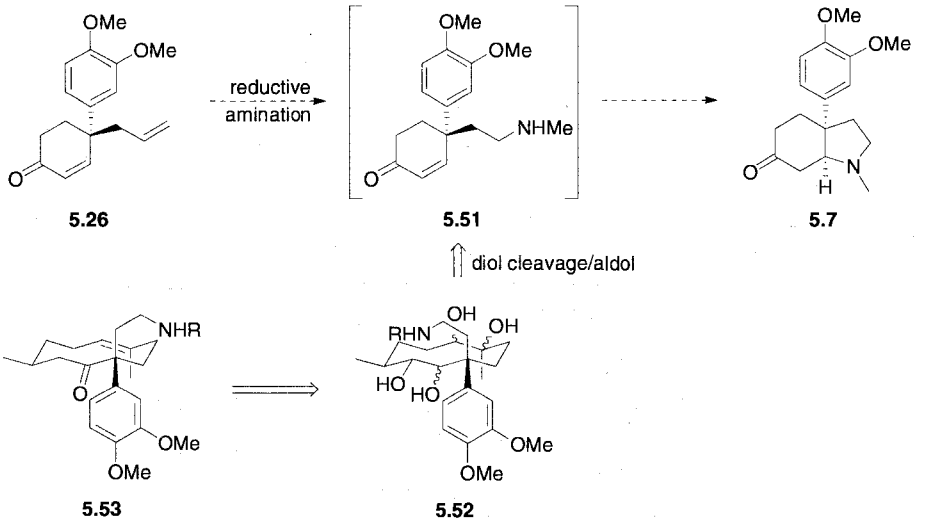
Scheme 5.14: The formal synthesis of (-)-mesembrine



Investigations in the Total Synthesis of (-)-Mesembrine

It is not immediately evident why the conversion of **5.26** to mesembrine **5.7** is a four step procedure. One would think that the simple cleavage of the terminal olefin followed by a reductive amination would afford intermediate **5.51**, which should spontaneously cyclize to the natural product. While a reductive amination does indeed give mesembrine **5.7**, the ketone in the natural product is more reactive towards the reductive amination hence any mesembrine formed is immediately consumed and lost.

Scheme 5.15: A new approach to (-)-mesmebrine

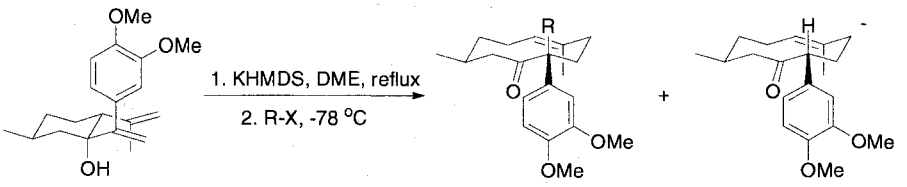


It is known that if **5.51** can be formed by other means, it will undergo a cyclization to give mesembrine **5.7**.[89] We thought we could accomplish this ourselves by generating compound **5.52** from **5.53**, the product of an anionic Oxy-Cope/alkylation reaction, using the same route as in our formal synthesis. Oxidative cleavage followed by an aldol condensation should give **5.51**, which under the conditions of the aldol reaction will cyclize to give the natural product. Not only would this drastically shorten our approach, it would also amount to a new total synthesis of (-)-mesembrine.

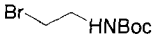
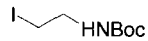
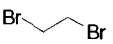
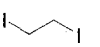
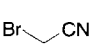
A New Anionic Oxy-Cope/Alkylation

To begin our new approach, we started by attempting to synthesize **5.53**, or a related compound that could be easily converted to **5.53**. A series of new electrophiles were screened in the anionic oxy-Cope/alkylation reaction of tertiary alcohol **5.29**, as summarized in Table 5.4. While the anionic oxy-Cope rearrangement in all cases worked, the alkylation to form the quaternary center was not successful with the relatively unreactive alkylating reagents employed. We were happy to find however that bromoacetonitrile[90] was acceptable as an electrophile, affording **5.54e** in a synthetically useful yield.

Table 5.3: Electrophiles used in the anionic oxy-Cope/alkylation reaction



5.29 **5.54a-e** **5.39**

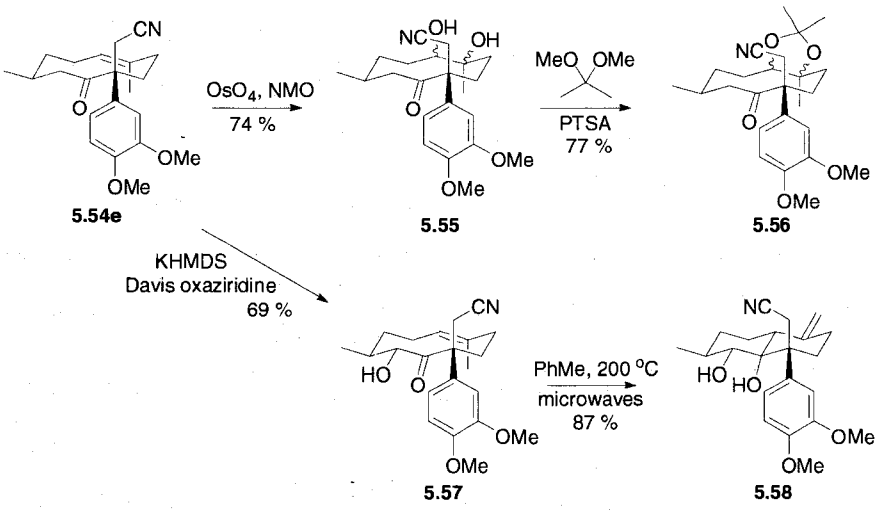
Entry	R-X	Yield (%) 5.54	5.39
a[91]		-	82
b[91]		-	86
c		-	85
d		-	91
e		57	30

Towards Cleavage of the Macrocycle

Having installed a functional group that can be transformed into the desired amine later in the synthesis, we examined whether or not compound **5.54e** would behave in a similar fashion to previous substrates in the dihydroxylation of the olefin and in the oxygenation adjacent to the carbonyl.

Both the dihydroxylation of **5.54e** to give **5.55** and the oxygenation of **5.54e** to give **5.57** were a success. As in the allyl derivative, **5.55** was unstable and needed to be protected as the acetonide **5.56** to be adequately characterized. Also, it was necessary to perform a transannular ene reaction on compound **5.57** to give *trans*-decalin **5.58** due to extreme line broadening in the NMR spectra of **5.57** which was not conducive to the correct identification of the compound.

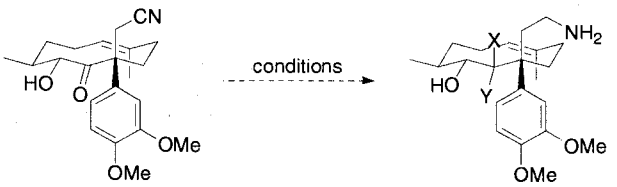
Scheme 5.16: Oxidation of the olefin djacent to the carbonyl



We next sought to investigate the reduction of ketone **5.57** to the corresponding diol. In the allyl analog **5.46**, only $LiAlH_4$ was sufficiently reactive to result in formation of the diol. In this case, the nitrile can also be reduced by $LiAlH_4$, and we wished to determine what effect this might have on the reduction.

In a very unfortunate turn of events, some of the only conditions effective in the reduction of the ketone in previous substrates cause decomposition of **5.57**. Limited in our choice of available reducing reagents, we sought to try a stepwise reduction, using conditions known to selectively reduce the nitrile to give **5.59b**, after which the ketone reduction could be attempted. Once again, we were met with failure in this reaction, with none of the conditions being effective in reducing the nitrile, returning starting material in all cases.

Table 5.4: Attempted reduction of compound 5.55



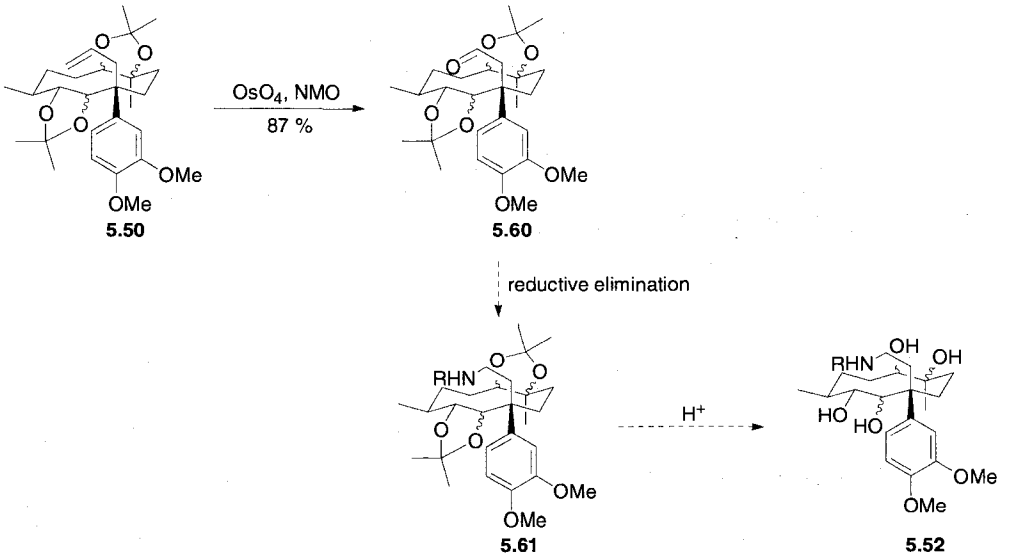
5.57

5.59a, X = H, Y = OH
5.59b, X, Y = O

Entry	Conditions	Desired Product	Outcome	Comments
1	$LiAlH_4$, THF	**5.59a**	decomposition	-
2	$LiAlH_4$, Et_2O	**5.59a**	decomposition	-
3	$NaBH_4$, $CoCl_2 \cdot 6H_2O$[92]	**5.59b**	starting material	-
4	$NaBH_4$, $NiCl_2 \cdot 6H_2O$[92]	**5.59b**	starting material	-
5	1. $(MeO_3)BF_4$, CH_2Cl_2 2. $NaBH_4$, MeOH[93]	**5.59b**	starting material	gives methyl amine

In a last ditch effort to salvage this approach to (-)-mesembrine, we returned to an intermediate developed in the formal synthesis. Could we cleave the olefin of compound **5.50** and perform a reductive amination to give **5.61**, simple deprotection of the acetonides would give us the key intermediate we were originally trying to synthesize, compound **5.52**. While olefin cleavage was a success, the product **5.60** was somewhat unstable and preliminary results suggested it would not be able to withstand the required reductive amination reaction conditions.

Scheme 5.17: A final effort at installing the amine



Conclusions

Using our quaternary carbon forming anionic oxy-Cope/alkylation protocol, we were able to achieve the formal enantioselective synthesis of (-)-mesembrine in just 11 steps from known starting materials, including those to transform our intermediate into the natural product. This is on par with other enantioselective routes to mesembrine. An effort to find a shorter route to a total synthesis of (-)-mesembrine encountered some unexpected pitfalls and the route was abandoned.

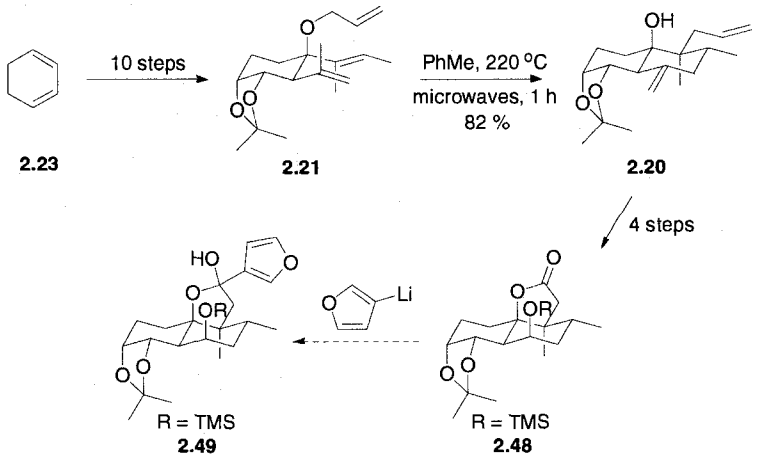
6

Summary and Outlook

Summary

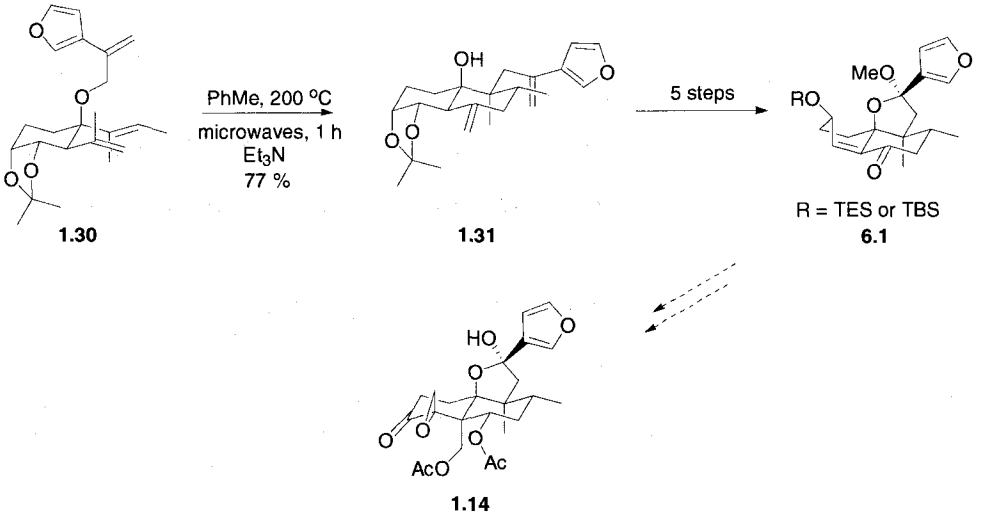
Total synthesis is often a labour of love. The most elegant and concise routes used in a syntheis seem in a paper or presentation to be simply a series of reactions performed in sequence. However, the amount of effort needed to develop and achieve a synthesis is often astounding and this is not always clear. Our pursuit of teucrolivin A is a perfect example of this; while just 10 steps on paper, the synthesis of compound **2.21** from 1,3-cyclohexadiene took almost 2 months to achieve on each run! However, we persevered and found that while the oxy-Cope/Claisen/ene reaction is useful in generating the skeleton of the natural product (compound **2.21** to **2.20**), the furanyl moiety could not be installed from intermediates arising from **2.20**.

Scheme 6.1: First approach to teucrolivin A



Our second generation approach required that the furan be installed prior to the pericyclic cascade, which culminated in the synthesis of **1.30**, which when heated gave the desired decalin **1.31**. Further elaboration established advanced intermediate **6.1**. A variety of attempts were made to install the quaternary center at the decalin ring junction, but none were successful. We concluded this was a result of a congested steric environment, and a propensity for the molecule to fragment by explusion of methoxide.

Scheme 6.2: Second approach to teucrolivin A



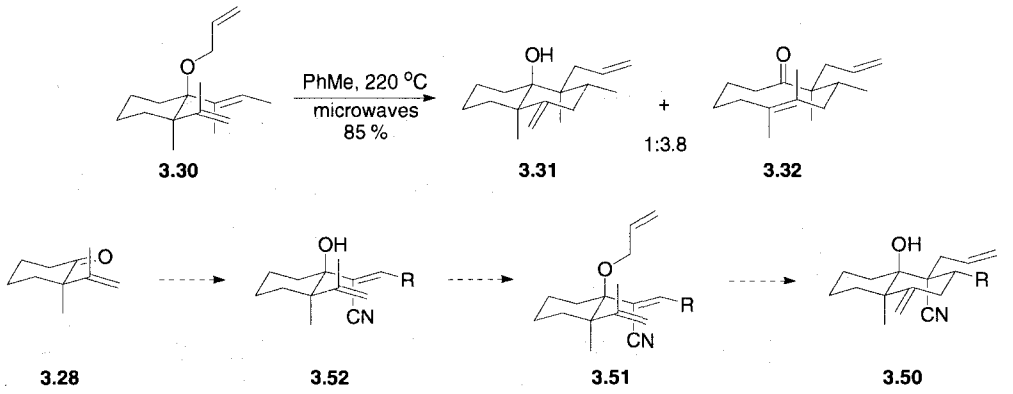
1.30 **1.31** **6.1**

1.14

In light of these results, we sought to determine whether or not the oxy-Cope/Claisen/ene reaction would tolerate the presence of a pre-installed quaternary center. After some effort we arrived at intermediate **3.30**, which when heated resulted in two products. One was the desired product **3.31** and the other was the product of the oxy-Cope/Claisen portion of the reaction, which has not been observed in any other case, and was the favored product of the reaction.

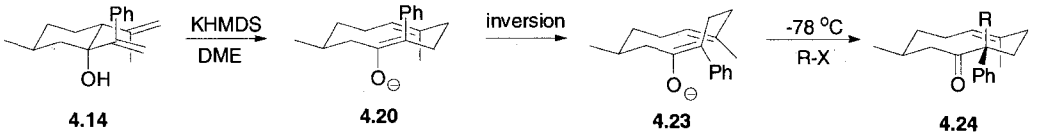
A detailed study with other substrates suggested this reaction is not favored because of unfavorable steric interactions. A preliminary attempt to solve this problem by using a functional group smaller then a methyl to form the quaternary center was hampered by the fact we could not achieve the synthesis of compound **3.52**.

Scheme 6.3: The oxy-Cope/Claisen/ene reaction with hindered substrates



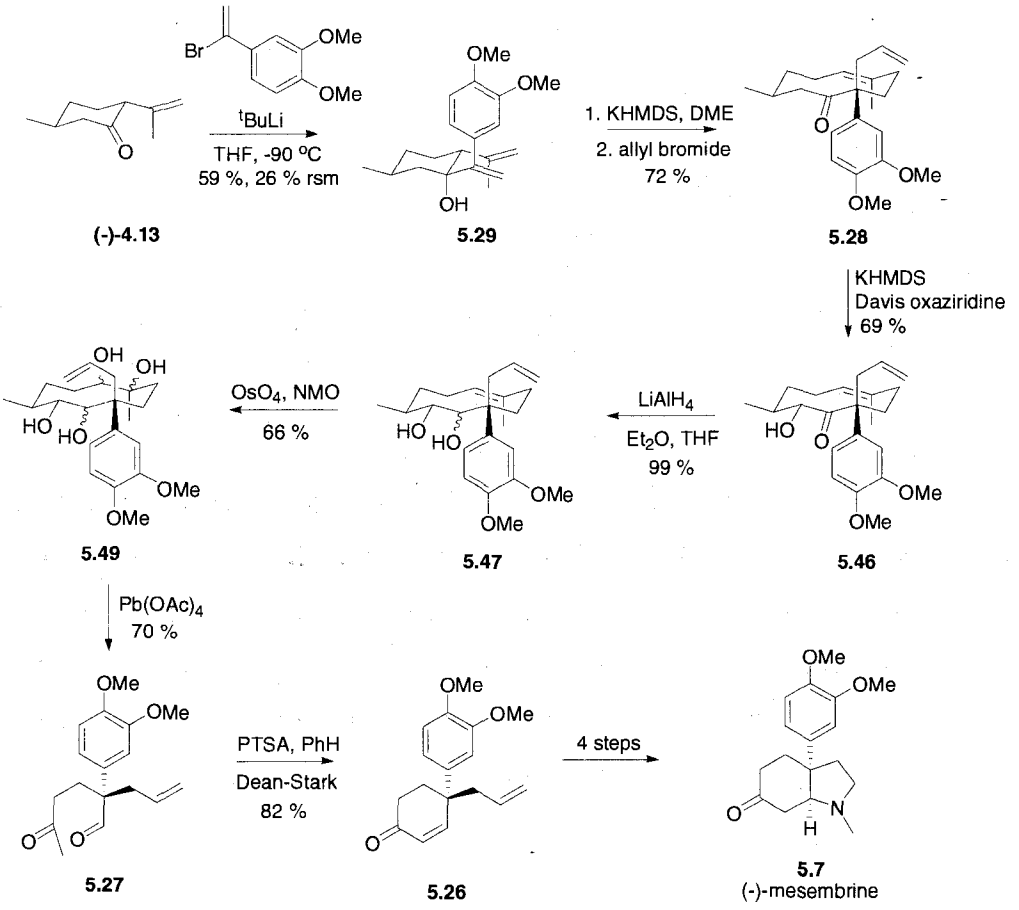
In addition to our synthetic pursuit of teucrolivin A, we also completed the development of an anionic oxy-Cope/alkylation reaction to generate quaternary centers, with a novel method of stereochemical control, as in the conversion of **4.14** to **4.24**.

Scheme 6.4: Anionic oxy-Cope/alkylation



Finally, this unique reaction was applied to the formal synthesis of (-)-mesembrine, which is summarized in Scheme 6.5.

Scheme 6.5: Summarized formal synthesis of (-)-mesembrine



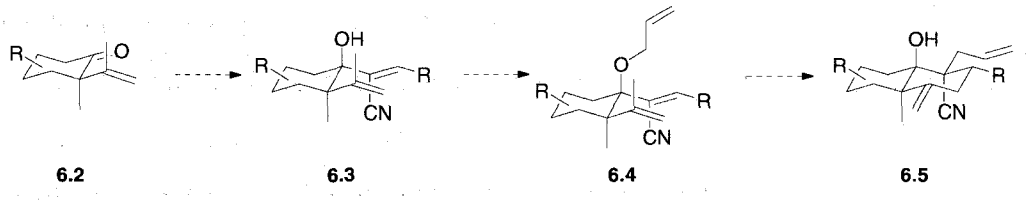
Outlook

It is a reasonable conclusion to state that the synthesis of teucrolivin A using an oxy-Cope/Claisen/ene reaction without the quaternary center in place prior to the reaction is not a viable route. As a result, the key to the synthesis lies with the inclusion of this key feature prior to the reaction, as was studied in Chapter 3.

Future efforts will be directed towards the successful generation of compounds such as **6.4**, which will ideally afford only *trans*-decalin products from the oxy-Cope/Claisen/ene reaction. Furthermore, it will necessary to include distal functionality in order to provide handles to install the specific structural features seen in teucrolivin A. There are obviously many approaches that can be taken to achieve this goal. It is important to note

that although we could alter our main strategy to access this natural product, we are most interested in completing the synthesis using our pericyclic cascade to establish the decalin core of the natural product.

Scheme 6.6: Possible route to the decalin of teucrolivin A



6.2 **6.3** **6.4** **6.5**

Having established the scope and sense of induction for the anionic oxy-Cope/alkylation reaction, efforts are now being directed towards confirming the novel mechanism by which the observed diastereoselectivity arises. As experimental evidence points towards a unique enolate isomeriation, calculations are being performed to validate this theory. Finally, the methodology is being applied to a more complex target. Our hope is to complete the synthesis of a classic target in total synthesis containing a quaternary center, morphine.

Final Comments

This thesis represents an in-depth study of the application of the oxy-Cope/Claisen/ene reaction towards the total synthesis of a complex diterpene natural product. In doing so, we have explored the limitations of this reaction, determining it is hindered when being used to construct congested carbon skeletons. Despite this there remains ample opportunity to develope substrates that will ultimately be useful in giving access to the required carbon system needed for generating teucrolivin A.

In addition, we described the development of a novel method for the construction of all-carbon quaternary centers using macrocyclic conformation as the control element. Our success in the synthesis of the alkaloid (-)-mesembrine opens the door to use this protocol

to synthesize bolder targets, and it is with much anticipation that we await the results of more detailed mechanistic studies.

Claims to Original Research

1. Developed a route to advanced intermediates en route towards the synthesis of teucrolivin A using the oxy-Cope/Claisen/ene reaction
2. Investigated several approaches to install the quaternary center at the decalin ring junction of teucrolivin A which were not successful
3. Generated a series of compounds to determine whether or not the oxy-Cope/Claisen/ene reaction would tolerate a quaternary center adjacent to the tertiary ether in the starting materials
4. It was found the oxy-Cope/Claisen/ene reaction does not tolerate these sterically hindered substrates
5. Completed a study of the scope and mechanism of an anionic oxy-Cope/alkylation reaction to generate quaternary carbon centers where the selectivity is governed by the conformational preferences of a macrocyclic enolate generated from the anionic oxy-Cope reaction
6. Applied the anionic oxy-Cope/alkylation reaction to the formal synthesis of (-)-mesembrine

Publications from this work

(2) "Diastereoselective Construction of Quaternary Carbons Via Macrocyclic Conformation. Formal Synthesis of (-)-Mesembrine" Arns, S. ; Barriault, L.; Lebrun, M. E.; Grisé, C. M.; Denissova, I. *J. Org. Chem.* **2007**, *72*, 9314.

(1) "A Concise Synthesis of the neo-Clerodane Skeleton of Teucrolivin A Using an Oxy-Cope/Claisen/ene Cascade" Arns, S.; Barriault, L. *J. Org. Chem.* **2006**, *71*, 1809.

Presentations from this work

(6) "Teucrolivin A: A Target For Total Synthesis Using A Pericyclic Reaction Cascade" University of Ottawa Synthesis Day, June **2007**.

(5) "Diastereoselective Construction of Quaternary Carbons Directed Via Macrocyclic Ring Conformation: (-)-Mesembrine" Gordon Research Conference in Natural Products, Tilton, NH, July **2006**.

(4) "Towards Teucrolivin A Via An Oxy-Cope/Claisen/Ene Cascade" University of Ottawa Synthesis Day, June **2005**.

(3) "Efforts Towards the Total Synthesis of Teucrolivin A Via The Oxy-Cope/Claisen/Ene Reaction" Symposium International de Synthese Organique de L'Universite de Montreal, University of Montreal, April **2005**.

(2) "Towards Teucrolivin A Via The Tandem Oxy-Cope/Claisen/Ene Reaction" Quebec-Ontario Mini-symposium in Synthetic and Bioorganic Chemistry. Gatineau, Quebec. October **2004**.

(1) "Towards Teucrolivin A Via The Tandem Oxy-Cope/Claisen/Ene Reaction" University of Ottawa Synthesis Day, February **2004**.

7

Experimental

General Experimental Procedures

All reactions were performed under argon or nitrogen unless otherwise dictated by the experimental protocol. Glassware was flame-dried under high vacuum, and each reaction vessel was equipped with a rubber septum and magnetic stir bar. Solvents were typically distilled prior to use. Et_2O and THF were distilled over sodium and benzophenone. DME was distilled over $LiAlH_4$. Toluene, CH_2Cl_2, DMF and Et_3N were distilled over CaH_2. All other solvents and chemicals were used without further purification unless otherwise noted.

Microwave-accelerated reactions were performed in either a CEM Corporation MARS microwave reactor or a CEM Corporation Discover LabMate microwave reactor using a quartz reaction vessel and a carboflon to assist in the absorption of microwaves. All microwave reactions were degassed with argon prior to heating.

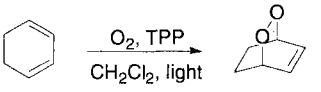
Reactions were monitored by TLC analysis using silica gel coated glass plates. TLC plates were developed by using UV irradiation, p-anisaldehyde staining solution, phosphomolybdic acid staining solution, potassium permanganate staining solution or iodine. Flash chromatography was carried out using 230-400 mesh silica gel.

NMR spectra were recorded on several instruments, including Bruker AVANCE 300 MHz and 400 MHz spectrometers, a Bruker AVANCE 500 MHz Wide Bore

spectrometer and a Varian INOVA 500 MHz spectrometer. Spectra were calibrated according to standardized chemical shifts[94] of the NMR solvent.

IR spectra were recorded on a Bomen Michaelson FT-IR spectrometer. HRMS spectra were otained on a Kratos Analytical Concept spectrometer and melting points were measured on a Gallenkamp P1106G Melting Point Apparatus.

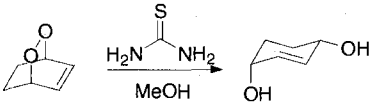
Experimental Data



2.23 **2.31**

2,3-Dioxa-bicyclo[2.2.2]octane (**2.31**)

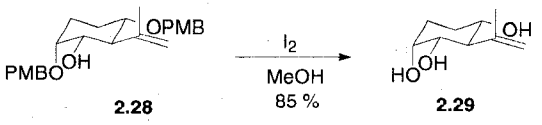
A solution of 1,3-cyclohexadiene (10.00 g, 124.8 mmol) in CH_2Cl_2 (500 mL) was degassed with O_2 for 15 minutes after which was added 5,10,15,20-tetraphenyl-21H,23H-porphine (abbreviated TPP, 275.2 mg, 0.4480 mmol). The resulting deep purple solution was irradiated with a 200 W tungsten lamp for 8 hours while being bubbled with a constant stream of O_2. The reaction mixture was concentrated to a total volume of 50 mL under reduced pressure and low heat, and this crude mixture was used directly in the next reaction.



2.31 **2.25**

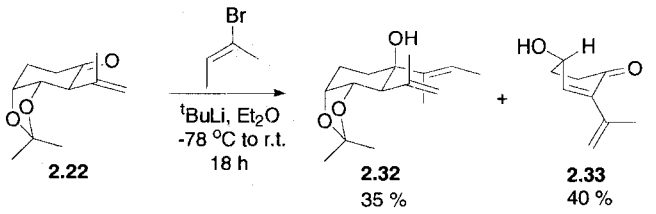
(±)-(1S,4R)-Cyclohex-2-ene-1,4-diol (**2.25**)

The crude mixture **2.31** was dissolved in MeOH (500 mL) and treated with thiourea (11.40 g, 149.8 mmol). The resulting mixture was stirred at room temperature for 18 hours, after which suspended solids in the reaction medium were removed by filtration through a short pad of silica. The solvent was removed under reduced pressure and the residue was preadsorbed onto silica gel (20 g). The product was isolated by flash chromatography (EtOAc) to yield **2.25** as a pink solid (11.87 g, 104.0 mmol, 83 % over 2 steps). It is also possible to not preadsorb the crude product on to silica and use it in the next step directly. Characterization data corresponds to that known in the literature.



(±)-(1S,2R,3S,4R)-3-(Prop-1-en-2-yl)cyclohexane-1,2,4-triol (**2.29**)

2.28 (7.21 g, 17.4 mmol) was dissolved in a 1 % w/v solution of I_2 in MeOH (200 mL) and the mixture was heated at reflux for 4 hours. The solution was cooled to room temperature and Na_2SO_3 was added in small portions until the solution became clear pale yellow. This mixture was filtered and the crude product was preadsorbed onto silica gel by evaporation of the solvent. Flash chromatography in EtOAc afforded **2.29** (2.52 g, 14.6 mmol, 85 %, R_f = 0.15) as a yellow oil. Spectroscopic data are in agreement with that found in the literature.



(±)-(3aR,4R,5S,7aS)-5-((E)-But-2-en-2-yl)-hexahydro-2,2-dimethyl-4-(prop-1-en-2-yl)benzo[d][1,3]dioxol-5-ol (**2.32**)

To a solution of E-2-bromo-2-butene (3.74 mL, 36.9 mmol) in ether (100 mL) cooled to -78 °C was added ^{t}BuLi (1.70 M in hexanes, 43.4 mL, 73.8 mmol) and the resulting solution was stirred for 2 hours. After this, a solution of **2.22** (2.22 g, 10.5 mmol) in ether (10 mL) was added, and the solution was stirred for 2 hours while warming to room temperature, and then for a further 16 hours at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the layers were separated. The aqueous layer was extracted with ether (3 × 50 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 20 % EtOAc/hexanes afforded **2.32** (984.0 mg, 3.68 mmol, 35 %, R_f = 0.50) as a pale yellow solid and **2.33** (642.9 mg, 4.22 mmol, 40 %, R_f = 0.15) as a colorless oil.

Data for **2.32**

M.p.: 85-86 °C

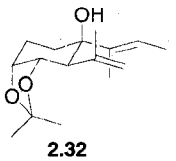
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.44 (q, J = 6.5 Hz, 1H), 4.96 (s, 1H), 4.78 (s, 1H), 4.28-4.24 (m, 2H), 2.45 (d, J = 8.7 Hz, 1 H), 2.19-1.90 (m, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.56 (d, J = 7.2 Hz, 3H), 1.51 (s, 3H), 1.34 (s, 3H), 1.27-1.23 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8 (C_4), 139.9 (C_4), 117.0 (CH), 113.6 (CH_2), 107.8 (C_4), 77.2 (CH), 73.1 (CH), 51.6 (CH), 31.0 (CH_2), 28.9 (CH_3), 26.5 (CH_3), 24.0 (CH_3), 22.4 (CH_2), 13.7 (CH_3), 13.4 (CH_3) One carbon (oxygen C_4) is not detected due to a long relaxation delay

FT-IR (neat, cm^{-1}): 3478 (b), 2987 (s), 2931 (s), 2874 (m)

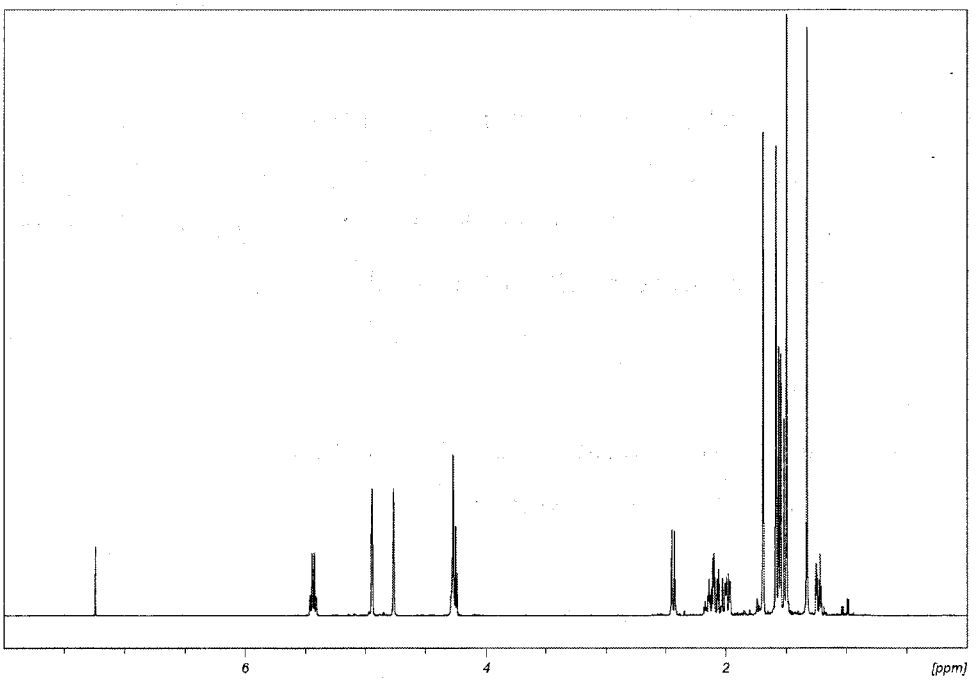
HRMS (EI): Calculated 266.1882 (M^+) for $C_{16}H_{26}O_3$, found 266.1921

Compound **2.33** is characterized in p. 111.

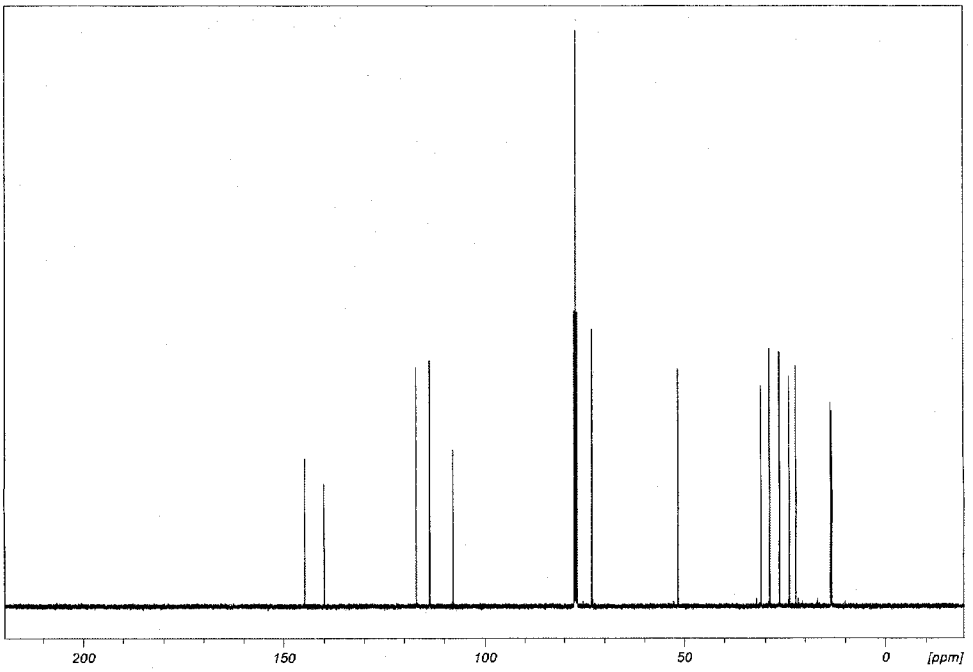


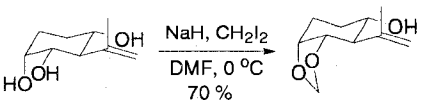
2.32

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





2.29 **2.34**

(±)-(3aR,4S,5R,7aS)-Hexahydro-4-(prop-1-en-2-yl)benzo[d][1,3]dioxol-5-ol (**2.34**)

To a solution of **2.29** (114.0 mg, 0.662 mmol) in DMF (7 mL) cooled to 0 °C was added NaH (60 % dispersion in oil, 158.9 mg, 3.97 mmol). The resulting mixture was stirred at 0 °C for 10 minutes after which was added diiodomethane (0.06 mL, 0.745 mmol). This mixture was stirred at room temperature for 18 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 50 % EtOAc/hexanes to afford **2.34** (88.9 mg, 0.463 mmol, 70 %, R_f = 0.50) as a yellow oil.

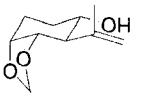
Data for **2.34**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.21 (s, 1H), 5.12-.511 (m, 1H), 4.98-4.93 (m, 2H), 4.05 (dd, J = 9.4, 4.8 Hz, 1H), 3.99-3.96 (m, 1H), 3.47(ddd, J = 10.6, 10.6, 3.8 Hz, 1H), 2.31-2.26 (m, 1H), 1.90-1.58 (m, 5H), 1.83 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.7 (C_4), 116.6 (CH_2), 94.6 (CH_2), 76.0 (CH), 74.3 (CH), 68.2 (CH), 55.4 (CH), 28.1 (CH_2), 23.7 (CH_2), 19.5 (CH_3)

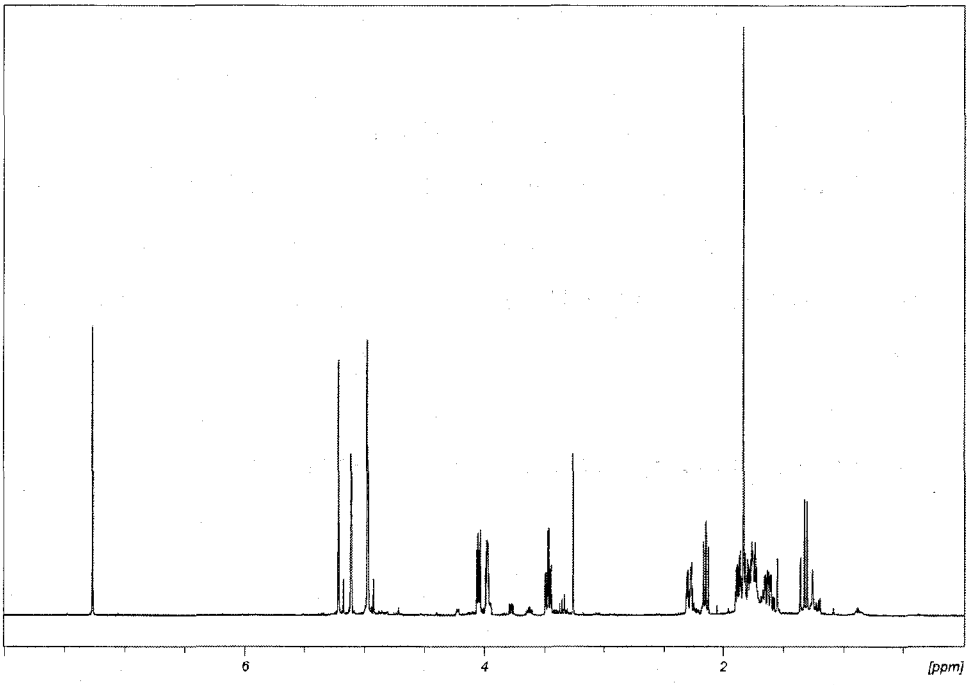
FT-IR (neat, cm^{-1}): 3411 (b), 3075 (w), 3941 (s), 2871 (s), 2771 (m)

HRMS (EI): Calculated 184.1099 (M^+) for $C_{10}H_{16}O_3$, found (M^+-H_2O) at 166.1010, actual value 166.0994

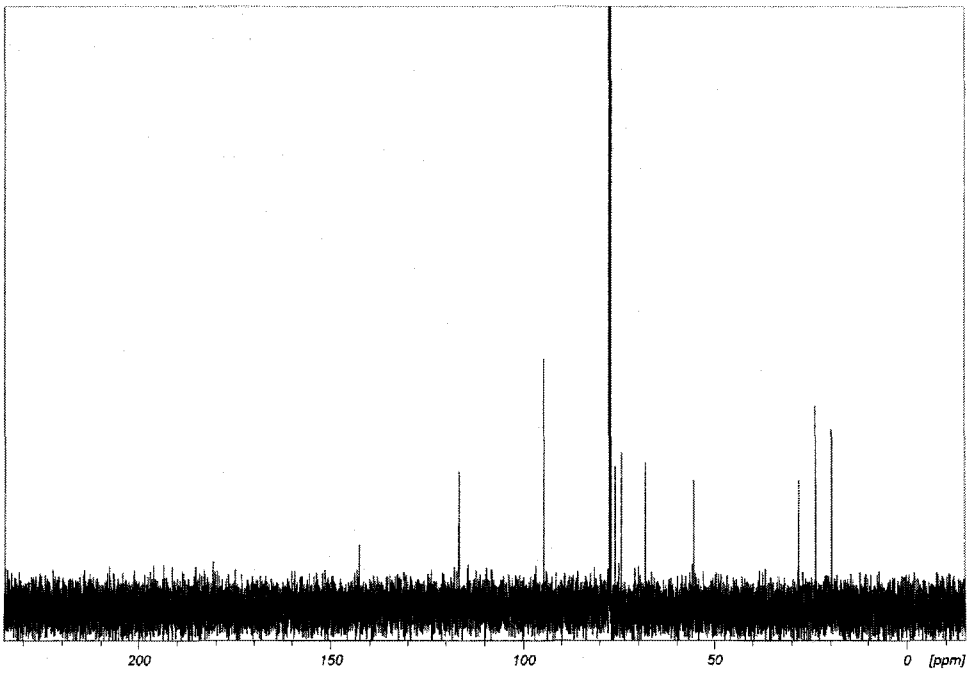


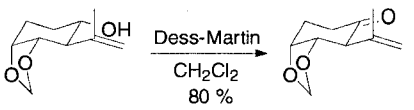
2.34

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.34 **2.35**

(±)-(3aR,4R,7aS)-Tetrahydro-4-(prop-1-en-2-yl)benzo[d][1,3]dioxol-5(6H)-one (**2.35**)

To a solution of **2.34** (12.7 mg, 0.0689 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (58.5 mg, 0.138 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (5 mL) followed by 5 minutes of stirring. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 30 % EtOAc/hexanes to afford **2.35** (10.0 mg, 0.0549 mmol, 80 %, R_f = 0.60) as a yellow oil.

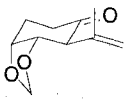
Data for **2.35**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16 (s, 1H), 5.06-5.05 (m, 1H), 4.77 (s, 1H), 4.74 (d, J = 1.4 Hz, 1H), 4.49-4.32 (m, 2H), 3.30 (d, J = 4.7 Hz, 1H), 2.57-2.45 (m, 1H), 2.26-2.11 (m, 2H), 2.09-2.00 (m, 1H), 1.79 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3 (C_4), 139.3 (C_4), 115.1 (CH_2), 94.2 (CH_2), 75.9 (CH), 72.3 (CH), 59.0 (CH), 34.3 (CH_2), 24.6 (CH_2), 22.1 (CH_3)

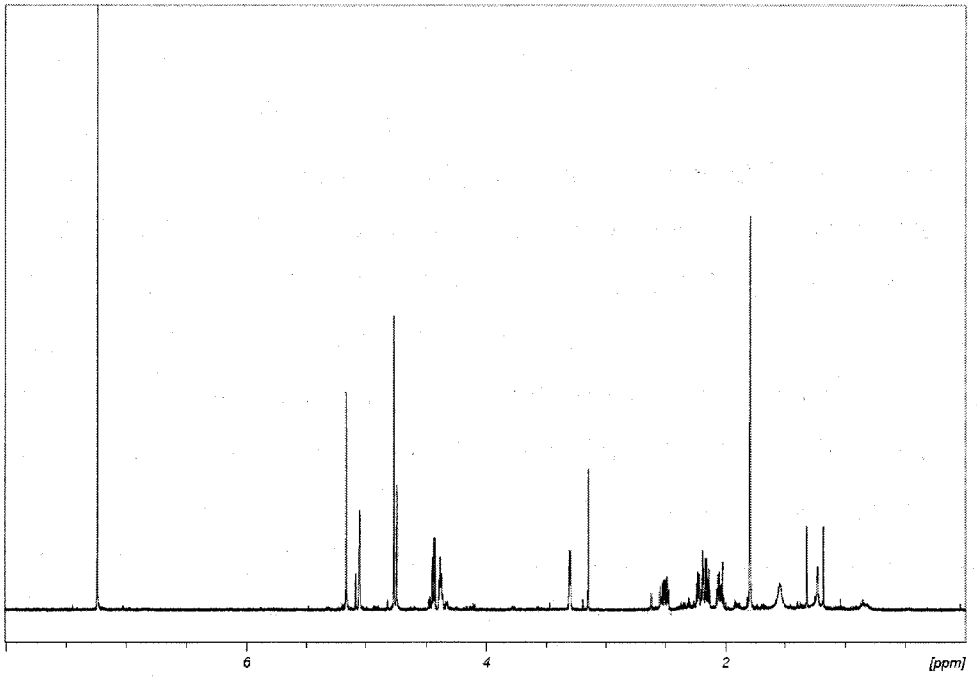
FT-IR (neat, cm^{-1}): 2925 (m), 2851 (m), 2753 (w), 1717 (s)

HRMS (EI): Calculated 182.0943 (M^+) for $C_{10}H_{14}O_3$, found 182.0929

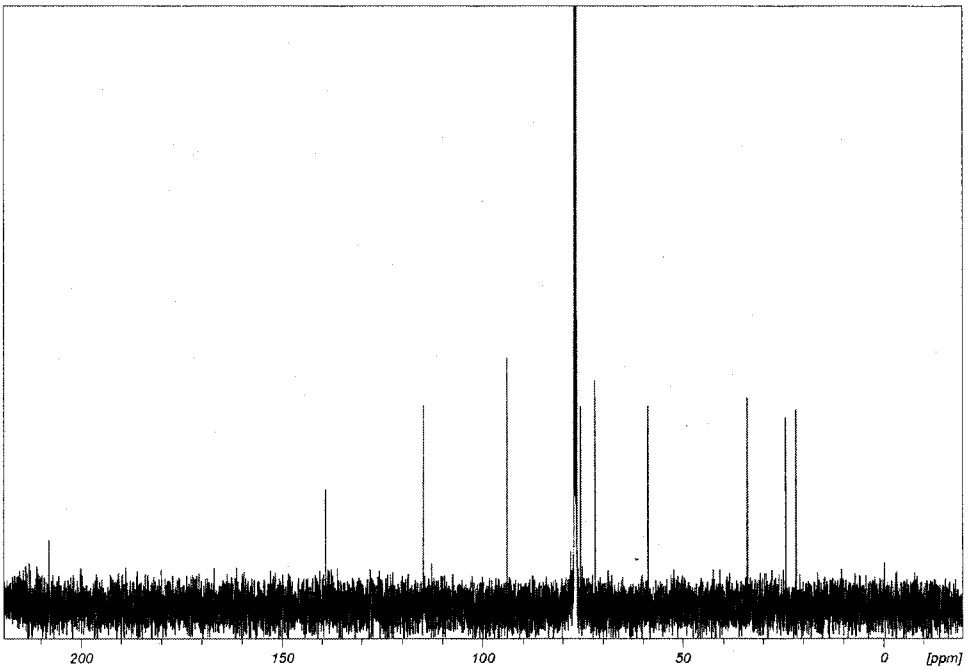


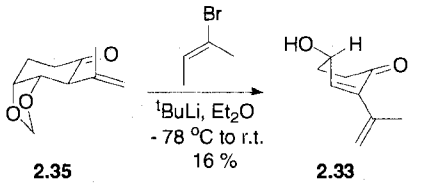
2.35

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)





2.35 **2.33**

(±)-4-Hydroxy-2-(prop-1-en-2-yl)cyclohex-2-enone (**2.33**)

To a solution of E-2-bromo-2-butene (0.02 mL, 0.197 mmol) in Et_2O (2 mL) cooled to -78 °C was added ^{t}BuLi (1.70 M in hexanes, 0.23 mL, 0.391 mmol) and the mixture was stirred at -78 °C for 2 hours. To this mixture was added **2.35** (10.0 mg, 0.0549 mmol) as a solution in Et_2O (2 mL) and the resulting solution was stirred at -78 °C for 2 hours, 2 hours while warming to room temperature and a further 16 hours at room temperature. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 50 % EtOAc/hexanes to give **2.33** (2.1 mg, 0.00881 mmol, 16 %, R_f = 0.45) as a colorless oil.

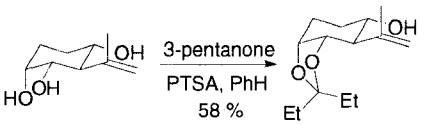
Data for **2.33**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79 (d, J = 2.5 Hz, 1H), 5.21 (s, 1H), 5.10 (s, 1H), 4.64-4.60 (m, 1H), 2.65 (ddd, J = 16.5, 4.4, 4.4 Hz, 1H), 2.45-2.39 (m, 1H), 2.38-2.32 (m, 1H), 2.05-1.94 (m, 1H), 1.92 (s, 3H), 1.72 (bs, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.6 (C_4), 147.3 (CH), 141.1 (C_4), 140.5 (C_4), 117.2 (CH_2), 67.1 (CH), 36.7 (CH_2), 32.8 (CH_2), 22.5 (CH_3)

FT-IR (neat, cm^{-1}): 3395 (b), 2953 (m), 2925 (m), 2874 (m), 2855 (m), 1673 (s)

HRMS (EI): Calculated 152.0873 (M^+) for $C_9H_{12}O_2$, found 152.0831



2.29 **2.36**

(±)-(3aR,4S,5R,7aS)-2,2-Diethyl-hexahydro-4-(prop-1-en-2-yl)benzo[d][1,3]dioxol-5-ol (**2.36**)

3-pentanone (0.38 mL, 3.59 mmol) and PTSA (6.8 mg, 0.0357 mmol) were added to a solution of **2.29** (61.9 mg, 0.359 mmol) in benzene (6 mL) and the resulting mixture was heated at reflux for 1 hour, using a Dean-Stark trap to remove H_2O. The mixture was cooled to room temperature and the reaction was quenched by adding saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 40 % EtOAc/hexanes, affording **2.36** (50.0 mg, 0.208, 58 %, $R_f = 0.55$) as a colorless oil.

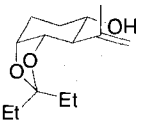
Data for **2.36**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.09 (s, 1H), 4.95 (s, 1H), 4.23-4.20 (m, 1H), 4.00 (dd, J = 9.5, 5.1 Hz, 1H), 3.44 (ddd, J = 10.6, 10.6, 7.8 Hz, 1H), 2.27-2.17 (m, 2H), 1.86-1.70 (m, 5H), 1.82 (s, 3H), 1.68-1.57 (m, 3H), 0.97 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.2 (C_4), 116.2 (CH_2), 112.9 (C_4), 76.8 (CH), 72.8 (CH), 68.5 (CH), 57.5 (CH), 30.7 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 24.1 (CH_2), 19.7 (CH_3), 8.9 (CH_3), 8.8 (CH_3)

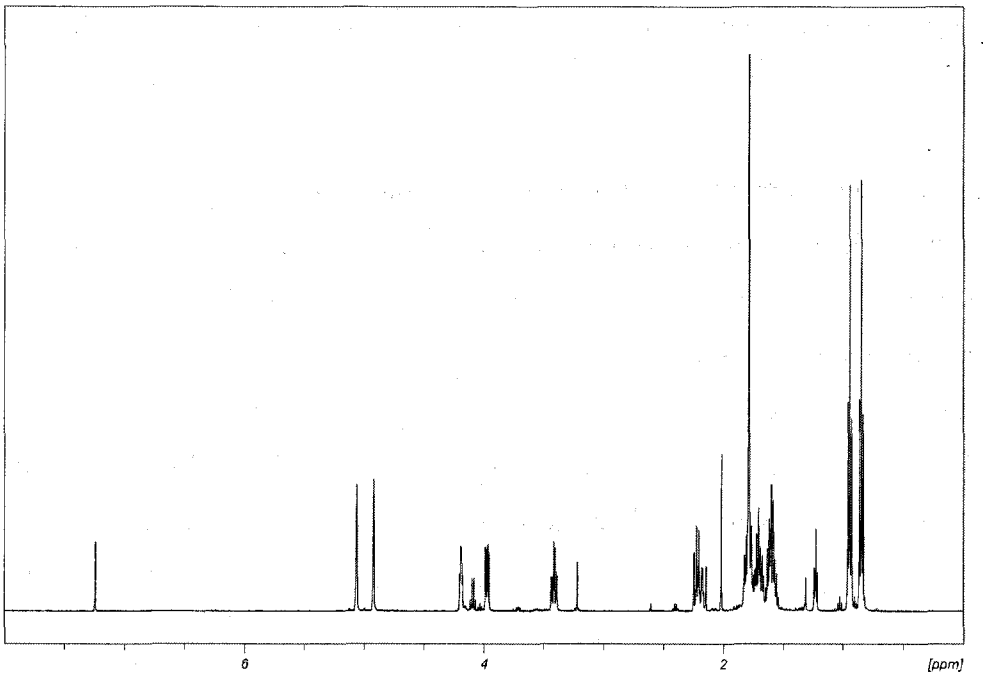
FT-IR (neat, cm^{-1}): 3423 (b), 3076 (w), 2968 (s), 2941 (s), 2875 (s)

HRMS (EI): Calculated 240.1725 (M^+) for $C_{14}H_{24}O_3$, found (M^+-Et) at 211.1339, actual value 211.1334

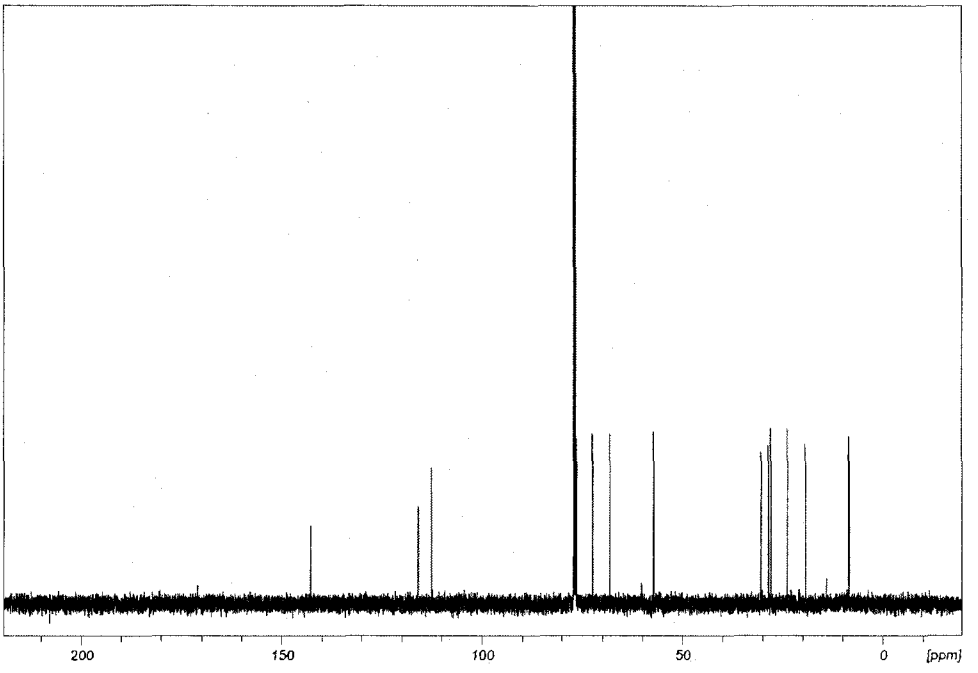


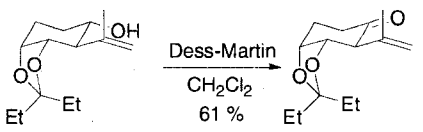
2.36

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.36 **2.37**

(±)-(3aR,4R,7aS)-2,2-Diethyl-tetrahydro-4-(prop-1-en-2-yl)benzo[d][1,3]dioxol-5(6H)-one (**2.37**)

To a solution of **2.36** (50.0 mg, 0.208 mmol) in CH_2Cl_2 (4 mL) was added Dess-Martin periodinane (176.4 mg, 0.416 mmol) and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction was quenched by adding saturated aqueous $NaHCO_3$ (5 mL) followed by 5 minutes of stirring. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 20 % EtOAc/hexanes to afford **2.37** (30.2 mg, 0.127 mmol, 61 %, $R_f = 0.45$) as a yellow oil.

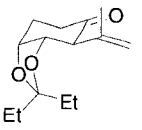
Data for **2.37**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.06 (s, 1H), 4.75 (s, 1H), 4.61 (dd, J = 7.3, 5.1 Hz, 1H), 4.56-4.52 (m, 1H), 3.26 (d, J = 5.1 Hz, 1H), 2.58-2.51 (m, 1H), 2.24-2.16 (m, 2H), 2.07-2.00 (m, 1H), 1.80 (s, 3H), 1.72 (q, J = 7.5 Hz, 2H), 1.66 (q, J = 7.6 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.1 (C_4), 139.6 (C_4), 115.0 (CH_2), 112.4 (C_4), 75.2 (CH), 72.0 (CH), 59.8 (CH), 34.3 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 24.9 (CH_2), 22.0 (CH_3), 8.9 (CH_3), 7.8 (CH_3)

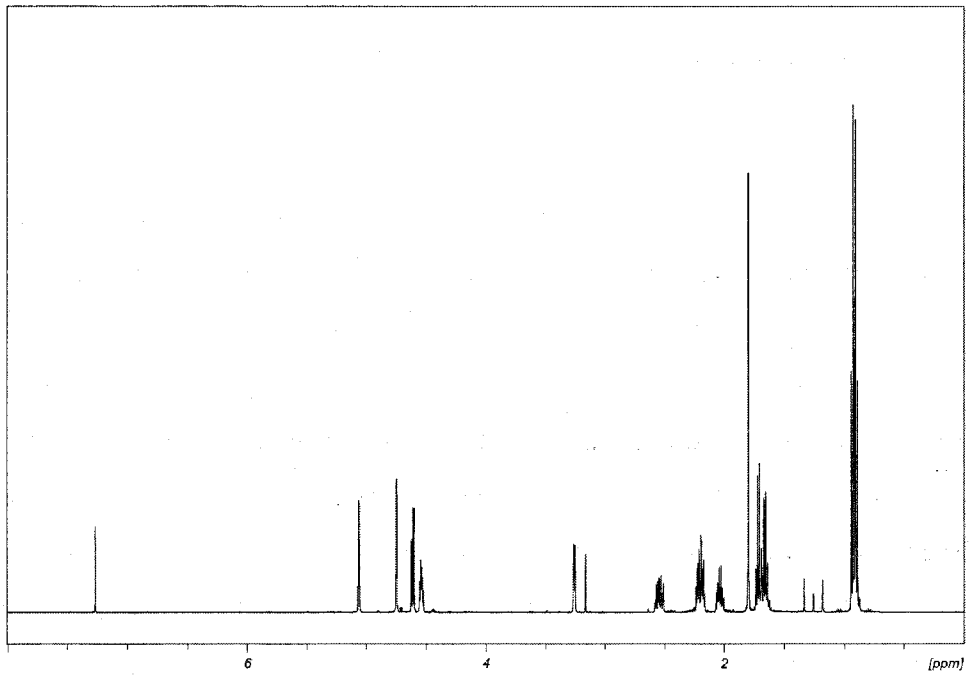
FT-IR (neat, cm^{-1}): 2980 (s), 2941 (s), 2883 (m), 1719 (s)

HRMS (EI): Calculated 238.1569 (M^+) for $C_{14}H_{22}O_3$, found 238.1562

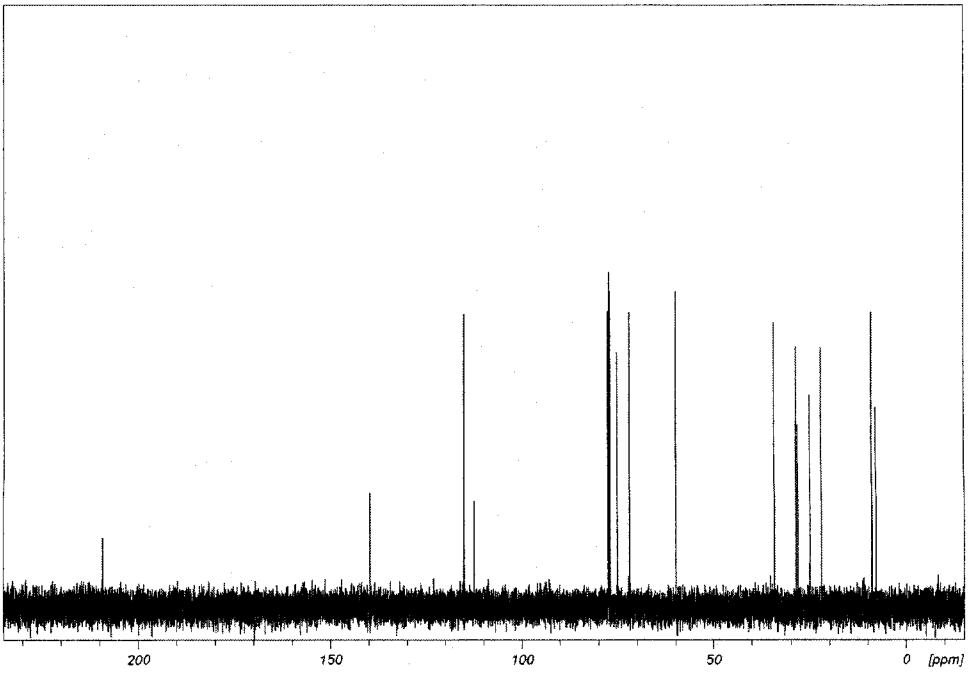


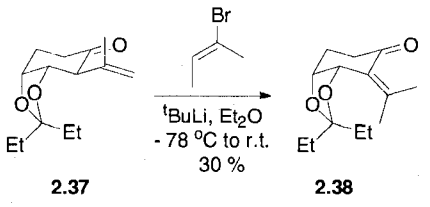
2.37

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.37 **2.38**

(±)-(3aR,7aS)-2,2-Diethyl-tetrahydro-4-(propan-2-ylidene)benzo[d][1,3]dioxol-5(6H)-one (**2.38**)

To a solution of E-2-bromo-2-butene (0.05 mL, 0.493 mmol) in Et_2O (4 mL) cooled to -78 °C was added ^{t}BuLi (1.70 M in hexanes, 0.23 mL, 0.391 mmol) and the mixture was stirred at -78 °C for 2 hours. To this mixture was added **2.37** (30.2 mg, 0.127 mmol) as a solution in Et_2O (2 mL) and the resulting solution was stirred at -78 °C for 2 hours then for a further 16 hours at room temperature. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 20 % EtOAc/hexanes to give **2.38** (9.1 mg, 0.0382 mmol, 30 %, $R_f = 0.40$) as a colorless oil.

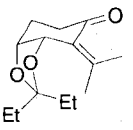
Data for **2.38**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.25 (d, J = 7.5 Hz, 1H), 4.55-4.53 (m, 1H), 2.66 (ddd, J = 13.7, 13.7, 4.5 Hz, 1H), 2.25-2.20 (m, 1H), 2.14 (s, 3H), 2.09-2.04 (m, 1H), 2.01 (s, 3H), 1.75-1.64 (m, 5H), 0.92 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.4 (C_4), 153.9 (C_4), 129.3 (C_4), 111.8 (C_4), 73.5 (CH), 72.8 (CH), 34.8 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 25.6 (CH_2), 24.2 (CH_3), 23.0 (CH_3), 9.0 (CH_3), 8.1 (CH_3)

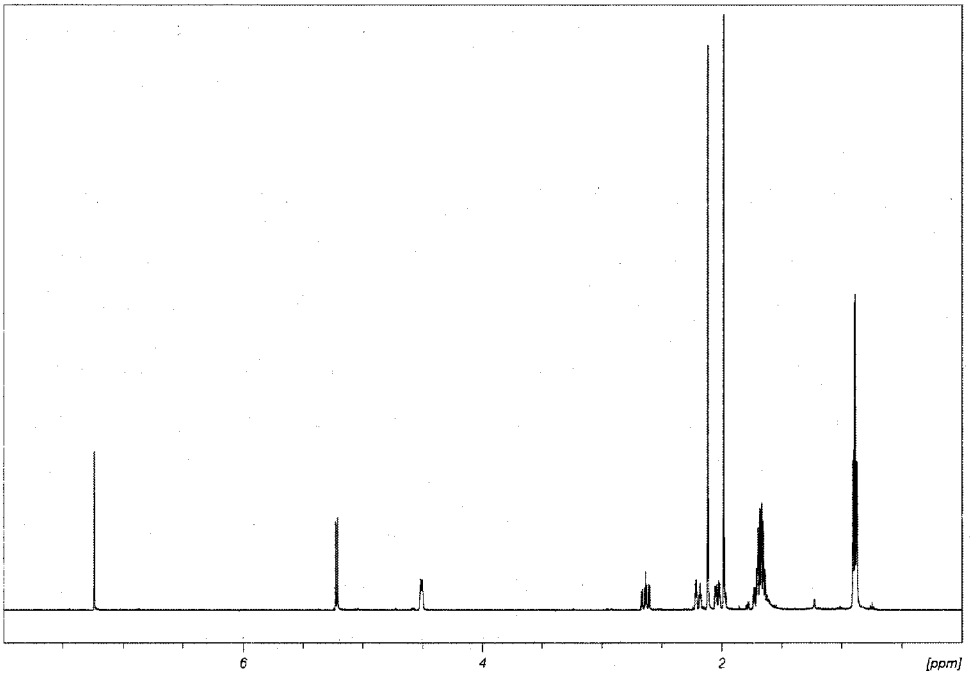
FT-IR (neat, cm^{-1}): 2971 (s), 2941 (s), 2887 (m), 1689 (s)

HRMS (EI): Calculated 238.1569 (M^+) for $C_{14}H_{22}O_3$, found (M^+-Et) at 209.1173, actual value 209.1178

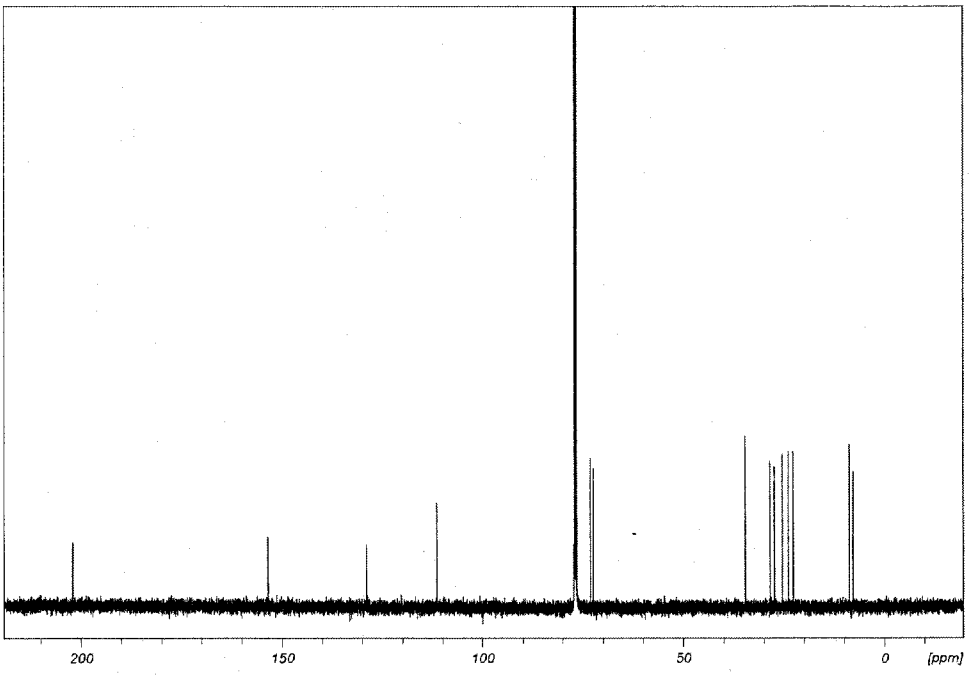


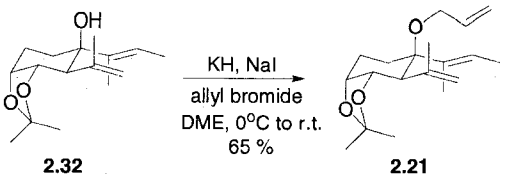
2.38

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





(±)-(3aR,4R,5S,7aS)-5-(Allyloxy)-5-((E)-but-2-en-2-yl)-hexahydro-2,2-dimethyl-4-(prop-1-en-2-yl)benzo[d][1,3]dioxole (**2.21**)

A mixture of NaI (4.2 mg, 0.0280 mmol) and KH (30 % dispersion in oil, 75.0 mg, 0.561 mmol) was washed with hexanes to remove mineral oil and was dried under high vacuum. These solids were suspended in DME (1.5 mL) and the mixture was cooled to 0 °C whereupon a solution of **2.32** in DME (1 mL) was added followed by 10 minutes of stirring. To this mixture was added allyl bromide (0.07 mL, 0.800 mmol), and the mixture was stirred while warming to room temperature for 2 hours, then at room temperature for 16 hours. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes yielded **2.21** (16.8 mg, 0.0548 mmol, 65 %, R_f = 0.50) as a yellow oil.

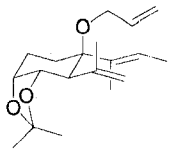
Data for **2.21**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.91-5.78 (m, 1H), 5.39 (q, J = 6.7 Hz, 1H), 5.27 (dd, J = 17.2, 1.7 Hz, 1H), 5.07 (dd, J = 9.9, 1.4 Hz, 1H), 4.88 (s, 1H), 4.72 (s, 1H), 4.41 (dd, J = 9.8, 4.7 Hz, 1H), 4.32-4.30 (m, 1H), 3.67 (m, 2H), 2.18 (d, J = 9.9 Hz, 1H), 2.07-1.83 (m, 2H), 1.79 (s, 3H), 1.69-1.62 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H), 1.50 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.0 (C_4), 136.1 (CH), 135.4 (C_4), 120.5 (CH), 115.3 (CH_2), 114.5 (CH_2), 107.9 (C_4), 83.7 (C_4), 76.9 (CH), 62.5 (CH), 56.1 (CH_2), 31.7 (CH), 28.8 (CH_2), 26.6 (CH_3), 26.0 (CH_3), 22.5 (CH_3), 14.3 (CH_2), 13.7 (CH_3), 13.5 (CH_3)

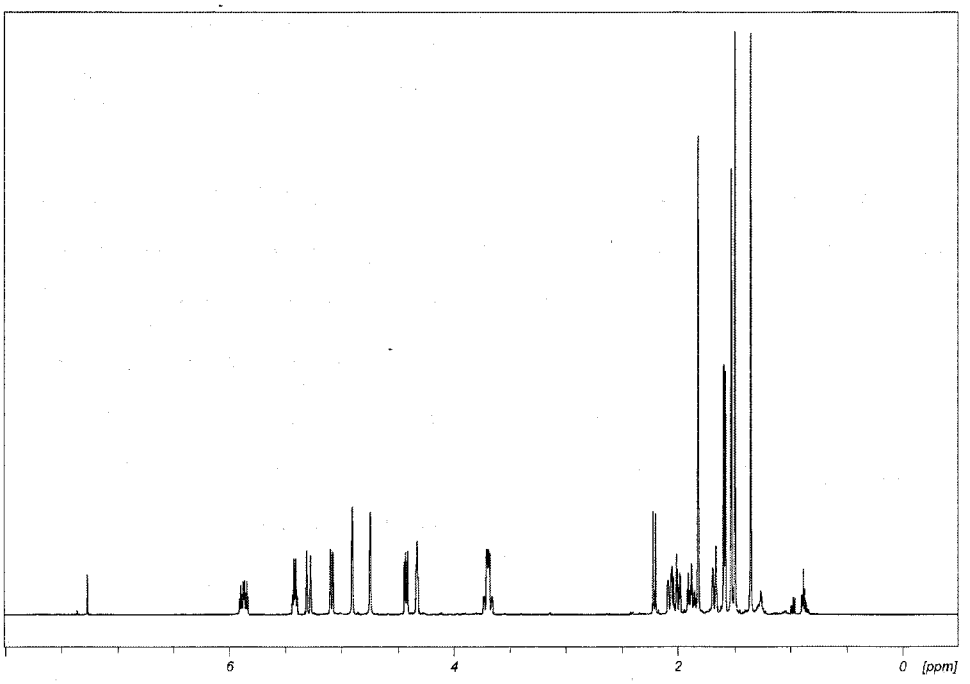
FT-IR (neat, cm^{-1}): 2984 (s), 2968 (s), 2933 (s), 2871 (s), 1643 (m)

HRMS (EI): Calculated 306.2195 (M^+) for $C_{19}H_{30}O_3$, found 306.2333

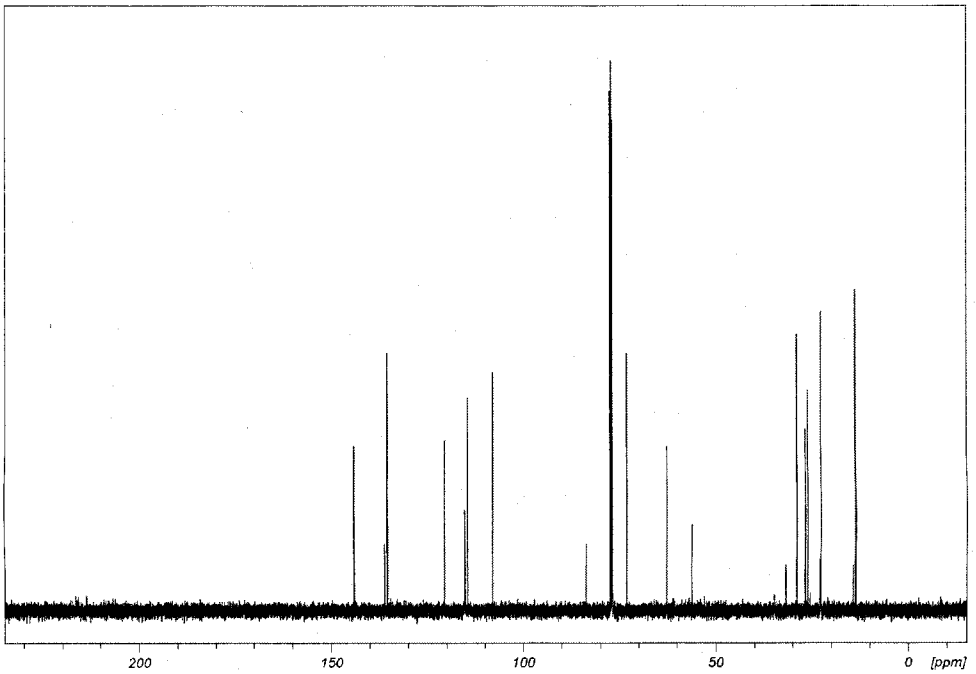


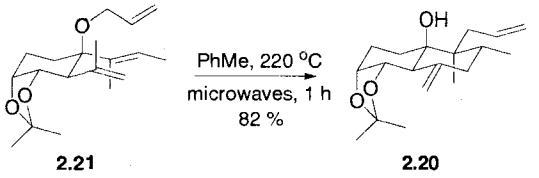
2.21

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.21 **2.20**

(±)-(3aR,5aR,6S,7R,9aS,9bS)-6-Allyl-decahydro-2,2,6,7-tetramethyl-9-methylenenaphtho[2,1-d][1,3]dioxol-5a-ol (**2.20**)

A sample of **2.21** (25.5 mg, 0.0832 mmol) was dissolved in toluene (13 mL) and placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated and the product was recovered by flash chromatography in 10 % EtOAc/hexanes, affording **2.20** (19.9 mg, 0.0649 mmol, 82 %, $R_f = 0.40$) as a yellow oil.

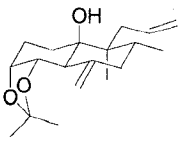
Data for **2.20**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11-6.02 (m, 1H), 5.06 (d, J = 17.2 Hz, 1H), 5.02 (s, 1H), 4.98 (d, J = 10.1 Hz, 1H), 4.94 (s, 1H), 4.33 (dd, J = 8.6, 5.4 Hz, 1H), 4.27-4.24 (m, 1H), 2.34 (dd, J = 15.4, 9.2 Hz), 2.29 (d, J = 8.8 Hz, 1H), 2.20-2.04 (m, 5H), 1.95-1.88 (m, 2H), 1.68-1.61 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H), 0.89 (d, J = 6.3 Hz, 3H), 0.88 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.1 (C_4), 138.2 (CH), 116.4 (CH_2), 109.5 (CH_2), 107.8 (C_4), 79.5 (C_4), 74.9 (CH), 72.8 (CH), 47.1 (CH), 44.8 (C_4), 41.1 (CH_2), 40.0 (CH_2), 34.2 (CH), 28.6 (CH_3), 26.3 (CH_2), 26.2 (CH_3), 22.5 (CH_2), 16.9 (CH_3), 15.9 (CH_3)

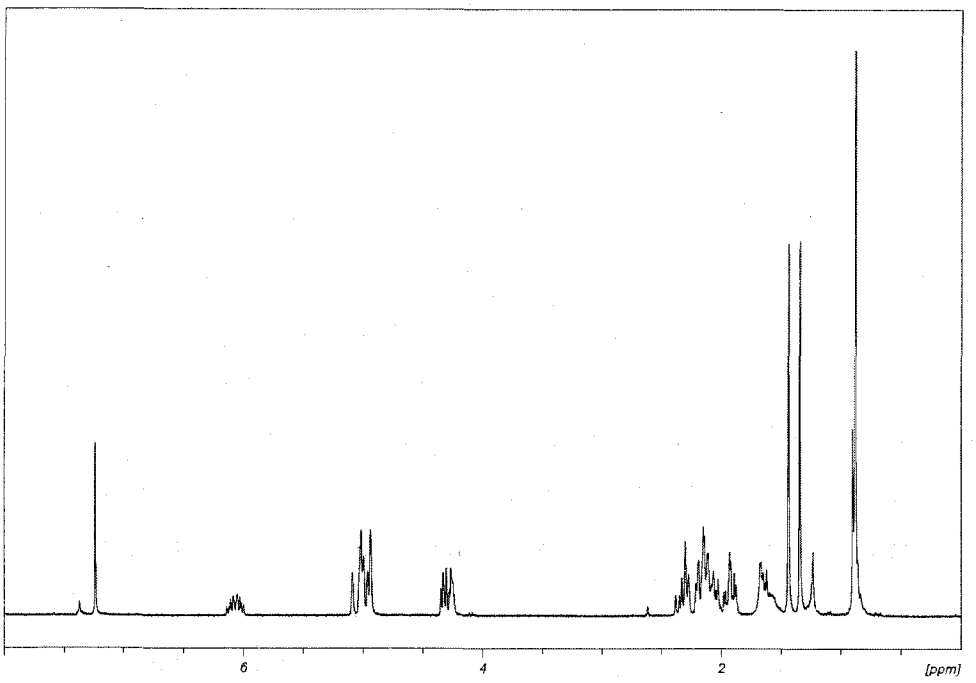
FT-IR (neat, cm^{-1}): 3561 (b), 2983 (s), 2956 (m), 2937 (s), 2880 (s)

HRMS (EI): Calculated 306.2195 (M^+) for $C_{19}H_{30}O_3$, found 306.2199

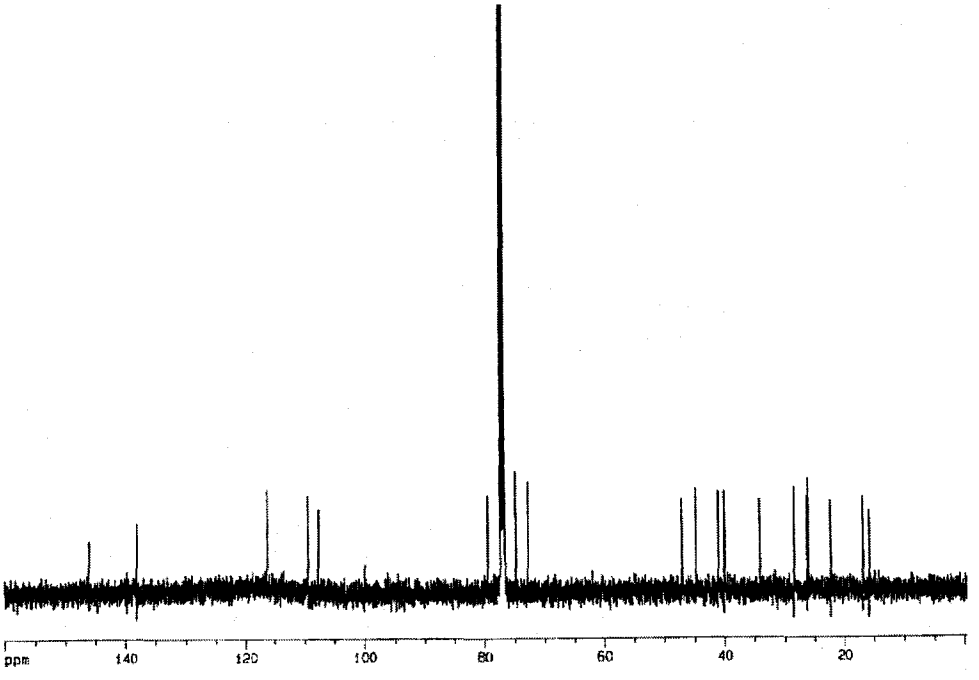


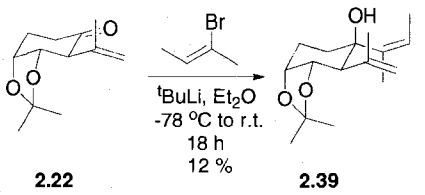
2.20

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.22 **2.39**

(±)-(3aR,4R,5S,7aS)-5-((Z)-But-2-en-2-yl)-hexahydro-2,2-dimethyl-4-(prop-1-en-2-yl)benzo[d][1,3]dioxol-5-ol (**2.39**)

To a solution of Z-2-bromo-2-butene (0.26 mL, 5.1 mmol) in ether (5 mL) cooled to -78 °C was added ^{t}BuLi (1.55 M in hexanes, 3.31 mL, 5.13 mmol), and the resulting solution was stirred for 2 hours. After this, a solution of **2.22** (134.6 mg, 0.640 mmol) in ether (8 mL) was added, and the solution was stirred for 2 hours while warming to room temperature, and then for a further 16 hours at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the layers were separated. The aqueous layer was extracted with ether (3 × 20 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 20 % EtOAc/hexanes afforded **2.39** (19.8 mg, 0.0743 mmol, 12 %, R_f = 0.50) as a pale yellow oil.

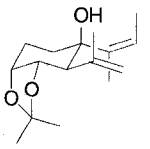
Data for **2.39**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.30 (dq, J = 7.4, 1.4 Hz, 1H), 5.08 (s, 1H), 4.94 (s, 1H), 4.32-4.28 (m, 2H), 2.59 (d, J = 9.0, 1H), 2.21-2.13 (m, 2H), 2.05-1.99 (m, 1H), 1.89 (s, 3H), 1.82 (bs, 1H), 1.79 (dd, J = 7.5, 1.4 Hz, 3H), 1.69 (s, 3H), 1.54 (s, 3H), 1.52-1.50 (m, 1H), 1.37 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.5 (C_4), 139.7 (C_4), 120.5 (CH), 113.3 (CH_2), 107.7 (C_4), 80.1 (C_4) 77.6 (CH), 73.0 (CH), 51.5 (CH), 31.0 (CH_2), 28.7 (CH_3), 26.4 (CH_3), 25.2 (CH_3), 23.4 (CH_3), 22.0 (CH_2), 15.2 (CH_3)

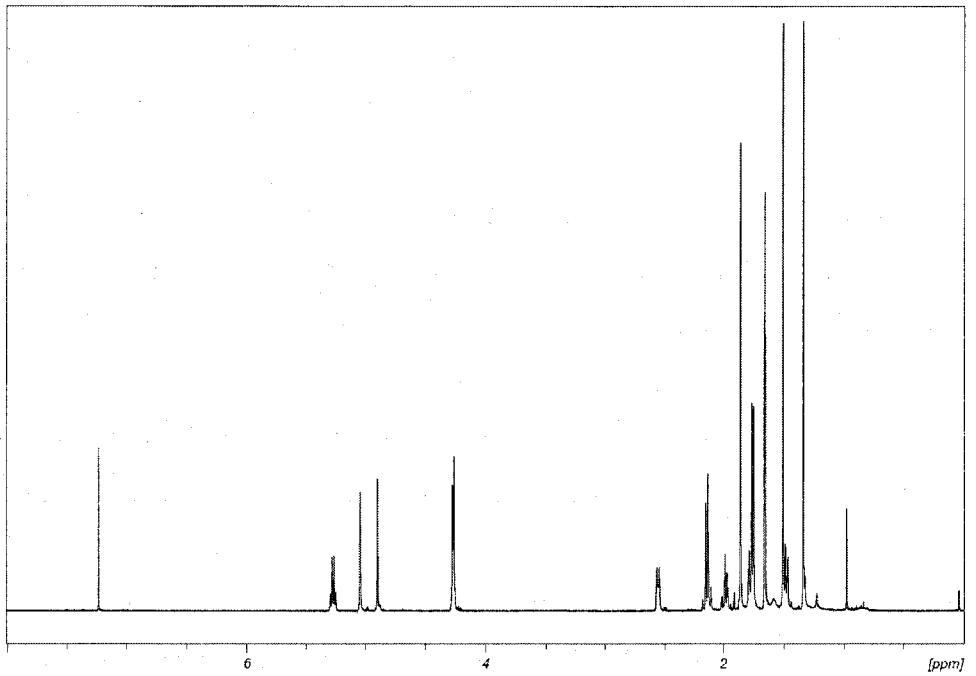
FT-IR (neat, cm^{-1}): 3492 (b), 2986 (s), 2967 (s), 2934 (m), 2871 (m)

HRMS (EI): Calculated 266.1882 (M^+) for $C_{16}H_{26}O_3$, found 266.1890

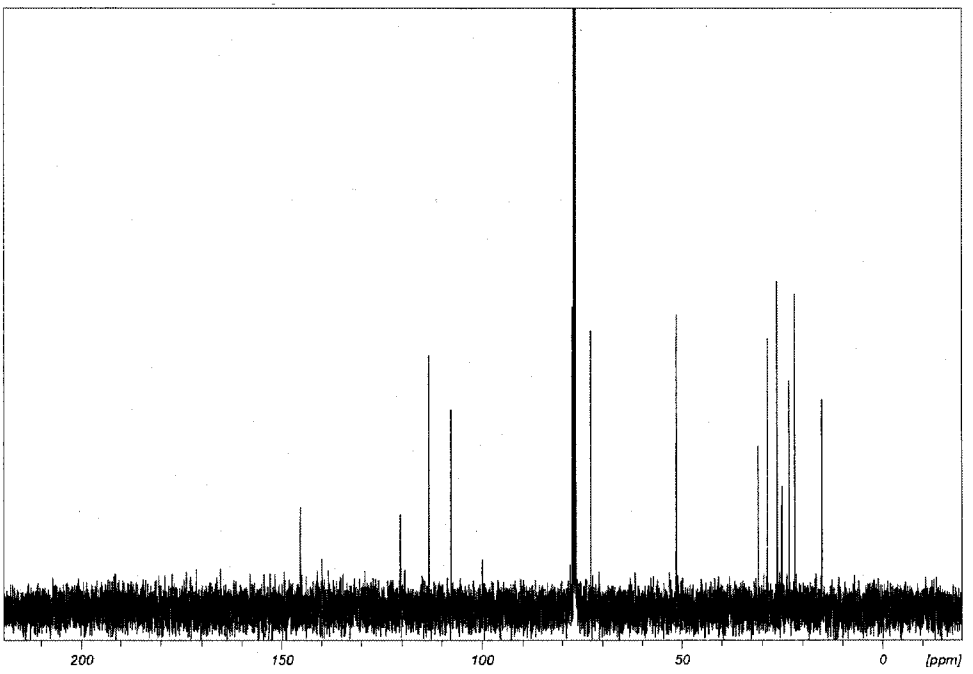


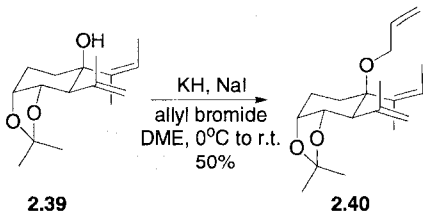
2.39

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.39 **2.40**

(±)-(3aR,4R,5S,7aS)-5-(Allyloxy)-5-((Z)-but-2-en-2-yl)-hexahydro-2,2-dimethyl-4-(prop-1-en-2-yl)benzo[d][1,3]dioxole (**2.40**)

NaI (0.6 mg, 0.004 mmol) was placed in a flask and flame dried, then KH (30 % dispersion in oil, 34.7 mg, 0.519 mmol) was added and washed with hexanes to remove mineral oil. The solids were dried under high vacuum and suspended in DME (1.5 mL). The mixture was cooled to 0 °C whereupon a solution of **2.39** (19.8 mg, 0.0743 mmol) in DME (2 mL) was added followed by 10 minutes of stirring. To this mixture was added allyl bromide (0.06 mL, 0.7 mmol), and the reaction was stirred while warming to room temperature for 2 hours, then at room temperature for 16 hours. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes yielded **2.40** (11.4 mg, 0.0372 mmol, 50 %, $R_f = 0.60$) as a yellow oil.

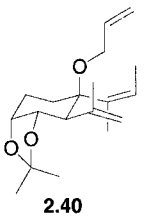
Data for **2.40**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.96-5.87 (m, 1H), 5.42 (qd, J = 7.4, 1.2 Hz, 1H), 5.28 (dddd, J = 17.3, 1.9, 1.9, 1.9 Hz, 1H), 5.09 (dddd, J = 10.6, 1.8, 1.8, 1.8 Hz, 1H), 5.02 (s, 1H), 4.90 (s, 1H), 4.51 (dd, J = 9.9, 4.9 Hz, 1H), 4.34-4.32 (m, 1H), 3.80 (dddd, J_{AB} = 13.2 Hz, J = 4.4, 1.8, 1.8 Hz, 1H), 3.74 (dddd, J_{AB} = 13.2 Hz, J = 4.7, 1.7, 1.7 Hz, 1H), 2.32 (d, J = 9.9 Hz, 1H), 2.03-1.91 (m, 2H), 1.88 (s, 3H), 1.86-1.79 (m, 2H), 1.67 (dd, J = 7.4, 1.3 Hz, 3H), 1.64 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.4 (C_4), 138.7 (C_4), 135.5 (CH), 125.5 (CH), 115.5 (CH_2), 114.7 (CH_2), 108.0 (C_4), 84.6 (C_4), 73.2 (CH_2), 62.5 (CH), 53.0 (CH), 32.3 (CH) 29.9 (CH_3), 26.8 (CH_3), 26.7 (CH_2), 24.4 (CH_3), 22.1 (CH_2), 15.7 (CH_3), 15.6 (CH_3)

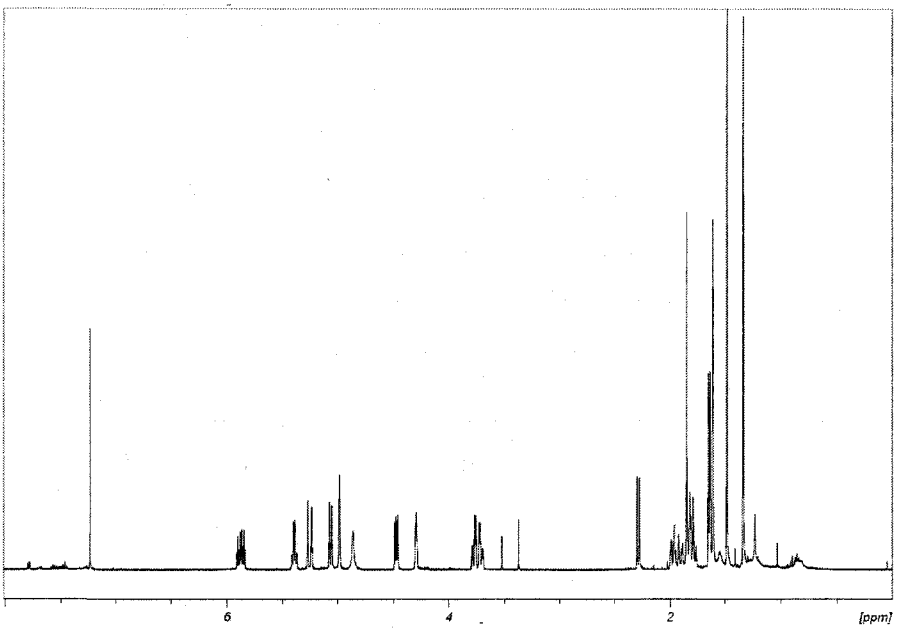
FT-IR (neat, cm^{-1}): 2991 (s), 2934 (s), 2871 (m), 1642 (w)

HRMS (EI): Calculated 306.2195 (M^+) for $C_{19}H_{30}O_3$, found 306.2216

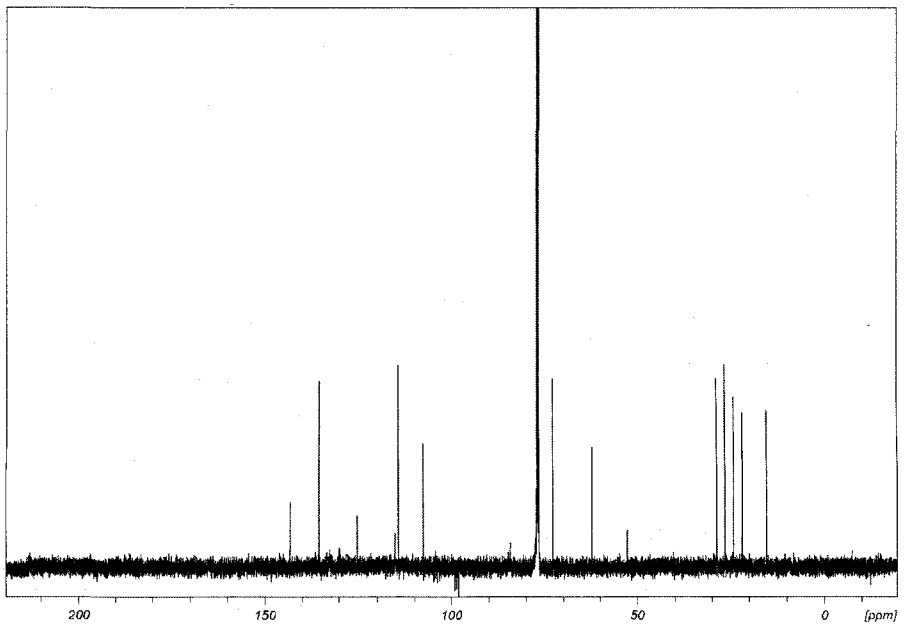


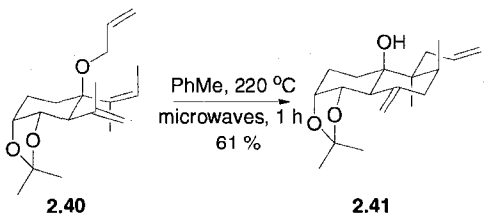
2.40

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.40 **2.41**

(±)-(3aR,5aR,6S,7S,9aS,9bS)-6-Allyl-decahydro-2,2,6,7-tetramethyl-9-methylenenaphtho[2,1-d][1,3]dioxol-5a-ol (**2.41**)

A sample of **2.40** (11.4 mg, 0.0372 mmol) was dissolved in toluene (13 mL) and placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 20 % EtOAc/hexanes, affording **2.41**(7.0 mg, 0.023 mmol, 61 %, $R_f = 0.50$) as a colorless oil.

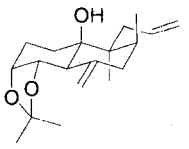
Data for **2.41**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.87-5.79 (m, 1H), 5.14-5.11 (m, 4H), 4.37 (dd, J = 8.9, 5.2 Hz, 1H), 4.30-4.29 (m, 1H), 2.59 (ddd, J = 13.6, 13.6, 5.6 Hz, 1H), 2.53 (d, J = 9.0 Hz, 1H), 2.08-2.00 (m, 3H), 1.94-1.88 (m, 1H), 1.80-1.67 (m, 2H), 1.63-1.57 (m, 2H), 1.49 (s, 3H), 1.38 (s, 3H), 1.11 (s, 3H), 1.05 (d, J = 7.3 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.0 (C_4), 135.0 (CH), 118.1 (CH_2), 112.3 (CH_2), 108.0 (C_4), 79.5 (C_4), 74.6 (CH), 73.0 (CH), 47.6 (CH), 42.9 (C_4), 39.9 (CH_2), 38.4 (CH), 37.4 (CH_2), 28.9 (CH_3), 26.5 (CH_3), 26.0 (CH_2), 23.8 (CH_3), 22.2 (CH_2), 17.1 (CH_3)

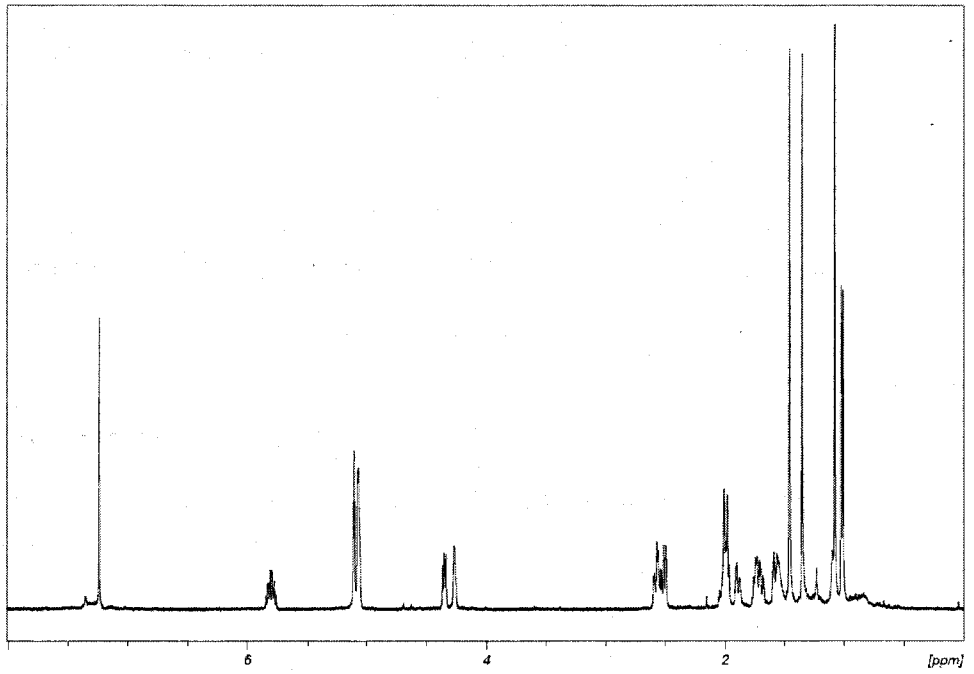
FT-IR (neat, cm^{-1}): 3506 (b), 2979 (s), 2932 (s), 2800 (m)

HRMS (EI): Calculated 306.2195 (M^+) for $C_{19}H_{30}O_3$, found 306.2214

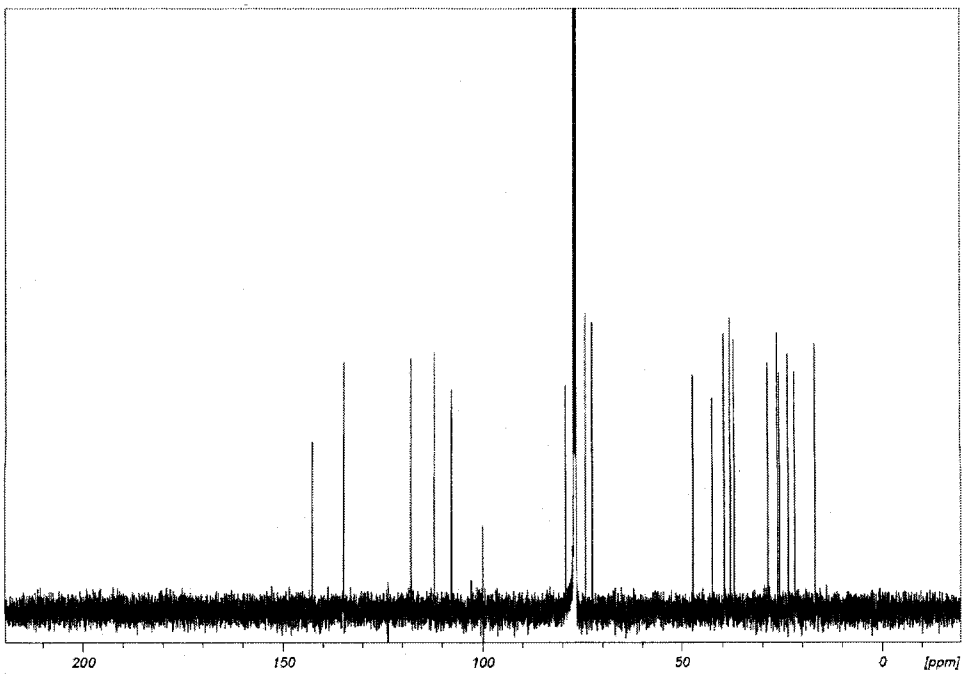


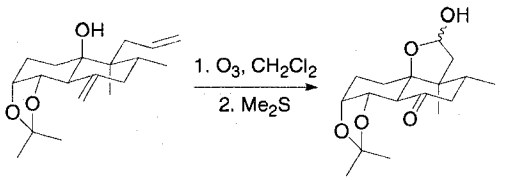
2.41

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

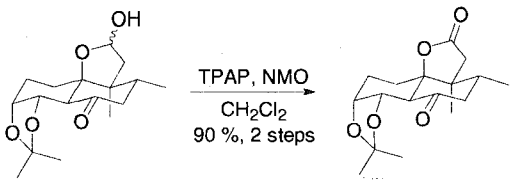




2.20 **2.45**

(±)-(3aS,4R,6aS,7S,8R,10aR)-7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[d]naphthalene-2-ol-6-one (**2.45**)

A solution of **2.20** (131.1 mg, 0.428 mmol) was dissolved in CH_2Cl_2 (25 mL) and degassed by bubbling with O_2 for 10 minutes. The resulting mixture was cooled to -78 °C and bubbled with O_3 until a pale blue color persisted in the solution. The reaction was quenched by adding Me_2S (excess), followed by stirring while warming to room temperature over 0.5 hours. The resulting solution was concentrated under reduced pressure to give an orange oil (133.5 mg), which was used without purification in the next step of the synthesis.



2.45 **2.46**

(±)-(3aS,4R,6aS,7S,8R,10aR)-7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[d]naphthalene-2,6-dione (**2.46**)

To a solution of crude **2.45** (133.5 mg) in CH_2Cl_2 (25 mL) was added 4Å molecular sieves (213.9 mg, 500 mg/mmol starting material), NMO (75.2 mg, 0.642 mmol) and TPAP (6.5 mg, 0.018 mmol). The resulting dark orange solution was stirred for 2 hours, whereupon it had turned black. The solution was filtered through a short pad of silica, and the filter cake was washed with 10 % MeOH/EtOAc (100 mL). The mother liquor was concentrated under reduced pressure, and the product was isolated by flash chromatography in 60 % EtOAc/hexanes to afford lactone **2.46** (118.7 mg, 0.385 mmol, 90 % over 2 steps, $R_f = 0.50$) as a white solid.

