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LIST OF ABBREVIATIONS

acac     acetylacetonate  
BBN      borabicyclo[3.3.1]nonane  
BINAP    2,2'-bis(diphenylphosphino)-1,1'-binaphthyl  
BINOL    [1,1']-binaphthalenyl-2,2'-dil  
Bn       benzyl  
Bu       butyl  
DBU      1,8-diazabicyclo[5.4.0]undec-7-ene  
DCC      1,3-dicyclohexylcarbodiimide  
DCM      dichloromethane  
de       diastereomeric excess  
DME      1,2-dimethoxyethane  
DMF      N,N-dimethylformamide  
DIBAL    diisobutylaluminum hydride  
DPS      tertiarybutyldiphenylsilyl  
dr       diastereomeric ratio  
ee       enantiomeric excess  
eq       equivalent  
Et       ethyl  
EtOAc    ethyl acetate  
Et₂O     diethylether  
Et₃N     triethylamine  
HPLC     high pressure liquid chromatography
ABSTRACT

The tandem oxy-Cope/ene reaction allows the rapid construction of complex structures in a few steps. It was notably used in the total synthesis of (+)-arteannium M where the cascade revealed to be highly diastereoselective and enantioselective. The hypothesis that the retention of chirality based on the rigidity of an intermediate atropisomer devoid of stereogenic centers was proposed.

This document presents a study of the enantioselectivity of the tandem oxy-Cope/ene reaction and provides an explanation for the decrease in chirality observed during the cascade. Different variables of the reaction and of the starting material were analyzed to explain the retention of chirality.

The efforts of our group in the development of tandem reactions led to the discovery of a novel cascade that involves 4 pericyclic reactions: the oxa-Cope/Claisen/ene/Claisen cascade. This sequence of reactions was briefly investigated to determine its scope and limitations, notably by changing the substituent on the alkyne and on the tertiary alcohol of 150.
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À mes très chers parents, Claudette et Michel
CHAPTER 1

1.1 Introduction

Discovered at the beginning of the 20th century and studied from 1930 to 1970, the concept of atropisomerism has regained its interest in the last decade due to the finding of novel synthetic targets which exist as atropisomers. Although, the subject of atropisomerism has been studied for 40 years, it is still not well understood. The complexity of this concept and the difficulty in identifying the existence of atropisomers are two factors which contribute to the lack of knowledge of this phenomenon.

The chirality induced by the restricted rotation in a compound can produce enantiomers and diastereomers devoid of stereogenic carbons. One challenge concerning atropisomerism is obtaining chiral atropisomers. In the beginning, a racemic synthesis was performed followed by a resolution to derive one of the chiral entities (which lead to the loss of half of the material). Recent strategies developed in total synthesis allow the formation of atropdiastereomers, due to the presence of a remote chiral center on the molecule, followed by the removal of this stereogenic center to achieve the preparation of a chiral atropisomer.

The study presented herein aims to analyze the formation and the immediate asymmetric induction of a series of chiral 10-membered-ring atropisomers that are generated as intermediates in a tandem oxy-Cope/ene reaction. An explanation for the preservation of the chirality during the cascade reaction is presented based on the rigidity of these atropisomers and the speed of the different processes involved in the tandem reaction.
1.2 Overview of the atropoisomerism

An atropisomer is defined as a stereoisomer resulting from the restricted internal rotation about one or several single bonds where the energy of activation of rotation is high enough to allow the isolation of the rotamers\(^1\). The limitation in rotation of the chiral entity usually comes from steric congestion. Atropoisomerism was first observed in 1922 by Christie and Kenner on biphenyl compounds\(^2\). The 6,6'-dinitro-2,2'-diphenic acid 1 and 2 (figure 1) were resolved from their brucine salts and the demonstration of their optical activities refuted the hypothesis that biaryl systems exist in a planar form (which would be non chiral). In these compound, the chirality comes from the presence of bulky ortho substituents on the aromatic ring that forces the molecule to adopt a twisted conformation and prevents an easy rotation of the single bond linking the two aromatic rings. It was proved that the two entities (1 and 2) could be racemized when heated. Such structures were later called “atropisomers” by Kuhn in 1933\(^3\), from Greek where \(a\) means “not” and \(tropos\) means “turn”.

![Figure 1. First example of atropoisomerism by Christie and Kenner](image)

The racemization observed when an atropisomer is heated is responsible for the difficulty of establishing the minimum energy of activation to rotation for the existence of atropoisomerism in a compound. One way to determine the occurrence of atropoisomerism is the recognition of two related isomers by a spectroscopic method\(^4\). However, such a definition of these rotamers is not very realistic because, depending on the instrument used, the lifetime of an atropisomer could be very short (the lifetime being determined by the frequencies). For example, the use of NMR can establish the lifetime of two exchanging rotamers of about \(10^{-2}\) sec, but the lifetime determined by vibrational
spectroscopy can be as low as $10^{-12}$ sec. In 1983, Oki\textsuperscript{4} defined more reasonably that an atropisomer exists when its isolation is possible and its optical activity half-life is at least 1000 seconds at room temperature. The corresponding energy barrier to rotation is established in function of the temperature and it is notably 22.3 kcal/mol at 300K.

1.3 Atropisomerism of the sp\textsuperscript{2}-sp\textsuperscript{2} Single Bond Type

The restricted rotation about a sp\textsuperscript{2}-sp\textsuperscript{2} single bond is the first example of atropisomerism observed\textsuperscript{2} and is also the most commonly known type. Most cases of atropisomerism related to this category involve biphenyl structures. The restriction of rotation required for the formation of atropisomer is mostly due to the presence of ortho substituents on the aromatic rings. Several trends linked to the size of the substituents were observed on a series of atropisomers\textsuperscript{1}. Most tetra-ortho-substituted biphenyls 3 (figure 2) can be resolved, except if at least two of the substituents are methoxys or fluorines (considered as small substituents). In the case of tri-ortho-substituted biaryls (4), most are optically stable providing that the three ortho-groups are large. In general, the presence of a small substituent among these groups greatly eases the racemization of the isomer. In the case of di-ortho-substituted biphenyls, these atropisomers are resolvable only when the two groups are large, a case most notable with 1,1'-binaphtyl structures (5). Finally, the rotation in mono-ortho-substituted biaryls is usually too fast to allow the isolation of one optically active isomer.

![Figure 2. Tetra, tri and di-ortho-substituted biphenyls](image-url)
The effect of the size of the *ortho*-substituents, which controls the energy barrier to rotation, was established based on the racemization of biphenyl atropisomers and follows the order I > Br >> CH₃ > Cl > NO₂ > COOH >> OCH₃ > F > H. This trend is in accordance with the van der Waals radii of these groups. The presence of substituents in the *meta* position on the biphenyls also contributes to the barrier to rotation. Such substituents help to prevent the loss of chirality by the so-called “buttressing effect”. During the racemization process, the *ortho* substituents bend away from each other (when the two phenyl rings are coplanar) and by the same token, bend toward the groups in the *meta* position. The presence of a substituent at the meta position thus reduces the rate of racemization due to the repulsion between the *ortho* and *meta* groups.

The rings in a biaryl species do not exist in a coplanar arrangement due to the hindrance of the *ortho* substituents. If the two aromatic rings were coplanar, the system would have a maximum resonance but it would suffer severe steric interactions between the *ortho* groups. A maximum energy is thus obtained when the two phenyls are at 0 and 180° to each other. These two maxima can have different values depending on the *ortho*-substituents. The two halves of the curve on figure 3 correspond to the two enantiomers of a biphenyl compound, which explains the symmetry of the curve. Two local maxima are observed at −90° and 90°. These high energy orientations are attributable to the complete absence of resonance in the biaryl system at these angles. However, these maxima can be much lower than presented in the figure (possibly a minimum) if the size of the *ortho* substituents is favorable. The angle between two phenyl rings giving the lowest energy is usually around ±44° and ±136°. These angles are compromises between the steric hindrance (destabilizing) and the resonance (stabilizing) in the system. The height of the minima and maxima and the shape of the energy curve can vary greatly depending on the substituents on the biphenyl system.
Figure 3. *Energy profile for the rotation of biphenyl structures*

Several bridged biphenyl structures have been described in the literature and the analysis of their optical stabilities demonstrated their existence as atropisomers. The resolution of biaryls bearing a two-atom bridge such as $6^6$ (figure 4) was possible, however these species were not very stable and racemized within a few hours. Longer bridged biphenyls $7$ (three-atom) proved to be more enantiomerically stable than their two-atom counterparts. Bridges consisting of four atoms have also been prepared$^7$ and resolved, but most of these compounds racemized very rapidly ($8$). Nevertheless, ortho-bridged structures are generally less optically stable than their corresponding non-bridged biphenyls. This decrease in stability could be attributed to the reduction of the dominant van der Waals interaction of the ortho substituents.

Figure 4. *Bridged biphenyl atropisomers*
The atropisomerism of sp\(^2\)-sp\(^2\) single bonds is not limited to biphenyl structures, it is also applicable to other species in which the rotation about such a bond is restricted. Moreover, the atropisomerism does not only create enantiomers, but generates diastereomers as well. Amides and thioamides are among the structures that may exist as atropodiastereomers. These functionalities are known to be planar or almost planar due to the delocalisation of the pair of electrons of the nitrogen into the carbonyl or thiocarbonyl. The presence of substituents on the amide affects the conformational equilibrium and consequently, introduces diastereoselectivity by favoring one amide conformation over another. This isomerism is particularly important in benzamides. Staab notably showed the atropisomerism of the benzamide 9 (figure 5) in which the activation energy for the equilibrium between the Z and the E form is relatively high (32.0 kcal/mol)\(^8\). The hindrance of the three tert-butyls on the phenyl favors the Z isomer (9) at equilibrium because the steric interaction between the tert-butyl and the methyl groups is less important than in the E isomer (10) (tert-butyl/benzyl interaction). Stable diastereomers were also observed on thiobenzamides. The principle is the same as with the benzamides in which the rotation around the thiocarbonyl-nitrogen bond is restricted due to steric factors. Mannschreck\(^9\) measured that the energy of activation for the rotation of thioamide 11 (Z) to its isomer 12 (E) as being approximately 27 kcal/mol. These two atropisomers were isolated.