Data for **2.46**

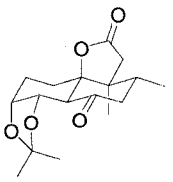
M.p.: 169-170 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.66 (dd, J = 8.8, 5.0 Hz, 1H), 4.33-4.30 (m, 1H), 2.53 (d, J = 9.1 Hz, 1H), 2.46-2.43 (m, 2H), 2.31 (ddd, J = 13.9, 13.9, 4.0 Hz, 2H), 2.15-1.91 (m, 3H), 1.67-1.61 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.8 (C_4), 173.9 (C_4), 108.4 (C_4), 93.3 (C_4), 72.0 (CH), 71.7 (CH), 53.4 (C_4), 45.1 (CH), 44.9 (CH_2), 40.4 (CH_2), 38.4 (CH), 28.2 (CH_3), 27.7 (CH_2), 26.1 (CH_3), 22.1 (CH_2), 17.1 (CH_3), 12.0 (CH_3)

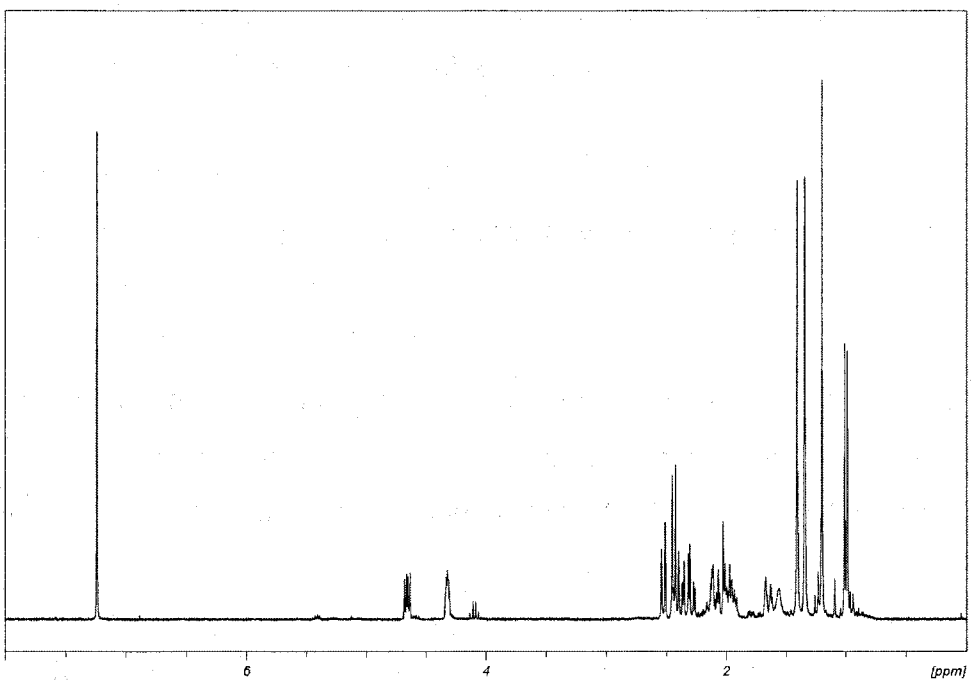
FT-IR (neat, cm^{-1}): 2959 (s), 2927 (s), 2854 (m), 1780 (s), 1727 (s)

HRMS (EI): Calculated 308.1624 (M^+) for $C_{17}H_{24}O_5$, found 308.1629

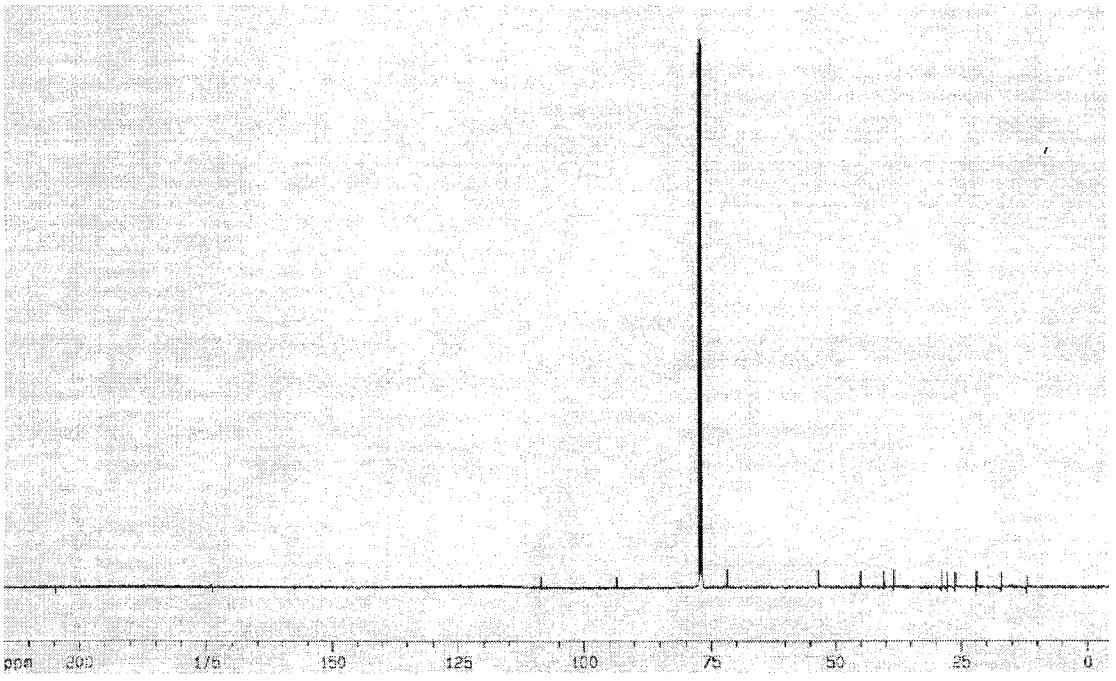


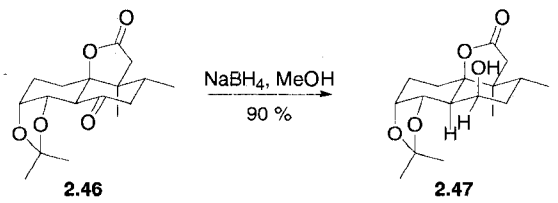
2.46

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.46 **2.47**

(±)-(3aS,4R,6R,6aS,7S,8R,10aR)-7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-octahydro-1-oxa-cyclopenta[d]naphthalene-6-ol-2-one (**2.47**)

To a solution of **2.46** (38.5 mg, 0.124 mmol) in MeOH (5 mL) was added $NaBH_4$ (32.3 mg, 0.373 mmol) and the resulting solution was stirred at room temperature for 3 hours. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL) followed by 1 hour of vigorous stirring. The MeOH was removed by evaporation, and the resulting aqueous solution was extracted with EtOAc (4 × 10 mL). The layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 60 % EtOAc/hexanes afforded **2.47** (34.9 mg, 1.12 mmol, 90 %, $R_f = 0.55$) as a colorless oil.

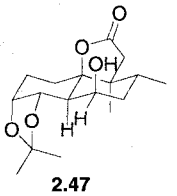
Data for **2.47**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.46 (dd, J = 9.6, 4.8 Hz, 1H), 4.31 (s, 1H), 4.08 (s, 1H), 2.44-2.37 (m, 2H), 2.12-2.02 (m, 4H), 1.95-1.91 (m, 1H), 1.82-1.78 (m, 1H), 1.73 (ddd, J = 13.2, 13.2, 5.5 Hz, 1H), 1.57-1.54 (m, 2H), 1.43 (s, 3H), 1.35 (s, 3H), 0.95 (s, 3H), 0.90 (d, J = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1 (C_4), 108.3 (C_4), 89.3 (C_4), 73.7 (CH), 72.4 (CH), 64.1 (CH), 44.5 (C_4), 43.5 (CH), 40.4 (CH_2), 36.3 (CH_2), 28.8 (CH_3), 28.5 (CH), 27.7 (CH_2), 26.4 (CH_3), 22.1 (CH_2), 16.6 (CH_3), 12.0 (CH_3)

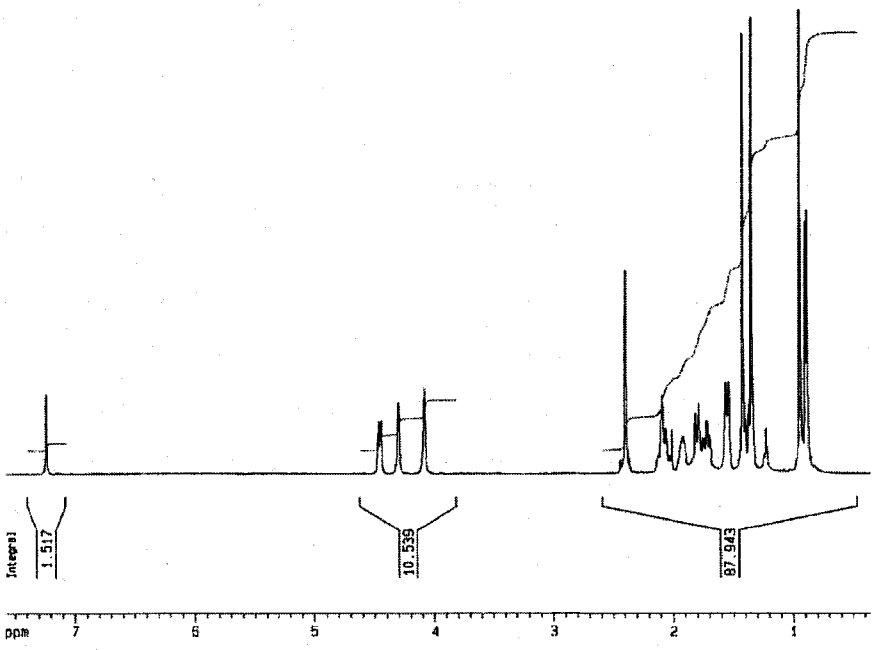
FT-IR (neat, cm^{-1}): 3492 (b), 2982 (m), 2964 (m), 2933 (m), 2881 (m), 1772 (s)

HRMS (EI): Calculated 310.1780 (M^+) for $C_{17}H_{26}O_5$, found (M^+-CH_3) at 295.1530, actual value 295.1546

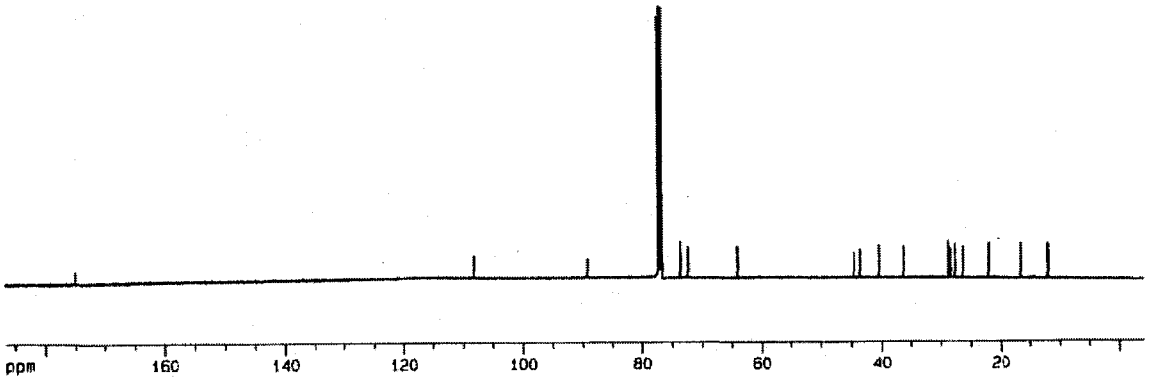


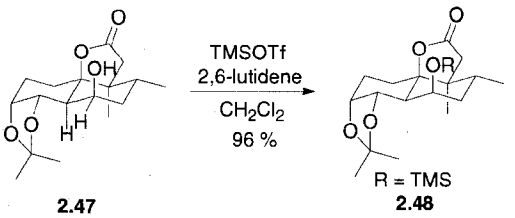
2.47

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.47 **2.48**

(±)-(3aS,4R,6R,6aS,7S,8R,10aR)-7,8-(2,2-Dimethyl[1,3]dioxol)-3a,4-dimethyl-6-(trimethylsilyloxy)-octahydro-1-oxa-cyclopenta[d]naphthalene-2-one (**2.48**)

A solution of **2.47** (10.1 mg, 0.0325 mmol) in CH_2Cl_2 (2 mL) cooled to -78 °C was treated with 2,6-lutidene (0.02 mL, 0.172 mmol) followed by TMSOTf (0.01 mL, 0.0579 mmol), and the resulting mixture was stirred for 0.5 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and warming to room temperature. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), then the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 30 % EtOAc/hexanes yielded **2.48** (12.0 mg, 0.0314 mmol, 96 %, R_f = 0.50) as a white solid.

Data for **2.48**

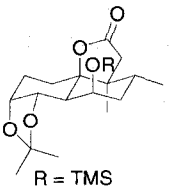
M.p.: 187-188 °C

^{1}H NMR (300 MHz, C_6D_6): δ = 4.53 (dd, J = 9.7, 4.8 Hz, 1H), 4.21 (ddd, J = 3.2, 3.2, 3.2 Hz, 1H), 4.08-4.06 (m, 1H), 2.12-2.09 (m, 2H), 1.88-1.84 (m, 3H), 1.44 (ddd, J = 14.0, 3.3, 3.3 Hz, 1H), 1.41-1.34 (m, 5H), 1.29 (s, 3H), 1.05-0.95 (m, 2H), 0.51 (d, J = 7.0 Hz, 3H), 0.39 (s, 3H), 0.19 (s, 9H)

^{13}C NMR (75 MHz, C_6D_6): δ = 173.8 (C_4), 107.7 (C_4), 100.2 (C_4), 87.3 (C_4), 74.6 (CH), 72.8 (CH), 64.4 (CH), 44.7 (CH), 43.9 (CH_2), 40.4 (CH_2), 37.1 (CH), 29.1 (CH_3), 28.4 (CH_2), 26.6 (CH_3), 22.7 (CH_2), 16.6 (CH_3), 11.8 (CH_3), 0.2 (3 × CH_3)

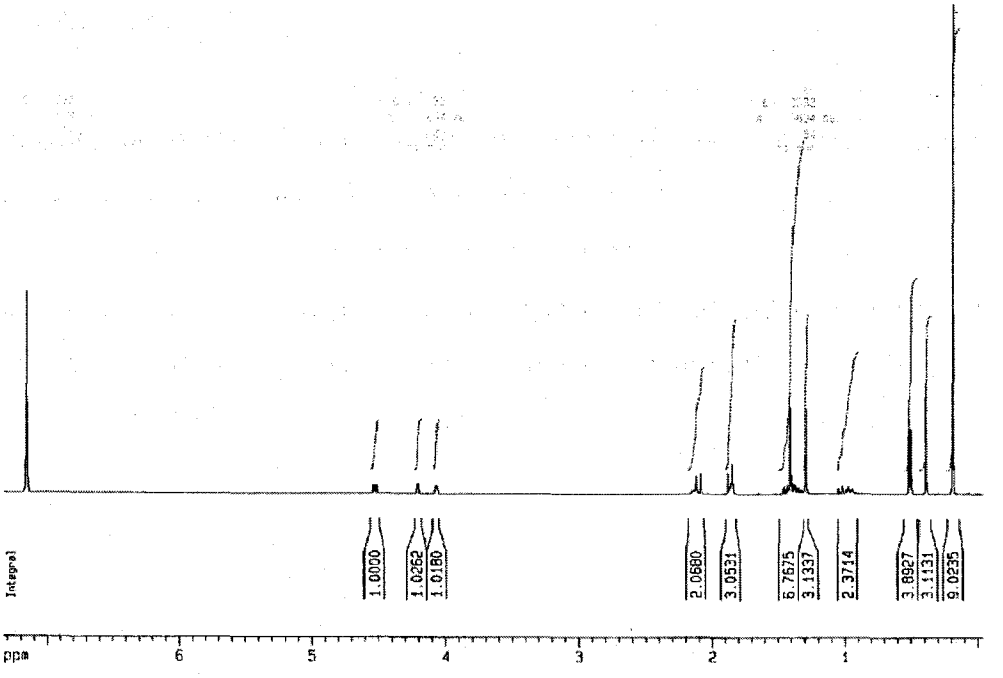
FT-IR (neat, cm^{-1}): 2982 (m), 2960 (m), 2934 (m), 2895 (m), 2888 (m), 1774 (s)

HRMS (EI): Calculated 382.2176 (M^+) for $C_{20}H_{34}O_5Si$, found (M^+-CH_3) at 367.1942, actual value 367.1941

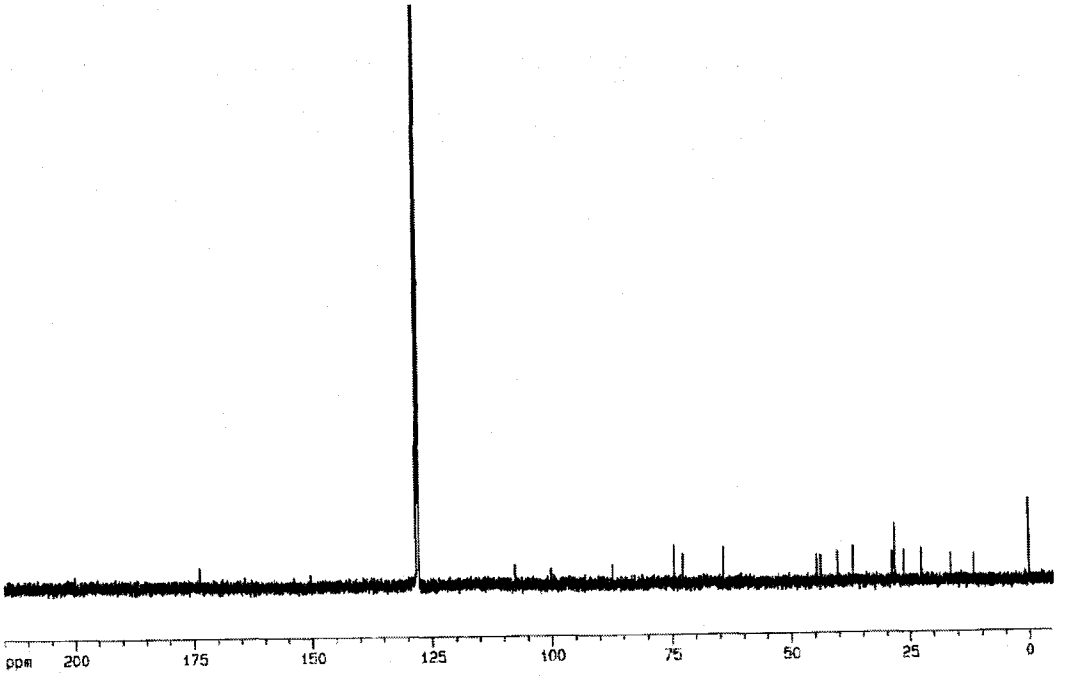


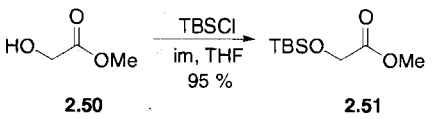
2.48

^{1}H NMR (300 MHz, C_6D_6)



^{13}C NMR (75 MHz, C_6D_6)





2.50 **2.51**

(Tert-butyl-dimethyl-silanyloxy)-acetic acid methyl ester (**2.51**)

A solution of **2.50** (27.29 g, 303.0 mmol) in THF (600 mL) was treated with imidazole (61.88 g, 909.0 mmol) followed by TBSCl (54.80 g, 364.0 mmol), and the mixture was stirred at room temperature for 16 hours. After this the reaction was quenched by adding saturated aqueous NH_4Cl (500 mL). The layers were separated, the aqueous layer was extracted with Et_2O (3 × 400 mL) and the combined organic layers were washed with H_2O (200 mL), 1M HCl (300 mL) and saturated aqueous NaCl (200 mL). The resulting solution was dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes gave **2.51** (58.81 g, 287.8 mmol, 95 %, R_f = 0.65) as a clear yellow liquid.

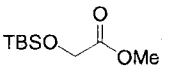
Data for **2.51**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.20 (s, 2H), 3.68 (s, 3H), 0.87(s, 9H), 0.05, (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1 (C_4), 61.6 (CH_2), 51.6 (CH_3), 25.7 (3 × CH_3), 18.3 (C_4), -5.6 (2 × CH_3)

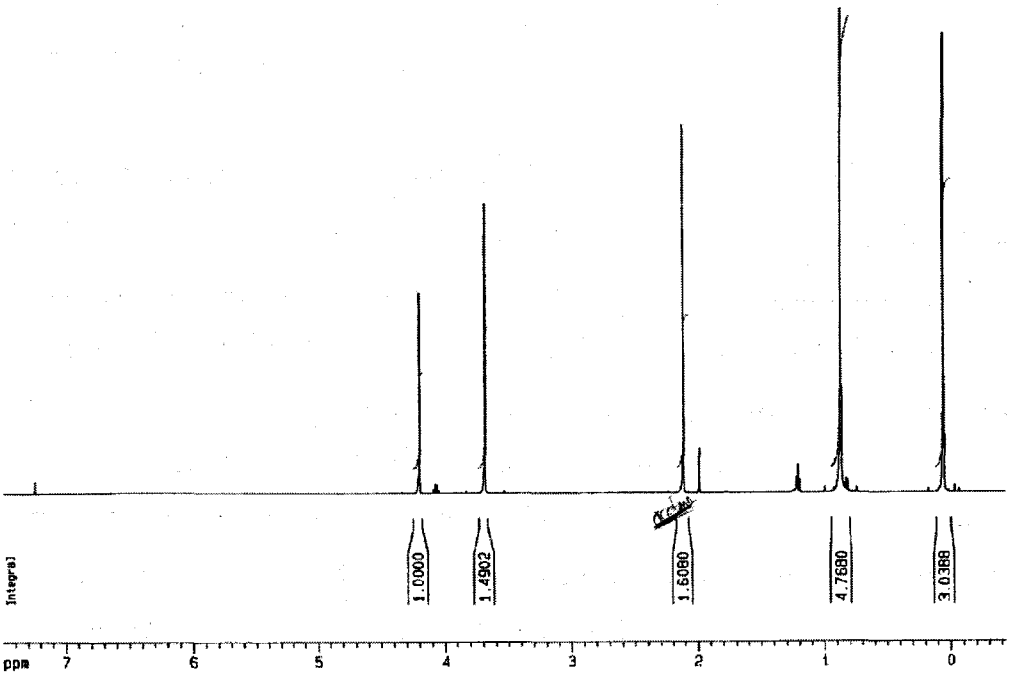
FT-IR (neat, cm^{-1}): 2954 (m), 2931 (m), 2896 (m), 2859 (m), 1765 (s)

HRMS (EI): Calculated 204.1182 (M^+) for $C_9H_{20}O_3Si$, found (M^+-^{t}Bu) at 147.0480, actual value 147.0477

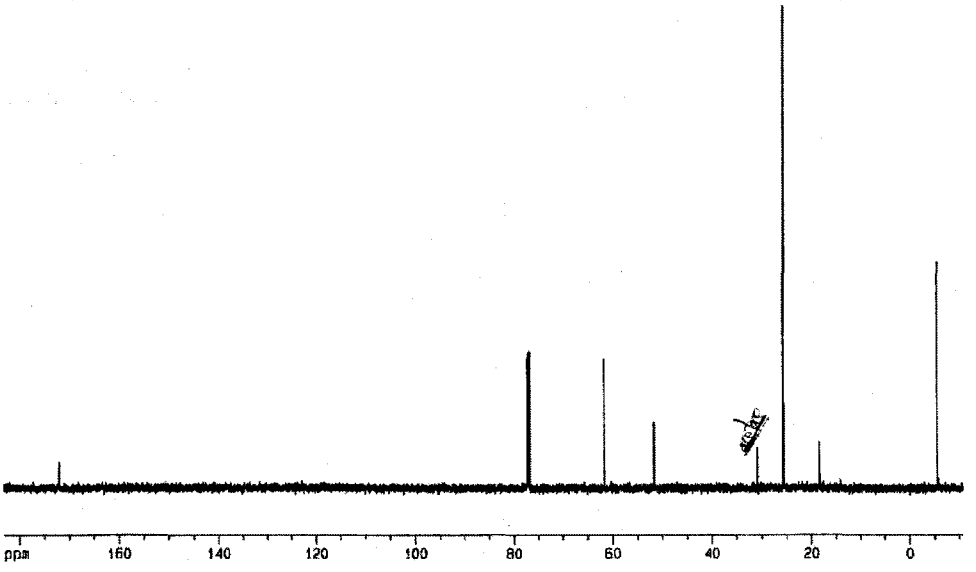


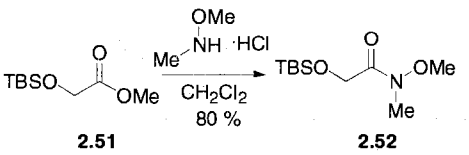
2.51

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





2.51 **2.52**

2-(Tert-butyl-dimethyl-silanyloxy)-N-methoxy-N-methyl-acetamide (**2.52**)

To a solution of N,O-dimethylhydroxylamine hydrochloride (15.64 g, 106.3 mmol) in CH_2Cl_2 (350 mL) cooled to 0 °C was added trimethyaluminum (2 M in hexanes, 80.2 mL, 160.3 mmol) and the resulting solution was stirred at 0 °C for 25 minutes. To this was added a solution of **2.51** (11.90 g, 58.20 mmol) in CH_2Cl_2 (150 mL), and the mixture was stirred at 0 °C for 20 minutes, whereupon the reaction was quenched by the careful addition of an aqueous solution of 1 M sodium tartrate/1 M NH_4Cl (300 mL). After 1 hour of vigorous stirring, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 20 % EtOAc/hexanes yielded **2.52** (11.11 g, 46.59 mmol, 80 %, R_f = 0.35) as a clear yellow liquid.

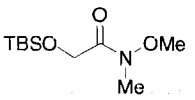
Data for **2.52**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.41 (s, 2H), 3.65 (s, 3H), 3.16 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0 (C_4), 61.7 (CH_2), 61.3 (CH_3), 60.3 (CH_3), 25.7 (3 × CH_3), 18.4 (C_4), -5.5 (2 × CH_3)

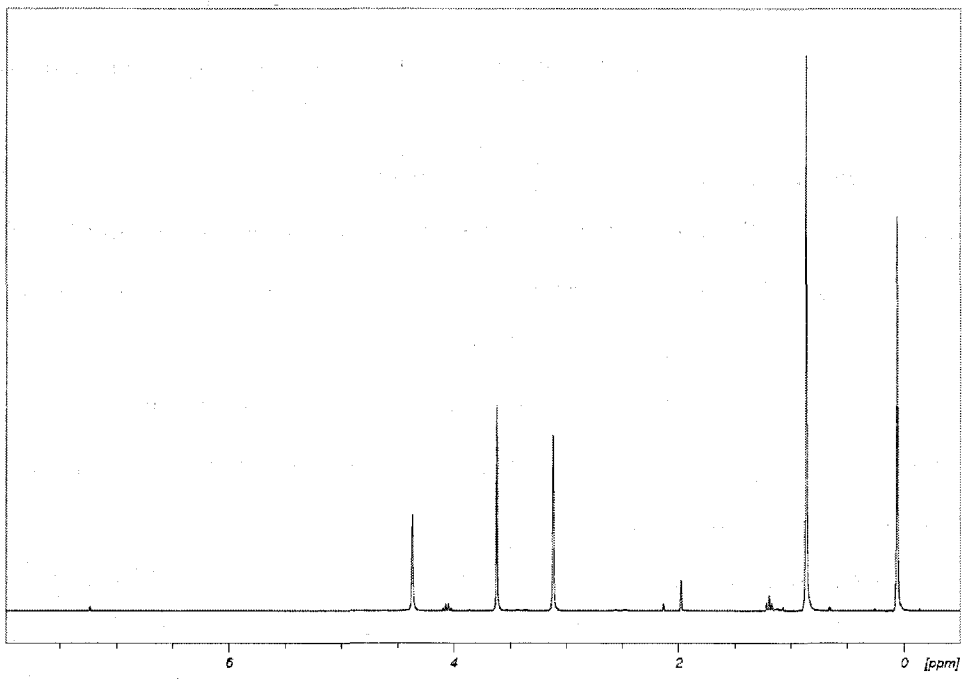
FT-IR (neat, cm^{-1}): 2954 (s), 2931 (s), 2897 (m), 2857 (s), 1695 (s)

HRMS (EI): Calculated 233.1447 (M^+) for $C_{10}H_{23}NO_3Si$, found (M^+-^{t}Bu) at 176.0762, actual value 176.0743

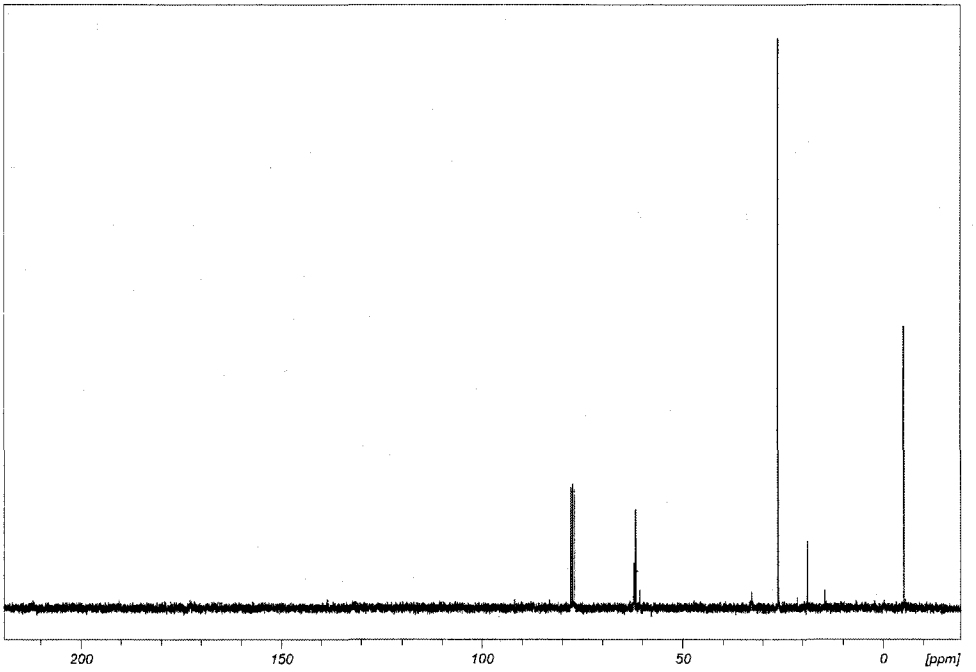


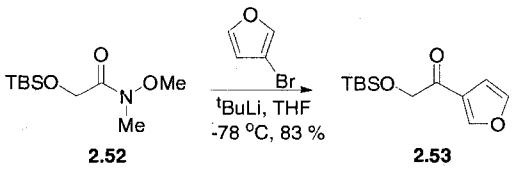
2.52

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)





2-(Tert-butyl-dimethyl-silanyloxy)-1-(furan-3-yl)-ethanone (**2.53**)

To a solution of freshly prepared 3-bromofuran (3.90 mL, 43.1 mmol) in THF (150 mL) cooled to -78 °C was added ^{t}BuLi (1.70 M in hexanes, 50.8 mL, 86.4 mmol) and the mixture was stirred for 2 hours at -78 °C, giving an orange solution. To this mixture was added a solution of **2.52** (5.03 g, 21.5 mmol) in THF (50 mL), followed by 0.5 hours stirring at -78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (200 mL) at -78 °C then warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Subsequent purification by flash chromatography in 10 % EtOAc/hexanes yielded **2.53** (4.27 g, 17.8 mmol, 83 %, Rf = 0.50) as a clear colorless liquid.

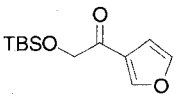
Data for **2.53**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27-8.26 (m, 1H), 7.41 (dd, J = 1.7, 1.7 Hz, 1H), 6.79 (dd, J = 1.9, 0.7, 1H), 4.52 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1 (C_4), 148.4 (CH), 143.4 (CH), 124.5 (C_4), 108.7 (CH), 69.0 (CH_2), 25.8 (3 × CH_3), 18.3 (C_4), -5.5 (2 × CH_3)

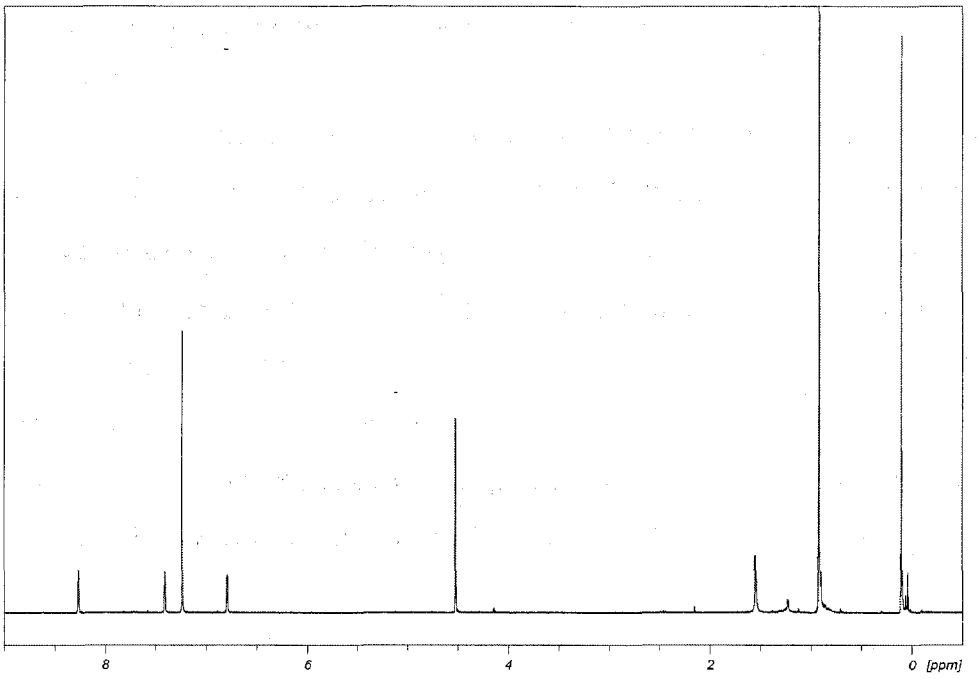
FT-IR (neat, cm^{-1}): 2955 (s), 2931 (s), 2887 (m), 2858 (s), 1674 (s)

HRMS (EI): Calculated 240.1182 (M^+) for $C_{12}H_{20}O_3Si$, found (M^+-^{t}Bu) at 183.0476, actual value 183.0477

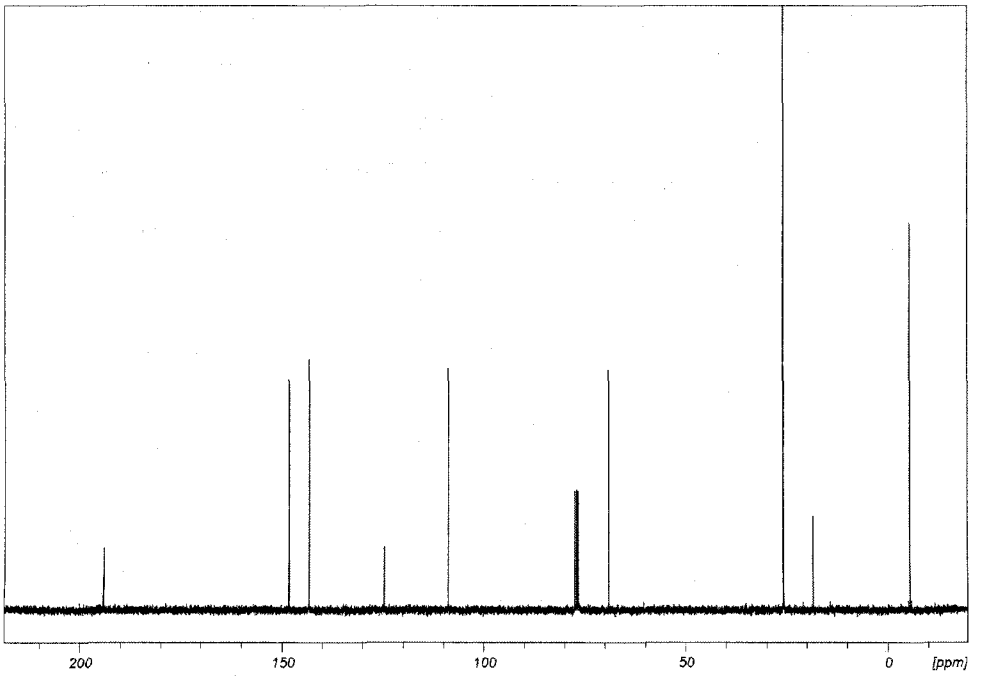


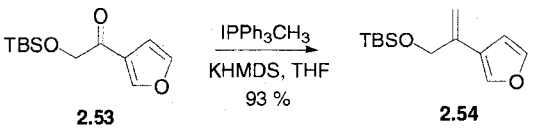
2.53

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)





Tert-butyl-(2-furan-3-yl-allyloxy)-dimethyl-silane (**2.54**)

To a suspension of methyltriphenylphosphonium iodide (10.50 g, 26.00 mmol) in THF (100 mL) cooled to 0 °C was added KHMDS (5.18 g, 26.0 mmol) and the resulting yellow mixture was stirred at 0 °C for 0.5 hours. To this was then added a solution of **2.53** (4.27 g, 17.6 mmol) in THF (50 mL), followed by stirring at 0 °C for a further 0.5 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes yielded **2.54** (3.95 g, 16.6 mmol, 93 %) as a clear yellow liquid.

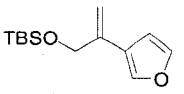
Data for **2.54**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.35 (dd, J = 1.7, 1.7 Hz, 1H), 6.52 (dd, J = 1.8, 0.8 Hz, 1H), 5.29 (s, 1H), 5.24 (s, 1H), 4.36 (s, 2H), 0.91 (s, 9H), 0.08 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8 (CH), 138.8 (C_4), 138.6 (CH), 124.0 (C_4), 109.5 (CH_2), 108.1 (CH), 64.6 (CH_2), 25.9 (3 × CH_3), 18.3 (C_4), -5.4 (2 × CH_3)

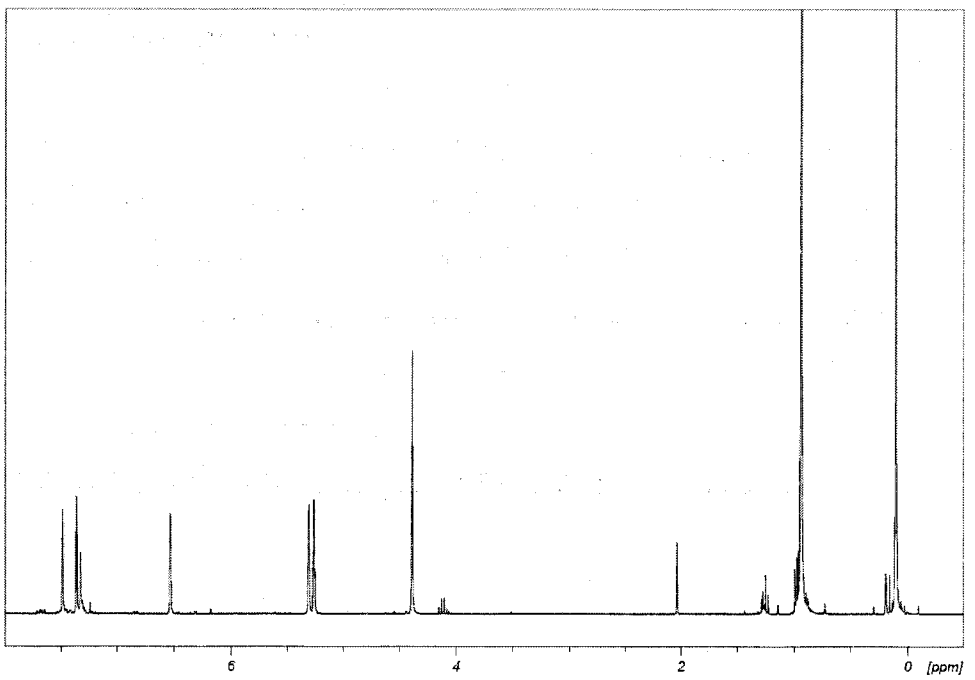
FT-IR (neat, cm^{-1}): 2956 (s), 2930 (s), 2886 (m), 2857 (m), 1642 (w)

HRMS (EI): Calculated 238.1389 (M^+) for $C_{13}H_{22}O_2Si$, found 238.1386

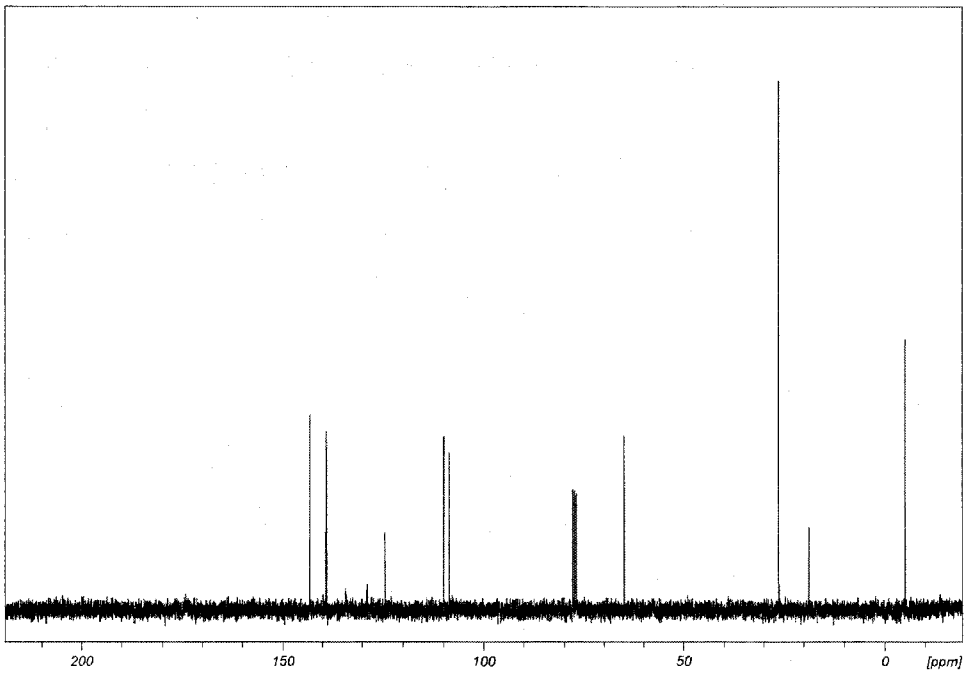


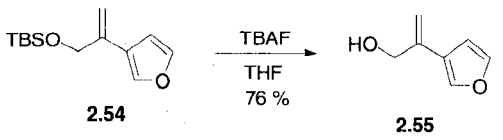
2.54

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)





2-(Furan-3-yl)-prop-2-en-1-ol (**2.55**)

A solution of **2.54** (3.95 g, 16.6 mmol) in THF (160 mL) was treated with TBAF (8.66 g, 33.1 mmol), and the resulting mixture was stirred at room temperature for 3 hours. Solid TBAF can be substituted with a solution of TBAF in THF in this protocol. The reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL), whereupon the layers were separated and the aqueous layer was extracted with Et_2O (3 × 75mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 40 % EtOAc/hexanes gave **2.55** (1.57 g, 12.6 mmol, 76 %, R_f = 0.50) as a clear yellow oil.

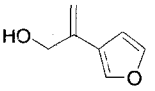
Data for **2.55**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.35 (s, 1H), 6.51 (s, 1H), 5.30 (s, 1H), 5.19 (s, 1H), 4.32 (s, 2H), 2.43 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1 (CH), 138.9 (CH), 138.8 (C_4), 123.8 (C_4), 110.4 (CH_2), 108.0 (CH), 64.6 (CH_2)

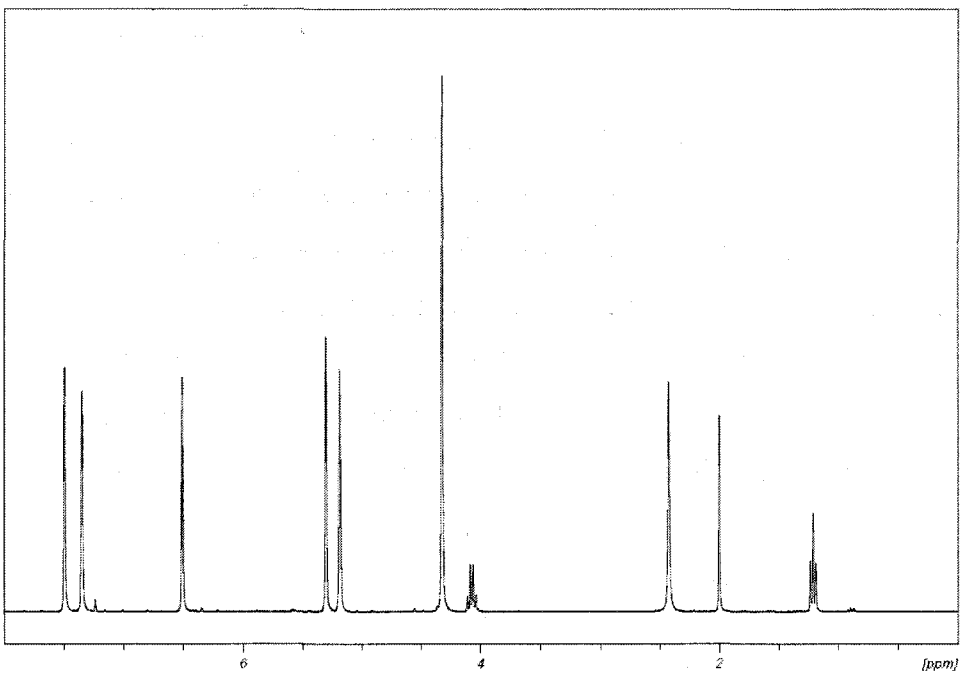
FT-IR (neat, cm^{-1}): 3347 (b), 2935 (m), 2870 (m), 1641 (m)

HRMS (EI): Calculated 124.0524 (M^+) for $C_7H_8O_2$, found 124.0525

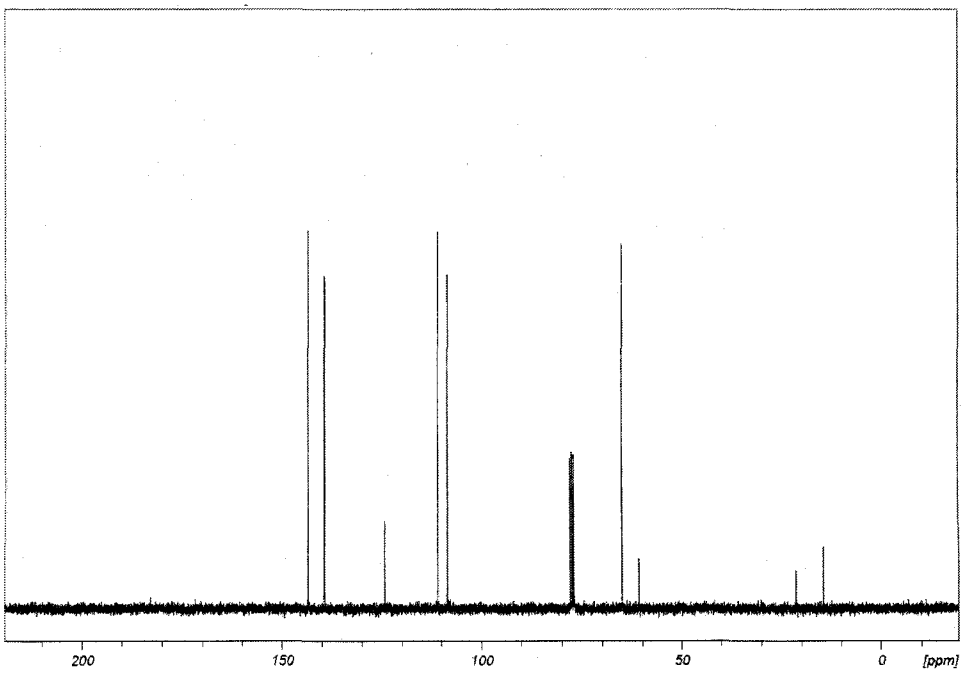


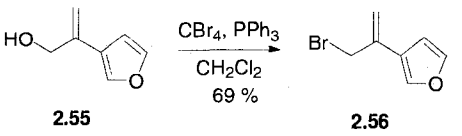
2.55

^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)





2.55 **2.56**

3-(1-Bromomethyl-vinyl)-furan (**2.56**)

To a solution of **2.55** (1.57 g, 12.6 mmol) in CH_2Cl_2 (100 mL) was added CBr_4 (5.24 g, 15.8 mmol) and the mixture was stirred for 5 minutes. To this was added a solution of PPh_3 (4.97 g, 18.9 mmol) in CH_2Cl_2 (25 mL). The resulting solution was stirred at room temperature for 2 hours, after which the reaction was quenched by the addition of hexanes (300 mL) which produced a white precipitate of triphenylphosphine oxide. The precipitate was removed by repeated filtration through a pad of Celite followed by removal of the solvent. Flash chromatography in 10 % EtOAc/hexanes afforded **2.56** (1.63 g, 8.7 mmol, 69 %, $R_f = 0.60$) as a clear yellow liquid.

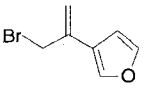
Data for **2.56**

^{1}H NMR (300 MHz, C_6D_6): δ = 7.31 (s, 1H), 6.95 (dd, J = 1.7, 1.7 Hz, 1H), 6.16-6.15 (m, 1H), 5.03 (s, 1H), 4.88 (s, 1H), 3.66 (s, 2H)

^{13}C NMR (75 MHz, C_6D_6): δ = 143.5 (CH), 140.1 (CH), 136.5 (C_4), 124.0 (C_4), 114.8 (CH_2), 108.4 (CH), 33.3 (CH_2)

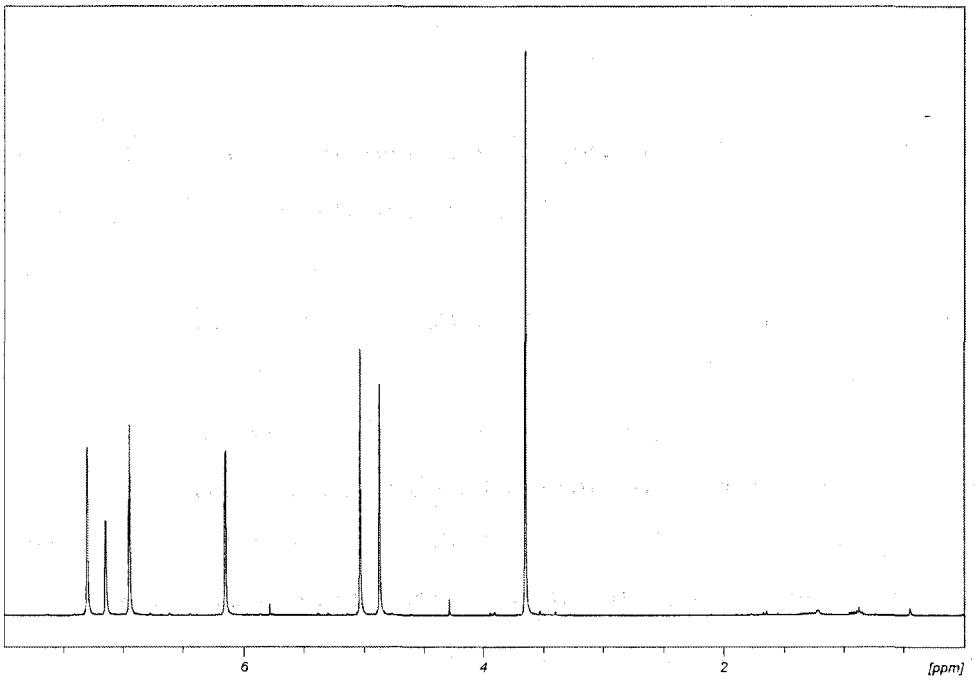
FT-IR (neat, cm^{-1}): 3125 (m), 3095 (s), 2969 (s), 1635 (m)

HRMS (EI): Calculated 185.9680 (M^+) for C_7H_7BrO, found 185.9664

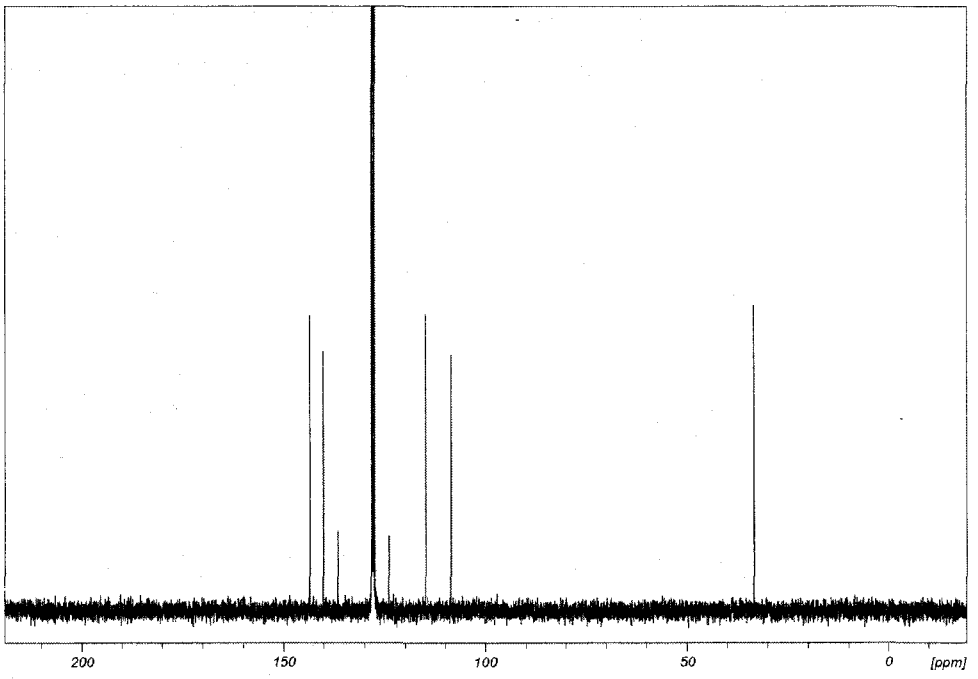


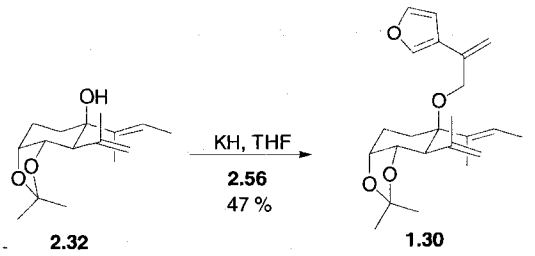
2.56

^{1}H NMR (300 MHz, C_6D_6)



^{13}C NMR (75 MHz, C_6D_6)





(±)-(3aR,4R,5S,7aS)-5-(2-(Furan-3-yl)allyloxy)-5-((E)-but-2-en-2-yl)-hexahydro-2,2-dimethyl-4-(prop-1-en-2-yl)benzo[d][1,3]dioxole (**1.30**)

KH (60 % dispersion in oil, 5.91 g, 44.2 mmol) was washed with hexanes to remove mineral oil and was dried under high vacuum. These solids were suspended in THF (40 mL) and the mixture was cooled to 0 °C whereupon a solution of **2.32** (1.68 g, 6.32 mmol) in THF (10 mL) was added followed by 10 minutes of stirring. To this mixture was added **2.56** (4.29 g, 23.0 mmol), and the mixture was stirred while warming to room temperature for 2 hours, then at room temperature for 16 hours. The reaction was quenched by adding saturated aqueous NH_4Cl (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **1.30** (1.10 g, 2.96 mmol, 47 %, $R_f = 0.45$) as a yellow oil.

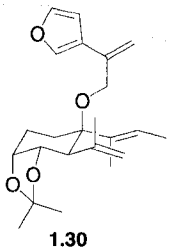
Data for **1.30**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.22 (s, 1H), 7.06 (s, 1H), 6.34 (s, 1H), 5.50 (q, J = 6.7 Hz, 1H), 5.44 (s, 1H), 5.33 (s, 1H), 5.06 (s, 1H), 4.98 (s, 1H), 4.56 (dd, J = 9.9, 4.8 Hz, 1H), 4.18-4.17 (m, 1H), 3.91 (d, J_{AB} = 13.5 Hz, 1H), 3.83 (d, J_{AB} = 13.5 Hz, 1H), 2.45 (d, J = 10.0 Hz, 1H), 2.08-2.02 (m, 2H), 1.99 (s, 3H), 1.75-1.67 (m, 2H), 1.56 (s, 3H), 1.55 (s, 3H), 1.52 (d, J = 6.7 Hz, 3H), 1.38 (s, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 144.0 (C_4), 143.0 (CH), 138.4 (CH), 137.0 (C_4), 136.3 (C_4), 124.7 (C_4), 120.4 (CH), 115.0 (CH_2), 109.5 (CH_2), 108.0 (CH), 108.5 (C_4), 84.3 (C_4), 76.7 (CH), 72.9 (CH), 62.8 (CH_2), 56.2 (CH), 28.8 (CH_3), 26.5 (CH_3), 26.0 (CH_2), 22.6 (CH_2) 22.6, (CH_3), 13.5 (CH_3), 13.2 (CH_3)

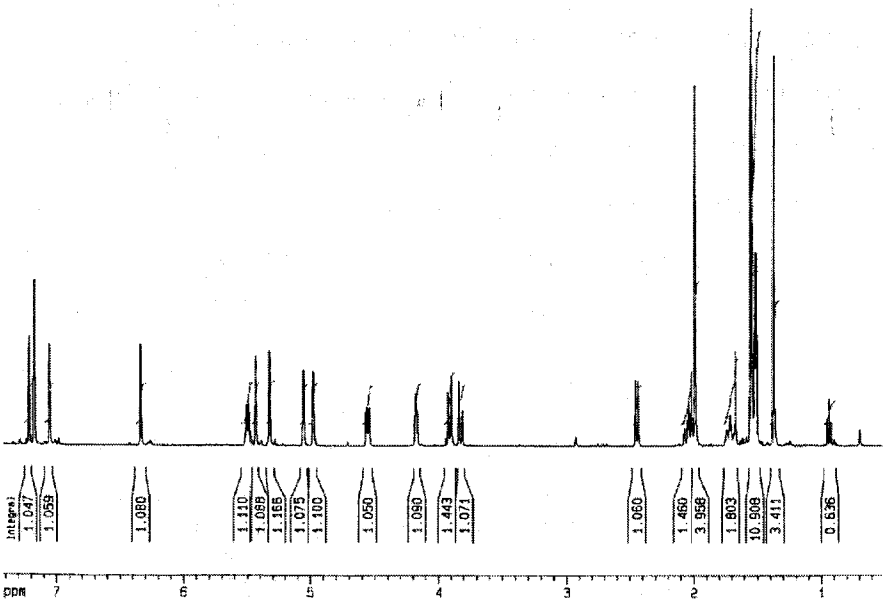
FT-IR (neat, cm^{-1}): 2983 (s), 2972 (s), 2932 (s), 2872 (w), 1641 (m)

HRMS (EI): Calculated 372.2301 (M^+) for $C_{23}H_{32}O_4$, found 372.2299

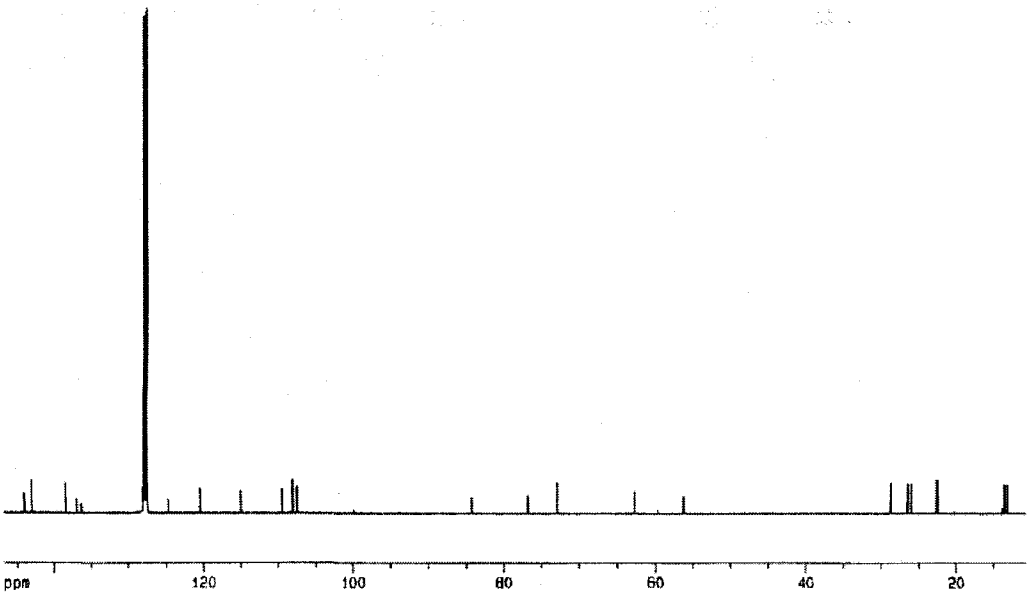


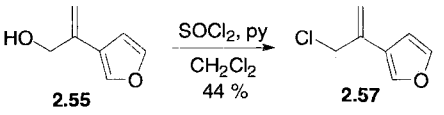
1.30

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





3-(1-Chloromethyl-vinyl)-furan (**2.57**)

To a solution of **2.55** (111.3 mg, 0.987 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added pyridine (0.44 mL, 5.44 mmol) followed by $SOCl_2$ (0.16 mL, 2.20 mmol). The reaction was stirred at 0 °C for 0.5 hours, then for a further 16 hours at room temperature after which it was quenched by the careful addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated, and the product was isolated by flash chromatography in 20 % EtOAc/hexanes to afford **2.57** (56.8 mg, 0.398 mmol, 44 %, R_f = 0.45) as a colorless liquid.

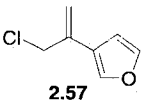
Data for **2.57**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.27 (s, 1H), 6.97 (s, 1H), 6.19 (s, 1H), 5.15 (s, 1H), 5.03 (s, 1H), 4.52 (d, J_{AB} = 12.5 Hz, 1H), 4.35 (d, J_{AB} = 12.5 Hz, 1H)

^{13}C NMR (125 MHz, C_6D_6): δ = 143.8 (CH), 140.2 (CH), 134.9 (C_4), 124.3 (C_4), 114.3 (CH_2), 108.5 (CH), 63.8 (CH_2)

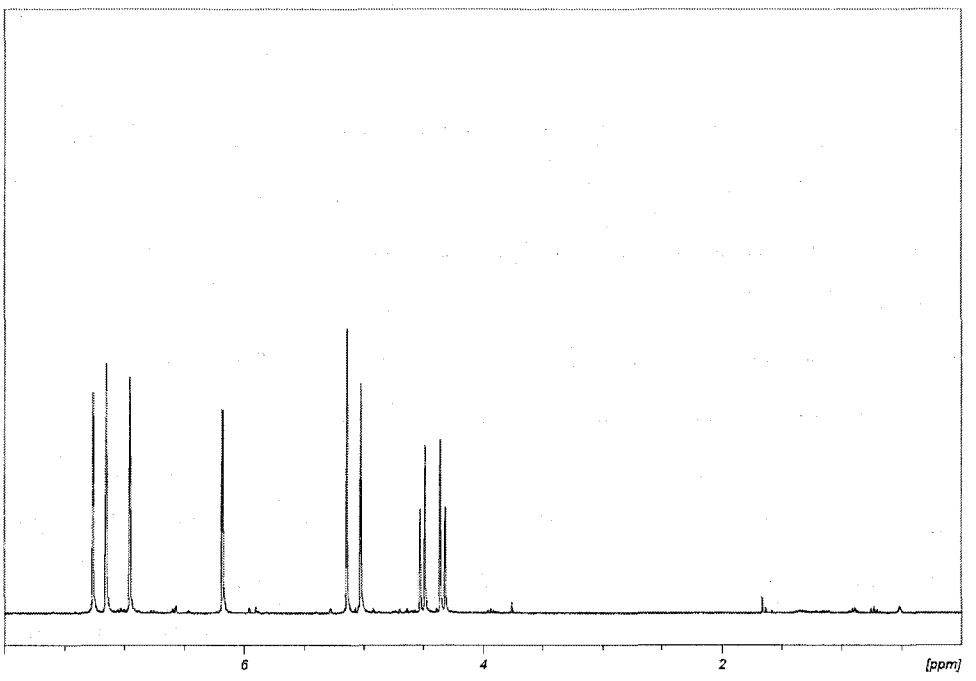
FT-IR (neat, cm^{-1}): 3125 (w), 2940 (m), 2879 (m), 1642 (s)

HRMS (EI): Calculated 142.0185 (M^+) for C_7H_7ClO, found (M^+-Cl) at 107.0486, actual value 107.0497

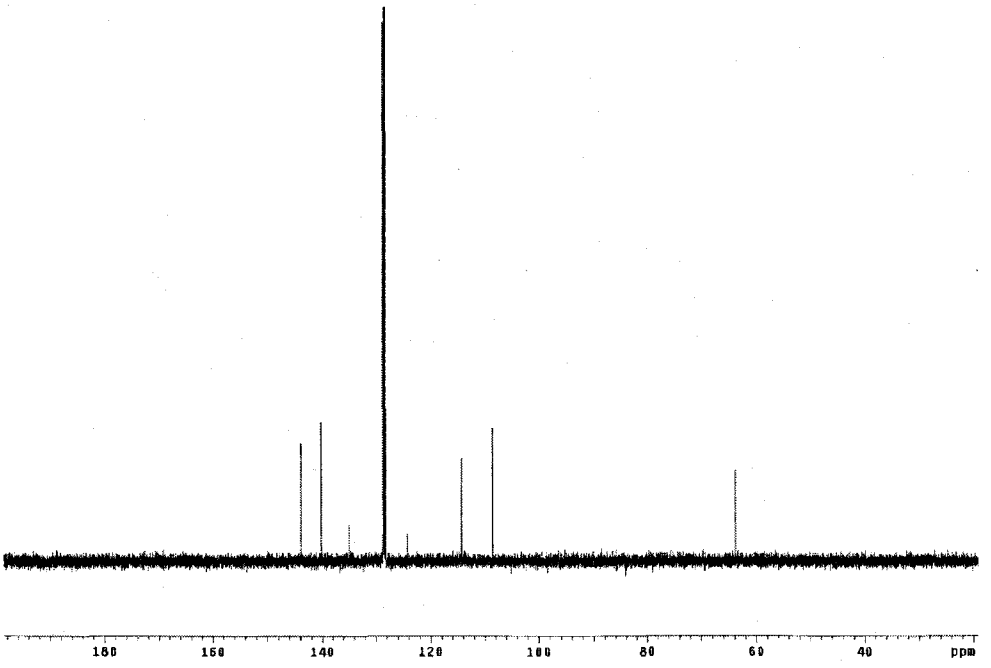


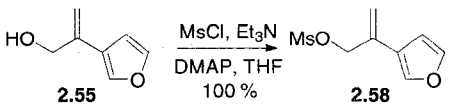
2.57

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





Methanesulfonic acid 2-furan-3-yl allyl ester (**2.58**)

A solution of **2.55** (96.5 mg, 0.777 mmol) in THF (10 mL) cooled to 0 °C was treated with DMAP (19.0 mg, 0.156 mmol), Et_3N (0.33 mL, 2.37 mmol) and MsCl (0.07 mL, 0.904 mmol). The reaction was warmed to room temperature and stirred for 4 hours after which an additional aliquot of MsCl (0.30 mL, 3.88 mmol) was added. The resulting mixture was stirred at room temperature for 16 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated, and the product was isolated by flash chromatography in 40 % EtOAc/hexanes to afford **2.58** (157.1 mg, 0.777 mmol, 100 %, R_f = 0.50) as a colorless liquid.

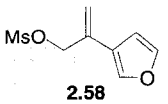
Data for **2.58**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.31 (s, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.19 (d, J = 0.7 Hz, 1H), 5.16 (s, 1H), 4.99 (s, 1H), 4.55 (s, 2H), 2.20 (s, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 144.0 (CH), 140.3 (CH), 133.7 (C_4), 123.9 (C_4), 115.8 (CH_2), 108.4 (CH), 71.0 (CH_2), 37.8 (CH_3)

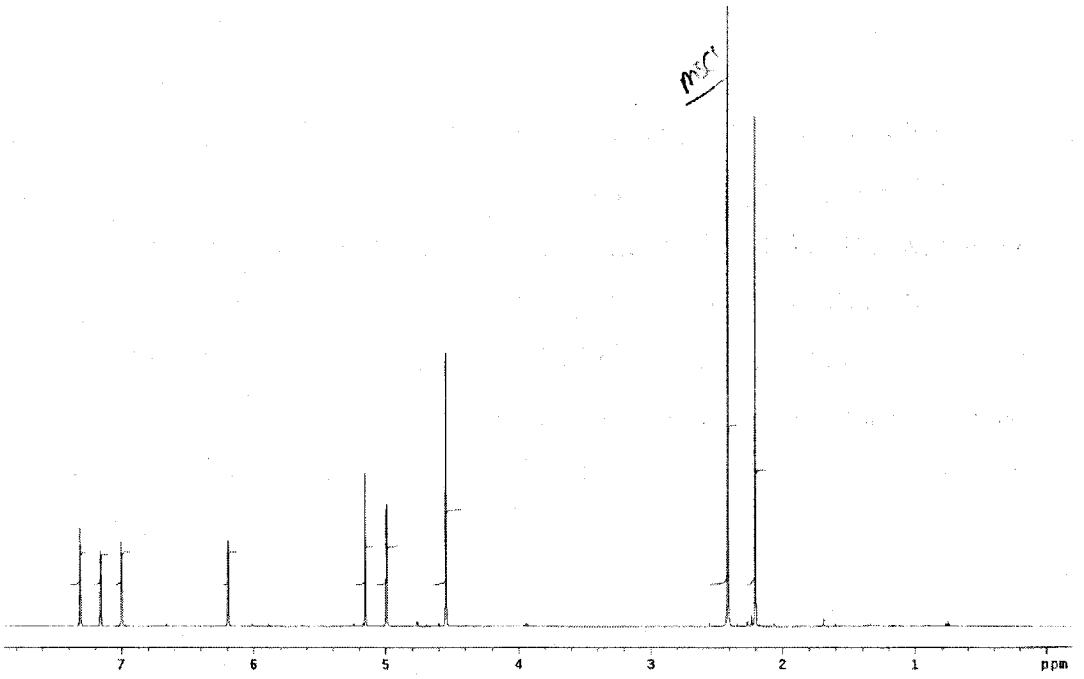
FT-IR (neat, cm^{-1}): 3124 (m), 3027 (m), 2937 (m), 1642 (s)

HRMS (EI): Calculated 202.0300 (M^+) for $C_8H_{10}O_4S$, found 202.0288

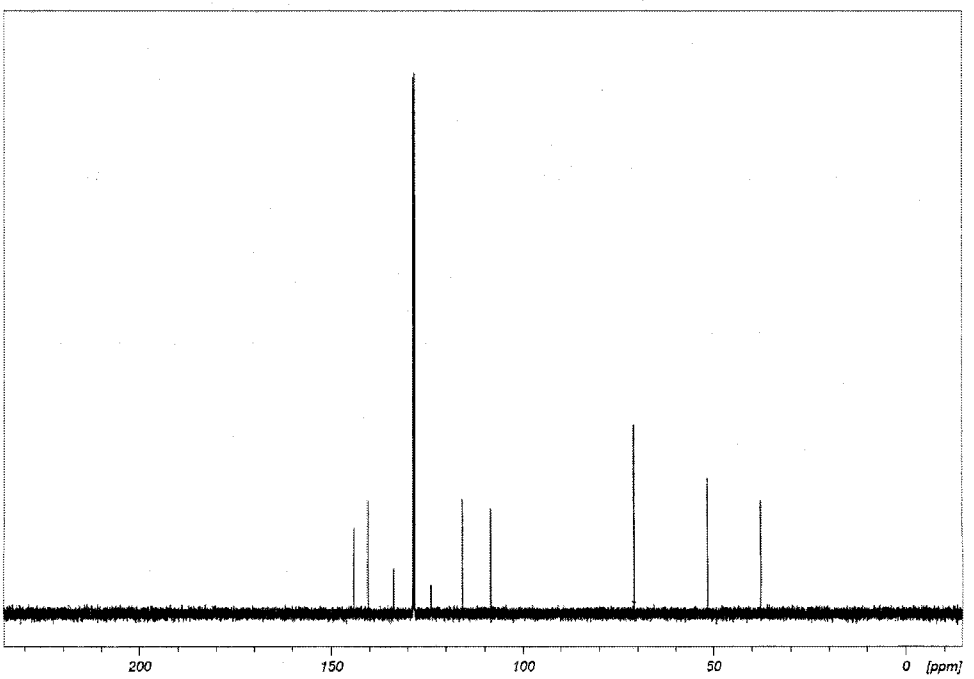


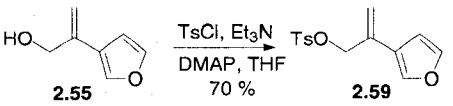
2.58

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





Toluene-4-sulfonic acid 2-furan-3-yl-allyl ester (**2.59**)

To a solution of alcohol **2.55** (27.0 mg, 0.217 mmol) in THF (2 mL) was added Et_3N (0.09 mL, 0.646 mmol), DMAP (5.3 mg, 0.0434 mmol) and tosyl chloride (50.0 mg, 0.262 mmol). The mixture was stirred at room temperature for 20 h, after which the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with Et_20 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 30 % EtOAc/hexanes afforded **2.59** (43.2 mg, 0.152 mmol, 70 %, R_f = 0.45) as a yellow oil.

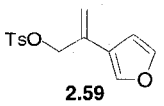
Data for **2.59**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.3 Hz, 2H), 7.38 (s, 1H), 7.33-7.22 (m, 2H), 7.31 (s, 1H), 6.42 (dd, J = 1.9, 0.9, 1H), 5.39 (s, 1H), 5.19 (s, 1H), 4.73 (s, 2H), 2.43 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.9 (C_4), 143.3 (CH), 139.4 (CH), 133.0 (C_4), 132.4 (C_4), 129.8 (2 × CH), 128.0 (2 × CH), 123.1 (C_4), 115.6 (CH_2), 107.8 (CH), 71.4 (CH_2), 21.6 (CH_3)

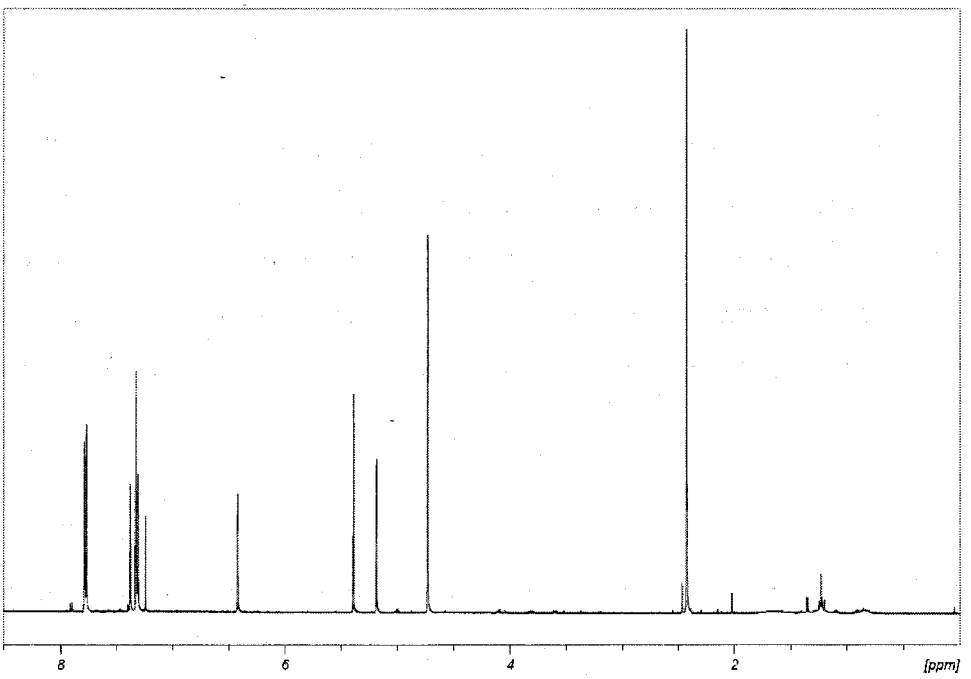
FT-IR (neat, cm^{-1}): 3148 (w), 2960 (s), 2922 (m)

HRMS (EI): Calculated 278.0613 (M^+) for $C_{14}H_{14}O_4S$, found 278.0633

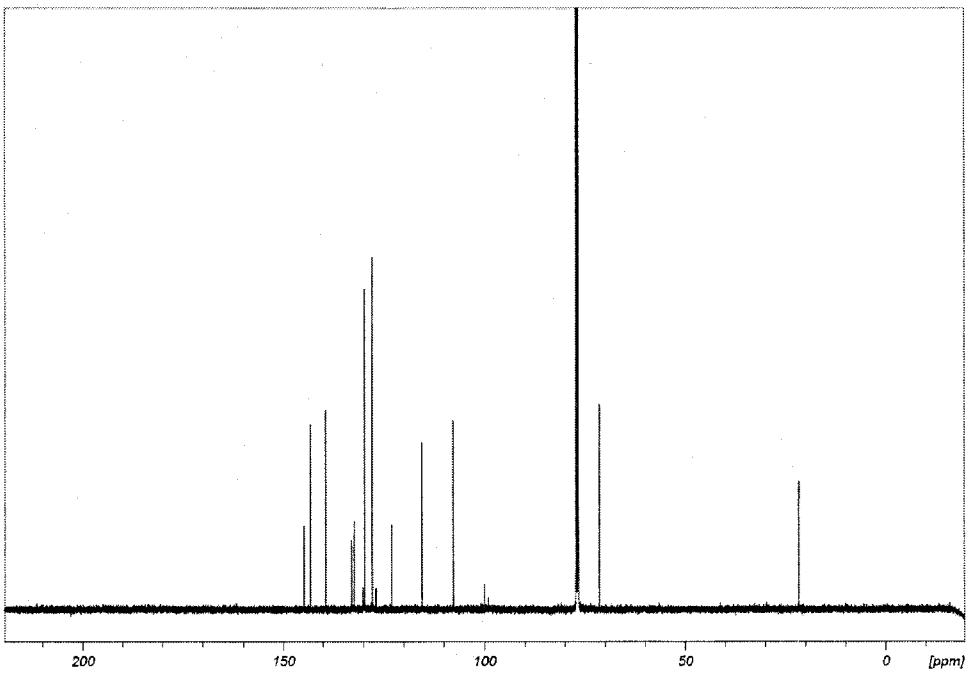


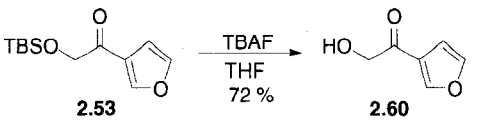
2.59

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





1-Furan-3-yl-2-hydroxyethanone (**2.60**)

A solution of **2.53** (210.2 mg, 0.847 mmol) in THF (10 mL) was treated with TBAF (1.0 M in THF, 1.75 mL, 1.75 mmol) and the resulting mixture was stirred at room temperature for 1 hour. The crude reaction mixture was concentrated under reduced pressure and the product from the reaction was isolated by flash chromatography in 50 % EtOAc/hexanes to afford **2.60** (78.9 mg, 0.626 mmol, 72 %, $R_f = 0.50$) as a white solid.

Data for **2.60**

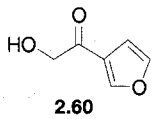
M.p.: 146-147 °C

^{1}H NMR (500 MHz, C_6D_6): δ = 7.04 (dd, J = 1.4, 0.8 Hz, 1H), 6.68 (dd, J = 1.7, 1.4 Hz, 1H), 6.36 (dd, J = 1.9, 0.8 Hz, 1H), 4.00 (s, 2H), 3.24 (bs, 1H)

^{13}C NMR (125 MHz, C_6D_6): δ = 193.6 (C_4), 147.4 (CH), 144.5 (CH), 128.7 (C_4), 108.5 (CH), 66.4 (CH_2)

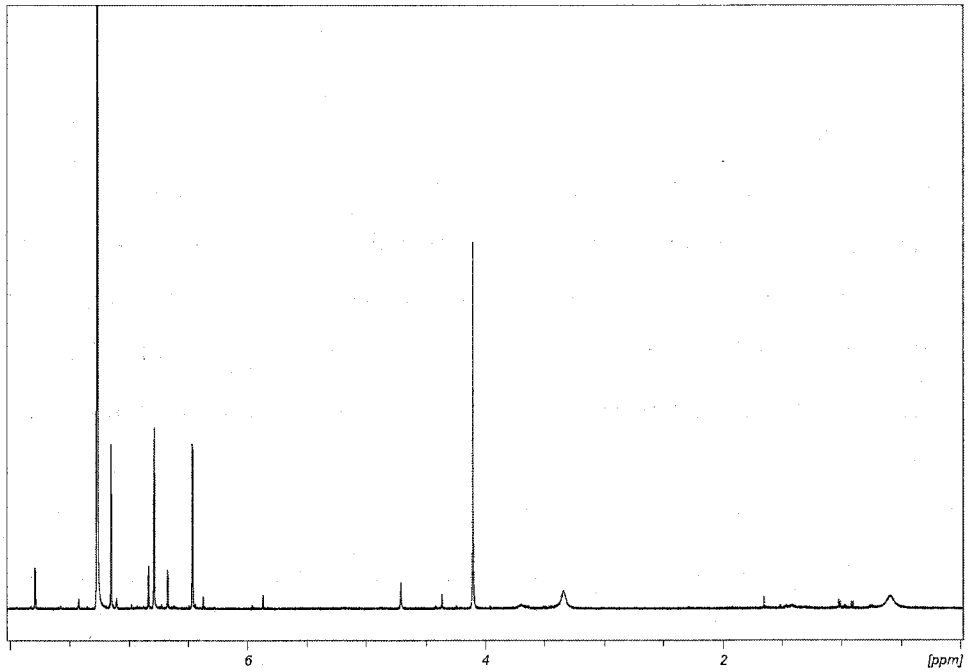
FT-IR (neat, cm^{-1}): 3387 (b), 2917 (m), 2858 (m), 1686 (s)

HRMS (EI): Calculated 126.0317 (M^+) for $C_6H_5O_3$, found 126.0334

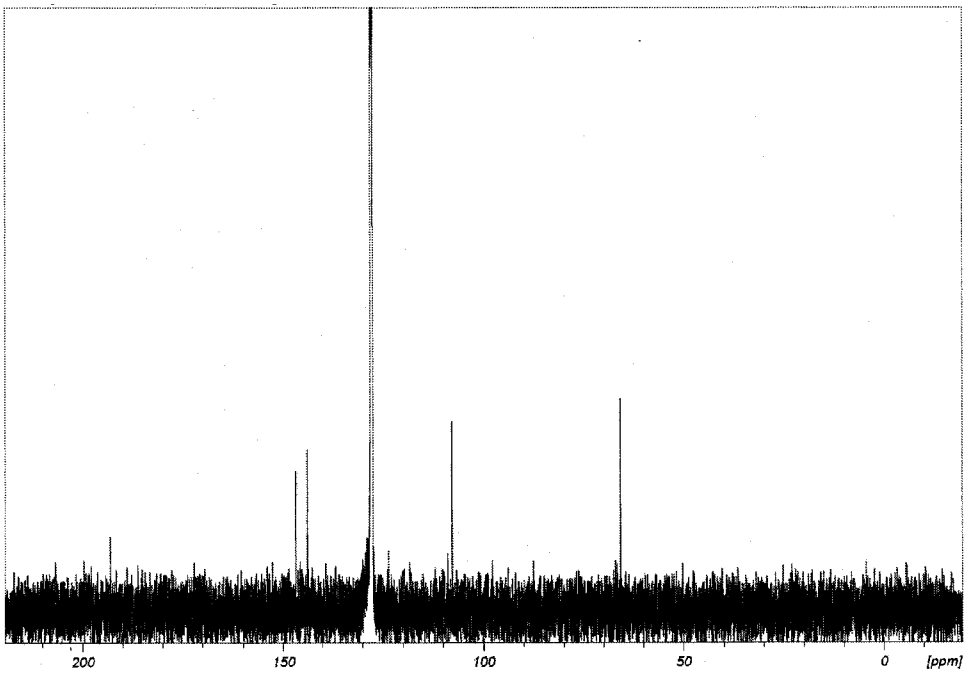


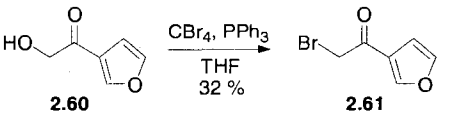
2.60

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





2-Bromo-1-furan-3-yl-ethanone (**2.61**)

A solution of **2.60** (37.1 mg, 0.294 mmol) in CH_2Cl_2 (5 mL) was treated with CBr_4 (121.9 mg, 0.368 mmol) and was stirred at room temperature for 10 min. To this mixture was added PPh_3 (115.7 mg, 0.441 mmol) and the resulting solution was stirred at room temperature for 1.5 hours. After the reaction was complete, the PPh_3O by-product was precipitated out of solution by pouring the reaction mixture into hexanes (100 mL) followed by filtration through a short pad of Celite. The mother liquor was concentrated under reduced pressure and the residue was preadsorbed onto silica gel (10 mL). The product was isolated by flash chromatography in 20 % EtOAc/hexanes to afford **2.61** (17.5 mg, 0.0926 mmol, 32 %, R_f = 0.55) as a yellow solid. This compound is unstable and cannot be stored.

Data for **2.61**

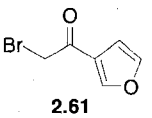
M.p.: 41 °C

^{1}H NMR (500 MHz, d_6-acetone): δ = 8.53 (d, J = 1.3 Hz, 1H), 7.23 (s, 1H), 6.84 (d, J = 0.9 Hz, 1H), 4.52 (s, 2H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 187.2 (C_4), 150.6 (CH), 146.4 (CH), 126.2 (C_4), 110.0 (CH), 33.9 (CH_2)

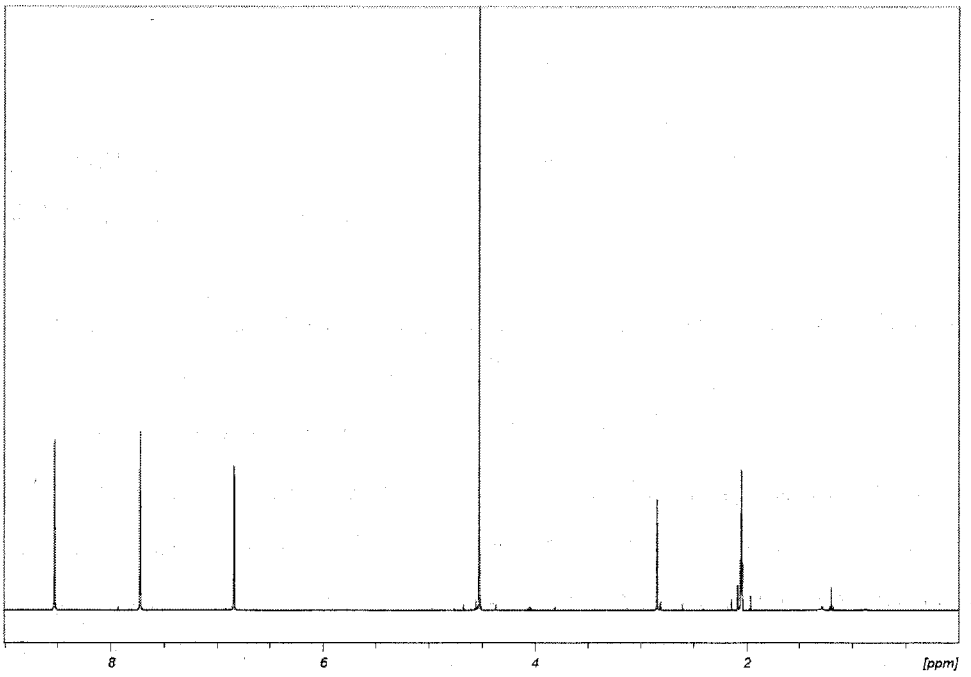
FT-IR (neat, cm^{-1}): 3135 (m), 2941 (m), 1674 (s)

HRMS (EI): Calculated 187.9473 (M^+) for $C_6H_5O_2Br$, found 187.9490

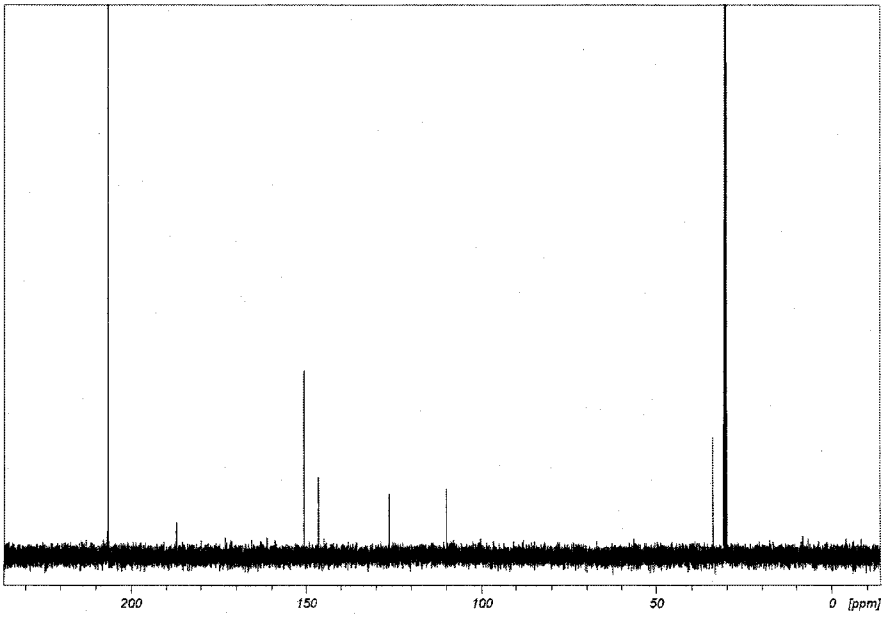


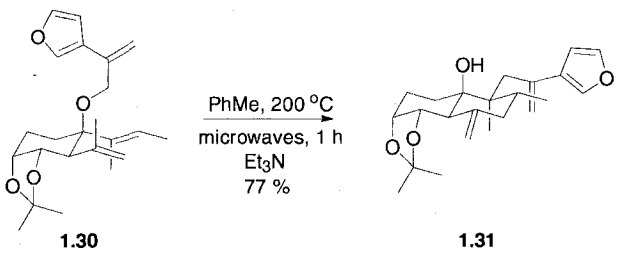
2.61

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





1.30 **1.31**

(±)-(3aR,5aR,6S,7R,9aS,9bS)-6-(2-(Furan-3-yl)allyl)-decahydro-2,2,6,7-tetramethyl-9-methylenenaphtho[2,1-d][1,3]dioxol-5a-ol (**1.31**)

A sample of **1.30** (257.8 mg, 0.692 mmol) and Et_3N (0.48 mL, 3.46 mmol) was dissolved in toluene (13 mL) and placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 200 °C over 20 minutes, then for 1 hour at 200 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 20 % EtOAc/hexanes, affording **1.31** (198.5 mg, 0.533 mmol, 77 %, R_f = 0.50) as a yellow oil.

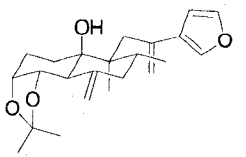
Data for **1.31**

^{1}H NMR (300 MHz, C_6D_6): δ = 7.47 (s, 1H), 7.04 (dd, J = 1.7, 1.7 Hz, 1H), 6.29 (dd, J = 0.9, 0.9 Hz, 1H), 5.22 (s, 1H), 5.17 (s, 1H), 5.01 (s, 1H), 4.94 (s, 1H), 4.31 (dd, J = 8.8, 5.7 Hz, 1H), 4.12 (ddd, J = 4.0, 4.0, 4.0 Hz, 1H), 2.43 (d, J_{AB} = 14.4 Hz, 1H), 2.34 (d, J_{AB} = 14.4 Hz, 1H), 1.97-1.74 (m, 6H), 1.67-1.51 (m, 3H), 1.48 (s, 3H), 1.32 (s, 3H), 0.79 (s, 3H), 0.70 (d, J = 6.5 Hz, 3H)

^{13}C NMR (75 MHz, C_6D_6): δ = 145.7 (C_4), 143.3 (CH), 140.3 (CH), 139.6 (C_4), 129.6 (C_4), 114.9 (CH_2), 110.5 (CH_2), 109.3 (CH), 107.7 (C_4), 78.6 (C_4), 74.8 (CH), 73.2 (CH), 48.1 (CH), 46.4 (C_4), 42.0 (CH_2), 39.8 (CH), 37.7 (CH_2), 28.7 (CH_3), 26.8 (CH_2), 26.2 (CH_3), 23.1 (CH_2), 17.6 (CH_3), 15.1 (CH_3)

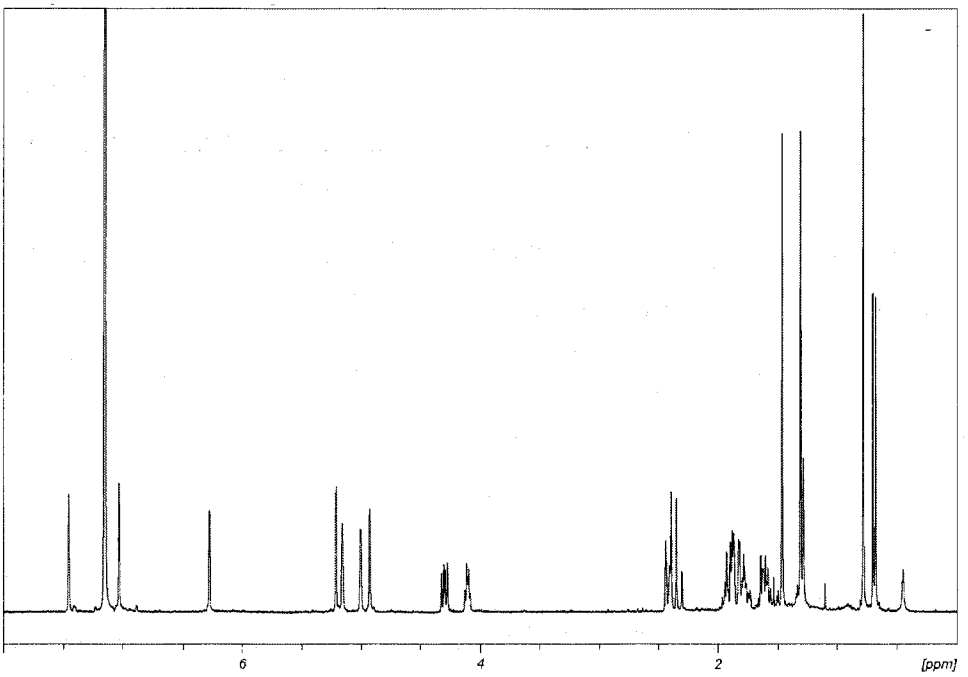
FT-IR (neat, cm^{-1}): 3552 (b), 2983 (s), 2933 (m), 2873 (w)

HRMS (EI): Calculated 372.2301 (M^+) for $C_{23}H_{32}O_4$, found 372.2280

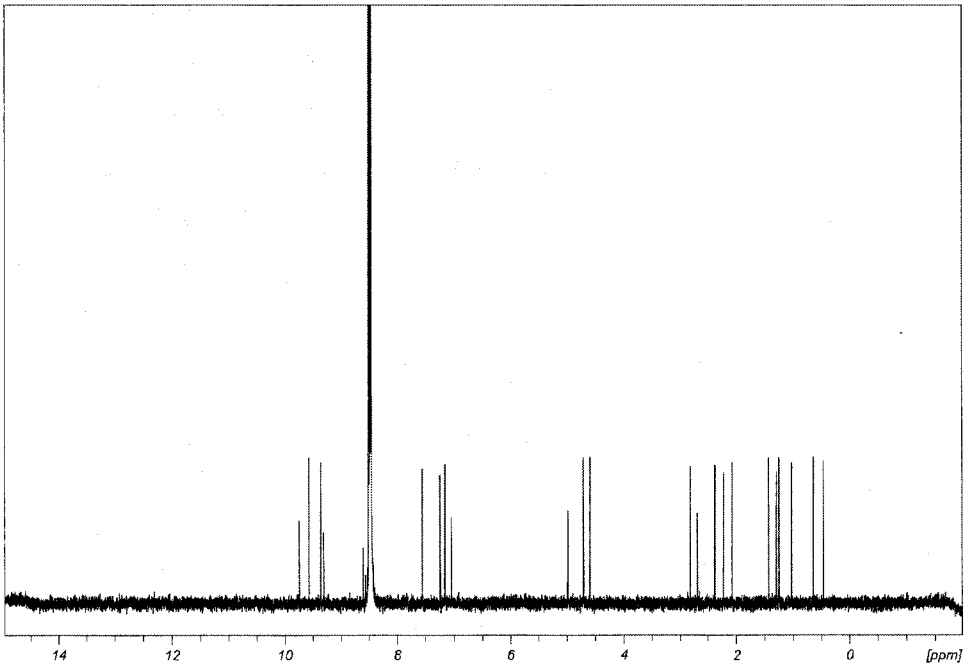


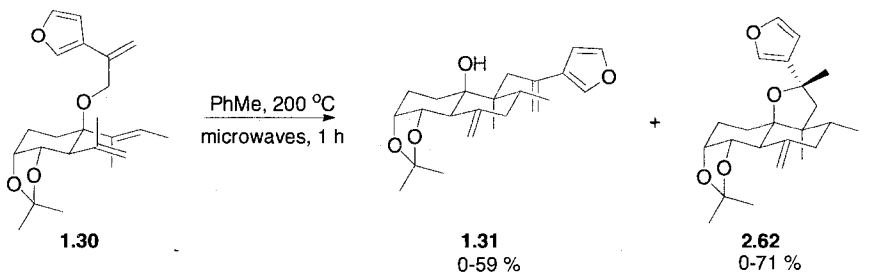
1.31

^{1}H NMR (300 MHz, C_6D_6)



^{13}C NMR (75 MHz, C_6D_6)





1.30 **1.31** 0-59 % **2.62** 0-71 %

(±)-(2S,3aS,4R,6aS,7S,8R,10aR)-2-(Furan-3-yl)-2,3a,4-trimethyl-6-methylene-decahydro-1-oxa-cyclopenta[d]naphthalene-7,8-diol acetonide (**2.62**)

This product is observed as an occasional side product (or the only product) from the microwave accelerated oxy-Cope/Claisen/ene reaction of **1.30**. Its isolation can be suppressed by performing the reaction in the presence of Et_3N. This compound is a white solid.

Data for **2.62**

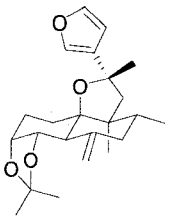
M.p.: 160-161 °C

^{1}H NMR (400 MHz, C_6D_6): δ = 7.06 (dd, J = 1.7, 1.7 Hz, 1H), 6.98 (dd, J = 1.1, 1.1 Hz, 1H), 6.34-6.33 (m, 1H), 5.37 (s, 1H), 5.14 (d, J = 1.7 Hz, 1H), 4.68 (dd, J = 9.6, 5.0 Hz, 1H), 4.26-4.23 (m, 1H), 2.34 (d, J = 9.6 Hz, 1H), 2.13-2.07 (m, 2H), 1.95-1.87 (m, 2H), 1.82-1.77 (m, 3H), 1.57-1.49 (m, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.33-1.28 (m, 1H), 0.75 (d, J = 6.7 Hz, 3H), 0.71 (s, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 145.2 (C_4), 143.2 (CH), 137.2 (CH), 136.4 (C_4), 110.1 (CH), 108.6 (CH_2), 107.5 (C_4), 89.2 (C_4), 76.6 (C_4), 76.1 (CH), 73.3 (CH), 48.8 (C_4), 48.6 (CH), 47.0 (CH_2), 41.3 (CH_2), 38.1 (CH), 33.7 (CH_3), 29.4 (CH_3), 27.6 (CH_2), 26.8 (CH_3), 22.7 (CH_2), 16.8 (CH_3), 13.8 (CH_3)

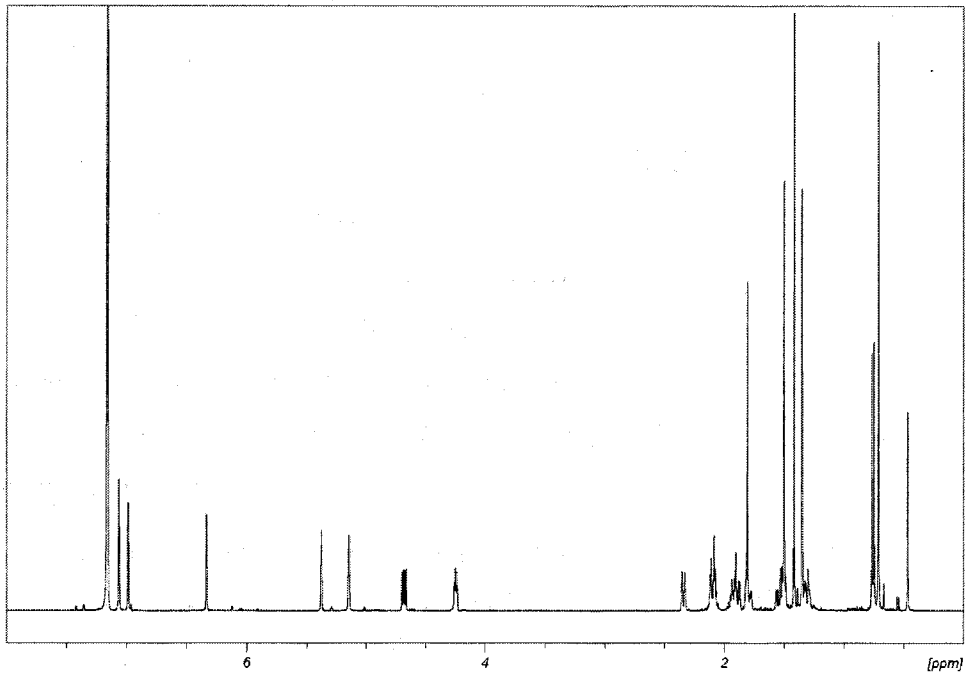
FT-IR (neat, cm^{-1}): 2960 (s), 2933 (s), 2875 (m), 1650 (w)

HRMS (EI): Calculated 372.2301 (M^+) for $C_{23}H_{32}O_4$, found 372.2319

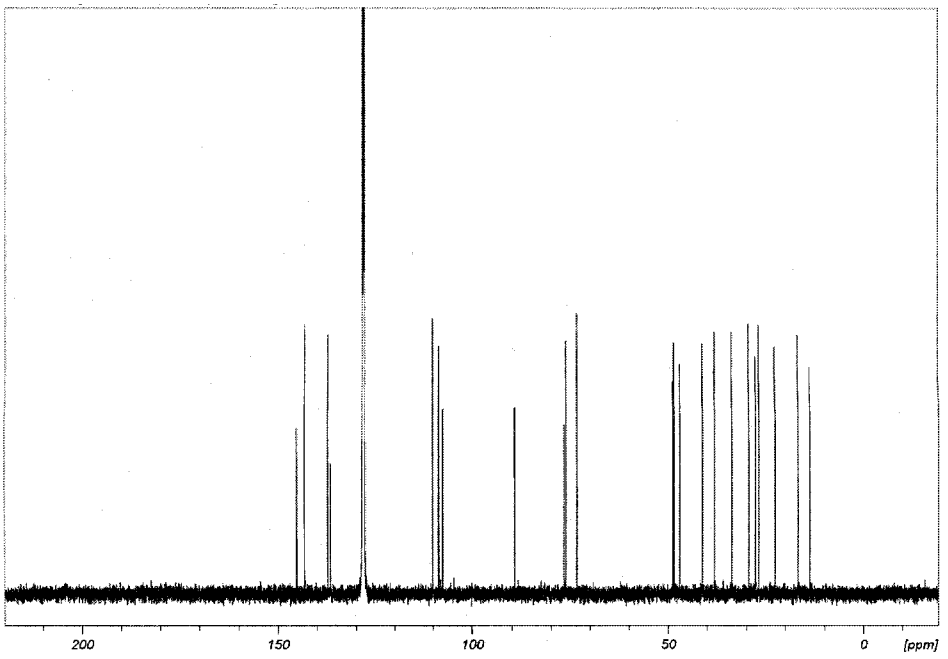


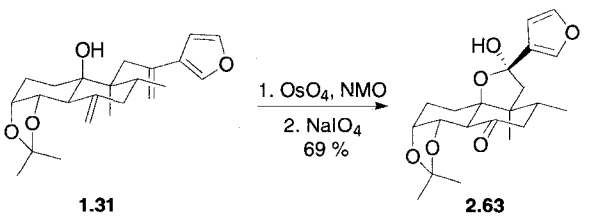
2.62

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



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





1.31 **2.63**

(±)-(2R,3aS,4R,6aS,6bS,9aR,11aR)-2-(Furan-3-yl)-2-hydroxy-3a,4,8,8-tetramethyl-octahydro-1,7,9-trioxa-dicyclopenta[d,h]naphthalene-6-one (**2.63**)

To a solution of **1.31** (130.0 mg, 0.372 mmol) in a 5:1 THF/H_2O (15 mL) was added NMO (163.8 mg, 1.40 mmol) followed by OsO_4 (4 % solution in H_2O, 0.26 mL, 0.0408 mmol), and the mixture was stirred at room temperature for 4 hours. After this, solid $NaIO_4$ (895.7 mg, 4.19 mmol) was added to the mixture, which was stirred for a further 16 hours. The reaction was quenched by the addition of saturated Na_2SO_3 followd by 0.5 hours of vigorous stirring. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 60 % EtOAc/hexanes gave **2.63** (91.0 mg, 0.242 mmol, 69 %, R_f = 0.50) as a white solid.