![Diagram of benzamides and thiobenzamides](image)

**Figure 5. Atropisomerism in benzamides and thiobenzamides**
1.4 Atropisomerism of the sp²-sp³ Single Bond Type

The atropisomerism observed around sp²-sp³ single bonds is more complex than in the case of the limited rotation of an sp²-sp² bond. This complication comes from the presence of three substituents (sp³) on one of the atoms of the bond (compared to two substituents on an sp² atom). Thus, a greater number of conformations can be adopted by the system, depending on the size of the different substituents. Four of these conformations are illustrated in figure 6. In the case where X is small, the rotamers with X eclipsing A, B or C (13 and analogues) would represent energy minima (double bonds tend to be eclipsed with single bonds). By the same token, the conformers in which Y eclipses A, B or C (14, 16 and analogue) would correspond to energy maxima. In the case when X is large, all the rotamers in which either X or Y eclipse A, B or C (13, 14, 16 and analogues) would represent maxima, whereas the conformers in which both X and Y are in intermediate positions between two substituents would correspond to minima (15 and analogues). In fact, in most examples of the atropisomerism around sp²-sp³ single bond, the sp² atom is part of an aromatic ring. In these cases, X and Y are relatively equal in size and the situation is simplified because the energies of conformers 13 and 16 are similar. Moreover, if A is relatively small compared to B and C, then only the conformers 13 and 16 (minima) and the energy barrier between them (maxima) really have to be considered.

![Figure 6. Conformations of a sp²-sp³ single bond](image)

The first example of sp²-sp³ atropisomerism was observed by Chandross and Sheley in 1968 on the 9-mesitylfluorene compound 17¹⁰ (figure 7). The analysis of the NMR spectra of 17 revealed that the two methyls of the mesityl (2- and 6–position) were
not equivalent below 200°C. The analysis of NMR spectra of 18 showed that this compound is less stable than 17. The distinction between the two ortho-methyls exists until the sample is heated to 150°C. Finally, the 9-chloro mesithylfluorene appeared to be even less stable than the previous two isomers, with the NMR of 19 showing only a broad signal for the same two methyls of the mesityl at room temperature. It was later calculated that the energy of rotation for the mesithylfluorenes 17, 18 and 19 was >25, 20.2 and 16.2 kcal/mol\(^{11}\) respectively (which is in accordance with the experimental results). The decrease of the energy barrier with the enlargement of the 9-substituent was explained by the increase of the ground state energy of 17, 18 and 19. Analysis of conformers 13 and 16 of figure 6 shows a steric interaction between X and Y with A in these minimum energy rotamers. Increasing the size of the A substituent raises the ground state energy of such conformers.

**Figure 7. Mesithylfluorenes prepared by Chandross and Sheley\(^{10}\)**

Several other examples of sp\(^2\)-sp\(^3\) single bond restricted rotation were observed for derivatives of fluorenes. These analogues were prepared to analyze the effect on the atropisomerism of the presence of substituents on the fluorene or on the 9-aryl part of these structures. It was noteworthy that in the case of an aromatic substituent bearing two different ortho-groups, the more stable conformer was the one in which the smaller group was over the plane of the fluorene. Nakamura and Oki determined that rotamer 20 (figure 8) was more stable than 21 and the energy barrier measured for this isomerisation was 27.1 kcal/mol\(^{12}\). It should also be noted that substituents on the fluorene part of these compounds increases the energy barrier to rotation. The increase of the size of one substituent (B or C) makes rotation around the sp\(^2\)-sp\(^3\) single bond more difficult due to steric hindrance. Kajigaeshi showed that the energy barrier for the rotation between 22
and 23 was 21.4 kcal/mol. This group successfully isolated these two species\textsuperscript{13}. It was believed that both solvation and entropy played a role in the stability of one conformer over another\textsuperscript{4}.

![Chemical structures](image)

**Figure 8. Effect of substituents on 9-aryl of fluorene derivatives**

1.5 Atropisomerism of the sp\textsuperscript{3}-sp\textsuperscript{3} Single Bond Type

Examples of atropisomerism around sp\textsuperscript{3}-sp\textsuperscript{3} bonds are not legion. The high steric restriction required for the observation of isomerism around such a bond has been observed on only a few compounds. Yamamoto and Oki are among the pioneers in research on this type of atropisomers and have observed the phenomenon on triptycene derivatives. The rigidity of the quaternary center along with the presence of bulky substituents on systems like 24 (figure 9) allowed the isolation of 24, 25 and 26\textsuperscript{13}. The activation energy for the rotation from 24 to 25 and 26 was 33.2 kcal/mol. Upon the establishment of equilibrium, the form 25 (and 26) was found to be slightly favored over 24 (2:1 ratio) due to the presence of the benzyl group between the two phenyls in the latter rotamer. A resolution was performed on enantiomers 25 and 26. Upon basic hydrolysis of one of the ester moieties, prior to esterification of the resulting acid with (-}


\(\text{\textsuperscript{14}}\) menthol. 24 was optically inactive due to a plane of symmetry in its structure and represents an atropdiastereomer of 25 and 26.

\[
\begin{align*}
\text{Bn} & \quad \text{Me} & \quad \text{COOMe} \\
\text{Me} & \quad \text{Me} & \quad \text{COOMe} \\
\text{Me} & \quad \text{Bn} & \quad \text{COOMe} \\
\end{align*}
\]

\(24\) \(25\) \(26\)

Figure 9. Atropisomerism in \(sp^3\)-\(sp^3\) single bond molecules

A few atropisomers having triptycene structures bearing tertiary and even a secondary substituents at the 9-position were identified\(^4\). However, the isolation of these isomers at room temperature required the presence of bulky substituents on the aromatic rings of the triptycene to prevent rotation of the atropisomer from occurring too rapidly.

1.6 Trans-cycloalkenes

The limited freedom incurred by the presence of an \(E\) olefin on a cyclic structure may introduce atropisomerism to a ring. When the transannular portion of the methylene chain on a trans-cycloalkene is short enough, the structures may exist as enantiomer even though the molecule is devoid of stereogenic centers. Atropisomerism in cycloalkenes was first observed by Cope and co-workers in 1962 when they isolated \(cis\)-\(trans\)-1,5-cyclooctadiene 27\(^{15}\) (figure 10). The chirality observed in this compound was explained by the high rigidity of the structure in addition to the interaction of trans-annular hydrogens which prevents the rotation of the \(E\) olefin. Resolution of the less rigid \(trans\)-cyclooctene 28\(^{16}\) was accomplished by Cope in the same year. Treatment of a racemic mixture of 28 with platinum dichloride and (+)-1-phenyl-2-aminopropane afforded two diastereomeric complexes. Separation of the two species followed by removal of the

21
chiral auxiliary furnished the optically active cycloalkene 28. The absolute configurations of the two cyclooctenes were later established by the preparation of known derivative structures. Larger cycloalkenes were also prepared, but the saturated segment of these rings, being quite long, complicated their isolation. Applying the resolution method presented above to a racemic mixture of trans-cyclononene 29 could not produce the chiral olefin because the racemization was too rapid at room temperature. However, a fast resolution of the nine-member-ring alkene mixture followed by immediate chilling to −80°C allowed the observation of the optical activity of 29 at 0°C. On the other hand, trans-cyclodecene 30 could not be resolved even at low temperature. The high degree of flexibility of this molecule permitted rapid swivelling between enantiomers, thus preventing their isolation. The barrier to rotation of the trans-cyclooctene 28, nonene 29 and decene 30 were measured and reported as 35.6, 20.0 and 10.7 kcal/mol respectively. From these energies, the half-lives of the optical activity at room temperature of the olefins were calculated and correspond to $10^5$ years for the trans-cyclooctene, 10 seconds for the cyclononene and $10^{-4}$ seconds for the cyclodecene. The inability to isolate a stable enantiomer of 30 was thus explained. It was later calculated that the minimum energy conformations of these trans-cycloalkenes (28, 29 and 30) are the crown-like geometries. In the case of the 8-membered-ring, the energy difference between the crown-like and the chair-like conformation was as high as 3.14 kcal/mol.

Figure 10. Trans-cycloalkenes of different sizes

The superior flexibility of the trans-cyclodecene 30 which account for its inability to be resolved was of particular interest. Different analogues of this cyclic olefin were prepared and their optical stabilities were analysed. The addition of a methyl group on each side of the E olefin permitted the resolution of trans-1,2-dimethylocyclodecene 31 (figure 11) in 1980 by Marshall. The presence of the methyl substituents on the double
bond raised the activation energy to racemization by increasing steric interactions when the double bond rotated. This strategy was applied to the preparation of the *trans*-1,2-cycloundecene 32 and was successful in producing a stable optically active isomer. However, the resolution of the larger *trans*-1,2-dimethylcyclodecene was not achieved. It was assumed that this structure racemized below room temperature.

![Figure 11. Trans-1,2-dimethylcyclodecene and undecene](image)

Despite of their high rigidity, the cycloalkenes bearing two *E* olefins proved to be enantiomerically unstable. The rate constant for the conversion of *trans*-1,2-divinylcyclohexane 33 to 35 (figure 12) was measured based on the racemization of this compound\(^{23}\). Cope reaction followed by the inversion of the 10-membered intermediate 34 and the reverse-Cope reaction resulted in the loss of chirality of 33. Wharton evaluated the ring strain of the cyclodecadiene 34 as 12 kcal/mol relative to the divinylcyclohexane 33.

![Figure 12. Racemization of the divinylcyclohexane 33 via a Cope/reverse-Cope process](image)

1.7 Actual use and Challenge of Atropisomerism

Over the years, chemists have developed various methods to use the chirality of atropisomers in order to introduce enantioselectivity into achiral compounds. Most
known examples of these strategies are the use of binaphthyl structures. BINAP 36 (figure 13) is a binaphthyl bearing a phosphine at the 2- and 2'-positions that act as an asymmetric ligand to a metal. When used with a ruthenium (II) salt, 36 forms a chiral complex that performs catalytic asymmetric hydrogenation in excellent yields and enantioselectivities. Moreover, BINAP is commercially available in both enantiomeric forms. Either enantiomer of the final product could be obtained based on the BINAP isomer used. Another well-known biaryl used in organic chemistry is BINOL-H (37). This complex consists of a mixture of a binaphthol and lithium aluminium hydride that enantioselectively reduces ketones by using the axial chirality of the atropisomer.