Data for **2.63**

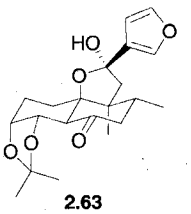
M.p.: 166-167 °C

^{1}H NMR (500 MHz, C_6D_6): δ = 7.50 (d, J = .07 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 6.31 (s, 1H), 5.19 (dd, J = 8.8, 5.2 Hz, 1H), 4.44-4.42 (m, 1H), 2.64 (d, J = 8.9 Hz, 1H), 2.38 (s, 1H), 2.25-2.15 (m, 3H), 2.05-1.92 (m, 3H), 1.87-1.81 (m, 1H), 1.66 (s, 2H), 1.61 (s, 3H), 1.52 (s, 3H), 0.73 (s, 3H), 0.45 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 205.9 (C_4), 143.5 (CH), 139.6 (CH), 133.0 (C_4), 108.8 (CH), 107.7 (C_4), 101.6 (C_4), 92.9 (C_4), 72.9 (CH), 55.5 (CH), 49.2 (C_4), 48.9 (CH_2), 45.7 (CH_2), 38.2 (CH), 30.7 (CH), 29.2 (CH_3), 28.0 (CH_2), 26.6 (CH_3), 23.0 (CH_2), 16.7 (CH_3), 12.6 (CH_3)

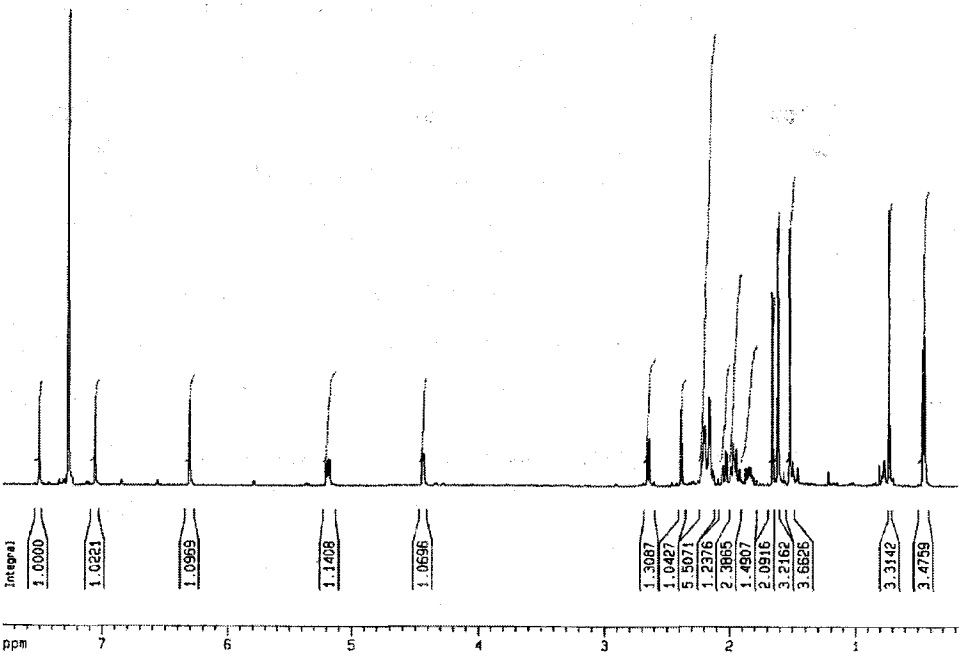
FT-IR (neat, cm^{-1}): 3411(b), 2981 (m), 2934 (m), 2878 (m), 1722 (s)

HRMS (EI): Calculated 376.1886 (M^+) for $C_{21}H_{28}O_6$, found (M^+-H_2O) at 358.1791, actual value 358.1780

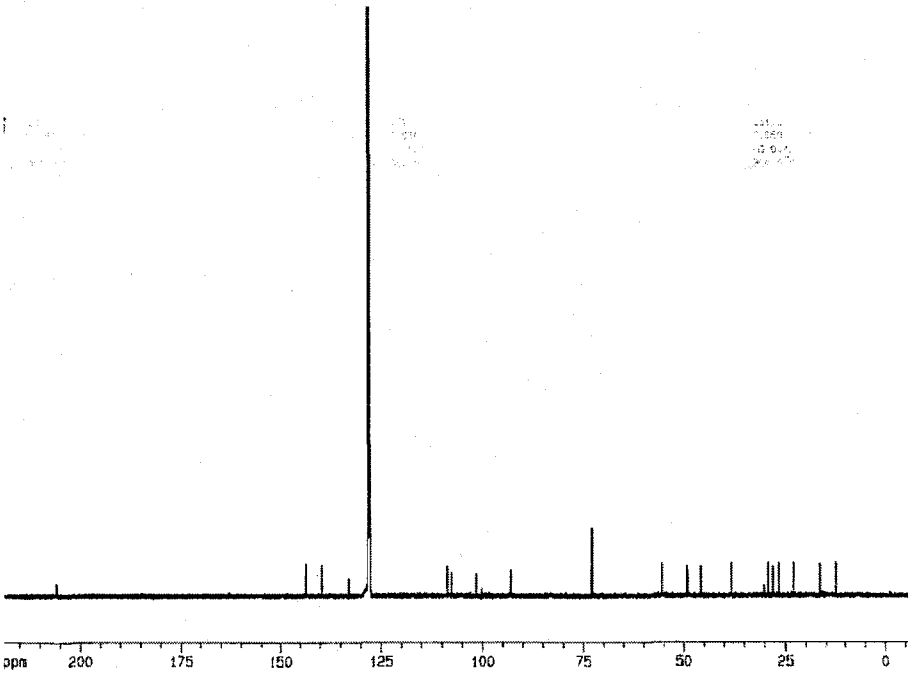


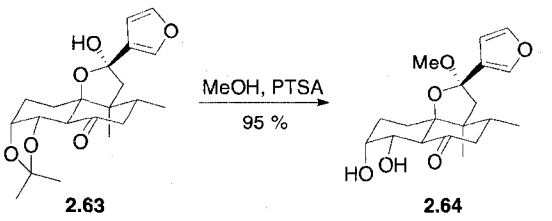
2.63

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





2.63 **2.64**

(±)-(2R,3aS,4R,6aS,7S,8R,10aR)-2-(Furan-3-yl)-octahydro-7,8-dihydroxy-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6(6aH)-one (**2.64**)

A solution of **2.63** (86.3 mg, 0.229 mmol) in MeOH (8 mL) was treated with PTSA (4.3 mg, 0.0229 mmol) and the resulting solution was stirred at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (8 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 80 % EtOAc/hexanes afforded **2.64** (76.5 mg, 0.218 mmol, 95 %, R_f = 0.55) as a white solid.

Data for **2.64**

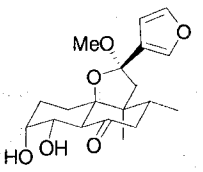
M.p.: 160-161 °C

^{1}H NMR (500 MHz, C_6D_6): δ = 7.48 (d, J = 0.7 Hz, 1H), 7.09 (dd, J = 1.7, 1.7 Hz, 1H), 6.20-6.19 (m, 1H), 4.60 (dd, J = 9.9, 2.6 Hz, 1H), 4.29-4.28 (m, 1H), 4.18 (s, 1H), 3.03 (s, 3H), 2.85 (d, J = 9.9 Hz, 1H), 2.24 (s, 2H), 2.21-2.15 (m, 1H), 2.10-2.04 (m, 2H), 2.00-1.92 (m, 3H), 1.81-1.75 (m, 2H), 0.73 (s, 3H), 0.43 (d, J = 6.8, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 212.8 (C_4), 143.9 (CH), 141.1 (CH), 129.0 (C_4), 108.9 (CH), 105.1 (C_4), 93.4 (C_4), 69.6 (CH), 68.1 (CH), 52.9 (CH), 50.7 (CH_3), 50.1 (CH_2), 48.1 (C_4), 45.2 (CH_2), 37.3 (CH), 27.6 (CH_2), 26.0 (CH_2), 16.5 (CH_3), 12.6 (CH_3)

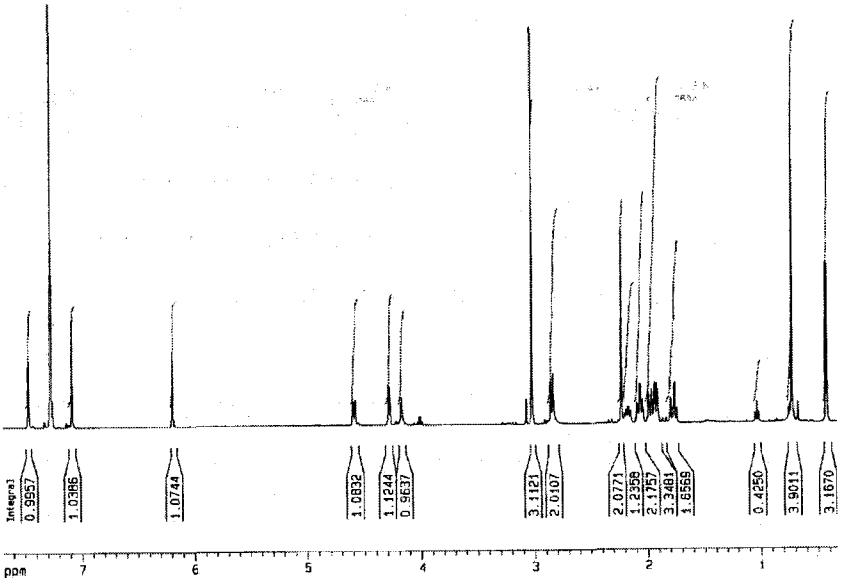
FT-IR (neat, cm^{-1}): 3450 (b), 2966 (s), 2935 (s), 2882 (m), 1712 (s)

HRMS (EI): Calculated 350.1729 (M^+) for $C_{19}H_{26}O_6$, found 350.1709

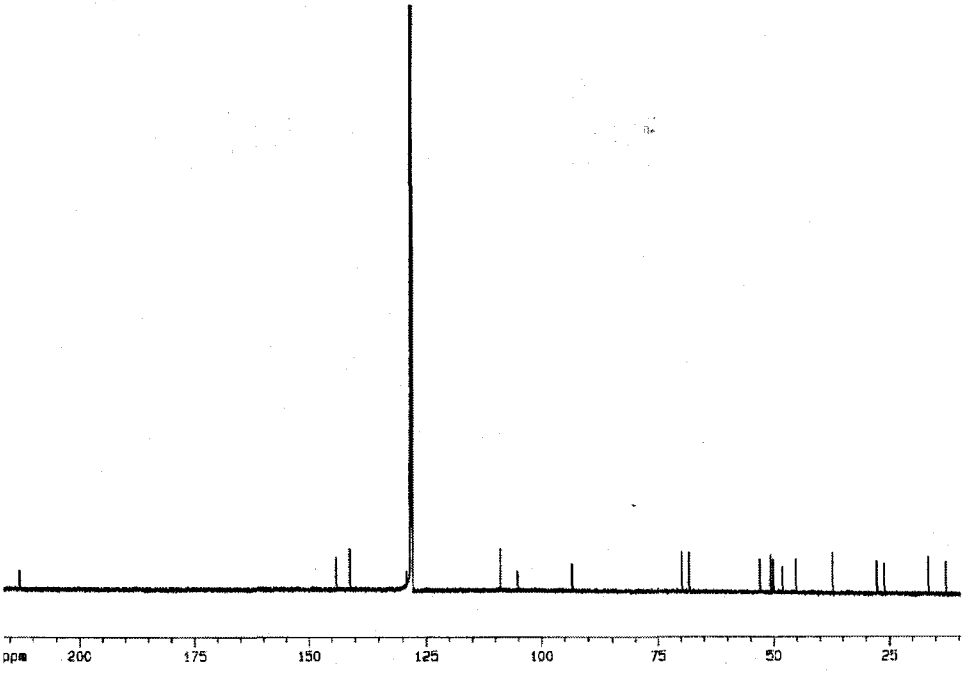


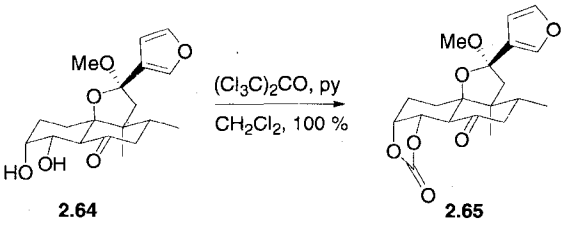
2.64

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





2.64 **2.65**

(±)-(2R,3aS,4R,6aS,7S,8R,10aR)-2-(Furan-3-yl)-2-methoxy-3a,4-dimethyl-octahydro-1,7,9-trioxa-dicyclopenta[d,h]naphthalene-6,8-dione (**2.65**)

To a solution of pyridine (0.14 mL, 1.91 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added triphosgene (85.0 mg, 0.286 mmol) followed by 10 minutes of stirring. A solution of **2.64** (67.0 mg, 0.191 mmol) in CH_2Cl_2 (5 mL) was added via cannula followed by stirring at 0 °C for 0.5 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 50 % EtOAc/hexanes gave **2.65** (72.0 mg, 0.191 mmol, 100 %, R_f = 0.50) as a white solid.

Data for **2.65**

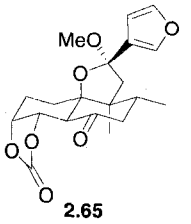
M.p.: 189-190 °C

^{1}H NMR (500 MHz, C_6D_6): δ = 7.40 (s, 1H), 7.06 (s, 1H), 6.10 (s, 1H), 5.24 (dd, J = 9.2, 6.2 Hz, 1H), 4.15-4.14 (m, 1H), 2.28 (s, 3H), 2.37 (d, J = 9.4 Hz, 1H), 2.12 (d, J_{AB} = 13.6 Hz, 1H) 2.08-2.02 (m, 1H), 2.02 (d, J_{AB} = 13.6 Hz, 1H), 1.91-1.87 (m, 2H), 1.75-1.70 (m, 2H), 1.64 (dd, J = 13.3, 13.3 Hz, 1H), 1.44-1.37 (m, 1H), 0.50 (s, 3H), 0.36 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 203.9 (C_4), 154.8 (C_4), 144.1 (CH), 141.1 (CH), 128.3 (C_4), 108.6 (CH), 105.8 (C_4), 91.6 (C_4), 75.1 (CH), 73.9 (CH), 53.5 (C_4), 50.9 (CH_3), 49.7 (CH), 48.4 (CH_2), 44.7 (CH_2), 37.9 (CH), 27.3 (CH_2), 22.1 (CH_2), 16.4 (CH_3), 12.4 (CH_3)

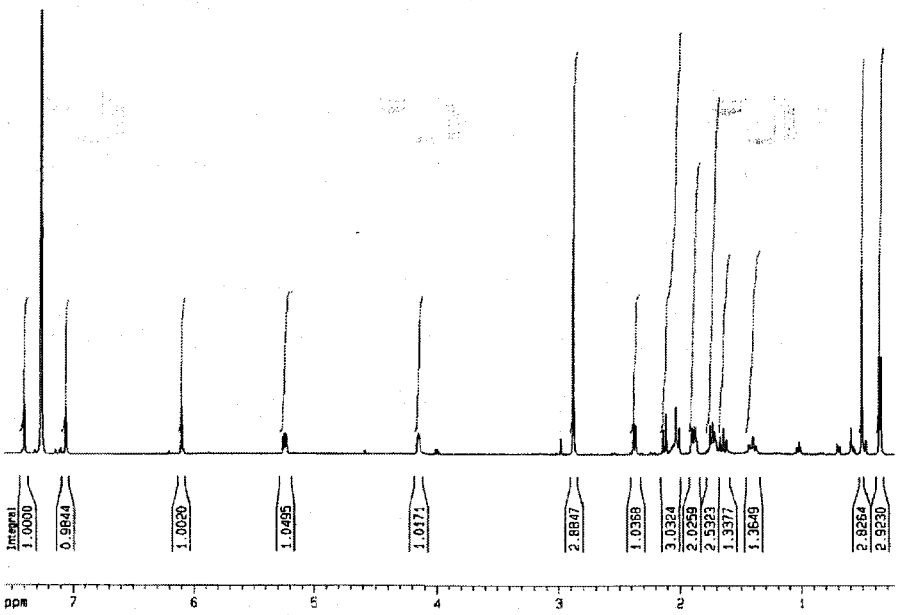
FT-IR (neat, cm^{-1}): 2963 (m), 2939 (m), 2887 (m), 1806 (s), 1717 (s)

HRMS (EI): Calculated 376.1522 (M^+) for $C_{20}H_{24}O_7$, found 376.1520

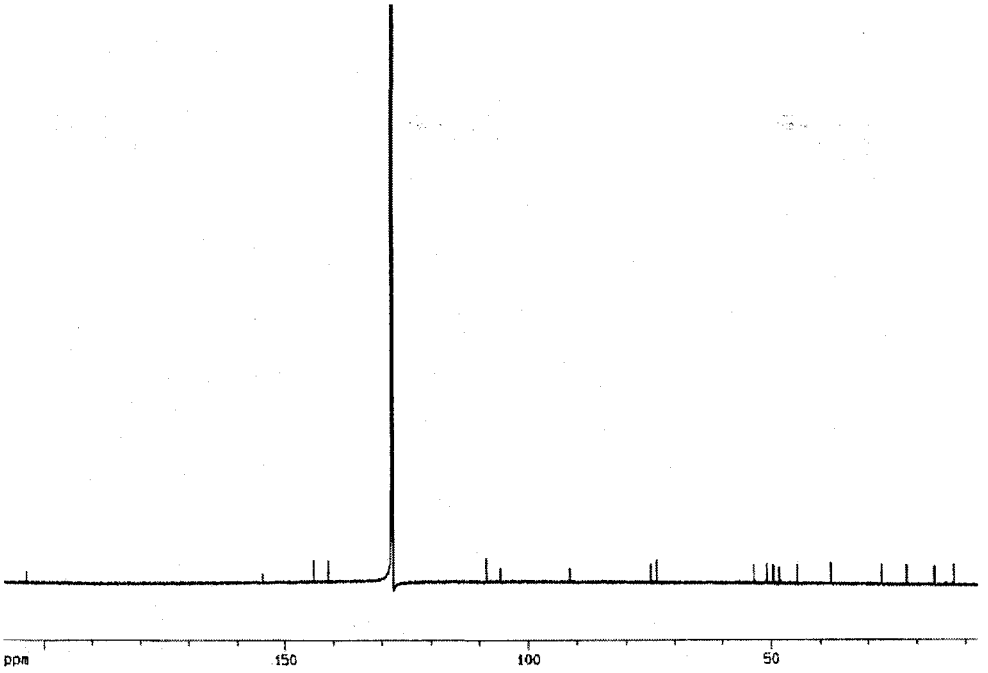


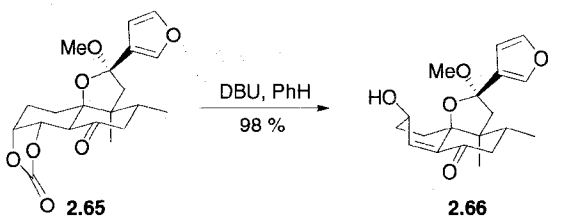
2.65

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





(±)-(2R,3aS,4R,8R,10aS)-2-(Furan-3-yl)-3,3a,4,5,9,10-hexahydro-8-hydroxy-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6(8H)-one (**2.66**)

To a solution of **2.65** (69.6 mg, 0.185 mmol) in benzene (10 mL) was added DBU (0.24 mL, 1.60 mmol) and the resulting mixture was stirred at room temperature for 0.5 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 80 % EtOAc/hexanes yielded **2.66** (60.0 mg, 0.181 mmol, 98 %, R_f = 0.50) as a colorless oil.

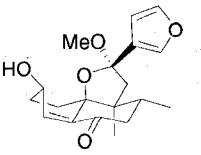
Data for **2.66**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.27 (dd, J = 0.8, 0.8 Hz, 1H), 6.97 (dd, J = 1.7, 1.7 Hz, 1H), 6.94 (dd, J = 4.3, 1.5 Hz, 1H), 6.13-6.12 (m, 1H), 3.92-3.89 (m, 1H), 3.05 (s, 3H), 2.37 (d, J_{AB} = 13.6 Hz, 1H), 2.29 (d, J_{AB} = 13.6 Hz, 1H), 2.23-2.13 (m, 3H), 2.11-2.06 (m, 1H), 1.91 (dd, J = 16.2, 12.9 Hz, 1H), 1.86-1.80 (m, 1H), 1.73-1.64 (m, 2H), 0.67 (s, 3H), 0.41 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 198.5 (C_4), 143.8 (CH), 141.0 (CH), 140.3 (CH), 137.3 (C_4), 128.8 (C_4), 109.0 (CH), 105.1 (C_4), 85.8 (C_4), 63.2 (CH), 51.5 (CH_2), 50.4 (CH_3), 48.3 (C_4), 43.6 (CH_2), 32.8 (CH), 27.2 (CH_2), 26.3 (CH_2), 15.8 (CH_3), 14.0 (CH_3)

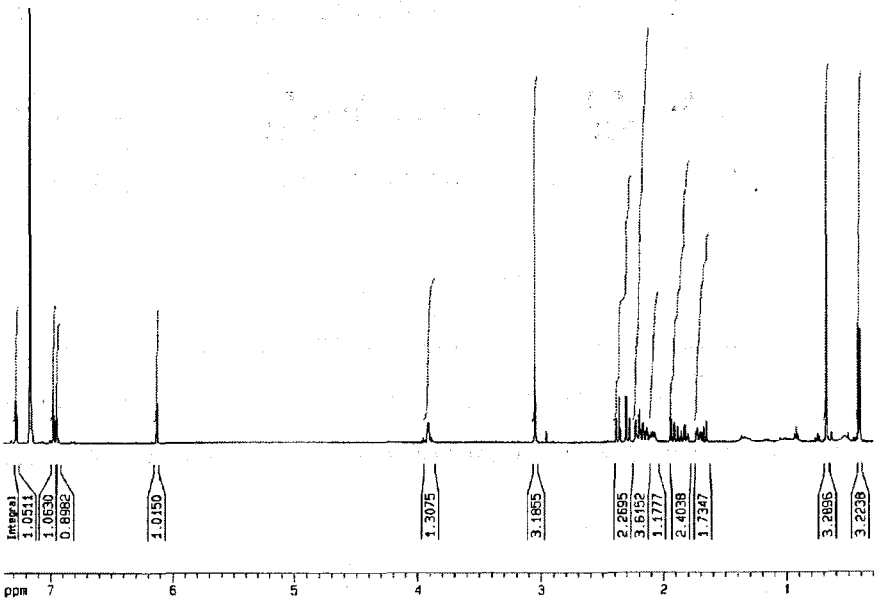
FT-IR (neat, cm^{-1}): 3414 (b), 2971 (m), 2943 (m), 2891 (m), 1694 (s)

HRMS (EI): Calculated 332.1624 (M^+) for $C_{19}H_{24}O_5$, found (M^+-H_2O) at 314.1518, actual value 314.1508

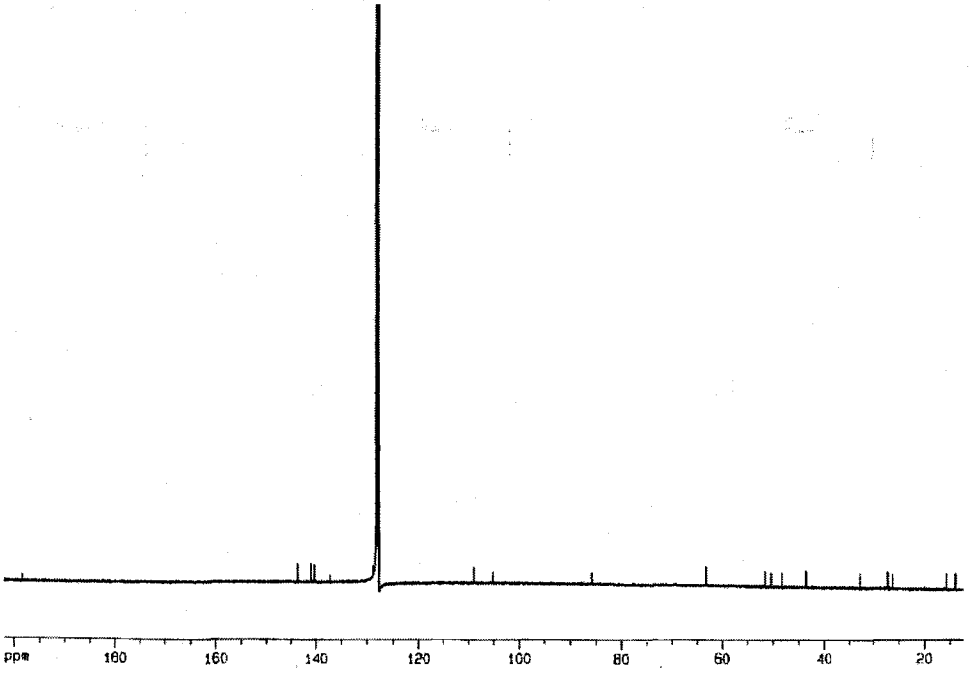


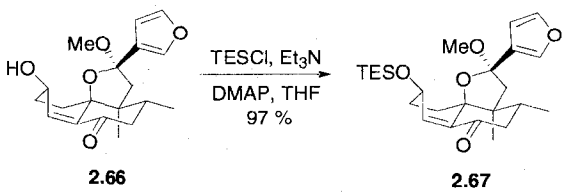
2.66

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





2.66 **2.67**

(±)-(2R,3aS,4R,8R,10aS)-8-Triethylsilyloxy-2-(furan-3-yl)-3,3a,4,5,9,10-hexahydro-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6(8H)-one (**2.67**)

A solution of **2.66** (57.0 mg, 0.171 mmol) in THF (15 mL) was treated with Et_3N (0.25 mL, 1.80 mmol), DMAP (2.0 mg, 0.0171 mmol) and TESCl (0.05 mL, 0.298 mmol) and the resulting solution was stirred at room temperature for 18 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, the aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes yielded **2.67** (74.0 mg, 1.66 mmol, 97 %, R_f = 0.75) as a colorless oil.

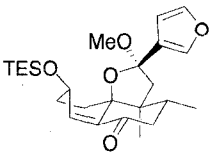
Data for **2.67**

^{1}H NMR (500 MHz, d_6-acetone): δ = 7.52 (dd, J = 1.7, 1.7 Hz, 1H), 7.40 (d, J = 0.7 Hz, 1H), 6.64 (dd, J = 4.2, 1.5 Hz, 1H), 6.32 (d, J = 1.0 Hz, 1H), 4.43-4.41 (m, 1H), 3.01 (s, 3H), 2.62 (d, J_{AB} = 13.7 Hz, 1H), 2.36 (d, J_{AB} = 13.7 Hz, 1H), 2.30-2.13 (m, 5H), 1.93 (ddd, J = 13.1, 13.0, 3.0 Hz, 1H), 1.78-1.75 (m, 1H), 1.09 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.65 (q, J = 7.9 Hz, 6H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 200.1 (C_4), 145.2 (CH), 142.0 (CH), 141.4 (CH), 138.1 (C_4), 130.0 (C_4), 110.4 (CH), 106.3 (C_4), 87.0 (C_4), 65.1 (CH), 52.3 (CH_2), 51.1 (CH_3), 49.6 (C_4), 44.5 (CH_2), 34.0 (CH), 29.2 (CH_2), 27.4 (CH_2), 16.8 (CH_3), 14.9 (CH_3), 7.7 (3 × CH_3), 6.0 (3 × CH_2)

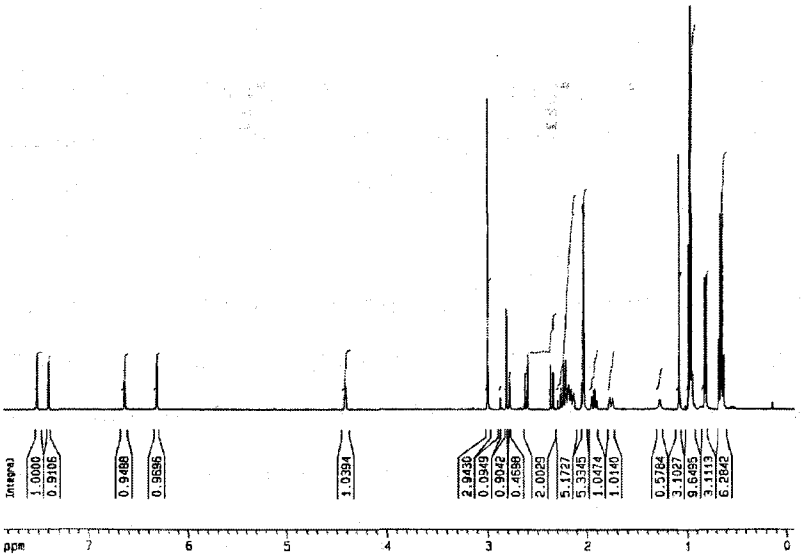
FT-IR (neat, cm^{-1}): 2957 (s), 2915 (m), 2877 (m), 2822 (w), 1698 (s)

HRMS (EI): Calculated 446.2489 (M^+) for $C_{25}H_{38}O_5Si$, found 446.2494

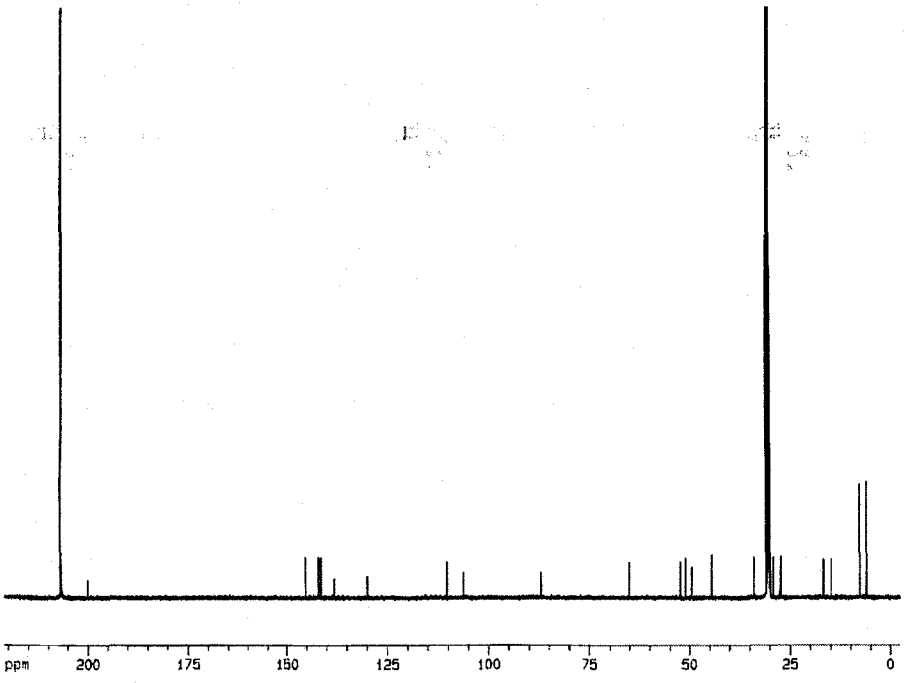


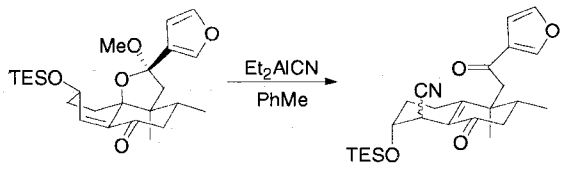
2.67

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





2.67 **2.71**

(±)-(2R,5S,6R)-2-(Triethylsilyloxy)-5-(2-(furan-3-yl)-2-oxoethyl)-1,2,3,4,5,6,7,8-octahydro-5,6-dimethyl-8-oxonaphthalene-1-carbonitrile (**2.71**)

2.67 (21.4 mg, 0.0479 mmol) was dissolved in toluene (10 mL) and Et_2AlCN (1.0 M in toluene, 0.14 mL, 0.140 mmol) was added dropwise over 10 min. This mixture was stirred at room temperature for 0.5 hours and was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Gradient flash chromatography in hexanes to 5 % EtOAc/hexanes afforded **2.71** (**A**) (0.0136 mmol, 28 %, R_f = 0.60) as a colorless oil and **2.71** (**B**) (3.5 mg, 0.00793 mmol, 17 %, R_f = 0.50) as a colorless oil.

Data for **2.71** (**A**)

^{1}H NMR (400 MHz, C_6D_6): δ = 7.34 (dd, J = 1.4, 0.9 Hz, 1H), 6.83 (dd, J = 1.8, 1.5 Hz, 1H), 6.58 (dd, J = 1.9, 0.8 Hz, 1H), 4.24-4.22 (m, 1H), 3.94 (d, J = 3.3 Hz, 1H), 2.56 (d, J_{AB} = 16.7 Hz, 1H), 2.32 (d, J_{AB} = 16.7 Hz, 1H), 2.29-2.25 (m, 1H), 2.22-2.20 (m, 1H), 2.19-1.86 (m, 4H), 1.45-1.39 (m, 1H), 0.87 (t, J = 7.9 Hz, 9H), 0.76 (s, 3H), 0.49-0.43 (m, 9H)

^{13}C NMR (100 MHz, C_6D_6): δ = 194.4 (C_4), 191.4 (C_4), 164.0 (C_4), 147.2 (CH), 144.7 (CH), 128.8 (C_4), 125.3 (C_4), 119.5 (C_4), 108.9 (CH), 67.1 (CH), 46.3 (CH_2), 42.2 (C_4), 41.6 (CH_2), 34.5 (CH), 33.3 (CH), 27.5 (CH_2), 22.9 (CH_2), 19.8 (CH_3), 15.5 (CH_3), 7.0 (3 × CH_3), 4.9 (3 × CH_2)

FT-IR (neat, cm^{-1}): 2957 (m), 2913 (m), 2877 (m), 2241 (w), 1668 (s)

HRMS (EI): Calculated 441.2335 (M^+) for $C_{25}H_{35}NO_4Si$, found (M^+-Et) at 412.1983, actual value 412.1944

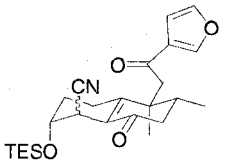
Data for **2.71 (B)**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.24 (dd, J = 1.4, 0.9 Hz, 1H), 6.75 (dd, J = 1.8, 1.5 Hz, 1H), 6.46 (dd, J = 1.9, 0.8 Hz, 1H), 4.34 (d, J = 5.2 Hz, 1H), 3.92-3.87 (m, 1H), 2.48 (d, J_{AB} = 17.9 Hz, 1H), 2.33-2.27 (m, 1H), 2.23-2.01 (m, 5H), 1.90-1.79 (m, 2H), 0.98 (t, J = 7.9 Hz, 9H), 0.50 (q, J = 7.8 Hz, 6H), 0.44 (s, 3H), 0.34 (d, J = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 194.1 (C_4), 191.8 (C_4), 164.1 (C_4), 147.2 (CH), 144.6 (CH), 129.1 (C_4), 127.2 (C_4), 118.5 (C_4), 108.7 (CH), 67.4 (CH), 44.9 (CH_2), 41.8 (C_4), 41.6 (CH_2), 34.6 (CH), 34.2 (CH), 29.4 (CH_2), 26.9 (CH_2), 18.8 (CH_3), 15.7 (CH_3), 7.1 (3 $\times$ CH_3), 5.1 (3 $\times$ CH_2)

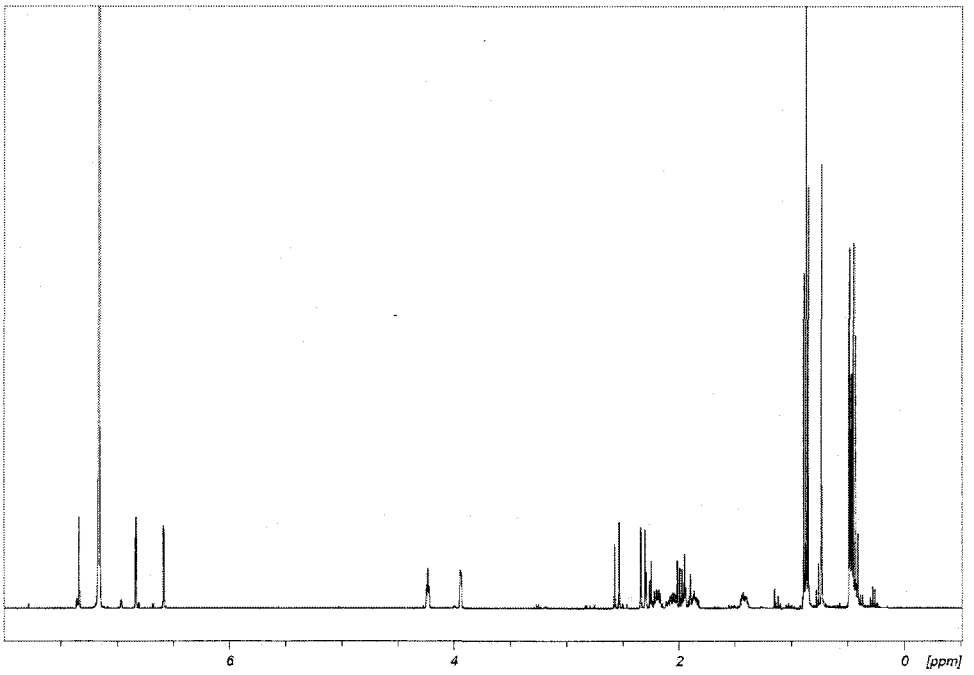
FT-IR (neat, cm^{-1}): 2957 (m), 2913 (m), 2877 (m), 2244 (w), 1669 (s)

HRMS (EI): Calculated 441.2335 (M^+) for $C_{25}H_{35}NO_4Si$, found (M^+-Et) at 412.1967, actual value 412.1944

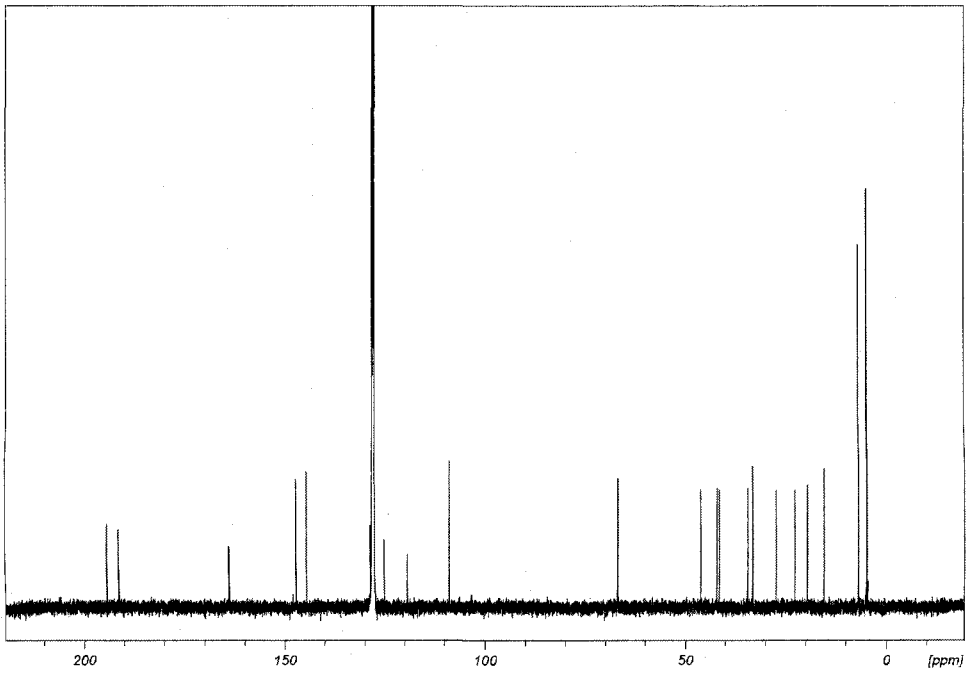


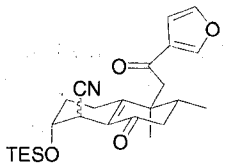
2.71 (A)

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



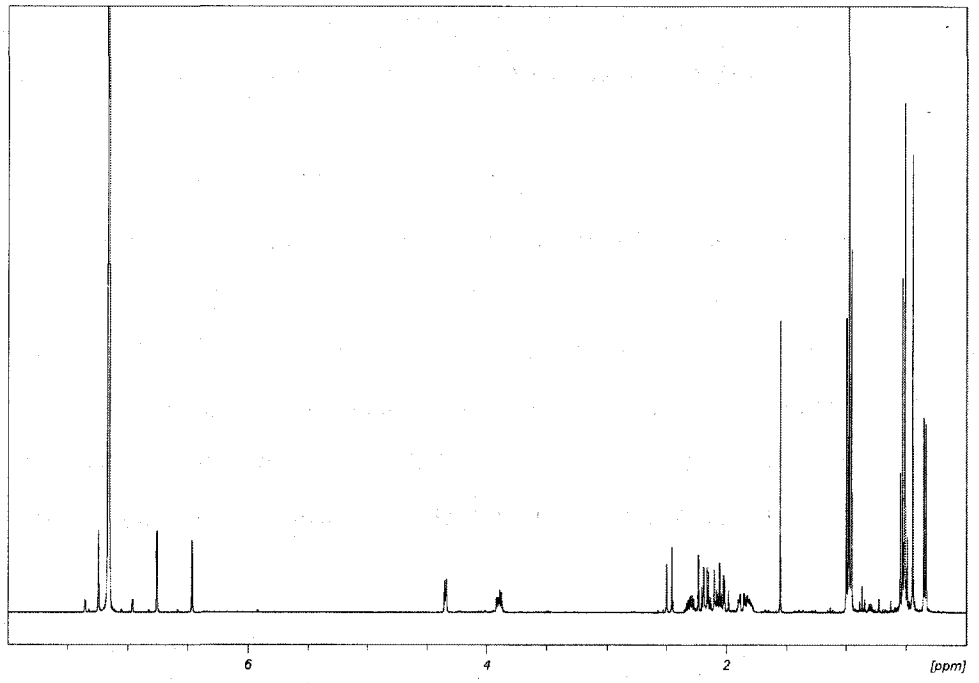
^{13}C NMR (100 MHz, C_6D_6)



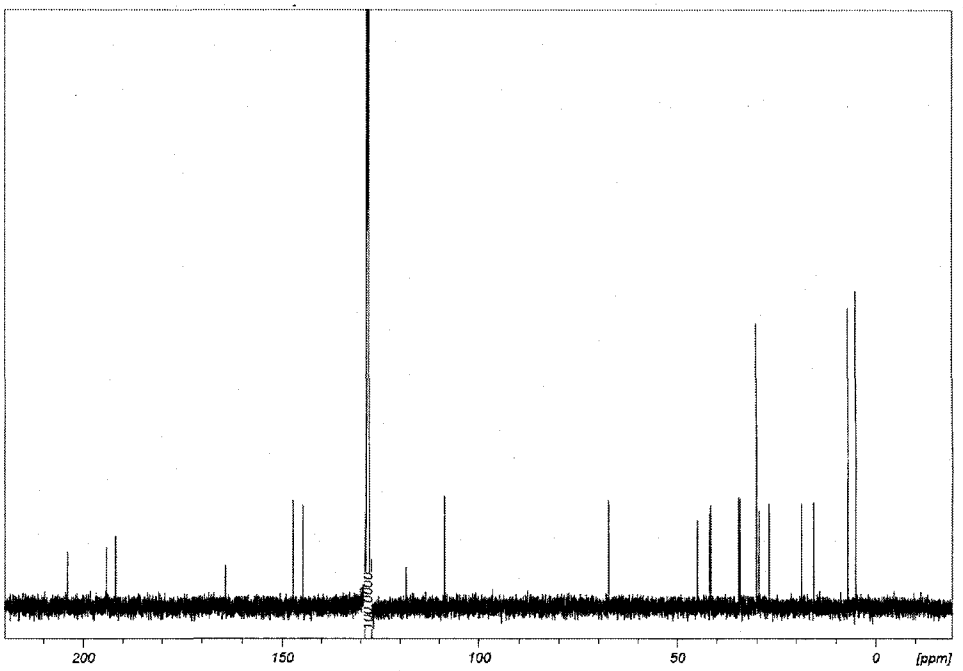


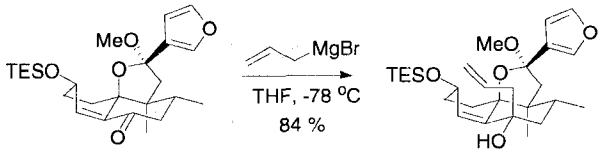
2.71 (B)

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



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





2.67 **2.73**

(±)-(2R,3aS,4R,6S,8R,10aS)-6-Allyl-8-(triethylsilyloxy)-2-(furan-3-yl)-3,3a,4,5,6,8,9,10-octahydro-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6-ol (**2.73**)

To a solution of **2.67** (14.5 mg, 0.0325 mmol) in THF (4 mL) cooled to -78 °C was added allyl magnesium bromide (1.0 M in THF, 0.10 mL, 0.100 mmol) and the resulting solution was stirred at -78 °C for 0.5 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded **2.73** (13.2 mg, 0.0270 mmol, 84 %, R_f = 0.45) as a colorless oil.

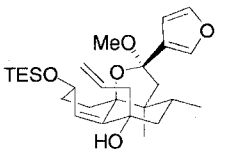
Data for **2.73**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.54 (dd, J = 1.6, 0.9 Hz, 1H), 7.01 (dd, J = 1.7, 1.7 Hz, 1H), 6.55 (dd, J = 4.7, 1.3 Hz, 1H), 6.25 (dd, J = 1.9, 0.9 Hz, 1H), 6.04-5.96 (m, 1H), 5.09-5.02 (m, 2H), 4.36-4.34 (m, 1H), 3.10 (s, 3H), 2.68-2.61 (m, 2H), 2.45 (d, J_{AB} = 13.5 Hz, 1H), 2.35 (d, J_{AB} = 13.5, 1H), 2.32-2.16 (m, 3H), 1.90-1.86 (m, 1H), 1.81-1.74 (m, 1H), 1.45 (dd, J = 13.2, 2.8 Hz, 1H), 1.20-1.12 (m, 2H), 1.05 (t, J = 8.0 Hz, 9H), 0.76 (s, 3H), 0.66 (q, J = 8.0 Hz, 6H), 0.54 (d, J = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 143.6 (CH), 142.1 (C_4), 140.1 (CH), 135.0 (CH), 130.8 (CH), 129.2 (C_4), 118.3 (CH_2), 109.6 (CH), 104.9 (C_4), 86.9 (C_4), 72.8 (C_4), 65.0 (CH), 51.3 (CH_2), 50.0 (CH_3), 49.6 (C_4), 45.7 (CH_2), 42.4 (CH_2), 31.6 (CH), 28.9 (CH_2), 27.4 (CH_2), 16.4 (CH_3), 13.7 (CH_3), 7.3 (3 × CH_3), 5.4 (3 × CH_2)

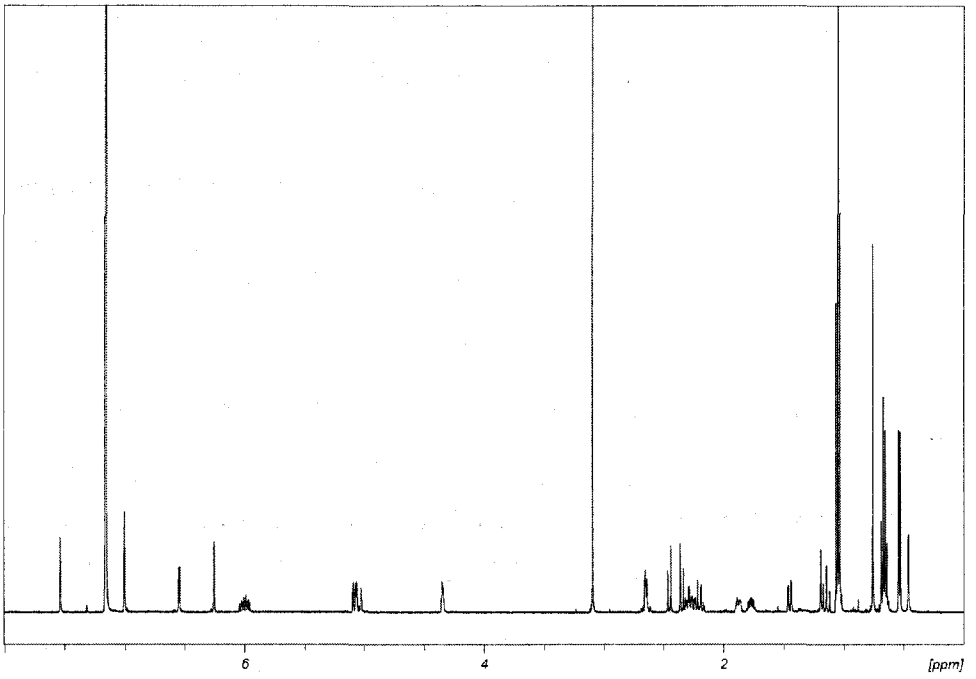
FT-IR (neat, cm^{-1}): 3461 (b), 2956 (s), 2936 (s), 2913 (m), 2876 (s)

HRMS (EI): Calculated 488.2958 (M^+) for $C_{28}H_{44}O_5Si$, found (M^+-OMe) at 457.2752, actual value 457.2774

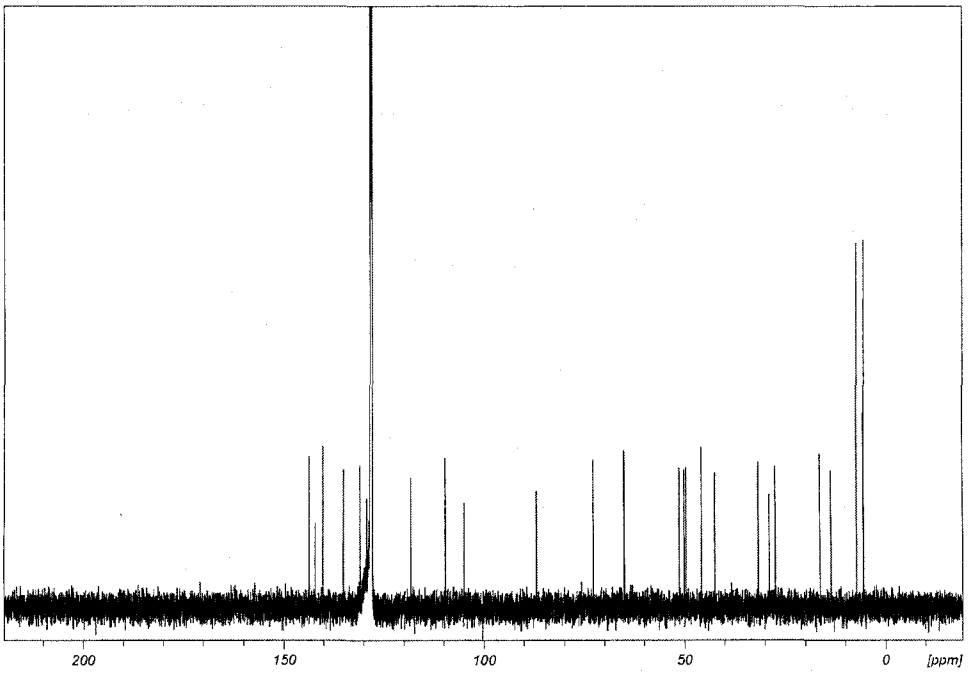


2.73

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



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



2.73 **2.75**

(±)-(2R,3aS,4R,6S,8R,10aS)-6-Allyl-2-(furan-3-yl)-3,3a,4,5,6,8,9,10-octahydro-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6,8-diol (**2.75**)

This product was observed in attempts at performing an anionic oxy-Cope rearrangement using compound **2.73**.

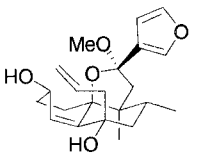
Data for **2.75**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.51 (dd, J = 1.6, 0.8 Hz, 1H), 7.00 (dd, J = 1.7, 1.7 Hz, 1H), 6.34 (dd, J = 4.8, 1.4 Hz, 1H), 6.23 (dd, J = 1.8, 0.8 Hz, 1H), 6.01-5.90 (m, 1H), 5.09-5.00 (m, 2H), 4.12-4.10 (m, 1H), 3.05 (s, 3H), 2.59 (d, J = 7.4 Hz, 2H), 2.45 (d, J_{AB} = 13.5 Hz, 1H), 2.32 (d, J_{AB} = 13.5 Hz, 1H), 2.25-2.11 (m, 2H), 1.96 (ddd, J = 13.1, 13.1, 2.8 Hz, 1H), 1.79-1.72 (m, 2H), 1.47 (dd, J = 13.1, 2.7 Hz, 1H), 1.38-1.11 (m, 3H), 0.80 (s, 3H), 0.56 (d, J = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 143.6 (CH), 142.8 (C_4), 140.1 (CH), 134.9 (CH), 130.3 (CH), 129.1 (C_4), 118.3 (CH_2), 109.6 (CH), 104.9 (C_4), 86.7 (C_4), 72.8 (C_4), 64.0 (CH_3), 51.2 (CH_2), 50.1 (CH), 49.5 (C_4), 45.7 (CH_2), 42.4 (CH_2), 31.5 (CH), 27.9 (CH_2), 27.0 (CH_2), 16.5 (CH_3), 13.7 (CH_3)

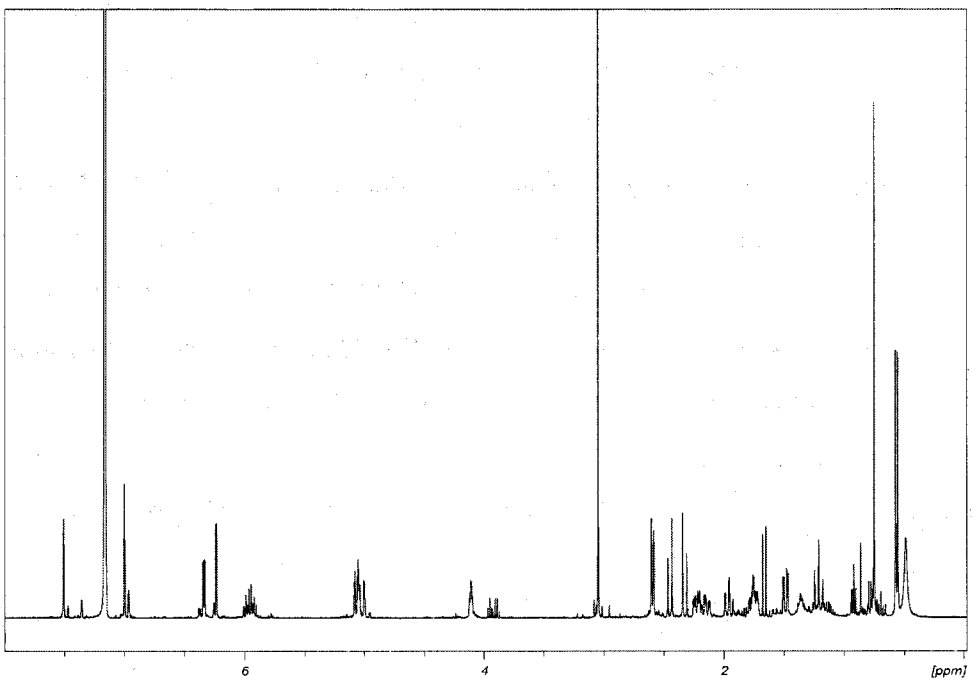
FT-IR (neat, cm^{-1}): 3368 (b), 2960 (s), 2933 (s), 2875 (m), 1636 (w)

HRMS (EI): Calculated 374.2093 (M^+) for $C_{22}H_{30}O_5$, found 374.2079

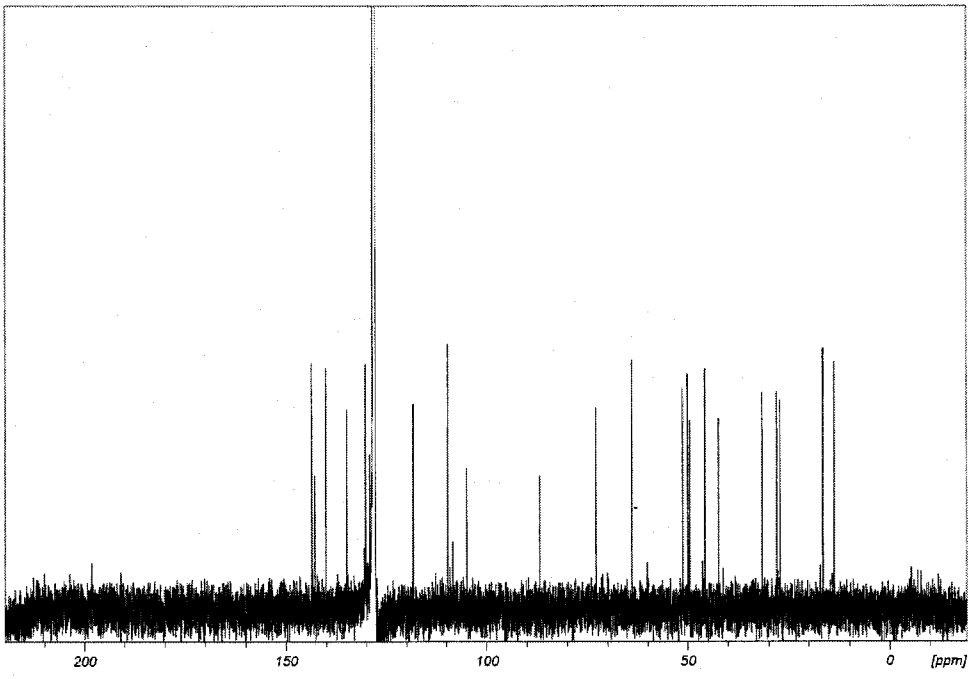


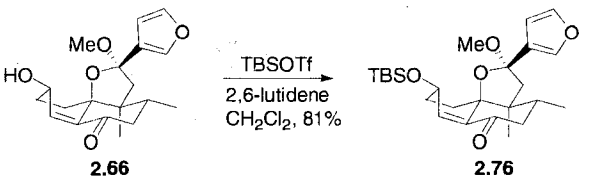
2.75

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



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





2.66 **2.76**

(±)-(2R,3aS,4R,8R,10aS)-8-(Tert-butyl-dimethylsilyloxy)-2-(furan-3-yl)-3,3a,4,5,9,10-hexahydro-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6(8H)-one (**2.76**)

A solution of **2.66** (38.3 mg, 0.115 mmol) in CH_2Cl_2 (6 mL) was cooled to 0 °C and treated with 2,6-lutidine (0.13 mL, 1.12 mmol) and then TBSOTf (0.05 mL, 0.218 mmol). This mixture was stirred at 0 °C for 2 hours after which it was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded **2.76** (41.5 mg, 0.0929 mmol, 81 %, R_f = 0.50) as a colorless oil.

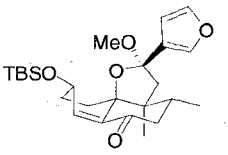
Data for **2.76**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.32 (dd, J = 1.7, 0.9 Hz, 1H), 7.12 (dd, J = 43, 1.6 Hz, 1H), 6.99 (dd, J = 1.8, 1.8 Hz, 1H), 6.15 (dd, J = 1.8, 0.9 Hz, 1H), 4.17-4.15 (m, 1H), 3.10 (s, 3H), 2.39 (d, J_{AB} = 13.6 Hz, 1H), 2.32 (d, J_{AB} = 13.6 Hz, 1H), 2.32-2.19 (m, 3H), 2.14-2.07 (m, 1H), 2.00 (ddd, J = 16.1, 16.1, 2.9 Hz, 1H), 1.89 (dd, J = 16.2, 12.9 Hz, 1H), 1.82-1.78 (m, 1H), 0.93 (s, 9H), 0.69 (s, 3H), 0.40 (d, J = 6.8 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 198.7 (C_4), 143.9 (CH), 141.0 (CH), 140.6 (CH), 137.1 (C_4), 128.9 (C_4), 109.1 (CH), 105.2 (C_4), 86.1 (C_4), 64.4 (CH), 51.7 (CH_2), 50.4 (CH_3), 48.4 (C_4), 43.6 (CH_2), 33.0 (CH), 28.3 (CH_2), 26.5 (CH_2), 26.1 (3 × CH_3), 18.4 (C_4), 15.8 (CH_3), 14.1 (CH_3), -4.5 (CH_3), -4.8 (CH_3)

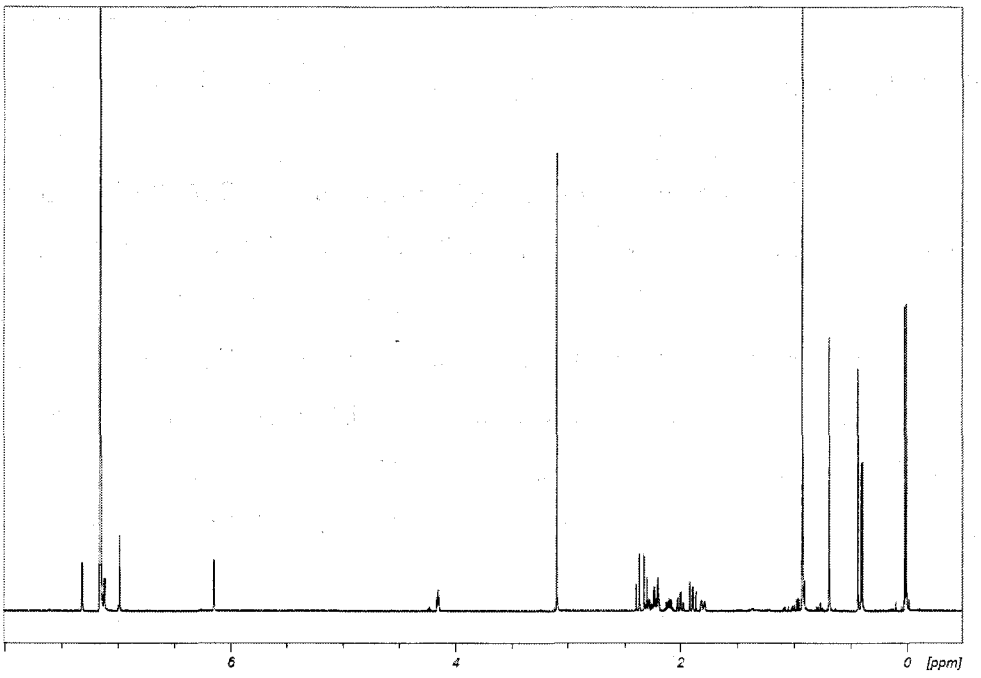
FT-IR (neat, cm^{-1}): 2955 (m), 2932 (m), 2886 (m), 2856 (m), 1698 (s)

HRMS (EI): Calculated 446.2489 (M^+) for $C_{25}H_{38}O_5Si$, found 446.2504

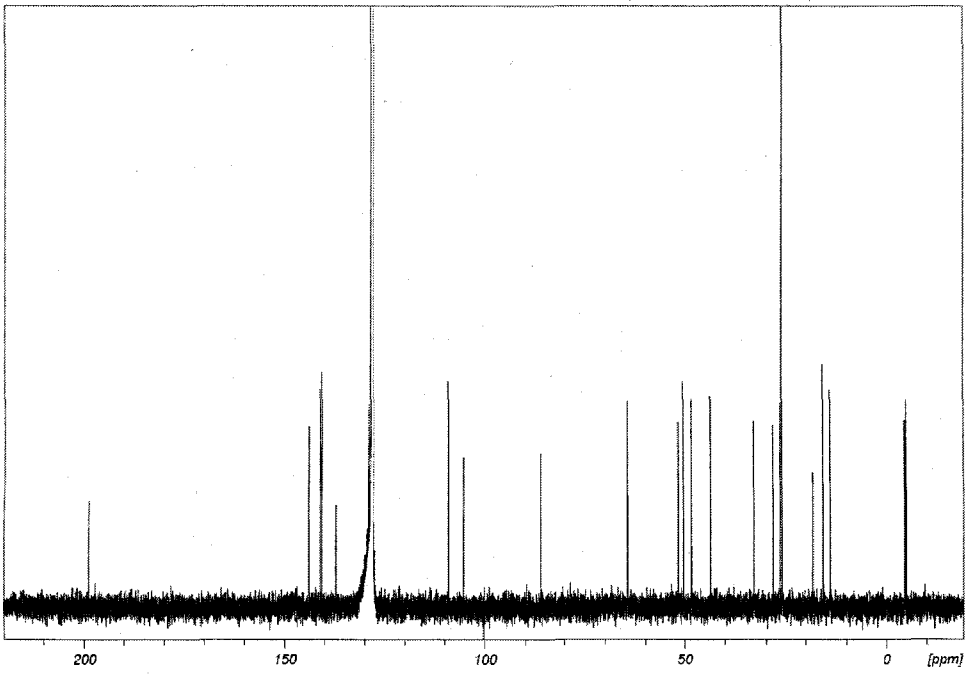


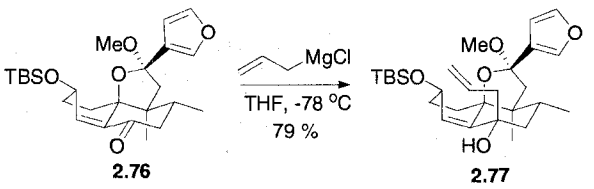
2.76

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



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





(±)-(2R,3aS,4R,6S,8R,10aS)-6-Allyl-8-(tert-butyl-dimethylsilyloxy)-2-(furan-3-yl)-3,3a,4,5,6,8,9,10-octahydro-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan-6-ol (**2.77**)

To a solution of **2.76** (49.5, 0.111 mmol) in THF (10 mL) cooled to -78 °C was added allyl magnesium chloride (2.0 M in THF, 0.17 mL, 0.340 mmol) and the resulting solution was stirred at -78 °C for 0.5 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded tertiary alcohol **2.77** (42.2 mg, 0.0864 mmol, 79 %, R_f = 0.65) as a colorless oil.

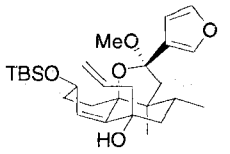
Data for **2.77**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.53 (dd, J = 1.5, 0.8 Hz, 1H), 7.01 (dd, J = 1.7, 1.7 Hz, 1H), 6.51 (dd, J = 4.7, 1.3 Hz, 1H), 6.25 (dd, J = 1.8, 0.8 Hz, 1H), 6.04-5.93 (m, 1H), 5.09-5.02 (m, 2H), 4.34-4.32 (m, 1H), 3.09 (s, 3H), 2.69-2.58 (m, 2H), 2.45 (d, J_{AB} = 13.5 Hz, 1H), 2.34 (d, J_{AB} = 13.5 Hz, 1H), 2.30-2.12 (m, 3H), 1.85-1.74 (m, 2H), 1.44 (dd, J = 13.1, 2.8 Hz, 1H), 1.26-1.10 (m, 2H), 1.00 (s, 9H), 0.76 (s, 3H), 0.53 (d, J = 6.8 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 143.6 (CH), 142.0 (C_4), 140.1 (CH), 135.0 (CH), 130.8 (CH), 129.2 (C_4), 118.3 (CH_2), 109.6 (CH), 104.9 (C_4), 87.0 (C_4), 72.8 (C_4), 65.4 (CH), 51.3 (CH_2), 50.0 (CH_3), 49.6 (C_4), 45.7 (CH_2), 42.5 (CH_2), 31.7 (CH), 28.8 (CH_2), 27.3 (CH_2), 26.3 (3 × CH_3), 18.5 (C_4), 16.5 (CH_3), 13.6 (CH_3), -4.0 (CH_3), -4.5 (CH_3)

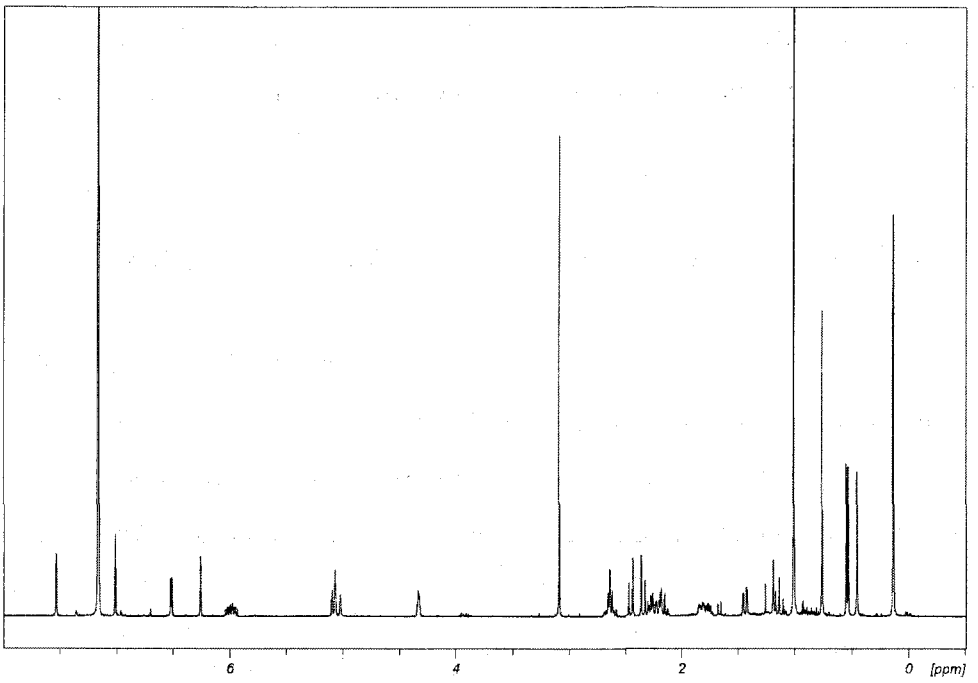
FT-IR (neat, cm^{-1}): 3457 (b), 2956 (s), 2930 (s), 2882 (m)

HRMS (EI): Calculated 488.2958 (M^+) for $C_{28}H_{44}O_5Si$, found 488.2922

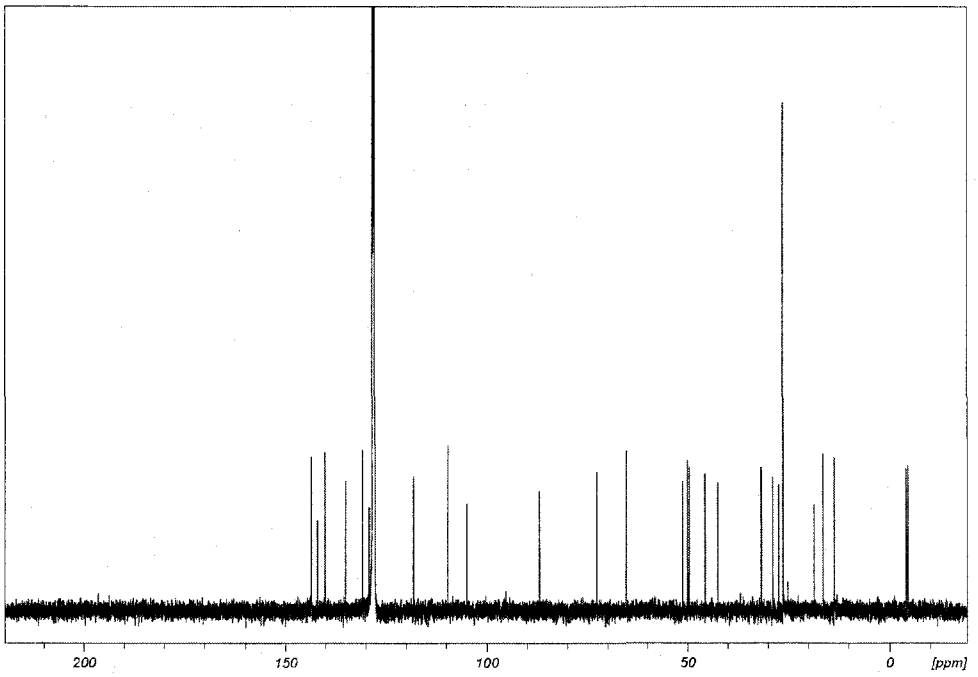


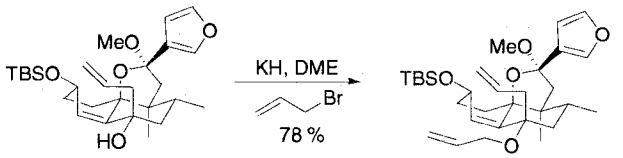
2.77

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



^{13}C NMR (125 MHz, C_6D_6)





2.77 **2.82**

(±)-(2R,3aS,4R,6S,8R,10aS)-6-Allyl-6-(allyloxy)-8-(tert-butyl-dimethylsilyloxy)-2-(furan-3-yl)-3,3a,4,5,6,8,9,10-octahydro-2-methoxy-3a,4-dimethyl-2H-naphtho[1-b]furan (**2.82**)

To a solution of dry KH (15.0 mg, 0.374 mmol) in DME (6 mL) cooled to 0 °C was added a solution of **2.77** (36.5 mg, 0.0747 mmol) in DME (2 mL) and the resulting mixture was stirred at 0 °C for 10 mintues. This was then treated with allyl bromide (0.03 mL, 0.354 mmol) and stirred for 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **2.82** (28.6 mg, 0.0541 mmol, 78 %, $R_f = 0.60$) as a colorless oil.

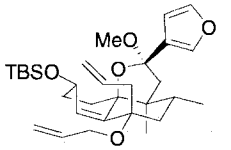
Data for **2.82**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.59 (d, J = 0.7 Hz, 1H), 7.02 (d, J = 1.5 Hz, 1H), 6.31 (d, J = 3.7 Hz, 1H), 6.27 (d, J = 0.7 Hz, 1H), 6.24-6.16 (m, 1H), 6.03-5.95 (m, 1H), 5.51 (dd, J = 17.1, 1.7 Hz, 1H), 5.16-5.08 (m, 3H), 4.25 (dd, J = 4.2, 4.2 Hz, 1H), 3.94-3.80 (m, 2H), 3.11 (s, 3H), 2.86 (dd, J = 14.2, 9.3 Hz, 1H), 2.68 (dd, J = 14.2, 4.6 Hz, 1H), 2.48 (d, J_{AB} = 13.4 Hz, 1H), 2.34 (d, J_{AB} = 13.4 Hz, 1H), 2.34-2.25 (m, 2H), 2.07 (ddd, J = 12.9, 12.9, 2.0 Hz, 1H), 1.87-1.80 (m, 2H), 1.56 (dd, J = 12.9, 12.9 Hz, 1H), 1.39-1.35 (m, 1H), 0.99 (s, 9H), 0.73 (s, 3H), 0.58 (d, J = 6.8 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 144.0 (CH), 140.5 (CH), 137.8 (C_4), 136.7 (CH), 135.8 (CH), 131.6 (CH), 129.6 (C_4), 117.6 (CH_2), 115.1 (CH_2), 109.9 (CH), 105.1 (C_4), 87.0 (C_4), 79.4 (C_4), 65.0 (CH), 62.9 (CH_2), 51.4 (CH_2), 50.6 (CH_3), 49.2 (C_4), 46.8 (CH_2), 35.1 (CH_2), 31.1 (CH), 28.7 (CH_2), 27.0 (CH_2), 26.5 (3 × CH_3), 18.8 (C_4), 16.9 (CH_3), 13.9 (CH_3), -4.1 (CH_3), -4.3 (CH_3)

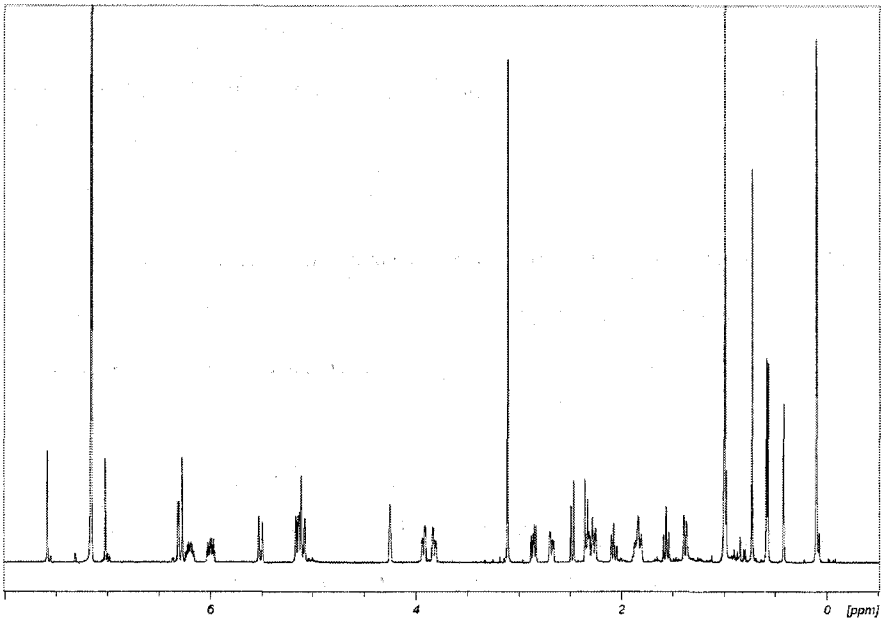
FT-IR (neat, cm^{-1}): 2956 (s), 2930 (s), 2886 (m), 2857 (s), 1638 (w)

HRMS (EI): Calculated 528.3271 (M^+) for $C_{31}H_{48}O_5Si$, found (M^+-OMe) at 497.3044, actual value 497.3087

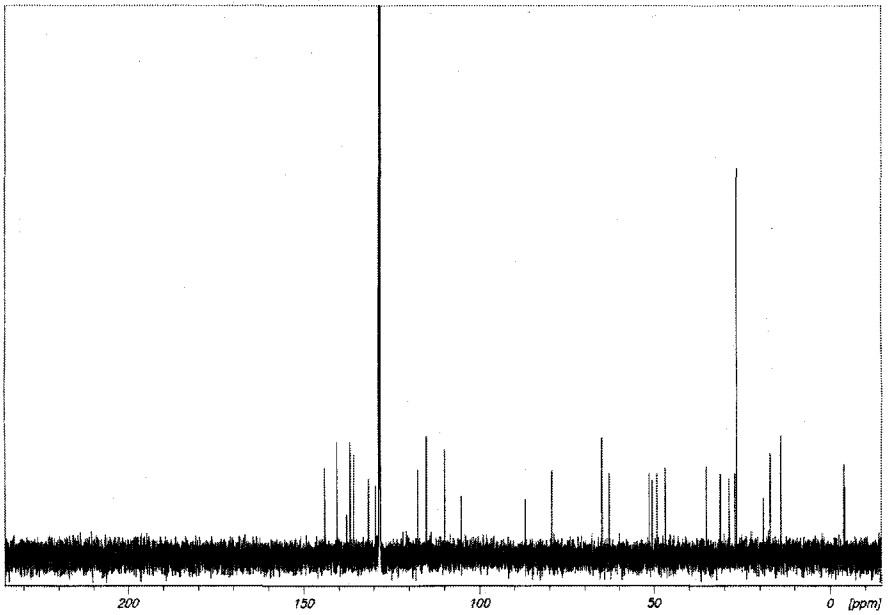


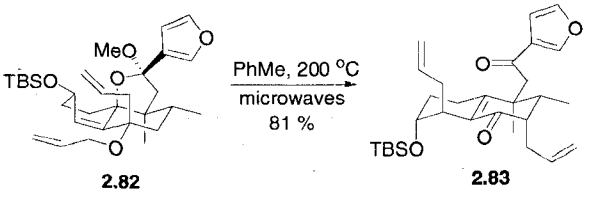
2.82

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





2.82 **2.83**

(±)-(2S,3R,4S,7R,8R)-2,8-Diallyl-7-(tert-butyl-dimethylsilyloxy)-4-(2-(furan-3-yl)-2-oxoethyl)-3,4,5,6,7,8-hexahydro -3,4-dimethylnaphthalen-1(2H)-one (**2.83**)

A sample of **2.82** (21.1 mg, 0.0399 mmol) was dissolved in toluene (4 mL) and placed in a microwave vessel for the CEM Corporation Discover microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 200 °C over 10 minutes, then for 0.5 hours at 200 °C. Upon cooling, the reaction mixture was concentrated and the product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording **2.83** (16.1 mg, 0.0324 mmol, 81 %, $R_f = 0.65$) as a colorless oil.

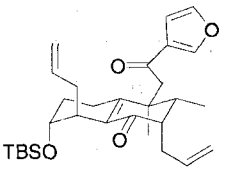
Data for **2.83**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.32 (s, 1H), 6.78 (dd, J = 1.4, 1.4 Hz, 1H), 6.62 (dd, J = 0.8, 0.8 Hz, 1H), 6.02-5.93 (m, 1H), 5.86-5.44 (m, 1H), 5.08-5.00 (m, 4H), 4.05 (dd, J = 2.0, 2.0 Hz, 1H), 3.13 (d, J = 10.3 Hz, 1H), 3.05-2.99 (m, 1H), 2.82-2.79 (m, 1H), 2.64 (d, J_{AB} = 13.6 Hz, 1H), 2.59-2.55 (m, 1H), 2.54 (d, J_{AB} = 13.6 Hz, 1H), 2.32-2.23 (m, 2H), 2.08 (ddd, J = 14.7, 8.9, 8.9 Hz, 1H), 1.79-1.74 (m, 1H), 1.69 (dd, J = 19.0, 5.2 Hz, 1H), 1.55-1.51 (m, 1H), 1.43 (ddd, J = 12.9, 12.9, 5.5 Hz, 1H), 1.11 (s, 3H), 0.93 (s, 9H), 0.74 (d, J = 6.9 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H)

^{13}C NMR (75 MHz, C_6D_6): δ = 198.0 (C_4), 192.5 (C_4), 155.3 (C_4), 147.4 (CH), 144.4 (CH), 137.8 (CH), 137.1 (CH), 133.2 (C_4), 129.8 (C_4), 116.2 (CH_2), 116.0 (CH_2), 109.0 (CH), 66.5 (CH), 48.0 (CH_2), 47.9 (CH), 43.6 (C_4), 41.1 (CH), 39.8 (CH), 38.5 (CH_2), 31.9 (CH_2), 25.9 (3 × CH_3), 24.6 (CH_2), 23.2 (CH_3), 22.7 (CH_2), 18.1 (C_4), 9.3 (CH_3), -4.4 (CH_3), -4.7 (CH_3)

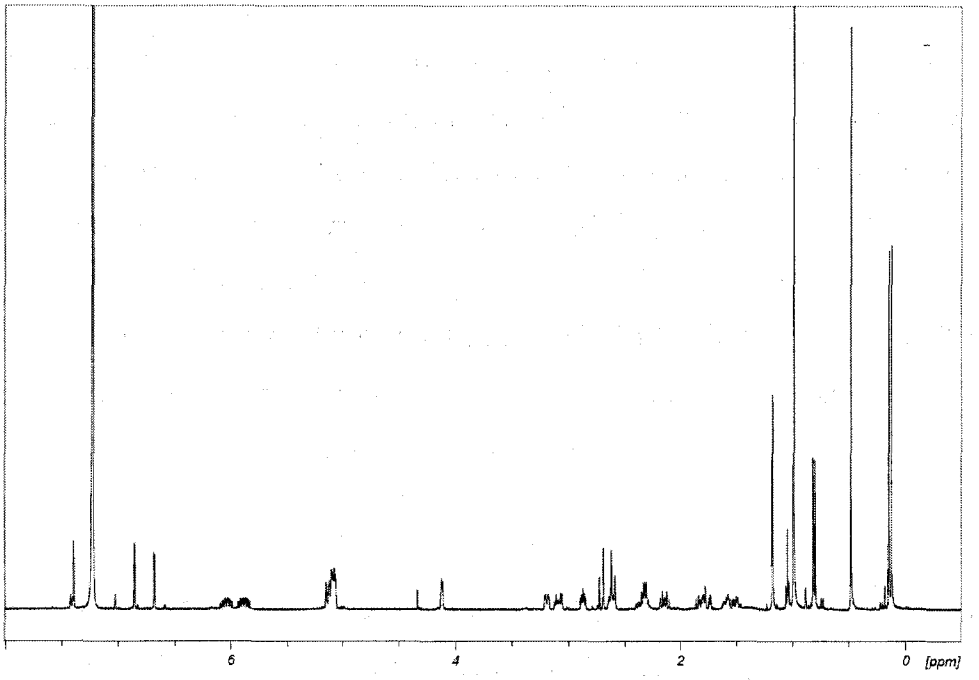
FT-IR (neat, cm^{-1}): 2952 (s), 2929 (s), 2855 (m), 1667 (s)

HRMS (EI): Calculated 496.3009 (M^+) for $C_{30}H_{44}O_4Si$, found 496.3018

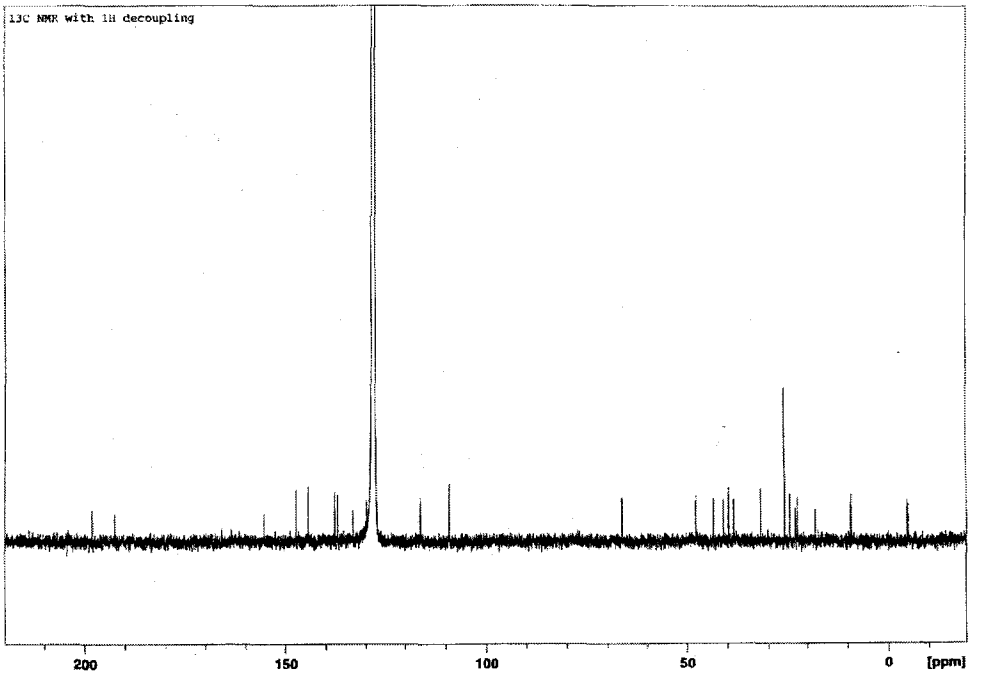


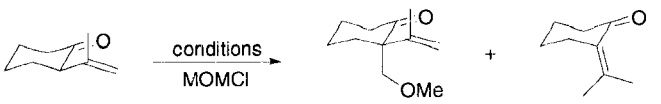
2.83

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (75 MHz, C_6D_6)





3.10 **3.11** 24 % **3.12** 24 %

2-(Methoxymethyl)-2-(prop-1-en-2-yl)cyclohexanone (**3.11**)

A solution of NaHMDS (2.67 g, 14.6 mmol) in THF (10 mL) was cannulated into a solution of ketone **3.10** (2.01 g, 14.5 mmol) in THF (25 mL) and the resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated, the aqueous layer was extracted with Et_2O (3 × 30 mL), then the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 30 % CH_2Cl_2/hexanes afforded **3.11** (628.0 mg, 3.45 mmol, 24%, R_f = 0.45) as a colorless liquid. Also recovered was enone **3.12**[59] (482.9 mg, 3.49 mmol, 24 %, R_f = 0.35) as a colorless liquid.

Data for **3.11**

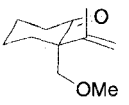
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (s, 1H), 4.81 (s, 1H), 3.51 (d, J_{AB} = 9.4 Hz, 1H), 3.34 (d, J_{AB} = 9.4 Hz, 1H), 3.31 (s, 3H), 2.51-2.42 (m, 1H), 2.35-2.31 (m, 1H), 2.26 (ddd, J = 14.1, 3.2, 3.2 Hz, 1H), 1.99-1.93 (m, 1H), 1.77-1.56 (m, 4H), 1.73 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.5 (C_4), 143.1 (C_4), 115.2 (CH_2), 76.8 (CH_2), 59.6 (CH_3), 59.4 (C_4), 40.2 (CH_2), 32.5 (CH_2), 27.3 (CH_2), 21.7 (CH_2), 20.3 (CH_3)

FT-IR (neat, cm^{-1}): 3087 (w), 2929 (s), 2821 (w), 1709 (s), 1633 (w)

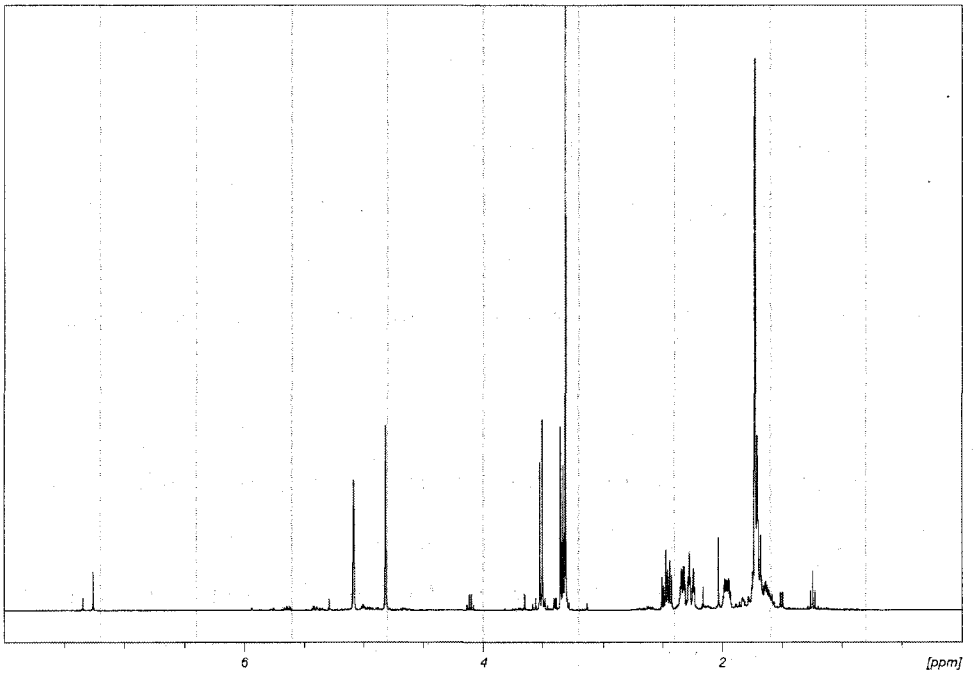
HRMS (EI): Calculated 182.1307 (M^+) for $C_{11}H_{18}O_2$, found 182.1309

Compound **3.12** has been previously characterized by Clement and Barriault.

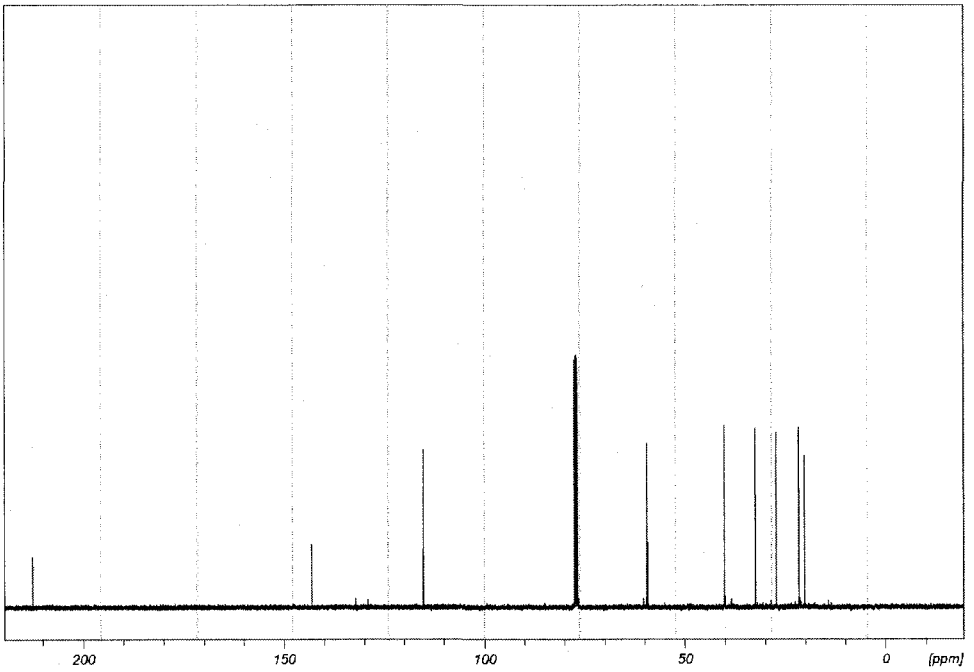


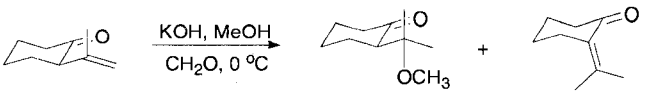
3.11

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.10 → **3.13** 17 % + **3.12** 37 %

2-(2-Methoxypropan-2-yl)cyclohexanone (**3.13**)

A solution of **3.10** (161.9 mg, 1.17 mmol) in 10 % KOH/MeOH (10 mL) was cooled to 0 °C. To this stirring solution was added a solution of formaldehyde (37 % in H_2O, 0.08 mL, 1.23 mmol) in MeOH (2 mL) dropwise over 0.5 hours. The resulting solution was stirred for 2 hours while slowly warming to room temperature whereupon it was quenched by the addition of 1 M HCl (5 mL). The mixture was further diluted by the addition of saturated aqueous NH_4Cl (20 mL), and this mixture was then extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Gradient flash chromatography in 2 % EtOAc/hexanes to 10 % EtOAc/hexanes) afforded **3.13** (33.7 mg, 0.198 mmol, 17 %, R_f = 0.40) as a colorless oil. Also recovered was the conjugated enone **3.12** (59.2 mg, 0.428 mmol, 37 %, R_f = 0.50) as a colorless oil.

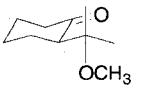
Data for **3.13**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15 (s, 3H), 2.54 (dd, J = 12.1, 5.1 Hz, 1H), 2.34-2.23 (m, 3H), 2.07-2.01 (m, 1H), 1.94-1.89 (m, 1H), 1.76-1.44 (m, 3H), 1.29 (s, 3H), 1.20 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.9 (C_4), 75.2 (C_4), 58.4 (CH_3), 48.4 (CH), 44.1 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 25.6 (CH_2), 23.4 (CH_3), 21.3 (CH_3)

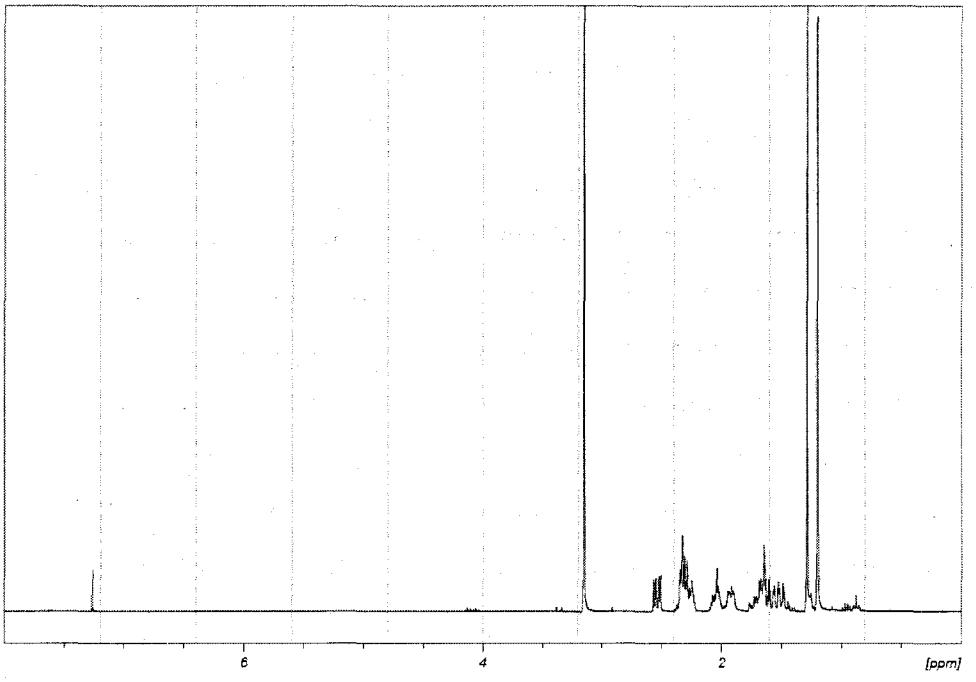
FT-IR (neat, cm^{-1}): 2967 (m), 2936 (m), 2867 (m), 2825 (w), 1709 (s)

HRMS (EI): Calculated 170.1307 (M^+) for $C_{10}H_{18}O_2$, found 170.1283

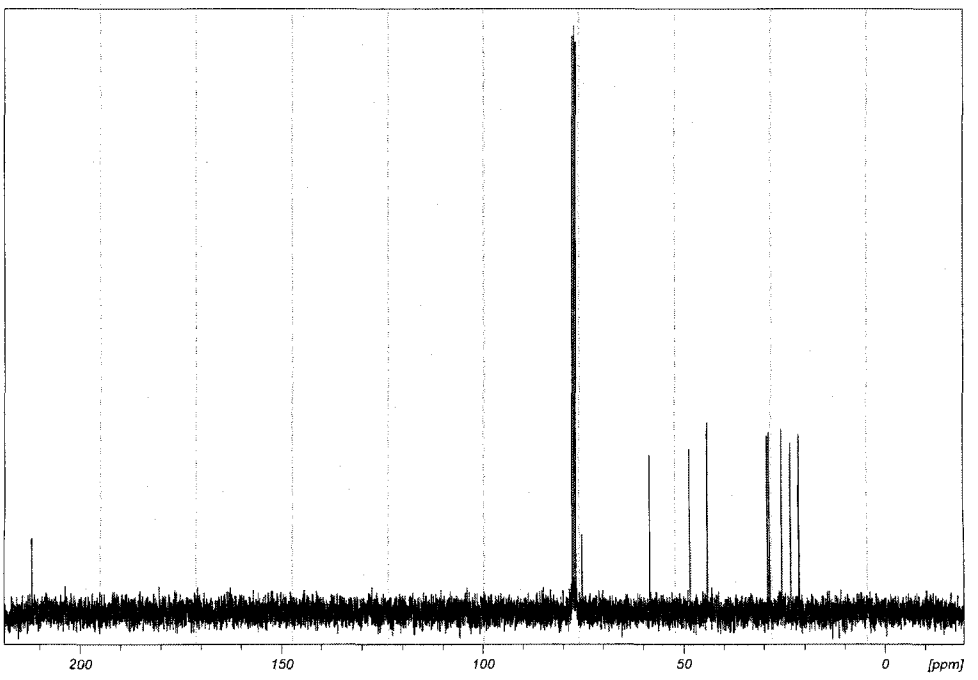


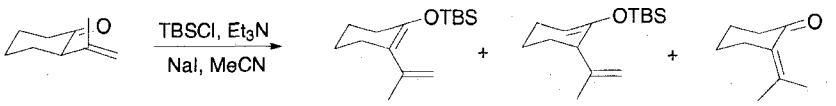
3.13

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.10 **3.16** 21 % **3.17** 6 % **3.12** 52 %

A solution of **3.10** (151.2 mg, 1.09 mmol) in acetonitrile (10 mL) was treated with Et_3N (0.18 mL, 1.29 mmol) followed by TBSCl (197.9 mg, 1.31 mmol) and then NaI (196.8 mg, 1.31 mmol). The reaction mixture was shielded against light and stirred at room temperature for 16 hours after which is was quenched by the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with hexanes (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in hexanes afforded silyl enol ether **3.17** (16.1 mg, 0.0678 mmol, 6 %, R_f = 0.60) as a colorless oil. Also recovered were **3.16** (51.8 mg, 0.205 mmol, 21 %, R_f = 0.50) as a colorless oil and conjugated enone **3.12** (78.1 mg, 0.565 mmol, 52 %, R_f = 0.05) as a colorless oil after increasing the polarity of the eluting solvent.

(2-(Prop-1-en-2-yl)cyclohex-1-enyloxy)(tert-butyl))dimethylsilane (**3.16**)

Data for **3.16**

^{1}H NMR (400 MHz, C_6D_6): δ = 5.04-5.03 (m, 1H), 5.01-5.00 (m, 1H), 2.15-2.12 (m, 2H), 2.02-1.99 (m, 2H), 2.00 (s, 3H), 1.52-1.42 (m, 4H), 1.01 (s, 9H), 0.13 (s, 6H)

^{13}C NMR (100 MHz, C_6D_6): δ = 145.6 (C_4), 144.5 (C_4), 118.3 (C_4), 113.3 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 26.1 (3 × CH_3), 23.7 (CH_2), 23.4 (CH_2), 23.0 (CH_3), 18.4 (C_4), -3.6 (2 × CH_3)

FT-IR (neat, cm^{-1}): 2933 (s), 2886 (m), 2875 (m)

HRMS (EI): Calculated 252.1909 (M^+) for $C_{15}H_{28}OSi$, found 252.1925

(6-(Prop-1-en-2-yl)cyclohex-1-enyloxy)(tert-butyl))dimethylsilane (**3.17**)

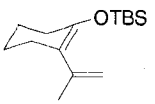
Data for **3.17**

^{1}H NMR (400 MHz, C_6D_6): δ = 4.99-4.97 (m, 1H), 4.92-4.90 (m, 2H), 2.84 (dd, J = 5.4, 5.4 Hz, 1H), 2.04-1.88 (m, 2H), 1.73 (m 3H), 1.69-1.52 (m, 3H), 1.41-1.32 (m, 1H), 0.99 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 151.3 (C_4), 147.0 (C_4), 112.6 (CH_2), 105.0 (CH), 48.3 (CH), 29.2 (CH_2), 25.9 (3 × CH_3), 24.5 (CH_2), 20.8 (CH_2), 20.2 (CH_3), 18.3 (C_4), -4.4 (CH_3), -4.5 (CH_3)

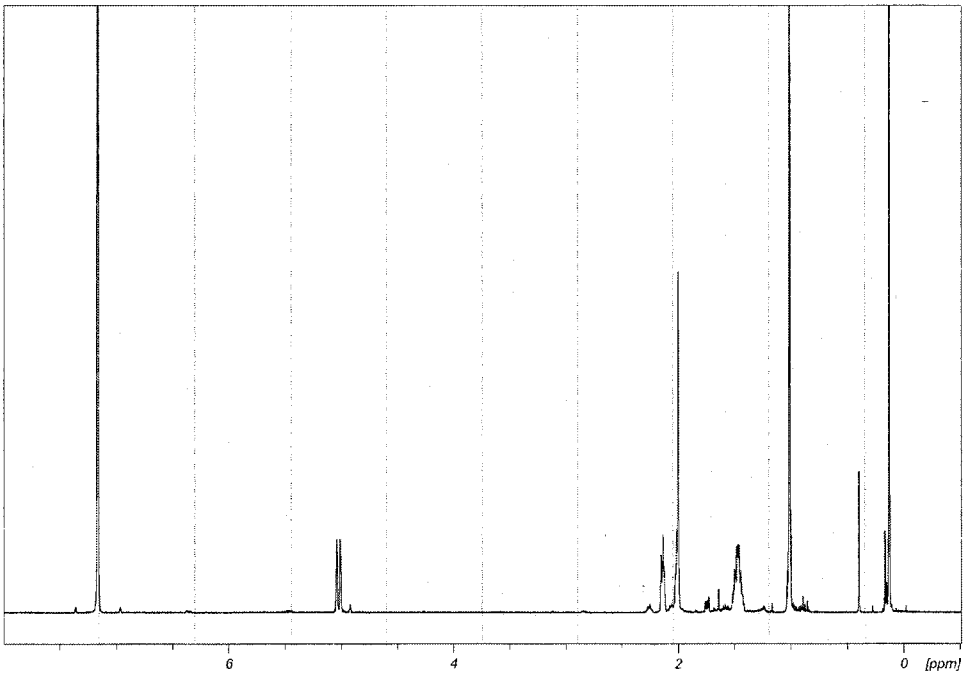
FT-IR (neat, cm^{-1}): 3048 (w), 2933 (s), 2882 (m), 2863 (s)

HRMS (EI): Calculated 252.1909 (M^+) for $C_{15}H_{28}OSi$, found 252.1903

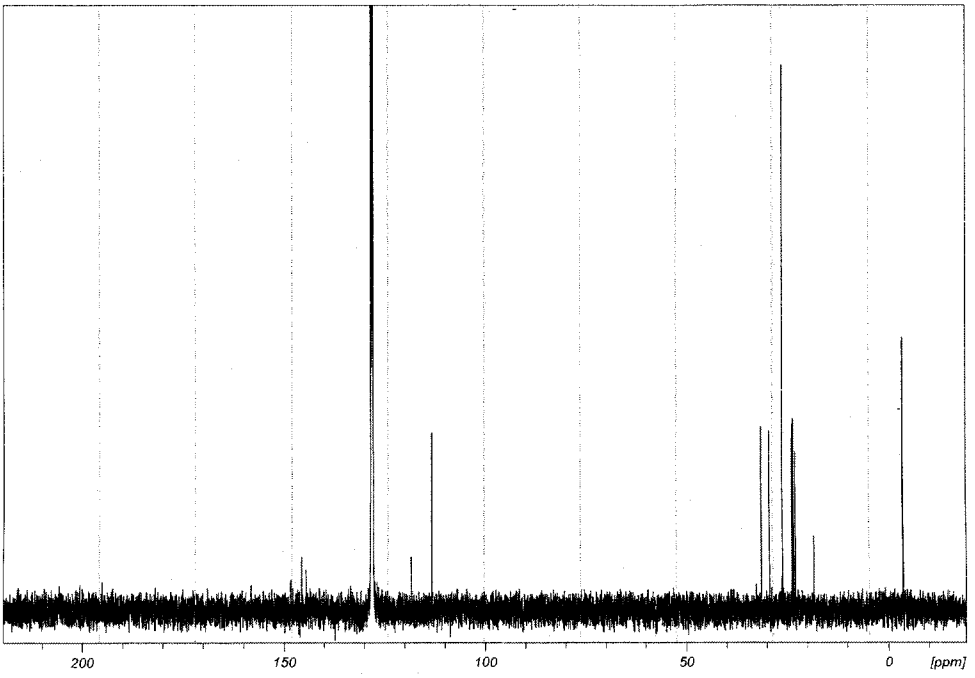


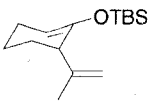
3.16

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



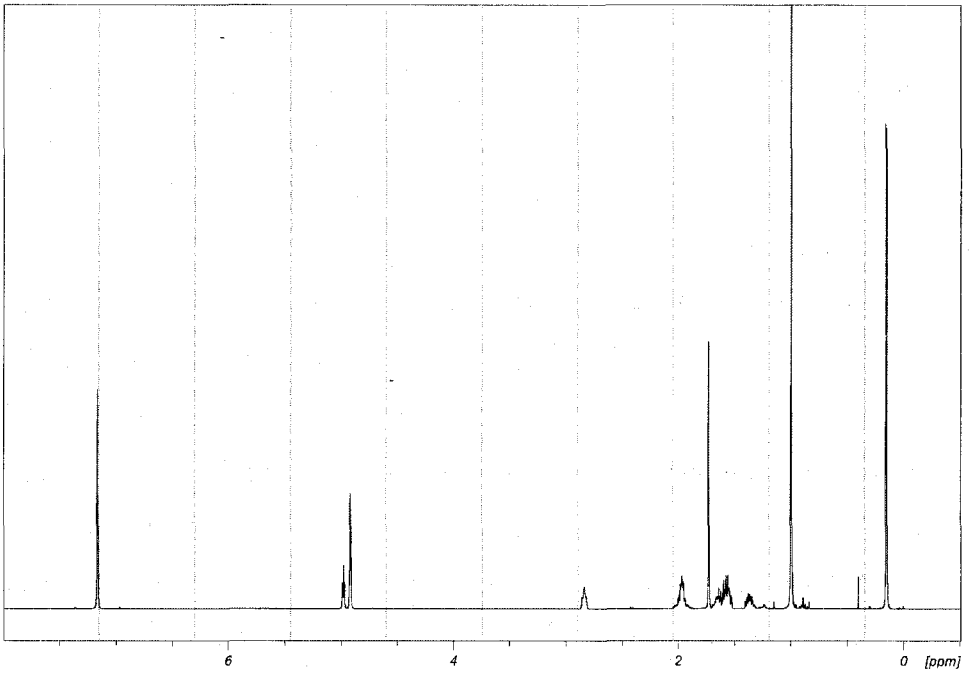
^{13}C NMR (100 MHz, C_6D_6)



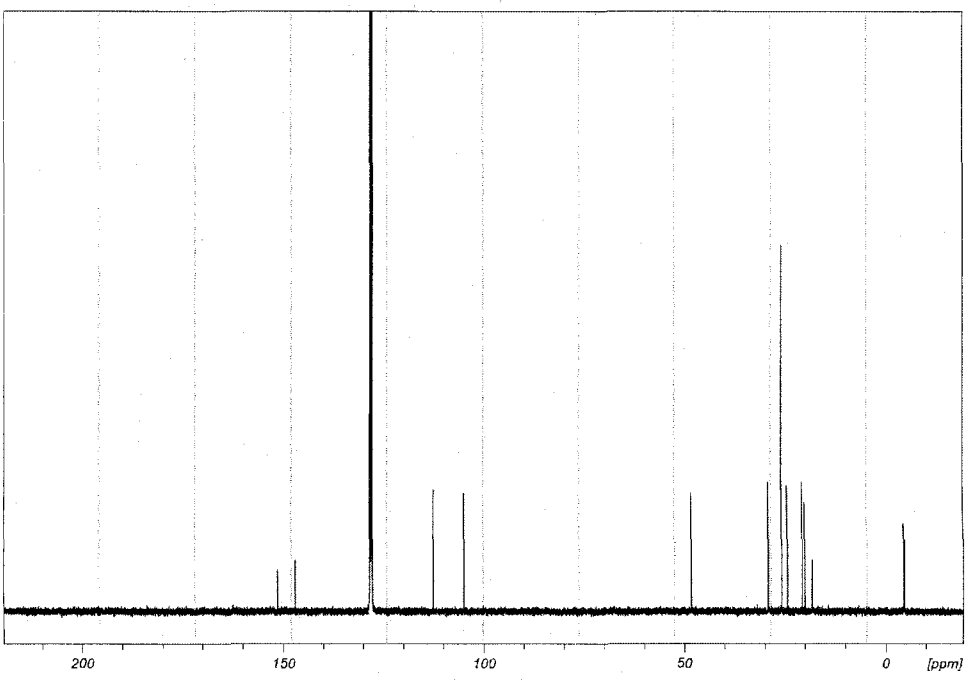


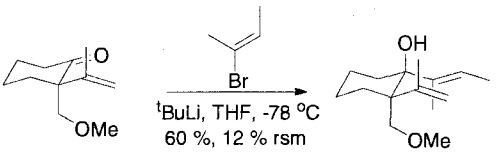
3.17

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



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





3.11 **3.18**

(±)- (1R, 2S)-1-((E)-But-2-en-2-yl)-2-(methoxymethyl)-2-(prop-1-en-2-yl)cyclohexanol (**3.18**)

A solution of *E*-2-bromo-2-butene (0.67 mL, 6.61 mmol) in THF (25 mL) was cooled to -78 °C and treated with ^{t}BuLi (1.35 M in pentane, 9.79 mL, 13.2 mmol) and the resulting clear yellow solution was stirred at -78 °C for 0.5 hours. A solution of **3.11** (628.0 mg, 3.45 mmol) in THF (5 mL) was then cannulated into the reaction and the resulting mixture was stirred at -78 °C for 4 hours upon which no more progression was observed. The reaction was quenched by the addition of saturated aqueous NH_4Cl followed by warming to room temperature. The layers were separated, the aqueous layer was extracted with Et2O (3 × 30 mL), then the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **3.18** (492.8 mg, 2.07 mmol, 60 %, R_f = 0.50) as a colorless oil. Also recovered was **3.11** (75.5 mg, 0.414 mmol, 12 %, R_f = 0.30) as a colorless oil.

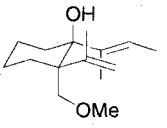
Data for **3.18**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.32 (qd, J = 6.5, 0.9 Hz, 1H), 5.17 (s, 1H), 4.98 (s, 1H), 3.70 (d, J_{AB} = 9.0 Hz, 1H), 3.57 (d, J_{AB} = 9.0 Hz, 1H), 3.34 (s, 3H), 2.55 (d, J = 2.7 Hz, 1H), 2.02-1.94 (m, 2H), 1.78-1.70 (m, 1H), 1.73 (s, 3H), 1.63-1.44 (m, 5H), 1.60 (d, J = 6.7 Hz, 3H), 1.58 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (C_4), 141.0 (C_4), 119.9 (CH), 115.2 (CH_2), 74.5 (C_4), 71.5 (CH_2), 59.3 (CH_3), 52.0 (C_4), 33.5 (CH_2), 27.4 (CH_2), 22.9 (CH_3), 21.3 (2 × CH_2), 15.0 (CH_3), 13.9 (CH_3)

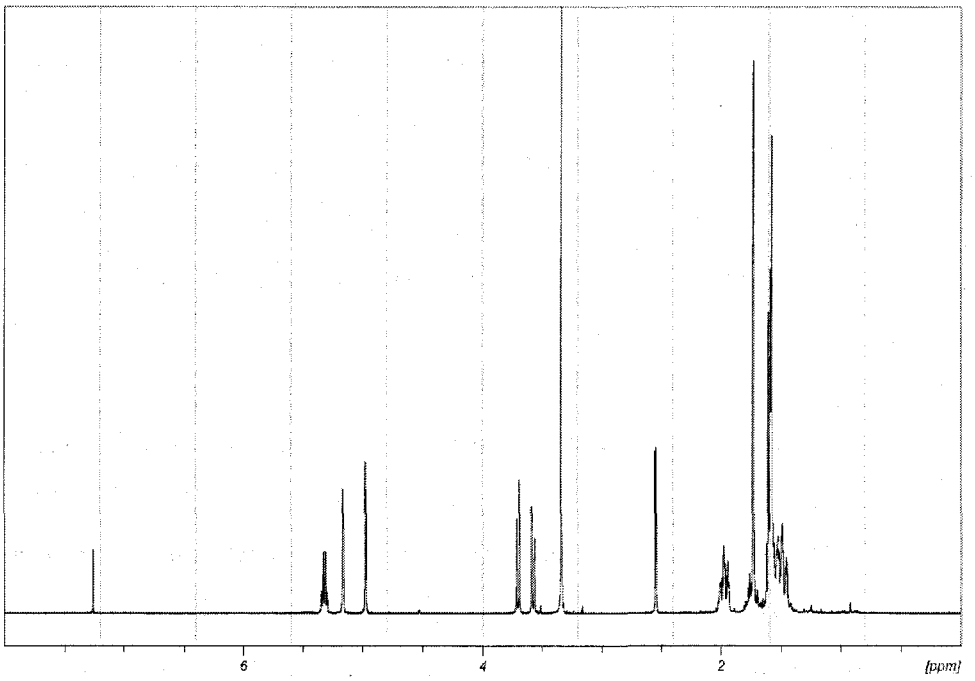
FT-IR (neat, cm^{-1}): 3545 (b), 2967 (s), 2918 (s), 2965 (s)

HRMS (EI): Calculated 238.1933 (M^+) for $C_{15}H_{26}O_2$, found 238.1896

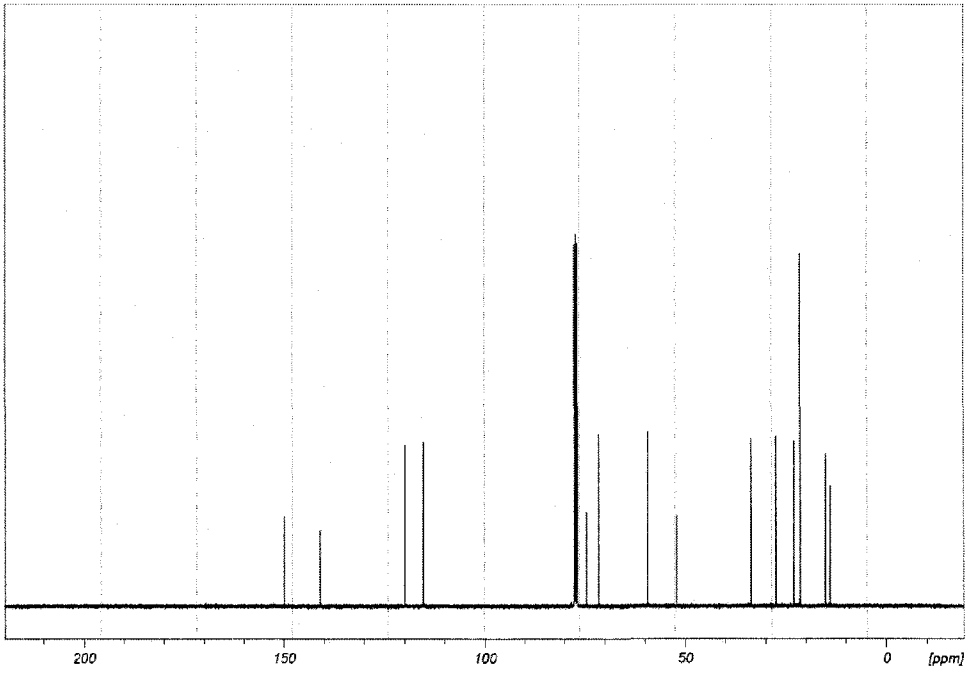


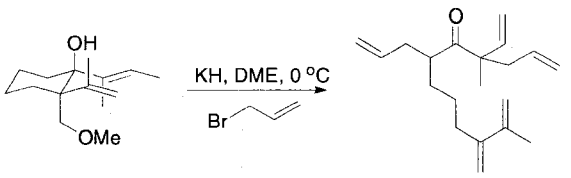
3.18

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.18 **3.20**

6-Allyl-4,11-dimethyl-10-methylene-4-vinyldodeca-1,11-dien-5-one (**3.20**)

A suspension of KH (17.4 mg, 0.434) in DME (3 mL) was cooled to 0 °C. To this was added a solution of tertiary alcohol **3.18** (25.8 mg, 0.108 mmol) in DME (3 mL) and the resulting mixture was stirred for 10 minutes. The mixture was then treated with allyl bromide (0.02 mL, 0.236 mmol) and the reaction was stirred at 0 °C for 2 h whereupon it did not undergo any further progression. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and then the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded ketone **3.20** (12.3 mg, 0.0429 mmol, 39 %, R_f = 0.75) as a colorless oil. This compound was isolated as an unassigned mixture of diastereomers. Also recovered was starting material **3.18** (7.4 mg, 0.0310 mmol, 29 %, R_f = 0.40) as a colorless oil.

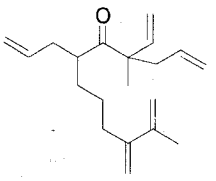
Data for **3.20**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (ddd, J = 17.4, 10.7, 5.3 Hz, 1H), 5.71-5.59 (m, 2H), 5.25 (dd, J = 10.8, 0.6 Hz, 1H), 5.17 (dd, J = 17.4, 0.8 Hz, 1H), 5.06-4.90 (m, 8H), 2.94-2.87 (m, 1H), 2.41-2.18 (m, 5H), 2.10-2.02 (m, 1H), 1.89 (s, 3H), 1.62-1.54 (m, 1H), 1.43-1.34 (m, 3H), 1.19 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.5 (2 × C_4), 147.7 (C_4), 147.6 (C_4), 142.8 (2 × C_4), 140.6 (2 × CH), 136.1 (2 × CH), 134.4 (CH), 134.3 (CH), 118.1 (2 × CH_2), 116.8 (2 × CH_2), 116.0 (2 × CH_2), 112.6 (2 × CH_2), 112.3 (CH_2), 112.2 (CH_2), 54.5 (2 × C_4), 46.1 (2 × CH), 41.6 (2 × CH_2), 36.6 (CH_2), 36.5 (CH_2), 33.9 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 31.7 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 21.3 (2 × CH_3), 19.5 (2 × CH_3)

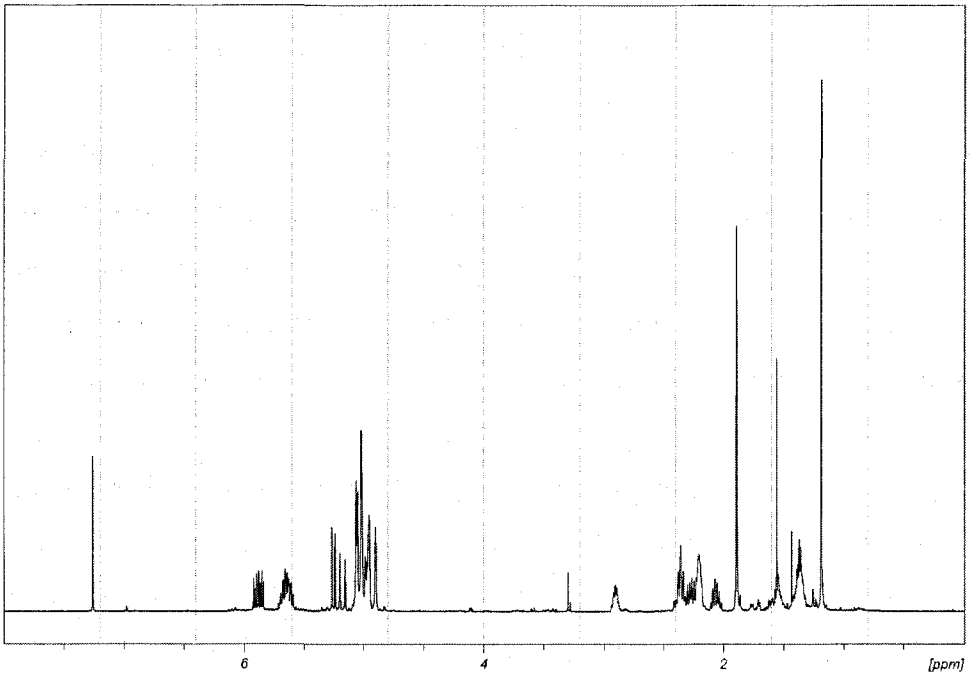
FT-IR (neat, cm^{-1}): 3078 (m), 2977 (m), 2942 (s), 2863 (m), 1704 (s)

HRMS (EI): Calculated 286.2297 (M^+) for $C_{20}H_{30}O$, found 286.2261

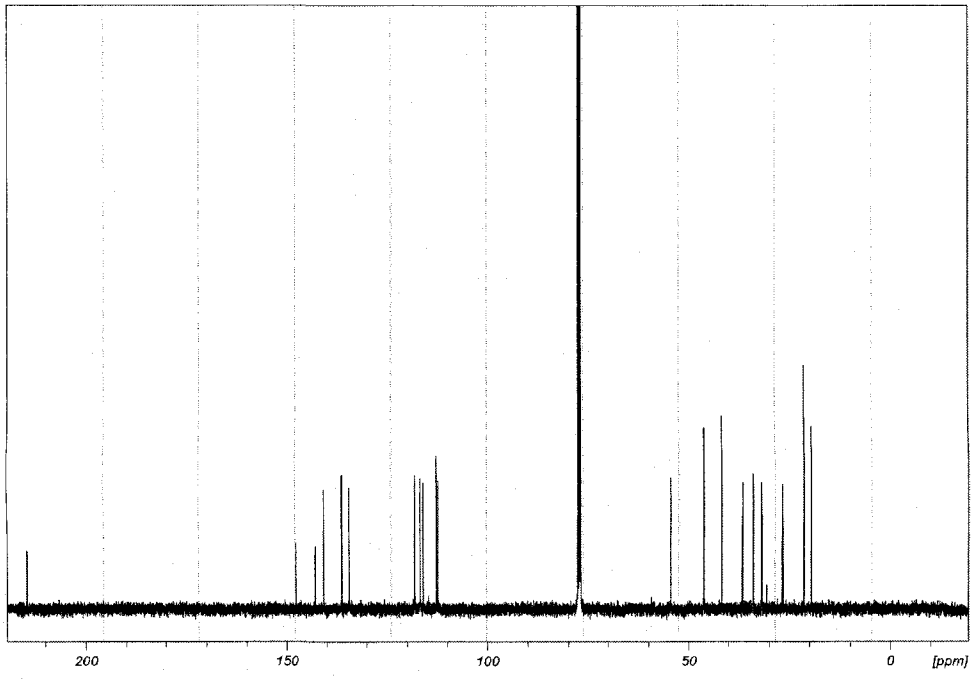


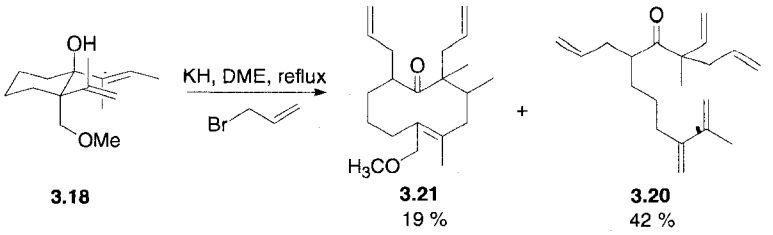
3.20

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.18 **3.21** 19 % **3.20** 42 %

2,10-Diallyl-6-(methoxymethyl)-2,3,5-trimethylcyclodec-5-enone (**3.21**)

A suspension of KH (41.7 mg, 1.04) in DME (5 mL) was cooled to 0 °C. To this was added a solution of tertiary alcohol **3.18** (41.7 mg, 0.260 mmol) in DME (5 mL) and the resulting mixture was stirred for 10 minutes. The mixture was then treated with allyl bromide (0.05 mL, 0.591 mmol) and the reaction was stirred while warming to reflux after which is was stirred for 1 hour whereupon it did not undergo any further progression. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and then the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded ketone **3.20** (31.3 mg, 0.109 mmol, 42 %, R_f = 0.75) as a colorless oil. Also recovered was ketone **3.21** (15.8 mg, 0.0496 mmol, 19 %, R_f = 0.35) as a colorless oil. The relative stereochemistry of **SA-1244** is unassigned.

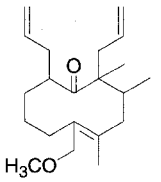
Data for **3.21**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78-5.61 (m, 1H), 5.04-4.91 (m, 4H), 4.27 (d, J_{AB} = 10.4 Hz, 1H), 3.96 (d, J_{AB} = 10.4 Hz, 1H), 3.28 (s, 3H), 2.68-2.63 (m, 1H), 2.59-2.51 (m, 2H), 2.38-2.26 (m, 3H), 2.10 (d, J = 13.3 Hz, 1H), 1.98 (dd, J = 13.7, 7.7 Hz, 1H), 1.87-1.82 (m, 1H), 1.81-1.59 (m, 4H), 1.58 (s, 3H), 1.47-1.36 (m, 2H), 1.15 (s, 3H), 0.92 (d, J = 6.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.0 (C_4), 135.8 (CH), 135.6 (CH), 134.5 (C_4), 131.6 (C_4), 117.5 (CH_2), 117.2 (CH_2), 71.1 (CH_2), 58.0 (CH_3), 52.5 (C_4), 49.3 (CH), 46.1 (CH_2), 40.6 (CH), 39.8 (CH_2), 39.2 (CH_2), 30.4 (CH_2), 28.5 (CH_2), 26.9 (CH_2), 19.9 (CH_3), 16.6 (CH_3), 14.3 (CH_3)

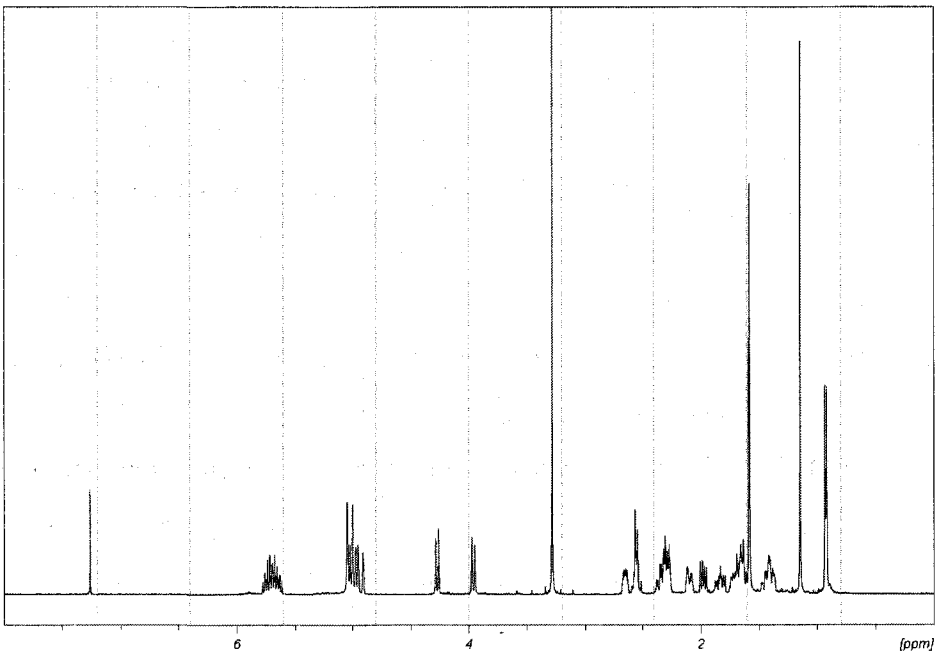
FT-IR (neat, cm^{-1}): 2962 (s), 2855 (m), 1687 (s)

HRMS (EI): Calculated 318.2559 (M^+) for $C_{21}H_{34}O_2$, found 318.2560

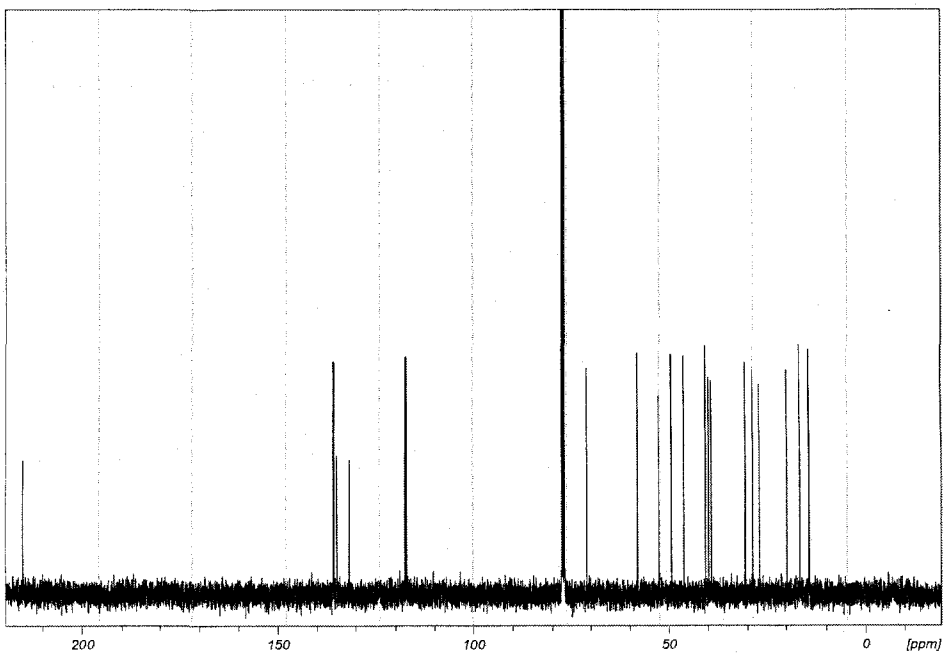


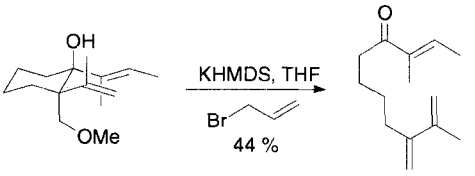
3.21

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.18 **3.22**

E-3,10-Dimethyl-9-methyleneundeca-2,10-dien-4-one (**3.22**)

A solution of tertiary alcohol **3.18** (29.0 mg, 0.122 mmol) in THF (5 mL) cooled to 0 °C was treated with solid KHMDS (97.1 mg, 0.487 mmol), followed by 10 minutes of stirring. The mixture was then treated with allyl bromide (0.02 mL, 0.236 mmol) and the reaction was stirred for 2 hours at 0 °C, warmed to room temp over 1 hour then stirred for a further 3 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (03 × 10 mL) and then the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded ketone **3.22** (11.3 mg, 0.0584 mmol, 44 %, R_f = 0.50) as a colorless oil. Also recovered was starting material **3.18** (5.1 mg, 0.0214 mmol, 18 %, R_f = 0.45) as a colorless oil.

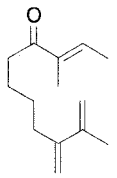
Data for **3.22**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (q, J = 6.9 Hz, 1H), 5.07 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.95 (s, 1H), 2.65 (t, J = 7.3 Hz, 2H), 2.28 (t, J = 7.8 Hz, 2H), 1.90 (s, 3H), 1.85 (d, J = 6.9 Hz, 3H), 1.77 (s, 3H), 1.66-1.60 (m, 2H), 1.52-1.45 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.1 (C_4), 147.9 (C_4), 142.8 (C_4), 138.6 (C_4), 137.0 (CH), 112.6 (CH_2), 112.2 (CH_2), 37.2 (CH_2), 33.7 (CH_2), 28.8 (CH_2), 25.1 (CH_2), 21.3 (CH_3), 14.9 (CH_3), 11.2 (CH_3)

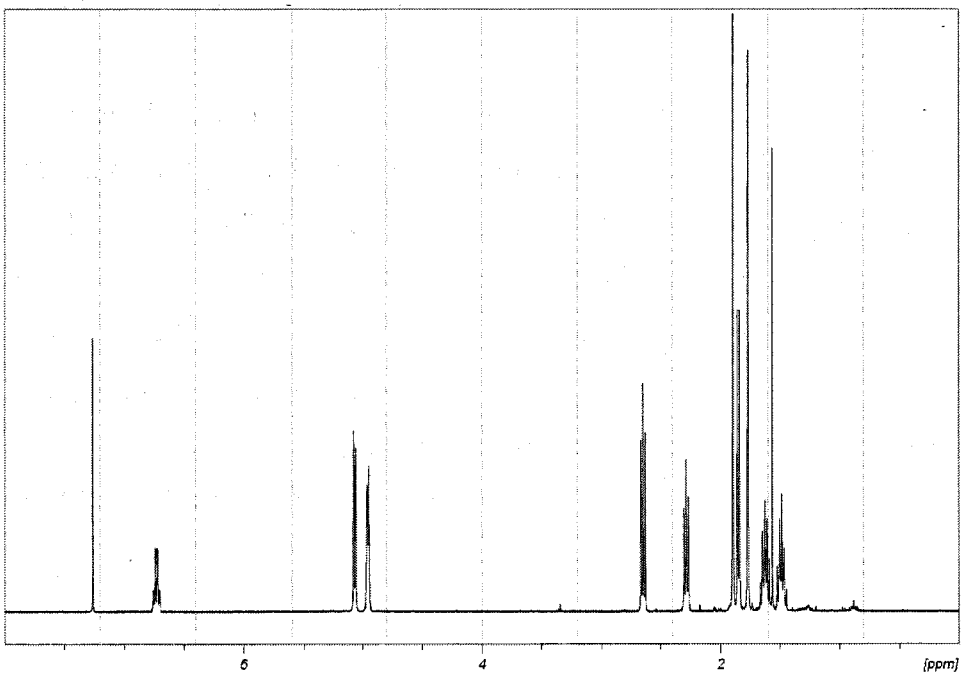
FT-IR (neat, cm^{-1}): 2936 (m), 2856 (m), 1667 (s)

HRMS (EI): Calculated 206.1671 (M^+) for $C_{14}H_{22}O$, found 206.1654

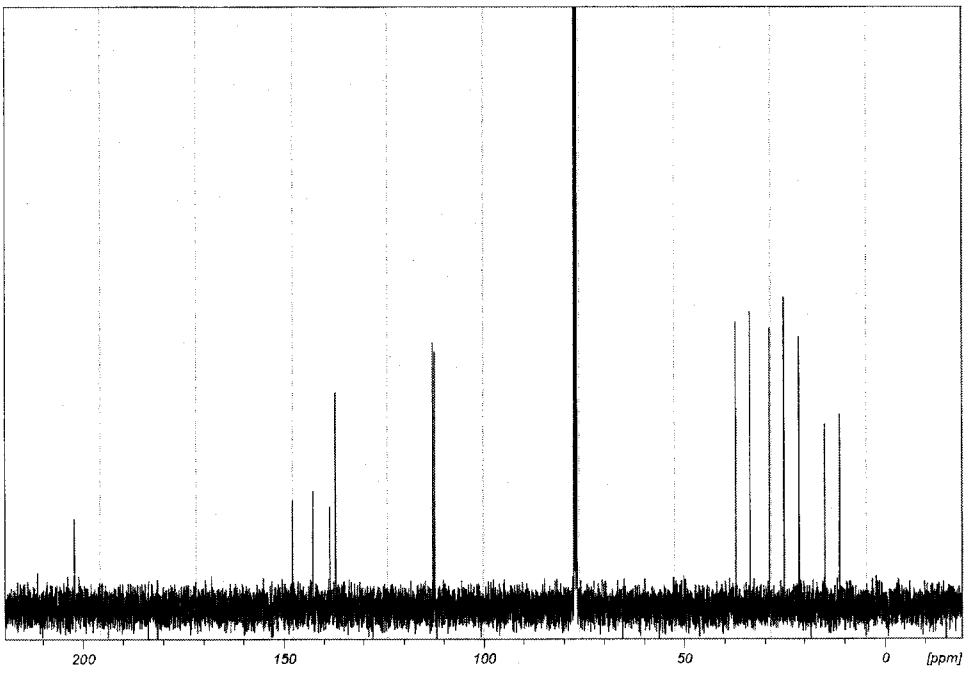


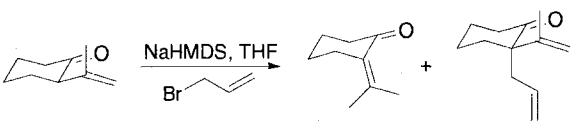
3.22

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.10 **3.12** 22 % **3.23** 61 %

2-Allyl-2-isopropenyl-cyclohexanone (**3.23**)

Ketone **3.10** (1.09 g, 7.92 mmol) was dissolved in THF (50 mL) and treated with a solution of NaHMDS (1.45 g, 7.92 mmol) in THF (30 mL). After 10 minutes, allyl bromide (0.74 mL, 8.75 mmol) was added to the reaction. The resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded ketone **3.23** (861.9 mg, 4.83 mmol, 61 %, $R_f = 0.60$) as a colorless oil and enone **3.12** (240.8 mg, 1.74 mmol, 22 %, $R_f = 0.50$) as a colorless oil.

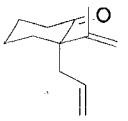
Data for **3.23**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65-5.55 (m, 1H), 5.03 (s, 1H), 4.95 (s, 1H), 4.93-4.90 (m, 1H), 4.76 (s, 1H), 2.48-2.35 (m, 2H), 2.25-2.12 (m, 3H), 1.97-1.91 (m, 1H), 1.73 (dddd, J = 13.1, 13.1, 4.1, 4.1 Hz, 1H), 1.64-1.49 (m, 2H), 1.59 (s, 3H), 1.41 (ddd, J = 13.8, 13.8, 3.8 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.7 (C_4), 143.7 (C_4), 134.8 (CH), 117.1 (CH_2), 114.1 (CH_2), 58.2 (C_4), 40.4 (CH_2), 40.4 (CH_2), 35.1 (CH_2), 27.9 (CH_2), 21.6 (CH_2), 20.0 (CH_3)

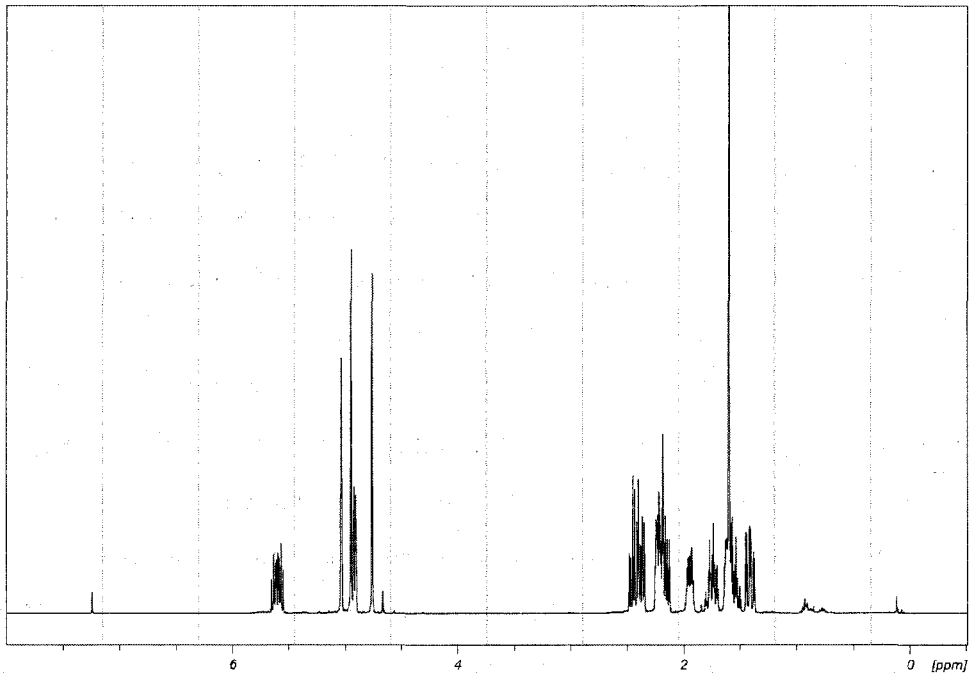
FT-IR (neat, cm^{-1}): 2942 (s), 2867 (s), 1706 (s)

HRMS (EI): Calculated 178.1358 (M^+) for $C_{12}H_{18}O$, found 178.1356

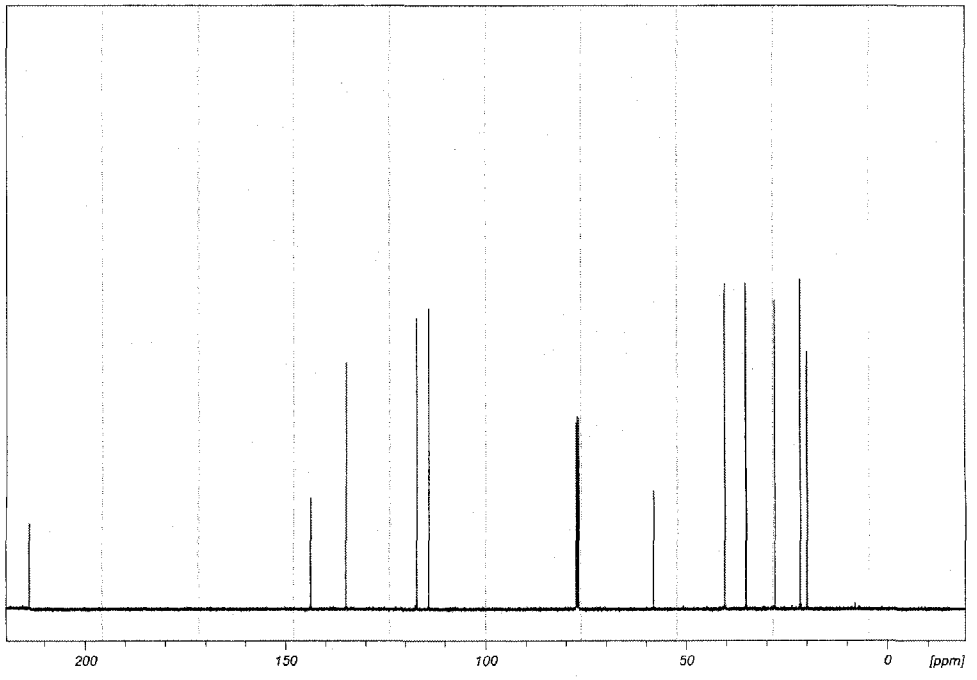


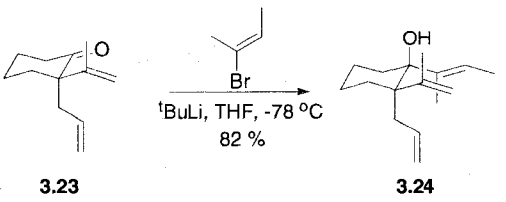
3.23

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.23 **3.24**

(±)-(1R, 2R)-2-Allyl-1-((E)-but-2-en-2-yl)-2-(prop-1-en-2-yl)cyclohexanol (**3.24**)

E-2-bromo-2-butene (1.28 mL, 12.6 mmol) was dissolved in THF (40 mL), cooled to -78 °C and treated with ^{t}BuLi (1.35 M in hexanes, 18.7 mL, 25.2 mmol). The resulting clear yellow solution was stirred at -78 °C for 0.5 hours whereupon a solution of **3.23** (750.7 mg, 4.21 mmol) in THF (20 mL) was added by cannulation. This mixture was stirred at -78 °C for 2 hours, allowed to slowly warm to room temperature and was left to stir at room temperature for a further 16 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the crude product in 5 % EtOAc/hexanes gave **3.24** (804.8 mg, 3.34 mmol, 82 %, R_f = 0.55) as a colorless oil.

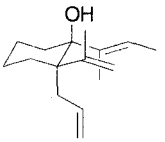
Data for **3.24**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55-5.45 (m, 1H), 5.38 (q, J = 6.2 Hz, 1H), 5.15 (s, 1H), 5.11-5.07 (m, 1H), 5.01-4.98 (m, 1H), 4.95 (s, 1H), 2.61-2.55 (m, 1H), 2.48 (dd, J = 14.7, 8.9 Hz, 1H), 2.35 (d, J = 2.6 Hz, 1H), 2.13-1.98 (m, 2H), 1.75-1.64 (m, 1H), 1.71 (s, 3H), 1.59 (d, J = 8.7 Hz, 3H), 1.58 (s, 3H), 1.55-1.35 (m, 4H), 1.29-1.24 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6 (C_4), 141.1 (C_4), 135.9 (CH), 120.1 (CH), 116.5 (CH_2), 115.9 (CH_2), 76.2 (C_4), 50.4 (C_4), 34.6 (CH_2), 33.3 (CH_2), 28.9 (CH_2), 23.1 (CH_3), 21.2 (CH_2), 20.7 (CH_2), 15.3 (CH_3), 13.9 (CH_3)

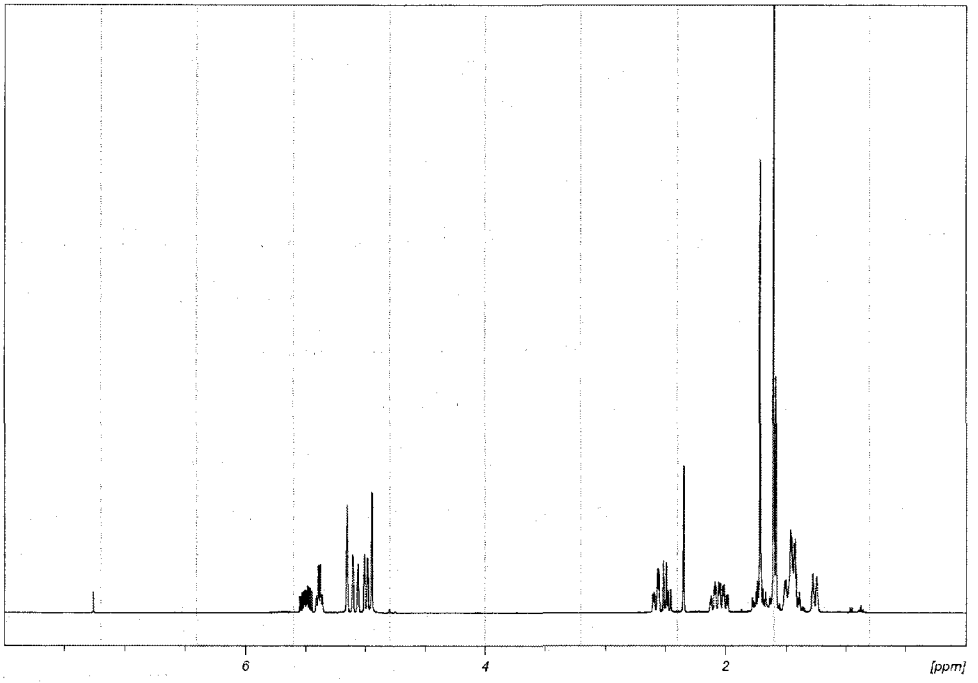
FT-IR (neat, cm^{-1}): 3550 (b), 2956 (s), 2928 (s), 2864 (s), 1640 (w), 1617 (w)

HRMS (EI): Calculated 234.1984 (M^+) for $C_{16}H_{26}O$, found 234.1997

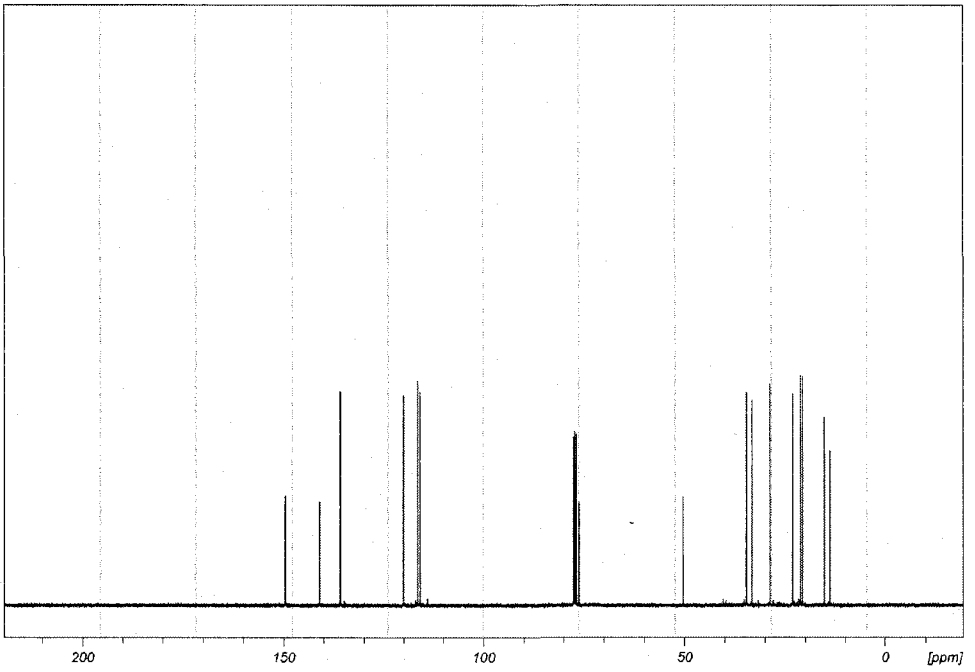


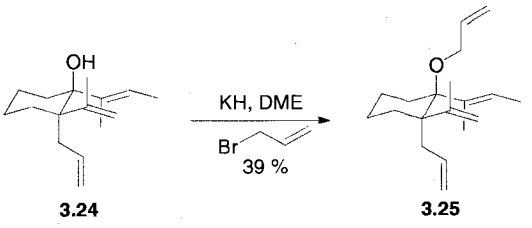
3.24

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.24 **3.25**

(±)-(1R,2R)-1-Allyl-2-allyloxy-2-((E)-but-2-en-2-yl)-1-(prop-1-en-2-yl)cyclohexane (**3.25**)

To a suspension of KH (59.9 mg, 1.49 mmol) in DME (5 mL) cooled to 0 °C was added a solution of **3.24** (87.5 mg, 0.373 mmol) in DME (3 mL) and the resulting mixture was stirred for 10 minutes. This mixture was treated with allyl bromide (0.07 mL, 0.827 mmol) and the reaction was stirred for 2 hours warming to room temperature and then for a further 16 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in hexanes gave allyl ether **3.25** (39.8 mg, 0.145 mmol, 39 %, $R_f = 0.80$) as a colorless oil.

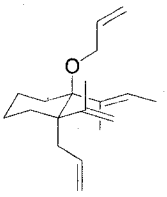
Data for **3.25**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96-5.86 (m, 1H), 5.71-5.61 (m, 1H), 5.33-5.28 (m, 2H), 5.07 (dq, J = 10.5, 1.6 Hz, 1H), 5.06-4.94 (m, 3H), 4.69 (s, 1H), 3.78-3.73 (m, 1H), 3.49-3.45 (m, 1H), 2.46-2.36 (m, 2H), 2.28 (dd, J = 12.9, 12.9, 4.4 Hz, 1H), 2.06-1.98 (m, 1H), 1.89 (s, 3H), 1.61 (dd, J = 6.7, 1.1 Hz, 3H), 1.56-1.36 (m, 5H), 1.53 (s, 3H), 1.30-1.27 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4 (C_4), 136.7 (CH), 136.1 (CH), 123.8 (CH), 115.9 (CH_2), 115.2 (CH_2), 114.7 (CH_2), 86.1 (C_4), 63.0 (CH_2), 49.0 (C_4), 35.7 (CH_2), 28.3 (CH_2), 24.2 (CH_3), 21.7 (CH_2), 20.6 (CH_2), 15.8 (CH_3), 13.9 (CH_3) Two carbons are absent (olefin C_4 and alkyl CH_2), even after attempts to detect them with long relaxation delays, heating and the use of HMBC.

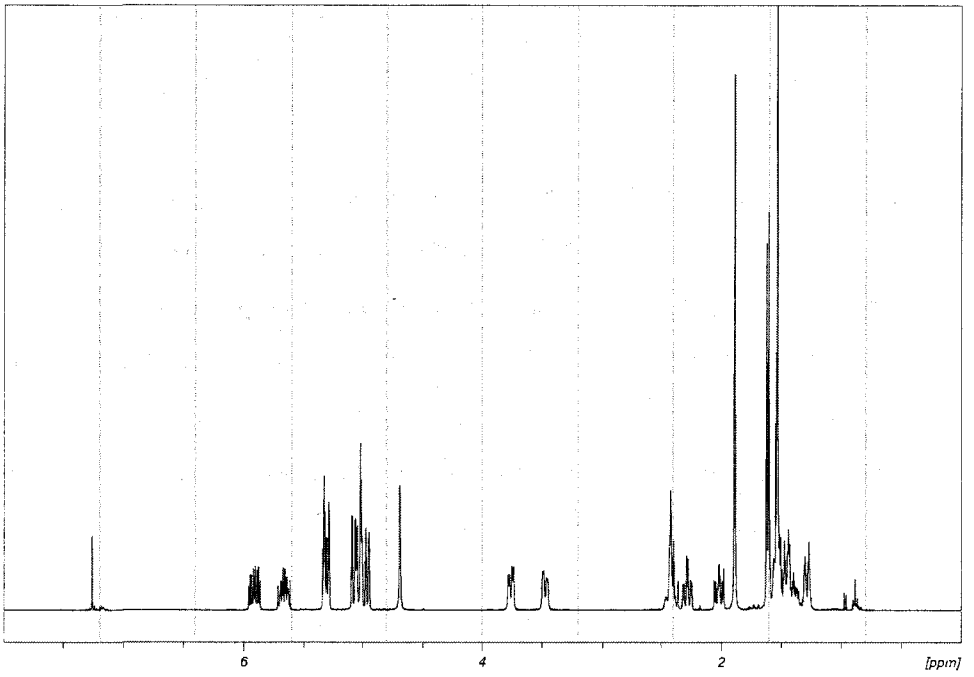
FT-IR (neat, cm^{-1}): 3079 (m), 2979 (s), 2927 (s), 2863 (s), 1629 (w)

HRMS (EI): Calculated 274.2297 (M^+) for $C_{19}H_{30}O$, found 274.2272

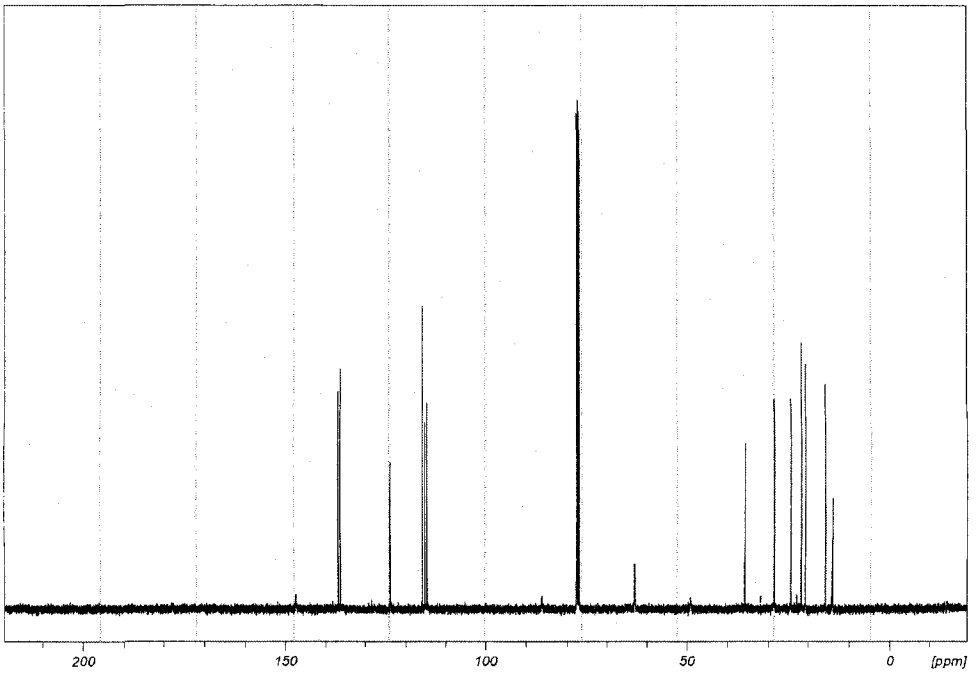


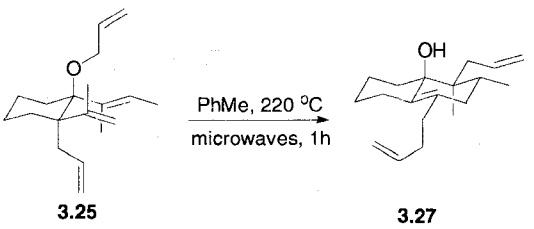
3.25

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.25 **3.27**

(±)-(3R,4S,4aS)-4-Allyl-1-(but-3-enyl)-2,3,4,4a,5,6,7,8-octahydro-3,4-dimethylnapthalen-4a-ol (**3.27**)

A sample of **3.25** (63.9 mg, 0.233 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered from the complex mixture of products by flash chromatography in 5 % EtOAc/hexanes, affording **3.27** (6.4 mg, 0.0233 mmol, 10 %, R_f = 0.55) as a colorless oil.

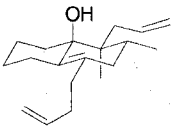
Data for **3.27**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.16-6.08 (m, 1H), 5.83-5.75 (m, 1H), 5.05 (dd, J = 17.1, 1.2 Hz, 1H), 5.01-4.92 (m, 3H), 2.52 (d, J = 15.0 Hz, 1H), 2.31 (dd, J_{AB} = 15.4 Hz, J = 8.3 Hz, 1H), 2.21 (dddd, J_{AB} = 15.4 Hz, J = 6.1, 1.7, 1.7 Hz, 1H), 2.17-1.99 (m, 5H), 1.85-1.79 (m, 2H), 1.77-1.68 (m, 2H), 1.57 (s, 1H), 1.54-1.49 (m, 3H), 1.46 (s, 1H), 1.17-1.08 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.71 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.0 (C_4), 138.8 (C_4), 132.3 (CH), 131.5 (CH), 115.4 (CH_2), 114.5 (CH_2), 77.1 (C_4), 43.1 (C_4), 39.9 (CH_2), 37.2 (CH_2), 33.2 (CH_2), 32.9 (2 × CH_2), 30.2 (CH), 26.6 (CH_2), 26.0 (CH_2), 21.7 (CH_2), 16.7 (CH_3), 15.6 (CH_3)

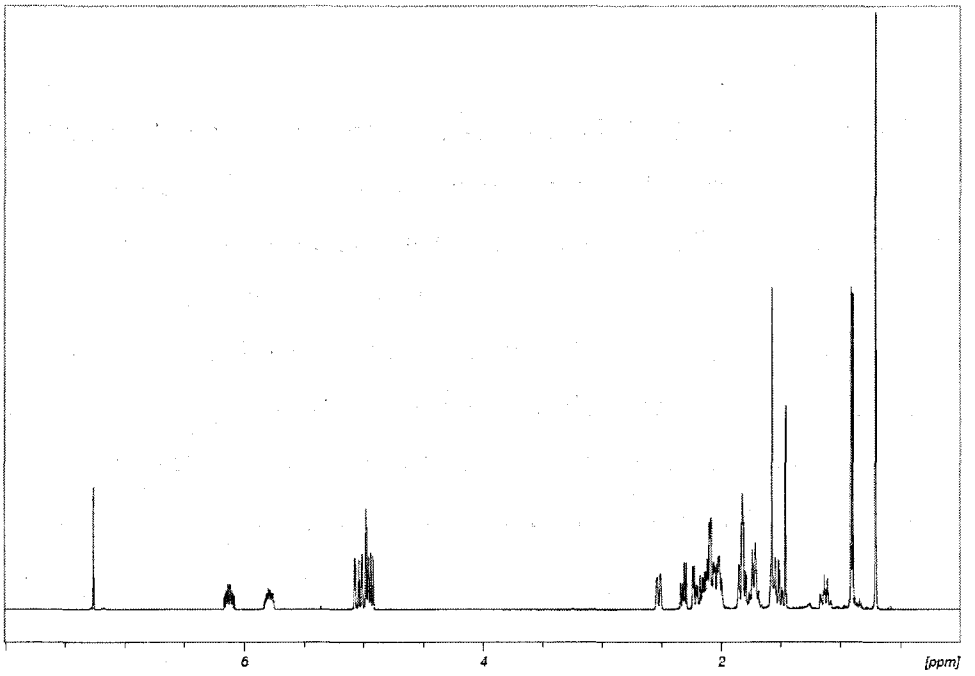
FT-IR (neat, cm^{-1}): 3554 (b), 3484 (b), 2975 (s), 2956 (s), 2930 (s), 1636 (w)

HRMS (EI): Calculated 274.2297 (M^+) for $C_{19}H_{30}O$, found 274.2304

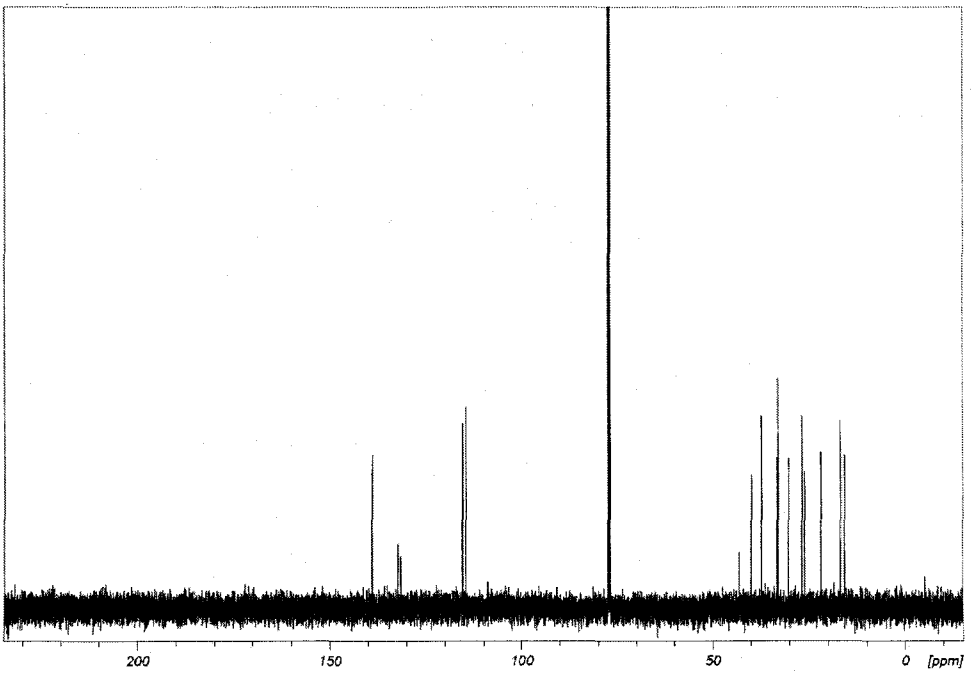


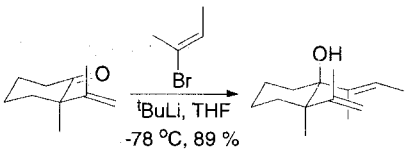
3.27

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





3.28 **3.29**

(±)-(1R, 2S)-1-((E)-But-2-en-2-yl)-2-methyl-2-(prop-1-en-2-yl)cyclohexanol (**3.29**)

E-2-bromo-2-butene (1.87 mL, 18.4 mmol) was dissolved in THF (40 mL), cooled to -78 °C and treated with ^{t}BuLi (1.70 M, 21.7 mL, 36.9 mmol). This mixture was stirred for 0.5 hours giving a clear yellow solution whereupon a solution of **3.28** (936.0 mg, 6.15 mmol) in THF (20 mL) was added via cannula. The reaction was stirred for 1 hour at -78 °C whereupon it was quenched with saturated aqueous NH_4Cl. After warming to room temperature the layers were separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes gave **3.29** (1146.0 mg, 5.50 mmol, 89 %, $R_f = 0.45$) as a colorless oil.

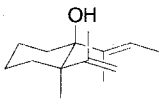
Data for **3.29**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.37 (q, J = 6.5 Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 2.39 (d, J = 2.4 Hz, 1H), 2.26-2.17 (m, 1H), 2.10-2.01 (m, 1H), 1.81-1.70 (m, 1H), 1.70 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.56-1.47 (m, 3H), 1.44-1.38 (m, 1H), 1.18 (s, 3H), 1.10-1.04 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0 (C_4), 141.2 (C_4), 119.9 (CH), 113.4 (CH_2), 76.3 (C_4), 47.0 (C_4), 34.0 (CH_2), 32.9 (CH_2), 23.7 (CH_3), 21.6 (CH_2), 21.3 (CH_2), 19.7 (CH_3), 15.1 (CH_3), 13.9 (CH_3)

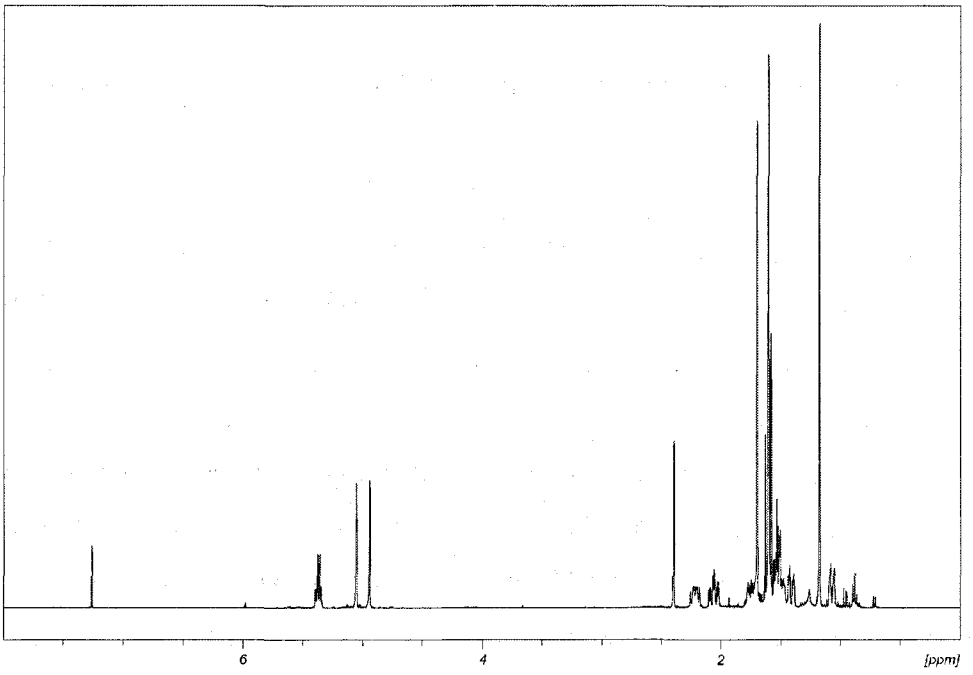
FT-IR (neat, cm^{-1}): 3473 (b), 2956 (s), 2921 (s), 2865 (s), 1621 (m)

HRMS (EI): Calculated 208.1827 (M^+) $C_{14}H_{24}O$, found 208.1838

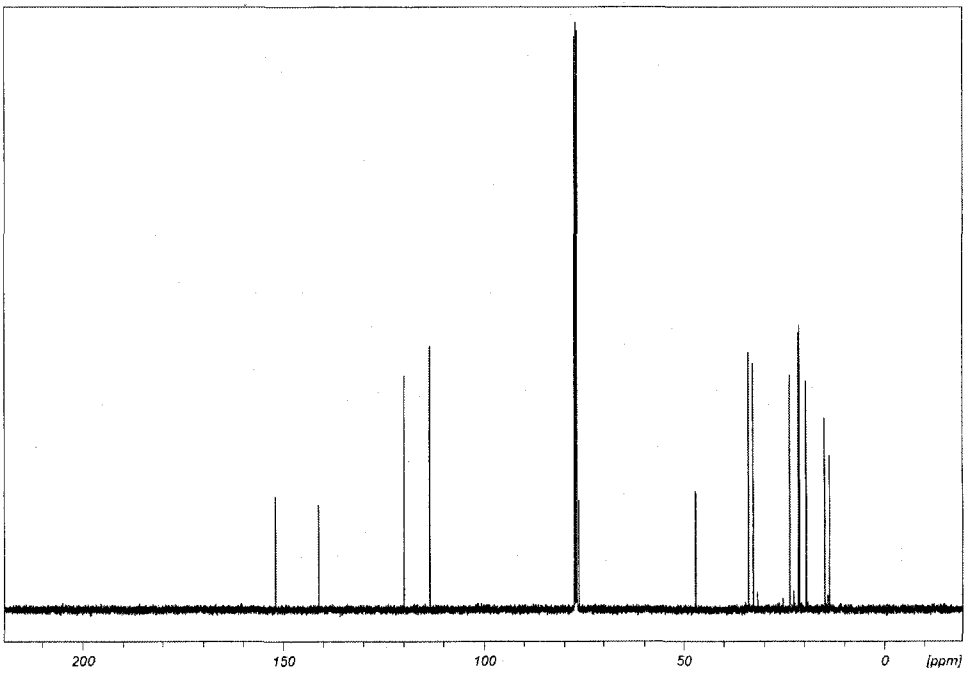


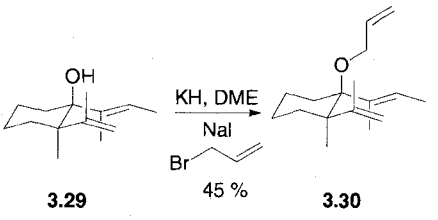
3.29

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.29 **3.30**

(±)-(1R, 2S)-1-(Allyloxy)-1-((E)-but-2-en-2-yl)-2-methyl-2-(prop-1-en-2-yl)cyclohexane (**3.30**)

NaI (121.7 mg, 0.812 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 4.34 g, 32.5 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (50 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.29** (1.69 g, 8.11 mmol) in DME (30 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (1.37 mL, 16.2 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in hexanes gave allyl ether **3.30** (908.8 mg, 3.66 mmol, 45 %, R_f = 0.85) as a colorless oil.

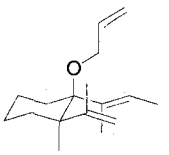
Data for **3.30**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96-5.89 (m, 1H), 5.32-5.26 (m, 2H), 5.07 (dq, J = 10.5, 1.6 Hz, 1H), 4.83-4.82 (m, 1H), 4.75 (s, 1H), 3.73 (dddd, J_{AB} = 12.8, J = 5.4, 1.6, 1.6 Hz, 1H), 3.46-3.42 (m, 1H), 2.47-2.41 (m, 1H), 1.96 (s, 3H), 1.93-1.86 (m, 1H), 1.60 (dq, J = 6.7, 1.0 Hz, 3H), 1.56-1.48 (m, 5H), 1.52 (s, 3H), 1.05-1.01 (m, 1H), 1.04 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4 (C_4), 136.1 (CH), 123.3 (CH), 114.6 (CH_2), 113.1 (CH_2), 85.8 (C_4), 63.0 (CH_2), 45.8 (C_4), 33.0 (CH_2), 28.0 (CH_2), 23.8 (CH_3), 21.5 (CH_2), 21.2 (CH_2), 21.1 (CH_3), 15.0 (CH_3), 13.7 (CH_3) One carbon is absent (olefin C_4), even after attempts to detect it with long relaxation delays, heating and the use of HMBC.

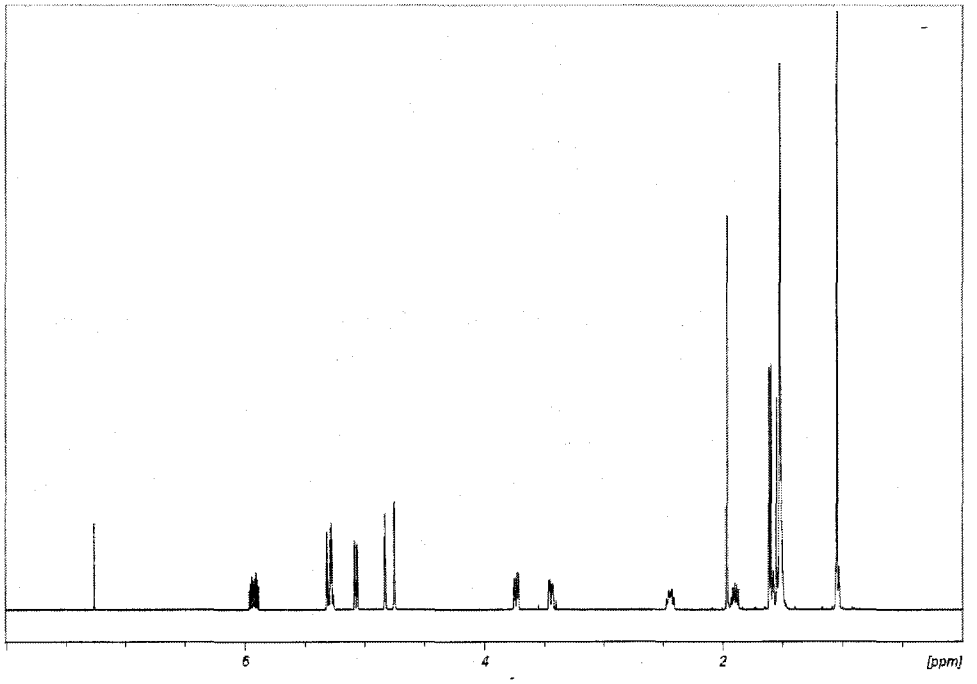
FT-IR (neat, cm^{-1}): 2956 (s), 2927 (s), 2860 (s), 1652 (w), 1626 (m)

HRMS (EI): Calculated 248.2140 (M^+) $C_{17}H_{28}O$, found 248.2124

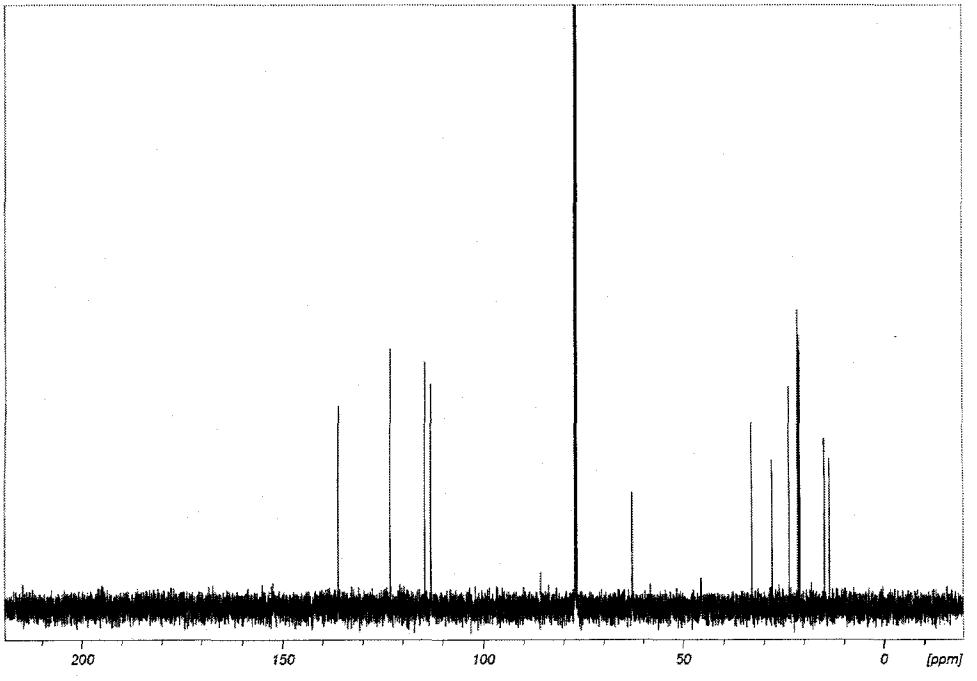


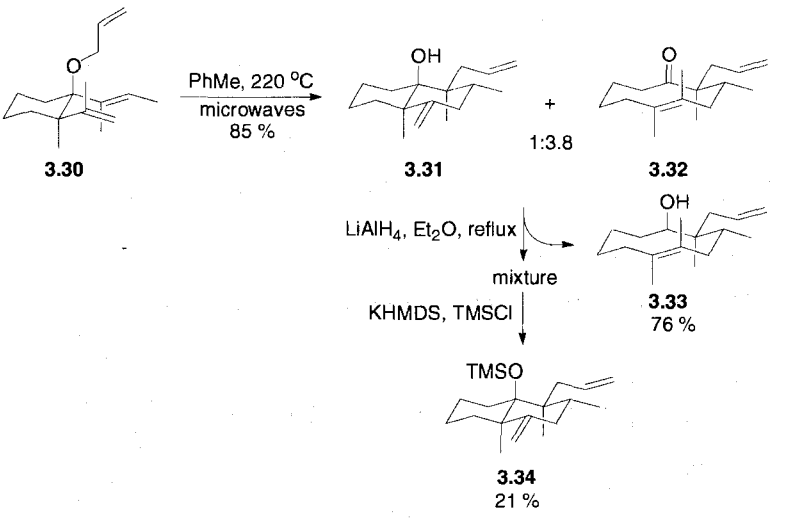
3.30

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(E, 1S, 2S, 3R)-2-Allyl-2,3,5,6-tetramethylcyclodec-5-enol (**3.33**)

A sample of **3.30** (908.8 mg, 3.66 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording an inseparable 1:3.8 mixture of tertiary alcohol **3.31** and ketone **3.32** (775.6 mg, 3.12 mmol, 85 %, $R_f = 0.50$) as a colorless oil.

The mixture of **3.31** and **3.32** (48.8 mg, 0.196 mmol) was dissolved in THF (10 mL) and it was treated with $LiAlH_4$ (29.8 mg, 0.743 mmol). The resulting gray mixture was heated at reflux for 16 hours after which it was cooled to room temperature and quenched by the careful addition of an aqueous 1.0 M solution of sodium tartrate. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 20 % EtOAc/hexanes affording secondary alcohol **3.33** (37.0 mg, 0.148 mmol, 76 %, $R_f = 0.60$) as a colorless oil. Also recovered was an inseparable mixture of unreacted ketone **3.31** and tertiary alcohol **3.32** (3.7 mg, 0.0149 mmol, 8 %, $R_f = 0.95$) as a colorless oil.

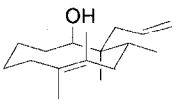
Data for **3.33**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06-5.95 (m, 1H), 5.05-5.00 (m, 1H), 4.97 (d, J = 10.0 Hz, 1H), 3.61 (d, J = 10.2 Hz, 1H), 2.67 (dd, J = 13.8, 10.2 Hz, 1H), 2.56-2.50 (m, 1H), 2.29 (dd, J = 14.7, 5.9 Hz, 1H), 1.99 (dd, J = 14.7, 9.0 Hz, 1H), 1.89-1.75 (m, 2H), 1.81 (s, 3H), 1.78 (s, 3H), 1.70-1.48 (m, 5H), 1.45-1.33 (m, 3H), 0.99 (s, 3H), 0.92 (d, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5 (CH), 129.9 (C_4), 129.8 (C_4), 116.1 (CH_2), 77.8 (CH), 46.0 (C_4), 39.8 (CH_2), 38.4 (CH_2), 35.9 (CH), 34.0 (CH_2), 32.1 (CH_2), 25.1 (CH_2), 24.7 (CH_2), 22.7 (CH_3), 20.1 (CH_3), 19.7 (CH_3), 17.2 (CH_3)

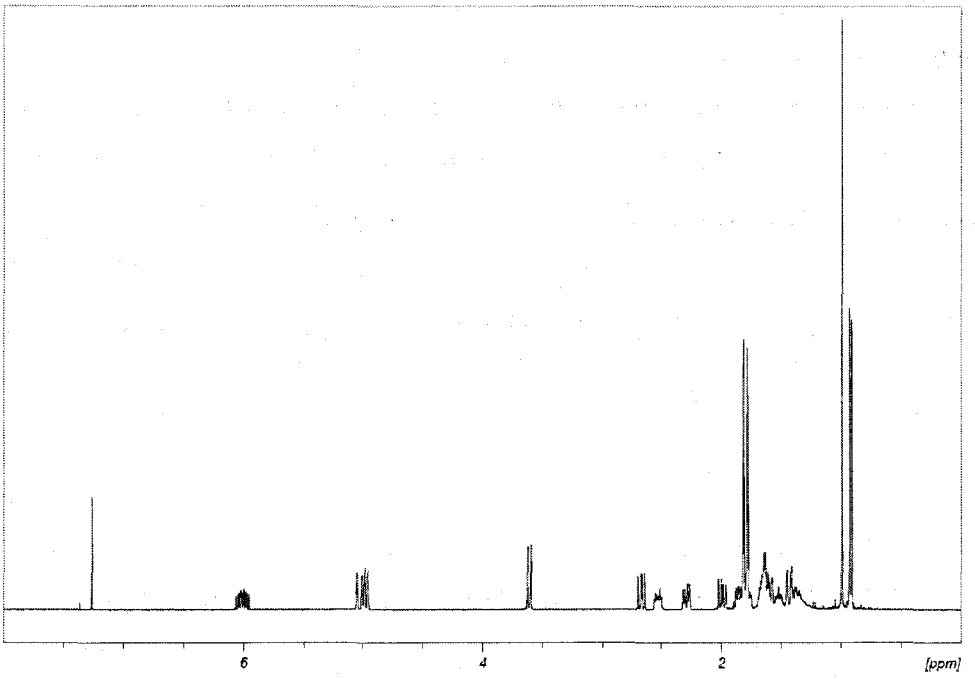
FT-IR (neat, cm^{-1}): 3472 (b), 2962 (s), 2923 (s), 2857 (s), 1634 (w)

HRMS (EI): Calculated 250.2297 (M^+) $C_{17}H_{30}O$, found 250.2288

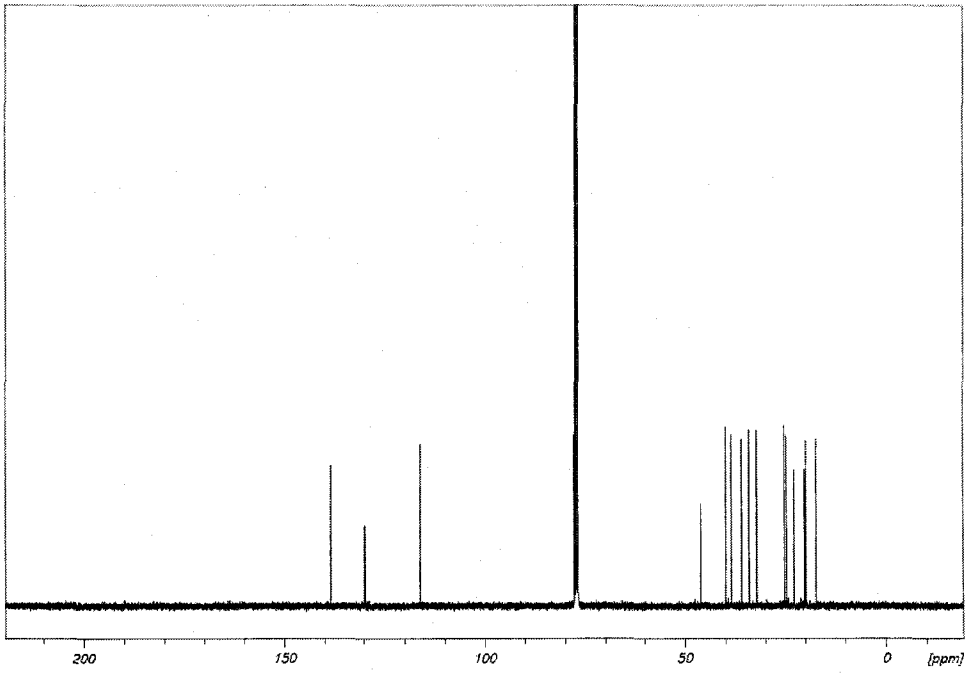


3.33

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



(±)-((1S, 2R, 4aR, 8aS)-1-Allyl-decahydro-1,2,4a-trimethyl-4-methylenenapthalen-8a-yloxy)trimethylsilane (**3.34**)

The mixture of **3.31** and **3.32** (256.4 mg, 1.03 mmol) was dissolved in THF (15 mL) and treated with solid KHMDS (823.7 mg, 4.13 mmol) and TMSCl (0.52 mL, 4.10 mmol). The reaction was stirred at room temperature for 0.5 h whereupon the reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in hexanes, affording silyl ether **3.34** (69.2 mg, 0.216 mmol, 21 %, R_f = 0.90) as a colorless oil.

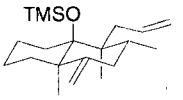
Data for **3.34**

^{1}H NMR (400 MHz, C_6D_6): δ = 5.97-5.86 (m, 1H), 5.06 (dddd, J = 17.0, 1.7, 1.7, 1.7 Hz, 1H), 5.02-4.98 (m, 1H), 4.84 (dd, J = 1.9, 1.9 Hz, 1H), 4.70 (dd, J = 1.7, 1.7 Hz, 1H), 2.46 (dd, J = 15.3, 7.0 Hz, 1H), 2.31-2.24 (m, 1H), 2.10 (dddd, J = 15.3, 7.4, 1.3, 1.3 Hz, 1H), 2.06-1.96 (m, 3H), 1.66-1.53 (m, 3H), 1.52-1.39 (m, 3H), 1.29-1.22 (m, 1H), 1.09 (s, 3H), 0.83 (d, J = 3.9 Hz, 3H), 0.82 (d, J = 2.7 Hz, 3H), 0.25 (s, 9H)

^{13}C NMR (100 MHz, C_6D_6): δ = 155.4 (C_4), 139.1 (CH), 115.6 (CH_2), 106.1 (CH_2), 87.8 (C_4), 45.7 (C_4), 45.3 (C_4), 41.8 (CH_2), 39.1 (CH_2), 39.0 (CH), 35.7 (CH_2), 27.3 (CH_2), 24.9 (CH_3), 22.1 (CH_2), 20.8 (CH_2), 17.3 (CH_3), 16.2 (CH_3), 3.3 (3 × CH_3)

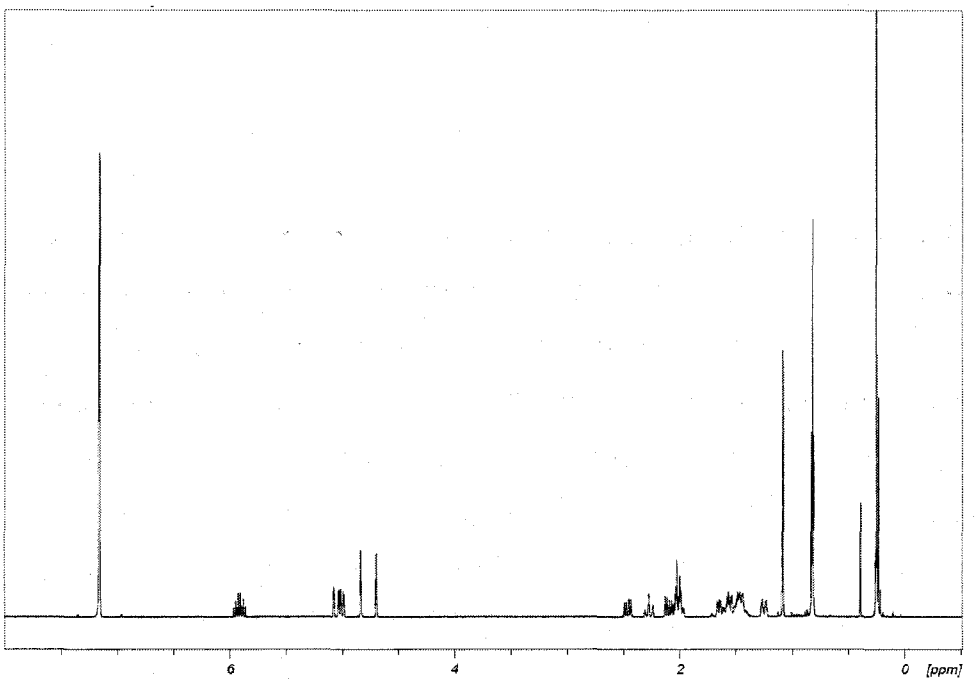
FT-IR (neat, cm^{-1}): 3079 (w), 3017 (w), 2953 (s), 1641 (w)

HRMS (EI): Calculated 320.2535 (M^+) for $C_{20}H_{36}OSi$, found 320.2532

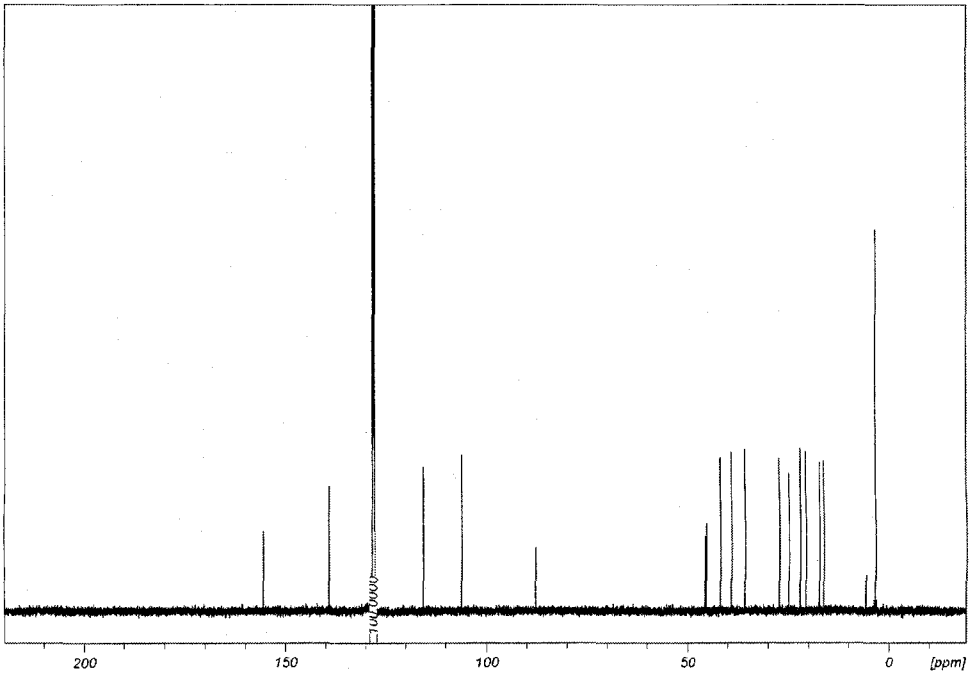


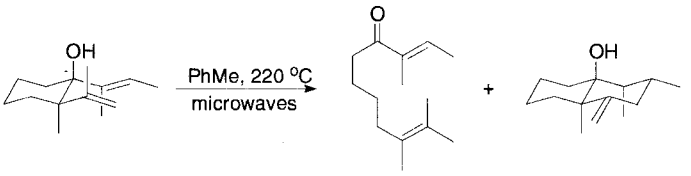
3.34

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



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





3.29 **3.40** 71 % **3.41** 17 %

E-3,9,10-Trimethylundeca-2,9-dien-4-one (**3.40**)

A sample of **3.29** (101.3 mg, 0.486 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The products were recovered by flash chromatography in 5 % EtOAc/hexanes, affording ketone **3.40** (72.1 mg, 0.346 mmol, 71 %, $R_f = 0.35$) as a colorless oil and tertiary alcohol **3.41** (17.4 mg, 0.0835 mmol, 17 %, $R_f = 0.30$) as a colorless oil, which was not sufficiently pure for characterization.

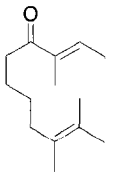
Data for **3.40**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (q, J = 6.8 Hz, 1H), 2.63 (t, J = 7.5 Hz, 2H), 2.02 (t, J = 7.7 Hz, 2H), 1.85 (d, J = 6.9 Hz, 3H), 1.76 (s, 3H), 1.63 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.60-1.53 (m, 2H), 1.39-1.33 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2 (C_4), 138.5 (C_4), 137.0 (CH), 127.7 (C_4), 124.2 (C_4), 37.3 (CH_2), 34.4 (CH_2), 28.2 (CH_2), 25.2 (CH_2), 20.7 (CH_3), 20.3 (CH_3), 18.4 (CH_3), 14.9 (CH_3), 11.2 (CH_3)

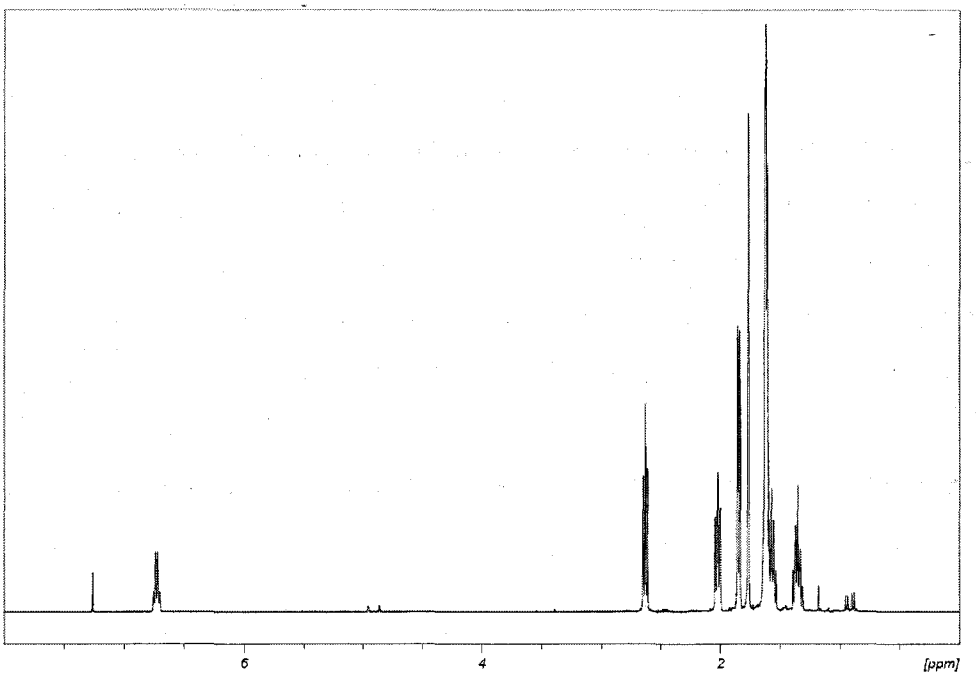
FT-IR (neat, cm^{-1}): 2987 (m), 2925 (s), 2860 (s), 1669 (s)

HRMS (EI): Calculated 208.1827 (M^+) $C_{14}H_{24}O$, found 208.1818

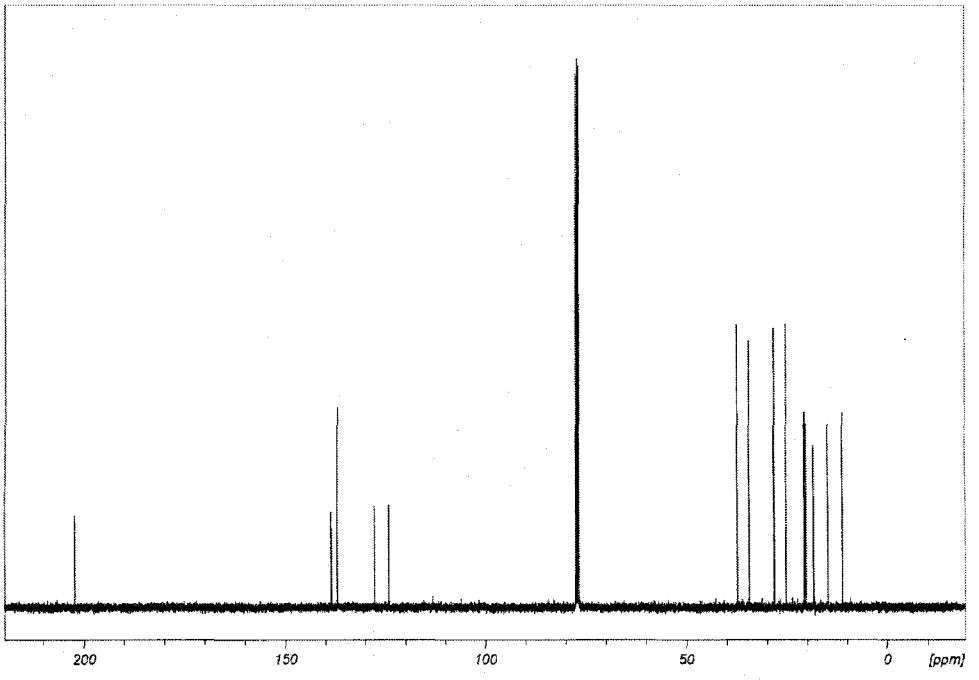


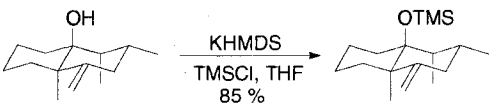
3.40

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.41 **3.42**

(±)-((1R,2R,4aR,8aS)-Decahydro-1,2,4a-trimethyl-4-methylenenapthalen-8a-yloxy)trimethylsilane (**3.42**)

Impure tertiary alcohol **3.41** (17.4 mg, 0.0835 mmol) was dissolved in THF (3 mL) and treated with solid KHMDS (66.0 mg, 0.331 mmol) and TMSCl (0.04 mL, 0.315 mmol). The reaction was stirred at room temperature for 0.75 h whereupon the reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in hexanes, affording silyl ether **3.42** (19.9 mg, 0.0709 mmol, 85 %, R_f = 0.80) as a colorless oil.

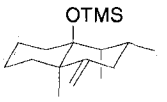
Data for **3.42**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.65 (dd, J = 2.0, 2.0 Hz, 1H), 4.48 (dd, J = 1.5, 1.5 Hz, 1H), 2.33-2.26 (m, 1H), 2.23 (dd, J = 12.9, 12.9 Hz, 1H), 1.99 (ddd, J = 13.7, 13.7 4.4 Hz, 1H), 1.92-1.87 (m, 2H), 1.67-1.58 (m, 1H), 1.56-1.48 (m, 4H), 1.27 (ddd, J = 13.7, 2.9, 2.9 Hz, 1H), 1.15 (d, J = 11.5 Hz, 1H), 1.09 (d, J = 0.5 Hz, 3H), 0.91 (d, J = 7.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.07 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (C_4), 105.5 (CH_2), 82.7 (C_4), 46.1 (CH), 44.4 (C_4), 36.5 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 31.7 (CH), 23.4 (CH_3), 21.8 (CH_2), 21.3 (CH_2), 19.1 (CH_3), 11.0 (CH_3), 2.3 (3 × CH_3)

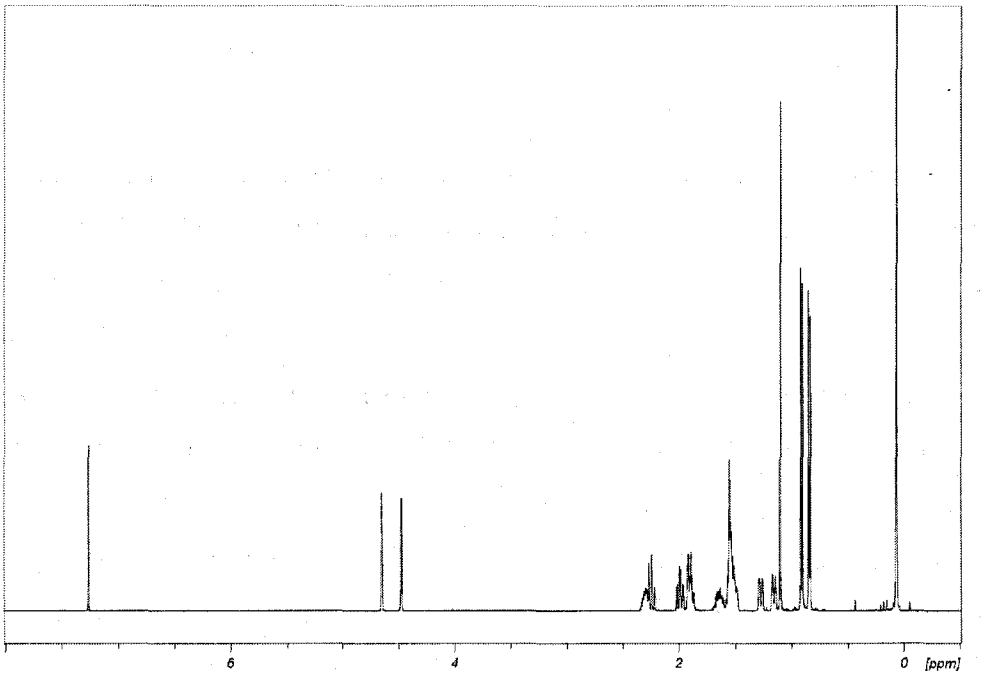
FT-IR (neat, cm^{-1}): 3010 (w), 2953 (s), 2926 (m), 1643 (w)

HRMS (EI): Calculated 280.2222 (M^+) for $C_{17}H_{32}OSi$, found 280.2220

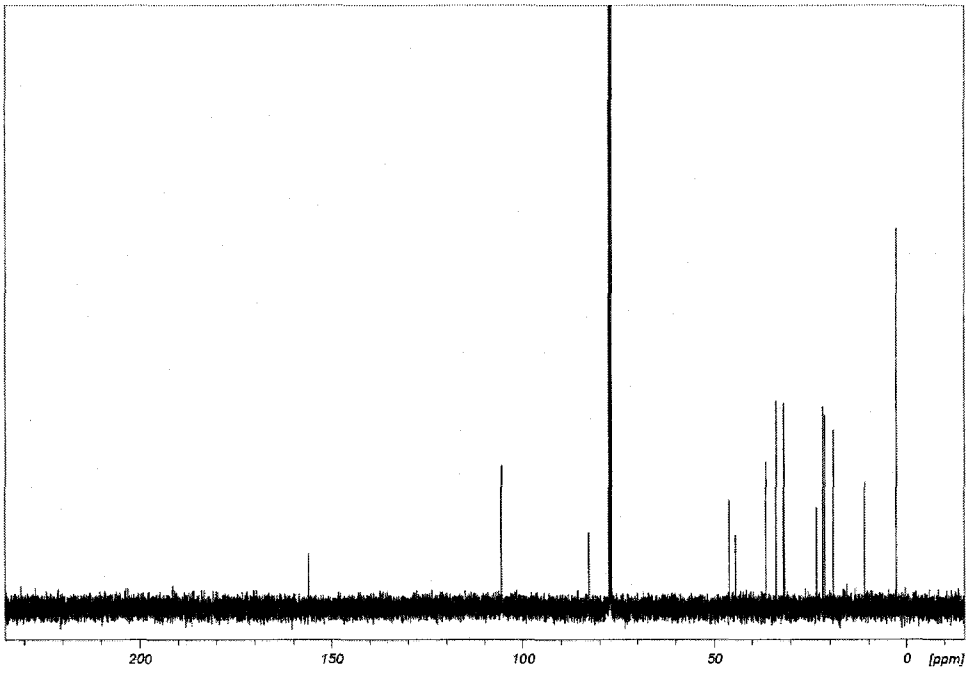


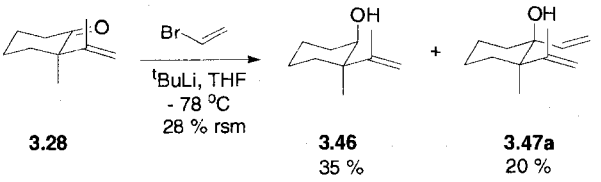
3.42

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





3.28 **3.46** 35 % **3.47a** 20 %

(±)-(1R, 2S)-2-Methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (**3.47a**)

A solution of vinyl bromide (1.0 M in THF, 2.62 mL, 2.62 mmol) was diluted with THF (2.5 mL), cooled to -78 °C and treated with ^{t}BuLi (1.70 M, 3.08 mL, 5.24 mmol). After stirring for 0.5 hours a solution of **3.28** (200.0 mg, 1.31 mmol) in THF (10 mL) was added via cannula and the mixture was stirred for 3 hours at -78 °C followed by 14 hours of stirring at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by gradient flash chromatography in 2 to 10 % EtOAc/hexanes gave the desired product **3.47a** (47.2 mg, 0.262 mmol, 20 %, R_f = 0.58) as a colorless oil, returned starting material **3.28** (55.0 mg, 0.361 mmol, 28 %, R_f = 0.55) as a colorless oil, and secondary alcohol **3.46** (69.8 mg, 0.453 mmol, 35 %, R_f = 0.45) as a colorless oil.

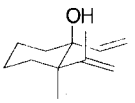
Data for **3.47a**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (dd, J = 17.1, 10.8 Hz, 1H), 5.17 (dd, J = 17.2, 1.7 Hz, 1H), 5.05-5.04 (m, 1H), 4.97 (dd, J = 10.8, 1.7 Hz, 1H), 4.94 (s, 1H), 2.15 (ddd, J = 12.4, 12.4, 5.5 Hz, 1H), 2.04 (bs, 1H), 1.77 (s, 3H), 1.75-1.60 (m, 2H), 1.56-1.46 (m, 3H), 1.42-1.38 (m, 1H), 1.19 (s, 3H), 1.17-1.12 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1 (C_4), 144.4 (CH), 114.1 (CH_2), 112.0 (CH_2), 74.2 (C_4), 46.4 (C_4), 33.3 (CH_2), 33.0 (CH_2), 23.9 (CH_3), 21.5 (CH_2), 21.0 (CH_2), 19.5 (CH_3)

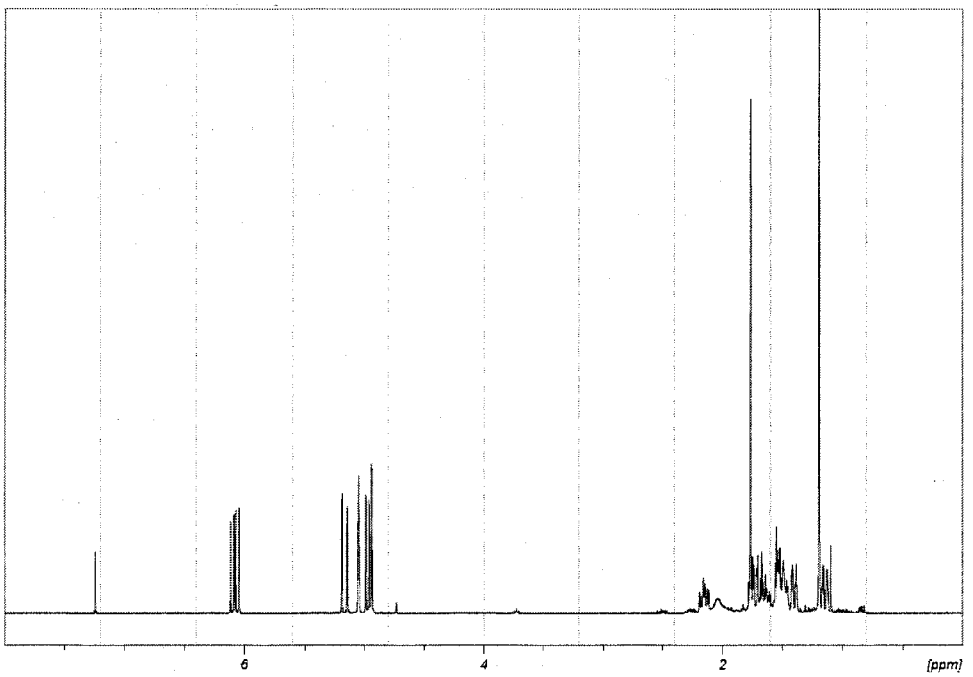
FT-IR (neat, cm^{-1}): 3438 (b), 2987 (s), 2929 (s), 2867 (s), 1625 (m)

HRMS (EI): Calculated 180.1514 (M^+) for $C_{12}H_{20}O$, found 180.1508

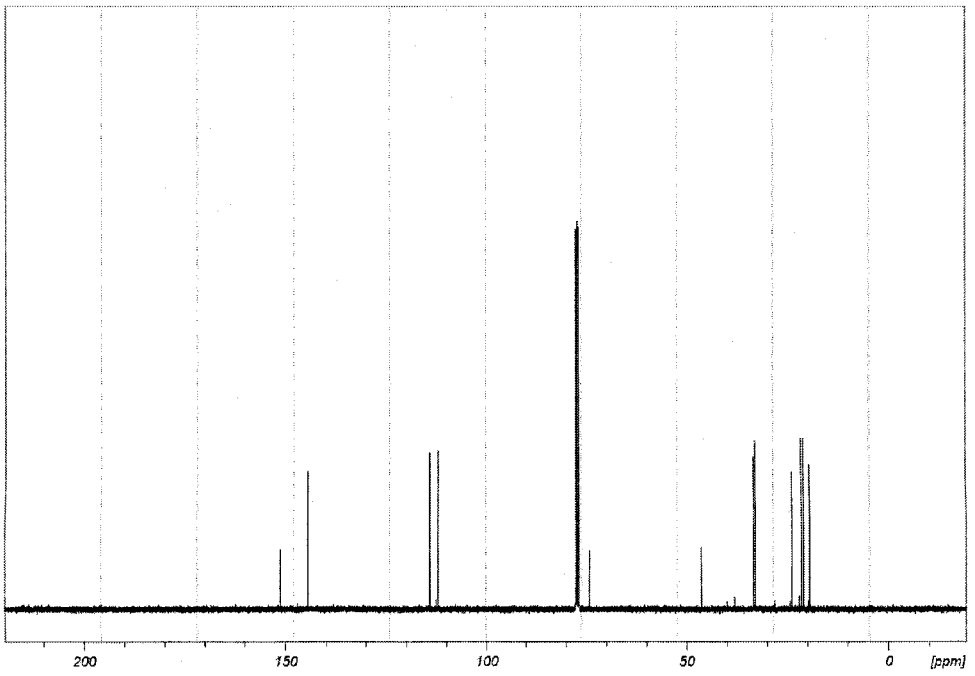


3.47a

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



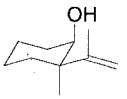
Data for **3.46**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98-4.96 (m, 1H), 4.89 (s, 1H), 3.72 (s, 1H), 1.83 (ddd, J = 12.5, 12.5, 3.8 Hz, 1H), 1.78 (s, 3H), 1.77-1.48 (m, 6H), 1.44-1.39 (m, 1H), 1.34-1.29 (m, 1H), 1.07 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6 (C_4), 112.1 (CH_2), 70.7 (CH), 43.0 (C_4), 29.4 (CH_2), 27.7 (CH_2), 21.7 (CH_2), 21.4 (CH_3), 19.7 (CH_2), 19.2 (CH_3)

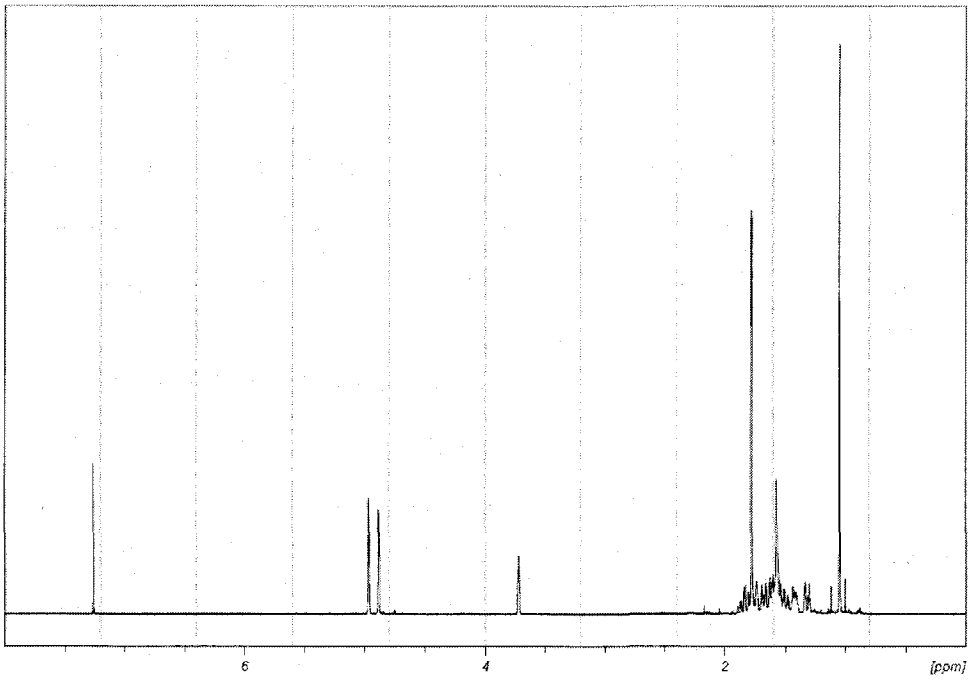
FT-IR (neat, cm^{-1}): 3415 (b), 2932 (s), 2867 (s), 1636 (w)

HRMS (EI): Calculated 154.1358 (M^+) for $C_{10}H_{18}O$, found 154.1370

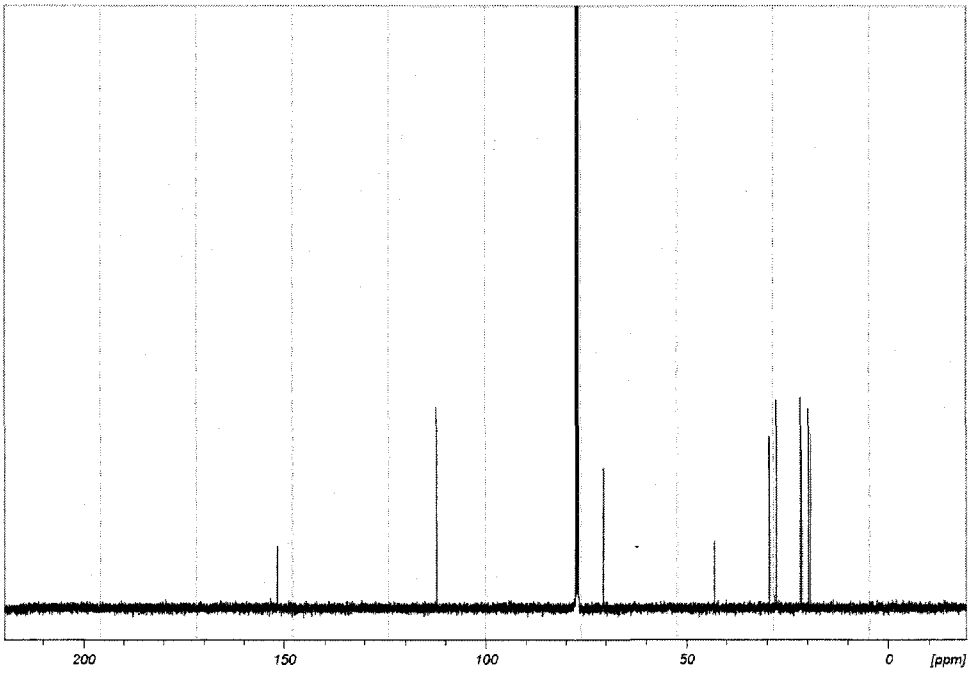


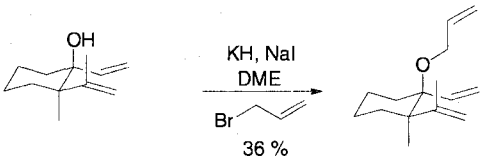
3.46

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.47a **3.43a**

(±)-(1R, 2S)-1-(Allyloxy)-2-methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexane (**3.43a**)

NaI (3.9 mg, 0.0260 mmol) was placed in a flask and flame dried. To this flask was added KH (140.0 mg, 1.05 mmol) and the solids were suspended in DME (5 mL). This suspension was cooled to 0 °C and to it was added a solution of **3.47a** (47.2 mg, 0.262 mmol) in DME (5 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.05 mL, 0.591 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in hexanes gave allyl ether **3.43a** (21.8 mg, 0.0989 mmol, 36 %, $R_f = 0.80$) as a colorless oil.