![Figure 13. BINAP-Ru(II) and BINOL-H](image)

The major concern about atropisomerism in the last 5 years is the synthesis of atropisomeric natural products. The challenge in the preparation of such compounds is the control of the atropisomerism when this chirality is installed and also its maintenance during the synthesis. Vancomycin 38 (figure 14) represents a very complex structure bearing three notable stereochemical elements of atropisomerism. Several research groups around the world have tackled the synthesis of this powerful antibiotic with three syntheses of the aglycon completed thus far (Evans\textsuperscript{24}, Nicolaou\textsuperscript{25} and Boger\textsuperscript{26}).
These syntheses of vancomycin required the elaboration of strategies to control the three elements of atropisomerism of this structure. All these strategies are based on an atropdiastereselectivity generated in the molecules. One of these strategies consists in the installation of a substituent on an aromatic ring to force the formation of an atropdiastereomer over a second one. This approach was notably used by Evans\textsuperscript{24} where he placed a nitro group on the top-left aromatic ring of the vancomycin precursor 38a to force the formation of atropdiastereomer 38b when the 16-membered ring was formed (figure 15). The presence of the bulky nitro group (pointing exo on the product) allowed the formation of 38b with the chlorine atom of the phenyl pointing inside the 16-membered ring, as present in vancomycin. The nitro group was later removed upon its reduction followed by a Sandmeyer reaction.
Figure 15. Control of atropisomerism due to the installation of a substituent on an aromatic ring

Another strategy that is used in synthesis of chiral atropisomers is the thermal equilibration. Upon the formation of an atropisomer, different modifications of this structure may transform the atropisomer in a higher energy conformer compare to a second one. Thermal equilibration allows the atropdiastereomer to adopt a lower energy conformation. This strategy was also used by Evans in his total synthesis of vancomycin (figure 16). 38d was produced with high diastereoselectivity upon the thermal equilibration of 38c to obtain the correct atropisomerism on the bottom-left ring of vancomycin.

Figure 16. Thermal equilibration as atropdiastereomer control strategy
A frequently used strategy in the formation of chiral atropdiastereomer is the used 1,3-allylic strain between a chiral center in α of an aromatic ring and a substituent on the phenyl. The presence of this interaction favors the formation of an atropdiastereomer over another due to a significant difference in activation energy between two transition states when the atropisomer is formed.

1.8 Aim of this project

The study described herein aims to explain the enantioselectivity of a tandem oxy-Cope/ene reaction. An intermediate in this cascade is a 10-member-ring enol devoid of chiral centers bearing three olefins. The optical stability of this atropisomer was analysed based on the chirality of the resultant product of the tandem process. The decrease in enantioselectivity observed on certain products will be discussed according to the rigidity of the intermediate atropisomer, the nature of the substrates used, but also due to the rate of the different processes involved in the cascade reaction.
CHAPTER 2

2.1 Introduction

In 2001, the first total synthesis of (+)-arteannium M (42 in scheme 1) was accomplished in the laboratory of Dr Barriault. Starting from S-isopiperitenone 39, a chiral ketone readily available from (+)-limonene, the synthesis of the natural product was achieved in only 10 steps and 14% overall yield. The key step of the synthesis was a tandem oxy-Cope/ene reaction that was realized by heating the 1,2-divinylcyclohexenol 40 at 220°C in a sealed tube in the presence of DBU to afford a 55-60% yield of bicyclic compound 41. The tandem reaction proved to be highly diastereoselective (de >98%) and enantioselective (ee = 78%) affording compound 41 with inversion of configuration at the C₁ and C₂ centers. Further transformations led to (+)-arteannium M.

![Scheme 1. Total synthesis of (+)-Arteannium M](image)

The relative and absolute stereochemistry of 41 (1S, 2R) was established by a single crystal structure of derivative 44r (figure 17). The enantioselectivity was determined by 500MHz $^1$H NMR analysis of the Mosher ester 45 (diastereomeric excess of 78%).
Scheme 2. Determination of the enantioselectivity of 41

Figure 17. Single crystal structure of 44r

The high diastereoselectivity of the tandem process was rationalized based on the proposed mechanism and transition states shown in figure 18. Firstly, the oxy-Cope reaction takes place on the 1,2-divinylcyclohexenol 40 to give the 10-membered-ring enol 46 devoid of chiral center. A rapid diastereoselective tautomerization then occurs to furnish the enone 47 via a stereofacial protonation. During this process, the proton has to approach perpendicular to the π system of the double bond and only one face of the olefin is thus accessible (the β-face), since the other face is blocked by the ring. The quite
flexible enone 47 could adopt different conformations, so the two possible transition states A and B can lead to the formation of diastereomers 41 and 48 respectively via a transannular ene reaction. A close examination of the 2 transition states reveals that in A, the alkyl chain is in a pseudoaxial position, whereas in B, the alkyl chain is oriented pseudoequatorial, thus favoring the production of 41 over 48. This results in an inversion of configuration at the C₁ and C₂ chiral centers on compound 41.

![Diagram](image)

**Figure 18. Diastereoselectivity of the tandem oxy-Cope/ene reaction**

The enantioselectivity of the tandem oxy-Cope/ene reaction was explained by the highly rigid atropisomer 46. The 10-membered-ring enol 46 contains two E and one Z olefins (relative to the carbon framework) which make this ring very strained. In order to invert from 46 to ent-46 (figure 19), the enol moiety has to rotate inside the ring, which is highly energetically demanding. At the same time, the competitive stereofacial protonation on the β-face of the olefin can occur. As a lower energy process, tautomerization occurs in preference to inversion of the ring. It was believed that the energy of inversion of the ring 46 is so high that this process does not occur, even at 220°C.
2.2 Our Approach

We decided to investigate the tandem oxy-Cope/ene reaction in order to explain the enantioselectivity of this process in greater details. One of the objectives of this project was to prepare a series of 1,2-divinylcyclohexenols of type 49 (figure 20) and to perform the tandem reaction to observe the effect of different variables (i.e. base used, substituents on the divinylcyclohexenols) on the enantioselectivity of the cascade products 50. Moreover, a microwave oven was used for the study instead of conventional heating because the former accelerates the oxy-Cope/ene reaction (1 hour for completion using microwaves compared to 24 hours for conventional heating) without any significant effect on the yield, diastereoselectivity or enantioselectivity.

Figure 20. Approach for the study of the enantioselectivity of the tandem oxy-Cope/ene reaction
2.3 Results and Discussion

2.3.1 Initial Results

Two 1,2-divinylcyclohexenols were used as models for the study of the enantioselectivity of the tandem oxy-Cope/ene reaction. The first model alcohol 51 (scheme 3) bears a methyl group on the vinyl moiety in α of the hydroxyl, whereas the other compound bears a phenyl at the same position (52). These compounds were obtained by a halogen-metal exchange of 2-bromopropene and α-bromostyrene respectively using tert-butyllithium, followed by the addition of S-isopiperitone (>98% ee) 39 29. A first test of the tandem reaction was attempted on these model molecules (51 and 52). When compound 51 was heated to 220°C in toluene for an hour using a microwave oven, bicyclic 53 was observed in 60% yield along with 55 in a diastereomeric ratio of 15:1 (isolated). Heating 52 in the same conditions afforded 54 as the sole diastereomer in 93% yield.

![Scheme 3. Preparation of the model 1,2-divinylcyclohexenols and the tandem oxy-Cope/Ene reaction](image)

The method for determination of the enantiomeric excess of the oxy-Cope/ene products was established on compound 53. The first attempt to determine the ee was by the preparation of Mosher ester derivatives (scheme 4). Esterification of 53 with (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) using different coupling agents failed to give 56. The preparation of the less crowded Mosher's ester 59 was then attempted. After the directed epoxidation of 53 using vanadyl acylacetonate 30, the
epoxide 57 was opened using DIBAL\(^{31}\) to give secondary alcohol 58. Unfortunately, the esterification of 58 to the Mosher’s ester 59 also failed, so this approach for determination of the enantioselectivity was forsaken.

**Scheme 4. Attempts to prepare the Mosher’s ester derivatives of 53**

The use of a chiral HPLC column salvaged the legitimacy of the determination of the enantiomeric excess. After multiple tries to identify which chiral column separated the two enantiomers of 53 and 54\(^{32}\), the ChiralPak AS (4.6 X 250 mm) chiral column equipped on our Waters HPLC 2690 proved to be best for this task. For all the results that follow, a racemic mixture of these compounds was prepared and separated using the chiral column prior to the injection of the oxy-Cope/ene product obtained from an enantio pure starting material.

### 2.3.2 Effect of DBU and Various Other Bases on the Tandem Oxy-Cope/Ene Reaction

The first facet of the tandem oxy-Cope/ene reaction that was studied was the effect of different bases. It had previously been observed that the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) favored the formation of the oxy-Cope/ene product 61 over the formation of the retroene product 62 (scheme 5). In some cases, the
presence of DBU was essential to obtain the oxy-Cope/ene product, otherwise a complex mixture of products was generated\(^{29}\).