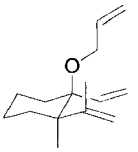
Data for **3.43a**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93-5.83 (m, 2H), 5.26 (dddd, J = 17.3, 1.9, 1.9, 1.9 Hz, 1H), 5.22 (dd, J = 11.2, 1.6 Hz, 1H), 5.05 (dddd, J = 10.5, 1.6, 1.6, 1.6 Hz, 1H), 5.00-4.95 (m, 2H), 4.74 (d, J = 1.6 Hz, 1H), 3.71-3.69 (m, 2H), 2.46-2.38 (m, 1H), 1.94 (d, J = 0.9 Hz, 3H), 1.76-1.73 (m, 1H), 1.67-1.60 (m, 1H), 1.58-1.49 (m, 4H), 1.16-1.12 (m, 1H), 1.03 (d, J = 0.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6 (C_4), 141.3 (CH), 136.6 (CH), 116.4 (CH_2), 114.6 (CH_2), 113.2 (CH_2), 81.2 (C_4), 62.8 (CH_2), 45.2 (C_4), 31.8 (CH_2), 25.5 (CH_2), 24.2 (CH_3), 21.4 (CH_2), 21.3 (CH_2), 21.0 (CH_3)

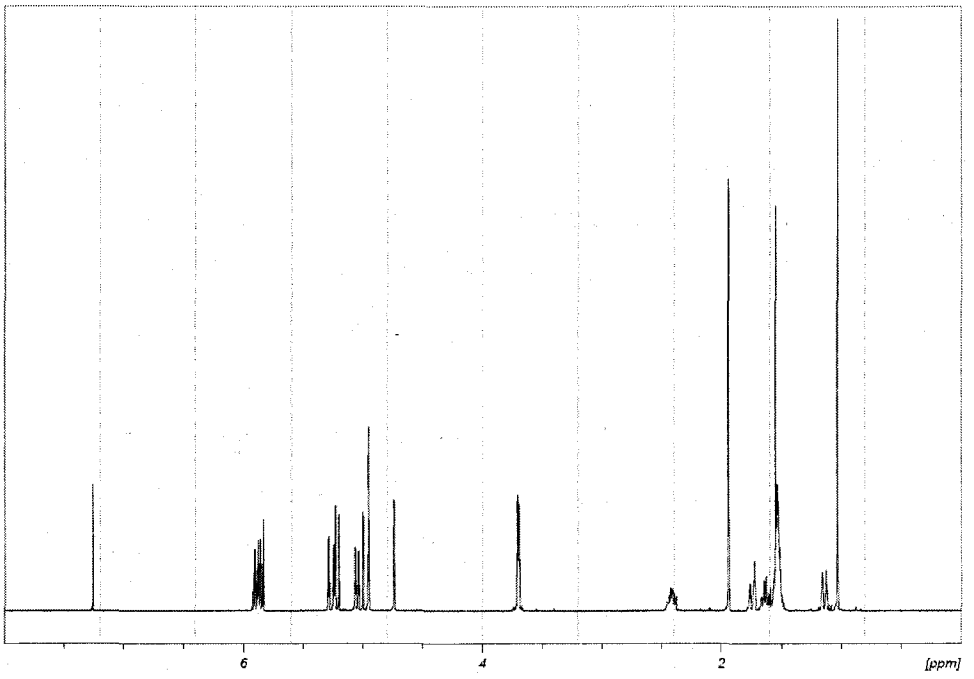
FT-IR (neat, cm^{-1}): 2987 (m), 2927 (s), 1644 (w), 1626 (m)

HRMS (EI): Calculated 220.1827 (M^+) for $C_{15}H_{24}O$, found 220.1803

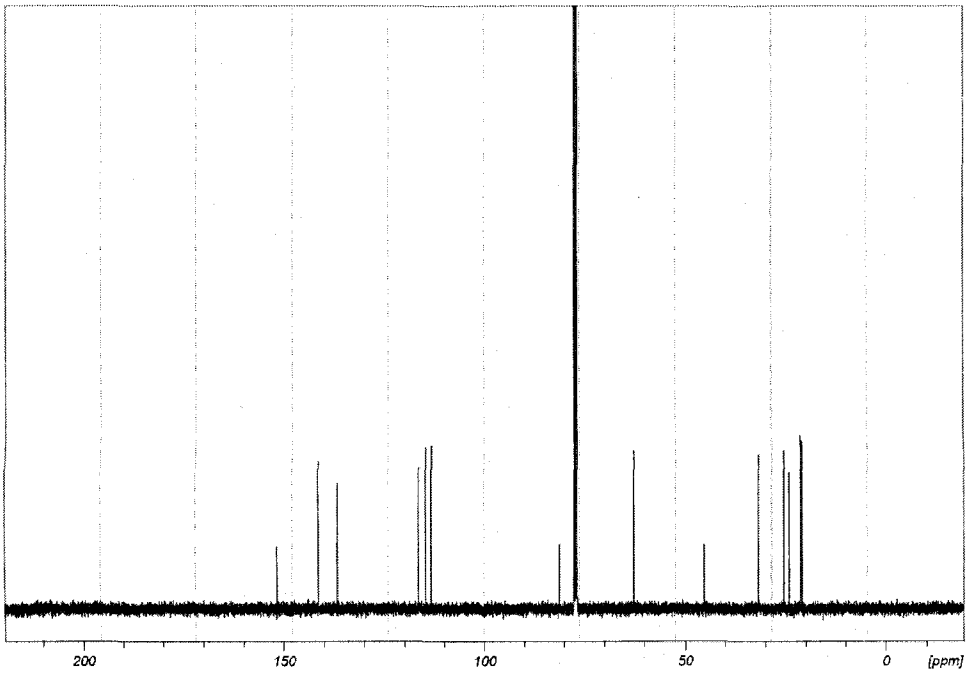


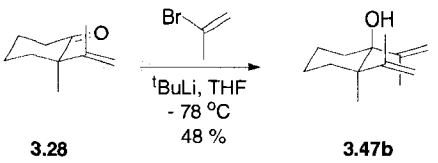
3.43a

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.28 **3.47b**

(±)-(1R, 2S)-2-Methyl-1,2-di(prop-1-en-2-yl)cyclohexanol (**3.47b**)

2-bromopropene (0.23 mL, 2.63 mmol) was dissolved in THF (10 mL), cooled to -78 °C and treated with ^{t}BuLi (1.70 M, 3.10 mL, 5.27 mmol). This mixture was stirred for 0.5 hours giving a clear yellow solution whereupon a solution of **3.28** (200.0 mg, 1.31 mmol) in THF (2 mL) was added via cannula. The reaction was stirred for 2 hours at -78 °C whereupon it was quenched with saturated aqueous NH_4Cl. After warming to room temperature the layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes gave **3.47b** (122.5 mg, 0.630 mmol, 48 %, $R_f = 0.35$) as a colorless oil.

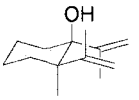
Data for **3.47b**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.07-5.05 (m, 1H), 4.96 (s, 1H), 4.96-4.92 (m, 1H), 4.74 (q, J = 0.6 Hz, 1H), 2.41 (bs, 1H), 2.24-2.17 (m, 1H), 2.00 (ddd, J = 14.1, 14.1, 4.6 Hz, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.72-1.65 (m, 1H), 1.58-1.46 (m, 4H), 1.21 (s, 3H), 1.11-1.06 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8 (C_4), 151.0 (C_4), 113.5 (CH_2), 112.4 (CH_2), 76.3 (C_4), 46.5 (C_4), 33.6 (CH_2), 33.3 (CH_2), 23.9 (CH_3), 22.3 (CH_3), 21.4 (CH_2), 21.2 (CH_2), 19.3 (CH_3)

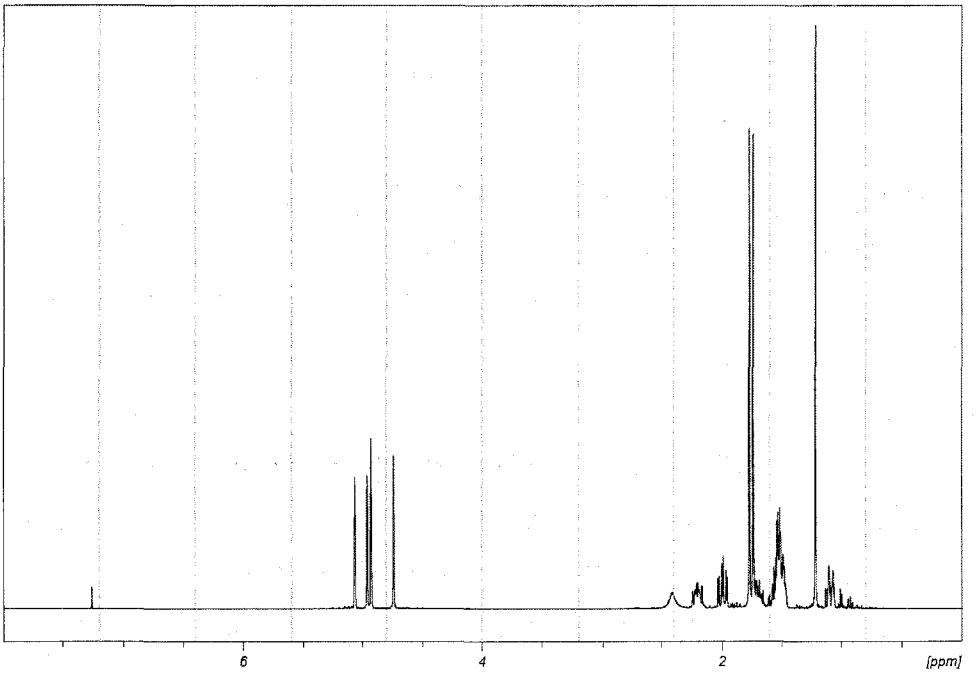
FT-IR (neat, cm^{-1}): 3551 (b), 2957 (s), 2924 (s), 2866 (s), 1622 (m)

HRMS (EI): Calculated 194.1671 (M^+) for $C_{13}H_{22}O$, found 194.1674

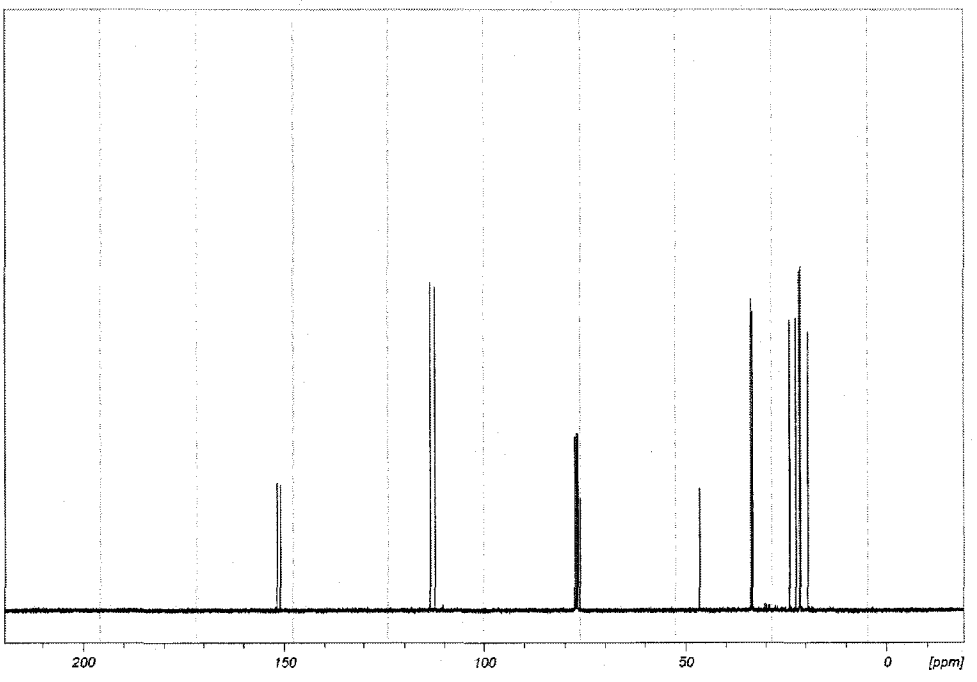


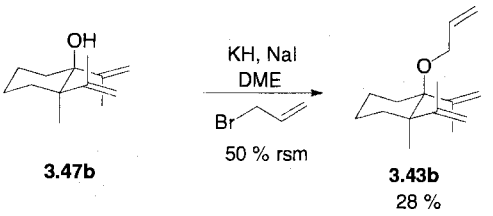
3.47b

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(1R, 2S)-1-(Allyloxy)-2-methyl-1,2-di(prop-1-en-2-yl)cyclohexane (**3.43b**)

NaI (9.4 mg, 0.0627 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 337.2 mg, 2.52 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (10 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.47b** (122.5 mg, 0.630 mmol) in DME (10 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.11 mL, 1.30 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in hexanes gave allyl ether **3.43b** (41.8 mg, 0.178 mmol, 28 %, R_f = 0.80) as a colorless oil. Also recovered was starting material **3.47b** (61.3 mg, 0.315 mmol, 50 %, R_f = 0.15) as a colorless oil.

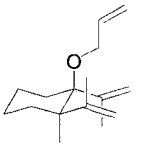
Data for **3.43b**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97-5.87 (m, 1H), 5.30 (dddd, J = 17.3, 1.9, 1.9, 1.9 Hz, 1H), 5.08 (dddd, J = 10.5, 1.6, 1.6, 1.6 Hz, 1H), 5.07-5.05 (m, 1H), 4.87-4.85 (m, 1H), 4.82 (s, 1H), 4.73 (s, 1H), 3.79 (dddd, J_{AB} = 12.7 Hz, J = 5.3, 1.6, 1.6 Hz, 1H), 3.55 (dddd, J_{AB} = 12.7 Hz, J = 4.6, 1.7, 1.7 Hz, 1H), 2.49-2.41 (m, 1H), 1.98 (d, J = 0.9 Hz, 3H), 1.94-1.86 (m, 1H), 1.70 (s, 3H), 1.70-1.65 (m, 1H), 1.58-1.45 (m, 4H), 1.11 (d, J = 0.6 Hz, 3H), 1.09-1.04 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3 (C_4), 147.3 (C_4), 136.1 (CH), 115.6 (CH_2), 114.9 (CH_2), 113.4 (CH_2), 85.2 (C_4), 63.3 (CH_2), 45.7 (C_4), 33.4 (CH_2), 28.1 (CH_2), 24.0 (CH_3), 21.6 (CH_2), 21.6 (CH_3), 21.3 (CH_2), 21.3 (CH_3)

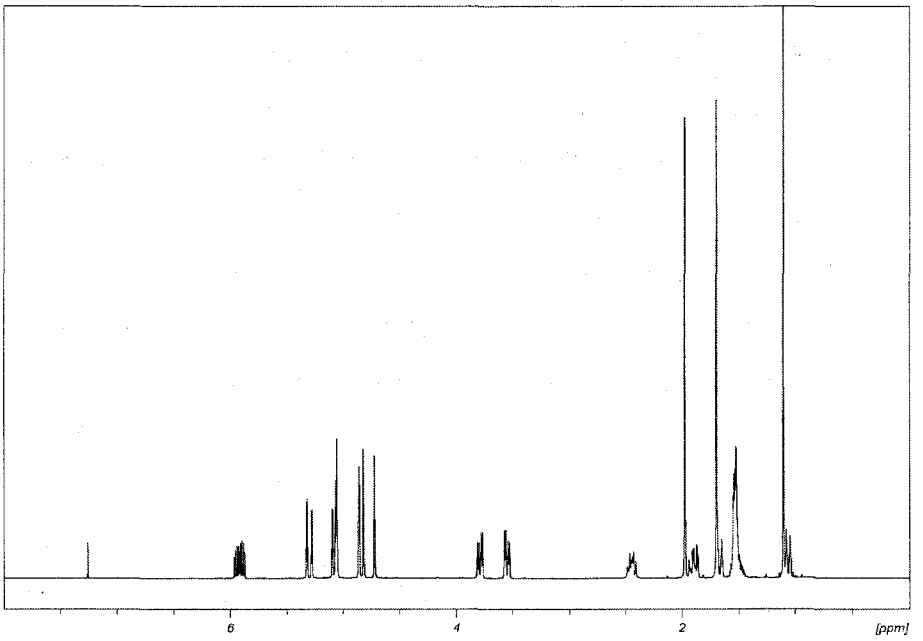
FT-IR (neat, cm^{-1}): 2959 (s), 2928 (s), 1652 (w), 1628 (m)

HRMS (EI): Calculated 234.1984 (M^+) for $C_{16}H_{26}O$, found 234.2044

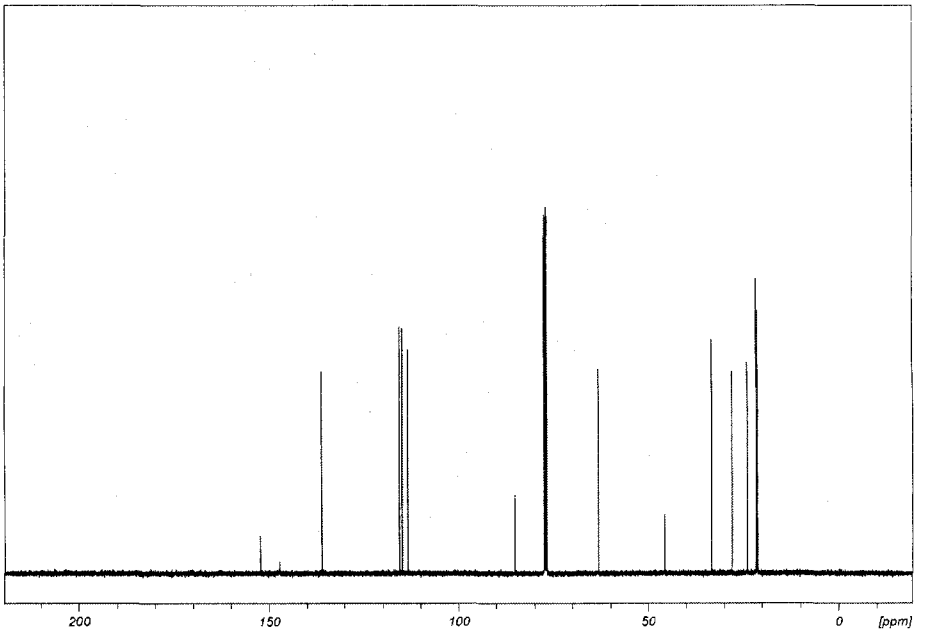


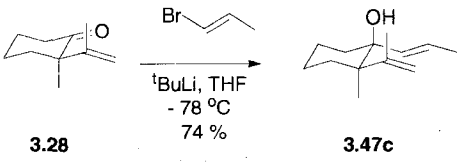
3.43b

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(1R, 2S)-2-Methyl-2-(prop-1-en-2-yl)-1-((E)-prop-1-enyl)cyclohexanol (**3.47c**)

Trans-1-bromopropene (0.34 mL, 3.96 mmol) was dissolved in THF (8 mL), cooled to -78 °C and treated with ^{t}BuLi (1.70 M, 4.66 mL, 7.29 mmol). This mixture was stirred for 0.5 hours whereupon a solution of **3.28** (200.0 mg, 1.31 mmol) in THF (2 mL) was added via cannula. The reaction was stirred for 2 hours at -78 °C whereupon it was quenched with saturated aqueous NH_4Cl. After warming to room temperature the layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes gave **3.47c** (189.4 mg, 0.974 mmol, 74 %, R_f = 0.40) as a colorless oil.

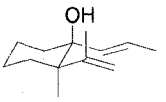
Data for **3.47c**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (dq, J = 15.4, 1.4 Hz, 1H), 5.54 (dq, J = 15.4, 6.2 Hz, 1H), 5.06-5.05 (m, 1H), 4.93 (s, 1H), 2.15 (ddd, J = 12.0, 12.0, 5.9 Hz, 1H), 2.06 (bs, 1H), 1.77 (d, J = 0.9 Hz, 3H), 1.72-1.60 (m, 2H), 1.67 (dd, J = 6.2, 1.4 Hz, 3H), 1.56-1.39 (m, 4H), 1.18 (s, 3H), 1.16-1.11 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3 (C_4), 137.3 (CH), 122.3 (CH), 113.9 (CH_2), 73.6 (C_4), 46.4 (C_4), 33.6 (CH_2), 32.9 (CH_2), 23.8 (CH_3), 21.5 (CH_2), 21.0 (CH_2), 19.5 (CH_3), 17.9 (CH_3)

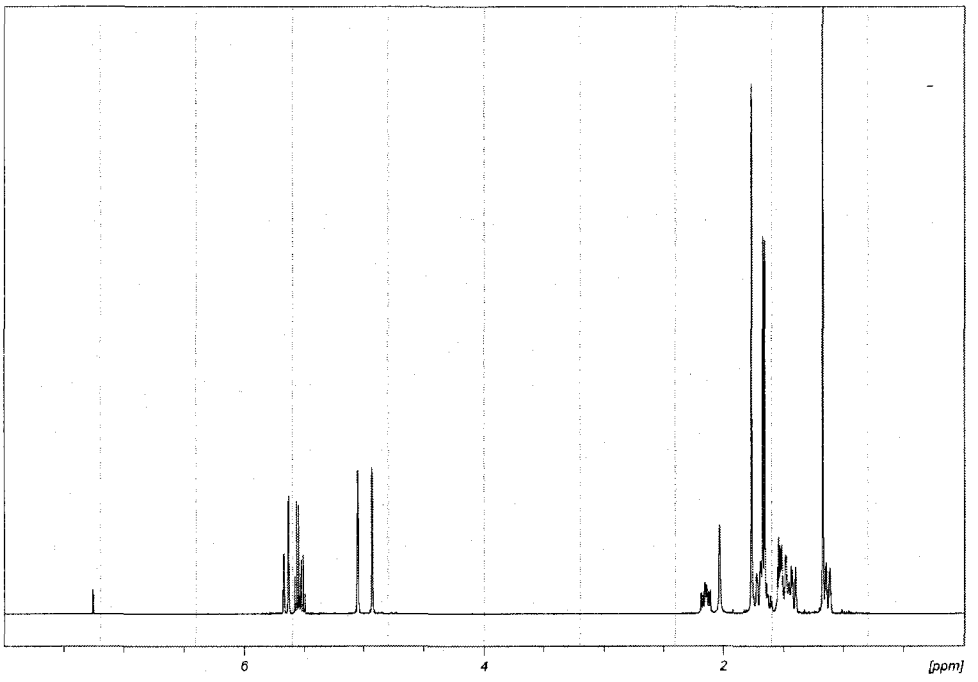
FT-IR (neat, cm^{-1}): 3542 (b), 2921 (s), 2867 (s), 1623 (m)

HRMS (EI): Calculated 194.1671 (M^+) for $C_{13}H_{22}O$, found 194.1665

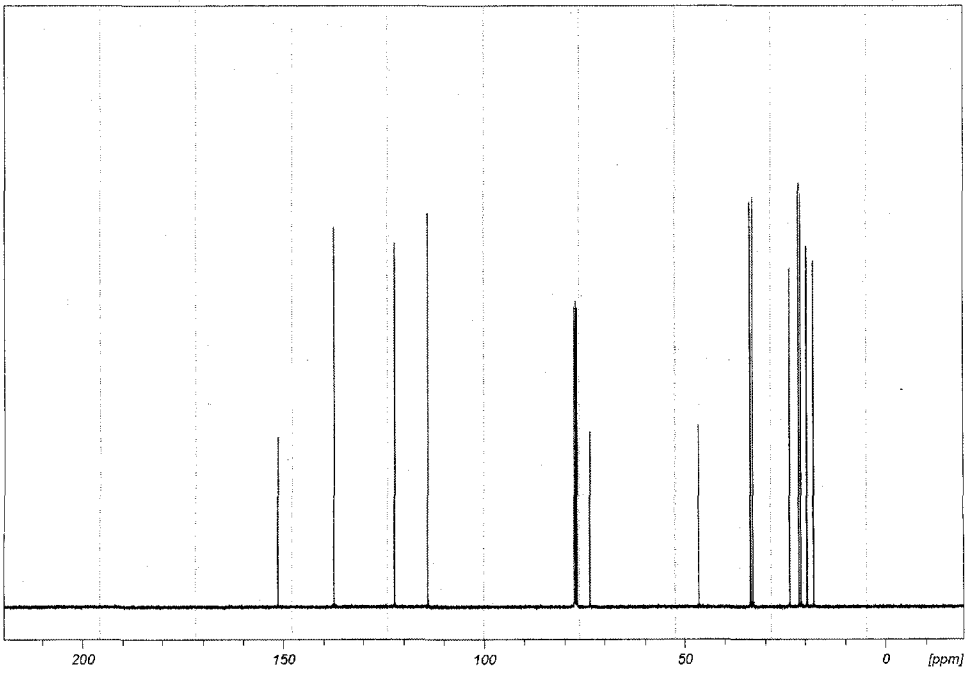


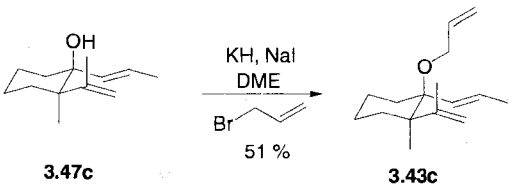
3.47c

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(1R,2S)-1-Allyloxy-2-methyl-2-(prop-1-en-2-yl)-1-((E)-prop-1-enyl)cyclohexane (**3.43c**)

NaI (14.6 mg, 0.0974 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 521.3 mg, 3.90 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (15 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.47c** (189.4 mg, 0.975 mmol) in DME (15 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.16 mL, 1.98 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in hexanes gave allyl ether **3.43c** (116.7 mg, 0.498 mmol, 51 %, R_f = 0.80) as a colorless oil.

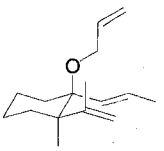
Data for **3.43c**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93-5.88 (m, 1H), 5.51 (dd, J = 16.1, 1.4 Hz, 1H), 5.40 (dq, J = 16.1, 6.1 Hz, 1H), 5.26 (dddd, J = 17.5, 1.9, 1.9, 1.9 Hz, 1H), 5.05 (dddd, J = 10.5, 1.7, 1.7, 1.7 Hz, 1H), 4.97-4.96 (m, 1H), 4.74 (d, J = 1.8 Hz, 1H), 3.73-3.64 (m, 2H), 2.44-2.37 (m, 1H), 1.94 (d, J = 1.0 Hz, 3H), 1.75-1.70 (m, 1H), 1.71 (dd, J = 6.2, 1.4 Hz, 3H), 1.63-1.48 (m, 5H), 1.15-1.11 (m, 1H), 1.02 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7 (C_4), 136.8 (CH), 134.2 (CH), 126.8 (CH), 114.4 (CH_2), 113.1 (CH_2), 80.8 (C_4), 62.6 (CH_2), 45.5 (C_4), 31.8 (CH_2), 26.3 (CH_2), 24.2 (CH_3), 21.4 (CH_2), 21.4 (CH_3), 21.2 (CH_2), 18.2 (CH_3)

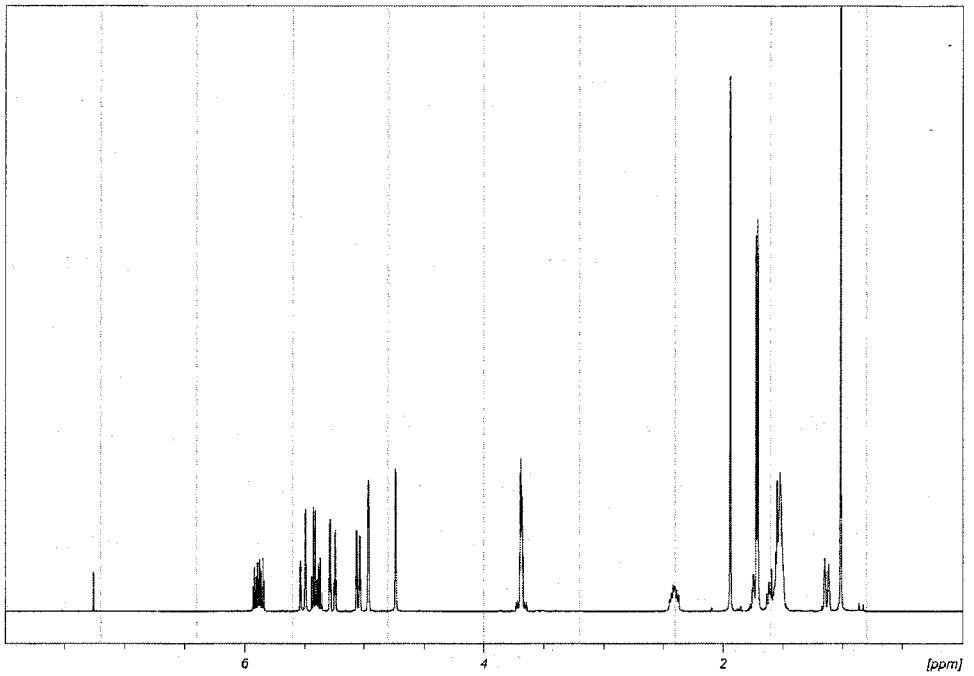
FT-IR (neat, cm^{-1}): 3087 (m), 2987 (s), 2956 (s), 2863 (s), 1648 (m)

HRMS (EI): Calculated 234.1984 (M^+) for $C_{16}H_{26}O$, found 234.1966

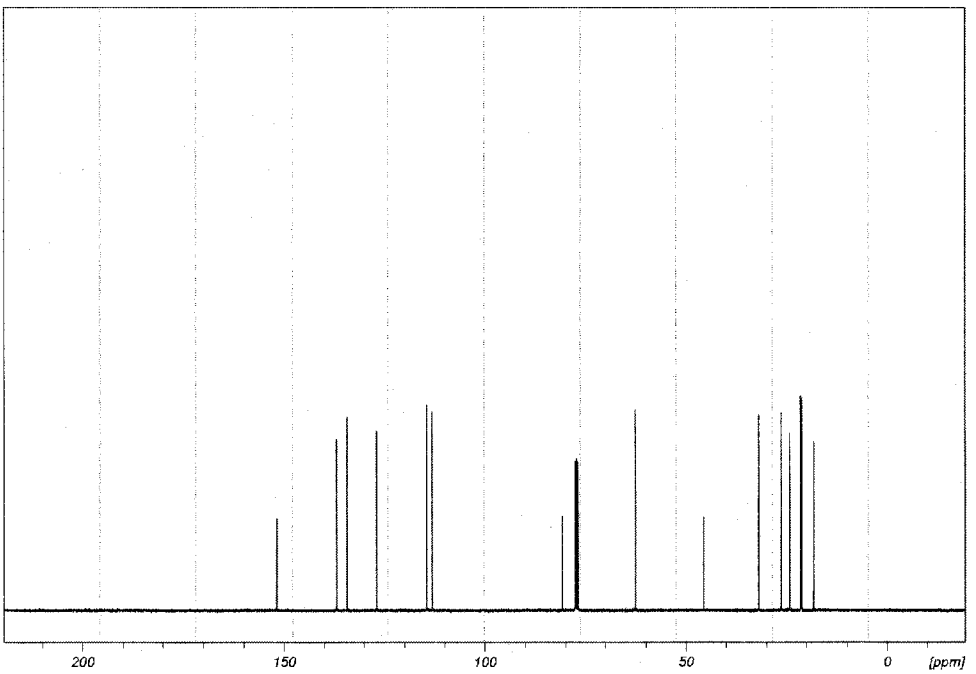


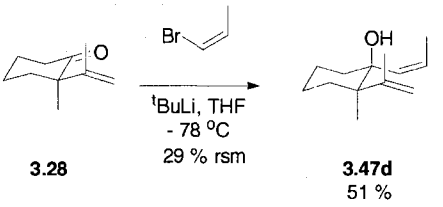
3.43c

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(1R, 2S)-2-Methyl-2-(prop-1-en-2-yl)-1-((Z)-prop-1-enyl)cyclohexanol (**3.47d**)

Cis-1-bromopropene (0.34 mL, 4.00 mmol) was dissolved in THF (8 mL), cooled to -78 °C and treated with ^{t}BuLi (1.70 M, 4.70 mL, 7.99 mmol). This mixture was stirred for 0.5 hours whereupon a solution of **3.28** (200.0 mg, 1.31 mmol) in THF (2 mL) was added via cannula. The reaction was stirred for 2 hours at -78 °C whereupon it was quenched with saturated aqueous NH_4Cl. After warming to room temperature the layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes gave **3.47d** (129.8 mg, 0.668 mmol, 51 %, R_f = 0.40) as a colorless oil. Also recovered starting material **3.28** (58.1 mg, 0.382 mmol, 29 %, R_f = 0.20) as a colorless oil.

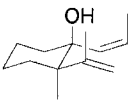
Data for **3.47d**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (dq, J = 12.1, 1.7 Hz, 1H), 5.39 (dq, J = 12.2, 7.0 Hz, 1H), 5.06-5.05 (m, 1H), 4.99 (s, 1H), 2.16-2.08 (m, 2H), 1.88 (d, J = 0.9 Hz, 3H), 1.80 (dd, J = 7.1, 1.7 Hz, 3H), 1.72-1.59 (m, 3H), 1.55-1.50 (m, 2H), 1.48-1.42 (m, 1H), 1.21 (s, 3H), 1.16-1.11 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9 (C_4), 135.4 (CH), 124.5 (CH), 114.0 (CH_2), 76.3 (C_4), 46.7 (C_4), 34.2 (CH_2), 32.9 (CH_2), 23.5 (CH_3), 21.5 (CH_2), 20.8 (CH_2), 19.8 (CH_3), 14.2 (CH_3)

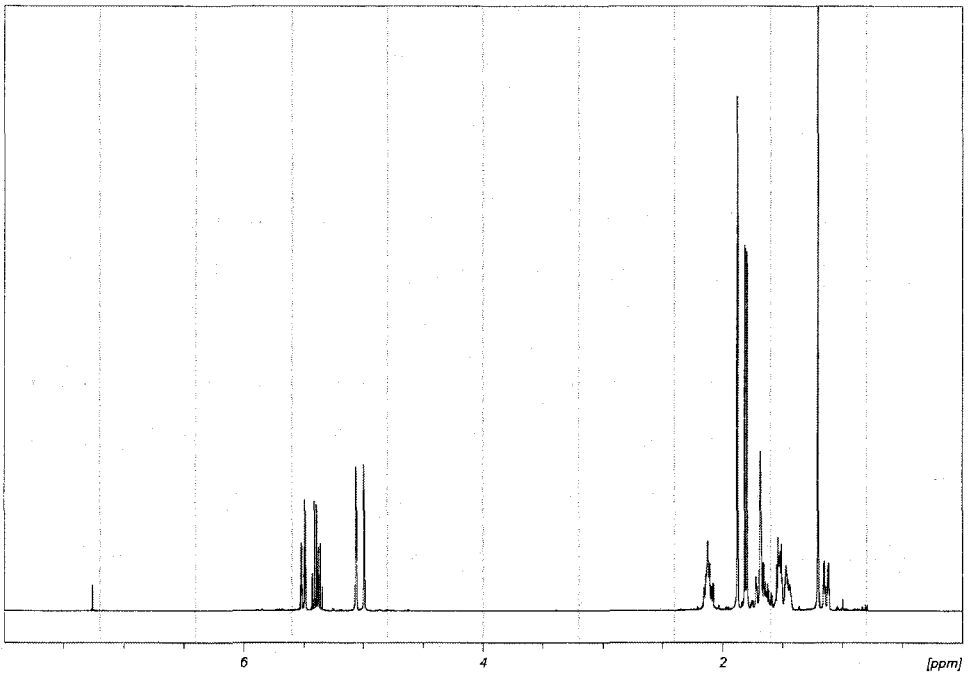
FT-IR (neat, cm^{-1}): 3551 (b), 2928 (s), 2865 (s), 1623 (w)

HRMS (EI): Calculated 194.1671 (M^+) for $C_{13}H_{22}O$, found 194.1667

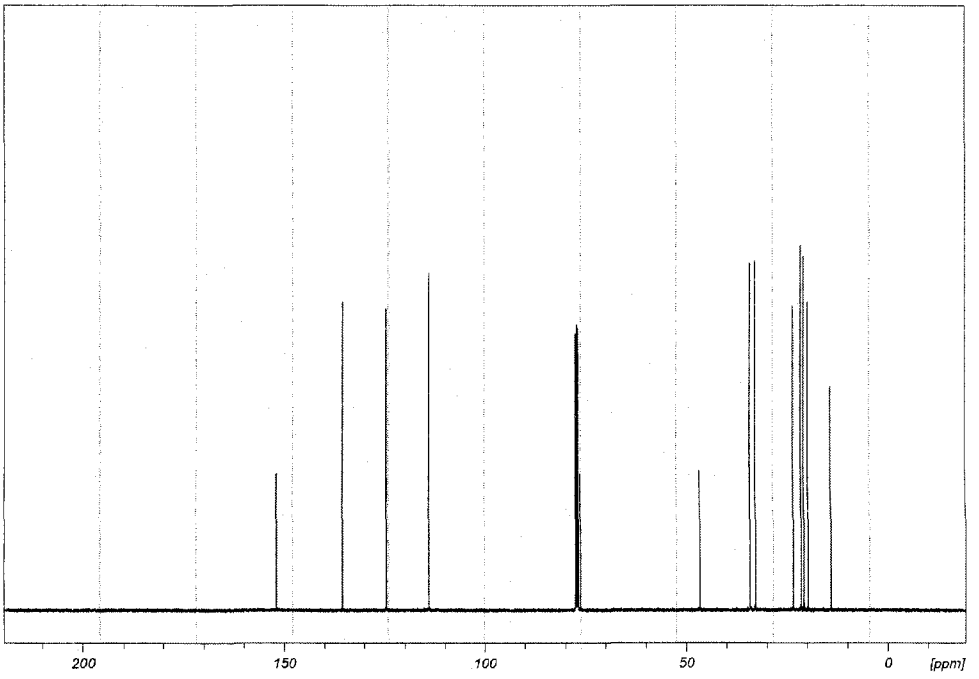


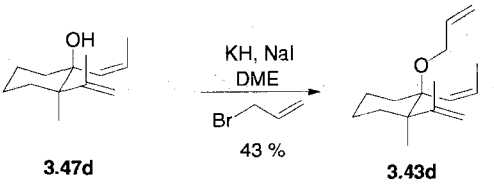
3.47d

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.47d **3.43d**

(±)-(1R,2S)-1-Allyloxy-2-methyl-2-(prop-1-en-2-yl)-1-((Z)-prop-1-enyl)cyclohexane (**3.43d**)

NaI (10.0 mg, 0.0667 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 357.2 mg, 2.67 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (12 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.47d** (129.8 mg, 0.668 mmol) in DME (12 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.11 mL, 1.30 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 25 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in hexanes gave allyl ether **3.43d** (68.0 mg, 0.290 mmol, 43 %, R_f = 0.80) as a colorless oil.

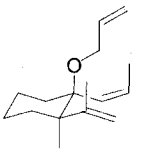
Data for **3.43d**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88-5.79 (m, 1H), 5.47 (dq, J = 12.4, 7.3 Hz, 1H), 5.18 (dddd, J = 17.3, 1.8, 1.8, 1.8 Hz, 1H), 4.97 (dddd, J = 10.5, 1.6, 1.6, 1.6 Hz, 1H), 4.91 (dq, J = 12.4, 1.8 Hz, 1H), 4.81-4.79 (m, 1H), 4.73 (s, 1H), 3.70 (ddd, J_{AB} = 12.7 Hz, J = 1.6, 1.6 Hz, 1H), 3.63 (ddd, J_{AB} = 12.7 Hz, J = 1.7, 1.7 Hz, 1H), 2.35-2.27 (m, 1H), 1.86 (d, J = 0.9 Hz, 3H), 1.78 (ddd, J = 14.8, 3.2, 3.2 Hz, 1H), 1.61-1.53 (m, 1H), 1.56 (dd, J = 7.3, 1.8 Hz, 3H), 1.49-1.43 (m, 2H), 1.39-1.33 (m, 2H), 1.05-1.00 (m, 1H), 1.02 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2 (C_4), 136.6 (CH), 131.3 (CH), 127.7 (CH), 114.7 (CH_2), 113.7 (CH_2), 83.6 (C_4), 62.8 (CH_2), 46.2 (C_4), 32.1 (CH_2), 30.1 (CH_2), 24.2 (CH_3), 21.5 (CH_2), 21.3 (CH_3), 20.9 (CH_2), 15.0 (CH_3)

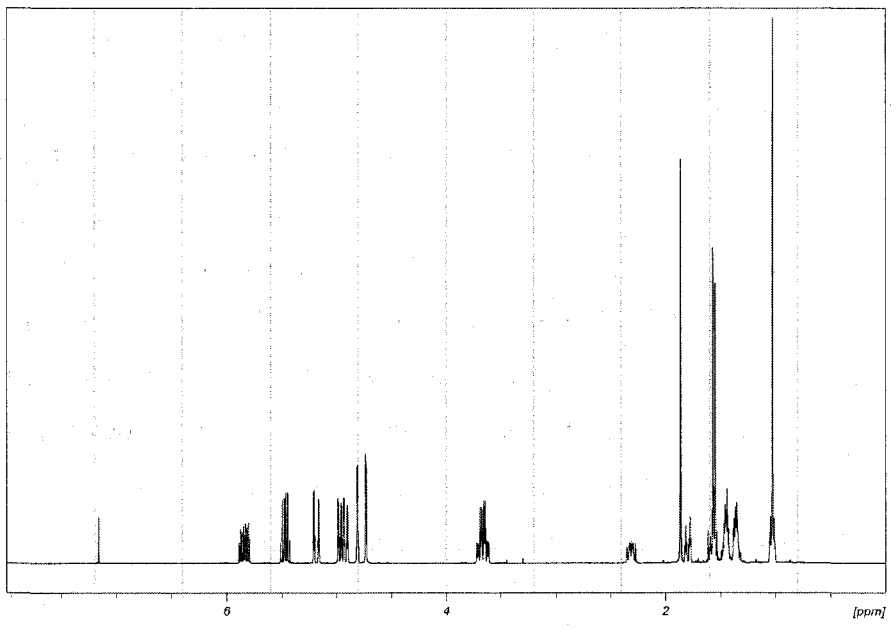
FT-IR (neat, cm^{-1}): 2994 (s), 2960 (s), 2923 (s), 2867 (s), 1627 (w)

HRMS (EI): Calculated 234.1984 (M^+) for $C_{16}H_{26}O$, found 234.1978

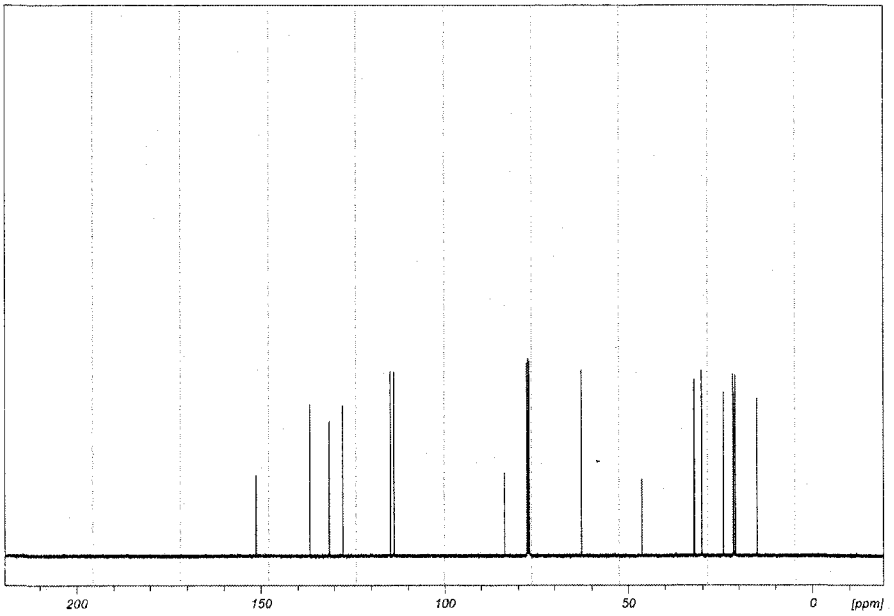


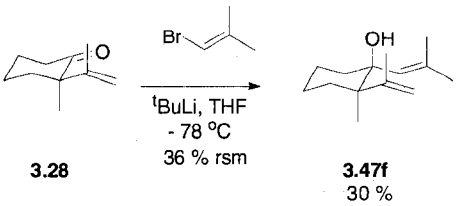
3.43d

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(1R, 2S)-2-Methyl-1-(2-methylprop-1-enyl)-2-(prop-1-en-2-yl)cyclohexanol (**3.47f**)

1-bromo-2-methyl-1-propene (0.27 mL, 2.64 mmol) was dissolved in THF (10 mL), cooled to -78 °C and treated with ^{t}BuLi (1.70 M, 3.10 mL, 5.27 mmol). This mixture was stirred for 0.5 hours giving a clear yellow solution whereupon a solution of **3.28** (200.0 mg, 1.31 mmol) in THF (5 mL) was added via cannula. The reaction was stirred for 3 hour at -78 °C, warmed to room temperature and then stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous NH_4Cl, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes gave **3.47f** (82.1 mg, 0.394 mmol, 30 %, R_f = 0.55) as a colorless oil and returned starting material **3.28** (71.1 mg, 0.467 mmol, 36 %, R_f = 0.45) as a colorless oil.

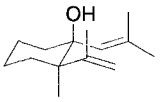
Data for **3.47f**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34-5.32 (m, 1H), 5.05-5.04 (m, 1H), 4.97 (s, 1H), 2.12 (ddd, J = 12.8, 12.8, 6.2 Hz, 1H), 2.02 (bs, 1H), 1.85 (d, J = 0.5 Hz, 3H), 1.80 (d, J = 1.3 Hz, 3H), 1.70-1.60 (m, 3H), 1.68 (d, J = 1.2 Hz, 3H), 1.54-1.42 (m, 3H), 1.20 (s, 3H), 1.16-1.10 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0 (C_4), 132.2 (C_4), 129.5 (CH), 113.9 (CH_2), 75.3 (C_4), 46.8 (C_4), 34.3 (CH_2), 33.0 (CH_2), 28.3 (CH_3), 23.4 (CH_3), 21.6 (CH_2), 21.0 (CH_2), 19.9 (CH_3), 18.8 (CH_3)

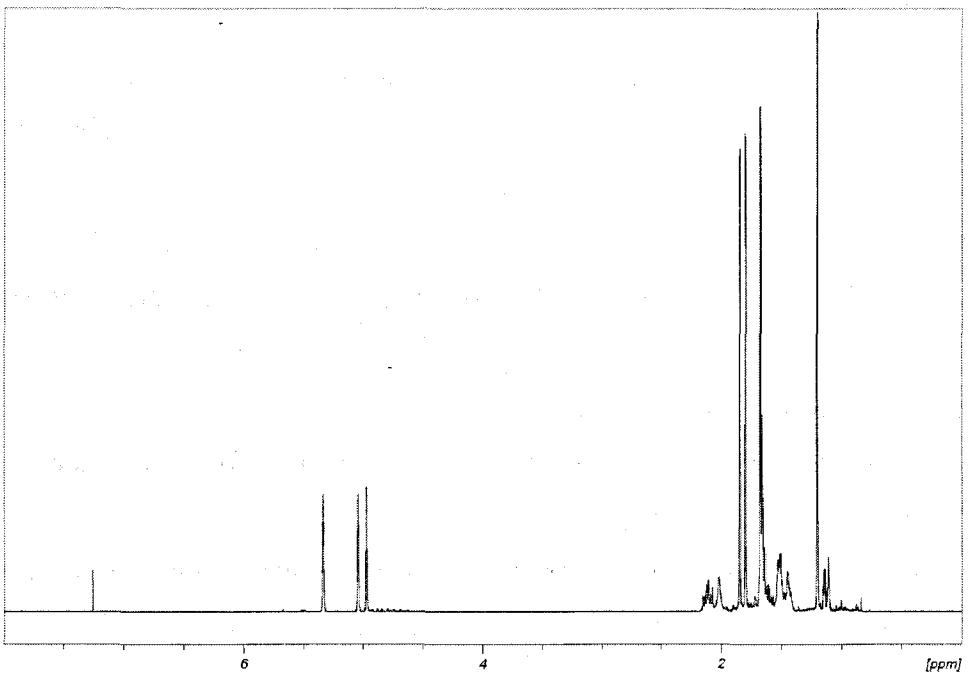
FT-IR (neat, cm^{-1}): 3551 (b), 2926 (s), 2870 (m), 1621 (w)

HRMS (EI): Calculated 208.1827 (M^+) for $C_{14}H_{24}O$, found 208.1828

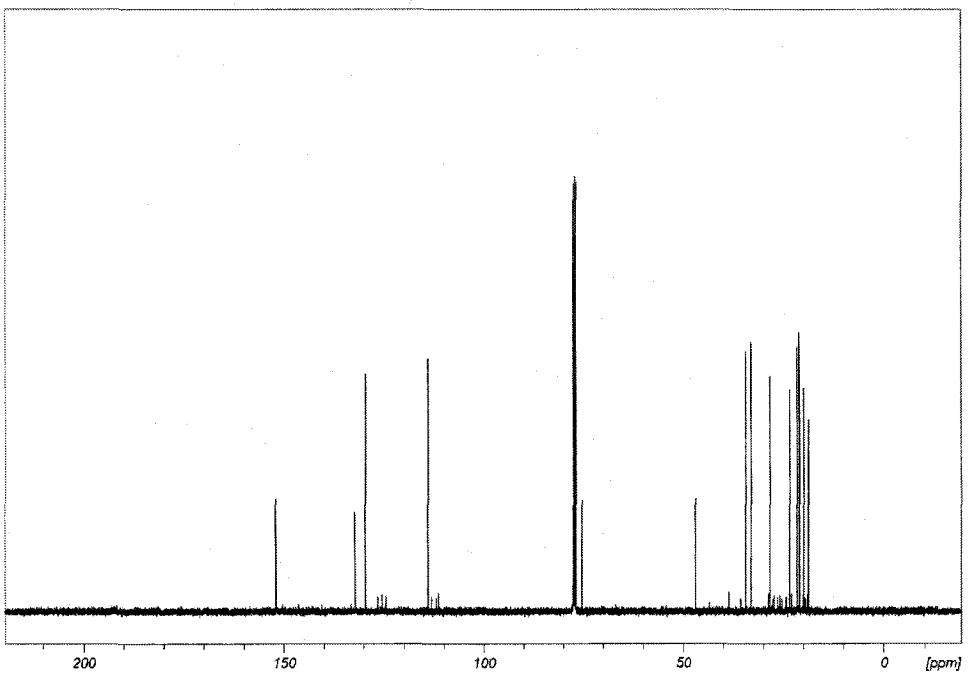


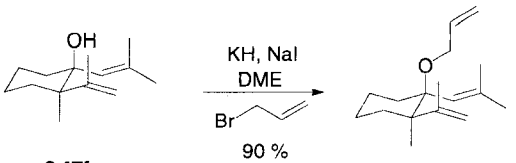
3.47f

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.47f
30 %

3.43f

(±)-(1R,2S)-1-Allyloxy-2-methyl-1-(2-methylprop-1-enyl)-2-(prop-1-en-2-yl)cyclohexane (**3.43f**)

NaI (3.4 mg, 0.0227 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 120.6 mg, 0.902 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (10 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.47f** (47.0 mg, 0.226 mmol) in DME (3 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.04 mL, 0.473 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in hexanes gave allyl ether **3.43f** (50.5 mg, 0.203 mmol, 90 %, R_f = 0.85) as a colorless oil.

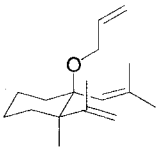
Data for **3.43f**

^{1}H NMR (500 MHz, C_6D_6): δ = 5.97-5.89 (m, 1H), 5.34 (dddd, J = 17.2, 1.9, 1.9, 1.9 Hz, 1H), 5.08-5.04 (m, 2H), 5.01 (s, 1H), 4.83 (s, 1H), 3.69-3.66 (m, 2H), 2.56-2.49 (m, 1H), 2.13 (d, J = 0.9 Hz, 3H), 1.75-1.73 (m, 1H), 1.70 (d, J = 1.3 Hz, 3H), 1.66 (d, J = 1.3 Hz, 3H), 1.51-1.42 (m, 4H), 1.34-1.31 (m, 1H), 1.18-1.15 (m, 1H), 1.13 (d, J = 0.5 Hz, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 151.2 (C_4), 136.7 (CH), 135.3 (C_4), 125.7 (CH), 114.8 (CH_2), 114.3 (CH_2), 83.0 (C_4), 62.8 (CH_2), 46.6 (C_4), 32.5 (CH_2), 30.7 (CH_2), 38.0 (CH_3), 24.4 (CH_3), 21.7 (CH_2), 21.5 (CH_3), 21.1 (CH_2), 19.8 (CH_3)

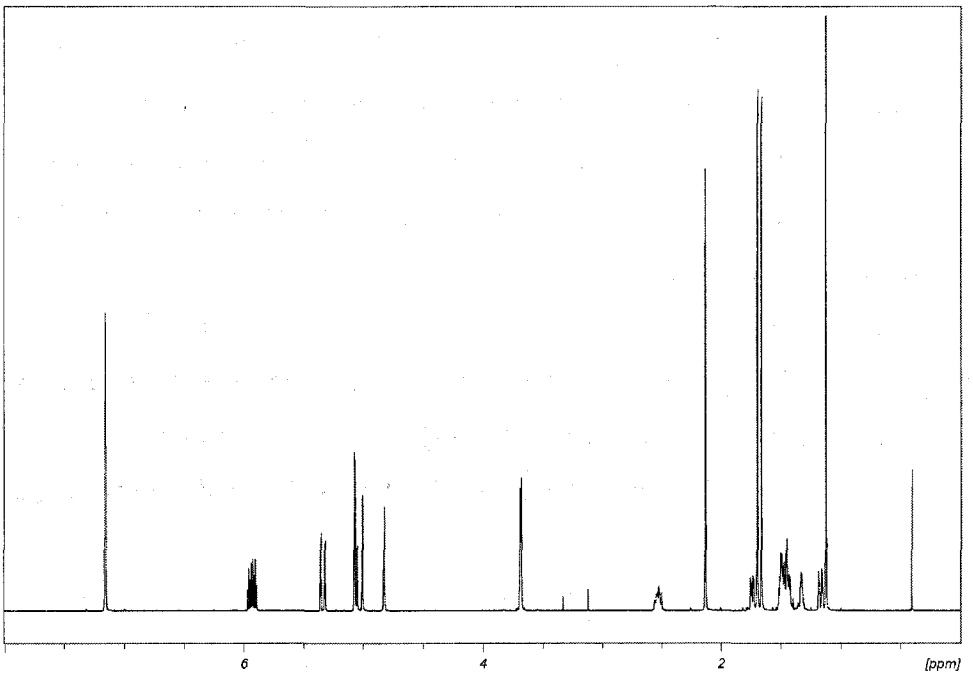
FT-IR (neat, cm^{-1}): 2961 (s), 2928 (s), 2867 (s), 1628 (m)

HRMS (EI): Calculated 248.2140 (M^+) for $C_{17}H_{28}O$, found 248.2157

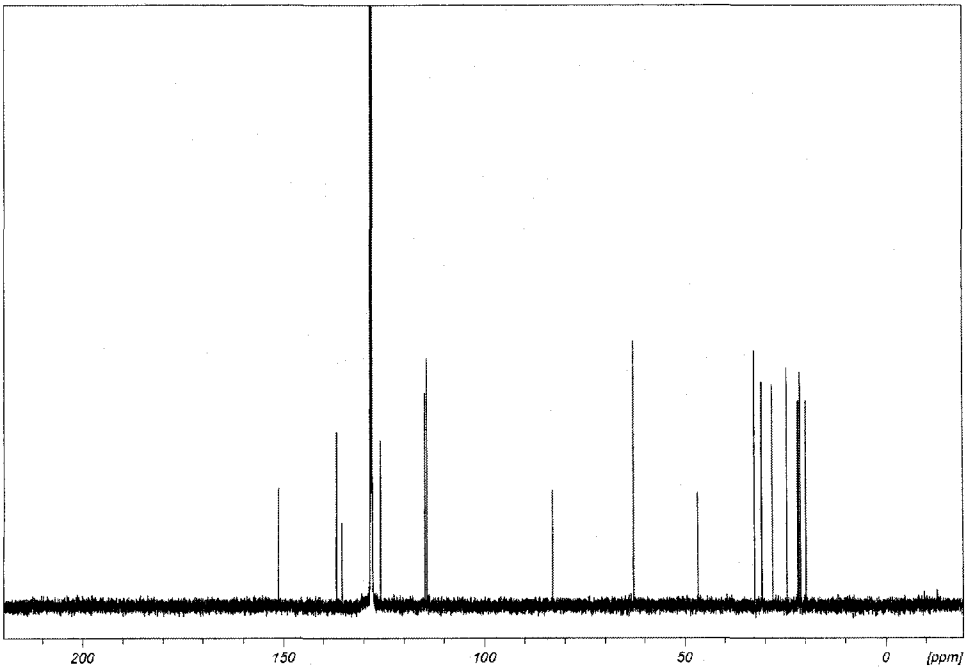


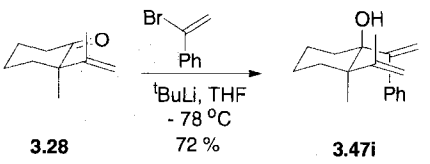
3.43f

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





3.28 **3.47i**

(±)-(1R, 2S)-2-Methyl-1-(1-phenylvinyl)-2-(prop-1-en-2-yl)cyclohexanol (**3.47i**)

A solution of α-bromostyrene (0.51 mL, 3.93 mmol) in THF (6 mL) was cooled to -90 °C and treated with ^{t}BuLi (1.70 M in hexanes, 4.62 mL, 7.85 mmol). The resulting black solution was stirred for 1 hour at -90 °C whereupon a solution of **3.28** (200.0 mg, 1.31 mmol) in THF (6 mL) was added to the reaction mixture. After a further 1 hour of stirring at -90 °C all starting material had been consumed and the reaction was quenched by the addition of water. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 5 % EtOAc/hexanes, affording alcohol **3.47i** (240.9 mg, 0.940 mmol, 72 %, R_f = 0.35) as a colorless oil.

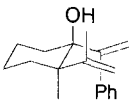
Data for **3.47i**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.22 (m, 5H), 5.28 (d, J = 1.1 Hz, 1H), 5.11 (d, J = 1.1 Hz, 1H), 5.03 (s, 1H), 4.98 (s, 1H), 2.28 (dd, J = 12.6, 6.2 Hz, 1H), 2.23 (d, J = 2.1 Hz, 1H), 2.19-2.11 (m, 1H), 1.87 (s, 3H), 1.82-1.71 (m, 2H), 1.63-1.53 (m, 3H), 1.27 (s, 3H), 1.16-1.11 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (C_4), 151.4 (C_4), 148.2 (C_4), 129.3 (2 × CH), 127.6 (2 × CH), 126.8 (CH), 117.3 (CH_2), 114.4 (CH_2), 76.8 (C_4), 47.1 (C_4), 36.2 (CH_2), 34.6 (CH_2), 24.3 (CH_3), 21.4 (2 × CH_2), 20.4 (CH_3)

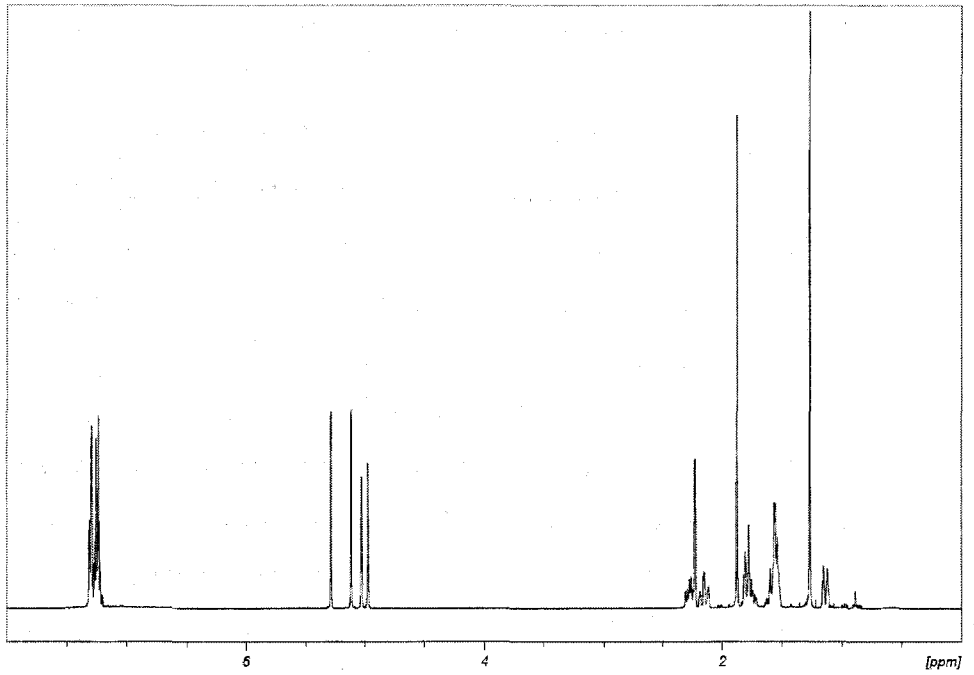
FT-IR (neat, cm^{-1}): 3540 (b), 3087 (w), 2958 (s), 2922 (s), 2856 (s), 1622 (w)

HRMS (EI): Calculated 256.1827 (M^+) for $C_{18}H_{24}O$, found 256.1811

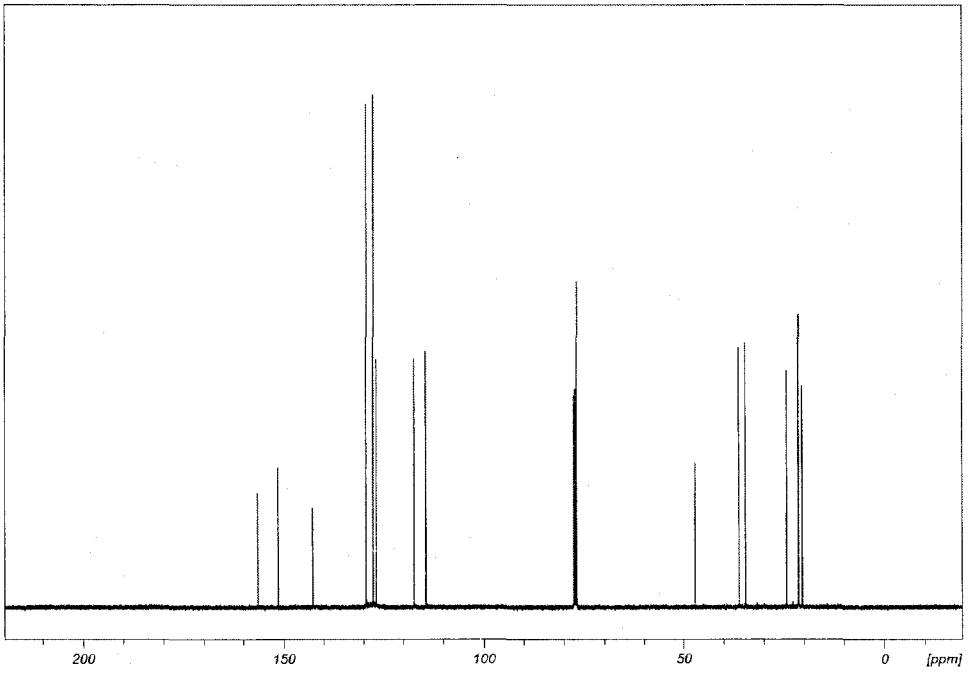


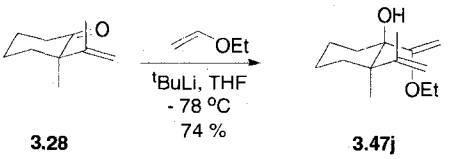
3.47i

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.28 **3.47j**

(±)-(1R, 2S)-1-(1-Ethoxyvinyl)-2-methyl-2-(prop-1-en-2-yl)cyclohexanol (**3.47j**)

A solution of ethyl vinyl ether (1.53 mL, 16.0 mmol) in THF (15 mL) was cooled to -78 °C and treated with ^{t}BuLi (1.70 M in hexanes, 4.71 mL, 8.01 mmol). After stirring at -78 °C for 5 minutes the reaction mixture was warmed to and stirred at 0 °C for 0.5 hours, then it was recooled to -78 °C. To this mixture was added a solution of **3.28** (122.0 mg, 0.801 mmol) in THF (5 mL) and the resulting mixture was stirred for 1 hour at -78 °C whereupon all the starting material had been consumed. The reaction was quenched by the addition of water and warmed to room temperature, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 5 % EtOAc/hexanes basified with Et_3N, affording alcohol **3.47j** (133.1 mg, 0.593 mmol, 74 %, R_f = 0.40) as a colorless oil.

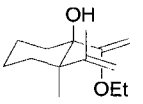
Data for **3.47j**

^{1}H NMR (400 MHz, C_6D_6): δ = 5.00-4.99 (m, 1H), 4.97 (s, 1H), 4.19 (d, J = 2.4 Hz, 1H), 3.83 (d, J = 2.4 Hz, 1H), 3.32-3.23 (m, 2H), 2.86 (bs, 1H), 2.39 (ddd, J = 13.0, 8.8, 8.8 Hz, 1H), 2.05-1.98 (m, 2H), 1.77-1.73 (m, 1H), 1.71 (s, 3H), 1.55-1.46 (m, 3H), 1.24 (d, J = 0.8 Hz, 3H), 1.18-1.12 (m, 1H), 0.98 (t, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 166.9 (C_4), 151.1 (C_4), 113.1 (CH_2), 81.3 (CH_2), 74.8 (C_4), 62.8 (CH_2), 46.5 (C_4), 34.2 (CH_2), 32.5 (CH_2), 23.3 (CH_3), 21.8 (CH_2), 21.2 (CH_2), 20.0 (CH_3), 14.3 (CH_3)

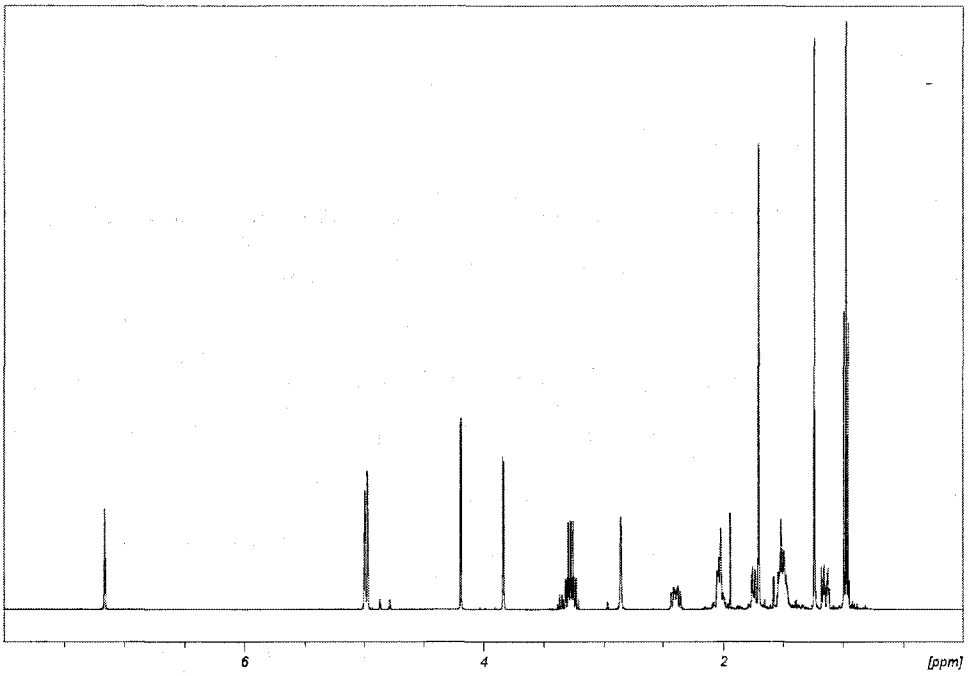
FT-IR (neat, cm^{-1}): 3569 (b), 3089 (w), 2959 (s), 2929 (s), 2867 (s)

HRMS (EI): Calculated 224.1776 (M^+) for $C_{14}H_{24}O_2$, found 224.1770

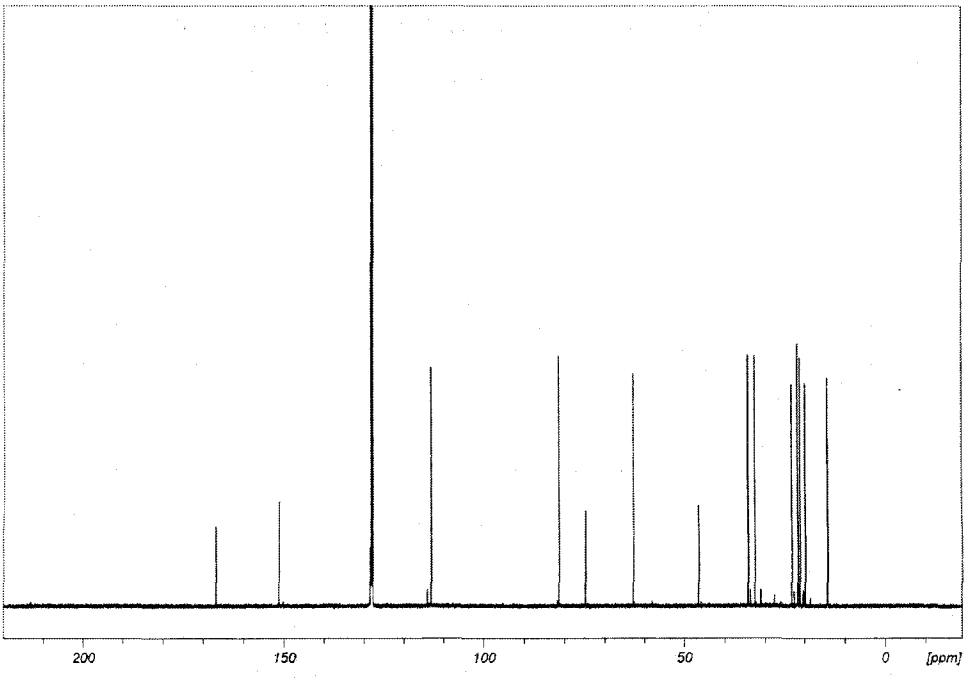


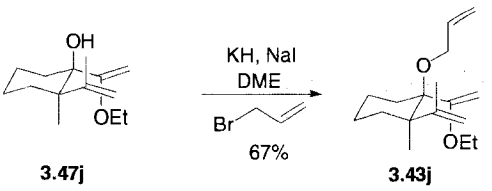
3.47j

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



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





3.47j **3.43j**

(±)-(1R,2S)-1-(Allyloxy)-1-(1-ethoxyvinyl)-2-methyl-2-(prop-1-en-2-yl)cyclohexane (**3.43j**)

NaI (8.9 mg, 0.0593 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 317.3 mg, 2.37 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (20 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.47j** (133.1 mg, 0.593 mmol) in DME (5 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.10 mL, 1.18 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in 1 % EtOAc/hexanes basified with Et_3N gave allyl ether **3.43j** (105.0 mg, 0.397 mmol, 67 %, R_f = 0.40) as a colorless oil.

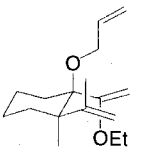
Data for **3.43j**

^{1}H NMR (500 MHz, C_6D_6): δ = 5.96-5.89 (m, 1H), 5.38 (dddd, J = 17.1, 1.7, 1.7, 1.7 Hz, 1H), 5.12 (s, 1H), 5.07 (dddd, J = 10.5, 1.7, 1.7, 1.7 Hz, 1H), 5.00 (d, J = 1.7 Hz, 1H), 4.18 (d, J = 2.0 Hz, 1H), 4.04 (d, J = 2.0Hz, 1H), 3.88 (dddd, J_{AB} = 12.7 Hz, J = 4.6, 1.7, 1.7 Hz, 1H), 3.71 (dddd, J_{AB} = 12.7 Hz, J = 5.4, 1.5, 1.5 Hz, 1H), 3.33 (qd, J = 6.8, 1.2 Hz, 2H), 2.58 (ddd, J = 12.7, 12.7, 5.6 Hz, 1H), 2.16 (d, J = 1.0 Hz, 3H), 2.04-1.98 (m, 1H), 1.70-1.66 (m, 1H), 1.56-1.41 (m, 4H), 1.29-1.20 (m, 1H), 1.21 (s, 3H), 1.06 (t, J = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 161.5 (C_4), 151.0 (C_4), 136.4 (CH), 114.9 (CH_2), 113.2 (CH_2), 84.4 (CH_2), 84.2 (C_4), 63.4 (CH_2), 62.4 (CH_2), 46.4 (C_4), 33.7 (CH_2), 26.2 (CH_2), 24.5 (CH_3), 21.7 (CH_2), 21.4 (CH_3), 21.3 (CH_2), 14.5 (CH_3)

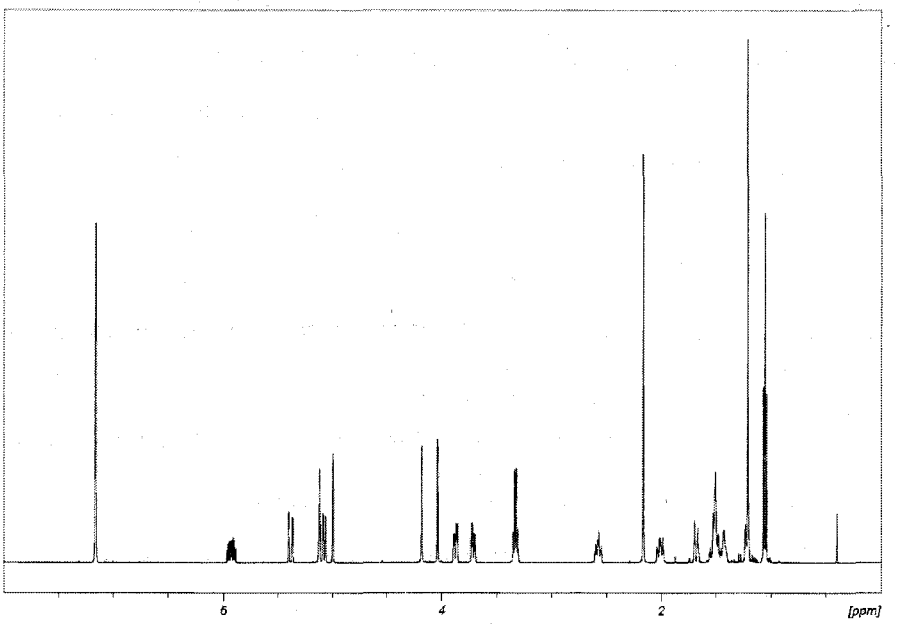
FT-IR (neat, cm^{-1}): 3097 (w), 2984 (m), 2928 (s), 1622 (m)

HRMS (EI): Calculated 264.2089 (M^+) for $C_{17}H_{28}O_2$, found 264.2080

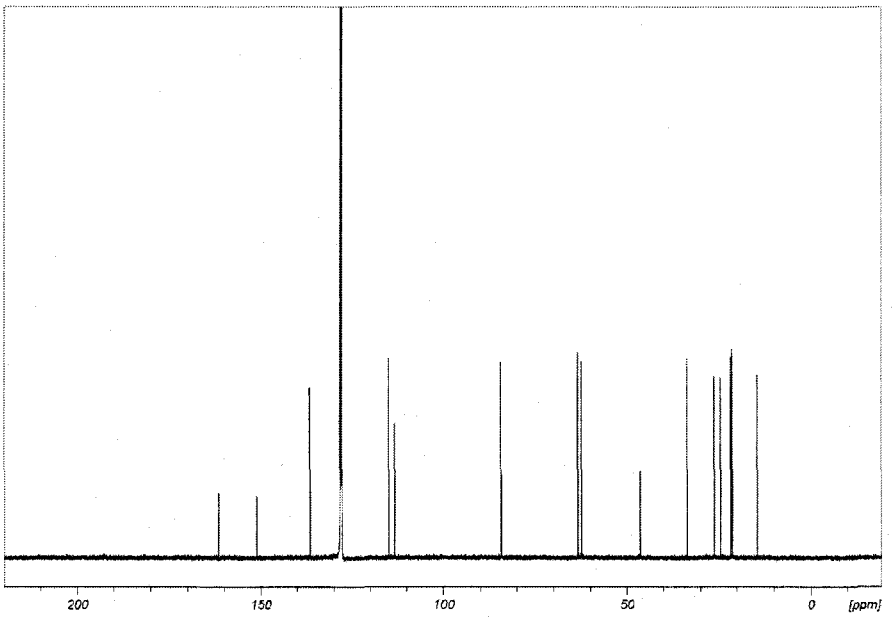


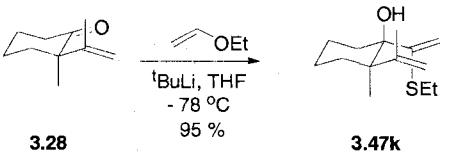
3.43j

^{1}H NMR (500 MHz, C_6D_6)



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





3.28 **3.47k**

(±)-(1R, 2S)-1-(1-(Ethylthio)vinyl)-2-methyl-2-(prop-1-en-2-yl)cyclohexanol (**3.47k**)

A solution of ethyl vinyl sulfide (1.61 mL, 15.9 mmol) in THF (15 mL) was cooled to -78 °C and treated with ^{t}BuLi (1.70 M in hexanes, 4.66 mL, 7.92 mmol). After stirring at -78 °C for 5 minutes the reaction mixture was warmed to and stirred at 0 °C for 0.5 hours, then it was recooled to -78 °C. To this mixture was added a solution of **3.28** (120.6 mg, 0.792 mmol) in THF (5 mL) and the resulting mixture was stirred for 1 hour at -78 °C whereupon all the starting material had been consumed. The reaction was quenched by the addition of water and warmed to room temperature, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 5 % EtOAc/hexanes basified with Et_3N, affording alcohol **3.47k** (180.7 mg, 0.752 mmol, 95 %, $R_f = 0.30$) as a yellow oil.

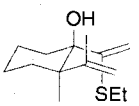
Data for **3.47k**

^{1}H NMR (400 MHz, C_6D_6): δ = 5.14 (d, J = 0.6 Hz, 1H), 5.05-5.03 (m, 1H), 4.94 (s, 1H), 4.80 (s, 1H), 2.88 (bs, 1H), 2.38-2.25 (m, 3H), 2.05-1.90 (m, 2H), 1.85 (d, J = 0.9 Hz, 3H), 1.74-1.70 (m, 1H), 1.49-1.40 (m, 3H), 1.22 (s, 3H), 1.11-1.04 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 154.2 (C_4), 151.1 (C_4), 114.2 (CH_2), 108.9 (CH_2), 77.4 (C_4), 46.9 (C_4), 34.7 (CH_2), 34.2 (CH_2), 27.8 (CH_2), 24.0 (CH_3), 21.7 (2 × CH_2), 20.2 (CH_3), 13.1 (CH_3)

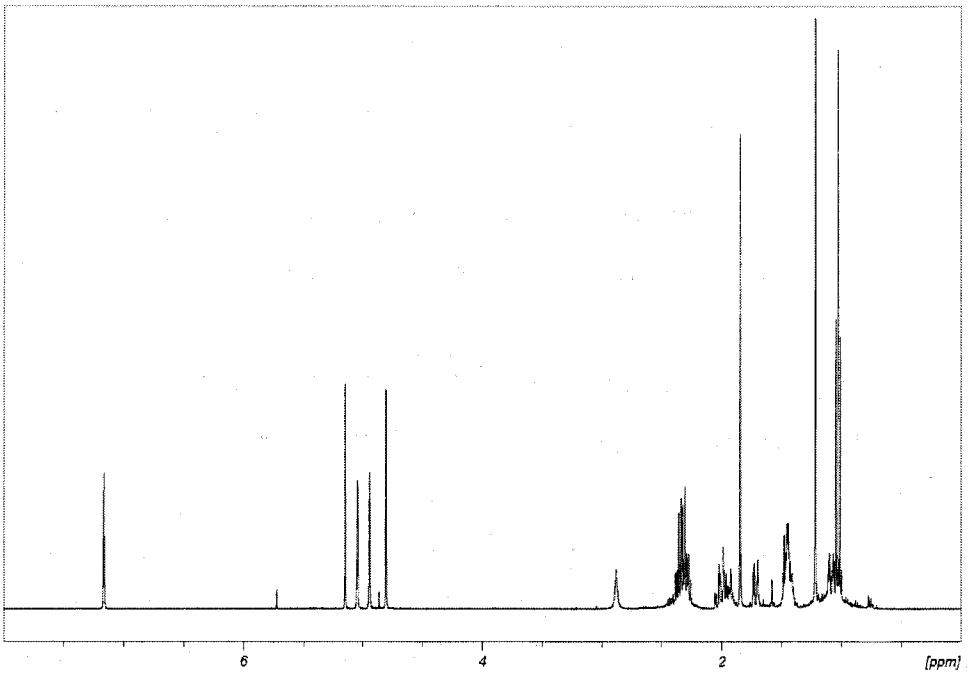
FT-IR (neat, cm^{-1}): 3516 (b), 2961 (s), 2926 (s), 2867 (s), 1622 (w)

HRMS (EI): Calculated 240.1548 (M^+) for $C_{14}H_{24}OS$, found 240.1555

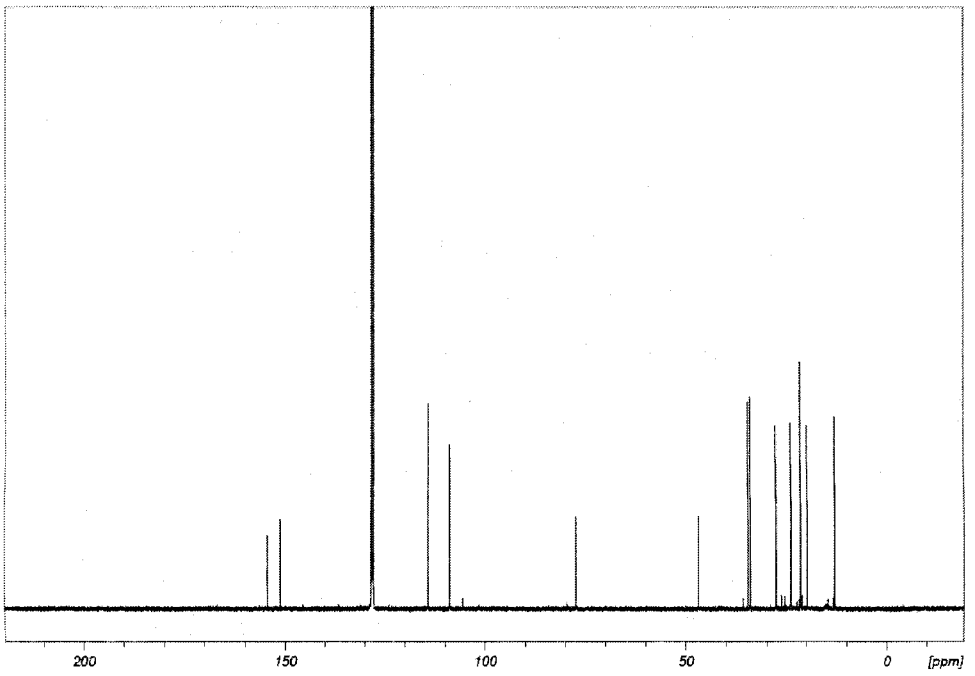


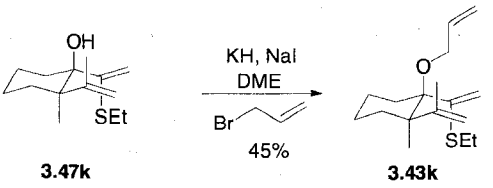
3.47k

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



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





3.47k **3.43k**

(±)-(1R, 2S)-(1-(1-(Allyloxy)-2-methyl-2-(prop-1-en-2-yl)cyclohexyl)vinyl)(ethyl)sulfane (**3.43k**)

NaI (11.3 mg, 0.0754 mmol) was placed in a flask and flame dried. To this flask was added KH (30 % in oil, 402.4 mg, 3.01 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. The solids were suspended in DME (20 mL) and this suspension was cooled to 0 °C after which was added a solution of **3.47k** (180.7 mg, 0.752 mmol) in DME (5 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.13 mL, 1.54 mmol). This final mixture was stirred at 0 °C for 3 hours then for 15 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in 2 % EtOAc/hexanes basified with Et_3N gave allyl ether **3.43k** (94.7 mg, 0.338 mmol, 45 %, Rf = 0.50) as a yellow oil.

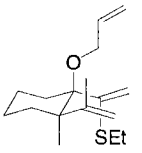
Data for **3.43k**

^{1}H NMR (400 MHz, C_6D_6): δ = 5.98-5.88 (m, 1H), 5.35 (dddd, J = 17.3, 1.9, 1.9, 1.9 Hz, 1H), 5.22 (s, 1H), 5.16 (dd, J = 1.8, 1.8 Hz, 1H), 5.09-5.05 (m, 2H), 4.94 (s, 1H), 3.87 (dddd, J_{AB} = 12.4 Hz, J = 5.6, 1.7, 1.7 Hz, 1H), 3.67 (dddd, J_{AB} = 12.4 Hz, J = 5.5, 1.5, 1.5 Hz, 1H), 2.55 (ddd, J = 17.7, 17.7, 5.8 Hz, 1H), 2.41-2.33 (m, 2H), 2.15 (d, J = 0.9 Hz, 3H), 2.07-1.99 (m, 1H), 1.81-1.78 (m, 1H), 1.54-1.36 (m, 4H), 1.30 (s, 3H), 1.21-1.17 (m, 1H), 1.01 (d, J = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 150.0 (C_4), 146.4 (C_4), 136.1 (CH), 115.2 (CH_2), 115.0 (CH_2), 109.0 (CH_2), 85.7 (C_4), 63.3 (CH_2), 47.1 (C_4), 34.1 (CH_2), 28.0 (CH_2), 26.4 (CH_2), 24.6 (CH_3), 21.9 (CH_3), 21.7 (CH_2), 21.5 (CH_2), 12.9 (CH_3)

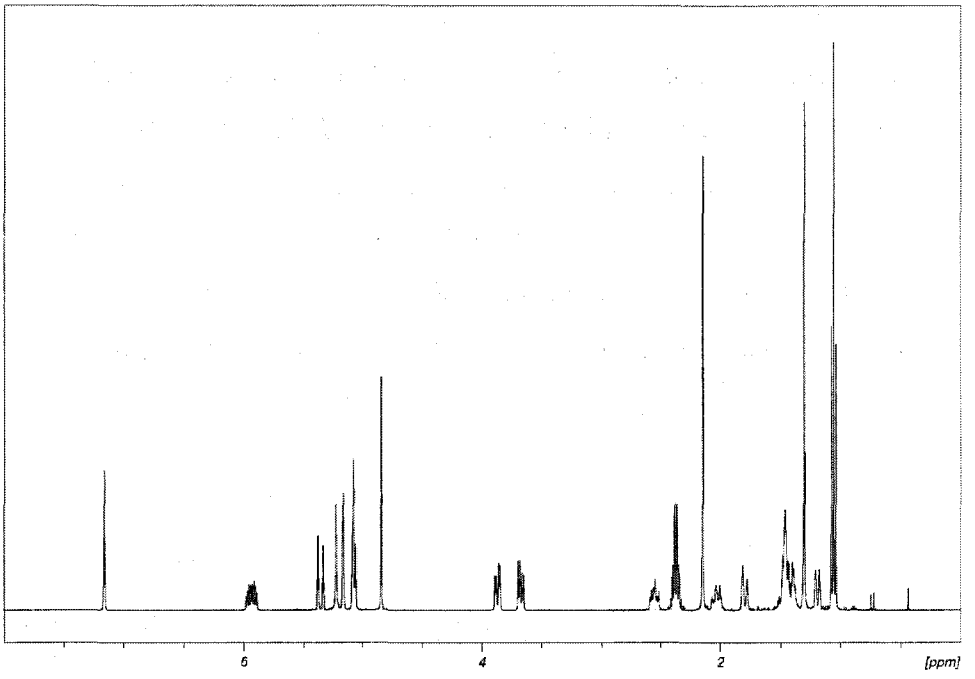
FT-IR (neat, cm^{-1}): 3094 (m), 2963 (s), 2928 (s), 1626 (w)

HRMS (EI): Calculated 280.1861 (M^+) for $C_{17}H_{28}OS$, found 280.1846

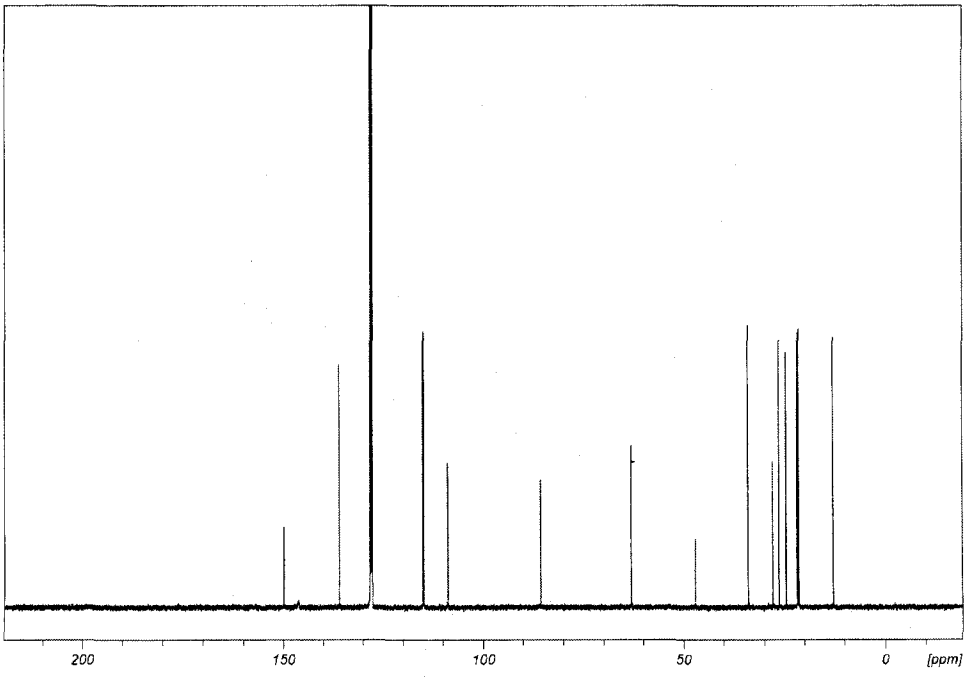


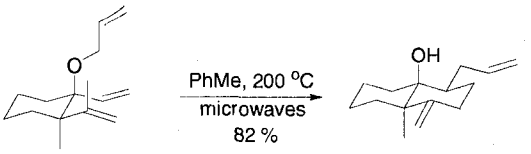
3.43k

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



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





3.43a **3.44a**

(±)-(4R, 4aS, 8aR)-4-Allyl-decahydro-8a-methyl-1-methylenenapthalen-4a-ol (**3.44a**)

A sample of **3.43a** (5.6 mg, 0.0254 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a brown oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording **3.44a** (4.6 mg, 0.0209 mmol, 82 %, $R_f = 0.60$) as a colorless oil.

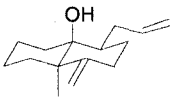
Data for **3.44a**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84-5.71 (m, 1H), 5.03-4.94 (m, 2H), 4.91 (dd, J = 1.8, 1.8 Hz, 1H), 4.73 (dd, J = 1.4, 1.4 Hz, 1H), 2.47 (ddddd, J = 14.1, 14.1, 5.1, 1.7, 1.7 Hz, 1H), 2.37-2.30 (m, 1H), 2.15 (ddd, J = 13.9, 5.6, 1.8 Hz, 1H), 1.91-1.83 (m, 1H), 1.81-1.73 (m, 4H), 1.69-1.51 (m, 6H), 1.41 (dd, J = 13.4, 4.4 Hz, 1H), 1.31-1.26 (m, 1H), 1.19 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6 (C_4), 138.6 (CH), 115.6 (CH_2), 109.6 (CH_2), 75.8 (C_4), 44.4 (C_4), 39.8 (CH), 34.1 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 21.4 (CH_3), 21.1 (CH_2), 21.0 (CH_2)

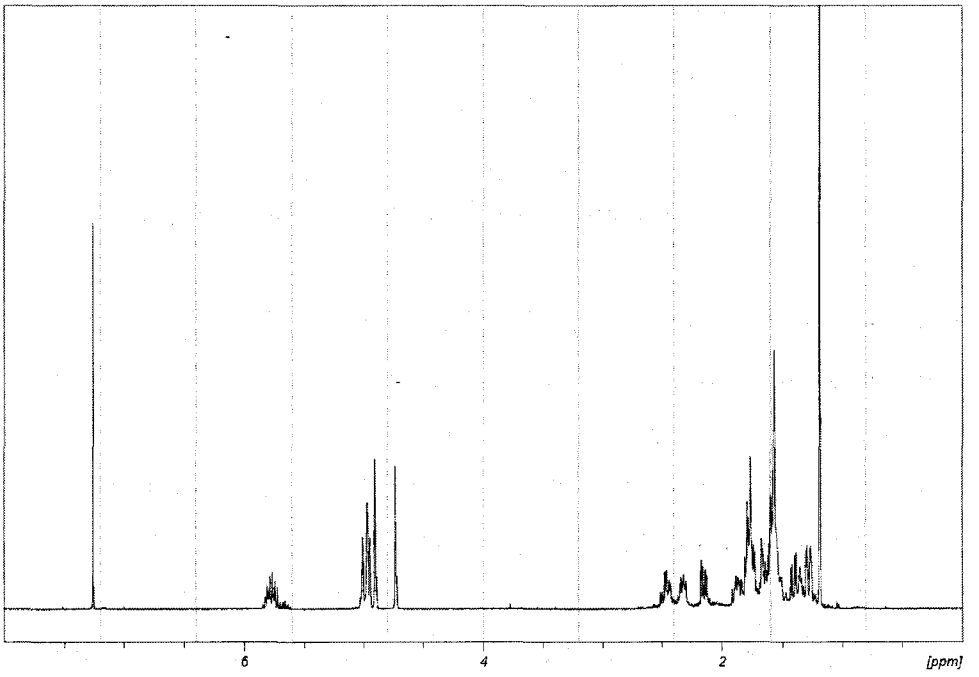
FT-IR (neat, cm^{-1}): 3573 (b), 3075 (w), 2979 (m), 2935 (s), 1637 (m)

HRMS (EI): Calculated 220.1827 (M^+) for $C_{15}H_{24}O$, found 220.1812

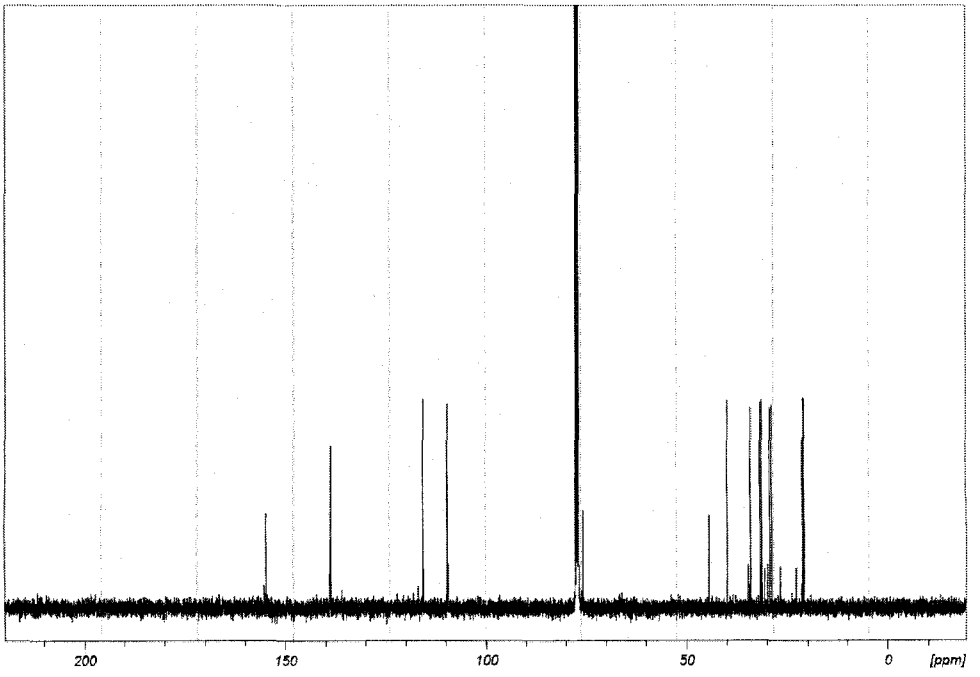


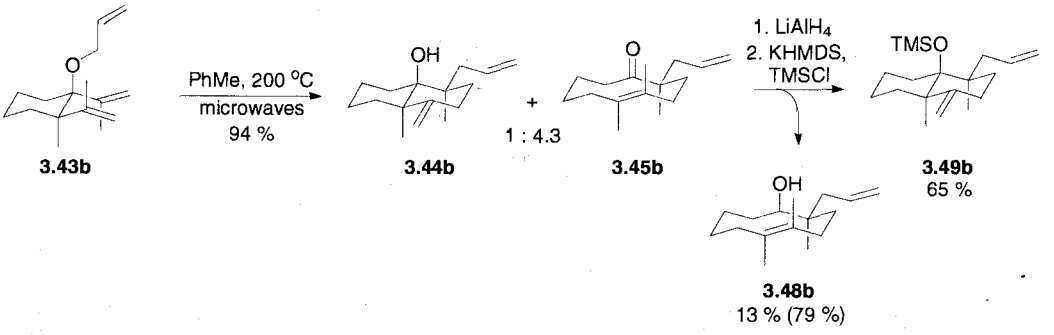
3.44a

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

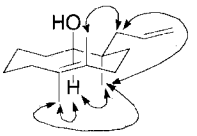




(±)-(E, 1S, 2R)-2-Allyl-2,5,6-trimethylcyclodec-5-enol (**3.48b**)

A sample of **3.43b** (41.8 mg, 0.178 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording an inseparable 1:4.3 mixture of tertiary alcohol **3.44b** and ketone **3.45b** (39.5 mg, 0.169 mmol, 94 %, $R_f = 0.60$) as a colorless oil.

The mixture of **3.44b** and **3.45b** (39.5 mg, 0.169 mmol) was dissolved in THF (5 mL) and it was treated with $LiAlH_4$ (25.6 mg, 0.675 mmol). The resulting gray mixture was heated at reflux for 16 hours after which it was cooled to room temperature and quenched by the careful addition of an aqueous 1.0 M solution of sodium tartrate. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 20 % EtOAc/hexanes affording secondary alcohol **3.48b** (25.9 mg, 0.110 mmol, 65 %, $R_f = 0.60$) as a colorless oil. Also recovered was an inseparable mixture of unreacted ketone **3.44b** and tertiary alcohol **3.45b** (5.3 mg, 0.0226 mmol, 13 %, $R_f = 0.95$) as a colorless oil.



NOESY correlations

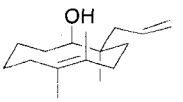
Data for **3.48b**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93-5.83 (m, 1H), 5.04-4.98 (m, 2H), 3.65 (dd, J = 10.0, 4.8 Hz, 1H), 2.64 (dd, J = 13.1, 13.1 Hz, 1H), 2.55-2.48 (m, 1H), 2.22 (dd, J = 13.6, 7.8 Hz, 1H), 1.85-1.80 (m, 2H), 1.83 (s, 3H), 1.77 (s, 3H), 1.72-1.56 (m, 7H), 1.35 (ddd, J = 14.8, 7.2, 1.3 Hz, 1H), 1.29-1.24 (m, 1H), 1.13-1.11 (m, 1H), 1.09 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6 (CH), 130.1 (C_4), 129.7 (C_4), 116.8 (CH_2), 76.2 (CH), 42.9 (C_4), 40.8 (CH_2), 35.9 (CH_2), 34.3 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 25.5 (CH_2), 23.5 (CH_2), 23.0 (CH_3), 21.7 (CH_3), 19.8 (CH_3)

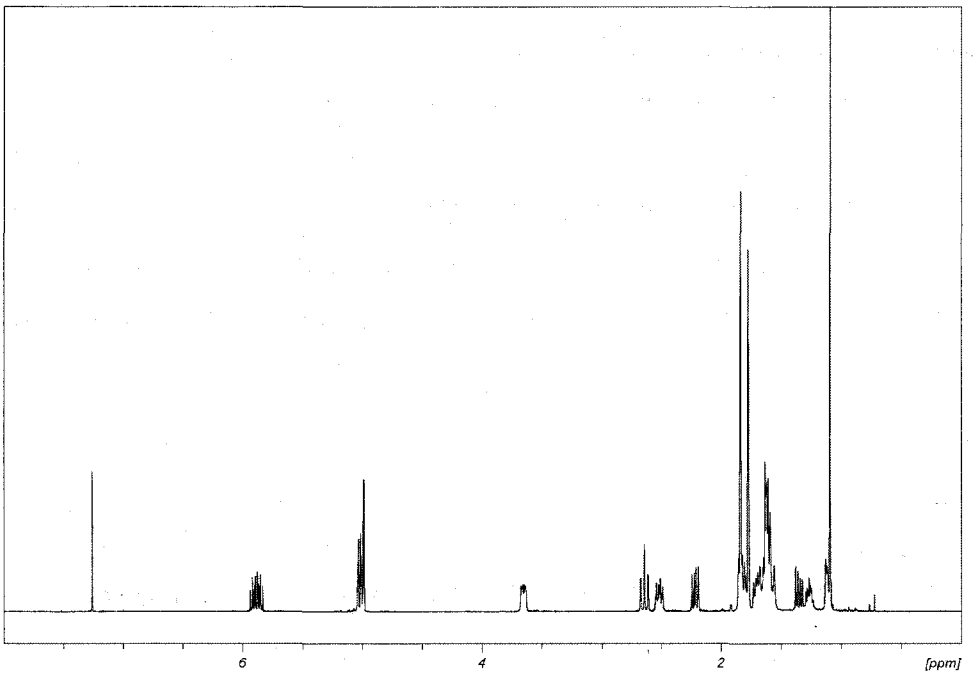
FT-IR (neat, cm^{-1}): 3391 (b), 2959 (w), 2919 (s), 1636 (w)

HRMS (EI): Calculated 236.2140 (M^+) for $C_{16}H_{28}O$, found 236.2154

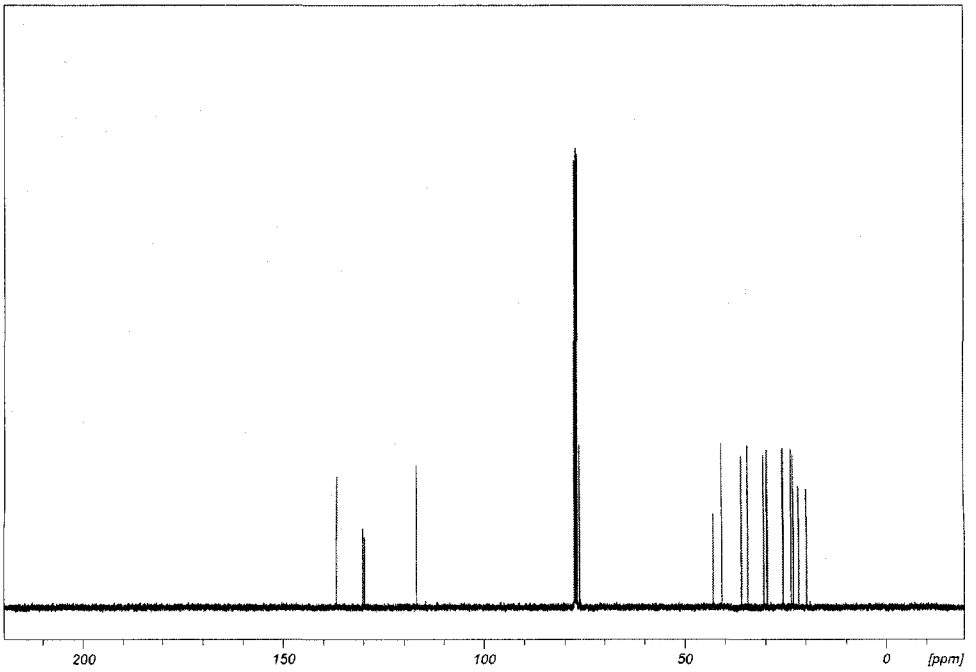


3.48b

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



(±)-((1R,4aR,8aS)-1-Allyl-decahydro-1,4a-dimethyl-4-methylenenapthalen-8a-yloxy)trimethylsilane (**3.49b**)

The recovered mixture of ketone **3.44b** and tertiary alcohol **3.45b** (5.3 mg, 0.0226 mmol) was dissolved in THF (3 mL) and treated with solid KHMDS (18.0 mg, 0.0902 mmol) and TMSCl (0.01 mL, 0.0788 mmol). The reaction was stirred at room temperature for 0.5 h whereupon the reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in hexanes, affording silyl ether **3.49b** (5.5 mg, 0.0179 mmol, 79 %, $R_f = 0.70$) as a colorless oil.

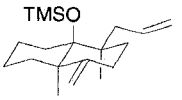
Data for **3.49b**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84-5.73 (m, 1H), 5.06-4.97 (m, 2H), 4.67 (dd, J = 1.8, 1.8 Hz, 1H), 4.51 (dd, J = 1.6, 1.6 Hz, 1H), 2.50 (ddddd J = 14.1, 14.1, 5.0, 1.8, 1.8 Hz, 1H), 2.15-2.00 (m, 3H), 1.95-1.88 (m, 1H), 1.78-1.69 (m, 1H), 1.66 (ddd, J = 13.4, 13.4, 5.0 Hz, 1H), 1.58-1.53 (m, 5H), 1.27-1.21 (m, 2H), 1.24 (d, J = 0.6 Hz, 3H), 1.04 (s, 3H), 0.14 (S, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7 (C_4), 136.2 (CH), 117.4 (CH_2), 105.8 (CH_2), 86.1 (C_4), 45.5 (C_4), 43.1 (CH_2), 41.7 (C_4), 35.3 (CH_2), 34.8 (CH_2), 39.4 (CH_2), 25.5 (CH_2), 25.4 (CH_3), 21.8 (CH_2), 20.6 (CH_2), 20.4 (CH_3), 3.1 (3 × CH_3)

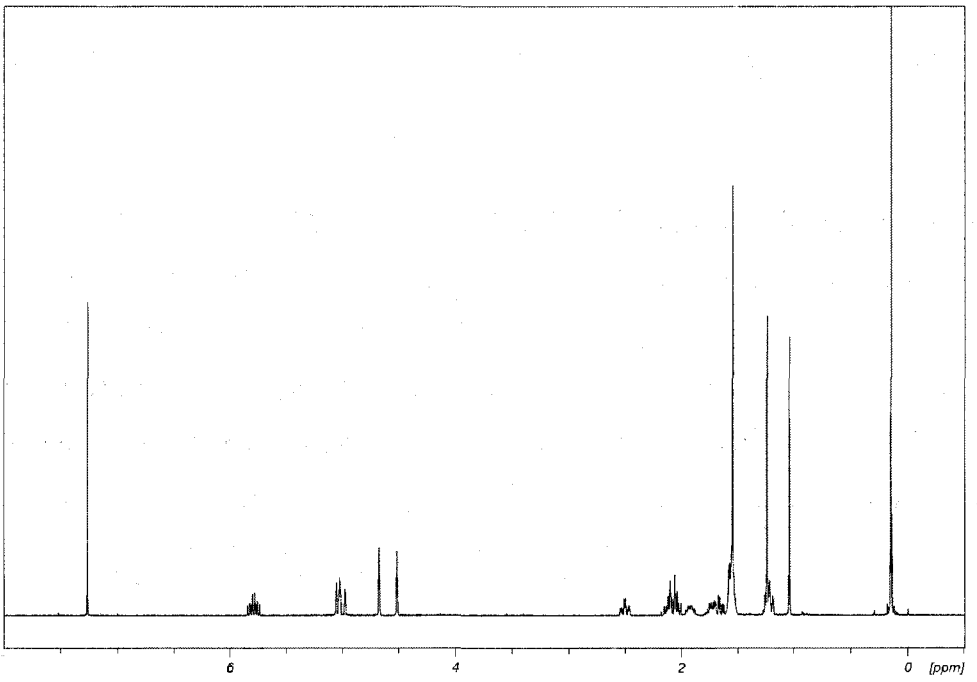
FT-IR (neat, cm^{-1}): 2949 (s), 2868 (s), 1640 (w)

HRMS (EI): Calculated 306.2379 (M^+) for $C_{19}H_{34}OSi$, found 306.2389

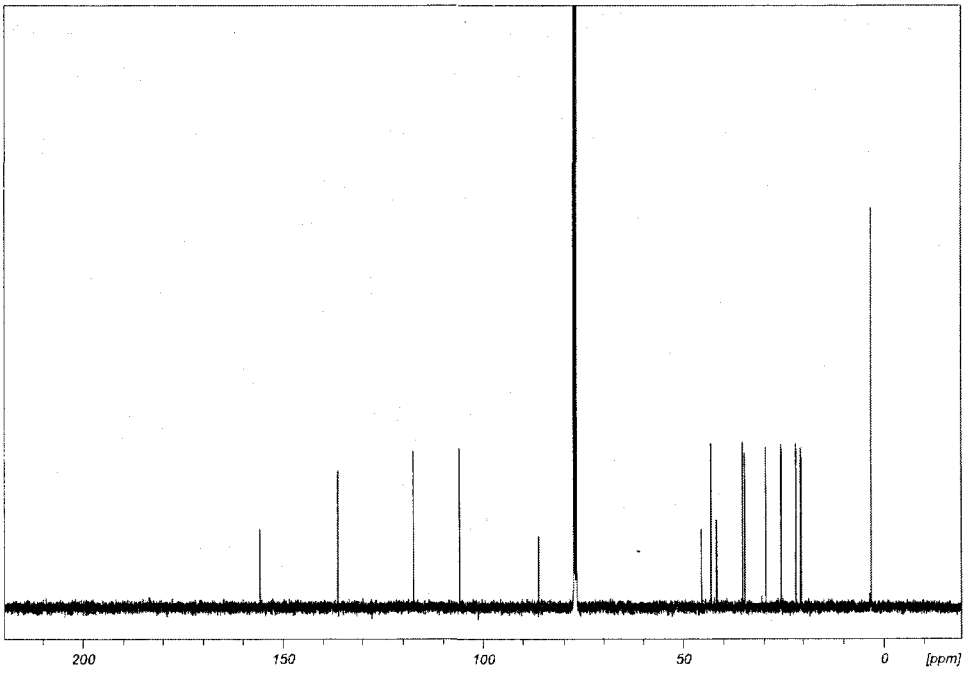


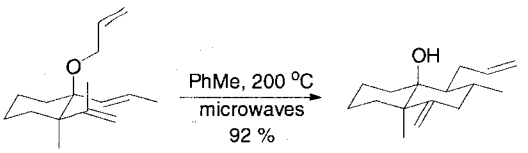
3.49b

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.43c **3.44c**

(±)-(3R, 4S, 4aS, 8aR)-4-Allyl-decahydro-3,8a-dimethyl-1-methylenenapthalen-4a-ol (**3.44c**)

A sample of **3.43c** (116.7 mg, 0.498 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording **3.44c** (106.8 mg, 0.456 mmol, 92 %, $R_f = 0.55$) as a colorless oil.

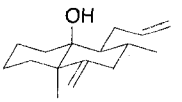
Data for **3.44c**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98-5.87 (m, 1H), 4.99 (dddd, J = 17.2, 1.7, 1.7, 1.7 Hz, 1H), 4.92 (dddd, J = 10.2, 1.4, 1.4, 1.4 Hz, 1H), 4.88-4.87 (m, 1H), 4.71-4.70 (m, 1H), 2.39-2.31 (m, 1H), 2.26-2.21 (m, 1H), 2.16 (dd, J = 14.0, 5.7 Hz, 1H), 2.11-2.03 (m, 1H), 1.87 (ddd, J = 12.2, 12.2, 5.5 Hz, 1H), 1.81-1.77 (m, 1H), 1.71-1.62 (m, 2H), 1.61-1.47 (m, 3H), 1.44-1.38 (m, 2H), 1.35 (d, J = 1.6 Hz, 1H), 1.29-1.24 (m, 1H), 1.15 (d, J = 0.6 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3 (C_4), 139.7 (CH), 114.6 (CH_2), 109.0 (CH_2), 76.7 (C_4), 46.9 (CH), 44.2 (C_4), 40.9 (CH_2), 34.3 (CH), 32.1 (CH_2), 31.2 (CH_2), 30.2 (CH_2), 21.5 (CH_3), 21.0 (CH_2), 20.9 (CH_2), 20.5 (CH_3)

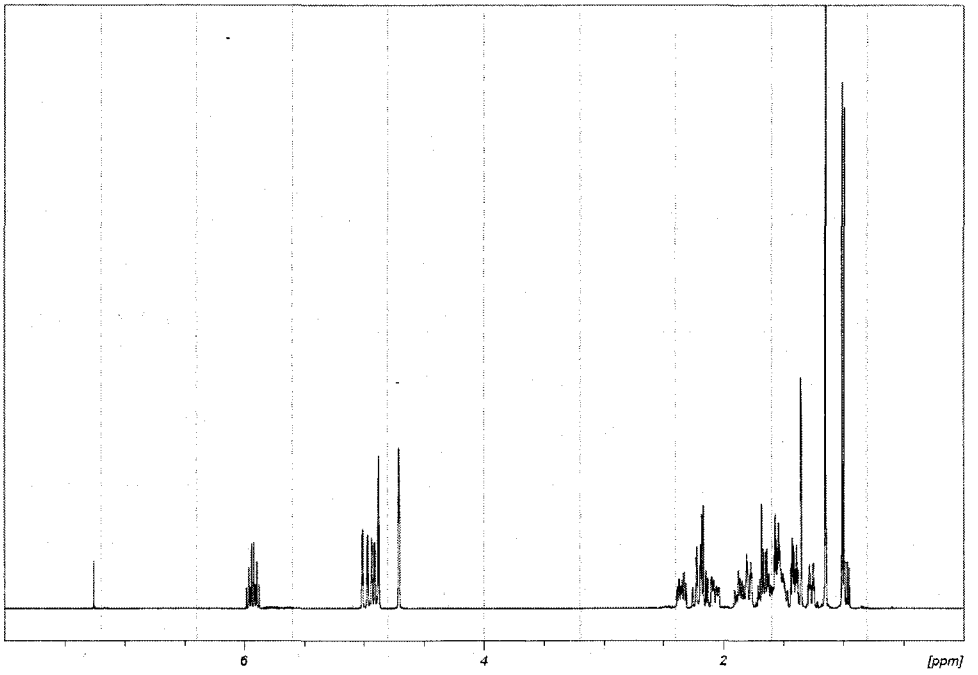
FT-IR (neat, cm^{-1}): 3566 (b), 2978 (m), 2941 (s), 2867 (s), 1637 (m)

HRMS (EI): Calculated 234.1984 (M^+) for $C_{16}H_{26}O$, found 234.1973

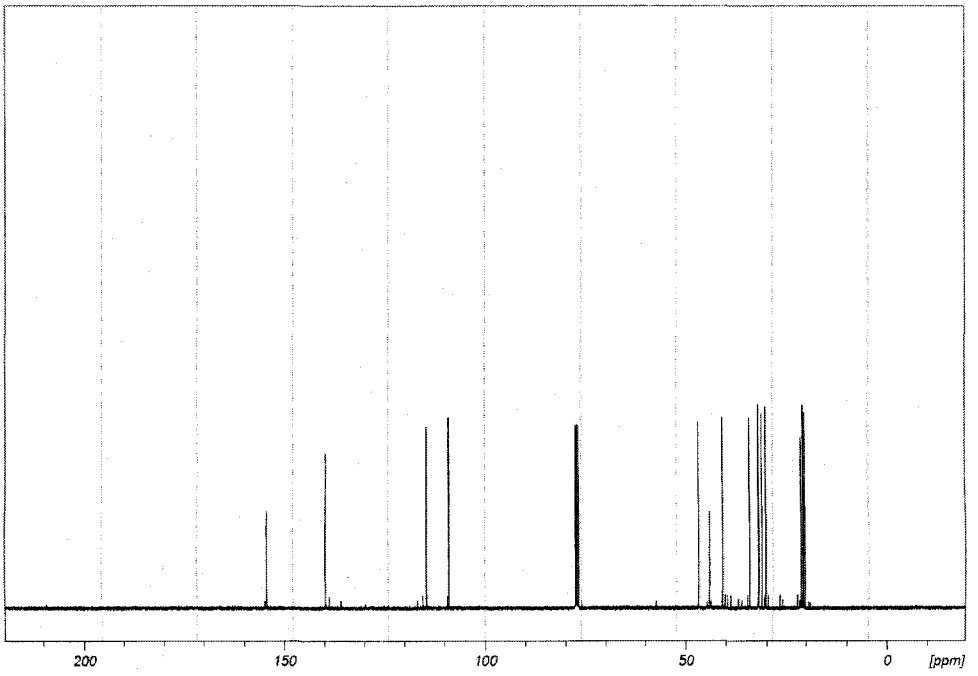


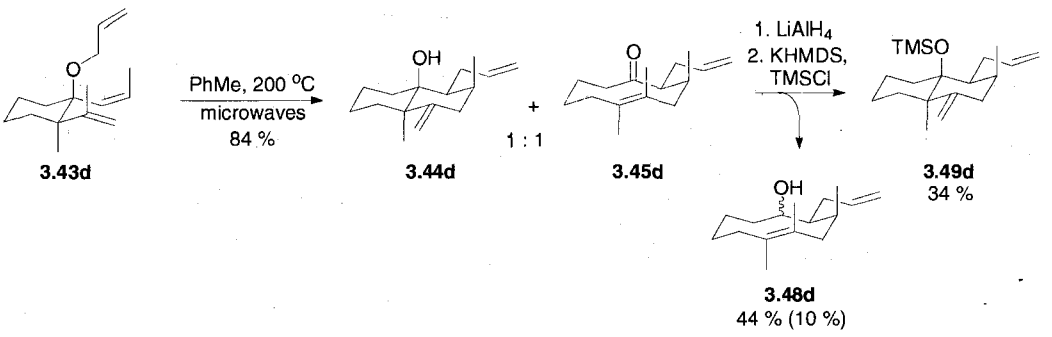
3.44c

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(E, 1S, 2S, 3S)/(E, 1R, 2S, 3S)-2-Allyl-3,5,6-trimethylcyclodec-5-enol (**3.48d**)

A sample of **3.43d** (68.0 mg, 0.290 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give an orange oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording an inseparable 1:1 mixture of tertiary alcohol **3.44d** and ketone **3.45d** (57.2 mg, 0.244 mmol, 84 %, $R_f = 0.55$) as a colorless oil.

The mixture of **3.44d** and **3.45d** (57.2 mg, 0.244 mmol) was dissolved in THF (5 mL) and it was treated with $LiAlH_4$ (37.0 mg, 0.975 mmol). The resulting gray mixture was heated at reflux for 16 hours after which it was cooled to room temperature and quenched by the careful addition of an aqueous 1.0 M solution of sodium tartrate. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 20 % EtOAc/hexanes affording secondary alcohol **3.48d** (19.7 mg, 0.0833 mmol, 34 %, $R_f = 0.65$) as a colorless oil. This product is an unassigned 1.6:1 mixture of diastereomers at the secondary alcohol. Also recovered was an inseparable mixture of unreacted ketone **3.44d** and tertiary alcohol **3.45d** (24.9 mg, 0.106 mmol, 44 %, $R_f = 0.95$) as a colorless oil.

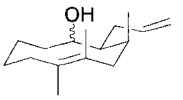
Data for **3.48d**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05-5.94 (m, 1H), 5.85, 5.75 (m, 1.6H), 5.11-5.05 (m, 2.6H), 5.03-4.98 (m, 2.6H), 3.59 (d, J = 11.1 Hz, 1.6H), 3.46-3.41 (m, 1H), 2.59-2.48 (m, 5.2H), 2.39-2.26 (m, 2.6H), 2.22-2.08 (m, 2.6H), 2.05-1.99 (m, 1.6H), 1.96-1.90 (m, 1H), 1.90 (s, 3H), 1.84 (s, 4.8H), 1.82-1.66 (m, 7.8H), 1.77 (s, 4.8H), 1.72 (s, 3H), 1.62-1.18 (m, 13H), 1.07-1.01 (m, 2.6H), 0.98-0.92 (m, 1H), 0.93 (d, J = 7.0 Hz, 4.8H), 0.91 (d, J = 7.0 Hz, 3H), 0.76-0.67 (m, 1.6H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9 (CH), 139.1 (CH), 129.8 (2 × C_4), 129.6 (C_4), 129.4 (C_4), 116.0 (CH_2), 115.3 (CH_2), 75.0 (CH), 73.4 (CH), 72.5 (CH_2), 42.1 (CH_2), 39.6 (CH), 38.7 (CH), 35.4 (CH_2), 34.3 (CH_2), 34.2 (CH_2), 33.7 (CH_2), 33.5 (CH), 32.6 (CH_2), 32.1 (CH_2), 29.3 (CH), 26.0 (CH_2), 25.8 (CH_2), 25.5 (CH_3), 25.3 (CH_3), 21.6 (CH_2), 19.8 (CH_3), 19.4 (CH_3), 18.6 (CH_2), 18.6 (CH_3), 17.3 (CH_3)

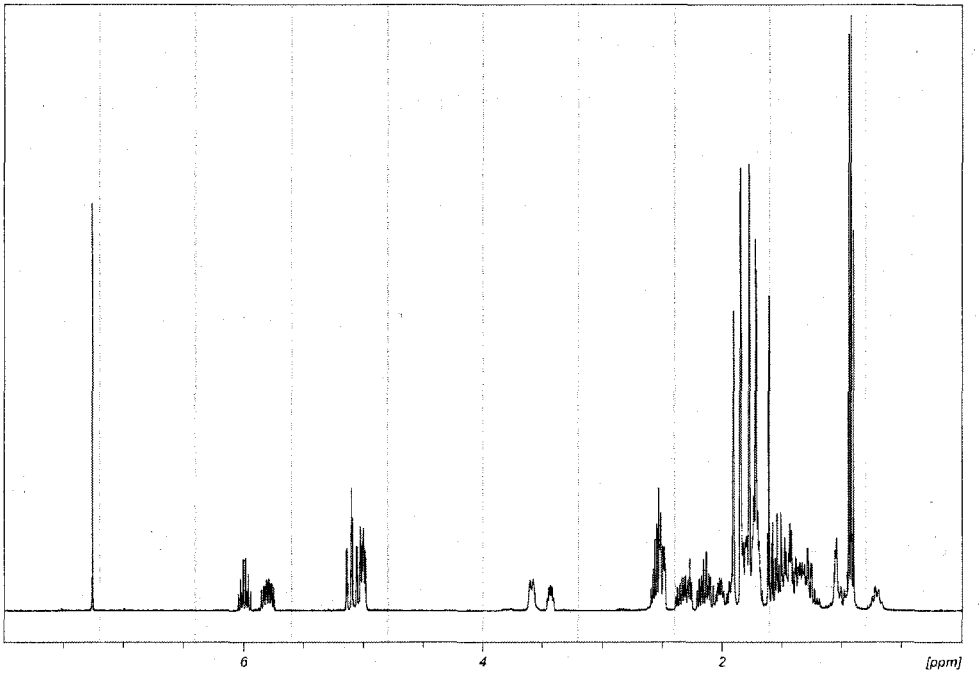
FT-IR (neat, cm^{-1}): 3382 (b), 2953 (s), 2929 (s), 2861 (s), 1638 (w)

HRMS (EI): Calculated 236.2140 (M^+) for $C_{16}H_{28}O$, found 236.2159

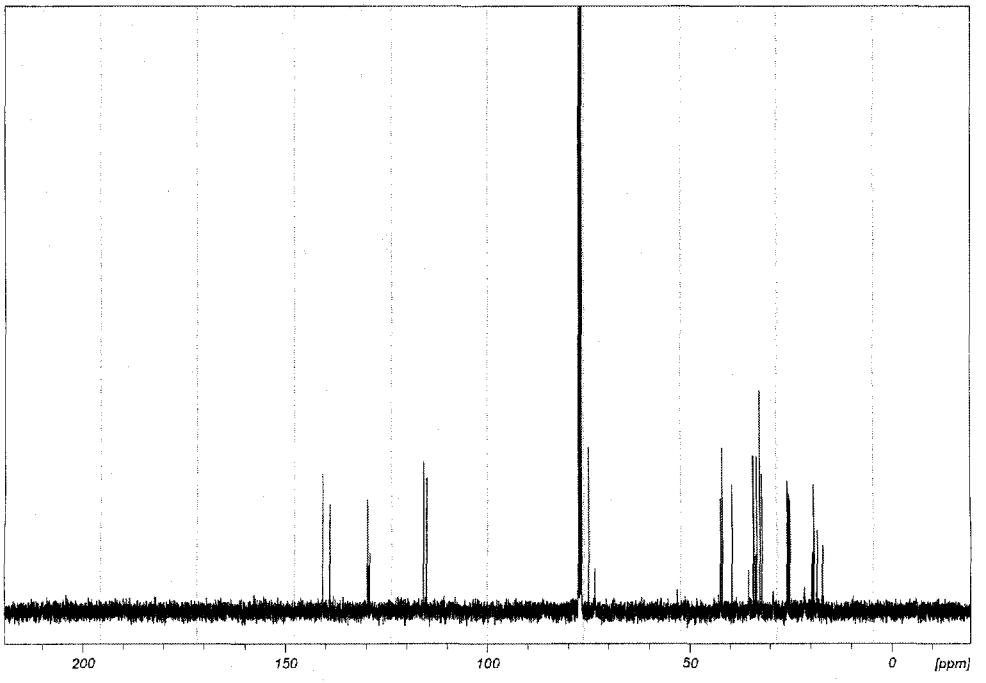


3.48d

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



(±)-((1S, 2S, 4aR, 8aS)-1-Allyl-decahydro-2,4a-dimethyl-4-methylenenapthalen-8a-yloxy)trimethylsilane (**3.49d**)

The recovered mixture of ketone **3.44d** and tertiary alcohol **3.45d** (24.9 mg, 0.106 mmol) was dissolved in THF (4 mL) and treated with solid KHMDS (156.8 mg, 0.786 mmol) and TMSCl (0.10 mL, 0.788 mmol). The reaction was stirred at room temperature for 0.5 h whereupon the reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in hexanes, affording silyl ether **3.49d** (10.0 mg, 0.0312 mmol, 10 %, $R_f = 0.70$) as a colorless oil.

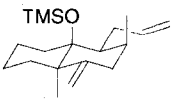
Data for **3.49d**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90-5.80 (m, 1H), 5.05 (dddd, J = 17.1, 1.7, 1.7, 1.7 Hz, 1H), 4.97-4.93 (m, 1H), 4.72 (s, 1H), 4.65 (s, 1H), 2.56-2.48 (m, 3H), 2.34-2.27 (m, 1H), 2.01 (ddd, J = 14.0, 8.3, 8.3 Hz, 1H), 1.89-1.73 (m, 3H), 1.67-1.50 (m, 5H), 1.20 (s, 3H), 1.16 (dd, J = 12.5, 3.0 Hz, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.13 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5 (C_4), 139.8 (CH), 114.7 (CH_2), 110.9 (CH_2), 92.1 (C_4), 56.2 (C_4), 55.7 (CH), 46.6 (CH_2), 37.2 (CH_2), 35.9 (CH), 35.4 (CH_2), 33.4 (CH_2), 29.5 (CH_3), 26.7 (CH_2), 25.1 (CH_2), 23.3 (CH_3), 3.3 (3 × CH_3)

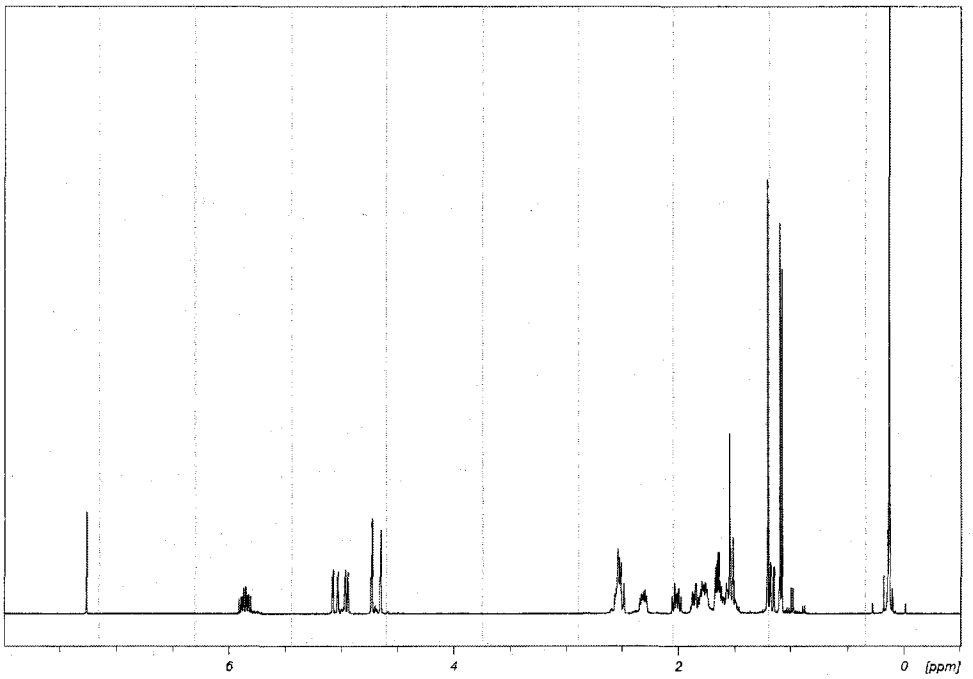
FT-IR (neat, cm^{-1}): 2949 (s), 2869 (m), 1621 (m)

HRMS (EI): Calculated 306.2379 (M^+) for $C_{19}H_{34}OSi$, found 306.2362

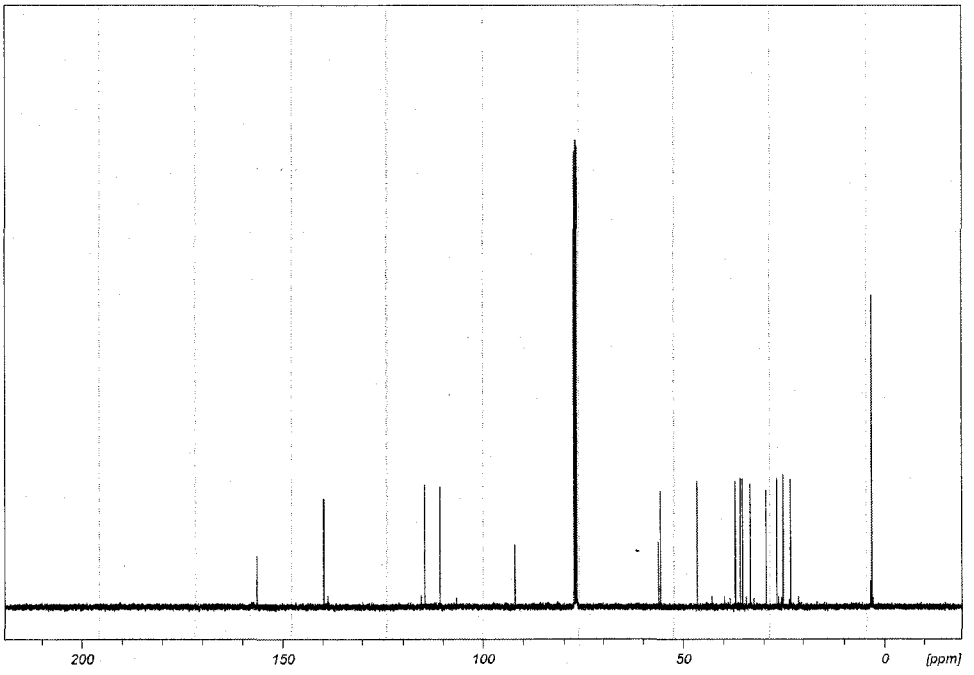


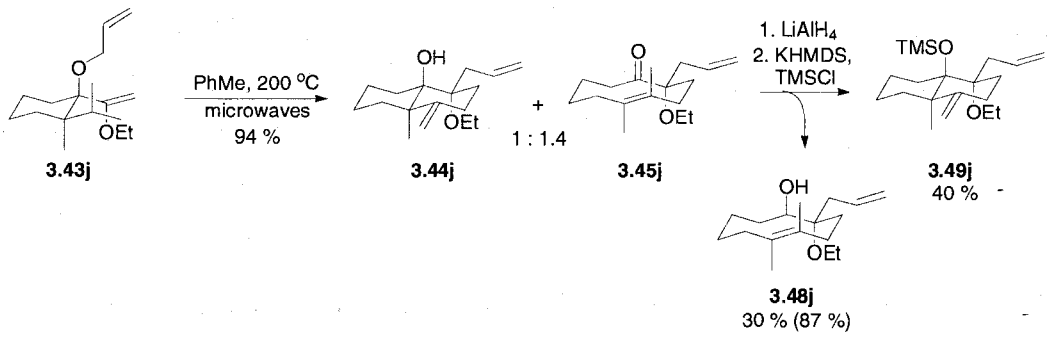
3.49d

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(E, 1S, 2S)-2-Allyl-2-ethoxy-5,6-dimethylcyclodec-5-enol (**3.48j**)

A sample of **3.43j** (17.5 mg, 0.0662 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 200 °C over 20 minutes, then for 1 hour at 200 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording an inseparable 1:1.4 mixture of tertiary alcohol **3.44j** and ketone **3.45j** (16.5 mg, 0.0624 mmol, 94 %, $R_f = 0.60$) as a colorless oil.

The mixture of **3.44j** and **3.45j** (16.5 mg, 0.0624 mmol) was dissolved in THF (5 mL) and it was treated with $LiAlH_4$ (9.5 mg, 0.250 mmol). The resulting gray mixture was heated at reflux for 16 hours after which it was cooled to room temperature and quenched by the careful addition of an aqueous 1.0 M solution of sodium tartrate. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 10 % EtOAc/hexanes affording secondary alcohol **3.48j** (6.7 mg, 0.0251 mmol, 40 %, $R_f = 0.50$) as a colorless oil. Also recovered was an inseparable mixture of unreacted ketone **3.44j** and tertiary alcohol **3.45j** (4.9 mg, 0.0185 mmol, 30 %, $R_f = 0.85$) as a colorless oil.

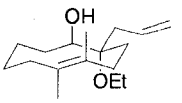
Data for **3.48j**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00-5.89 (m, 1H), 5.03-4.95 (m, 2H), 3.90 (d, J = 9.3 Hz, 1H), 3.52-3.40 (m, 2H), 2.70 (dd, J = 12.4, 12.4 Hz, 1H), 2.55-2.49 (m, 1H), 2.35 (dd, J = 2.0, 2.0 Hz, 1H), 2.27 (d, J = 7.7 Hz, 2H), 1.86-1.79 (m, 2H), 1.85 (s, 3H), 1.75 (s, 3H), 1.73-1.54 (m, 6H), 1.40-1.33 (m, 2H), 1.18 (t, J = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8 (CH), 130.9 (C_4), 129.1 (C_4), 116.5 (CH_2), 83.3 (C_4), 75.2 (CH), 56.9 (CH_2), 38.6 (CH_2), 34.2 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 25.5 (CH_2), 24.4 (CH_2), 21.1 (CH_3), 19.5 (CH_3), 16.3 (CH_3)

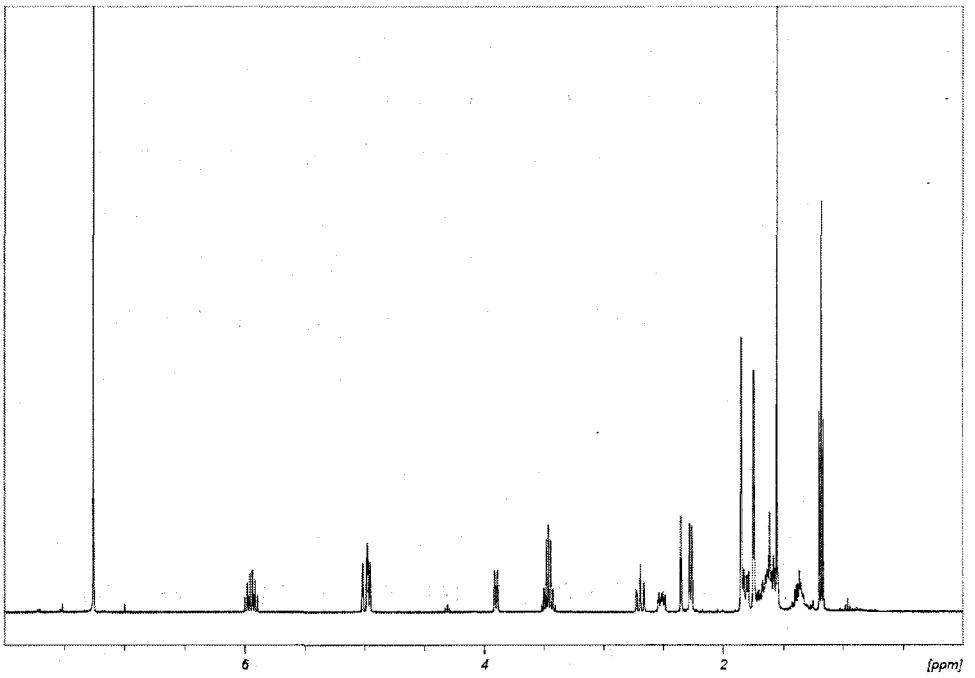
FT-IR (neat, cm^{-1}): 3588 (b), 3469 (b), 3079 (w), 2971 (m), 2920 (s), 1636 (m)

HRMS (EI): Calculated 266.2246 (M^+) for $C_{17}H_{30}O_2$, found 266.2235

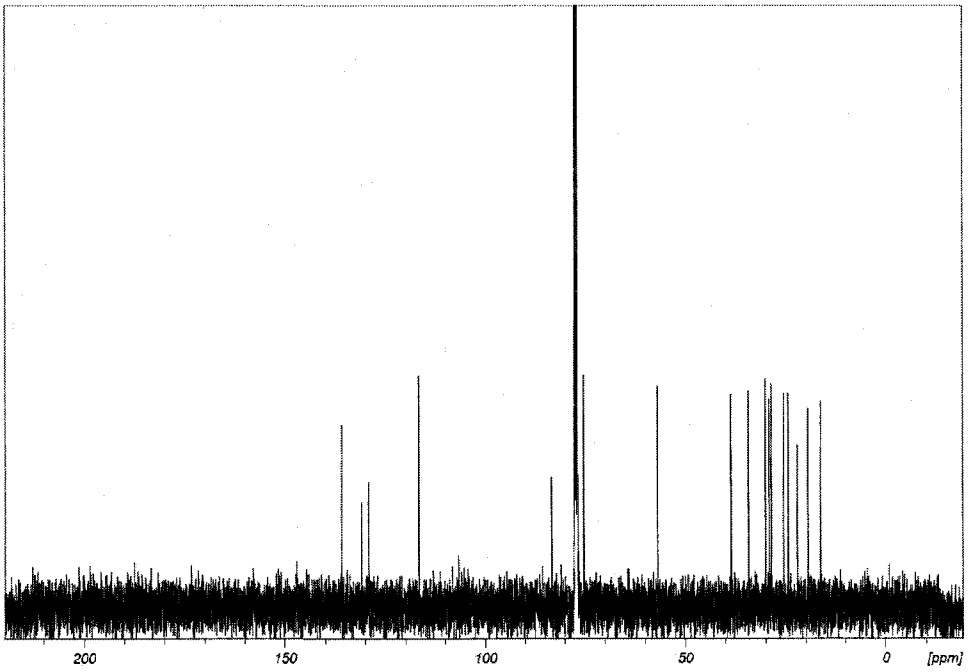


3.48j

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



(±)-((1S, 4aR, 8aR)-1-Allyl-1-ethoxy-decahydro-4a-methyl-4-methylenenapthalen-8a-yloxy)trimethylsilane (**3.49j**)

The recovered mixture of ketone **3.44j** and tertiary alcohol **3.45j** (4.9 mg, 0.0185 mmol) was dissolved in THF (5 mL) and treated with solid KHMDS (14.8 mg, 0.0742 mmol) and TMSCl (0.01 mL, 0.0788 mmol). The reaction was stirred at room temperature for 0.5 h whereupon the reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 2 % EtOAc/hexanes, affording silyl ether **3.49j** (5.3 mg, 0.0157 mmol, 87 %, R_f = 0.70) as a colorless oil.

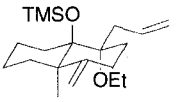
Data for **3.49j**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00-5.90 (m, 1H), 5.05-4.96 (m, 2H), 4.64 (dd, J = 1.8, 1.8 Hz, 1H), 4.49 (dd, J = 1.7, 1.7 Hz, 1H), 3.52-3.42 (m, 2H), 2.58-2.45 (m, 2H), 2.26 (dddd, J = 15.8, 8.2, 1.9, 1.9 Hz, 1H), 2.03-1.95 (m, 2H), 1.86-1.77 (m, 2H), 1.64 (ddd, J = 14.0, 14.0, 4.9 Hz, 1H), 1.61-1.47 (m, 5H), 1.28 (s, 3H), 1.21-1.17 (m, 1H), 1.14 (t, J = 6.9 Hz, 3H), 0.23 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7 (C_4), 136.7 (CH), 115.7 (CH_2), 105.5 (CH_2), 85.0 (C_4), 80.7 (C_4), 57.3 (CH_2), 44.9 (C_4), 39.1 (CH_2), 34.1 (CH_2), 30.8 (CH_2), 29.4 (CH_2), 25.7 (CH_2), 24.4 (CH_3), 21.5 (CH_2), 20.6 (CH_2), 16.0 (CH_3), 3.0 (3 × CH_3)

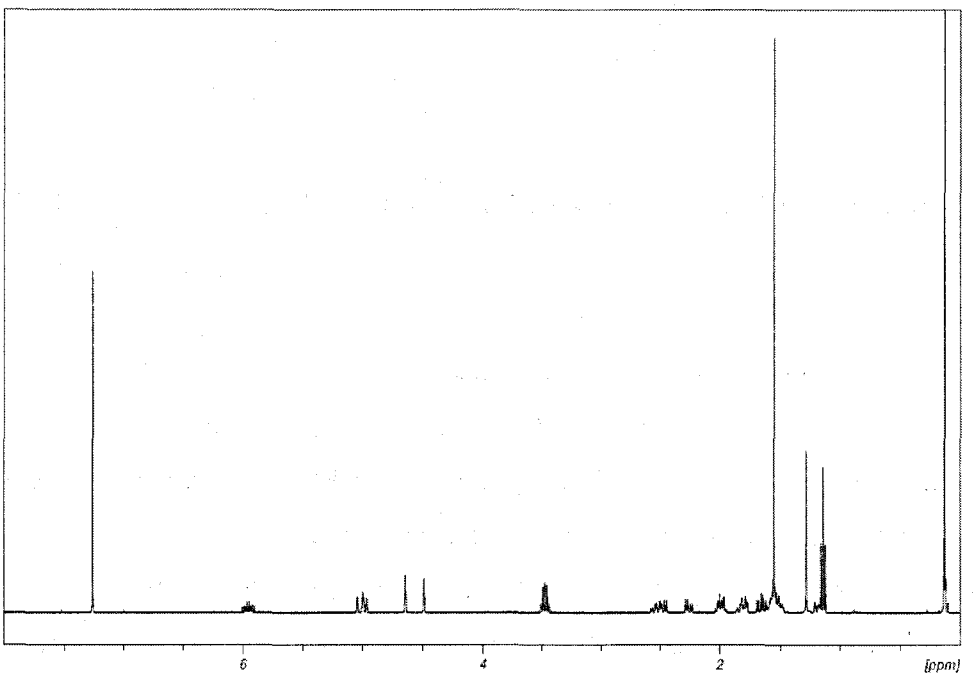
FT-IR (neat, cm^{-1}): 3079 (w), 3025 (w), 2952 (s), 2933 (s), 1636 (m)

HRMS (EI): Calculated 336.2485 (M^+) for $C_{20}H_{36}O_2Si$, found 336.2477

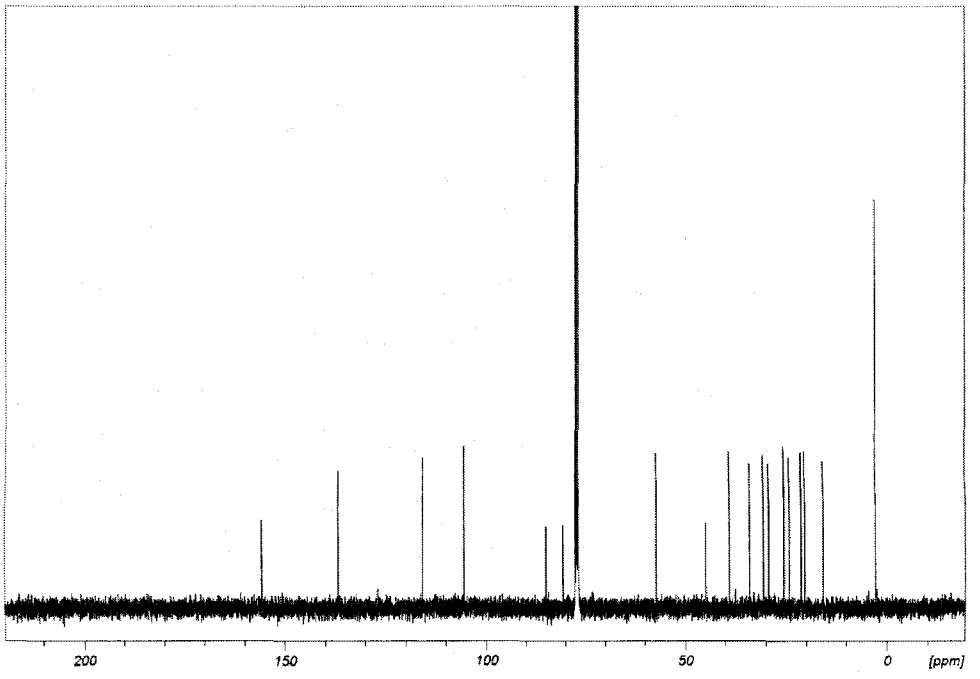


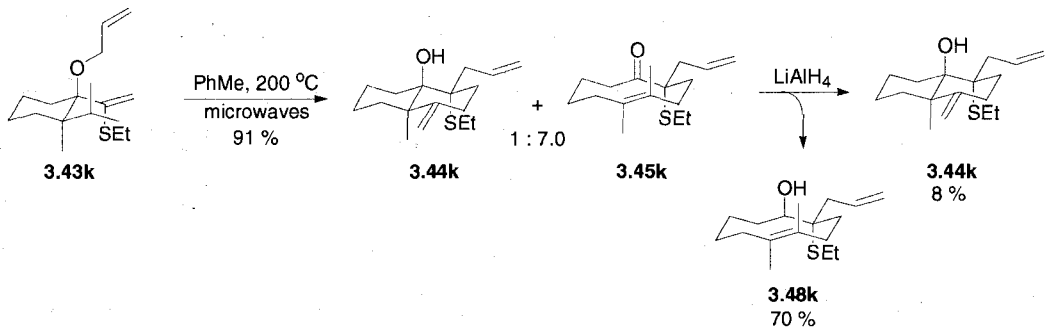
3.49j

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(4S, 4aR, 8aR)-4-Allyl-4-(ethylthio)-decahydro-8a-methyl-1-methylenenapthalen-4a-ol (**3.44k**)

A sample of **3.43k** (94.7 mg, 0.338 mmol) was dissolved in toluene (13 mL), placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 200 °C over 20 minutes, then for 1 hour at 200 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 5 % EtOAc/hexanes, affording an inseparable 1:7 mixture of tertiary alcohol **3.44k** and ketone **3.45k** (86.1 mg, 0.307 mmol, 91 %, $R_f = 0.50$) as a colorless oil.

The mixture of **3.44k** and **3.45k** (86.1 mg, 0.307 mmol) was dissolved in THF (10 mL) and it was treated with $LiAlH_4$ (46.6 mg, 1.23 mmol). The resulting gray mixture was heated at reflux for 16 hours after which it was cooled to room temperature and quenched by the careful addition of an aqueous 1.0 M solution of sodium tartrate. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 10 % EtOAc/hexanes affording tertiary alcohol **3.44k** (7.0 mg, 0.0250 mmol, 8 %, $R_f = 0.75$) as a colorless oil. Also recovered was secondary alcohol **3.48k** (60.7 mg, 0.215 mmol, 70 %, $R_f = 0.40$) as a yellow oil. See characterization data for **3.48k** below.

Data for **3.44k**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09-5.98 (m, 1H), 5.09-5.00 (m, 2H), 4.92 (dd, J = 1.6, 1.6 Hz, 1H), 4.74 (s, 1H), 2.76 (ddd, J = 7.3, 7.3, 6.0 Hz, 1H), 2.65-2.51 (m, 4H), 2.09 (ddd, J = 14.1, 3.4, 3.4 Hz, 1H), 1.95-1.79 (m, 4H), 1.77-1.68 (m, 1H), 1.67-1.53 (m, 5H), 1.62 (d, J = 1.3 Hz, 3H), 1.26-1.22 (m, 1H), 1.21 (t, J = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7 (C_4), 136.5 (CH), 116.7 (CH_2), 109.5 (CH_2), 79.9 (C_4), 55.4 (C_4), 45.8 (C_4), 41.3 (CH_2), 35.5 (CH_2), 34.9 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 25.4 (CH_3), 23.6 (CH_2), 21.2 (CH_2), 20.8 (CH_2), 14.2 (CH_3)

FT-IR (neat, cm^{-1}): 3557 (b), 3014 (w), 2932 (s), 2865 (m), 1636 (w)

HRMS (EI): Calculated 280.1861 (M^+) for $C_{17}H_{28}OS$, found 280.1846

(±)-(E, 1S, 2S)-2-allyl-2-(ethylthio)-5,6-dimethylcyclodec-5-enol (**3.48k**)

See experimental procedure above.

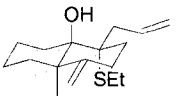
Data for **3.48k**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08-5.98 (m, 1H), 5.09-5.02 (m, 2H), 3.91 (dd, J = 9.8, 4.4 Hz, 1H), 3.00-2.94 (m, 1H), 2.68-2.47 (m, 4H), 2.23 (dddd, J = 14.7, 7.3, 1.2, 1.2 Hz, 1H), 1.97 (dd, J = 4.4, 1.1 Hz, 1H), 1.88 (s, 3H), 1.84-1.67 (m, 4H), 1.76 (s, 3H), 1.65-1.48 (m, 5H), 1.41-1.33 (m, 1H), 1.23 (t, J = 7.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0 (CH), 130.7 (C_4), 129.2 (C_4), 117.1 (CH_2), 75.9 (CH), 60.7 (C_4), 40.0 (CH_2), 34.2 (CH_2), 34.1 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 25.5 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 22.1 (CH_3), 19.8 (CH_3), 14.5 (CH_3)

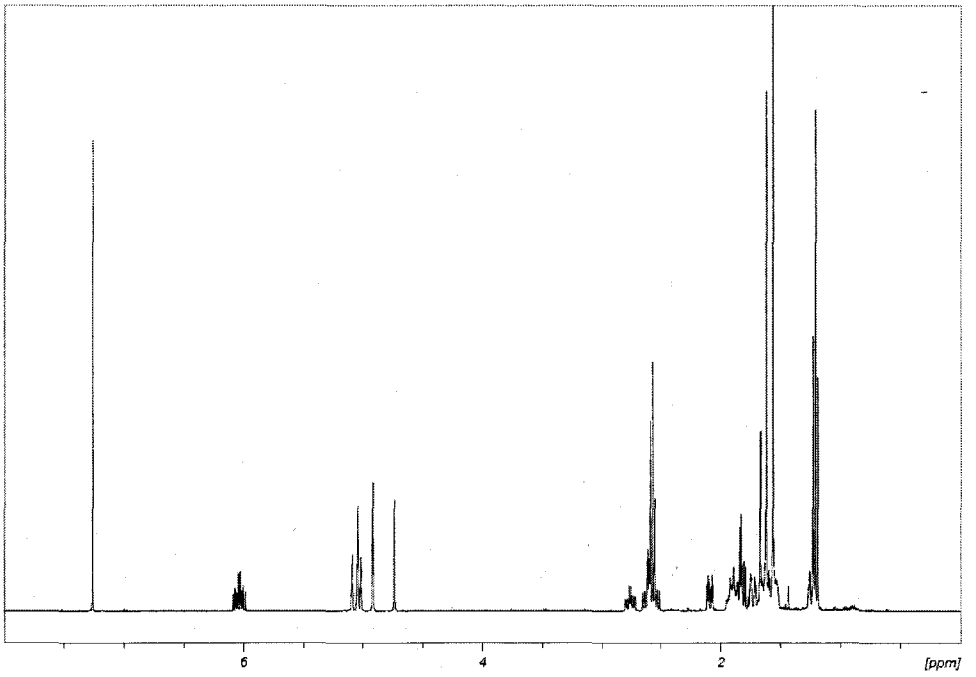
FT-IR (neat, cm^{-1}): 3473 (b), 3071 (w), 2963 (m), 2921 (s), 1636 (w)

HRMS (EI): Calculated 282.2017 (M^+) for $C_{17}H_{30}OS$, found 282.1996

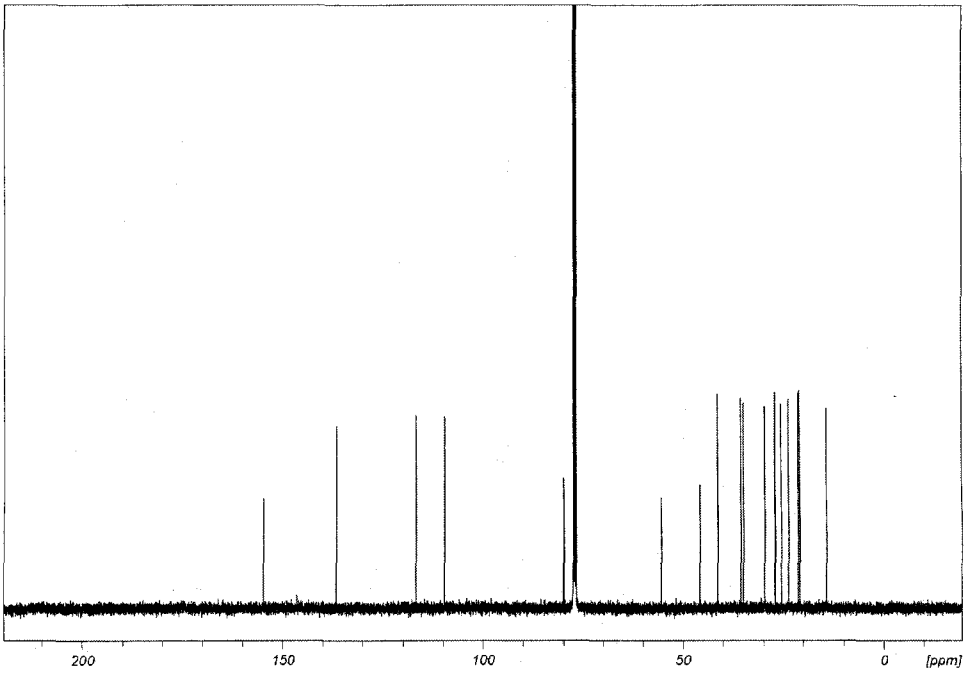


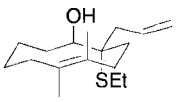
3.44k

^{1}H NMR (400 MHz, $CDCl_3$)



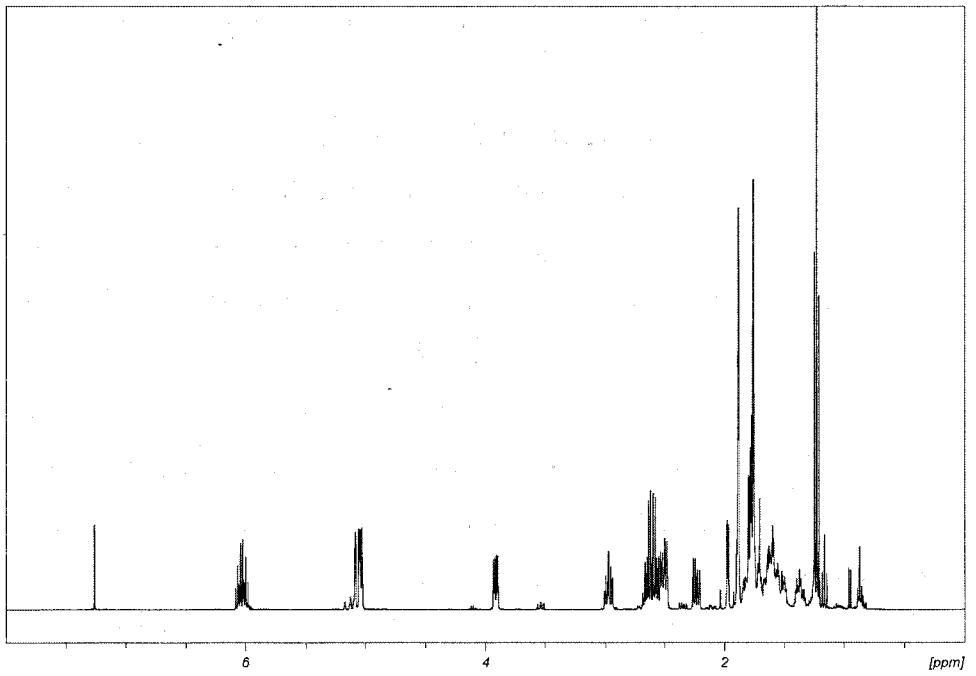
^{13}C NMR (100 MHz, $CDCl_3$)



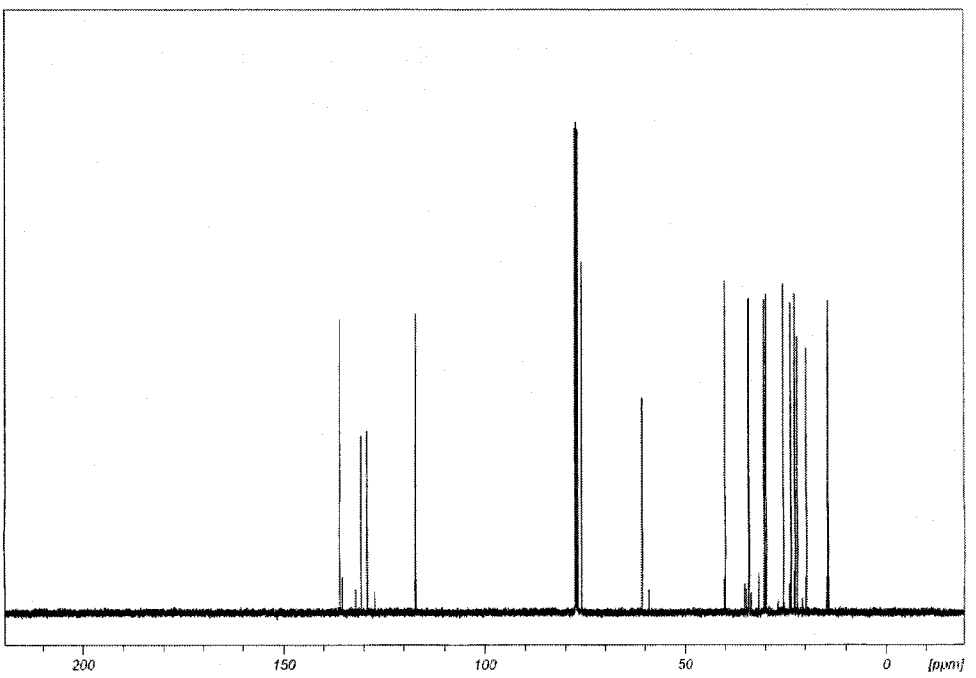


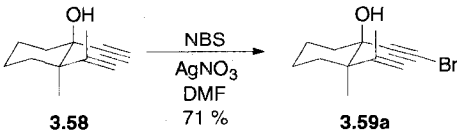
3.48k

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)- (1S,2S)-1-(2-Bromoethynyl)-2-methyl-2-(prop-1-en-2-yl)cyclohexanol (**3.59a**)

A solution of **3.58** (310.3 mg, 1.74 mmol) in DMF (15 mL) was treated with NBS (371.8 mg, 2.09 mmol) and $AgNO_3$ (354.8, 2.09 mmol), and the reaction was wrapped in foil to hide it from light. This mixture was stirred for 3 hours whereupon it was diluted with a 1:1 mixuture of Et_2O and hexanes (15 mL) and then quenched with saturated aqueous Na_2SO_3. Solids were removed from the biphasic mixture by filtration through a short pad of celite, followed by washing the filter cake with Et_2O. The aqueous phase was removed and extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with water (50 mL) and then brine (25 mL). The remaining organic phase was dried over $MgSO_4$, filtered and concentrated. Subsequent flash chromatography in 5 % EtOAc/hexanes gave **3.59a** (321.7 mg, 1.27 mmol, 71 %, $R_f = 0.65$) as a colorless liquid.

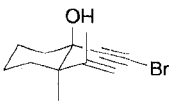
Data for **3.59a**

^{1}H NMR (400 MHz, C_6D_6): δ = 4.94 (s, 1H), 4.93-4.92 (m, 1H), 2.21 (d, J = 2.0 Hz, 1H), 2.05-2.00 (m, 1H), 1.90 (ddd, J = 12.7, 12.7, 4.4 Hz, 1H), 1.89 (s, 3H), 1.78-1.59 (m, 2H), 1.36-1.21 (m, 3H), 1.15 (d, J = 0.5 Hz, 3H), 1.11-1.05 (m, 1H)

^{13}C NMR (100 MHz, C_6D_6): δ = 150.3 (C_4), 114.8 (CH_2), 85.4 (C_4), 71.9 (C_4), 46.3 (C_4), 44.2 (C_4), 35.8 (CH_2), 31.7 (CH_2), 23.0 (CH_3), 21.4 (CH_2), 20.7 (CH_2), 20.5 (CH_3)

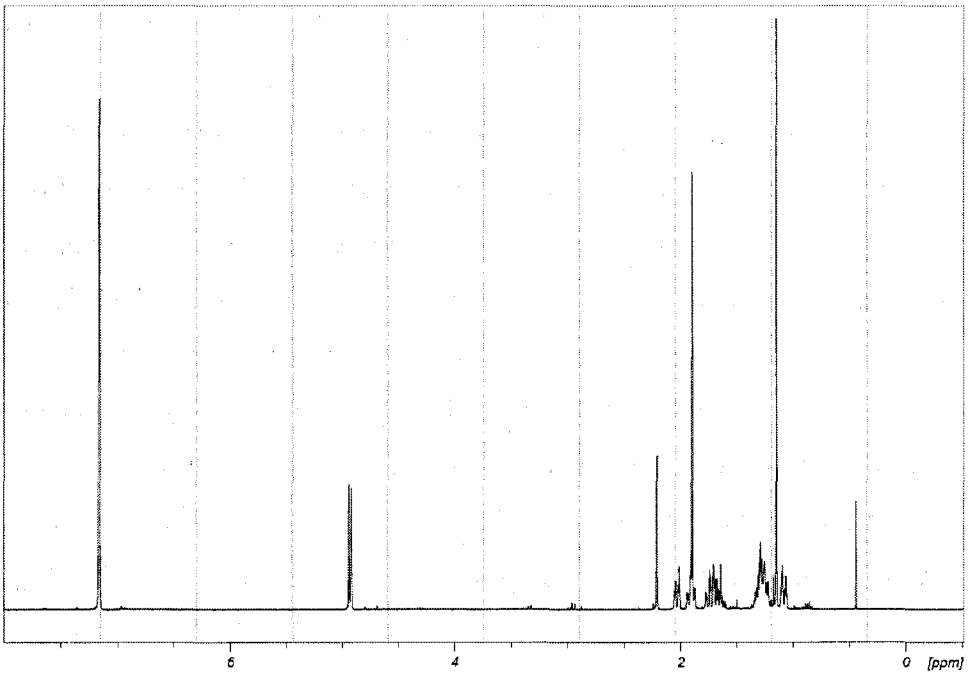
FT-IR (neat, cm^{-1}): 3534 (b), 2956 (s), 2932 (s), 2867 (m), 2200 (w)

HRMS (EI): Calculated 256.0463 (M^+) for $C_{12}H_{17}OBr$, found (M^+-CH_3) at 241.0235, actual value 241.0228

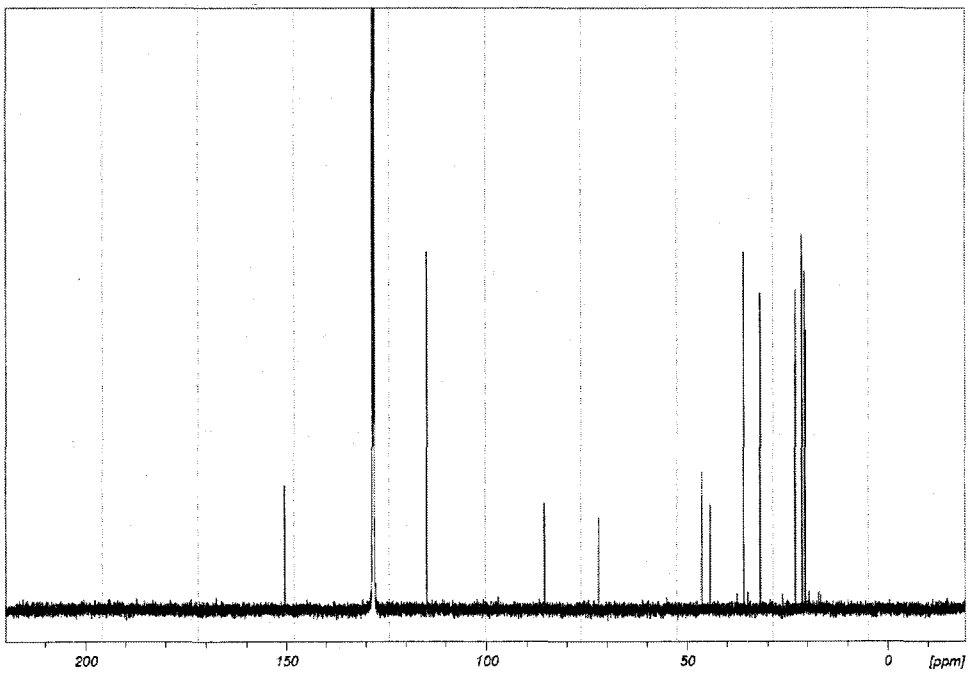


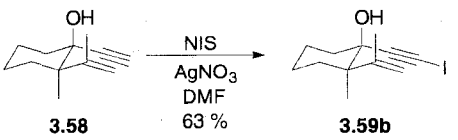
3.59a

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



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





(±)-(1S,2S)-1-(2-Iodoethynyl)-2-methyl-2-(prop-1-en-2-yl)cyclohexanol (**3.59b**)

A solution of **3.58** (127.8 mg, 0.717 mmol) in DMF (7 mL) was treated with NIS (193.5 mg, 0.860 mmol) and $AgNO_3$ (146.1, 0.860 mmol), and the reaction was wrapped in foil to hide it from light. This mixture was stirred for 3 hours whereupon it was diluted with a 1:1 mixuture of Et_2O and hexanes (7 mL) and then quenched with saturated aqueous Na_2SO_3. Solids were removed from the biphasic mixture by filtration through a short pad of celite, followed by washing the filter cake with Et_2O. The aqueous phase was removed and extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with water (30 mL) and then brine (15 mL). The remaining organic phase was dried over $MgSO_4$, filtered and concentrated. Subsequent flash chromatography in 5 % EtOAc/hexanes gave **3.59b** (137.4 mg, 0.452 mmol, 63 %, R_f = 0.45) as a colorless liquid.

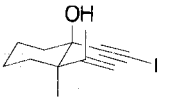
Data for **3.59b**

^{1}H NMR (400 MHz, C_6D_6): δ = 4.94 (s, 1H), 4.92-4.91 (m, 1H), 2.24 (d, J = 2.0 Hz, 1H), 2.06-2.01 (m, 1H), 1.91 (s, 3H), 1.90 (ddd, J = 13.6, 13.6, 4.3 Hz, 1H), 1.79-1.59 (m, 2H), 1.32-1.21 (m, 3H), 1.17 (d, J = 0.4 Hz, 3H), 1.11-1.06 (m, 1H)

^{13}C NMR (100 MHz, C_6D_6): δ = 150.3 (C_4), 114.8 (CH_2), 99.4 (C_4), 72.5 (C_4), 46.4 (C_4), 36.0 (CH_2), 31.7 (CH_2), 23.2 (CH_3), 21.4 (CH_2), 20.7 (CH_2), 20.5 (CH_3), -1.0 (C_4)

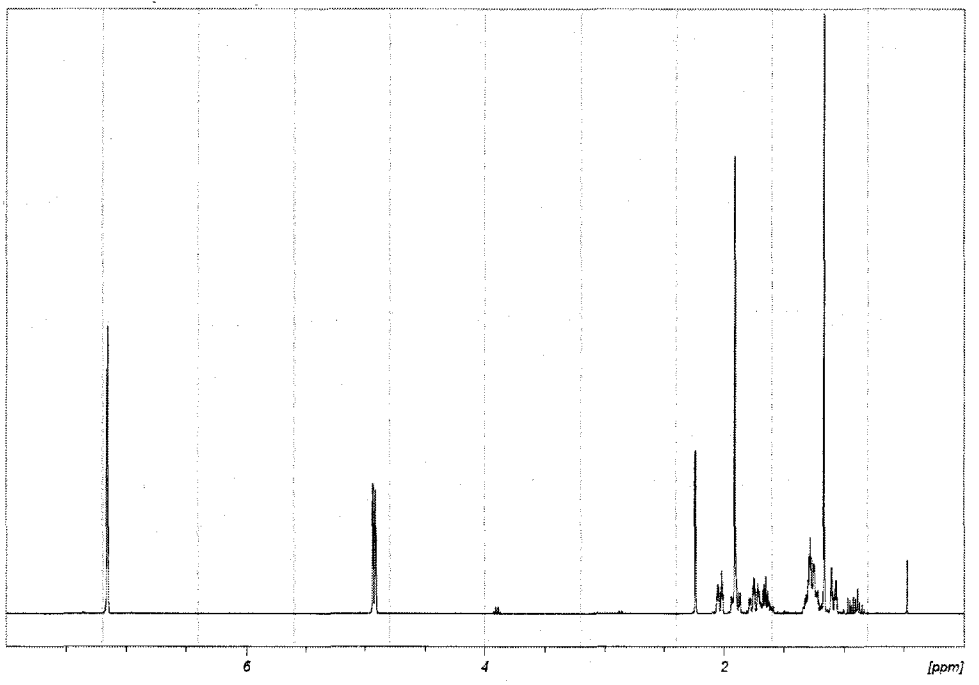
FT-IR (neat, cm^{-1}): 3515 (b), 2957 (s), 2931 (s), 2866 (m), 2170 (w)

HRMS (EI): Calculated 304.0324 (M^+) for $C_{12}H_{17}OI$, found (M^+-CH_3) at 289.0094, actual value 289.0089

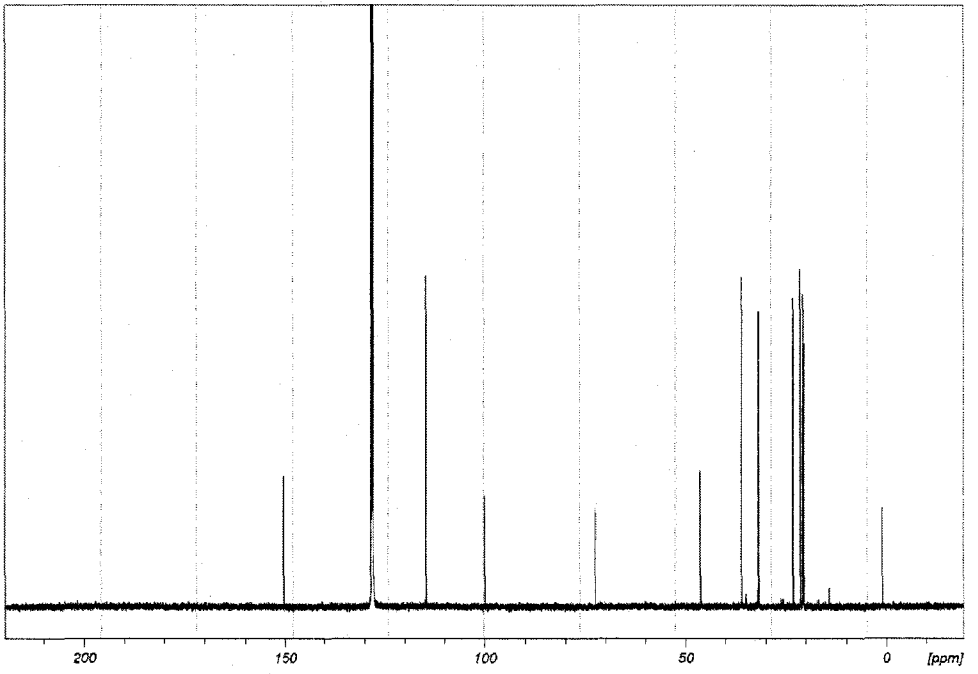


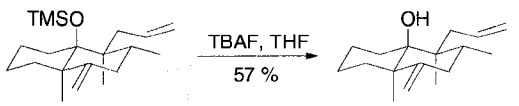
3.59b

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



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





3.34 **3.62**

(±)-(3R, 4S, 4aR, 8aR)-4-Allyl-decahydro-3,4,8a-trimethyl-1-methylenenapthalen-4a-ol (**3.62**)

A solution of **3.34** (359.0 mg, 1.12 mmol) in THF (12 mL) was treated with TBAF (1.0 M in THF, 2.24 mL, 2.24 mmol) and stirred at room temperature for 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 20 % EtOAc/hexanes, affording **3.62** (157.3 mg, 0.633 mmol, 57 %, $R_f = 0.50$) as a colorless oil.

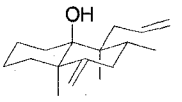
Data for **3.62**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11-6.02 (m, 1H), 4.98 (dddd, J = 17.1, 2.2, 2.2, 2.2 Hz, 1H), 4.93 (d, J = 11.7 Hz, 1H), 4.85 (s, 1H), 4.69 (s, 1H), 2.37-2.29 (m, 2H), 2.20-2.11 (m, 2H), 2.04 (dd, J = 13.9, 4.2 Hz, 1H), 1.96 (ddd, J = 12.2, 12.2, 3.7 Hz, 1H), 1.81-1.64 (m, 3H), 1.56-1.43 (m, 4H), 1.24-1.20 (m, 1H), 1.22 (s, 3H), 0.92 (s, 3H), 0.88 (d, J = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1 (C_4), 139.2 (CH), 115.3 (CH_2), 108.3 (CH_2), 80.3 (C_4), 45.8 (C_4), 45.1 (C_4), 42.3 (CH_2), 38.3 (CH_2), 35.6 (CH), 35.2 (CH_2), 27.2 (CH_2), 24.5 (CH_3), 21.3 (CH_2), 20.9 (CH_2), 18.5 (CH_3), 16.3 (CH_3)

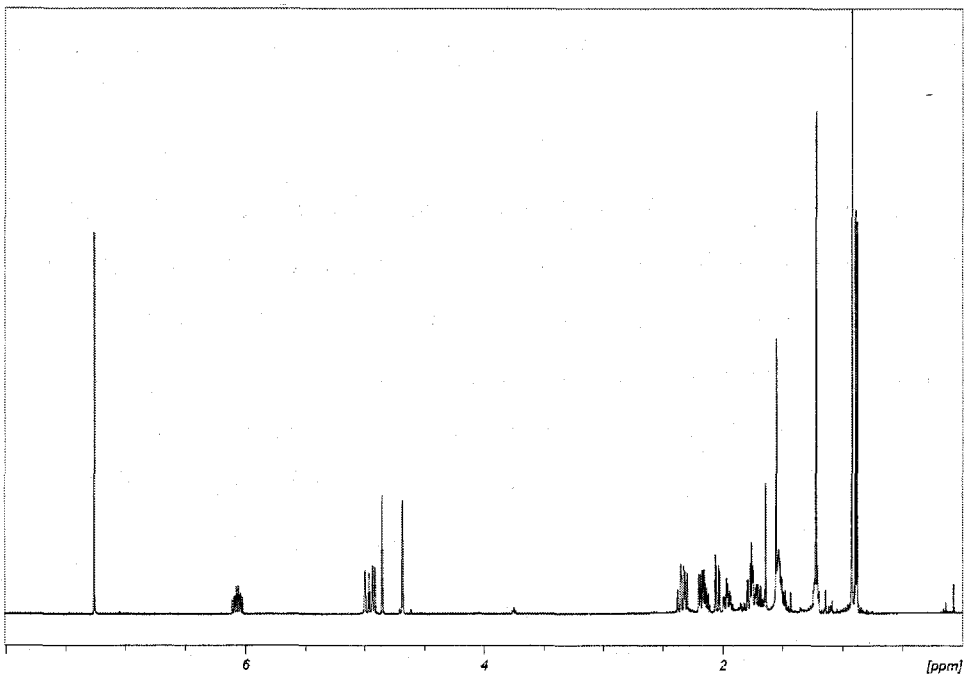
FT-IR (neat, cm^{-1}): 3573 (b), 3017 (w), 2984 (s), 2925 (s), 1633 (m)

HRMS (EI): Calculated 248.2140 (M^+) for $C_{17}H_{28}O$, found 248.2153

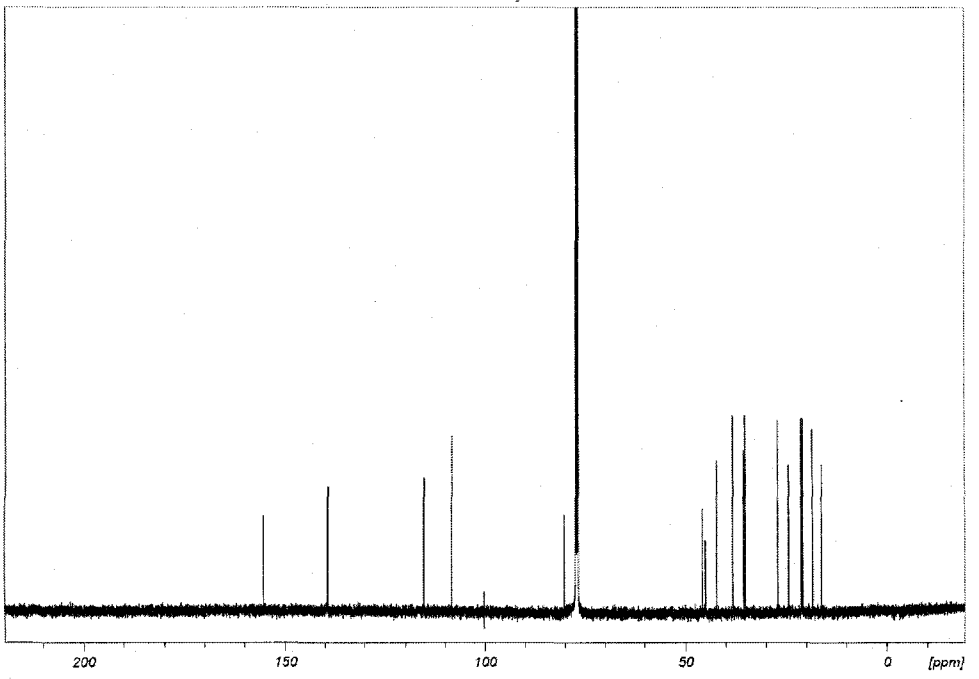


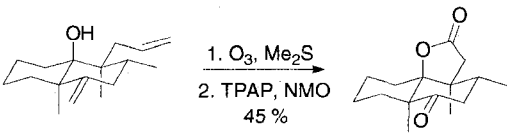
3.62

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.62 **3.63**

(±)-(3aS, 4R, 6aS, 10aS)-Octahydro-3a,4,6a-trimethyl-6aH-naptho[1-b]furan-2,6-dione (**3.63**)

A solution of **3.62** (157.3 mg, 0.633 mmol) in CH_2Cl_2 (10 mL) was degassed by bubbling with a stream of argon for 10 minutes and cooled to -78 °C. This solution was then bubbled with a stream of O_3 until the solution became blue (approximately 20 minutes). After this, the reaction was degassed by bubbling with a stream of argon for a further 10 minutes after which it was quenched by the addition of Me_2S (0.47 mL, 6.40 mmol). Warming to room temperature and concentration afforded **3.62int** as a brown oil which was used crude in the next step of the synthesis.

A solution of crude **3.62int** from the ozonolysis was dissolved in CH_2Cl_2 (10 mL) and cannulated into a flask containing dry molecular sieves (316.6 mg, 500 mg/mmol). This mixture was treated with NMO (148.4 mg, 1.27 mmol) and TPAP (22.3 mg, 0.0635 mmol) and stirred at room temperature for 2 hours. When complete, the mixture was filtered through a short pad of silica gel and the filter cake was washed with 5 % MeOH/EtOAc. The mother liquor was concentrated and the product was isolated by flash chromatography in 50 % EtOAc/hexanes affording **3.63** (71.5 mg, 0.286 mmol, 45 % over 2 steps, $R_f = 0.45$) as a white solid. A sample was recrystallized from CH_2Cl_2 and hexanes for X-ray analysis.

Data for **3.63**

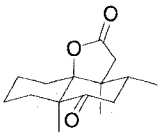
M.p.: 129-130 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.72 (dd, J = 13.9, 13.9 Hz, 1H), 2.54 (d, J_{AB} = 17.1 Hz, 1H), 2.37 (d, J_{AB} = 17.1 Hz, 1H), 2.15 (dd, J = 13.9, 4.3 Hz, 1H), 2.07-1.90 (m, 3H), 1.75-1.62 (m, 4H), 1.57-1.47 (m, 2H), 1.31 (s, 3H), 1.20 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.4 (C_4), 174.3 (C_4), 95.4 (C_4), 50.1 (C_4), 44.8 (C_4), 43.2 (CH_2), 41.2 (CH_2), 38.0 (CH), 28.4 (CH_2), 27.8 (CH_2), 21.3 (CH_3), 20.8 (CH_2), 19.5 (CH_2), 17.0 (CH_3), 14.3 (CH_3)

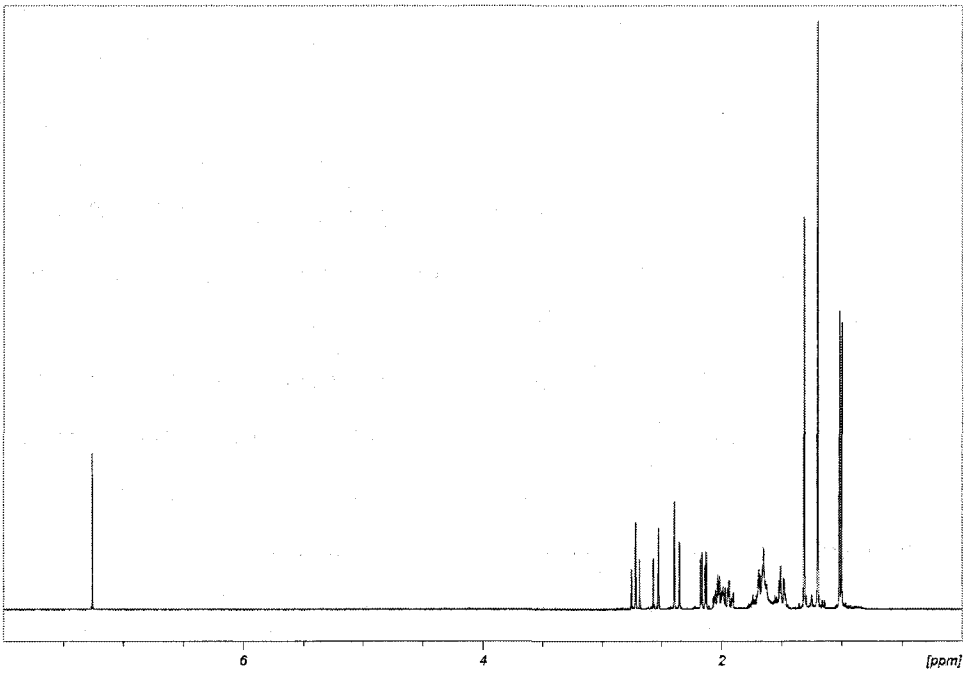
FT-IR (neat, cm^{-1}): 2967 (m), 2936 (m), 2871 (m), 1779 (s), 1714 (s)

HRMS (EI): Calculated 250.1569 (M^+) for $C_{15}H_{22}O_3$, found 250.1567

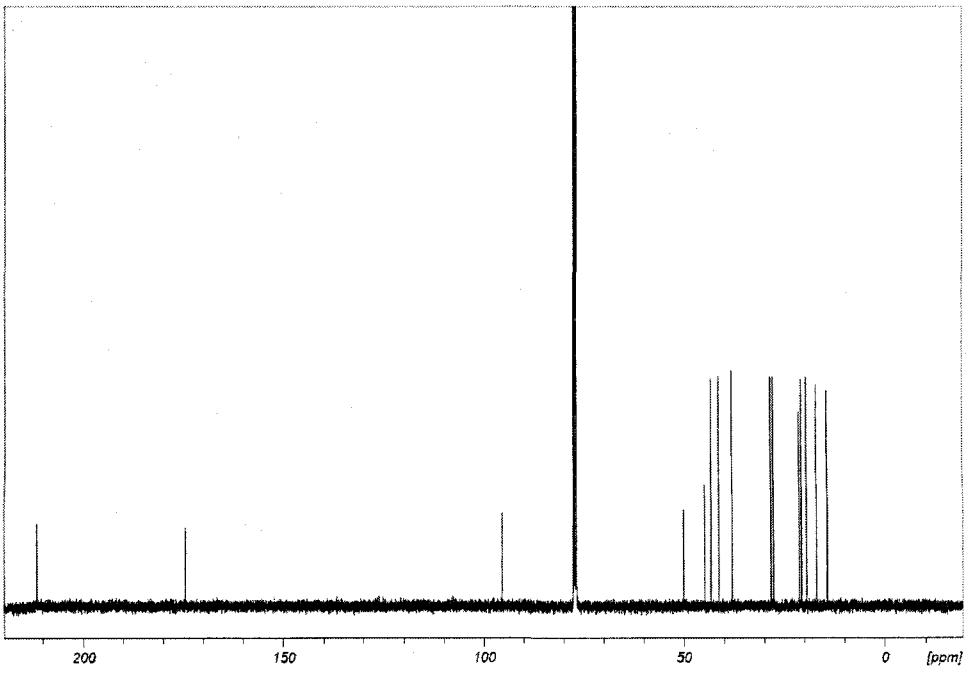


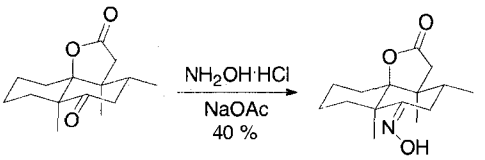
3.63

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





3.63 **3.64**

(±)-(E,3aS,4R,6aS,10aS)-Decahydro-6-hydroxyimino)-3a,4,6a-trimethylnaptho[1-b]furan-2-one (**3.64**)

A solution of **3.63** (71.5 mg, 0.286 mmol) in MeOH (5 mL) was treated with $NH_2OH{\cdot}HCl$ (39.7 mg, 0.571 mmol) and NaOAc (58.6 mg, 0.714 mmol). This mixture was heated at 50 °C for 20 hours after which all starting material had been consumed. Upon cooling, the reaction was diluted with H_2O (10 mL). Et_2O (15 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was recovered by flash chromatography in 50 % EtOAc/hexanes, affording **3.64** (30.6 mg, 0.115 mmol, 40 %, $R_f = 0.60$) as a white solid.

Data for **3.64**

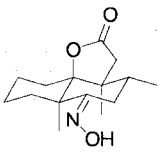
M.p.: 245-246 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (dd, J = 13.9, 13.9 Hz, 1H), 2.50 (d, J_{AB} = 17.2 Hz, 1H), 2.32 (d, J_{AB} = 17.2 Hz, 1H), 2.10 (ddd, J = 13.4, 13.4, 5.7 Hz, 1H), 1.94-1.87 (m, 1H), 1.78-1.71 (m, 2H), 1.69-1.51 (m, 7H), 1.31 (s, 3H), 1.10 (s, 3H), 1.00 (d, J = 6.6 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9 (C_4), 162.0 (C_4), 93.8 (C_4), 44.9 (C_4), 43.6 (CH_2), 43.3 (C_4), 36.5 (CH), 30.2 (CH_2), 27.8 (CH_2), 24.4 (CH_2), 22.4 (CH_3), 21.0 (CH_2), 19.8 (CH_2), 16.8 (CH_3), 14.3 (CH_3)

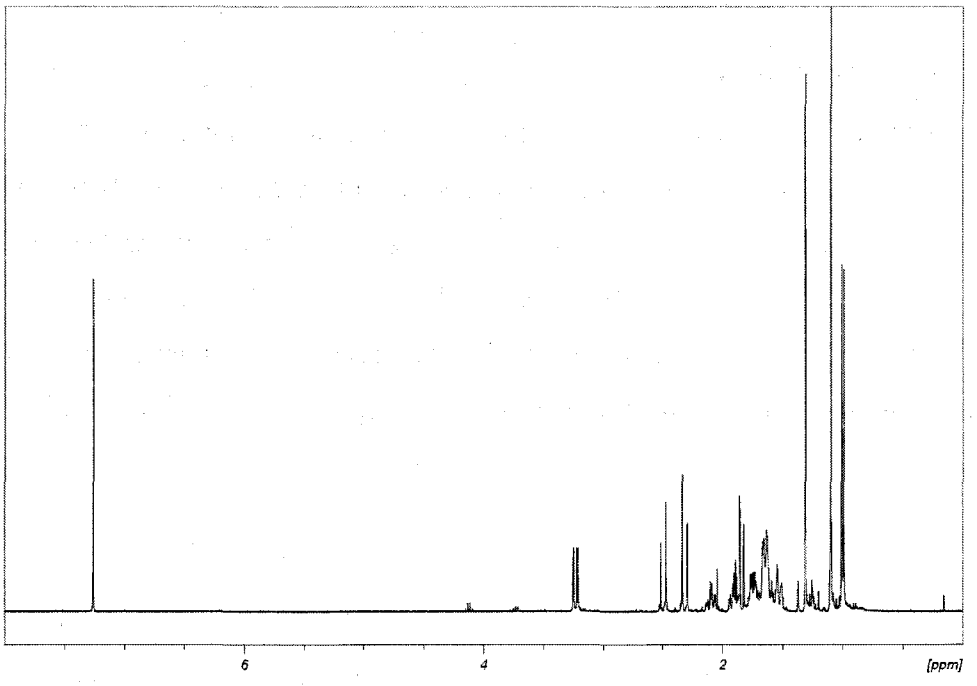
FT-IR (neat, cm^{-1}): 3233 (b), 3149 (b), 2963 (m), 2929 (m), 2882 (m), 1760 (s)

HRMS (EI): Calculated 265.1678 (M^+) for $C_{15}H_{23}NO_3$, found 265.1681

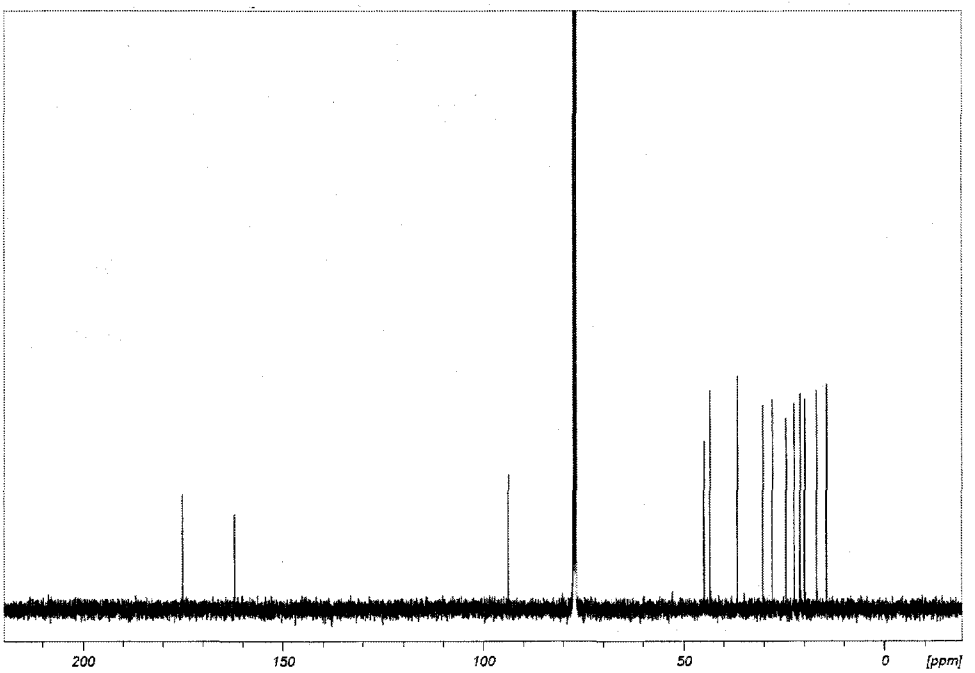


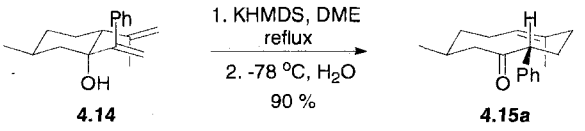
3.64

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-(E, 2S, 9S)-5,9-Dimethyl-2-phenylcyclodec-5-enone (**4.15a**)

Alcohol **4.14** (50.1 mg, 0.195 mmol) was dissolved in DME (3 mL) and treated with a solution of KHMDS (116.9 mg, 0.586 mmol) in DME (2 mL). The resulting mixture was heated at reflux for 15 minutes after which it was cooled to room temperature and then to -78 °C. The cooled solution was quenched with water followed by warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **4.15a** (45.1 mg, 0.176 mmol, 90 %, R_f = 0.50) as a white solid.

Data for **4.15a**

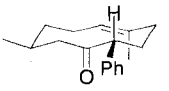
M.p.: 116-117 °C

^{1}H NMR (500 MHz, d_6-acteone): δ = 7.78-7.26 (m, 4H), 7.21-7.17 (m, 1H), 5.36 (d, J = 13.0 Hz, 1H), 3.72 (dd, J = 11.8, 1.6 Hz, 1H), 2.82-2.77 (m, 2H), 2.76-2.69 (m, 1H), 2.16-2.07 (m, 3H), 2.03-1.94 (m, 2H), 1.73-1.68 (m, 1H), 1.61 (dddd, J = 13.3, 3.6, 3.6, 1.9 Hz, 1H), 1.48 (s, 3H), 1.34-1.25 (m, 1H), 0.86 (d, J = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, d_6-acteone): δ = 206.7 (C_4), 142.2 (C_4), 139.2 (C_4), 129.9 (2 × CH), 129.1 (2 × CH), 128.1 (CH), 127.8 (CH), 61.7 (CH), 53.1 (CH_2), 42.1 (CH_2), 39.1 (CH_2), 36.3 (CH_2), 30.0 (CH), 28.8 (CH_2), 25.6 (CH_3), 16.8 (CH_3)

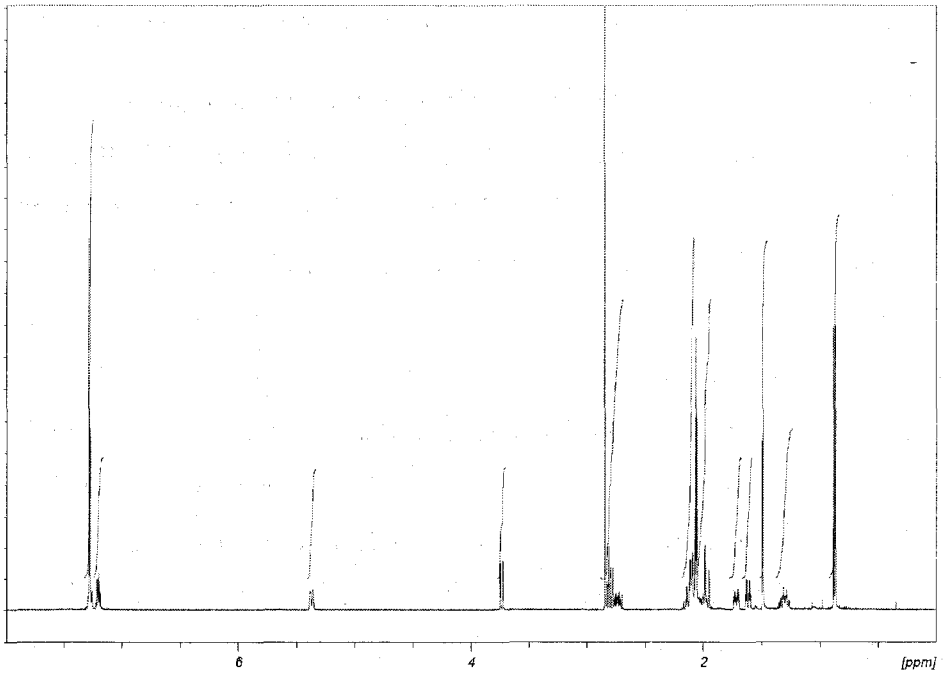
FT-IR (neat, cm^{-1}): 2928 (m), 2875 (m), 2845 (w), 1717 (s)

HRMS (EI): Calculated 256.1827 (M^+) for $C_{18}H_{24}O$, found 256.1822

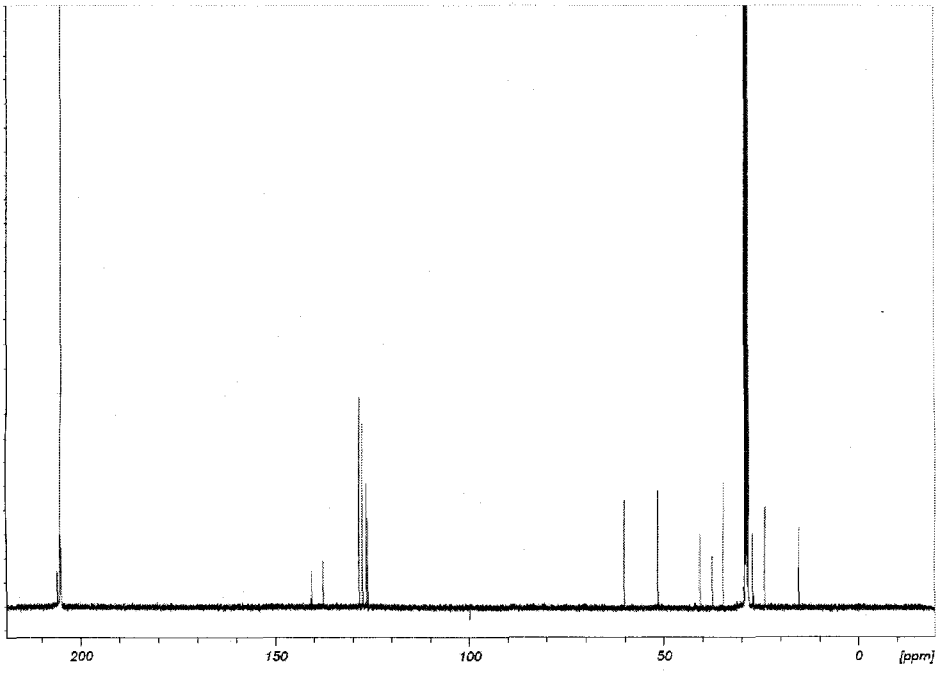


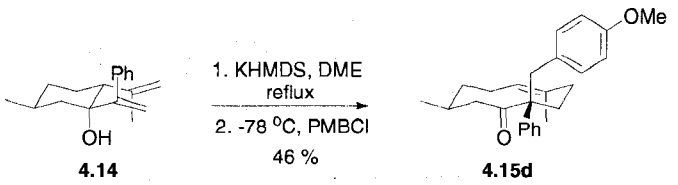
4.15a

^{1}H NMR (500 MHz, d_6-acteone)



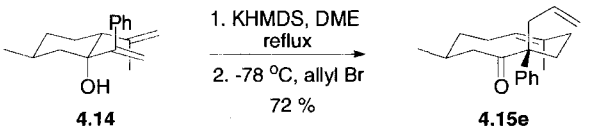
^{13}C NMR (125 MHz, d_6-acteone)





(±)-(E,2S,9S)-2-(4-Methoxybenzyl)-5,9-dimethyl-2-phenylcyclodec-5-enone (**4.15d**)

A solution of **4.14** (56.1 mg, 0.219 mmol) in DME (4 mL) was treated with a solution of KHMDS (131.0 mg, 0.657 mmol) in DME (3 mL). The resulting cloudy yellow solution was plunged into a pre-warmed oil bath and heated at 85 °C for 15 minutes whereupon it turned clear orange. This mixture was cooled to room temperature, then immediately to -78 °C after which it was treated with PMBCl (0.06 mL, 0.443 mmol). The reaction was stirred for a further 15 mintues and then it was quenched with water and warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 10 % EtOAc/hexanes, affording ketone **4.15d** (37.7 mg, 0.100 mmol, 46 %, R_f = 0.55) as a yellow oil. The product was difficult to characterize due to extreme line broadening in the NMR spectra, so it was characterized by derivatization to the ene reaction product. See compound **4.16**.



(±)-(E,2S,9S)-2-Allyl-5,9-dimethyl-2-phenylcyclodec-5-enone (**4.15e**)

Tertiary alcohol **4.14** (75.0 mg, 0.293 mmol) was dissolved in DME (5 mL) and to this was added a solution of KHMDS (175.0 mg, 0.878 mmol) in DME (3 mL). The resulting mixture was heated at reflux for 15 minutes after which is was cooled to room temperature and then -78 °C. To the cooled solution was added allyl bromide (0.05 mL, 0.585 mmol) and the mixture was stirred at -78 °C for 30 minutes. The reaction was quenched by the addition of water (8 mL) followed by warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Gradient flash chromatography from 2 to 5 % EtOAc/hexanes afforded **4.15e** (62.2 mg, 0.210 mmol, 72 %, R_f = 0.50) as a colorless oil.

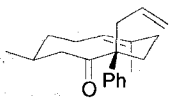
Data for **4.15e**

^{1}H NMR (500 MHz, d_6-acetone): δ = 7.35 (d, J = 7.8 Hz, 2H), 7.28 (dd, J = 7.8, 7.8 Hz, 2H), 7.16 (dd, J = 7.8, 7.8 Hz, 1H), 5.49 (d, J = 10.0 Hz, 1H), 5.30-5.25 (m, 1H), 5.17 (d, J = 17.1 Hz, 1H), 4.93 (d, J = 10.0 Hz, 1H), 3.30 (dd, J = 17.8 , 7.8 Hz, 1H), 3.25-3.17 (m, 2H), 2.86-2.82 (m, 2H), 2.40 (dd, J = 12.7, 12.7 Hz, 1H), 2.17-2.04 (m, 4H), 1.95 (dd, J = 24.2, 14.2 Hz, 1H), 1.71 (d, J = 13.7 Hz, 1H), 1.47 (s, 3H), 1.34 (ddd, J = 10.7, 10.7, 10.7 Hz, 1H), 0.94 (d, J = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 210.2 (C_4), 146.3 (C_4), 138.4 (CH), 135.4 (CH), 129.6 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 127.5 (CH), 118.5 (CH_2), 57.2 (C_4), 49.3 (CH_2), 38.7 (CH_2), 38.6 (CH_2), 36.5 (CH_2), 34.8 (CH_2), 29.1 (CH), 28.7 (CH_2), 25.8 (CH_3), 16.9 (CH_3)

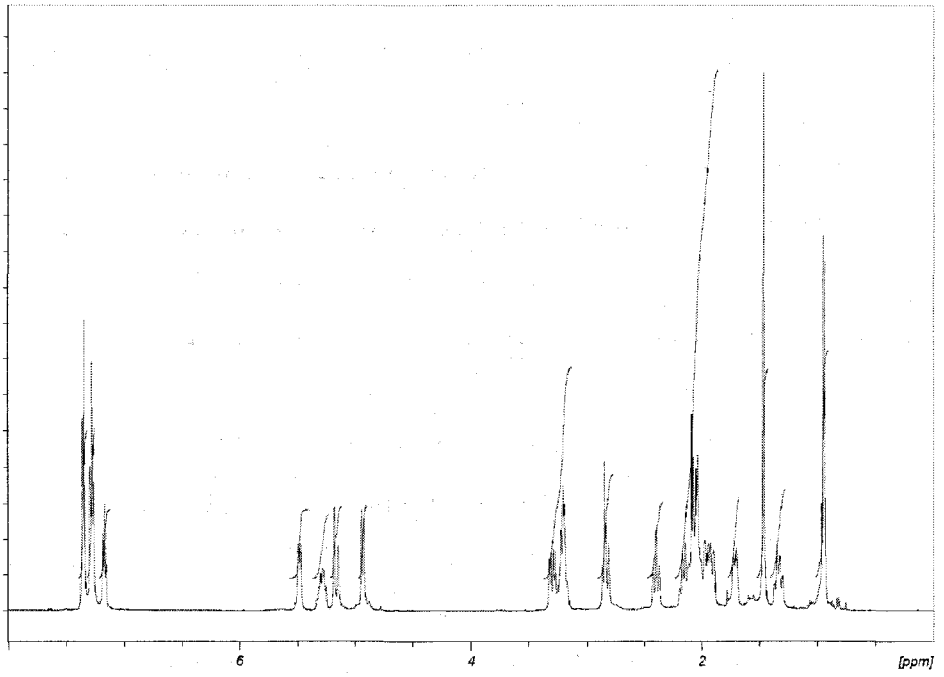
FT-IR (neat, cm^{-1}): 2951 (m), 2913 (m), 2865 (m), 1696 (s)

HRMS (EI): Calculated 296.2140 (M^+) for $C_{21}H_{28}O$, found 296.2112

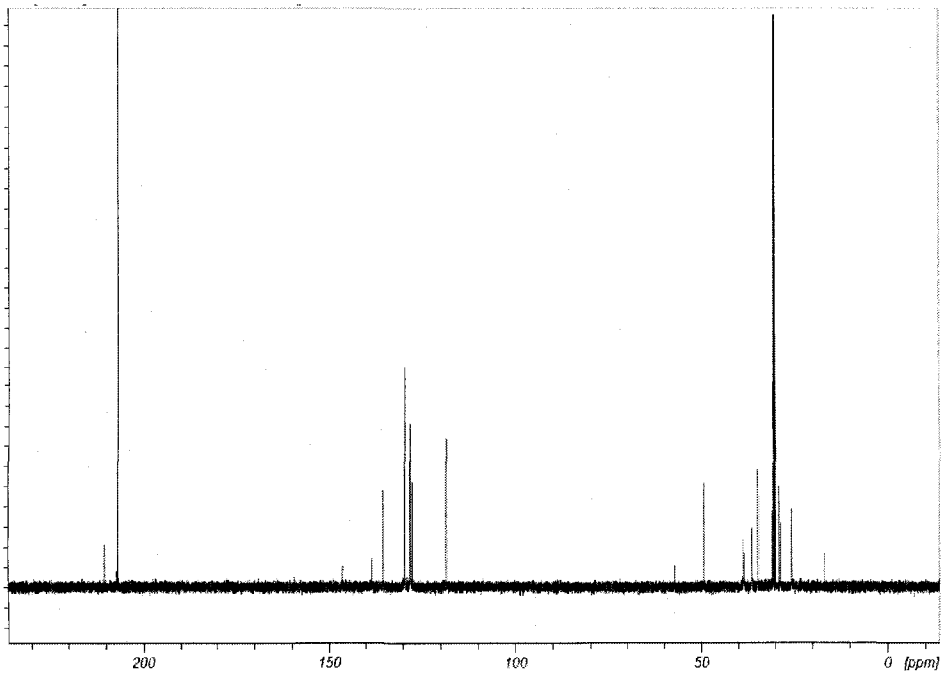


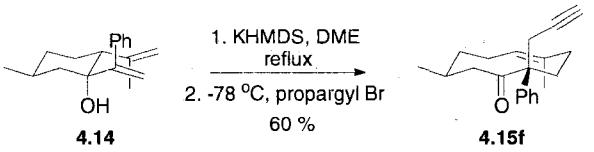
4.15e

^{1}H NMR (500 MHz, d_6-acetone)



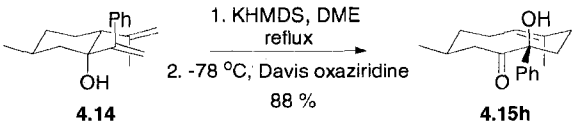
^{13}C NMR (125 MHz, d_6-acetone)





(±)-(E, 2S, 9S)-5,9-Dimethyl-2-phenyl-2-(prop-2-ynyl)cyclodec-5-enone (**4.15f**)

A solution of **4.14** (72.0 mg, 0.280 mmol) in DME (4 mL) was treated with a solution of KHMDS (168.0 mg, 0.842 mmol) in DME (2 mL). The resulting cloudy yellow solution was plunged into a pre-warmed oil bath and heated at 85 °C for 20 minutes whereupon it turned clear orange. This mixture was cooled to room temperature, then immediately to -78 °C after which it was treated with propargyl bromide (0.06 mL, 0.541 mmol). The reaction was stirred for a further 30 mintues and then it was quenched with water and warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 5 % EtOAc/hexanes, affording ketone **4.15f** (49.8 mg, 0.169 mmol, 60 %, R_f = 0.50) as a colorless oil. The product was difficult to characterize due to extreme line broadening in the NMR spectra, so it was fully characterized by derivatization to the ene reaction product.