<table>
<thead>
<tr>
<th>Base</th>
<th>oxy-Cope/ene (61)</th>
<th>Retroene (62)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3.5</td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>DBU (20eq)</td>
<td>20</td>
<td>1</td>
<td>75</td>
</tr>
</tbody>
</table>

**Scheme 5. Utility of DBU on the tandem oxy-Cope/ene reaction**

The oxy-Cope/ene process was performed using microwaves to heat to 220°C two model 1,2-divinylcyclohexenols in the presence of various bases in order to analyse the effect of the strength of these bases on the retention of chirality in the cascade reaction. All other factors in the reaction were held constant (i.e. concentration of substrate, time and temperature of the reaction, number of equivalents of base used). As shown in table 1, the yields obtained for the tandem reaction of 51 while using different bases were always moderate (28 to 60%) and the diastereomeric ratio, as previously mentioned, was 15:1 favoring 53 over 55. When a “proton sponge” was used as the base, the reaction led to the decomposition of the starting material (entry 6). The tandem reaction performed on 52 gave better yields (36 to 98%) and all reactions furnished 54 as the sole diastereomer. In the formation of both 53 and 54, the use of DBU as the base gave the best yields. The diastereoselectivity observed with 54 may be explained by the proposed mechanism in figure 18 (page 30). A comparison between divinylcyclohexenols 51 and 52 reveals the presence of a larger substituent on 52, which increases the difference of energy between the two possible transition states (A and B). Consequently, the diastereoselectivity of the tandem reaction was improved for 52. It should be noted that in the case of compound 41 (R=CH\(_2\)CH\(_2\)ODPS), only one diastereomer was observed (scheme 1, page 28).
Concerning the enantioselectivity of the tandem reaction, small differences in the transfer of chirality was observed on compound 53 depending on the base used. When the oxy-Cope/ene reaction was performed on 52, complete preservation of chirality was noticed in all cases. Only the presence of DBU induced a significant drop in enantioselectivity on the cascade reaction and this effect was particularly important for the bicyclic compound 54 (entry 2). The good yields and complete retention of chirality of the oxy-Cope/ene reaction performed with tetramethylethylenediamine (TMEDA) as a base justified its use later in the study (in comparison with DBU).

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base used</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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</thead>
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<td>R = Ph</td>
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<tr>
<td>2</td>
<td>DBU</td>
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<td>&gt; 98</td>
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</table>

**Table 1. Results for the tandem oxy-Cope/ene reaction with various bases**

Because of the significant decrease in chirality observed when DBU was used as a base on the oxy-Cope/ene reaction, its effect was further investigated. The tandem reaction was performed while changing the amount of DBU in the reaction (table 2). When the reaction was performed in the absence of the base, almost no loss of chirality was observed for both 53 and 54. Increasing the number of equivalents of DBU in the reaction with 1,2-divinylcyclohexenol 51 did not have a notable effect on the
enantioselectivity of the tandem reaction. Only a large excess of DBU (10 equivalents) affected the retention of chirality of product 53 (92.6% ee). On the other hand, addition of DBU to the reaction of the 1,2-divinylcyclohexenol 52 had an important impact on the enantioselectivity of the reaction, even in small quantities. The chirality of 54 was significantly decreased with as little as 0.5 equivalent of DBU (ee 83%). The addition of a greater amounts of DBU in the reaction reduced even more the chirality of the product. This observation suggested that there was an inverse relationship between the amount of DBU and the enantioselectivity. DBU is a relatively strong diamine base, so it is believed that the strength of the base played an important role in the decrease of chirality observed during the cascade reaction. In fact, according to the results presented in table 2, it appeared that the acidity of the proton in $\alpha$ of the ketone in compound 64 (figure 21) was related to the decrease in chirality of the tandem reaction. If $R$ is a phenyl ring, this proton becomes more acidic than when $R$ is a methyl, which might explain the greater reduction of chirality observed with this substrate.

<table>
<thead>
<tr>
<th>Entry</th>
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<tr>
<td></td>
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<tr>
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</tr>
<tr>
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</tr>
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</tr>
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<td>6</td>
<td>-</td>
<td>89</td>
<td>-</td>
<td>42.5</td>
</tr>
</tbody>
</table>

Table 2. Results of the tandem oxy-Cope/ene reactions with different amounts of DBU
Figure 21. Transition states of the tandem oxy-Cope/ene reaction

An important factor that contributes to the enantioselectivity of the oxy-Cope/ene reaction is the kinetic control of the overall process. It has been proven that the last step, the transannular ene reaction, is irreversible. The deuteration of the hydroxyl of 53 to furnish 66 (scheme 6) followed by exposure to the tandem reaction conditions showed absolutely no insertion of the deuterium into the exo cyclic double bond of 66 (after a reaction time of 1 hour in the microwave oven at 220°C). This experiment proved the irreversibility of the transannular ene reaction.

Scheme 6. Proof of the irreversibility of the transannular ene reaction

It is to be noted that the tandem oxy-Cope/ene reaction has also been realized in the presence of 2,6-di-tert-butyl-4-methylphenol (BHT), a radical scavenger, and the outcome of the reaction (yield, diastereo- and enantioselectivity) was approximately the
same as when the cascade was performed without this chemical. This observation tends to prove the concerted mechanism over a diradical mechanism for the reaction.

2.3.3 Anionic Oxy-Cope

The decrease in chirality of compound 54 in the presence of DBU was observed when the reaction was performed using microwave heat at 220°C. High temperature was essential for the occurrence of the tandem reaction, since the oxy-Cope is an energy demanding reaction and is the rate-determining step of this process. In order to study the effect of the temperature on the enantioselectivity of the oxy-Cope reaction, a lower temperature reaction was attempted. To accomplish this task, the oxy-Cope was performed as an anionic oxy-Cope. In 1975, Evans et al discovered that the oxy-Cope reaction can be catalyzed by the presence of a base\textsuperscript{33-34}. A clear acceleration by a factor of $10^{10}$ to $10^{17}$ and the use of milder conditions were observed when the hydroxyl of a divinyl system was converted to its alkoxide derivative. When attempted in our laboratory, the anionic oxy-Cope on the 1,2-divinylcyclohexenols 51 and 52 showed to be a complicated task. About a dozen different conditions were attempted before finding one which allowed the base catalyzed sigmatropic rearrangement to proceed. Some of these conditions are summarized in table 3. Interestingly, the conditions of entry 1 did not permit the reaction to occur, even if it was applicable to a very similar substrate (scheme 7)\textsuperscript{35}.
Table 3. Conditions for the anionic oxy-Cope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Eq of base</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KH / 18-Cr-6</td>
<td>5 / 5</td>
<td>THF, rt then reflux (24hrs+8hrs)</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>PdCl$_2$(PhCN)$_2$</td>
<td>0.2</td>
<td>THF, rt then reflux</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK / 18-Cr-6</td>
<td>5 / 5</td>
<td>DME, rt then reflux (2hrs+1hr)</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>$n$-BuLi / TMEDA</td>
<td>1.2 / 6</td>
<td>DME, rt then reflux (3hrs+5hrs)</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>KHMDS</td>
<td>5</td>
<td>DME, reflux 1.5hr</td>
<td>26.7 %</td>
</tr>
<tr>
<td>6</td>
<td>KHMDS</td>
<td>5</td>
<td>DME, reflux 1.25hr</td>
<td>40-75 %</td>
</tr>
</tbody>
</table>

Scheme 7. W. C. Still’s anionic oxy-Cope

The use of dimethoxyethane as the solvent was critical to the success of the reaction. In addition, KHMDS seemed to be the base of choice for the anionic oxy-Cope. This observation follows a common reactivity trend of the anionic oxy-Cope in which the rate of the reaction depends on the degree of cation coordination to the oxy anion. The time required for the reaction is also very important. Close monitoring of the reaction was essential because after a certain period of time, the product of the anionic oxy-Cope rapidly decomposes if the reaction was not quenched (entries 5-6, table 3). The use of the optimized conditions for the anionic oxy-Cope (entry 6: KHMDS, DME, 85°C, 1.25 hrs) resulted in the formation of compounds 67 and 70 in good yields (scheme 8).
Surprisingly, chiral HPLC analysis of these two enones showed racemic mixtures of 67 and 70, which is opposite to a common chemical trend in which, low temperatures improve the enantioselectivity of an asymmetric processes. To prove the loss of optical purity of 67 and 70 (avoid the possibility of two conformers on the HPLC spectra), these enones were heated using microwaves to perform the transannular ene reaction and the racemization of 53 and 54 was confirmed. Attempts to increase the enantioselectivity of the anionic oxy-Cope were done, notably by quenching the reaction at low temperature (-78°C) with a solution of acetic acid in THF and also by using a hindered source of proton (tert-butyl bromide). The latter experiment indicated that the loss of chirality was not caused by the approach of the proton to the olefin, but that the racemization must occur before the quench. In fact, the use of a hindered source of protons forces the protonation to occur only on the outside face of the olefin during the quench. This observation led to the hypothesis that the enolate form of 63 (figure 21, page 37) may have a low energy barrier of inversion.

![Scheme 8. Racemization observed on the anionic oxy-Cope](image)
2.3.4 Trapping the Enol Ether

In order to investigate the energy of inversion of enol 63 and its enolate form, the synthesis of enol ethers 72 and 74 was attempted (scheme 9). To demonstrate the chirality of these two atropisomers would prove with strong evidence, the high-energy barrier of inversion of these macrocycles. The hydroxyl on the model 1,2-divinylcyclohexenol 51 was first protected with a methyl by treating this compound with KH and 18-crown-6 followed by addition of dimethylsulfate to furnish 71. This ether was then heated in a microwave oven at 220°C for 5 hours in the presence of DBU, but the oxa-Cope reaction was not observed. Silyl enol ether 73, prepared from alcohol 52, also did not seem to undergo the sigmatropic rearrangement.

Scheme 9. Attempts to isolate the enol ethers 72 and 74

In fact, a recent experiment on compound 71 proved that the oxa-Cope reaction occurs but the 10-member ring 72 could not be isolated by the oxa-Cope reaction. 71 was prepared as its chiral entity ($[\alpha]_D^{20} +93.1^\circ$) and after its exposure to microwaves (220°C), compound 71 was recovered with a significant loss of chirality ($[\alpha]_D^{20} +13.0^\circ$). The only way to explain this decrease in chirality is that the oxa-Cope reaction takes place to produce 72. Once obtained, the 10-member ring may either perform the retro-oxa-Cope or invert to its enantiomer ent-72. Finally the retro-oxa-Cope on ent-72 occurs
to produce ent-71 and thus explains the decrease in chirality. The impossibility to isolate 72 is probably due to its greater ground-state energy. In thermodynamic condition, the oxa-Cope / retro-oxa-Cope equilibrium generates the most stable product, in this case 71.