4.14 **4.15h**

(±)-(E, 2S, 9S)-2-Hydroxy-5,9-dimethyl-2-phenylcyclodec-5-enone (**4.15h**)

Tertiary alcohol **4.14** (74.4 mg, 0.290 mmol) was dissolved dissolved in DME (4 mL) and treated with a solution of KHMDS (173.4 mg, 0.869 mmol) in DME (2 mL). The resulting mixture was heated at reflux for 15 minutes after which it was cooled to room temperature and then to -78 °C. To this was added a solution of the Davis oxaziridine (151.7 mg, 0.581 mmol) in DME (2 mL) and the mixture was stirred at -78 °C for 15 minutes. The reaction was quenched by the addition of water (10 mL) followed by warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **4.15h** (69.8 mg, 0.256 mmol, 88 %, $R_f = 0.65$) as a white solid.

Data for **4.15h**

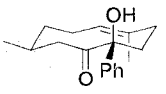
M.p.: 110-111 °C

^{1}H NMR (500 MHz, C_6D_6): δ = 7.60 (d, J = 7.9 Hz, 2H), 7.18-7.15 (m, 2H), 7.06 (dd, J = 7.3, 7.3 Hz, 1H), 5.37 (d, J = 9.8 Hz, 1H), 3.47 (dd, J = 17.5, 9.2 Hz, 1H), 3.06 (ddd, J = 13.8, 13.8, 3.5 Hz, 1H), 2.32 (ddd, J = 13.2, 13.2, 3.2 Hz, 1H), 2.18-2.08 (m, 2H), 1.96 (d, J = 13.1 Hz, 1H), 1.70-1.66 (m, 1H), 1.62 (s, 3H), 1.56-1.50 (m, 3H), 1.35 (ddd, J = 13.9, 3.4, 3.4 Hz, 1H), 1.13-1.06 (m, 1H), 0.69 (d, J = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 208.9 (C_4), 145.3 (C_4), 137.1 (C_4), 128.8 (2 × CH), 128.7 (CH), 127.8 (CH), 125.9 (2 × CH), 82.7 (C_4), 43.8 (CH_2), 41.6 (CH_2), 38.5 (CH_2), 35.6 (CH_2), 28.5 (CH), 28.2 (CH_2), 25.3 (CH_3), 16.7 (CH_3)

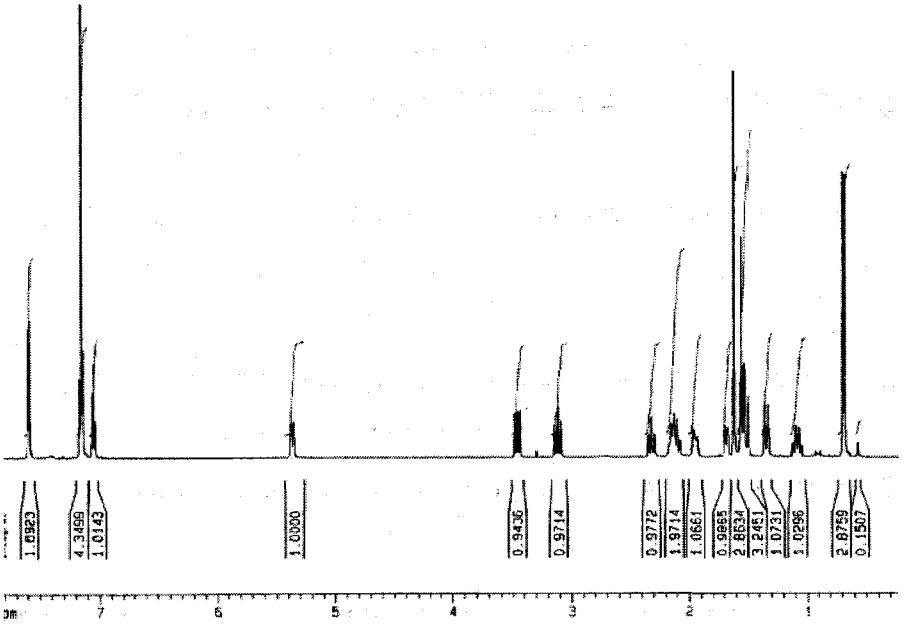
FT-IR (neat, cm^{-1}): 3472 (b), 2951 (s), 2914 (s), 2866 (m), 1692 (s)

HRMS (EI): Calculated 372.1776 (M^+) for $C_{18}H_{24}O_2$, found 372.1789

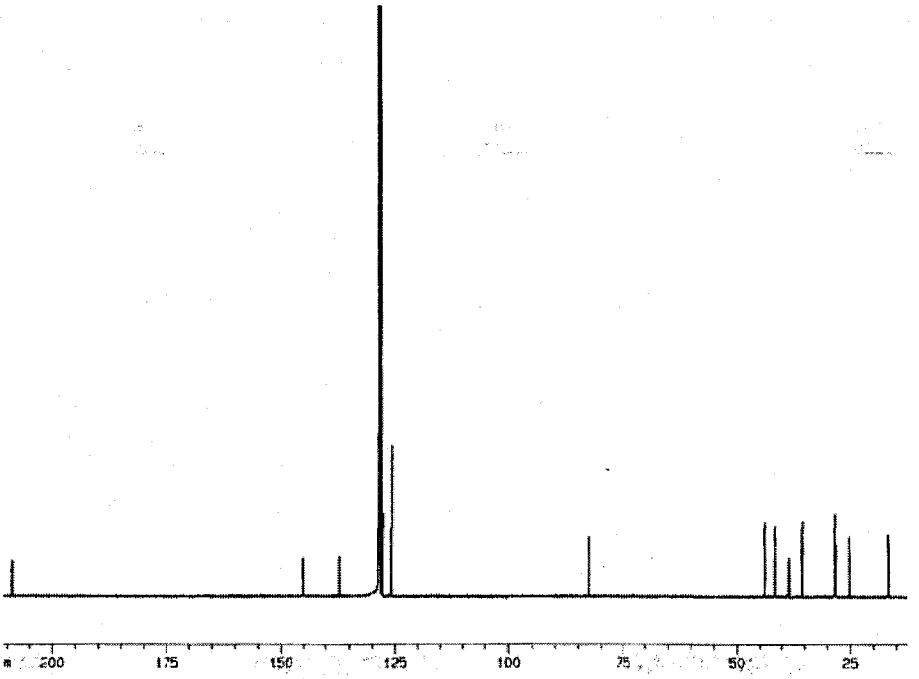


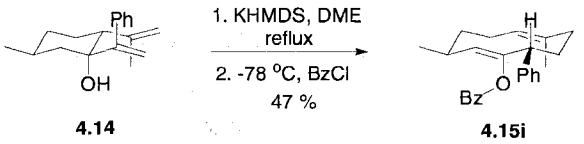
4.15h

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





4.14 **4.15i**

(±)-(3S, 10R)-3,7-Dimethyl-10-phenylcyclodeca-1,6-dienyl benzoate (**4.15i**)

Alcohol **4.14** (51.7 mg, 0.202 mmol) was dissolved in DME (3 mL) and treated with a solution of KHMDS (120.7 mg, 0.605 mmol) in DME (2 mL). The resulting mixture was heated at reflux for 15 minutes after which it was cooled to room temperature and then immediately to -78 °C. To the cooled solution was then added benzoyl chloride (0.047 mL, 0.403 mmol) and the mixture was stirred at -78 °C for 15 minutes. The reaction was quenched by the addition of water (10 mL) followed by warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **4.15i** (31.2 mg, 0.0948 mmol, 47 %, R_f = 0.50) as a white solid.

Data for **4.15i**

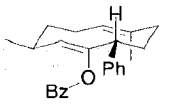
M.p.: 136-137 °C

^{1}H NMR (500 MHz, d_6-acetone): δ = 7.50 (dd, J = 8.3, 0.9 Hz, 2H), 7.40 (dd, J = 7.6, 7.6 Hz, 2H), 7.37-7.29 (m, 2H), 7.23-7.18 (m, 4H), 5.67 (d, J = 10.3 Hz, 1H), 5.16 (d, J = 10.7 Hz, 1H), 2.79 (ddd, J = 13.7, 13.7, 2.2 Hz, 1H), 2.53-2.49 (m, 1H), 2.39-2.31 (m, 2H), 2.17 (ddd, J = 14.2, 5.9, 1.9 Hz, 1H), 2.12-2.08 (m, 3H), 1.74 (s, 3H), 1.65 (dddd, J = 13.4, 2.9, 2.9, 2.9 Hz, 1H), 1.37-1.29 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 204.0 (C_4), 149.3 (C_4), 142.9 (C_4), 142.6 (C_4), 131.8 (CH), 131.7 (CH), 130.4 (C_4), 130.1 (2 × CH), 130.0 (2 × CH), 129.5 (2 × CH), 129.0 (2 × CH), 128.8 (CH), 119.6 (CH), 64.5 (CH), 38.6 (CH_2), 38.5 (CH_2), 33.6 (CH), 29.6 (CH_2), 28.4 (CH_2), 23.5 (CH_3), 16.9 (CH_3)

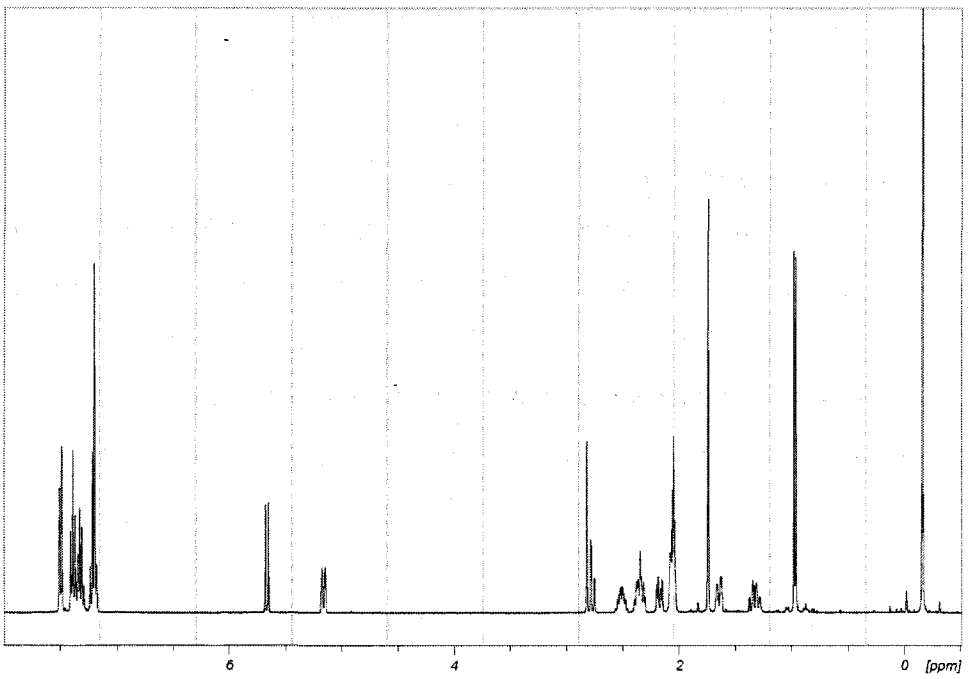
FT-IR (neat, cm^{-1}): 2961 (m), 2944 (m), 2911 (m), 1676 (s)

HRMS (EI): Calculated 360.2089 (M^+) for $C_{25}H_{28}O_2$, found 360.2091

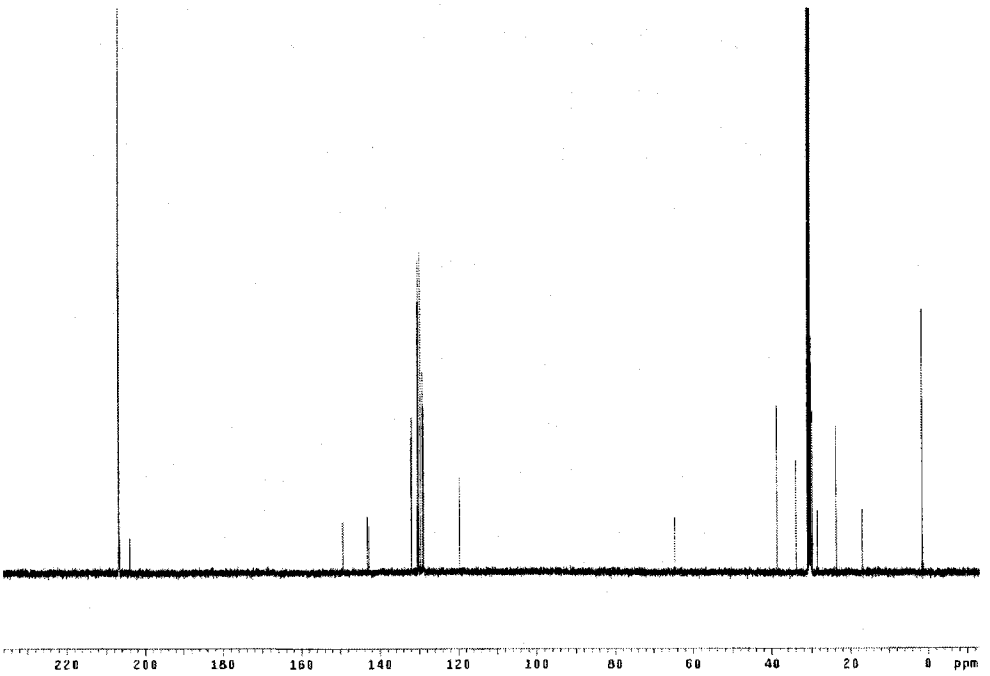


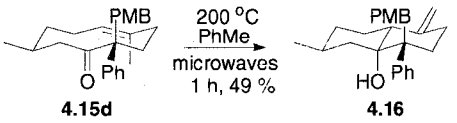
4.15i

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





4.15d **4.16**

(±)-(4S, 4aR, 6S, 8aR)-4-(4-Methoxybenzyl)-decahydro-6-methyl-1-methylene-4-phenylnapthalen-4a-ol (**4.16**)

A sample of **4.15d** (37.7 mg, 0.100 mmol) was dissolved in toluene (13 mL) and placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 200 °C over 20 minutes, then for 1 hour at 200 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 10 % EtOAc/hexanes, affording **4.16** (18.5 mg, 0.0491 mmol, 49 %, R_f = 0.40) as a white solid.

Data for **4.16**

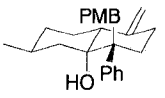
M.p.: 61-62 °C

^{1}H NMR (400 MHz, d_6-acetone): δ = 7.62 (d, J = 7.4 Hz, 2H), 7.33 (dd, J = 7.7, 7.7 Hz, 2H), 7.24-7.20 (m, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 4.81 (d, J = 1.4 Hz, 1H), 4.61 (d, J = 0.7 Hz, 1H), 3.76 (d, J_{AB} = 15.0 Hz, 1H), 3.67 (s, 3H), 3.37 (d, J_{AB} = 15.0 Hz, 1H), 2.66-2.52 (m, 3H), 2.15-2.12 (m, 1H), 1.98-1.96 (m, 1H), 1.74-1.58 (m, 5H), 1.46-1.39 (m, 2H), 1.06-0.93 (m, 1H), 0.83 (d, J = 6.4 Hz, 3H)

^{13}C NMR (100 MHz, d_6-acetone): δ = 158.9 (C_4), 151.0 (C_4), 143.4 (C_4), 131.9 (C_4), 131.9 (2 × CH), 131.4 (2 × CH), 128.0 (2 × CH), 126.9 (CH), 114.0 (2 × CH), 107.7 (CH_2), 77.7 (C_4), 55.4 (CH_3), 51.8 (C_4), 44.9 (CH), 42.0 (CH_2), 36.1 (CH_2), 35.5 (CH_2), 33.2 (CH_2), 30.4 (CH_2), 28.4 (CH), 26.1 (CH_2), 23.1 (CH_3)

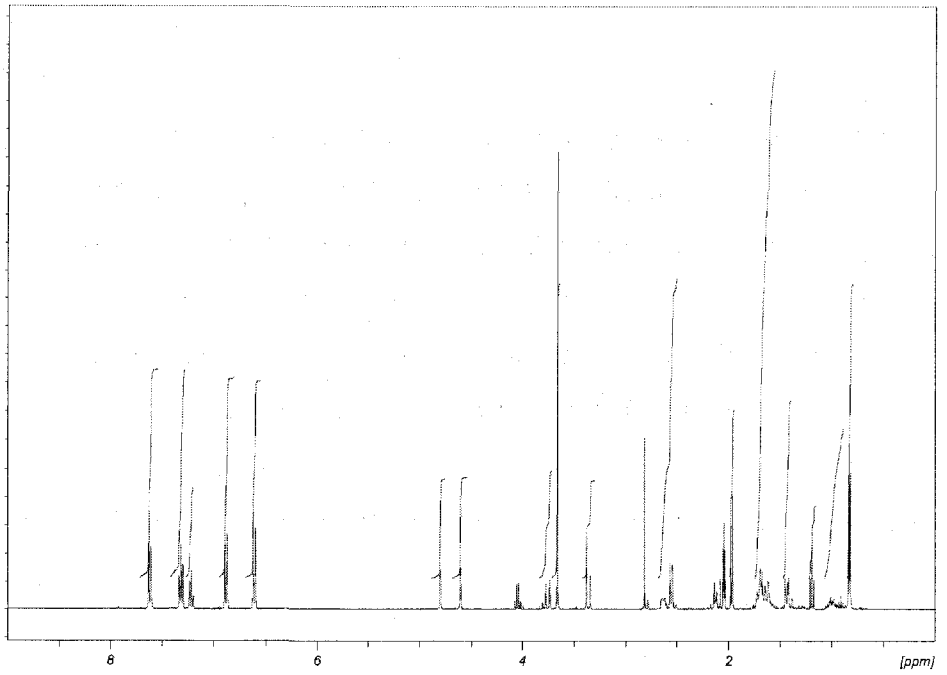
FT-IR (neat, cm^{-1}): 3559 (m), 2948 (m), 2928 (m), 2866 (w), 2847 (w)

HRMS (EI): Calculated 376.2402 (M^+) for $C_{26}H_{32}O_2$, found 376.2395

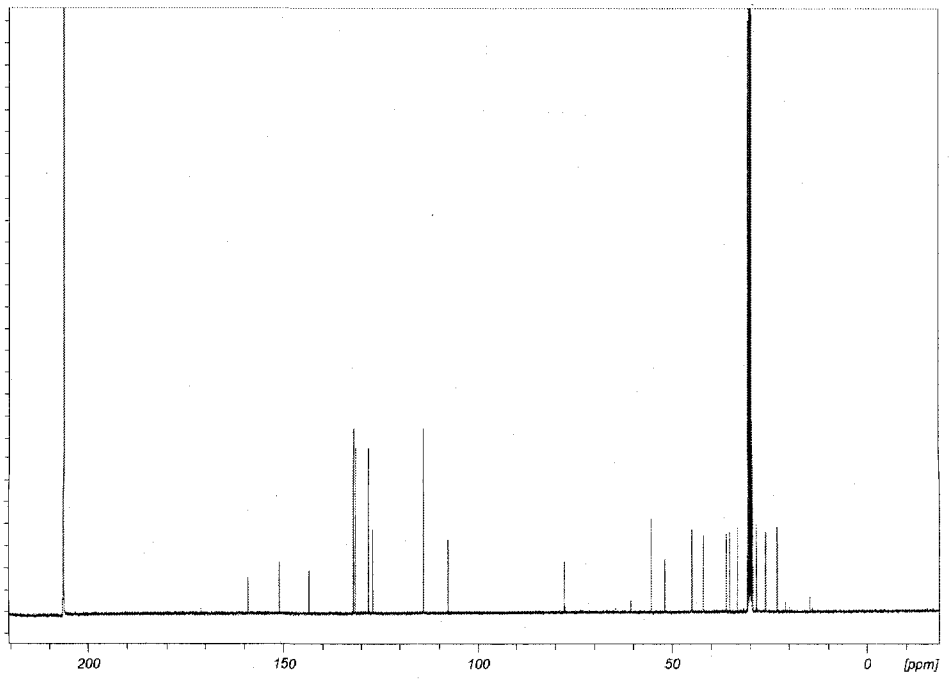


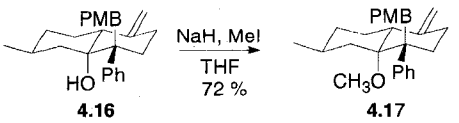
4.16

^{1}H NMR (400 MHz, d_6-acetone)



^{13}C NMR (100 MHz, d_6-acetone)





(±)-(1S, 4aR, 7S, 8aR)-1-(4-Methoxybenzyl)-decahydro-8a-methoxy-7-methyl-4-methylene-1-phenylnapthalene (**4.17**)

A solution of **4.16** (18.5 mg, 0.0491 mmol) in THF (4 mL) cooled to 0 °C was treated with NaH (60 % in oil, 15.7 mg, 0.393 mmol) and then stirred at 0 °C for 10 minutes. The mixture was then treated with MeI (0.02 mL, 0.320 mmol) and stirred for 1 hour while warming to room temperature and then for 16 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **4.17** (13.9 mg, 0.0356 mmol, 72 %, R_f = 0.55) as a white solid.

Data for **4.17**

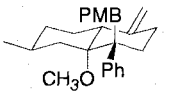
M.p.: 144-145 °C

^{1}H NMR (400 MHz, d_6-acetone): δ = 7.66 (bs, 2H), 7.34 (dd, J = 7.9, 7.9 Hz, 2H), 7.28-7.24 (m, 1H), 6.76 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 4.72 (d, J = 1.4 Hz, 1H), 4.52 (d, J = 1.2 Hz, 1H), 3.65 (s, 3H), 3.59 (d, J_{AB} = 14.4 Hz, 1H), 3.34 (d, J_{AB} = 14.4 Hz, 1H), 2.68-2.57 (m, 3H), 2.38 (s, 3H), 2.38-2.33 (m, 1H), 2.23-2.17 (m, 1H), 1.77-1.60 (m, 3H), 1.58-1.41 (m, 3H), 1.05 (dddd, J = 12.3, 12.3, 12.3, 4.2 Hz, 1H), 0.96 (d, J = 6.2 Hz, 3H)

^{13}C NMR (100 MHz, d_6-acetone): δ = 159.0 (C_4), 151.0 (C_4), 144.8 (C_4), 131.9 (2 × CH), 131.6 (C_4), 131.2 (2 × CH), 128.4 (CH), 127.2 (2 × CH), 113.8 (2 × CH), 106.5 (CH_2), 83.8 (C_4), 55.3 (CH_3), 52.1 (CH_3), 51.4 (C_4), 46.4 (CH), 38.3 (CH_2), 36.5 (CH_2), 35.2 (CH_2), 33.2 (CH_2), 30.5 (CH_2), 30.3 (CH), 26.4 (CH_2), 23.2 (CH_3)

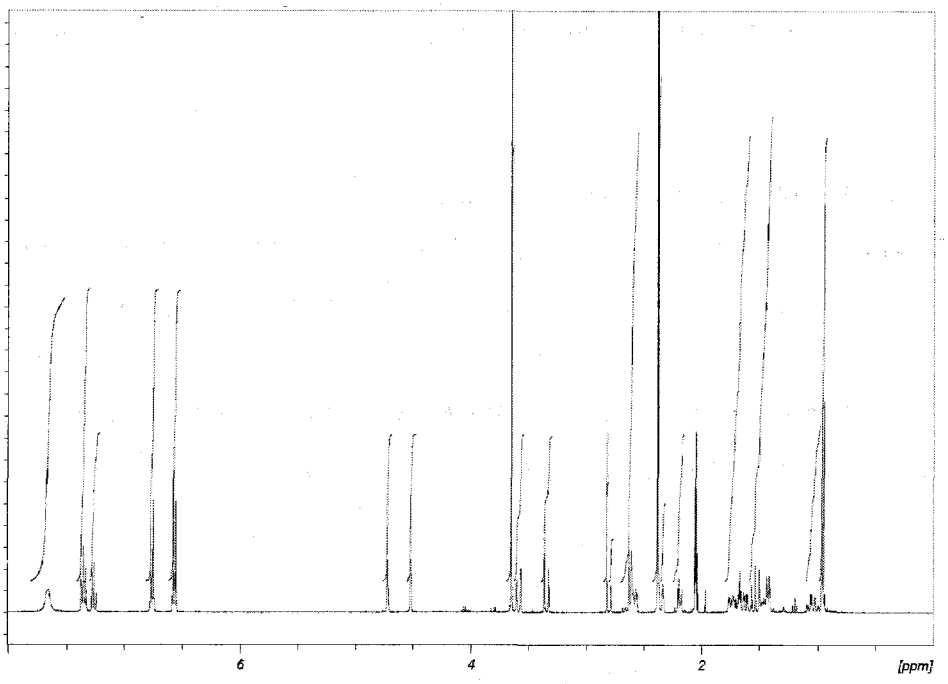
FT-IR (neat, cm^{-1}): 2925 (m), 2866 (m), 2835 (m), 1645 (m), 1606 (w)

HRMS (EI): Calculated 390.2559 (M^+) for $C_{27}H_{34}O_2$, found 390.2521

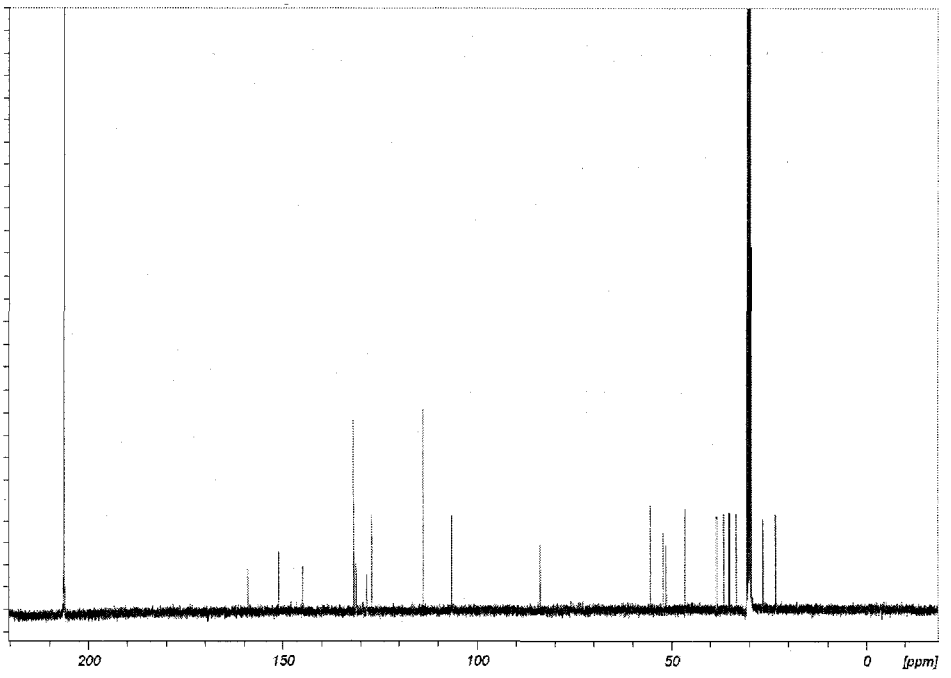


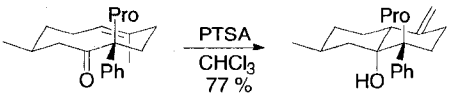
4.17

^{1}H NMR (400 MHz, d_6-acetone)



^{13}C NMR (100 MHz, d_6-acetone)





4.15f **4.18**

(±)-(4S,4aR,6S,8aR)-6-Methyl-1-methylene-4-phenyl-4-(prop-2-ynyl)-octahydro-napthalene-4a-ol (**4.18**)

To a solution of **4.15f** (24.9 mg, 0.0846 mmol) in $CHCl_3$ (4 mL) was added PTSA (1.6 mg, 0.00842 mmol), and the mixture was stirred at room temperature for 19 hours. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded **4.18** (19.1 mg, 0.0649 mmol, 77 %, R_f = 0.40) as a colorless oil.

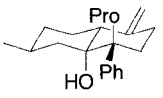
Data for **4.18**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (dd, J = 8.5, 1.0 Hz, 2H), 7.37 (dd, J = 8.5, 7.7 Hz, 2H), 7.29-7.26 (m, 1H), 4.98 (d, J = 1.5 Hz, 1H), 4.75 (d, *J* = 1.2 Hz, 1H), 3.15 (ddd, J_{AB} = 17.1 Hz, J = 2.2, 2.2 Hz, 1H), 3.07 (dd, J_{AB} = 17.1 Hz, J = 2.4 Hz, 1H), 2.61-2.55 (m, 1H), 2.48-2.38 (m, 2H), 2.26 (d, J = 11.2 Hz, 1H), 2.08 (ddd, J = 13.2, 3.2, 3.2 Hz, 1H), 1.83 (dd, J = 2.7, 2.7 Hz, 1H), 1.75-1.61 (m, 4H), 1.22 (bs, 1H), 1.17-1.14 (m, 1H), 1.05 (dd, J = 13.2, 11.7 Hz, 1H), 0.88 (dddd, J = 12.2, 12.2, 12.2, 4.2 Hz, 1H), 0.77 (d, J = 6.6 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.3 (C_4), 140.7 (C_4), 129.4 (2 × CH), 127.8 (2 × CH), 126.8 (CH), 109.0 (CH_2), 81.7 (C_4), 76.0 (C_4), 71.0 (CH), 50.1 (C_4), 44.1 (CH), 41.0 (CH_2), 34.4 (CH_2), 32.2 (CH_2), 31.2 (CH_2), 27.5 (CH), 25.1 (CH_2), 22.5 (CH_3), 21.7 (CH_2)

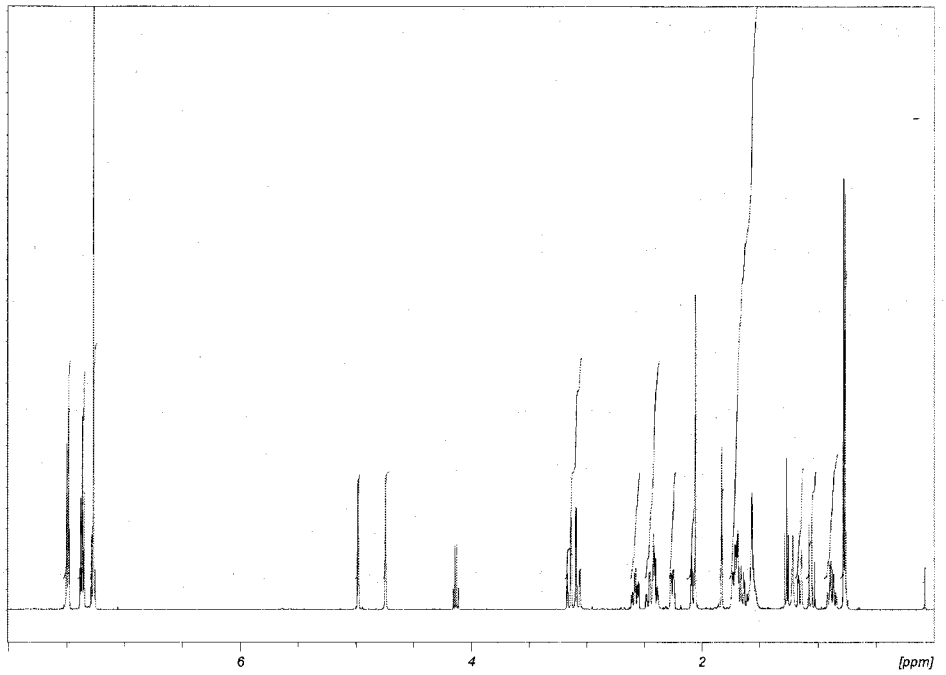
FT-IR (neat, cm^{-1}): 3565 (b), 2948 (s), 2926 (s), 2866 (m), 2115 (w)

HRMS (EI): Calculated 294.1984 (M^+) for $C_{21}H_{26}O$, found 294.1977

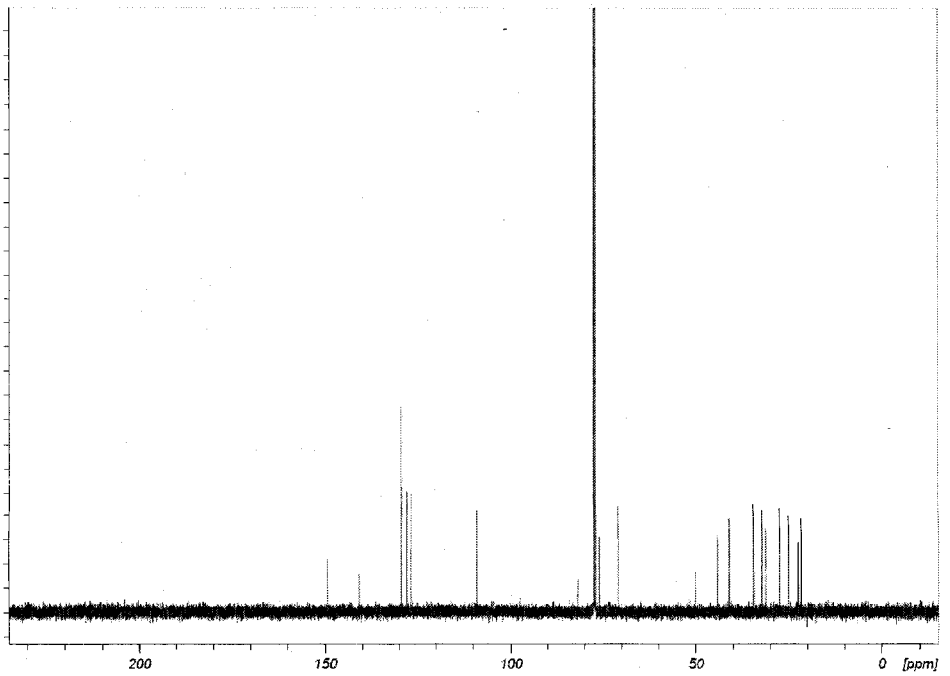


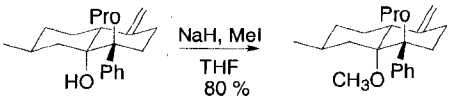
4.18

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)





4.18 **4.19**

(±)-(1S, 4aR, 7S, 8aR)-Decahydro-8a-methoxy-7-methyl-4-methylene-1-phenyl-1-(prop-2-ynyl)naphthalene (**4.19**)

To a solution of **4.18** (19.1 mg, 0.0649 mmol) in THF (3 mL) cooled to 0 °C was added NaH (60% in mineral oil, 5.2 mg, 0.130 mmol) and the mixture was stirred for 10 minutes. Iodomethane (0.01 mL, 0.160 mmol) was added to the solution, which was warmed to room temperature over 1 hour then stirred at room temperature for 16 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **4.19** (16.1 mg, 0.0522 mmol, 80 %, R_f = 0.55) as a white solid.

Data for **4.19**

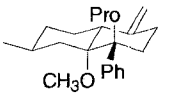
M.p.: 178-179 °C

^{1}H NMR (500 MHz, C_6D_6): δ = 7.50 (d, J = 7.3 Hz, 2H), 7.27-7.24 (m, 2H), 7.17 (dd, J = 7.1, 7.1 Hz, 1H), 5.08 (s, 1H), 4.88 (s, 1H), 3.08-3.02 (m, 1H), 2.82 (d, J = 2.4 Hz, 2H), 2.58 (s, 3H), 2.54 (dd, J = 8.1, 3.1 Hz, 2H), 2.30 (ddd, J = 12.4, 3.4, 3.4, 1H), 1.98-1.91 (m, 2H), 1.84-1.68 (m, 4H), 1.03-0.99 (m, 1H), 0.90 (dd, J = 12.0, 9.3 Hz, 1H), 0.85 (d, J = 6.6 Hz, 3H), 0.83-0.77 (m, 1H)

^{13}C NMR (125 MHz, C_6D_6): δ = 149.5 (C_4), 143.2 (C_4), 130.1 (2 × CH), 128.1 (2 × CH), 126.9 (CH), 107.6 (CH), 82.0 (C_4), 81.6 (C_4), 70.8 (CH), 52.6 (CH_3), 49.8 (C_4), 46.2 (CH), 36.1 (CH_2), 34.9 (CH_2), 32.7 (CH_2), 31.2 (CH_2), 30.0 (CH), 25.8 (CH_2), 24.5 (CH_2), 23.1 (CH_3)

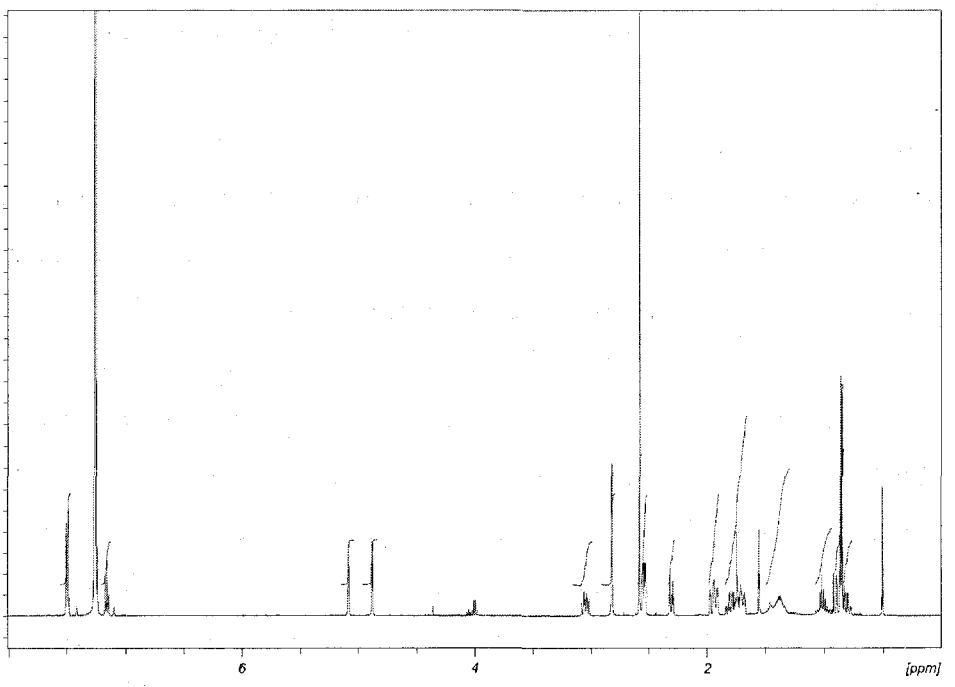
FT-IR (neat, cm^{-1}): 2936 (m), 2867 (s), 2855 (s), 2836 (s), 2115 (w)

HRMS (EI): Calculated 308.2140 (M^+) for $C_{22}H_{28}O$, found 308.2137

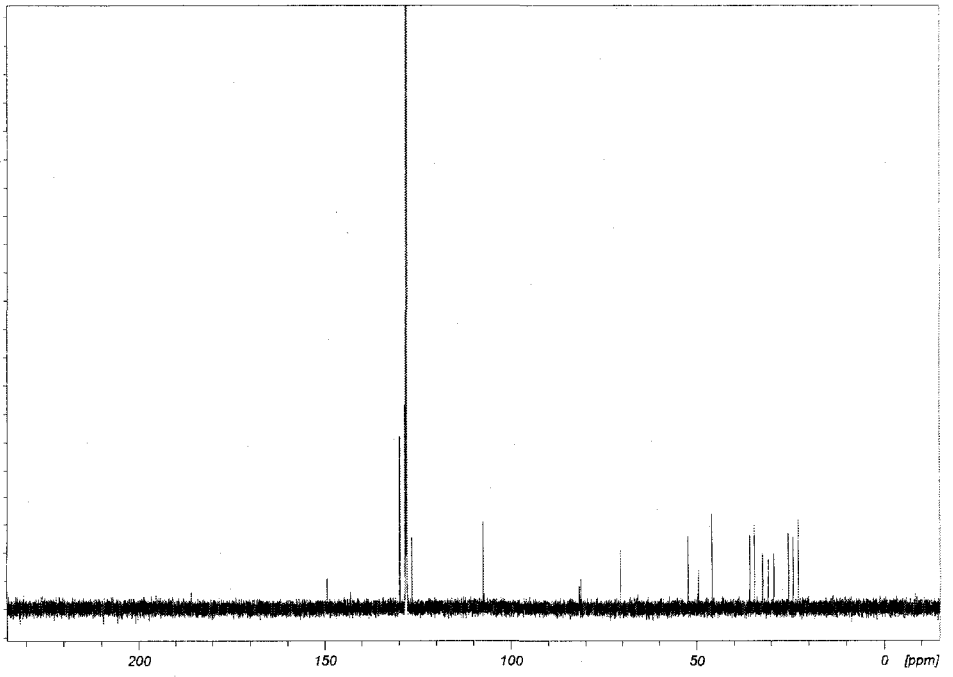


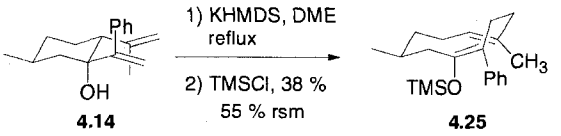
4.19

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





(±)-((S, 1Z, 5E)-5,9-Dimethyl-2-phenylcyclodeca-1,5-dienyloxy)trimethylsilane (**4.25**)

A solution of **4.14** (86.1 mg, 0.336 mmol) in DME (4 mL) was treated with a solution of KHMDS (201.0 mg, 1.01 mmol) in DME (2 mL). The resulting cloudy yellow solution was plunged into a pre-warmed oil bath and heated at 85 °C for 15 minutes whereupon it turned clear orange. This mixture was cooled to room temperature, then immediately to -78 °C after which it was treated with TMSCl (0.09 mL, 0.709 mmol). The reaction was stirred for a further 15 mintues and then it was quenched with water and warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in hexanes, affording silyl enol ether **4.25** (41.7 mg, 0.127 mmol, 38 %, R_f = 0.40) as a colorless oil. Also recovered was ketone **4.14** (47.4 mg, 0.185 mmol, 55 %, R_f = 0.50) as a colorless oil by increasing the polarity of the eluting solvent to 10 % EtOAc/hexanes.

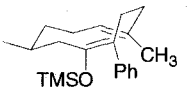
Data for **4.25**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.40 (d, J = 7.2 Hz, 2H), 7.21 (dd, J = 7.6, 7.6 Hz, 2H), 7.07 (dd, J = 7.5, 7.5 Hz, 1H), 5.32 (dd, J = 10.5, 4.6 Hz, 1H), 2.39-2.20 (m, 4H), 2.06-1.96 (m, 3H), 1.91-1.81 (m, 3H), 1.63 (s, 3H), 1.52-1.50 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), -0.13 (s, 9H)

^{13}C NMR (100 MHz, d_6-acetone): δ = 149.9 (C_4), 142.6 (C_4), 131.2 (2 × CH), 129.6 (CH), 129.2 (C_4), 128.2 (2 × CH), 126.3 (CH), 119.2 (C_4), 38.7 (CH_2), 37.0 (CH_2), 33.0 (CH_2), 30.8 (CH_2), 30.6 (CH), 23.5 (CH_2), 21.0 (CH_3), 17.1 (CH_3), -0.3 (3 × CH_3)

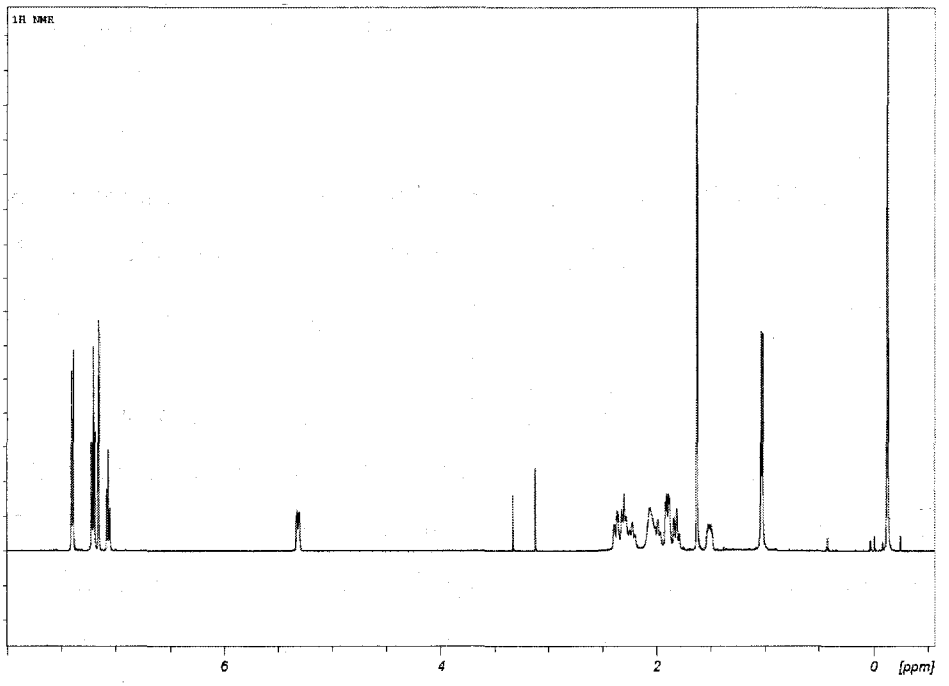
FT-IR (neat, cm^{-1}): 2953 (s), 2919 (s), 2854 (s), 1599 (m)

HRMS (EI): Calculated 328.2222 (M^+) for $C_{21}H_{32}OSi$, found 328.2212

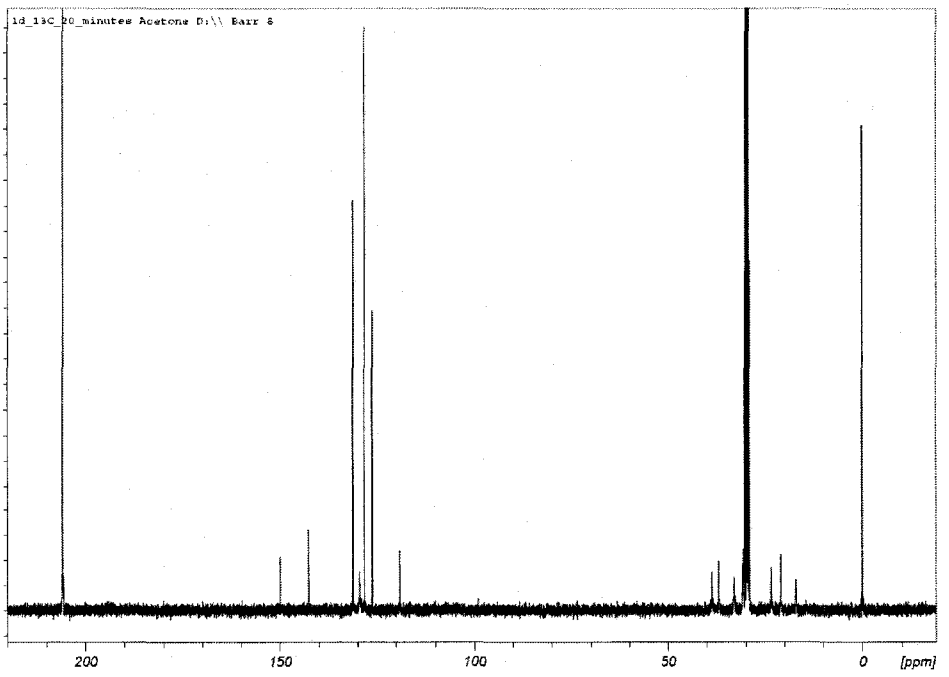


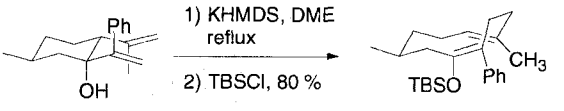
4.25

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



^{13}C NMR (100 MHz, d_6-acetone)





4.14 **4.26**

(±)-((S,1Z,5E)-5,9-Dimethyl-2-phenylcyclodeca-1,5-dienyloxy)-(tert-butyl)dimethylsilane (**4.26**)

A solution of **4.14** (49.6 mg, 0.193 mmol) in DME (3 mL) was treated with a solution of KHMDS (115.8 mg, 0.580 mmol) in DME (2 mL). The resulting cloudy yellow solution was plunged into a pre-warmed oil bath and heated at 85 °C for 15 minutes whereupon it turned clear orange. This mixture was cooled to room temperature, then immediately to -78 °C after which it was treated with TBSCl (58.3 mg, 0.387 mmol). The reaction was stirred for a further 15 mintues and then it was quenched with water and warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in hexanes, affording silyl enol ether **4.26** (57.6 mg, 0.155 mmol, 80 %, $R_f = 0.60$) as a colorless oil.

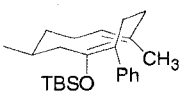
Data for **4.26**

^{1}H NMR (400 MHz, d_6-acetone): δ = 7.34-7.26 (m, 4H), 7.15 (dd, J = 7.2, 7.2 Hz, 1H), 5.14 (d, J = 8.5 Hz, 1H), 2.42-2.25 (m, 4H), 2.08-1.87 (m, 5H), 1.70 (s, 3H), 1.61-1.51 (m, 2H), 1.03 (d, J = 7.0 Hz, 3H), 0.75 (s, 9H), -0.02 (s, 3H), -0.59 (s, 3H)

^{13}C NMR (75 MHz, d_6-acetone): δ = 150.1 (C_4), 142.8 (C_4), 131.9 (2 × CH), 130.2 (CH), 129.0 (C_4), 128.7 (2 × CH), 126.7 (CH), 119.8 (C_4), 38.4 (CH_2), 37.3 (CH_2), 32.8 (CH_2), 31.3 (CH_2), 30.6 (CH), 26.4 (3 × CH_3), 23.5 (CH_2), 20.9 (CH_3), 18.8 (C_4), 17.2 (CH_3), -3.8 (CH_3), -4.6 (CH_3)

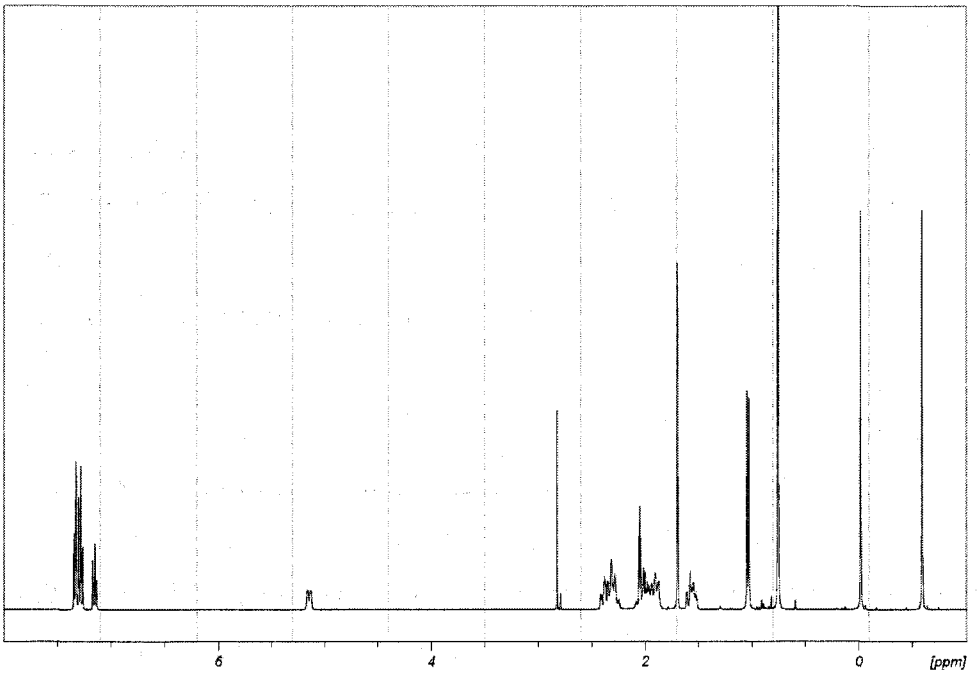
FT-IR (neat, cm^{-1}): 2960 (s), 2927 (s), 2855 (s), 1630 (m)

HRMS (EI): Calculated 370.2692 (M^+) for $C_{24}H_{38}OSi$, found 370.2700

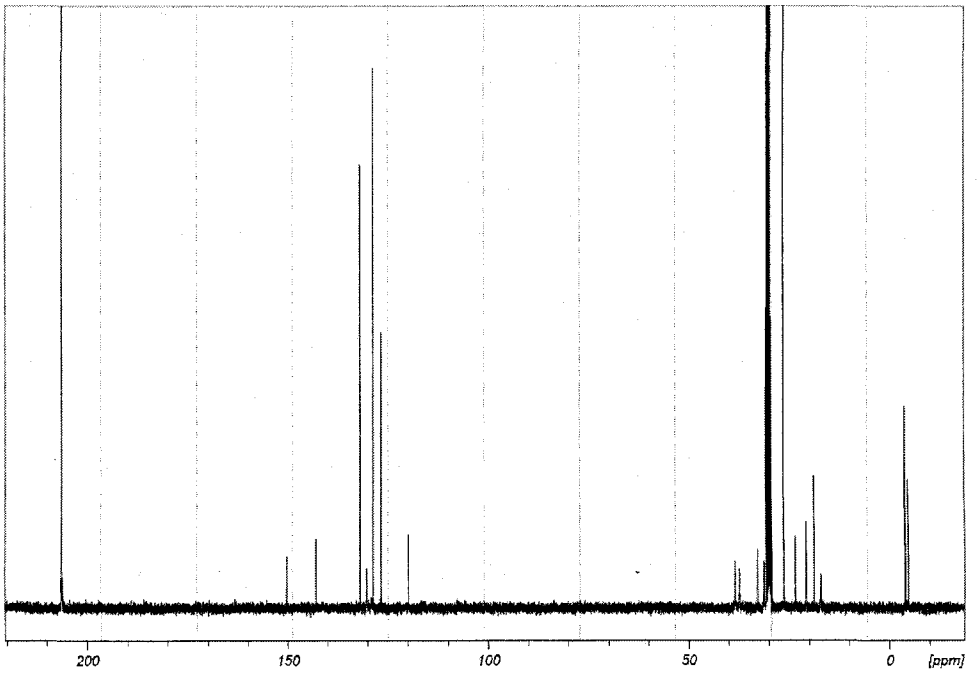


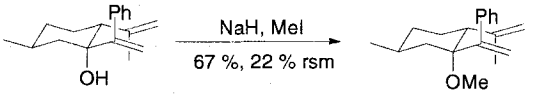
4.26

^{1}H NMR (400 MHz, d_6-acetone)



^{13}C NMR (75 MHz, d_6-acetone)





4.14

(±)-1-(1-((1R,2R,5S)-1-Methoxy-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)vinyl)benzene
This compound is mentioned in reference 72.

A solution of **4.14** (75.0 mg, 0.293 mmol) in THF (5 mL) was cooled to 0 °C and treated with NaH (60 % in oil, 93.6 mg, 2.34 mmol). This mixture was stirred for 10 minutes at 0 °C, then it was treated with MeI (0.11 mL, 1.76 mmol) followed by 2 hours stirring while warming to room temperature and then 18 hours stirring at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 5 % EtOAc/hexanes, affording the methyl ether (53.4 mg, 0.197 mmol, 67 %, R_f = 0.75) as a colorless oil. Starting material **4.14** was also recovered (16.3 mg, 0.0636 mmol, 22 %, R_f = 0.35) as a yellow liquid.

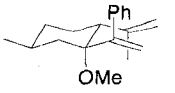
Data for the methyl ether

^{1}H NMR (400 MHz, d_6-acetone): δ = 7.33-7.24 (m, 5H), 5.24 (d, J = 2.4 Hz, 1H), 5.02 (d, J = 2.4 Hz, 1H), 4.81-4.78 (m, 2H), 3.17 (s, 3H), 2.31 (dd, J = 12.5, 3.5 Hz, 1H), 2.09 (dddd, J = 12.9, 12.9, 12.9, 3.7 Hz, 1H), 1.90 (ddd, J = 14.5, 14.5, 2.6 Hz, 1H), 1.82 (s, 3H), 1.73-1.67 (m, 1H), 1.66-1.55 (m, 1H), 1.45 (dddd, J = 12.8, 3.5, 3.5, 3.5, 1H), 0.95-0.82 (m, 2H), 0.79 (d, J = 6.6 Hz, 3H)

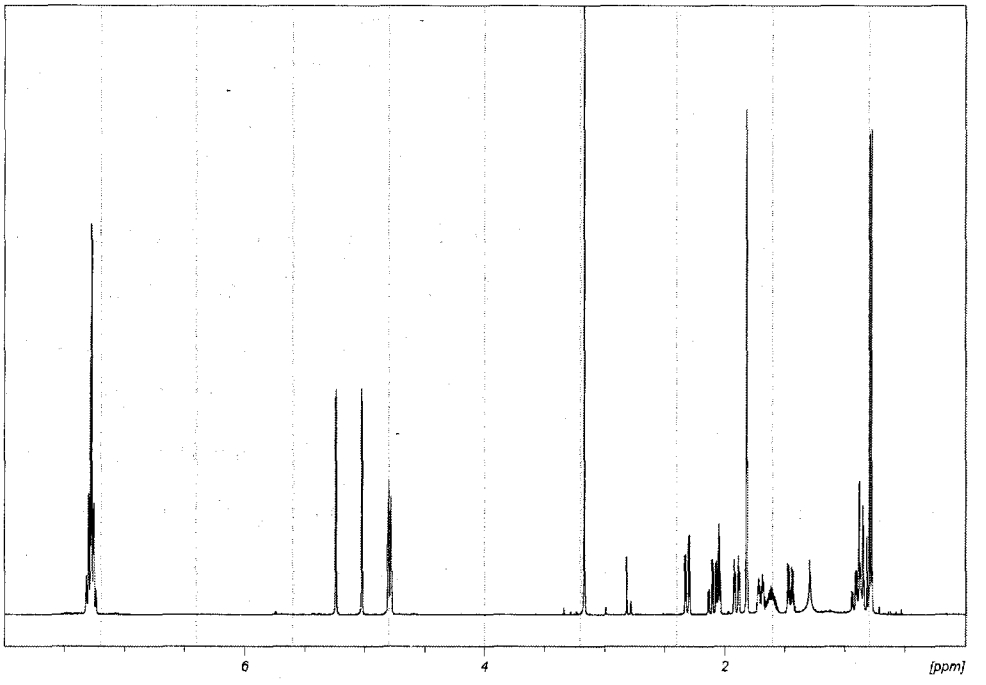
^{13}C NMR (100 MHz, d_6-acetone): δ = 150.7 (C_4), 149.0 (C_4), 143.8 (C_4), 129.5 (2 ×CH), 128.7 (2 ×CH), 127.7 (CH), 116.8 (CH_2), 114.2 (CH_2), 83.6 (C_4), 54.4 (CH_3), 49.7 (CH), 41.3 (CH_2), 35.8 (CH_2), 28.9 (CH_2), 28.4 (CH), 22.8 (CH_3), 22.6 (CH_3)

FT-IR (neat, cm^{-1}): 2948 (s), 2925 (s), 2873 (m), 2856 (m), 1638 (w), 1601 (w)

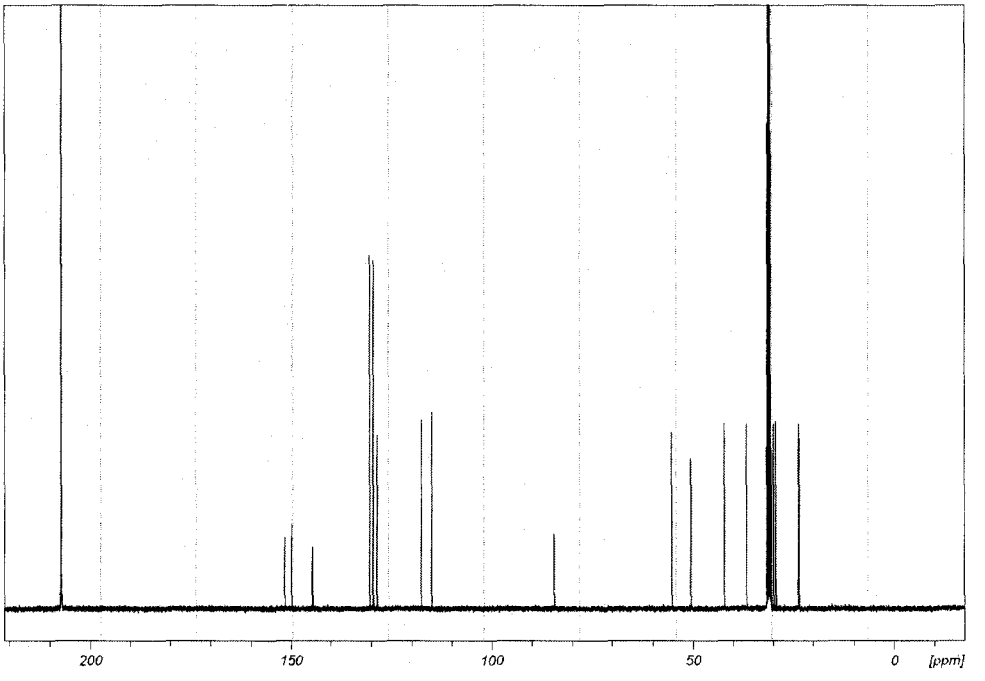
HRMS (EI): Calculated 270.1984 (M^+) for $C_{19}H_{26}O$, found 270.1987

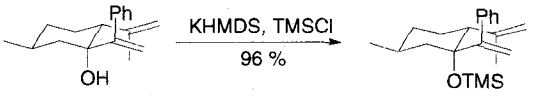


^{1}H NMR (400 MHz, d_6-acetone)



^{13}C NMR (100 MHz, d_6-acetone)





4.14 **4.27**

(±)-((1R,2R,5S)-5-Methyl-1-(1-phenylvinyl)-2-(prop-1-en-2-yl)cyclohexyloxy)trimethylsilane (**4.27**)

A stirring solution of **4.14** (103.0 mg, 0.402 mmol) in THF (5 mL) was treated with KHMDS (320.8 mg, 1.61 mmol) and then TMSCl (0.20 mL, 1.58 mmol). After 5 minutes of stirring at room temperature the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in hexanes, affording **4.27** (126.7 mg, 0.386 mmol, 96 %, R_f = 0.50) as a colorless oil.

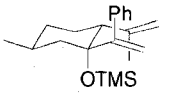
Data for **4.27**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30-7.19 (m, 5H), 5.38 (d, J = 2.0, 1H), 4.98 (d, J = 2.0 Hz, 1H), 4.82-4.81 (m, 1H), 4.78 (d, J = 2.5 Hz, 1H), 2.12 (dd, J = 12.3, 3.3 Hz, 1H), 1.91 (dddd, J = 7.5, 7.5, 7.5, 3.6 Hz, 1H), 1.82-1.65 (m, 3H), 1.79 (s, 3H), 1.47 (dddd, J = 12.9, 3.3, 3.3, 3.3 Hz, 1H), 1.09 (dd, J = 13.9, 12.3 Hz, 1H), 0.92-0.81 (m, 1H), 0.78 (d, J = 6.6 Hz, 3H), 0.17 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (C_4), 148.6 (C_4), 143.1 (C_4), 128.9 (2 × CH), 127.7 (2 × CH), 126.7 (CH), 116.1 (CH_2), 113.2, (CH_2), 82.2 (C_4), 53.4 (CH), 46.5 (CH_2), 34.9 (CH_2), 28.5 (CH_2), 27.9 (CH), 22.2 (CH_3), 22.1 (CH_3), 2.3 (3 × CH_3)

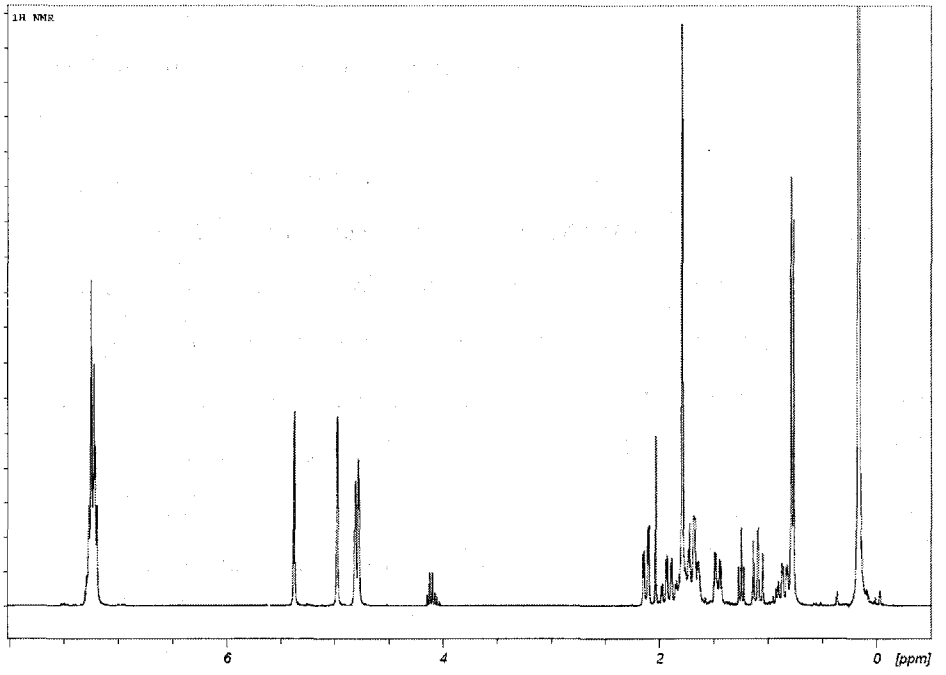
FT-IR (neat, cm^{-1}): 2951 (s), 2926 (s), 2867 (m), 1598 (w)

HRMS (EI): Calculated 328.2222 (M^+) for $C_{21}H_{32}OSi$, found 328.2228

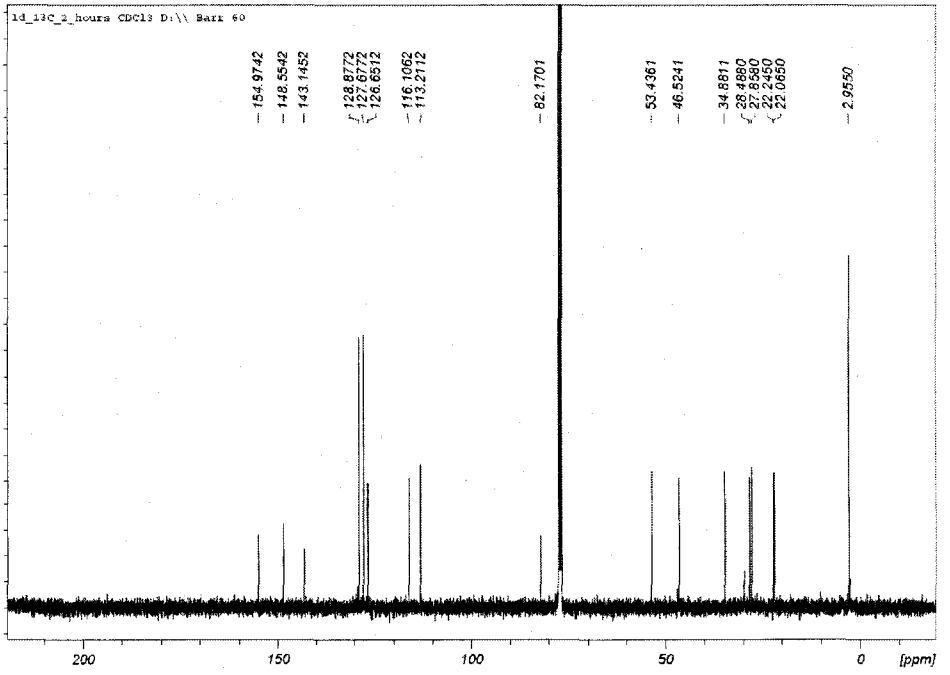


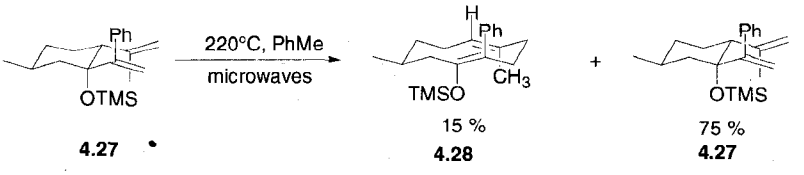
4.27

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)





(±)-((S,1E,5E)-5,9-Dimethyl-2-phenylcyclodeca-1,5-dienyloxy)trimethylsilane (**4.28**)

A sample of **4.27** (126.7 mg, 0.386 mmol) was dissolved in toluene (13 mL) and placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220 °C over 20 minutes, then for 1 hour at 220 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in hexanes, affording **4.28** (19.3 mg, 0.0587 mmol, 15 %, R_f = 0.40) as a colorless oil and returned starting material **4.27** (95.4 mg, 0.290 mmol, 75 %, R_f = 0.50) as a colorless oil.

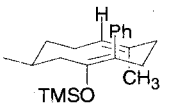
Data for **4.28**

^{1}H NMR (500 MHz, C_6D_6): δ = 7.48 (dd, J = 8.4, 1.3 Hz, 2H), 7.32 (dd, J = 7.4, 7.4 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 4.98 (d, J = 9.2 Hz, 1H), 3.00 (ddd, J = 12.8, 12.8, 5.0 Hz, 1H), 2.53 (dd, J = 14.3, 10.7 Hz, 1H), 2.48 (ddd, J = 12.7, 4.9, 4.9 Hz, 1H), 2.35-2.15 (m, 5H), 2.00-1.93 (m, 1H), 1.90 (s, 3H), 1.60 (dd, J = 14.5, 6.5 Hz, 1H), 1.09-0.98 (m, 1H), 0.90 (d, J = 7.1 Hz, 3H), 0.25 (s, 9H)

^{13}C NMR (100 MHz, d_6-acetone): δ = 151.0 (C_4), 143.7 (C_4), 130.5 (C_4), 129.8 (CH), 129.6 (2 × CH), 128.9 (2 × CH), 126.6 (CH), 120.4 (C_4), 44.1 (CH_2), 40.5 (CH_2), 39.9 (CH_2), 33.7 (CH), 32.8 (CH_2), 29.5 (CH_2), 26.3 (CH_3), 18.4 (CH_3), 0.84 (3 × CH_3)

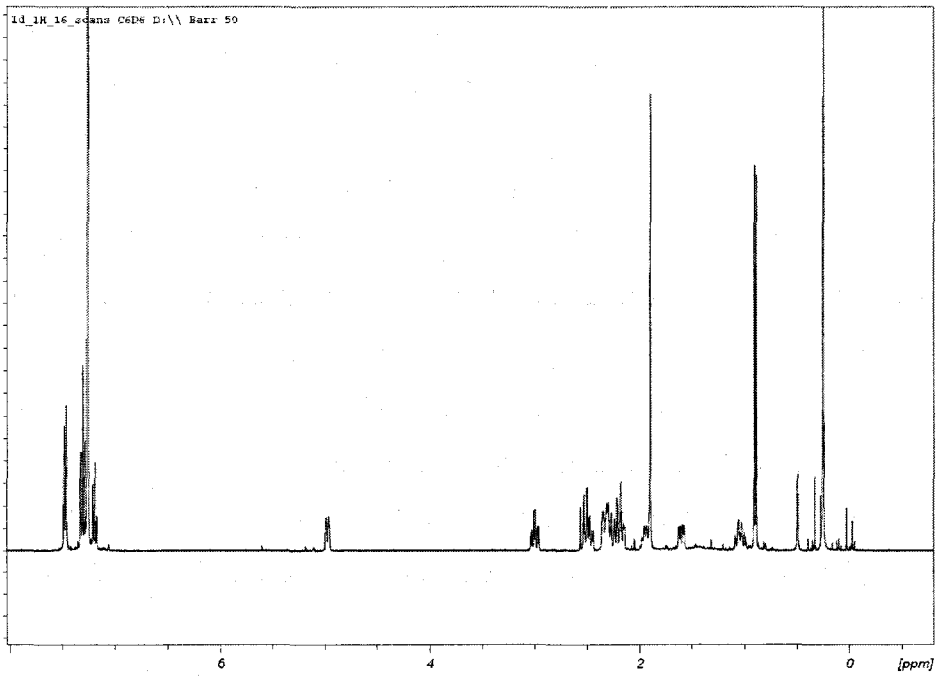
FT-IR (neat, cm^{-1}): 3033 (w), 3021 (w), 2953 (s), 2925 (s), 2871 (m)

HRMS (EI): Calculated 328.2222 (M^+) for $C_{21}H_{32}OSi$, found 328.2223

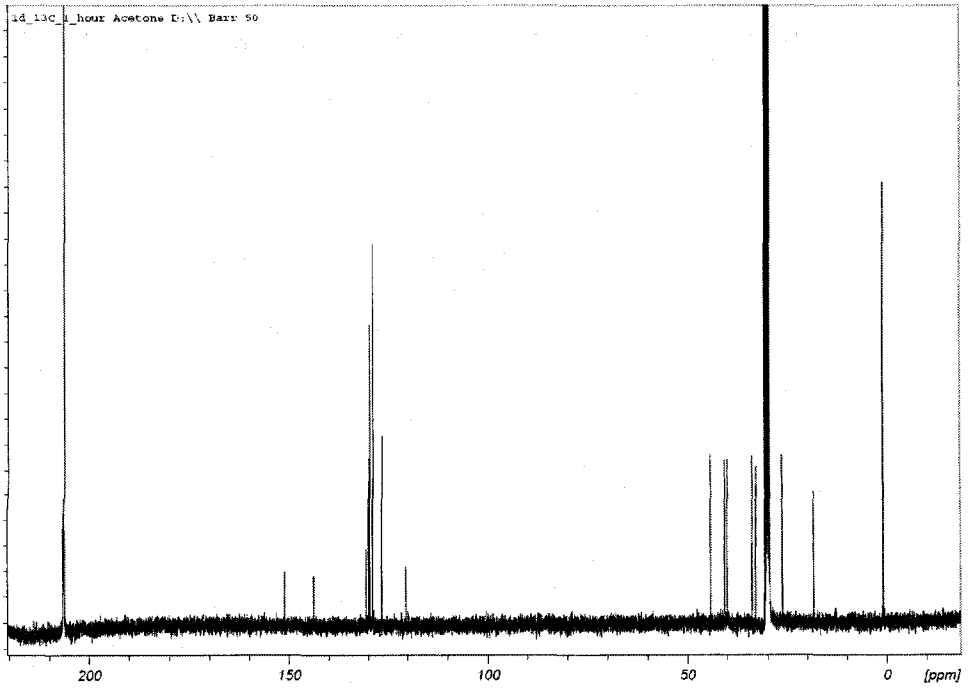


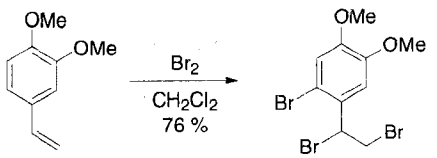
4.28

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (100 MHz, d_6-acetone)





5.34 **5.35**

1-Bromo-2-(1,2-dibromoethyl)-4,5-dimethoxybenzene (**5.35**)

To a solution of **5.34** (122.0 mg, 0.743 mmol) in CH_2Cl_2 (8 mL) was added Br_2 (0.05 mL, 1.49 mmol) to give a clear orange solution and the resulting mixture was stirred at room temperature for 2 hours, after which the solution turned clear yellow. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 followed by 10 minutes of stirring. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 20 % EtOAc/hexanes to afford **5.35** (226.4 mg, 0.562 mmol, 76 %, R_f = 0.50) as a white solid.

Data for **5.35**

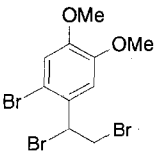
M.p.: 187-188 °C

^{1}H NMR (500 MHz, d_6-acetone): δ = 7.30 (s, 1H), 7.13 (s, 1H), 5.70 (dd, J = 10.3, 5.4 Hz, 1H), 4.44 (dd, J = 10.3, 10.3 Hz, 1H), 4.24 (dd, J = 10.3, 5.4 Hz, 1H), 3.87 (s, 6H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 152.0 (C_4), 151.0 (C_4), 130.8 (C_4), 116.7 (CH), 115.8 (C_4), 112.4 (CH), 57.1 (CH_3), 57.0 (CH_3), 51.4 (CH), 35.3 (CH_2)

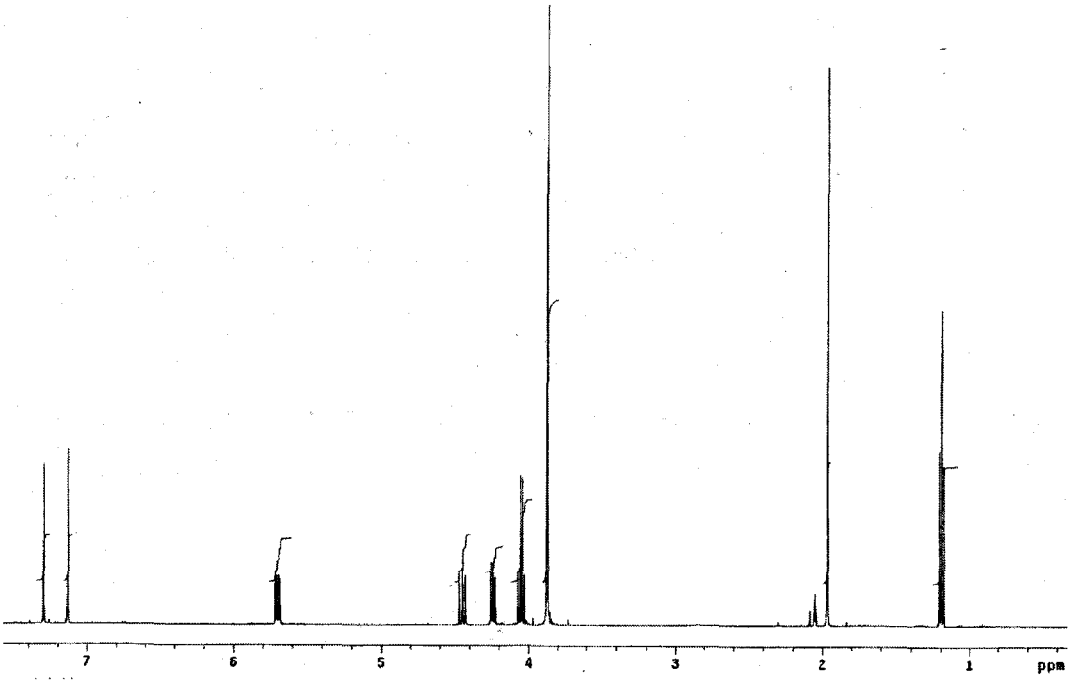
FT-IR (neat, cm^{-1}): 2964 (s), 2941 (s), 2905 (s), 2839 (m)

HRMS (EI): Calculated 399.8309 (M^+) for $C_{10}H_{11}O_2Br_3$, found 399.8321

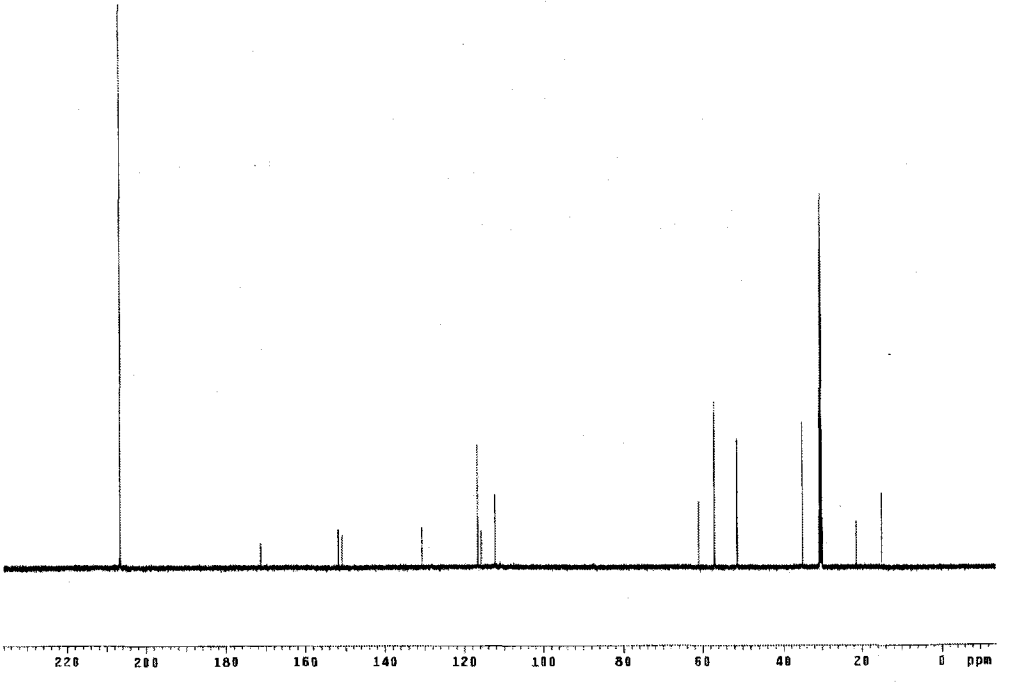


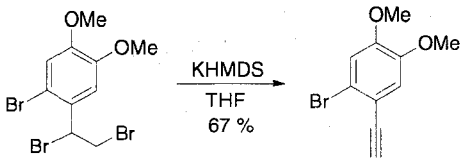
5.35

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





5.35 **5.36**

1-Bromo-2-ethynyl-4,5-dimethoxybenzene (**5.36**)

To a solution of **5.35** (80.6 mg, 0.200 mmol) in THF (3 mL) was added KHMDS (119.7 mg, 0.600 mmol) and the mixture was stirred for 1 hour at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in 5 % EtOAc/hexanes to afford **5.36** (32.3 mg, 0.134 mmol, 67 %, R_f = 0.40) as a white solid.

Data for **5.36**

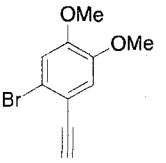
M.p.: 90-91 °C

^{1}H NMR (500 MHz, d_6-acetone): δ = 7.16 (s, 1H), 7.08 (s, 1H), 3.87 (s, 3H), 3.85 (s, 1H), 3.84 (s, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 152.2 (C_4), 150.1 (C_4), 117.5 (C_4), 117.5 (CH), 117.2 (C_4), 116.7 (CH), 83.3 (C_4), 82.5 (CH), 57.0 (CH_3), 56.9 (CH_3)

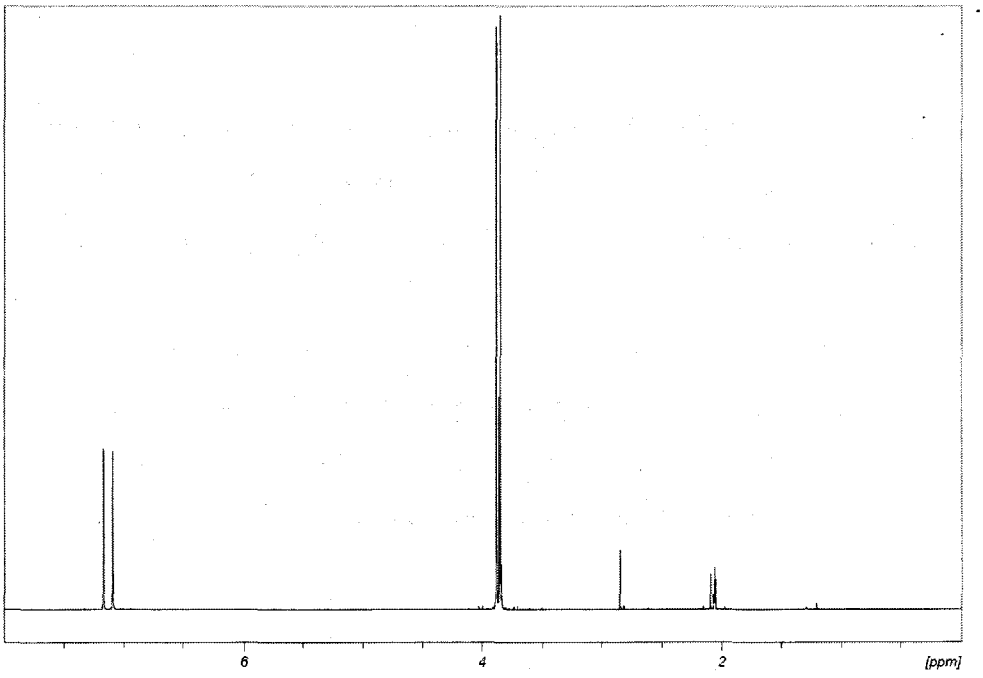
FT-IR (neat, cm^{-1}): 2960 (s), 2941 (s), 2905 (s), 2843 (m), 2100 (w)

HRMS (EI): Calculated 239.9786 (M^+) for $C_{10}H_9O_2Br$, found 239.9795

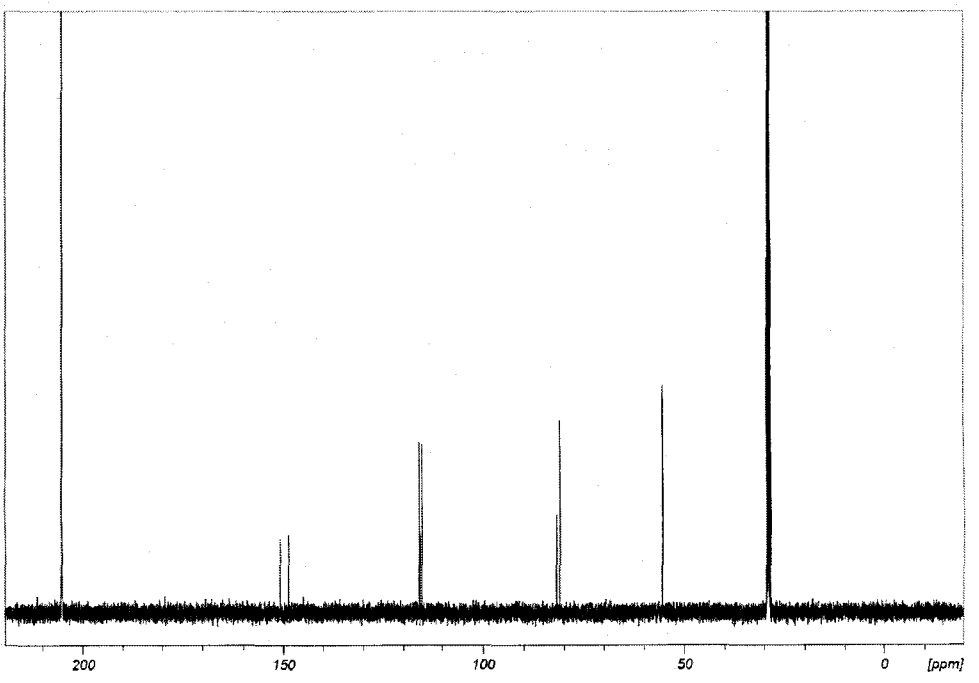


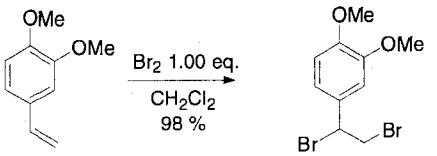
5.36

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





5.34 **5.37**

4-(1,2-Dibromoethyl)-1,2-dimethoxybenzene (**5.37**)

Bromine (1.52 mL, 29.7 mmol) was added slowly to a solution of **5.34** (4.87 g, 29.7 mmol) in CH_2Cl_2 (300 mL). The orange color of the bromine bleached immediately upon addition. The clear pale yellow reaction mixture was quenched by the addition of saturated aqueous Na_2SO_3 (300 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 20 % EtOAc/hexanes afforded **5.37** (9.44 g, 29.1 mmol, 98 %, R_f = 0.50) as a white solid. The flash must be performed quickly as the dibromide is unstable in the presence of silica gel.

Data for **5.37**

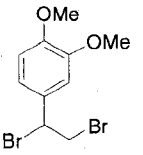
M.p.: 98 °C

^{1}H NMR (500 MHz, d_6-acetone): δ = 7.16 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 5.41-5.38 (m, 1H), 4.30 (dd, J = 10.3, 10.3 Hz, 1H), 4.20-4.17 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 151.5 (C_4), 150.9 (C_4), 132.8 (C_4), 122.0 (CH), 112.7 (CH), 112.5 (CH), 56.7 (CH_3), 56.5 (CH_3), 53.9 (CH), 36.5 (CH_2)

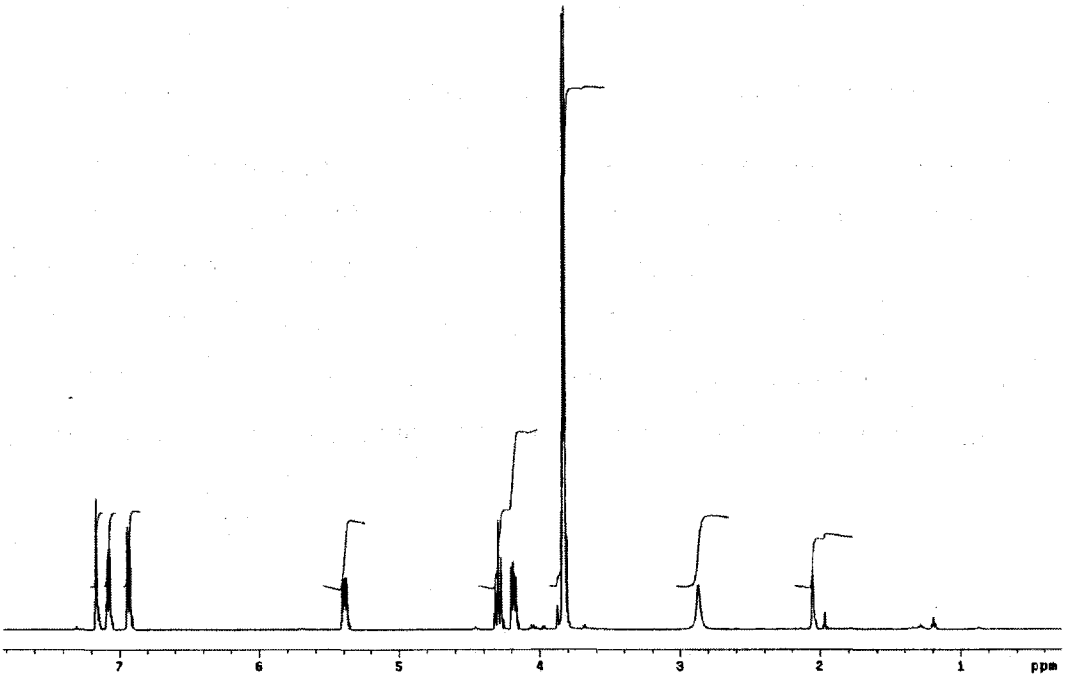
FT-IR (neat, cm^{-1}): 2995 (s), 2960 (s), 2941 (s), 2909 (s), 1602 (w)

HRMS (EI): Calculated 321.9204 (M^+) for $C_{10}H_{12}O_2Br_2$, found 321.9219

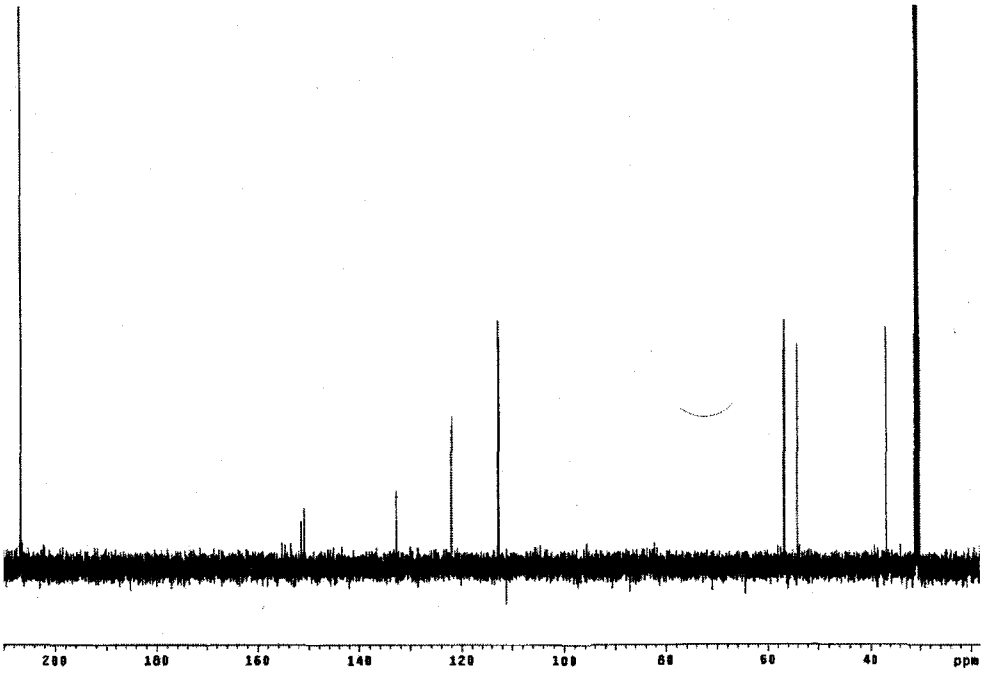


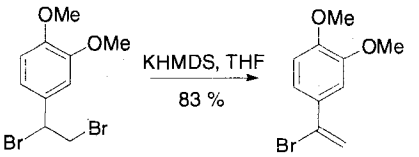
5.37

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)

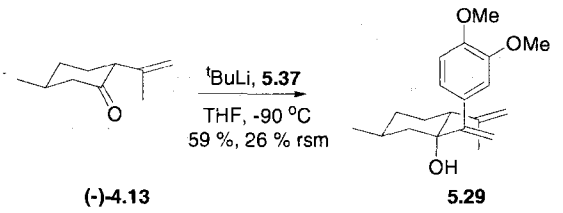




5.37 **5.38**

4-(1-Bromo-vinyl)-1,2-dimethoxybenzene (**5.38**)

A solution of **5.37** (5.03 g, 15.5 mmol) in THF (150 mL) was treated with KHMDS (3.25 g, 16.3 mmol) and the resulting mixture was stirred at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 20 % EtOAc/hexanes afforded **5.38** (3.13 g, 12.9 mmol, 83 %, R_f = 0.50) as a yellow liquid. This product rapidly decomposes and must be used immediately upon isolation.



(-)-4.13 5.29

(+)-(1R,2R,5S)-1-(1-(3,4-Dimethoxyphenyl)vinyl)-5-methyl-2-(prop-1-en-2-yl)cyclohexanol (**5.29**)

To a solution of vinyl bromide **5.37** (1.42 g, 5.83 mmol) in THF (30 mL) cooled to -90 °C was added ^{t}BuLi (1.70 M in hexanes, 6.86 mL, 11.66 mmol) and the resulting solution was stirred at -90 °C for 35 minutes. To this mixture was added a solution of ketone **(-)-4.13** (0.444 g, 2.91 mmol) in THF (10 mL) by cold cannulation, and the resulting solution was stirred at -90 °C for 0.5 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL) followed by warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded **5.29** (0.544 g, 1.72 mmol, 59 %, R_f = 0.40) as a colorless oil. Starting ketone **(-)-4.13** (0.115 g, 0.758 mmol, 26 %, R_f = 0.50) was also recovered.

Data for **5.29**

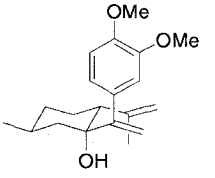
^{1}H NMR (500 MHz, d_6-acetone): δ = 6.94-6.84 (m, 2H), 6.78 (dd, J = 8.3, 2.0 Hz, 1H), 5.48 (d, J = 2.2 Hz, 1H), 4.90 (d, J = 2.4 Hz, 1H), 4.88-4.87 (m, 1H), 4.79-4.78 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.21 (d, J = 1.2 Hz, 1H), 2.54 (dd, J = 12.6, 3.5 Hz, 1H), 1.99 (dddd, J = 12.9, 12.9, 12.9, 3.7 Hz, 1H), 1.96-1.89 (m, 1H), 1.79 (s, 3H), 1.72-1.65 (m, 2H), 1.48-1.43 (dddd, J = 12.7, 3.4, 3.4, 3.4 Hz, 1H), 1.36 (dd, J = 13.4, 12.3 Hz, 1H), 0.96-0.87 (m, 1H), 0.82 (d, J = 6.6 Hz, 3H)

^{13}C NMR (75 MHz, d_6-acetone): δ = 158.6 (C_4), 150.0 (C_4), 149.7 (C_4), 149.6 (C_4), 136.3 (C_4), 122.5 (CH), 114.7 (CH), 114.5 (CH_2), 113.8 (CH_2), 112.3 (CH), 78.0 (C_4), 56.5 (CH_3), 56.4 (CH_3), 52.7 (CH), 49.8 (CH_2), 36.2 (CH_2), 29.7 (CH_2), 28.7 (CH), 23.5 (CH_3), 23.1 (CH_3)

FT-IR (neat, cm^{-1}): 3531 (b), 2947 (s), 2866 (m), 2839 (m)

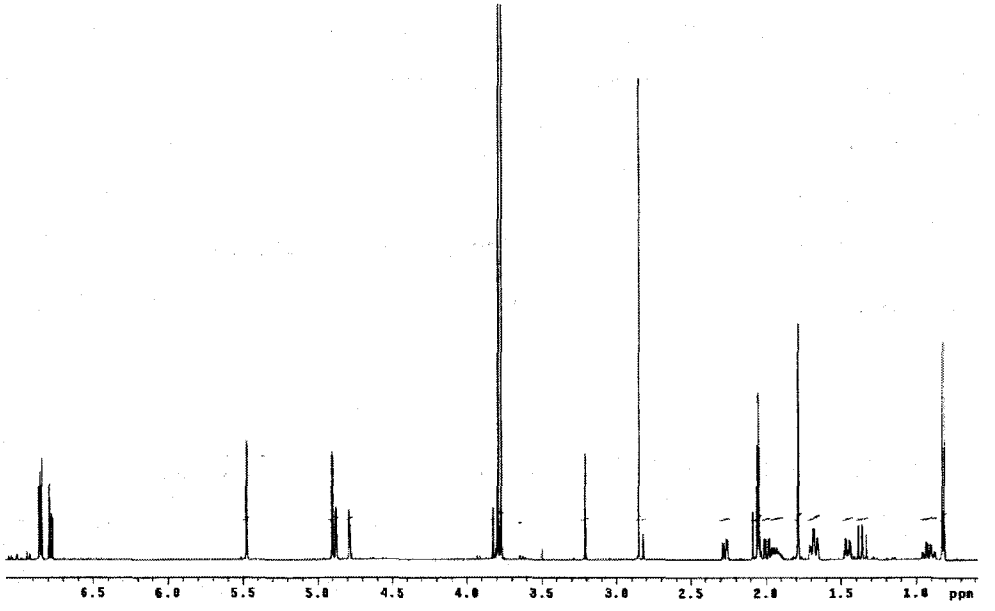
HRMS (EI): Calculated 316.2038 (M^+) for $C_{20}H_{28}O_3$, found 316.2058

$[\alpha]_D^{22}$: +34.1°, c = 19.1 mg/mL (CH_2Cl_2)

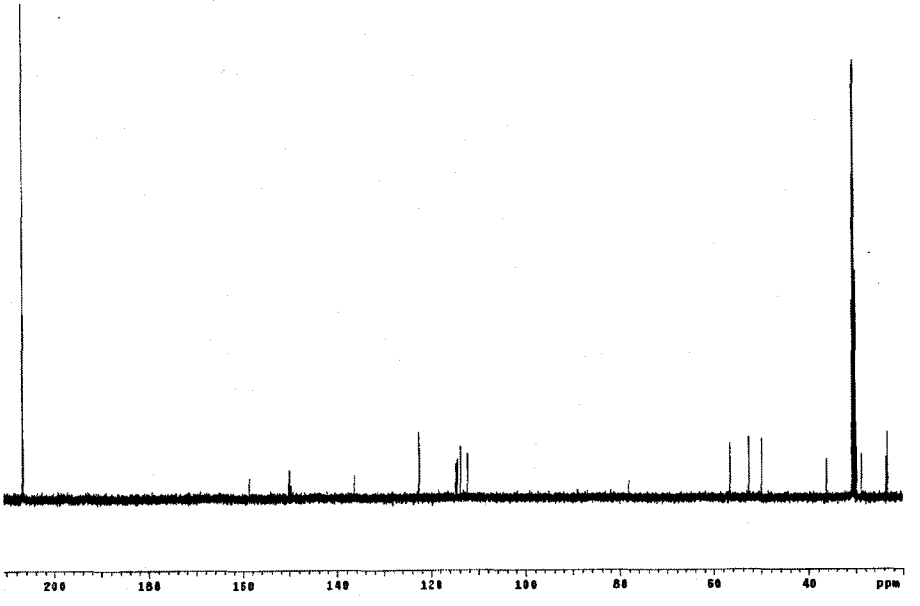


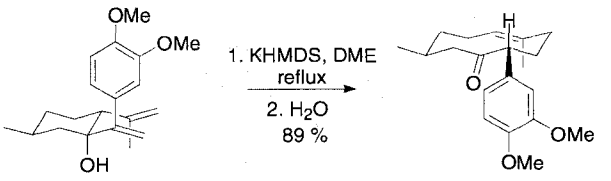
5.29

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (75 MHz, d_6-acetone)





5.29 **5.39**

(±)-(E,2R,9S)-2-(3,4-Dimethoxyphenyl)-5,9-dimethylcyclodec-5-enone (**5.39**)

Alcohol **5.29** (62.1 mg, 0.196 mmol) was dissolved in DME (5 mL) and treated with a solution of KHMDS (117.5 mg, 0.598 mmol) in DME (5 mL). The resulting mixture was heated at reflux for 20 minutes after which it was cooled to room temperature. The reaction was quenched by the addition of water (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 5 % EtOAc/hexanes afforded **5.39** (55.3 mg, 0.174 mmol, 89 %, $R_f = 0.50$) as a colorless oil.