![Equilibrium Diagram]

Figure 22. Oxa-Cope / retro-Oxa-Cope equilibrium

2.3.5 Substituents on the Vinyl of the 1,2-Divinylcyclohexenols

2.3.5.1 Absence of Substituent on the Vinyl

It had been observed that a change of substituent on the vinyl in α of the hydroxyl of compound 49 affected the enantioselectivity of the tandem oxy-Cope/ene reaction (table 2, page 36). To pursue the study of the retention of chirality of the cascade reaction, a series of 1,2-divinylcyclohexenols were prepared and subjected to the oxy-Cope/ene conditions to observe the effect of changing this substituent. The first scenario that was investigated is the absence of such a substituent at this position. Compound 68 was obtained by alkylation of ketone 39 with vinylmagnesium bromide and was immediately heated using microwaves to give 77 as a racemic mixture (scheme 10). When 68 was heated, a [3,3]-sigmatropic rearrangement first occurred to generate 75. The enol rapidly tautomerized to 76 via a stereofacial protonation on the β-face of the olefin. There are two possible transition states (A and ent-A) for the transannular ene reaction. However, in the case of the 1,2-divinylcyclohexenol (68) bearing no substituent on the vinyl in α of the hydroxyl, the two transition states are of equal energy due to their enantiomeric relationship and both pathway are followed. An equivalent mixture of 77 and 78 (mirror images) is obtained and thus, the chiral HPLC identified 77 as a racemic
compound. This experiment confirms the flexibility of the macrocycle 76 and the presence of the two possible transition states (A and ent-A). Moreover, this result indicates that a substituent on the vinyl in α of the hydroxyl on compound 49 is required for the retention of chirality during the oxy-Cope/ene cascade.

Scheme 10. Absence of a substituent on the vinyl in α of the hydroxyl of the 1,2-divinylcyclohexenol for the enantioselectivity of the oxy-Cope reaction

2.3.5.2 Preparation of Iodo Olefins

The installation of various substituents on the vinyl in α of the hydroxyl on compound 49 was accomplished by the addition of a series of lithio-olefins to S-isopiperitenone 39 to produce the desired 1,2-divinylcyclohexenols. The lithiated olefins were generated by halogen-metal exchange between tert-butyllithium and various bromo and iodo alkenes. Some of these iodo olefins were not commercially available, so they were prepared in our laboratory. The synthesis of the iodo alkenes began by mixing the aldehydes (79, 80 and 81) with carbon tetrabromide and triphenylphosphine to afford their corresponding dibromo olefins 82, 83 and 84 (scheme 11). The olefins when treated
with an excess of \( n \)-butyllithium underwent the Corey-Fuchs reaction\(^{37} \) to furnish alkynes 85, 86 and 87. Finally, installation of the iodo atom on the alkynes was performed using B-I-9-BBN followed by an acid quench to produce the iodo olefins 88, 89 and 90. The preparations of 89 and 90 were particularly difficult due to their high sensitivity to light.

Scheme 11. Preparation of the iodo olefins

2.3.5.3 Preparation of the 1,2-Divinylcyclohexenols

The 1,2-divinylcyclohexenols were obtained in good yields by the treatment of the bromo and iodo olefins with \( \text{tert} \)-butyllithium followed by the addition of the \( \text{S} \)-isopiperitenone 39 (scheme 12). In the case of compound 92, its preparation involved the treatment of enone 39 with a solution of lithiated 30M ethyl vinyl ether\(^{38} \).
Scheme 12. Preparation of the 1,2-divinylcyclohexenols

2.3.5.4 Tandem Oxy-Cope/Ene Reaction on Various 1,2-Divinylcyclohexenols

The oxy-Cope/ene cascade was applied to the 1,2-divinylcyclohexenols presented in scheme 12. The reaction was performed using DBU and TMEDA, but also in the absence of base in order to study the effect of a base on the enantioselectivity of the tandem reaction. A comparison of entries 1, 2 and 3 with entries 4, 5 and 6 respectively (table 4) confirmed the hypothesis that the acidity of the proton in $\alpha$ of the ketone on the compound 64 (figure 21, page 37) plays a role in the decrease in chirality of the tandem process. In fact, when the methyl of 51 is replaced by a trifluoromethyl (91), the decrease in enantioselectivity observed in compound 95 when DBU was used as a base was much more drastic (ee=69.5%) than in compound 53 (ee=92.6%). Trifluoromethyl, a strong electron-withdrawing group by inductive effect, can efficiently stabilize the negative charge formed when the proton in the $\alpha$ position is abstracted. Furthermore, the decrease in chirality in entries 4, 5 and 6 directly follows the strength of the base used for the reaction. The use of 10 equivalents of DBU in the reaction with compound 91 resulted in an ee of 70%, whereas an ee of 83% was measured when TMEDA was employed (TMEDA being a weaker base than DBU$^{39}$) and a complete retention of chirality was observed in the absence of base. This trend relating the strength of the base and the enantioselectivity of the oxy-Cope/ene cascade was confirmed with compounds 41, 54,
96 and 97 (tables 4, 5 and 6), where in all cases, the decrease in chirality was more important with DBU rather than with TMEDA as a base. All these results bring strong evidences that show the direct relationship between the acidity of the proton in \( \alpha \) of the ketone on the compound 64 (figure 21, page 37) and the decrease in enantioselectivity observed in the tandem oxy-Cope/ene reaction.

Entry 7 represents the tandem reaction segment of the total synthesis of (+)-arteannium M 42. The yield and enantioselectivity observed when the tandem reaction was performed using a microwave oven (66% yield and 82% ee) were quite similar to those obtained during the total synthesis where the cascade was realized using conventional heating (60% yield and 78% ee). However, performing the tandem reaction on substrate 40 with TMEDA instead of DBU (entry 8) showed that the synthesis of (+)-arteannium M could have been achieved in an enantiospecific manner (>98% ee).

![Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrat</th>
<th>Major Product</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51 R=CH₃</td>
<td>53 R=CH₃</td>
<td>DBU</td>
<td>60</td>
<td>92.6</td>
<td>15:1</td>
</tr>
<tr>
<td>2</td>
<td>51 R=CH₃</td>
<td>53 R=CH₃</td>
<td>TMEDA</td>
<td>48</td>
<td>&gt;98</td>
<td>15:1</td>
</tr>
<tr>
<td>3</td>
<td>51 R=CH₃</td>
<td>53 R=CH₃</td>
<td>No base</td>
<td>37-49</td>
<td>97.1</td>
<td>15:1</td>
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<tr>
<td>4</td>
<td>91 R=CF₃</td>
<td>95 R=CF₃</td>
<td>DBU</td>
<td>17</td>
<td>69.5</td>
<td>8.5:1</td>
</tr>
<tr>
<td>5</td>
<td>91 R=CF₃</td>
<td>95 R=CF₃</td>
<td>TMEDA</td>
<td>72</td>
<td>82.9</td>
<td>8.5:1</td>
</tr>
<tr>
<td>6</td>
<td>91 R=CF₃</td>
<td>95 R=CF₃</td>
<td>No base</td>
<td>76</td>
<td>&gt;98</td>
<td>8.5:1</td>
</tr>
<tr>
<td>7</td>
<td>40 R=CH₂CH₂ODPS</td>
<td>41 R=CH₂CH₂ODPS</td>
<td>DBU</td>
<td>66</td>
<td>82.2</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>8</td>
<td>40 R=CH₂CH₂ODPS</td>
<td>41 R=CH₂CH₂ODPS</td>
<td>TMEDA</td>
<td>37</td>
<td>&gt;98</td>
<td>&gt;25:1</td>
</tr>
</tbody>
</table>

Table 4. Tandem oxy-Cope/ene reactions on 1,2-divinylcyclohexenols bearing different substituents on the vinyl in \( \alpha \) of the hydroxyl
Experiments presented in entries 1 to 6 of table 5 were performed to study the effect of different aromatic ring substituents on the vinyl moiety. Entry 6 was attempted in order to determine the effect of having an electron rich phenyl substituent (para-methoxy phenyl) compared to entries 1 to 3. Unfortunately, the enantioselectivity of compound 98 could not be determined using our chiral column, as it was impossible to separate the two enantiomers of 98 with the ChiralPak AS column (only one peak was observed for a racemic mixture of 98). A higher enantioselectivity would have been expected for 98 compared to 54 due to the presence of the methoxy substituent that increases the electron density on the aromatic ring and and therefore, becomes less efficient for the stabilization of a negative charge. This expected increase in chirality would be due to the decrease in acidity of the proton in α of the ketone on the compound 64 (figure 21, page 37). The preparation of a 1,2-divinylcyclohexenol bearing a para-trifluoromethyl phenyl substituent was attempted, but its iodostyrene precursor was too sensitive to permit the synthesis. Entries 4 and 5 show an example of the oxy-Cope/ene cascade performed on a divinylcyclohexenol bearing a larger aromatic substituent. The bulkiness of the naphtyl group seems to allow a better retention of chirality. The presence of a larger group on the intermediate enol atropisomer could explain the better enantioselectivity by raising the activation energy of inversion of the ring.
Table 5. Tandem oxy-Cope/ene reactions on 1,2-divinylcyclohexenols bearing different aromatic substituents on the vinyl in α of the hydroxyl