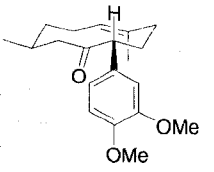
Data for **5.39**

^{1}H NMR (500 MHz, d_6-acetone): δ = 6.86 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.78 (dd, J = 8.2, 2.0 Hz, 1H), 5.33 (dd, J = 12.7, 1.8 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.65 (dd, J = 11.8, 1.5 Hz, 1H), 2.76 (dd, J = 16.6, 9.3 Hz, 1H), 2.72-2.65 (m, 1H), 2.15-2.08 (m, 4H), 2.00-1.96 (m, 2H), 1.73-1.68 (m, 1H), 1.62-1.57 (m, 1H), 1.48 (s, 3H), 1.32-1.24 (m, 1H), 0.87 (d, J = 7.1 Hz, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 207.8 (C_4), 150.9 (C_4), 149.9 (C_4), 139.2 (C_4), 134.6 (C_4), 127.7 (CH), 121.2 (CH), 113.4 (CH), 113.0 (CH), 61.2 (CH), 56.6 (CH_3), 56.5 (CH_3), 52.9 (CH_2), 42.1 (CH_2), 39.1 (CH_2), 36.3 (CH_2), 31.1 (CH), 28.8 (CH_2), 25.6 (CH_3), 16.8 (CH_3)

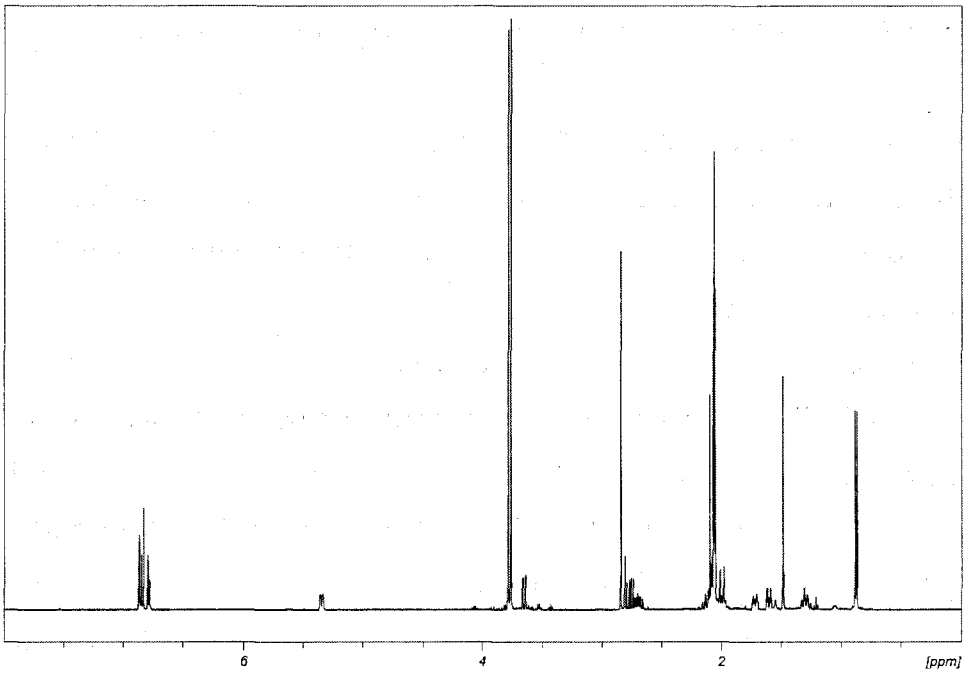
FT-IR (neat, cm^{-1}): 2949 (m), 2918 (m), 2870 (w), 2847 (w), 1702 (s)

HRMS (EI): Calculated 316.2038 (M^+) for $C_{20}H_{28}O_3$, found 316.2060

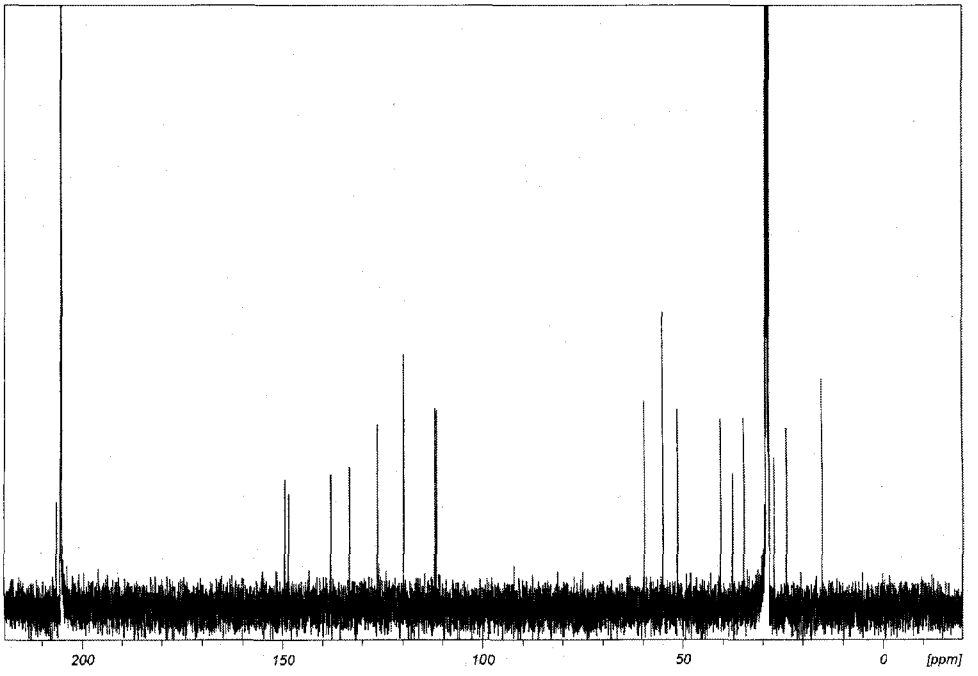


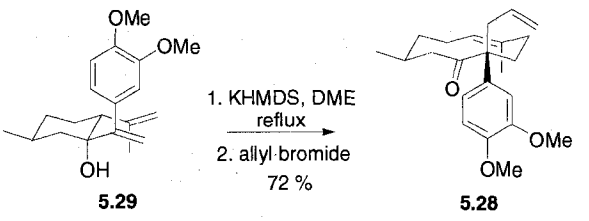
5.39

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





5.29 **5.28**

(+)-(E,2S,9S)-2-Allyl-2-(3,4-dimethoxyphenyl)-5,9-dimethylcyclodec-5-enone (**5.28**)

Alcohol **5.29** (749.5 mg, 2.37 mmol) was dissolved in DME (40 mL) and treated with a solution of KHMDS (1417.5 mg, 7.10 mmol) in DME (10 mL). The resulting mixture was heated at reflux for 15 minutes after which it was cooled to room temperature and then -78 °C. To the cooled solution was added allyl bromide (0.40 mL, 3.70 mmol) and the mixture was stirred at -78 °C for 30 minutes. The reaction was quenched by the addition of water (50 mL) followed by warming to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes afforded **5.28** (717.5 mg, 2.02 mmol, 72 %, R_f = 0.40) as a colorless oil.

Data for **5.29**

M.p.: 87-88 °C

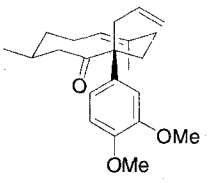
^{1}H NMR (500 MHz, d_6-acetone): δ = 6.92 (s, 1H), 6.90-6.83 (m, 2H), 5.45 (d, J = 10.3 Hz, 1H), 5.37-5.30 (m, 1H), 5.18 (d, J = 17.1 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.25 (dd, J = 17.8, 7.8 Hz, 1H), 3.18 (d, J = 6.4 Hz, 2H), 2.85-2.79 (m, 1H), 2.37 (dd, J = 12.5, 12.5 Hz, 1H), 2.17-2.07 (m, 2H), 1.99-1.94 (m, 2H), 1.89 (dd, J = 17.8, 13.2 Hz, 2H), 1.70 (d, J = 13.9 Hz, 1H), 1.45 (s, 3H), 1.36-1.27 (m, 1H), 0.93 (d, J = 7.1 Hz 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 210.0 (C_4), 150.4 (C_4), 149.4 (C_4), 138.6 (C_4), 138.4 (C_4), 135.7 (CH), 128.0 (CH), 120.2 (CH), 118.2 (CH_2), 112.9 (CH), 112.5 (CH), 56.7 (CH_3), 56.6 (C_4), 56.5 (CH_3), 48.9 (CH_2), 38.8 (CH_2), 38.4 (CH_2), 36.5 (CH_2), 35.0 (CH_2), 29.1 (CH), 28.7 (CH_2), 25.6 (CH_3), 16.9 (CH_3)

FT-IR (neat, cm^{-1}): 2951 (s), 2933 (s), 2846 (m), 1694 (s)

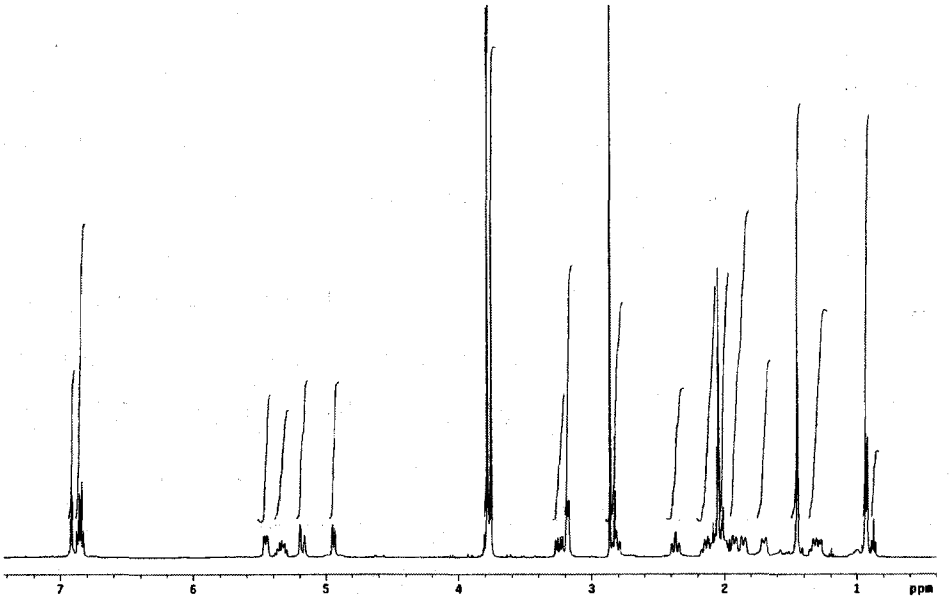
HRMS (EI): Calculated 356.2351 (M^+) for $C_{23}H_{32}O_3$, found 356.2352

$[\alpha]_D^{22}$: +61.5°, c = 24.0 mg/mL (CH_2Cl_2)

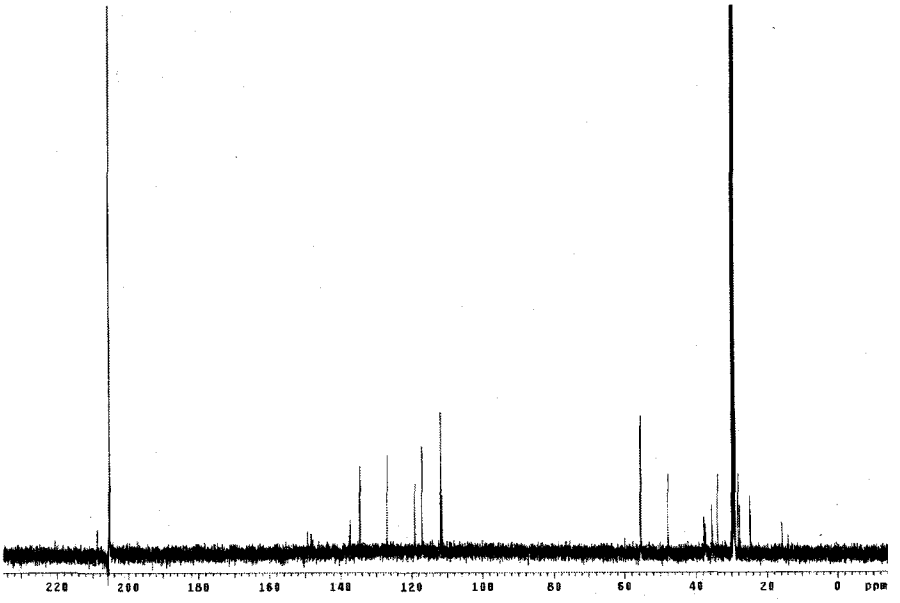


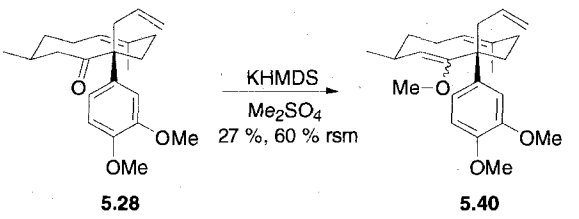
5.28

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





5.28 **5.40**

(±)-(3S, 6E, 10S)-10-Allyl-1-methoxy-10-(3,4-dimethoxyphenyl)-3,7-dimethylcyclodeca-1,6-diene (**5.40**)

Ketone **5.28** (32.9 mg, 0.0923 mmol) was dissolved in benzene (10 mL) and concentrated under reduced pressure three times to remove water and it was then dried under high vacuum for 1 hour. This compound was dissolved in THF (4 mL) and cooled to -78 °C. A solution of KHMDS (184.1 mg, 0.923 mmol) in THF (2 mL) was added via cannula and the resulting mixture was stirred at -78 °C for 15 min, then warmed to room temperature and stirred for 0.5 hours. The mixture was re-cooled to -78 °C and Me_2SO_4 (distilled twice over CaH_2, 0.01 ml, 0.107 mmol) was added dropwise, then stirred for 0.5 hours at -78 °C and then for 2 hours at room temperature. The reaction was quenched by the addition of H_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 10 % EtOAc/hexanes basified with Et_3N afforded **5.40** (9.2 mg, 0.0248 mmol, 27 %, Rf = 0.60) as a white solid. Starting material **5.28** (19.6 mg, 0.0553 mmol, 60 %, R_f = 0.35) was also recovered.

Data for **5.40**

M.p.: 102-103 °C

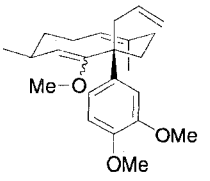
^{1}H NMR (500 MHz, d_6-acetone): δ = 6.95-6.90 (m, 1H), 6.88-6.85 (m, 2H), 5.31-5.23 (m, 1H), 5.08-5.04 (m, 2H), 4.88 (ddd, J = 10.7, 1.7, 1.7 Hz, 1H), 4.52 (d, J = 10.2 Hz, 1H), 3.77 (s, 6H), 3.07 (s, 3H), 3.02 (dd, J = 13.7, 9.1 Hz, 1H), 2.64-2.50 (m, 3H), 2.44-2.30 (m, 2H), 2.11-2.00 (m, 2H), 1.71 (s, 3H), 1.69-1.60 (m, 2H), 1.32-1.28 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 162.7 (C_4), 149.2 (C_4), 140.3 (C_4), 136.2 (CH), 132.4 (C_4), 130.7 (CH), 120.5 (CH_2), 120.4 (C_4), 117.8 (CH), 114.2 (CH), 113.1 (CH),

112.5 (CH), 63.0 (CH_3), 56.7 (CH_3), 56.5 (CH_3), 50.0 (C_4), 41.0 (CH_2), 38.1 (CH_2), 37.5 (CH_2), 34.1 (CH), 30.6 (CH_2), 25.2 (CH_2), 23.7 (CH_3), 16.6 (CH_3)

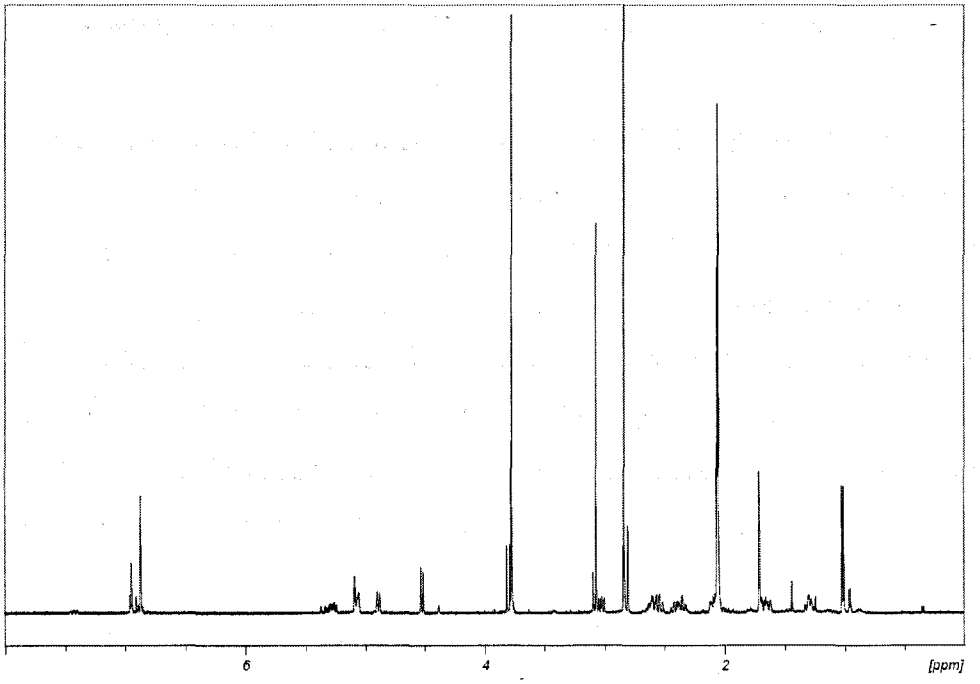
FT-IR (neat, cm^{-1}): 2957 (s), 2929 (w), 2839 (w), 1661 (w)

HRMS (EI): Calculated 370.2508 (M^+) for $C_{24}H_{34}O_3$, found 370.2504

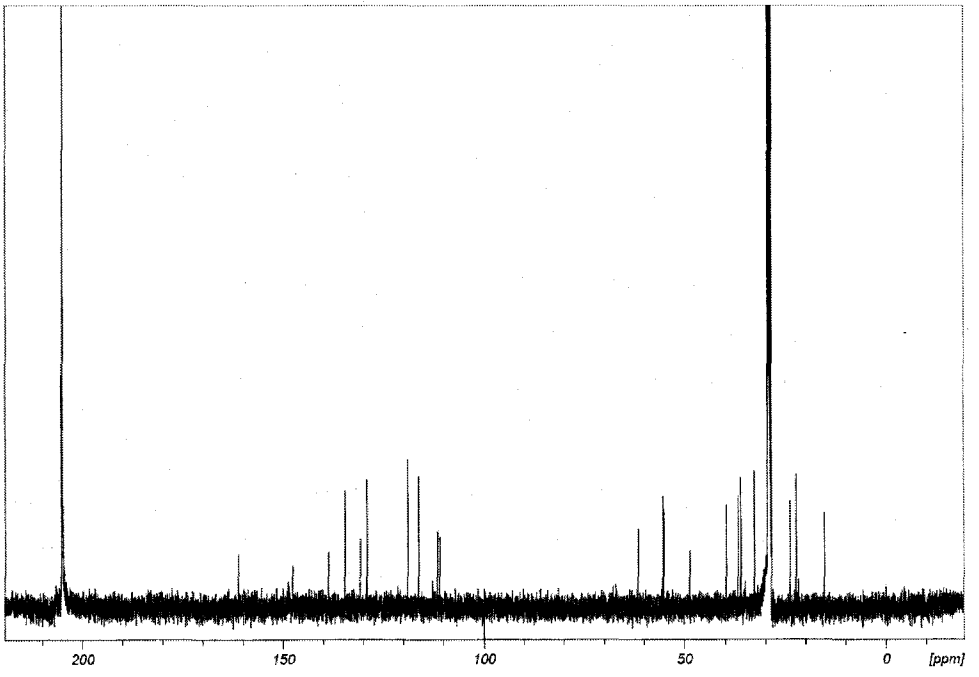


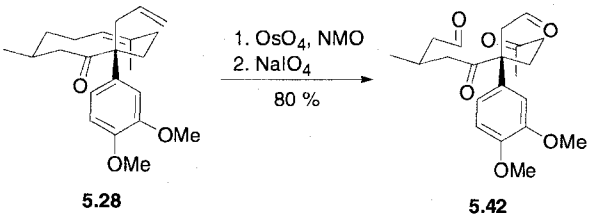
5.40

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)





5.28 **5.42**

(±)-(3S,6S)-3-(3,4-Dimethoxyphenyl)-6-methyl-4-oxo-3-(3-oxobutyl)nonanedial (**5.42**)

To a solution of **5.28** (27.4 mg, 0.0768 mmol) in a mixture of THF/ H_2O (5:1, 6 mL) was added NMO (9.0 mg, 0.0768 mmol) followed by OsO_4 (4% in H_2O, 0.05 mL, 0.00786 mmol) and the mixture was stirred at room temperature for 4 hours. To this was then added $NaIO_4$ (49.3 mg, 0.230 mmol) and the resulting mixture was stirred at room temperature for a further 16 h. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (5 mL). The layers were separated, the aqueous phase was extracted with Et_2O (3 × 10 mL), and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 80 % EtOAc/hexanes afforded **5.42** (24.0 mg, 0.0614 mmol, 80 %) as a colorless oil.

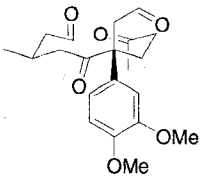
Data for **5.42**

^{1}H NMR (500 MHz, d_6-acetone): δ = 9.63 (t, J = 1.6 Hz, 1H), 9.59 (t, J = 1.9 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.89 (dd, J = 8.4, 2.3 Hz, 1H), 6.83 (d, J = 2.3 Hz, 1H), 3.81 (s, 6H), 2.51-2.47 (m, 1H), 2.35-2.29 (m, 5H), 2.26-2.20 (m, 2H), 2.18-2.07 (m, 1H), 2.05 (s, 3H), 1.95-1.91 (m, 1H), 1.50-1.43 (m, 1H), 1.29-1.20 (m, 2H), 0.71 (d, J = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, d_6-acetone): δ = 209.8 (C_4), 207.8 (C_4), 203.1 (CH), 202.2 (CH), 151.2 (C_4), 150.3 (C_4), 133.5 (C_4), 120.5 (CH), 113.3 (CH), 112.2 (CH), 57.1 (C_4), 56.7 (CH_3), 56.5 (CH_3), 47.7 (CH_2), 44.8 (CH_2), 42.3 (CH_2), 39.2 (CH_2), 29.7 (CH_3), 29.5 (CH), 29.3 (CH_2), 28.2 (CH_2), 20.2 (CH_3)

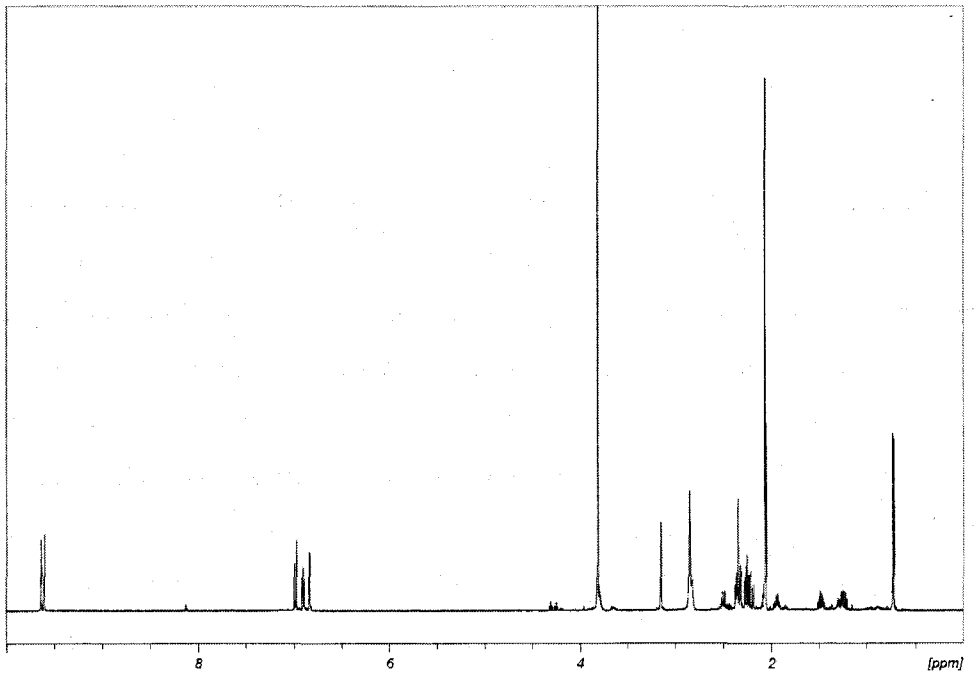
FT-IR (neat, cm^{-1}): 2956 (m), 2878 (m), 2838 (m), 1727 (s), 1712 (s)

HRMS (EI): Calculated 390.2042 (M^+) for $C_{22}H_{30}O_6$, found 390.2035

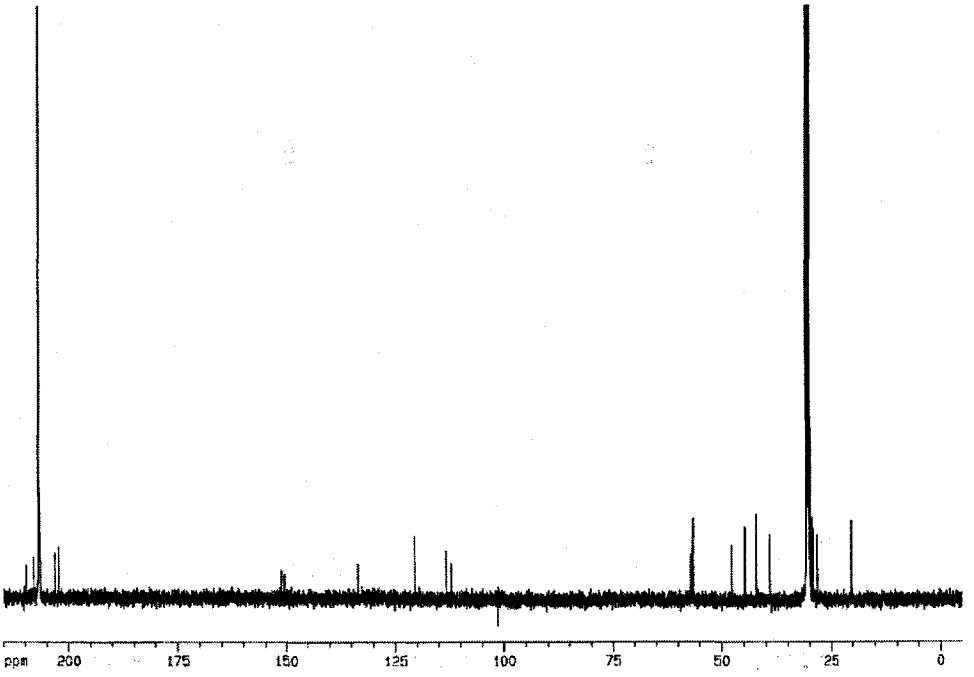


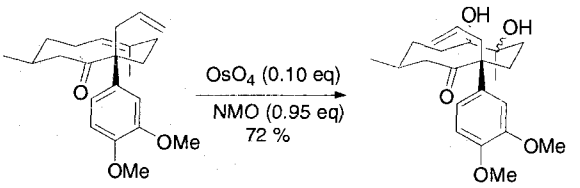
5.42

^{1}H NMR (500 MHz, d_6-acetone)



^{13}C NMR (125 MHz, d_6-acetone)

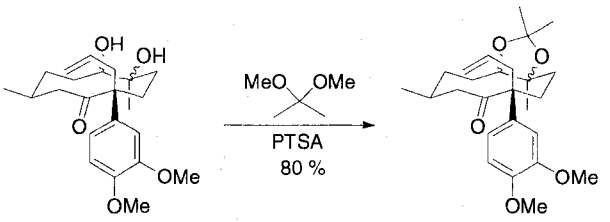




5.28 **5.43**

(±)-(2S,5R,6R,9S)-2-Allyl-5,6-dihydroxy-2-(3,4-dimethoxyphenyl)-5,9-dimethylcyclodecanone (**5.43**)

To a solution of **5.28** (23.1 mg, 0.0648 mmol) in THF/H_2O (5:1, 5 mL) was added NMO (7.2 mg, 0.0615 mmol) followed by OsO_4 (4% in H_2O, 0.04 mL, 0.00624 mmol), and the resulting clear yellow solution was stirred at room temperature for 3 hours. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 followed by 0.5 hours of vigorous stirring. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in 80 % EtOAc/hexanes to afford **5.43** (18.2 mg, 0.0467 mmol, 72 %, R_f = 0.50) as a yellow oil. This product rapidly decomposes, so it was used directly without full characterization in the next step.



5.43 **5.44**

(±)-(3aR,6S,9S,11aR)-6-Allyl-octahydro-6-(3,4-dimethoxyphenyl)-2,2,3a,9-tetramethylcyclodeca[d][1,3]dioxol-7-(8H)-one (**5.44**)

To a solution of **5.43** (14.6 mg, 0.0373 mmol) in acetone (3 mL) was added 2,2-dimethoxypropane (0.05 mL, 0.373 mmol) followed by PTSA (0.7 mg, 0.00368 mmol), and the mixture was stirred at room temperature for 10 minutes. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 20 % EtOAchexanes to afford **5.44** (12.9 mg, 0.0299 mmol, 80 %, $R_f = 0.60$) as a colorless oil.

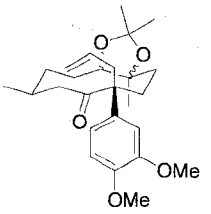
Data for **5.44**

^{1}H NMR (500 MHz, d_6-DMSO, spectrum recorded at 100 °C): δ = 6.86 (d, J = 8.1 Hz, 1H), 6.71-6.70 (m, 2H), 5.33-5.24 (m, 1H), 4.98 (d, J = 16.9 Hz, 1H), 4.90 (d, J = 9.9 Hz, 1H), 4.01 (dd, J = 5.8, 5.8 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.15 (dd, J = 18.7, 11.0 Hz, 1H), 2.83-2.63 (m, 2H), 2.44-2.40 (m, 2H), 2.32-2.26 (m, 1H), 2.04-1.93 (m, 2H), 1.71-1.65 (m, 1H), 1.56 (dd, J = 13.9, 13.9 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.31-1.26 (m, 2H), 1.17-1.10 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H), 0.94 (s, 3H)

^{13}C NMR (125 MHz, d_6-DMSO, spectrum recorded at 100 °C): δ = 210.8 (C_4), 148.0 (C_4), 147.3 (C_4), 133.7, (C_4) 133.3 (CH), 120.9 (CH), 117.0 (CH_2), 114.7 (CH), 111.7 (CH), 104.1 (C_4), 80.9 (CH), 76.3 (C_4), 60.2 (C_4), 55.9 (CH_3), 55.5 (CH_3), 44.8 (CH_2), 42.9 (CH_2), 30.5 (CH_2), 29.4 (CH_2), 27.8 (CH_3), 27.5 (CH), 26.8 (CH_3), 26.5 (CH_2), 23.6 (CH_2), 21.8 (CH_3), 20.3 (CH_3)

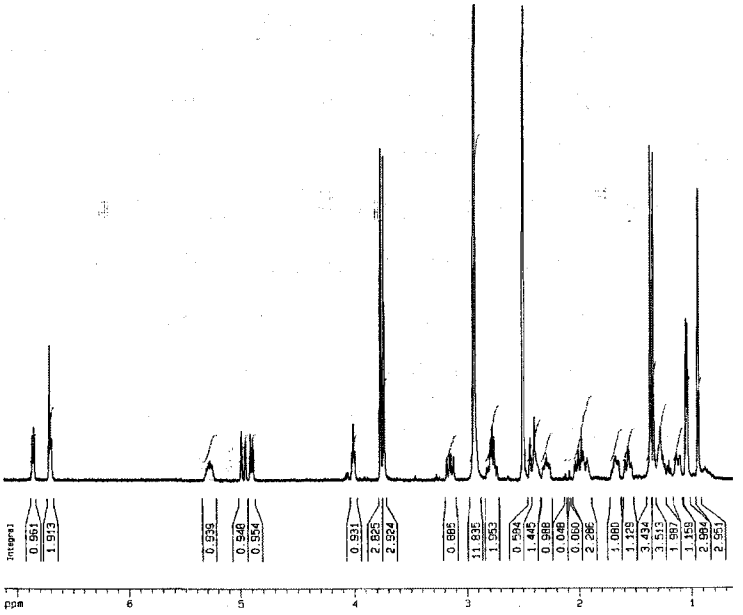
FT-IR (neat, cm^{-1}): 2956 (s), 2934 (s), 2870 (w), 2847 (m), 1701 (s)

HRMS (EI): Calculated 430.2719 (M^+) for $C_{26}H_{38}O_5$, found 430.2713

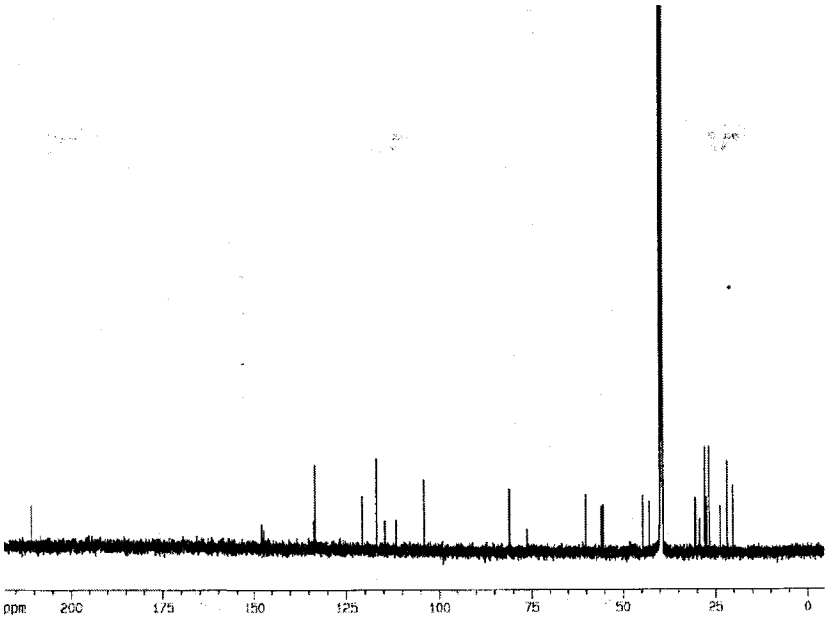


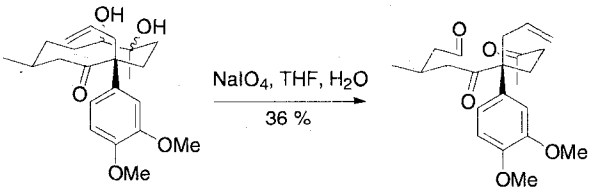
5.44

^{1}H NMR (500 MHz, d_6-DMSO, spectrum recorded at 100 °C)



^{13}C NMR (125 MHz, d_6-DMSO, spectrum recorded at 100 °C)

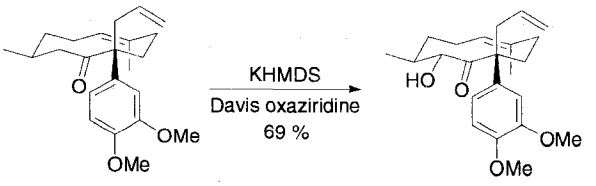




5.43 **5.45**

(±)-6-Allyl-6-(3,4-dimethoxy-phenyl)-3-methyl-5,9-dioxo-decanal (**5.45**)

To a solution of **5.43** (50.0 mg, 0.128 mmol) in THF/H_2O (5:1, 5 mL) was added NaIO4 (96.0 mg, 0.641 mmol), and the mixture was stirred at room temperature for 3 hours. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 followed by 0.5 hours of vigorous stirring. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in 80 % EtOAc/hexanes to afford **5.45** (18.2 mg, 0.0487 mmol, 36 %, R_f = 0.50) as a yellow oil. This product rapidly decomposes, but was observable by proton NMR.



5.28 **5.46**

(+)-(E, 2S, 9S, 10R)-2-Allyl-10-hydroxy-2-(3,4-dimethoxyphenyl)-5,9-dimethylcyclodec-5-enone (**5.46**)

To a solution of KHMDS (428.6 mg, 2.19 mmol) in THF (5 mL) cooled to -78 °C was added a solution of ketone **5.28** (153.2 mg, 0.430 mmol) in THF (5 mL). The resulting mixture was stirred at -78 °C for 0.5 hours after which the Davis oxaziridine (134.7 mg, 0.515 mmol) was added as a solution in THF (3 mL), followed by another 0.5 hours of stirring at -78 °C. The reaction was quenched by the addition of H_2O (15 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in 30 % EtOAc/hexanes to afford **5.46** (110.5 mg, 0.297 mmol, 69 %, Rf = 0.45) as a white solid.

Data for **5.46**

M.p.: 148-149 °C

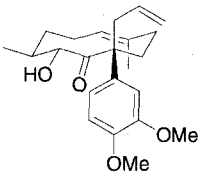
^{1}H NMR (500 MHz, d_6-DMSO, spectrum recorded at 100 °C): δ = 7.24 (d, J = 1.7 Hz, 1H), 7.01 (dd, J = 8.4, 1.4 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.53 (d, J = 6.7 Hz, 1H), 5.40-5.32 (m, 1H), 5.11 (d, J = 17.1 Hz, 1H), 5.00 (bs, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.31 (d, J = 8.0 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.41-3.37 (m, 1H), 3.16 (dd, J = 14.8, 8.1 Hz, 1H), 2.62 (dd, J = 13.2, 13.2 Hz, 1H), 2.36-2.30 (m, 1H), 2.09-2.05 (m, 1H), 1.98-1.88 (m, 5H), 1.46 (s, 3H), 1.34-1.30 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H)

^{13}C NMR: Carbon spectrum unavailable due to severe line broadening at room temperature. Heating over 70 °C resulted in decomposition at a rate that the carbon spectrum was not recordable before appreciable amounts of decomposition products were observed.

FT-IR (neat, cm^{-1}): 3492 (b), 2960 (s), 2929 (m), 2862 (m), 1696 (s)

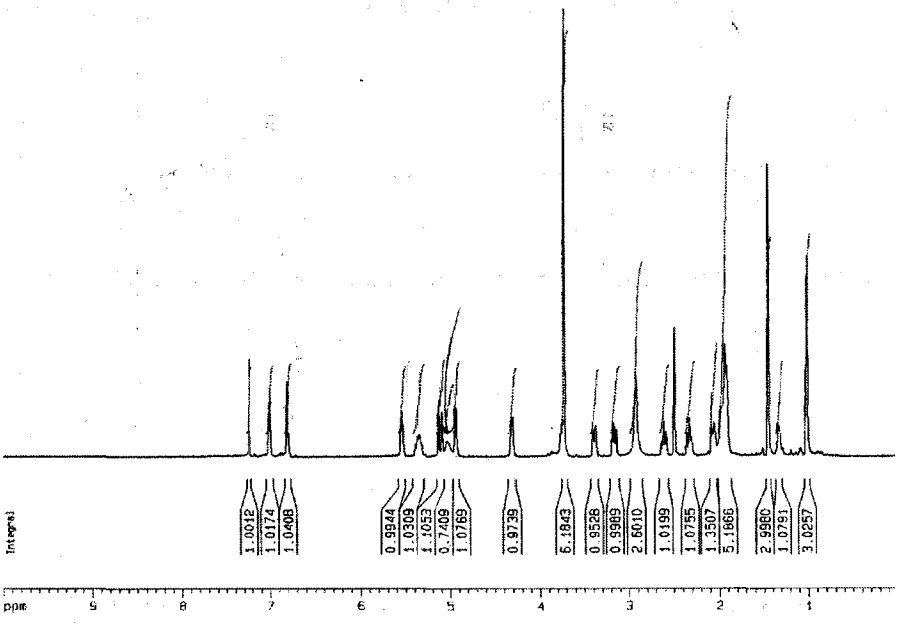
HRMS (EI): Calculated 372.2301 (M^+) for $C_{23}H_{32}O_4$, found 372.2299

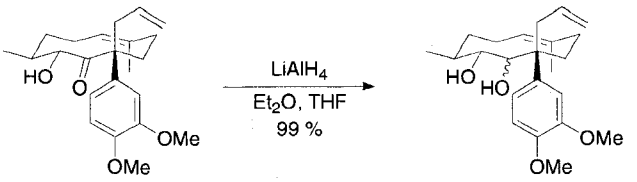
$[\alpha]_D^{22}$: +20.7°, c = 35.3 mg/mL (CH_2Cl_2)



5.46

^{1}H NMR (500 MHz, d_6-DMSO, spectrum recorded at 100 °C)





5.46 **5.47**

(-)-(E,1R,3S,10S)-3-Allyl-3-(3,4-dimethoxyphenyl)-6,10-dimethylcyclodec-6-ene-1,2-diol (**5.47**)

A solution of **5.46** (121.2 mg, 0.325 mmol) in THF (12 mL) cooled to 0 °C was treated with $LiAlH_4$ (61.6 mg, 1.62 mmol) and the resulting mixture was stirred for 0.5 hours. The reaction was quenched by the addition of 1M sodium tartrate (20 mL) followed by 2 hours of vigorous stirring. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 50 % EtOAc/hexanes giving **5.47** (122.8 mg, 0.324 mmol, 99 %, R_f = 0.50) as a white solid.

Data for **5.47**

M.p.: 136-137 °C

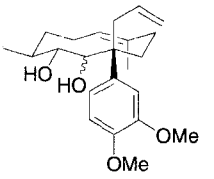
^{1}H NMR (500 MHz, C_6D_6): δ = 7.05 (s, 1H), 6.92 (dd, J = 8.3, 1.8 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 5.62-5.55 (m, 1H), 5.27 (d, J = 9.9 Hz, 1H), 5.19 (d, J = 17.1 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 4.41 (d, J = 4.3 Hz, 1H), 3.53 (s, 1H), 3.44 (s, 6H), 2.98 (dd, J = 15.1, 4.2 Hz, 1H), 2.82 (dd, J = 15.0, 8.5 Hz, 1H), 2.65 (dd, J = 13.5, 13.5 Hz, 1H), 2.47 (dd, J = 13.1, 13.1 Hz, 1H), 2.40-2.28 (m, 2H), 2.05 (d, J = 11.8 Hz, 1H), 1.99-1.91 (m, 1H), 1.86 (s, 3H), 1.76 (dd, J = 14.3, 7.4 Hz, 1H), 1.56-1.48 (m, 1H), 1.38-1.31 (m, 1H), 1.18 (s, 1H), 1.04-0.98 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H)

^{13}C NMR (125 MHz, C_6D_6): δ = 150.3 (C_4), 148.9 (C_4), 142.5 (C_4), 136.7 (C_4), 135.6 (CH), 128.7 (CH), 120.2 (CH), 117.6 (CH_2), 112.7 (CH), 112.2 (CH), 84.5 (CH), 75.2 (CH), 56.2 (CH_3), 56.0 (CH_3), 50.5 (C_4), 37.2 (CH_2), 36.7 (CH_2), 34.9 (CH_2), 32.9 (CH), 29.5 (CH_2), 28.2 (CH_2), 16.8 (CH_3), 15.8 (CH_3)

FT-IR (neat, cm^{-1}): 3524 (b), 2964 (s), 2929 (s), 2858 (s), 2835 (m)

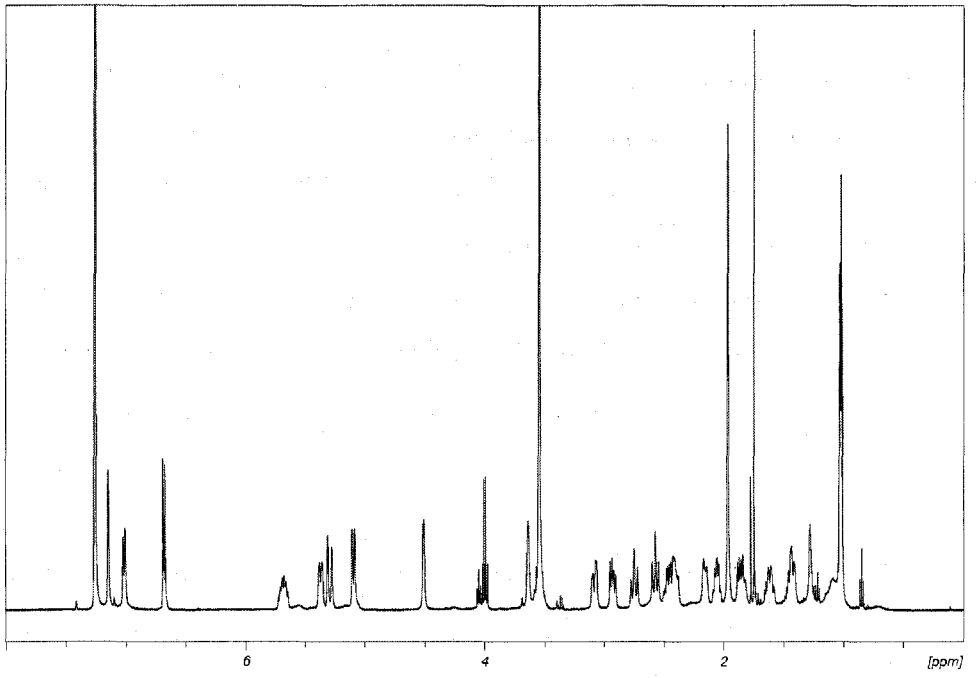
HRMS (EI): Calculated 374.2457 (M^+) for $C_{23}H_{34}O_4$, found 374.2446

$[\alpha]_D^{22}$: -5.1°, c = 24.0 mg/mL (CH_2Cl_2)

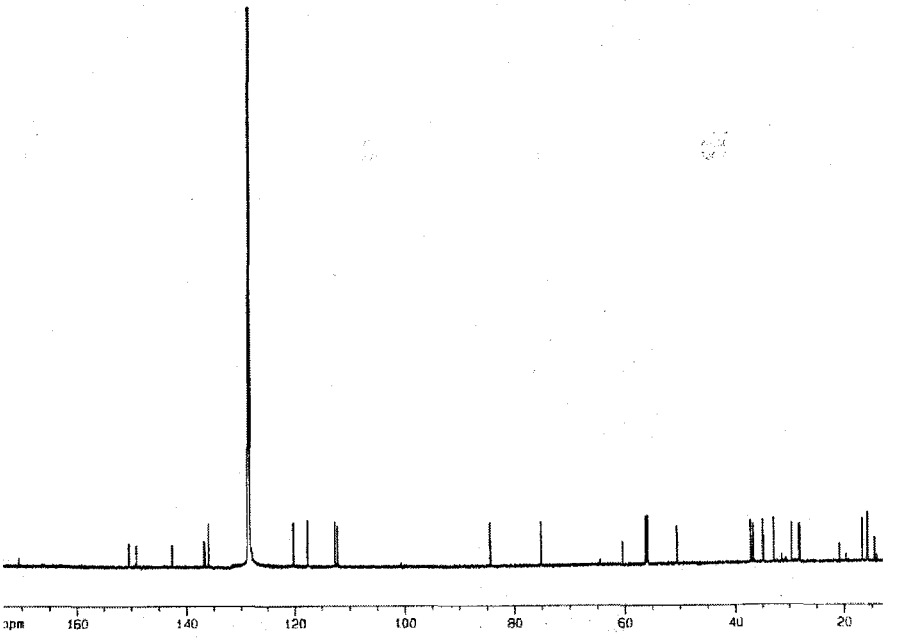


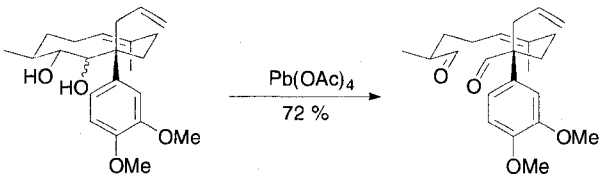
5.47

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





5.47 **5.48**

(±)-(E, 2S, 9S)-2-Allyl-2-(3,4-dimethoxyphenyl)-5,9-dimethyldec-5-enedial (**5.48**)

To a solution of **5.47** (71.4 mg, 0.191 mmol) in benzene (8 mL) was added $Pb(OAc)_4$ (338.1 mg, 0.763 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in 30 % EtOAc/hexanes to afford **5.48** (51.1 mg, 0.137 mmol, 72 %, $R_f = 0.60$) as a yellow oil.

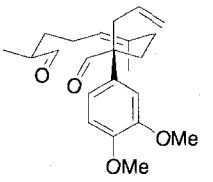
Data for **5.48**

^{1}H NMR (400 MHz, C_6D_6): δ = 9.44 (s, 1H), 9.29 (d, J = 1.8 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.71 (dd, J = 8.2, 2.3 Hz, 1H), 6.57 (d, J = 8.2 Hz, 1H), 5.68-5.57 (m, 1H), 5.07-4.98 (m, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 2.71-2.69 (m, 2H), 2.21-2.17 (m, 1H), 2.17-2.13 (m, 1H), 2.02-1.88 (m, 6H), 1.54 (s, 3H), 1.19-1.12 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 203.2 (CH), 200.9 (CH), 150.6 (C_4), 149.6 (C_4), 136.0 (C_4), 133.7 (CH), 131.1 (C_4), 124.4 (CH), 120.3 (CH), 118.4 (CH_2), 112.4 (CH), 111.9 (CH), 60.1 (C_4), 55.7 (CH_3), 55.5 (CH_3), 45.9 (CH), 37.0 (CH_2), 34.0 (CH_2), 31.3 (CH_2), 30.7 (CH_2), 25.6 (CH_2), 16.2 (CH_3), 13.3 (CH_3)

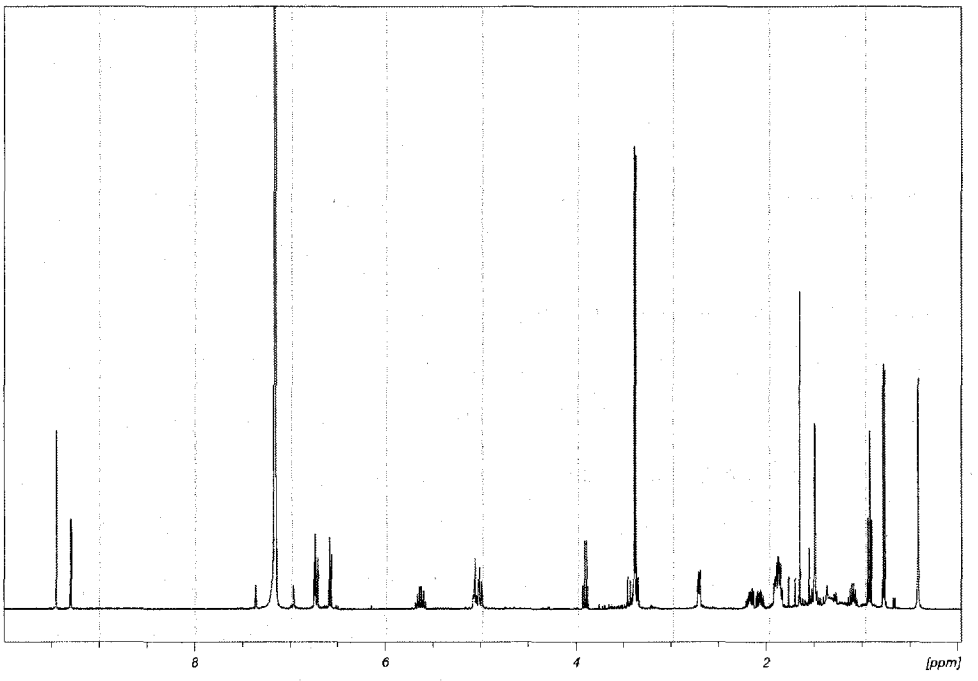
FT-IR (neat, cm^{-1}): 2933 (s), 2852 (m), 1721 (s), 1640 (w)

HRMS (EI): Calculated 372.2301 (M^+) for $C_{23}H_{32}O_4$, found 372.2331

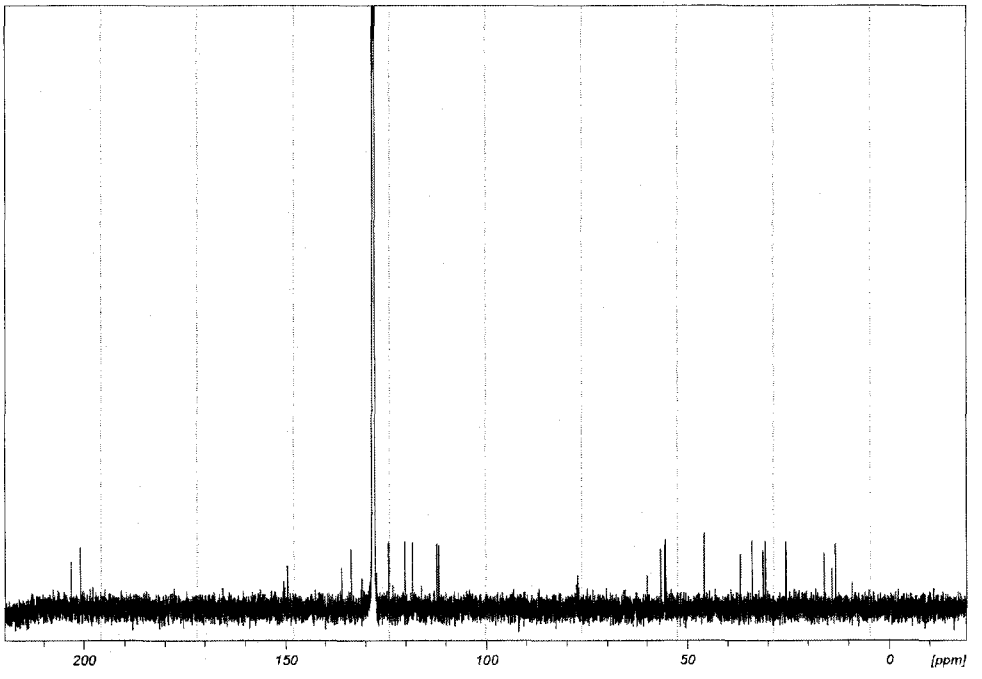


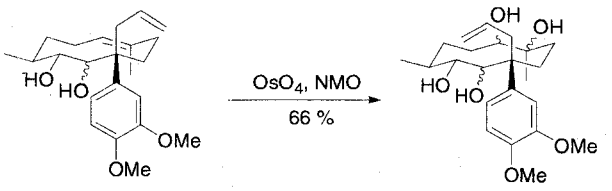
5.48

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



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

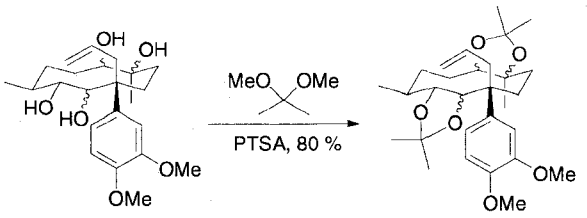




5.47 **5.49**

(±)-(5S,6R,8S)-8-Allyl-8-(3,4-dimethoxyphenyl)-1,5-dimethylcyclodecane-1,2,6,7-tetraol (**5.49**)

A solution of **5.47** (61.9 mg, 0.165 mmol) in THF/H_2O (5:1, 15 mL) was treated with NMO (17.4 mg, 0.149 mmol) and OsO_4 (4 % in H_2O, 0.11 mL, 0.0173 mmol) and stirred for 3 hours at room temperature. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (20 mL) followed by stirring for a further 0.5 hours. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in EtOAc afforded **5.49** (44.5 mg, 0.109 mmol, 66 %, R_f = 0.20) as a yellow oil. This product rapidly decomposed, so it was used directly without further purification or characterization in the next step of the sequence.



5.49 **5.50**

(±)-(5S,6R,8S)-8-Allyl-8-(3,4-dimethoxyphenyl)-1,5-dimethylcyclodecane-1,2,6,7-tetraol bis acetonide (**5.50**)

A solution of **5.49** (43.5 mg, 0.106 mmol) in acetone (8 mL) was cooled to 0 °C then treated with 2,2-dimethoxypropane (0.13 mL, 1.12 mmol) and PTSA (2.0 mg, 0.0105 mmol). The reaction mixture was stirred at 0 °C for 15 minutes and then was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 20 % EtOAc/hexanes afforded **5.50** (41.6 mg, 0.0852 mmol, 80 %, Rf = 0.50) as a colorless oil.

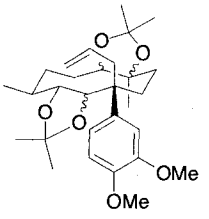
Data for **5.50**

^{1}H NMR (400 MHz, C_6D_6): δ = 7.47 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.6, 2.4 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 5.49-5.39 (m, 1H), 4.99 (d, J = 17.1 Hz, 1H), 4.90 (d, J = 10.1 Hz, 1H), 4.67 (d, J = 7.4 Hz, 1H), 4.38 (dd, J = 6.4, 6.4 Hz, 1H), 4.03 (dd, J = 4.0, 4.0 Hz, 1H), 3.62 (s, 3H), 3.43 (s, 3H), 3.15 (dd, J = 14.4, 4.8 Hz, 1H), 2.40 (dd, J = 14.2, 9.1 Hz, 1H), 2.29-2.24 (m, 1H), 2.19-1.94 (m, 5H), 1.76-1.67 (m, 1H), 1.63-1.50 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H), 0.71 (d, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 149.8 (C_4), 149.6 (C_4), 139.8 (C_4), 135.8 (CH), 121.7 (CH), 117.9 (CH_2), 116.1 (CH), 111.8 (CH), 106.3 (C_4), 106.2 (C_4), 83.7 (CH), 83.7 (C_4), 83.5 (CH), 82.2 (CH), 57.1 (CH_3), 56.0 (CH_3), 44.9 (C_4), 44.1 (CH_2), 38.3 (CH_2), 33.8 (CH_2), 33.7 (CH), 33.2 (CH_2), 29.5 (CH_3), 27.7 (CH_3), 27.1 (CH_3), 27.0 (CH_2), 23.7 (CH_3), 21.2 (CH_3), 20.2 (CH_3)

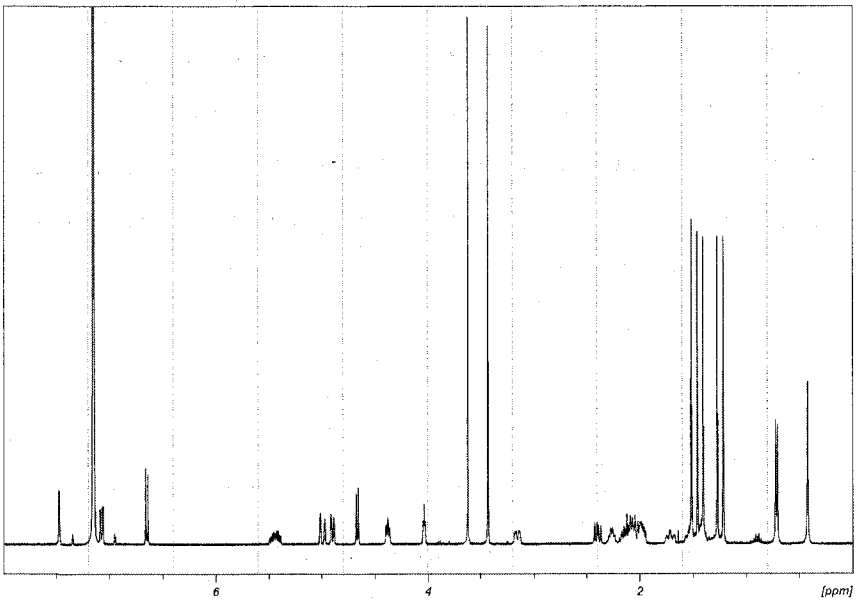
FT-IR (neat, cm^{-1}): 2998 (s), 2963 (s), 2940 (s), 2917 (s), 1652 (w)

HRMS (EI): Calculated 488.3138 (M^+) for $C_{29}H_{44}O_6$, found (M^+ - CH_3) at 473.2894, actual value 473.2903

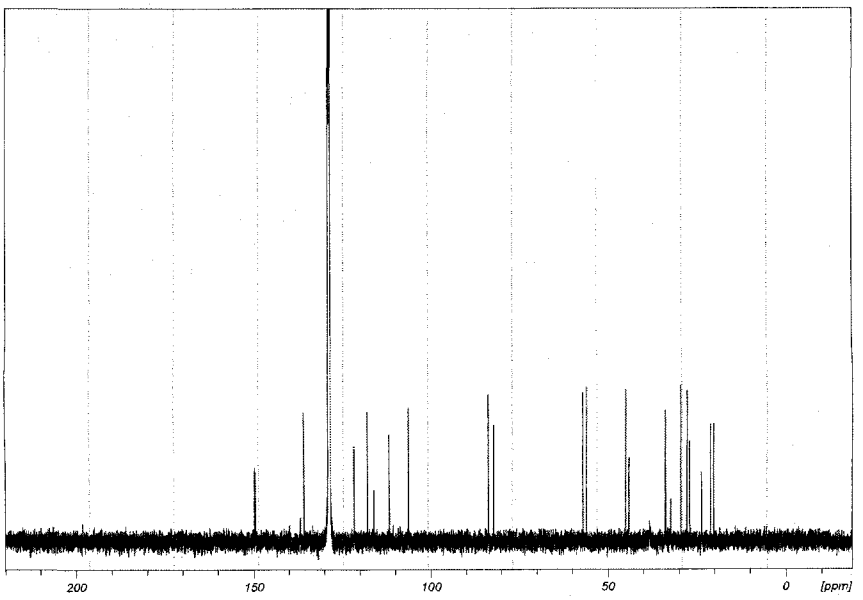


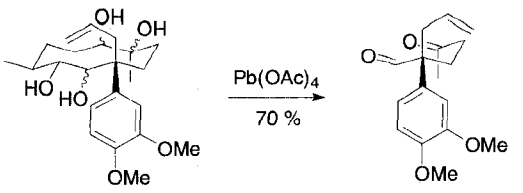
5.50

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



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





5.49 **5.27**

(-)-(S)-2-Allyl-2-(3,4-dimethoxyphenyl)-5-oxohexanal (**5.27**)

A solution of **5.49** (16.8 mg, 0.0411 mmol) in benzene (5 mL) was treated with $Pb(OAc)_4$ (109.4 mg, 0.247 mmol) and the resulting mixture was stirred at room temperature for 3 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 50 % EtOAc/hexanes afforded **5.27** (8.4 mg, 0.0289 mmol, 70 %, $R_f = 0.50$) as a colorless oil.

Data for **5.27**

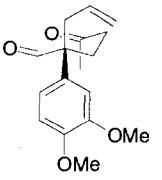
^{1}H NMR (400 MHz, C_6D_6): δ = 9.37 (s, 1H), 6.68 (d, J = 2.2 Hz, 1H), 6.63 (dd, J = 8.3, 2.3 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 5.57-5.48 (m, 1H), 4.97-4.91 (m, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 2.61-2.50 (m, 2H), 2.36-2.29 (m, 1H), 2.25-2.18 (m, 1H), 2.07-1.88 (m, 2H), 1.54 (s, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 205.5 (C_4), 200.9 (CH), 150.6 (C_4), 149.7 (C_4), 133.4 (CH), 130.8 (C_4), 120.2 (CH), 118.5 (CH_2), 112.4 (CH), 111.8 (CH), 56.0 (C_4), 55.6 (CH_3), 55.2 (CH_3), 37.8 (CH_2), 37.7 (CH_2), 29.4 (CH_3), 26.2 (CH_2)

FT-IR (neat, cm^{-1}): 2963 (w), 2940 (m), 2917 (w), 2836 (w), 1716 (s), 1652 (w)

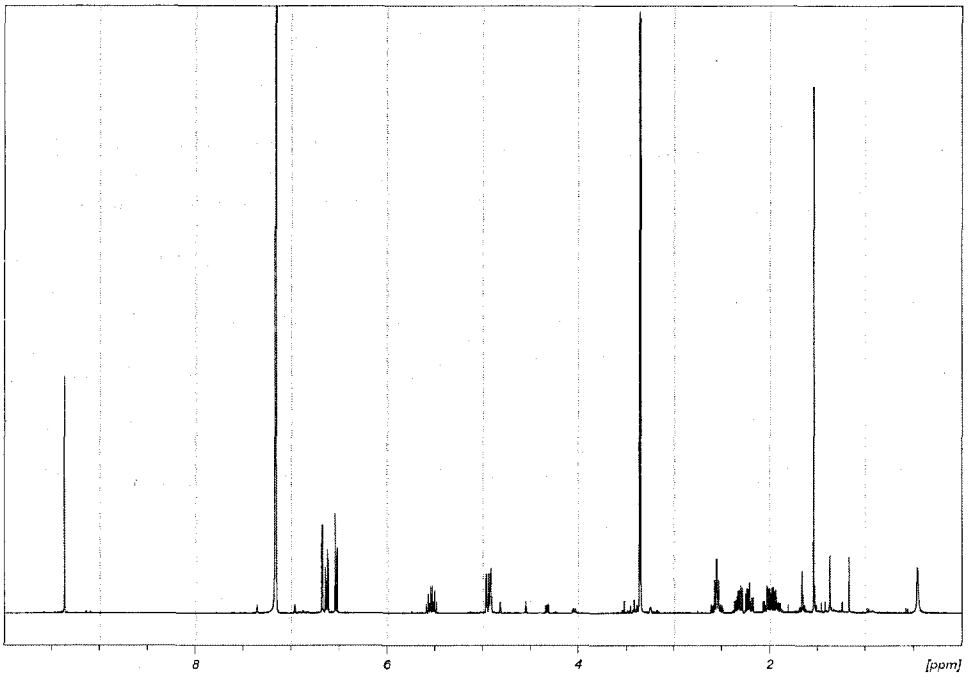
HRMS (EI): Calculated 290.1518 (M^+) for $C_{17}H_{22}O_4$, found 290.1503

$[\alpha]_D^{22}$: -8.1°, c = 12.2 mg/mL (CH_2Cl_2)

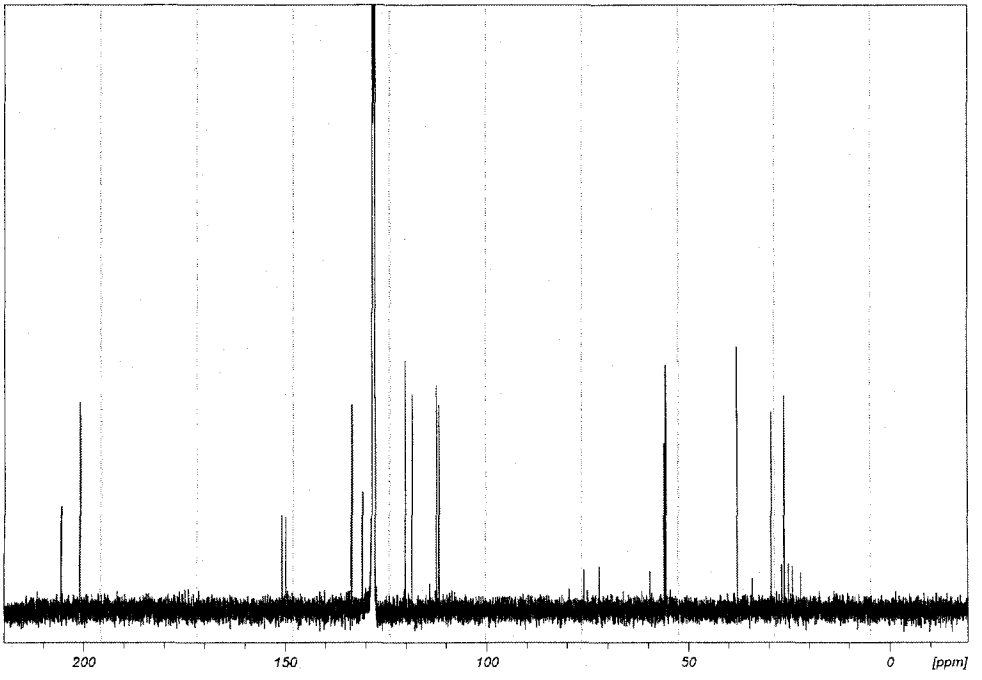


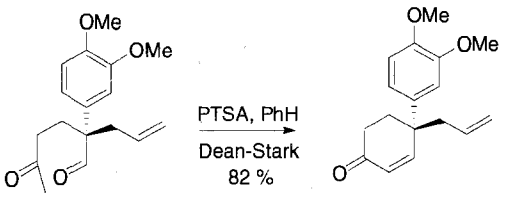
5.27

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



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





5.27 **5.26**

(-)-(R)-4-Allyl-4-(3,4-dimethoxyphenyl)cyclohex-2-enone (**5.26**)

A solution of **5.27** (10.5 mg, 0.0362 mmol) in benzene (5 mL) was treated with PTSA (0.7 mg, 0.00368 mmol). The flask containing the mixture was fitted with a Dean-Stark trap and reflux condenser and the mixture was heated at reflux for 1.5 hours. The reaction was then cooled to room temperature and then diluted with EtOAc (15 mL) and H_2O (15 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 50 % EtOAc/hexanes afforded **5.26** (8.1 mg, 0.0297 mmol, 82 %, $R_f = 0.55$) as a colorless oil.

Data for **5.26**

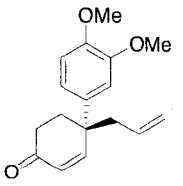
^{1}H NMR (500 MHz, C_6D_6): δ = 7.06 (d, J = 10.3 Hz, 1H), 6.84-6.81 (m, 3H), 6.17 (dd, J = 10.2, 0.5 Hz, 1H), 5.60-5.51 (m, 1H), 5.13-5.07 (m, 2H), 3.87 (s, 6H), 2.70 (ddd, J = 5.9, 1.4, 1.4 Hz, 1H), 2.49 (dd, J = 13.4, 8.5 Hz, 1H), 2.37-2.20 (m, 4H)

^{13}C NMR (125 MHz, C_6D_6): δ = 199.7 (C_4), 155.3 (CH), 149.2 (C_4), 148.1 (C_4), 135.4 (C_4), 133.6 (CH), 129.6 (CH), 119.5 (CH), 119.0 (CH_2), 111.1 (CH), 110.2 (CH), 65.1 (CH_3), 56.0 (CH_3), 46.4 (CH_2), 43.6 (C_4), 36.2 (CH_2), 34.6 (CH_2)

FT-IR (neat, cm^{-1}): 3002 (w), 2933 (m), 2840 (w), 1683 (s), 1633 (w)

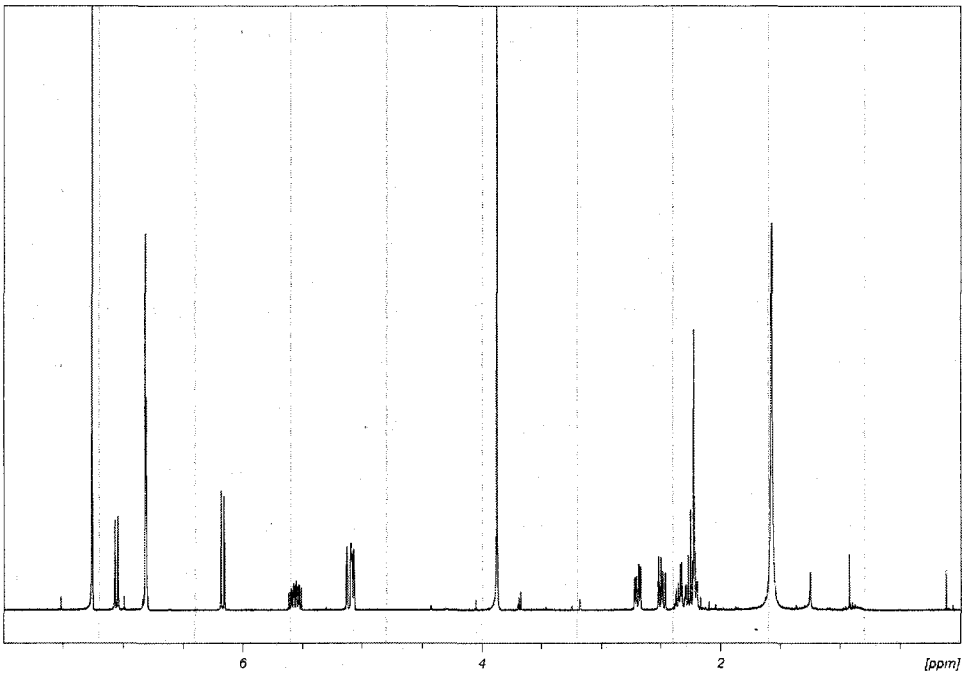
HRMS (EI): Calculated 272.1412 (M^+) for $C_{17}H_{20}O_3$, found 272.1432

$[\alpha]_D^{22}$: -81.5°, c = 8.1 mg/mL (CH_2Cl_2)

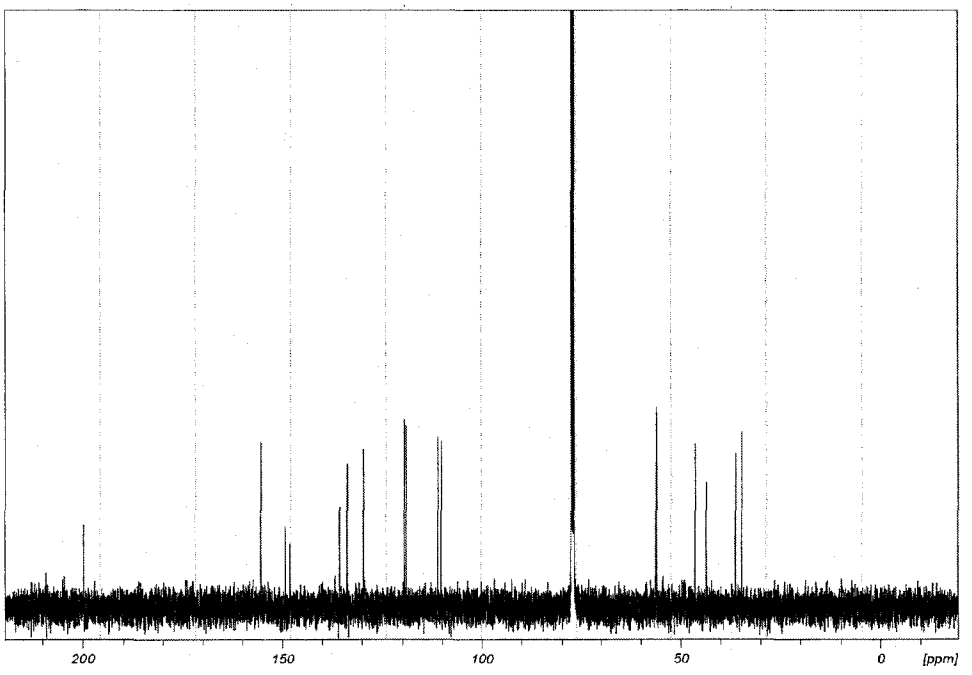


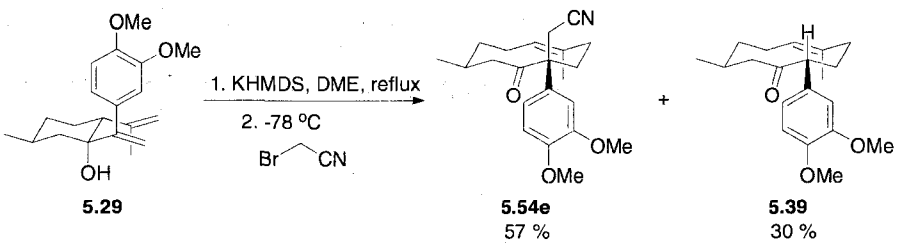
5.26

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR (125 MHz, C_6D_6)





5.29 **5.54e** 57 % **5.39** 30 %

(±)-2-((E,1S,8S)-1-(3,4-Dimethoxyphenyl)-4,8-dimethyl-1-oxocyclodec-4-enyl)acetonitrile (**5.54e**)

A solution of **5.29** (235.1 mg, 0.743 mmol) in DME (12 mL) was treated with a solution of KHMDS (444.6 mg, 2.23 mmol) in DME (5 mL). The resulting cloudy orange solution was plunged into a pre-warmed oil bath and heated at 85 °C for 15 minutes whereupon it turned clear orange. This mixture was cooled to room temperature, then immediately to -78 °C after which it was treated with bromoacetonitrile (0.10 mL, 1.50 mmol). The reaction was stirred for a further 15 mintues and then it was quenched with water and warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was isolated by flash chromatography in 40 % EtOAc/hexanes, affording ketone **5.54e** (151.1 mg, 0.425 mmol, 57 %, $R_f = 0.50$) as a yellow oil. Also recovered was intermediate **5.39** (70.5 mg, 0.223 mmol, 30 %, $R_f = 0.95$) as a yellow oil.

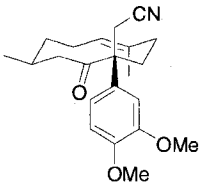
Data for **5.54e**

^{1}H NMR (500 MHz, d_6-DMSO): δ = 6.92-6.91 (m, 2H), 6.89-6.87 (m, 1H), 5.51 (d, J = 8.7 Hz, 1H), 3.85 (d, J_{AB} = 16.7 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.63 (d, J_{AB} = 16.7 Hz, 1H), 2.93 (dd, J = 18.1, 8.0 Hz, 1H), 2.86 (dd, J = 13.1, 13.1 Hz, 1H), 2.29 (dd, J = 13.1, 13.1 Hz, 1H), 2.08-1.91 (m, 6H), 1.65-1.62 (m, 1H), 1.39 (s, 3H), 1.27-1.20 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H)

^{13}C NMR (125 MHz, d_6-DMSO): δ = 206.0 (C_4), 148.4 (C_4), 147.9 (C_4), 136.2 (C_4), 134.9 (C_4), 127.0 (CH), 118.7 (CH), 118.6 (C_4), 111.5 (CH), 110.6 (CH), 55.7 (CH_3), 55.4 (CH_3), 53.8 (C_4), 47.2 (CH_2), 36.5 (CH_2), 35.7 (CH_2), 34.6 (CH_2), 27.4 (CH), 26.9 (CH_2), 24.4 (CH_3), 22.7 (CH_2), 15.8 (CH_3)

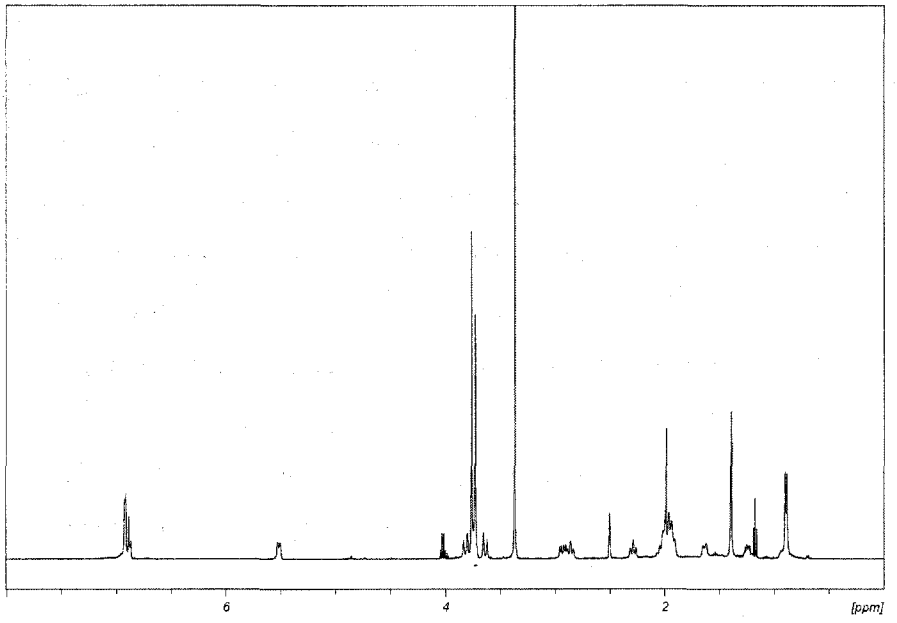
FT-IR (neat, cm^{-1}): 2956 (m), 2874 (m), 2252 (w), 1696 (s)

HRMS (EI): Calculated 355.2147 (M^+) for $C_{22}H_{29}NO_3$, found 355.2138

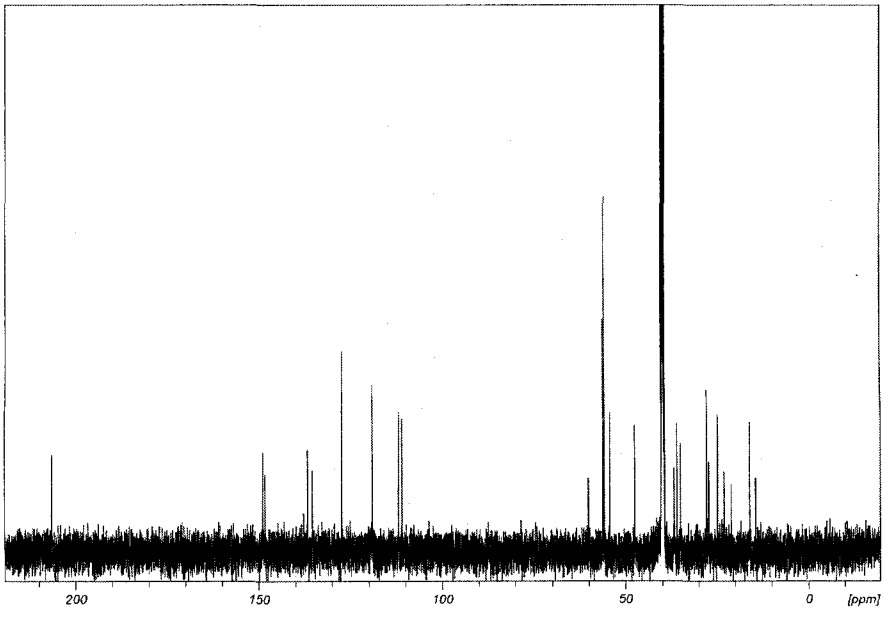


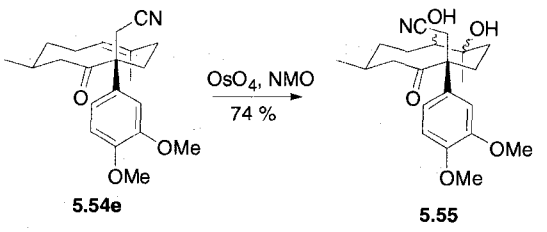
5.54e

^{1}H NMR (500 MHz, d_6-DMSO)



^{13}C NMR (125 MHz, d_6-DMSO)

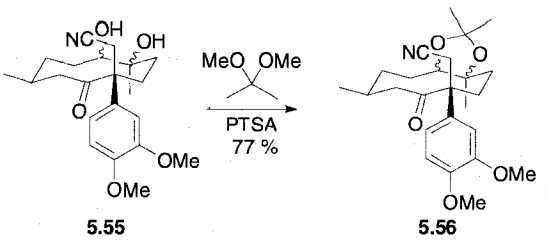




5.54e **5.55**

(±)-2-((1S, 2S, 7R, 8R)-7,8-Dihydro-1-(3,4-dimethoxyphenyl)-4,8-dimethyl-2-oxocyclodecyl)acetonitrile (**5.55**)

To a solution of **5.54e** (52.5 mg, 0.148 mmol) in THF/H_2O (5:1, 5 mL) was added NMO (34.6 mg, 0.295 mmol) followed by OsO_4 (4% in H_2O, 0.09 mL) and the resulting clear yellow solution was stirred at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 followed by 0.5 hours of vigorous stirring. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in EtOAc to afford **5.55** (42.7 mg, 0.110 mmol, 74 %) as a yellow oil. This product rapidly decomposed, so it was used directly without further purification or characterization in the next step of the sequence.



5.55 **5.56**

(±)-2-((3aR, 6S, 9S, 11aR)-Decahydro-6-(3,4-dimethoxyphenyl)-2,2,3a,9-tetramethyl-7-oxocyclodeca[d][1,3]dioxol-6-yl)acetonitrile (**5.56**)

To a solution of **5.55** (42.7 mg, 0.110 mmol) in acetone (5 mL) was added 2,2-dimethoxypropane (0.13 mL, 1.12 mmol) followed by PTSA (2.1 mg, 0.011 mmol) and the mixture was stirred at room temperature for 10 minutes. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated and the product was isolated by flash chromatography in 40 % EtOAc/hexanes to afford **5.56** (36.2 mg, 0.0843 mmol, 77 %, R_f = 0.55) as a white solid.

Data for **5.56**

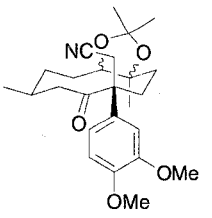
M.p.: 157-158 °C

^{1}H NMR (400 MHz, C_6D_6): δ = 6.70 (dd, J = 8.3, 2.3 Hz, 1H), 6.64 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 4.21-4.17 (m, 1H), 3.36 (s, 3H), 3.24 (s, 3H), 2.60-2.37 (m, 5H), 2.02-1.94 (m, 1H), 1.71-1.61 (m, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.34-1.20 (m, 2H), 1.24 (d, J = 7.0 Hz, 3H), 1.19-1.09 (m, 1H), 1.00 (s, 3H), 0.86 (dd, J = 15.7, 6.2 Hz, 1H)

^{13}C NMR (100 MHz, C_6D_6): δ = 210.6 (C_4), 150.6 (C_4), 150.2 (C_4), 131.5 (C_4), 119.4 (CH), 117.8 (C_4), 112.4 (CH), 110.7 (CH), 105.7 (C_4), 81.5 (CH), 75.0 (C_4), 58.4 (C_4), 55.6 (CH_3), 55.4 (CH_3), 42.2 (CH_2), 34.2 (CH), 30.7 (CH_2), 30.1 (CH_2), 28.8 (CH_3), 27.9 (CH_2), 27.6, (CH_3), 26.4 (CH_2), 25.5 (CH_2), 25.3 (CH_3), 23.0 (CH_3)

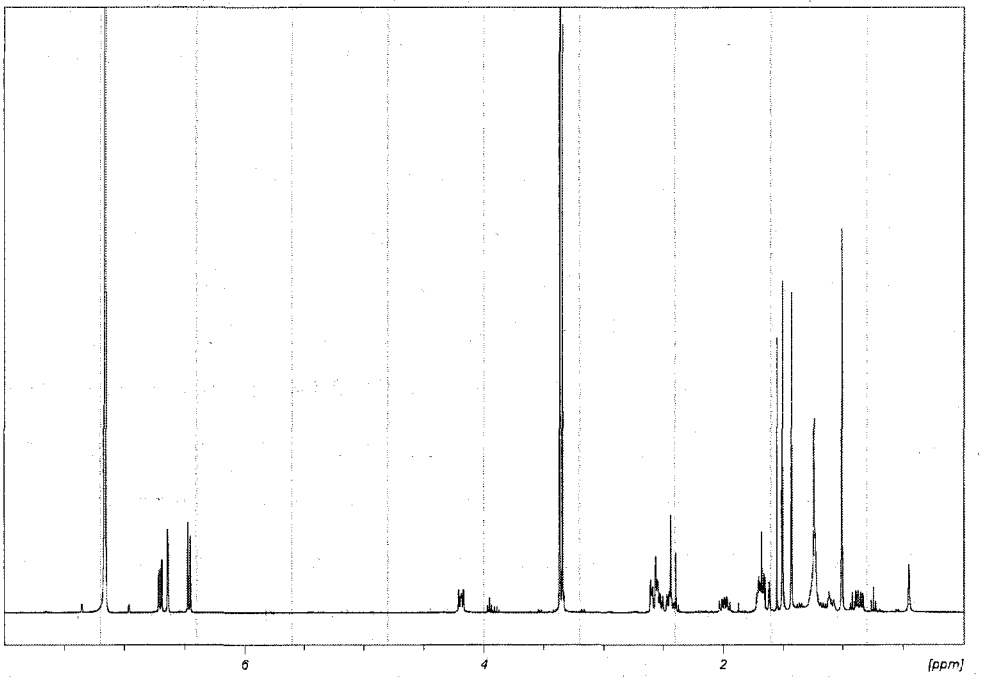
FT-IR (neat, cm^{-1}): 2979 (s), 2936 (m), 2223 (w), 1705 (s),

HRMS (EI): Calculated 429.2515 (M^+) for $C_{25}H_{35}NO_5$, found 429.2533

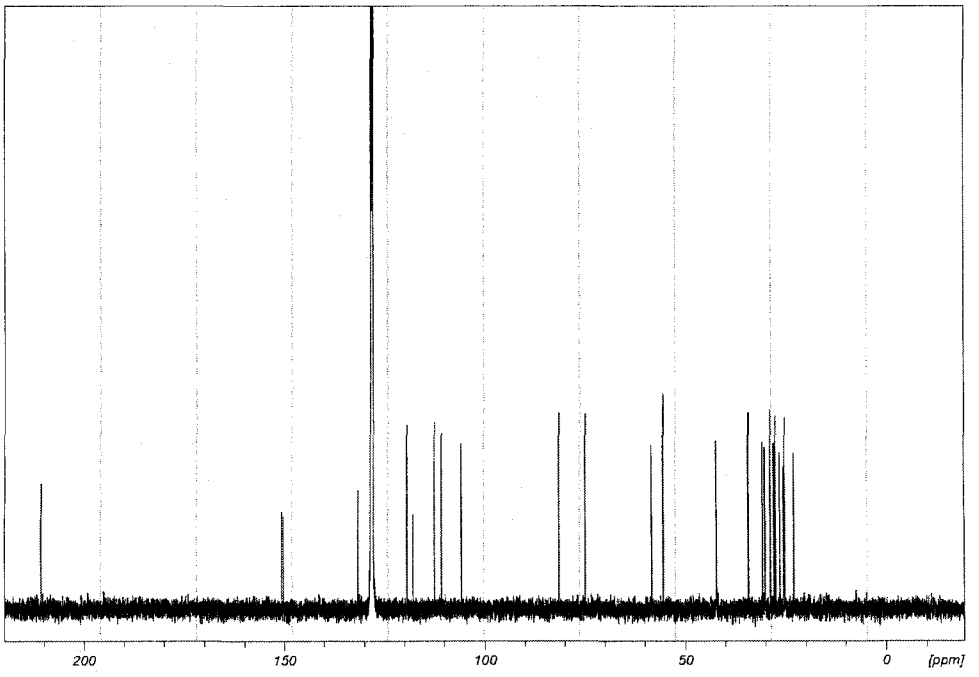


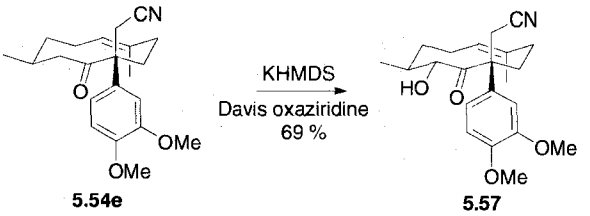
5.56

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



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

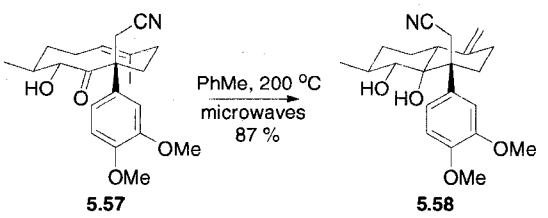




5.54e **5.57**

(±)-(1S, 8S, 9R)-(1-(3,4-Dimethoxyphenyl)-9-hydroxy-4,8-dimethyl-10-oxocyclodec-4-enyl)acetonitrile (**5.57**)

A solution of **5.54e** (79.9 mg, 0.225 mmol) in THF (3 mL) was cooled to -78 °C and treated with a solution of KHMDS (224.2 mg, 1.12 mmol) in THF (3 mL) whereupon the mixture was stirred at -78 °C for 0.5 hours giving a clear yellow solution. A solution of Davis' oxaziridine (70.5 mg, 0.270 mmol) in THF (1 mL) was then added to this solution and the resulting mixture was stirred for 0.5 hours at -78 °C whereupon the reaction was complete. The reaction was quenched by the addition of water followed by warming to room temperature where the layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 50 % EtOAc/hexanes afforded hydroxyketone **5.57** (57.6 mg, 0.155 mmol, 69 %, R_f = 0.45) as a colorless oil. This product was used in the next step without full characterization due to extreme line broadening in both the ^1H and ^{13}C spectra.



5.57 **5.58**

(±)-2-((1R, 2S, 4aR, 8S, 8aR)-Decahydro-1,8a-dihydroxy-8-(3,4-dimethoxyphenyl)-2-methyl-5-methylenenapthalen-8-yl)acetonitrile (**5.58**)

A sample of **5.57** (32.1 mg, 0.0864 mmol) was dissolved in toluene (13 mL) and placed in a quartz microwave vessel for the CEM Corporation MARS microwave reactor, and it was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 200 °C over 20 minutes, then for 1 hour at 200 °C. Upon cooling, the reaction mixture was concentrated to give a yellow oil. The product was recovered by flash chromatography in 40 % EtOAc/hexanes, affording **5.58** (27.8 mg, 0.0748 mmol, 87 %, $R_f = 0.50$) as a colorless oil.

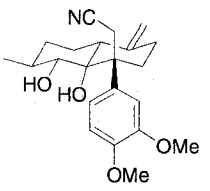
Data for **5.58**

^{1}H NMR (400 MHz, d_6-acetone): δ = 7.27 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.6, 2.5 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 4.86 (d, J = 1.7 Hz, 1H), 4.66 (d, J = 1.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.70 (d, J_{AB} = 17.4 Hz, 1H), 3.57 (d, J_{AB} = 17.4 Hz, 1H), 3.34 (dd, J = 9.6, 5.2 Hz, 1H), 2.99 (s, 1H), 2.62 (dddd, J = 13.8, 13.8, 4.7, 1.9 Hz, 1H), 2.47-2.31 (m, 3H), 1.78-1.71 (m, 3H), 1.68-1.53 (m, 2H), 1.51-1.42 (m, 1H), 1.07-0.97 (m, 1H), 0.83 (d, J = 6.5 Hz, 3H)

^{13}C NMR (100 MHz, d_6-acetone): δ = 149.8 (C_4), 149.5 (C_4), 148.9 (C_4), 136.8 (C_4), 120.5 (CH), 119.3 (C_4), 114.0 (CH), 112.2 (CH), 108.5 (CH_2), 79.7 (C_4), 77.5 (CH), 65.2 (CH_3), 56.0 (CH_3), 48.6 (C_4), 45.4 (CH), 36.2 (CH), 35.9 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 25.0 (CH_2), 21.7 (CH_2), 19.5 (CH_3)

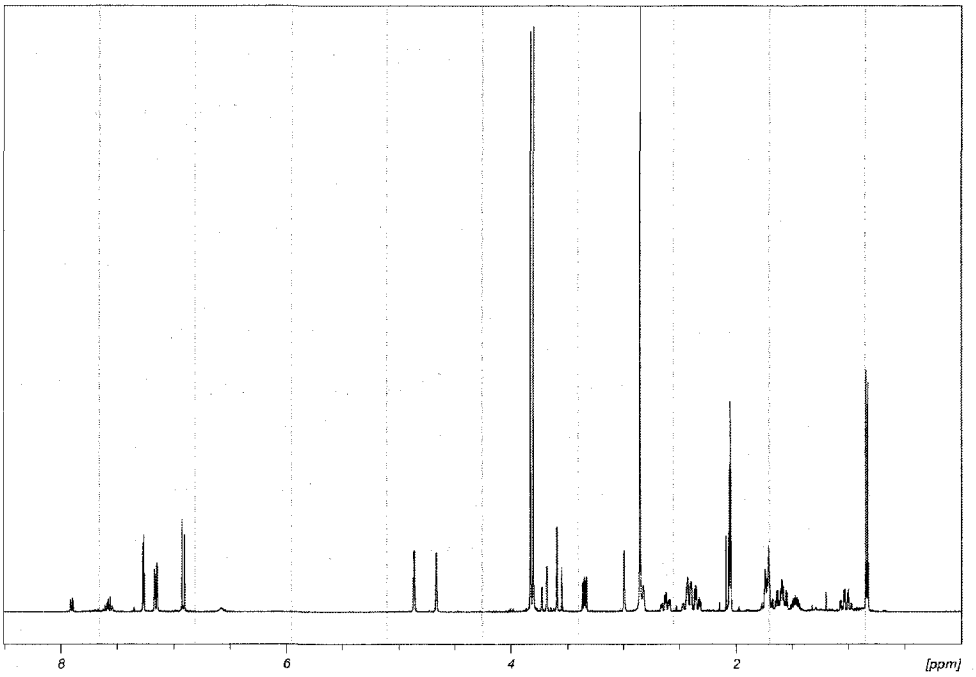
FT-IR (neat, cm^{-1}): 3537 (b), 2934 (m), 2868 (m), 2108 (w), 1606 (w)

HRMS (EI): Calculated 371.2097 (M^+) for $C_{22}H_{29}NO_4$, found 371.2091

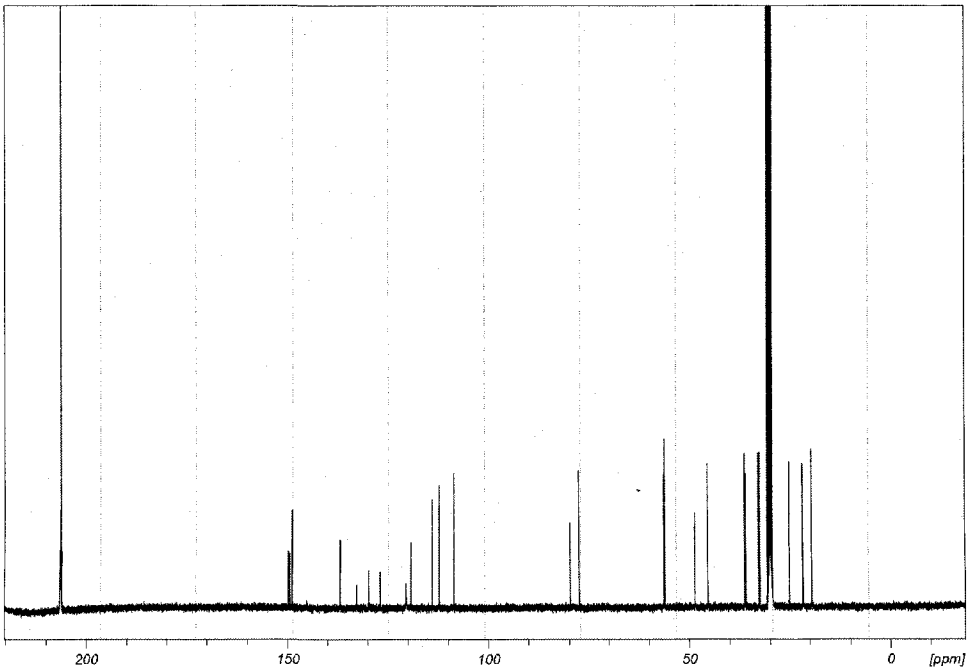


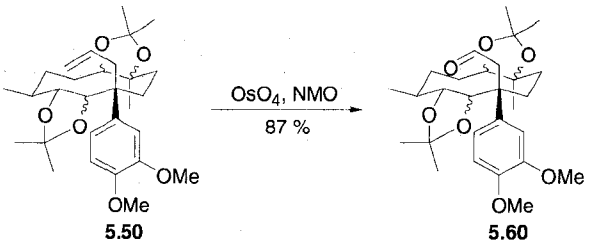
5.58

^{1}H NMR (400 MHz, d_6-acetone)



^{13}C NMR (100 MHz, d_6-acetone)





5.50 **5.60**

(±)-[1-(3,4-Dimethoxy-phenyl)-2,3,7,8-tetrahydroxy-4,8-dimethyl-cyclodecyl]-acetaldehyde bis acetonide (**5.60**)

A solution of **5.50** (35.4 mg, 0.0726 mmol) in THF/H_2O (5:1, 8 mL) was treated with NMO (25.5 mg, 0.218 mmol) and OsO_4 (4 % in H_2O, 0.12 mL, 0.0189 mmol) and stirred for 3.5 hours at room temperature. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (10 mL) followed by stirring for a further 0.5 hours. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography in 50 % EtOAc/hexanes afforded **5.60** (30.9 mg, 0.0630 mmol, 87 %, R_f = 0.65) as a colorless oil.

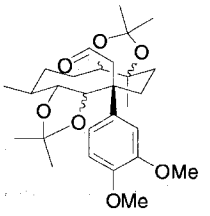
Data for **5.60**

^{1}H NMR (400 MHz, C_6D_6): δ = 9.36 (dd, J = 2.6, 2.6 Hz, 1H) 1.50 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 7.32 (d, J = 2.3 Hz, 1H), 7.03 (dd, J = 8.6, 2.3 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 4.56 (d, J = 7.2 Hz, 1H), 4.31 (dd, J = 7.0, 7.0 Hz, 1H), 3.89 (dd, J = 4.0, 4.0 Hz, 1H), 3.61 (s, 3H), 3.41 (s, 3H), 3.05 (dd, J = 15.6, 2.2 Hz, 1H), 2.45-2.37 (m, 2H), 2.18-1.87 (m, 6H), 1.81 (dd, J = 13.1, 6.4 Hz, 1H), 1.53-1.48 (m, 1H), 1.50 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 0.84 (d, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, C_6D_6): δ = 201.2 (CH), 149.5 (2 × C_4), 149.4 (C_4), 121.3 (CH), 115.3 (CH), 111.5 (CH), 105.6 (C_4), 105.5 (C_4), 83.3 (CH), 82.9 (C_4), 82.6 (CH), 81.2 (CH), 56.7 (CH_3), 55.4 (CH_3), 55.2 (C_4), 44.6 (CH_2), 28.3 (CH_2), 33.7 (CH_2), 31.3 (CH), 30.3 (CH_2), 29.1 (CH_3), 28.9 (CH_3), 27.1 (CH_2), 26.2 (CH_3), 22.7 (CH_3), 20.7 (CH_3), 19.9 (CH_3)

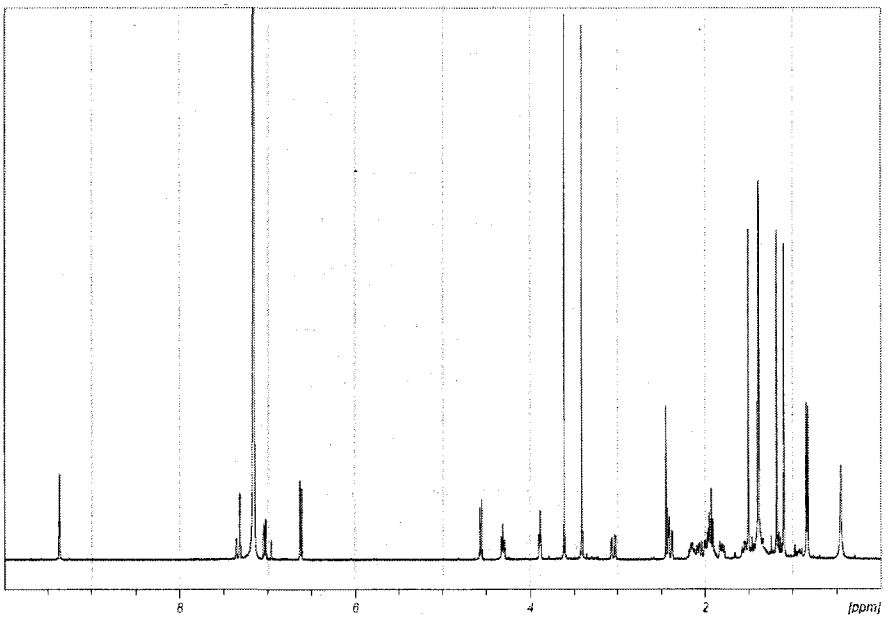
FT-IR (neat, cm^{-1}): 2926 (m), 2918 (m), 2847 (w), 1682 (s)

HRMS (EI): Calculated 490.2931 (M^+) for $C_{28}H_{42}O_7$, found 490.2914

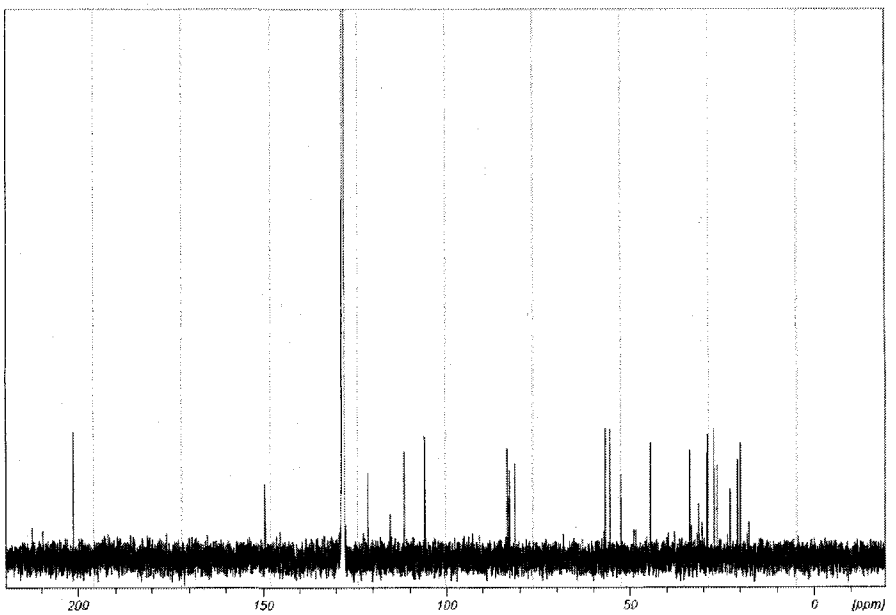


5.60

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



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



Glossary of Abbreviations

Bz	benzoyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EI	electron impact
FT-IR	Fourier transform infrared
HMRS	high resolution mass spectrometry
Im	imidazole
J	coupling constant in Hz
KHMDS	potassium hexamethyldisilylamide
m	multiplet
M	mol/L
M^+	molecular ion
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PMB	para-methoxybenzyl
PTSA	para-toluenesulfonic acid
q	quartet
R_f	retention factor
rsm	returned starting material
r.t.	room temperature

s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	5,10,15,20-tetraphenyl-21H,23H-porphine
UV	ultraviolet

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[11] FI_{50} is the feeding index of an insect antifeedant: The concentration which will stop consumption in 50 % of test cases.

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