The oxy-Cope/ene cascade applied to 92 gave a very interesting result. A bicyclic compound with an axial ethoxy substituent was produced as the major diastereomer with a diastereomeric ratio of 2.3:1 favoring 57 over 60 (entries 1, 2 and 3, table 6). After the [3,3]-sigmatropic rearrangement of 92 and the tautomerization to ketone 100 (figure 23) via a stereofacial approach of the proton on 99, it is believed that the ethoxy substituent activates the ketone in the α position and consequently, reduces the energy of activation of the ene reaction. The transannular ene reaction, being a lower energy process than the equilibrium between the conformers A and B, favors the formation of 96 over 101. Ene reactions are known to occur more rapidly when the carbonyl involved in the reaction is more electrophilic. The oxy-Cope/ene reaction performed on compound 91 (where R=CF₃, table 4) corroborates this hypothesis by producing a lower diastereoselectivity (8.5:1) of 95 (with an equatorial trifluoromethyl) compared to the tandem reaction realized on 51, which gave a diastereomeric ratio of 15:1 for 53 versus 55 (scheme 3, page 32). It is to be noted that the oxy-Cope/ene reaction does not proceed efficiently on 92 due to the sensibility of the enol ether and the presence of the ethoxy substituent. The decrease in reactivity due to the presence of an ether substituent on a 1,5-diene has previously been observed by our group and by Paquette. The formation of 96 as the
major diastereomer (axial substituent) observed when 92 was heated suggests that the ene reaction occurs more rapidly. This last information in addition to the low enantioselectivity observed suggest that the ene reaction is not responsible for the decrease in chirality of the oxy-Cope/ene cascade.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>26</td>
<td>74.3</td>
<td>2.3:1</td>
</tr>
<tr>
<td>2</td>
<td>TMEDA</td>
<td>15</td>
<td>81.8</td>
<td>2.3:1</td>
</tr>
<tr>
<td>3</td>
<td>No base</td>
<td>11</td>
<td>90.8</td>
<td>2.3:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Major diastereomer is 96

Table 6. Tandem oxy-Cope/ene reactions on the 1,2-divinylcyclohexenols bearing an ethoxy substituent on the vinyl in α of the hydroxyl

![Chemical Structures](image)

Figure 23. Transition states of the tandem oxy-Cope/ene reaction on 92
The relative stereochemistry of 96 and 101 were demonstrated by NMR analyses (figure 24). The first evidence of the orientation of the ethoxy substituent is the J coupling between H₄ and H₅ observed in ¹H NMR. For 96, the multiplicity of the peak for H₄ was a doublet of doublets (coupling with H₃c and H₃d), which appears as a triplet, with two small J values (2.5 Hz). For 101, the doublet of doublet of H₅ showed a small (4.6 Hz) and a large (11.3 Hz) coupling constant, which is typical of an axial proton due to the dihedral angle with an equatorial (H₃j) and an axial proton (H₃i) respectively (Karplus correlation⁴³). A number of different NOE studies of 96 proved the equatorial position of H₄. NOE effects were observed with H₅b, H₃c, H₃d, H₃e and H₃f when H₄ was irradiated. However, no NOE effect between H₄ and H₅e was noticeable, which would be expected if H₄ was in an axial position.
2.3.6 Importance of the $E$ Olefin

A close examination of atropisomer 63 (figure 21, page 37) shows that the rigidity of this 10-membered-ring is due to the presence of two $E$ and one $Z$ olefins (relative to the carbon framework). The two $E$ double bonds are required for the oxy-Cope reaction,
but the Z olefin is not involved anywhere in the tandem process. Its contribution to the retention of chirality during the cascade reaction has been studied. The presence of a Z olefin introduces rigidity to a medium-size ring, but certainly not as much as an E double bond, so its importance to the maintenance of the chirality is questionable. The removal of the Z olefin and the determination of the enantioselectivity of the tandem oxy-Cope/ene product would verify the utility of this double bond.

The removal of the Z olefin had to be performed without creating a new chiral center on the 1,2-divinylcyclohexenol (to avoid affecting the preservation of the chirality during the oxy-Cope/ene reaction due to the presence of a chiral center on the atropisomer). A direct reduction of the Z olefin was not considered because it would generate this undesired stereogenic center. To reduce this double bond without creating a chiral center, a 1,4-addition of a methylcuprate on enone 39 was performed to give the gem dimethyl ketone 102 (scheme 13). Compounds 103, 104 and 105 were then prepared in excellent yields by a halogen-metal exchange using tert-butyl lithium with the corresponding bromo and iodo olefins followed by addition of 102 (procedure mentioned above).

**Scheme 13. Preparation of the 5,5-dimethyl-1,2-divinylcyclohexanols**

Heating the 5,5-dimethyl-1,2-divinylcyclohexanols in the microwave oven produced the bicyclic compounds 106, 107 and 108 (table 7). Unfortunately, 106 was not separable using the ChiralPak AS column, but its optical rotation (-17.5°) indicated the presence of chirality. The determination of the enantioselectivity of 107 and 108 was accomplished using the chiral HPLC column. The yields obtained for the tandem oxy-
Cope/ene reaction on 104 (entries 2 and 3) were particularly high and in both cases, the enantioselectivity was excellent, even in presence of DBU as a base. It is believed that the absence of the Z olefin may lower the ground state energy of the starting material and the different intermediates of the tandem reaction (enol and ketone) thus preventing racemization by enlarging the required energy of activation to invert the 10-member ring enol. The retentions of chirality observed on 108 were similar to those of 107, but the yields of the reaction were lower when the reactions were performed in presence of TMEDA or absence of base. Nevertheless, all these results proved that the Z olefin present in the previous examples (table 1, 2 and 4) is not required to maintain the chirality during the oxy-Cope/ene process. The rigidity brought by the two E olefins to the atropisomer 63 (figure 21, page 37) is sufficient to avoid the inversion of this 10-membered-ring enol and allows an efficient preservation of the chirality along the cascade reaction.

![Image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrat</th>
<th>Producta</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>106 R=Me</td>
<td>DBU</td>
<td>56</td>
<td>Do not separate (HPLC)</td>
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<tr>
<td>2</td>
<td>104 R=Ph</td>
<td>107 R=Ph</td>
<td>DBU</td>
<td>93</td>
<td>95.2</td>
</tr>
<tr>
<td>3</td>
<td>104 R=Ph</td>
<td>107 R=Ph</td>
<td>TMEDA</td>
<td>100</td>
<td>98.2</td>
</tr>
<tr>
<td>4</td>
<td>105 R=CH₂CH₂OBPS</td>
<td>108b R=CH₂CH₂OH</td>
<td>DBU</td>
<td>92</td>
<td>95.6</td>
</tr>
<tr>
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<td>105 R=CH₂CH₂OBPS</td>
<td>108b R=CH₂CH₂OH</td>
<td>TMEDA</td>
<td>58</td>
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<tr>
<td>6</td>
<td>105 R=CH₂CH₂OBPS</td>
<td>108b R=CH₂CH₂OH</td>
<td>No base</td>
<td>40</td>
<td>97.7</td>
</tr>
</tbody>
</table>

*a all products were obtained with a dr >98%  
b 108 was obtained after a treatment with TBAF

Table 7. Tandem oxy-Cope/ene reaction on different 5,5-dimethyl-1,2-divinylcyclohexanols
2.3.7 Tandem Oxa-Cope/Claisen/Ene and the Explanation for the Decrease in Chirality

The aforementioned tandem oxy-Cope/ene reaction gives access to the 1S, 2R enantiomer of compound of type 50 (figure 20, page 31) when R-(+)-limonene is used in the first step of the synthesis. Of course, starting with S-(-)-limonene would produce the 1R, 2S enantiomer of 50 because of the intramolecular transfer of chirality. However, another approach to this enantiomer was proposed. The preparation of compound 111 would allow the introduction of a third reaction in the tandem oxy-Cope/ene process; the Claisen rearrangement (scheme 14). The presence of the allyl moiety on the oxygen of 111 should permit a Claisen rearrangement instead of the tautomerization process. The sigmatropic rearrangement should occur in a stereofacial manner due to the conformation of the macrocycle and lead to the formation of the enantiomer 112 (1R, 2S configuration).

This approach began with the preparation of 111 from the S-isopiperitenone 39 (scheme 14). Alkylation of the ketone with ethynylmagnesium chloride furnished a 5 to 1 mixture favoring diastereomer 109. Subsequent alkylation of the hydroxyl group using sodium hydride and allyl bromide in a 3 to 1 mixture of THF and DMF gave 110 in 51% yield (over 2 steps). The terminal alkyne was used instead of the vinyl because it was observed that compound 109, bearing a vinyl in place of the alkyne, is highly sensitive and decomposes spontaneously. Moreover, the alkylation of such a compound is impossible due to the hindrance around the hydroxyl. The reduction of alkyne 110 to the 1,2-divinylcyclohexenol 111 was achieved in the presence of Lindlar’s catalyst, hydrogen and quinoline in benzene. The crude product of this reduction was then heated in the microwave oven at 200°C for one hour in the presence of DBU to afford 112.
Scheme 14. Tandem oxa-Cope/Claisen/ene reaction

A proposed mechanism of this tandem reaction involving 3 pericyclic rearrangements is presented on figure 25. The oxa-Cope reaction first happens on 111 to give the enol ether 113. The alignment of the olefin on this system is suitable for the Claisen rearrangement to occur and to furnish enone 114. This sigmatropic rearrangement should happen through an approach of the allyl exclusively on the β-face of the E olefin since the other face is block by the ring. On 114, the allyl moiety is already in a pseudoequatorial position, so the transannular ene reaction occurs via transition state A (over transition state B where the allyl is pseudoaxial). The formation of 112 with retention of configuration at C₁ and C₂ is thus expected.
Figure 25. Proposed mechanism for the tandem oxa-Cope/Claisen/ene reaction

The analysis of 112 after chiral column separation revealed that this compound was racemic. To verify that the loss of chirality was not induced by the presence of DBU in the reaction mixture, the oxa-Cope/Claisen/ene cascade was performed in the absence of base, however 112 was again produced as a racemic mixture. In fact, the loss of chirality observed in the oxa-Cope/Claisen/ene can be rationalized based on figure 26. After the oxa-Cope reaction, two processes are in competition: the inversion of the macrocycle 113 and the Claisen rearrangement. In order to obtain a racemic mixture of 112, the inversion of the ring must be a lower energy pathway than the sigmatropic rearrangement. Therefore, once the equilibrium between 113 and its enantiomer (ent-113) took place, the Claisen rearrangement occurred on both enantiomers to produce enone 114 as a racemic mixture. The subsequent transannular ene reaction generates 112 as a racemic product. This result gives an approximation of the energy of inversion of the 10-membered-ring enol, which has to be lower than that of Claisen rearrangement.
Figure 26. Racemization of the tandem oxa-Cope/Claisen/ene reaction

The racemization observed during the oxa-Cope/Claisen/ene reaction can be rationalized by the Curtin-Hammett principle. This physico-organic rule stipulates that the ratio of products formed from conformational isomers is not determined by the conformation population ratio but by the energies of activation of a chemical reaction on both conformers\textsuperscript{36}. This principle is valid when the energy of activation of the reaction is greater (at least 10 times) than the barrier to conformational equilibration. Because the interconversion between the two conformers is so fast compared to the irreversible reaction, the ratio of products only depends on the energy of activation of the irreversible reaction. In the case of the tandem oxa-Cope/Claisen/ene reaction, the energy of activation of the Claisen reaction is the same for 113 and ent-113 (due to their enantiomeric relation), so an equivalent mixture of 114 and ent-114 is produced after the equilibrium between the two enol ethers took place (figure 27).
Figure 27. The Curtin-Hammett principle applied to the oxa-Cope/Claisen/ene reaction

The rationalization of the racemization that occurs during the tandem oxa-Cope/Claisen/ene reaction is vital to the explanation for the decrease in chirality observed in all of the previous results. The inversion of the 10-membered-ring enol (or its enolate form) being lower in energy than assumed, the decrease in chirality of the oxy-Cope/ene cascade can be explained depending on the conditions and substrates of the reaction. Upon completion of the oxy-Cope reaction, atropisomer 63 rapidly tautomerizes to enone 64 (figure 21, page 37). In the presence of a base strong enough to abstract the proton in \( \alpha \) of the ketone (\( \text{H}_\alpha \)), 64 can be deprotonated to produce the enolate 116 (figure 28). By increasing the lifetime of this species, the macrocycle can invert to ent-116 due to the relatively low energy of inversion of the ring. Reprotonation of the enolate ent-116 followed by the transannular ene reaction explain the partial formation of the enantiomer of 50.
The aforementioned results corroborate the explanation for the decrease in chirality previously mentioned. In table 1 (page 35), it was shown that DBU is the only base that significantly affects the retention of chirality of the tandem oxy-Cope/ene reaction. Actually, DBU is one of the strongest bases among those presented in this table. Proton $H_a$ of 64, being quite acidic due to the ketone in $\alpha$, can be removed by DBU to form the enolate 116 and allow the inversion of the atropisomer. It has also been observed that the 1,2-divinylcyclohexenol 49, bearing an electron-withdrawing group at the R position, undergoes the tandem reaction with a greater decrease in chirality. The presence of an anion-stabilizing group facilitates the abstraction of proton $H_a$ in compound 64 and consequently, increases the lifetime of enolate 116 and the subsequent inversion to its enantiomer. This was notably the case when the R group on compound 49 was a trifluoromethyl (91) or an aromatic substituent. The racemization of the anionic oxy-Cope is also explained by figure 28. After the 1,2-divinylcyclohexenols performed this base catalyzed sigmatropic rearrangement, the species that is present before the quench is the 10-membered-ring enolate. The protonation of the enolate is impossible due to the strongly basic conditions. Thus the lifetime of the enolates is sufficiently long to allow a complete equilibrium between 116 and ent-116, which gives a racemic mixture of enone 64 after the quench.
Based on the previous observations, the enantioselectivity of the oxy-Cope/ene cascade can be explained by two factors, the rigidity of the atropisomer 63 (figure 21, page 37) and the rate of the different processes involved in the tandem reaction. To avoid a direct inversion of the enol 63, this compound must have an energy of inversion high enough to prevent a rapid inversion of the macrocycle. However, as demonstrated by the oxa-Cope/Claisen/ene cascade, this inversion is still possible. The essential component in the retention of the chirality during the tandem reaction is the high rate of the reactions that take place. Typically, the shorter the lifetime of enol 63 and enolate 116, the higher the enantioselectivity of the oxy-Cope/ene product. Because the tautomerization from enol 63 to enone 64 is extremely fast, the duration of the existence of the enol is very short and this prevents the racemization of the product. Furthermore, the low activation energy of the intramolecular ene reaction also contributes to the reduction of the lifetime of 63 and consequently, avoid racemization during the tandem process. Finally, the irreversibility of the ene reaction prevents the racemization of the product once formed. With the results aforementioned, it can be stated that the activation energies of the inversion of the enol 63 and of its enolate analogue are greater than the activation energies of both the tautomerization and the transannular ene reaction.

Calculations using modeling softwares (Gaussian and PC Spartan) have been attempted, but they were forsaken due to their high complexity and their low precision. Both softwares cannot calculate directly the energy of inversion of 63 to ent-63 because this inversion is divided into 3 distinct movements. The values of these movements are required to calculate the activation energy of inversion. However, these values can hardly be determined and this would be achieved by using lots of approximation. The first approximation consists in the order in which these movements occur. The second and major approximation is related to the conformation of the ring after each movement. Usually when an activation energy calculation is submitted to a modeling software, a calculation of the minimum energy conformation is ask for prior to the activation energy calculation. In the case of the present study, the determination of the minimum energy conformation of the ring could not be ask for after each movement because this would bring the ring back to its original conformation. The calculation of the activation energy
could be done by giving an approximation of the position of every single atom of the ring after each movement, but the activation energy value thus obtained would be highly doubtful.

2.3.8 Anionic Oxy-Cope, A Novel Approach for Asymmetric Construction of Quaternary Centers

The enantioselective formation of quaternary centers has always represented one of the most complex challenges in organic chemistry. A few approaches have been developed to achieve this goal, but some limitations remain. The use of a chiral auxiliary for the asymmetric construction of the quaternary centers usually raises the problem of the removal of this moiety. Most of the actual methods which employ an auxiliary require harsh conditions to remove this substituent after the formation of the fully substituted carbon. On the other hand, the enantioselectivity of an asymmetric catalytic construction of quaternary centers is often sensitive to the substrate of the reaction.

We envisaged that the anionic oxy-Cope could represent a novel and versatile approach for the construction of quaternary stereocenters. The chiral environment created by the ring conformation should allow a good transfer of chirality. Instead of trapping the enolate 117 (figure 29) with a source of protons, the addition of an electrophile that favors C-alkylation would lead to the formation of the 10-membered-ring 118 bearing a quaternary center in α of the ketone. As mentioned in section 2.3.3, racemization that results from the anionic oxy-Cope performed on 1,2-divinylcyclohexenols of type 49 is due to the low energy of inversion of the enolate 117. The addition of a chiral center to an enolate (120) should lead to the formation of enone 121 with a high degree of enantioselectivity based on a diastereomeric relationship between two transition states for the alkylation. The presence of a third substituent on the olefin in α of the hydroxyl of 119 could produce this additional stereogenic center during the anionic oxy-Cope. This
approach would lead, after an electrophilic quench, to the formation of a 10-membered-ring enone 121 bearing contiguous quaternary and tertiary centers.

![Chemical Structures](image)

**Figure 29. Construction of quaternary centers via an anionic oxy-Cope**

The construction of the fully substituted carbon center was attempted on the 1,2-divinylcyclohexenol 122 (scheme 15). The preparation of this compound was achieved following the procedure presented above (halogen-metal exchange between butyllithium and an iodo olefin) and submitted to the optimized conditions of the anionic oxy-Cope (table 3, entry 6, page 39) to produce the enolate 123. Because of the low energy barrier of inversion of the enolate, two possible transition states (A and B) are present for the approach of the electrophile. Transition state A, where the propyl group is pseudoequatorial, is favored over transition state B in which the alkyl chain is in a pseudoaxial orientation. The alkylation of 123 occurs through a stereofacial approach of the electrophile on the β-face of the enol, since the other face of the olefin is hindered by the ring, to produce enone 124. The ozonolysis of both the enone and the Z olefin of 124 was performed followed by reduction using hydrogen and palladium on charcoal. Finally, the esterification of the acid moiety facilitated the isolation of the keto-ester 126 as the solely observed diastereomer. The absolute and relative stereochemistry of 126 has not yet been established. Attempts to do so using either crystallography or NMR studies on a cyclic derivative of 126 will be undertaken.
Scheme 15. Formation of quaternary centers and isolation of 126

The preparation of 126 was the only attempted example of this new approach for the construction of quaternary centers, due to time constraint. Research in our group is currently in progress to develop this novel strategy. However, the possibilities of this methodology already seem very promising. As shown in figure 30, the versatility of this approach is first based on the synthesis of a variety of divinylcyclohexenols 127 bearing a trisubstituted olefin in α of the hydroxyl. This task can easily be achieved by the preparation of different trisubstituted iodoolefins. The flexibility of this methodology would be demonstrated by quenching the anionic oxy-Cope with a series of electrophiles. Using an iodoalkyl electrophile would allow the preparation of the keto acids type 128, where R, R₁ and R₂ can be a variety of substituents. Trapping the enolate with Davies’ reagent should produce a quaternary center having an α-hydroxy acid contiguous with a tertiary center, which is a quite challenging combination of functional groups. A more interesting scenario is the use of a source of azide as electrophile, which would permit the preparation of a quaternary stereocenter bearing an azide moiety 130, which can easily be converted to the α amino acid in one step.
Figure 30. Possibilities of the novel approach for the formation of quaternary centers

2.4 Conclusion

This study constitutes an example of an asymmetric induction on a macrocycle without the use of a remote chiral center. The high enantioselectivity of the tandem oxy-Cope/ene reaction has been explained due to the rigidity of enol 63 and the rate of the different processes (inversion of the ring, tautomerization and ene reaction) involved in the cascade reaction. The decrease in chirality observed on some products of the tandem reaction has been rationalized by the relatively low energy barrier of inversion of the intermediate 10-member ring enol. The racemization of the anionic oxy-Cope was explained based on the same argument, involving the enolate intermediate of the base catalyzed sigmatropic rearrangement. The use of a rather strong base in addition to the presence of an electron-withdrawing group on the vinyl in \( \alpha \) of the hydroxyl of a 1,2-divinylcyclolhexenol contribute to the decrease in chirality. The enantioselectivity of the tandem process can be maximized depending on the substrate and on the base used for the reaction. Finally, the study of the anionic oxy-Cope led to the discovery of a novel approach for the asymmetric construction of quaternary centers.
CHAPTER 3

3.1 Introduction

The primary focus of our group is the development of novel tandem reactions and their use in total synthesis. This strategy allows the rapid and efficient construction of highly complex, functionalized cores of natural products in a minimal number of steps. It also permits the simultaneous installation of several stereogenic centers using traditional chemistry (figure 31).

Figure 31. Use of tandem reactions as a powerful synthetic tool

As presented in chapter 2, the first tandem reaction discovered in our laboratory is the oxy-Cope/ene cascade\(^{40}\), which was optimized and applied to the total synthesis of (+)-arteannium \(M^{27}\). The second generation of tandem reactions developed by our group is the oxy-Cope/ene/Claisen cascade. The utility of this reaction is justified by the facile construction of quaternary centers\(^{45}\). This tandem process involves 3 pericyclic reactions and is being used in our laboratory for the total synthesis of two natural products: the tetrodecamycin \(136\) and the agelasimine A \(139\) (scheme 16).
Scheme 16. Tandem reactions and their use in total synthesis

During the development of the third generation of tandem reactions in the tetrodecamycin synthesis, a novel cascade involving 4 pericyclic reactions was discovered. The synthesis of 136 begins with the alkylation of an isopropenylcuprate on cyclohexene oxide 140, followed by the oxidation of the resulting alcohol under Swern conditions to furnish ketone 141 (scheme 17). The addition of ethynylmagnesium chloride to the ketone and the subsequent allylic oxidation using selenium dioxide and tert-butyl hydroperoxide produced the diol 142 as the major diastereomer in 42% yield over two steps. Installation of an allyl group on the primary alcohol gave 134 which underwent a tandem oxy-Cope/ene/Claisen reaction when heated. In order to increase the yields of each steps of the synthesis, a large excess of the reagents for the allylation of the diol 142 was used (by J.M. Warrington, colleague). The reaction produced one compound, which when subjected to microwave heating gave a product (144) other than the one that was envisaged. The $^1$H NMR analysis notably showed four extra protons and the $^{13}$C NMR spectrum had three more carbons than expected. The unidentified
compound, which we assumed was a lactol, generated a white solid upon reduction with lithium aluminium hydride.

**Scheme 17. Discovery of the tandem oxa-Cope/Claisen/ene/Claisen reaction**

Analysis of the X-ray crystallograph revealed the presence of an additional allyl moiety on the olefin of the bicyclic compound 145 (figure 32). This observation corroborates the NMR data of the lactol 144. The analysis of the rest of the crystal structure confirmed that the two alcohols of 145 are syn (the tertiary hydroxyl and the methyl bearing the primary alcohol). The presence of the allyl on the quaternary center and its anti relation with the tertiary alcohol were also verified.
The formation of compound 145 can be explained by the excess of sodium hydride and allyl bromide used when the allylation of the primary alcohol was attempted (scheme 17). The use of a three to one mixture of THF and DMF allowed a complete alkylation of both the primary and the tertiary alcohols to furnish 143. The exposure of this compound to the microwave heating allowed a tandem reaction involving 4 pericyclic reactions, the oxa-Cope/Claisen/ene/Claisen cascade, to occur. A proposed mechanism of this novel tandem reaction is presented in figure 33. It is believed that the oxa-Cope reaction first takes place on 143 to produce allene 146. This system, which is highly strained due to the presence of an allene and an $E$ olefin (relative to the carbon framework) on the 10-membered ring, immediately undergoes a Claisen reaction to generate enone 147. Then, a transannular ene reaction occurs to form the two fused 6-membered rings 148. The presence of the allyl vinyl ether on 148 allows a second Claisen
reaction to occur. Finally, the aldehyde and the hydroxyl groups of 149 react to form the lactol 144 as an inseparable mixture of diastereomers.

![Chemical structures]

**Figure 33. Proposed mechanism of the tandem oxa-Cope/Claisen/ene/Claisen reaction**

The feasibility of applying this new tandem reaction to the fast construction of very complex tricyclic compounds sparked interest within our group. To this end, an investigation to determine the effects of the different substituents on the tertiary alcohol and the presence of a variety of groups on the alkyne 150 was performed (figure 34). The effect of the variation of the allyl moiety on the primary alcohol of 150 is already well understood in our laboratory, the actual study aims to explain the effects of changing the other functionalities of this compound. The presence of a substituent (R₁ and R₂) at the extremity of the allyl bound to the tertiary alcohol on 150 could notably permit the formation of a chiral center during the cascade. Besides, the use of a non-terminal alkyne could allow the preparation of tetrasubstituted olefins on the ring of the tricyclic compound of type 151.
3.2 Preliminary results

To evaluate the scope and limitations of the tandem oxa-Cope/Claisen/ene/Claisen reaction, a series of experiments were performed on various substrates. These substrates were prepared by the alkylation of different alkynes on ketone 141 followed by an allylic oxidation. The subsequent alkylation of the primary alcohol and the selective installation of a propargyl, a cinnamyl or a second allyl moiety on the tertiary alcohol produced the compounds 152, 155, 157, 158 and 160 (scheme 18). When heated using the microwave oven, two of these compounds underwent the desired tandem reaction to furnish the lactols 153 and 156. When substrate 152, a cyclohexanol bearing a propargyl moiety on the tertiary alcohol, was heated, it rearranged to furnish the compound 153 which has a stable allene bound to the olefin of the cycle. Heating compound 155 (which bears a non-terminal alkyne) gave access to compound 156 that has a fully substituted olefin on one of the two fused 6-membered ring. The structures of 153 was confirmed after its oxidation (TPAP and NMO) to its corresponding lactone (161 not shown). When the more functionalized substrates 157, 158 and 160 were heated in the microwave oven, the results obtained were not as promising as those of the initial investigation of this methodology. They produced mixtures of compounds, which were not separable in most cases. Moreover, examination of the TLC of these reactions showed no sign of the desired product (i.e. a lactol). It is believed that the presence of several olefins, alkynes and aromatic rings on the substrates could interfere with the
source of heat (microwaves) and cause either side-reactions and the decomposition of the starting material.

Scheme 18. Tandem oxa-Cope/Claisen/ene/Claisen reaction applied to various substrates

The tandem oxa-Cope/Claisen/ene/Claisen reaction applied to the substrate 152 to produce 153 was studied more in depth to identify the factors that may affect the cascade reaction (table 8). The choice of base, the source of heat and the temperature of the reaction were investigated in this part of the study performed by C. Grisé. At first glance,
it appeared that the use of a weaker base than DBU, such as triethylamine, would be a
better choice for the cascade reaction. 1,8-diazabicyclo[5.4.0]undec-7-ene is a base strong
enough to remove a proton on a terminal alkyne (at high temperature). Avoiding this
deprotonation would prevent side-reactions. It was observed that the tandem reaction
performed with triethylamine produced less side-products on the TLC. This fact is also
apparent by the better yields obtained with triethylamine than DBU for the tandem
reaction (table 8, entries 1 and 4). Moreover, the use of conventional heating instead of
the microwave oven facilitated the reaction with a low amount of undesired products, as
observed by thin layer chromatography. Finally, the temperature also plays an important
role in the outcome of the reaction. A variation of about 10°C during the reaction seems
to greatly affect the outcome of the tandem reaction (entries 3 to 5). The best yield
obtained for the formation of 153, using the optimized conditions (conventional heating,
triethylamine and 150°C) was 43%. It should be noted that the possible instability of the
allene moiety to the silica gel during purification may affect the yields determined in this
study.

![Chemical structures](image)

<table>
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<th>Entry</th>
<th>Heat source</th>
<th>Base (10eq)</th>
<th>Temperature (°C)</th>
<th>Time (hours)</th>
<th>Yield (isolated)</th>
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</tr>
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<tr>
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<td>Conventional</td>
<td>Et₃N</td>
<td>150</td>
<td>72</td>
<td>43%</td>
</tr>
</tbody>
</table>

Table 8. Study of the conditions for the tandem oxa-Cope/Claisen/ene/Claisen reaction
3.3 The “syn” series

The examples presented above in this chapter all used a cyclohexanol bearing an isopropenyl and an ethynyl in an anti relation 142 (scheme 19), which is the major diastereomer resulting from the addition of ethynylmagnesium chloride to ketone 141. The minor diastereomer of this alkylation, the cyclohexanol with the isopropenyl and the ethynyl syn to each other (162), has been briefly investigated. The two hydroxyls of the diols 142 and 162 were protected as their methoxy derivatives 163 and 164. When heated in a microwave oven, 163 produced diene 165 which has a Z olefin in α of the ring. However, heating compound 164 (syn substituents) generated diene 166 which has an E double bond (geometrical isomer of the previous compound). The possible structures of these two products as shown in scheme 19 were attributed according to the $^1$H NMR (coupling constant), $^{13}$C NMR, HMQC and NOE effects.

Scheme 19. Study comparing the anti and the “syn” series
A brief investigation of the mechanisms of the formation of 165 and 166 was undertaken. Substituting the proton on the terminal alkyne of 164 with a deuterium, followed by exposure of the deuterated compound 167 to the microwave heat furnished compound 168. This experiment displayed the movement of this deuterium atom during the reaction to the middle of the diene as shown in scheme 20. None of the actual accepted mechanisms in organic chemistry seem to explain the rearrangements that occur when 163 and 164 are heated. The study of this reaction involving the syn series substrates will be investigated in our laboratory.

![Scheme 20. Study of the rearrangement of 164](image)

3.4 Conclusion

The aforementioned project allowed the investigation of a novel tandem reaction which involves 4 pericyclic rearrangements, the oxa-Cope/Claisen/ene/Claisen cascade. Preliminary results of this study suggest the possibility of a rapid means for construction of highly complex tricyclic compounds, bearing notably a tetrasubstituted olefin and an allene. However, the use of more functionalized substrates for the new tandem reaction led to the formation of mixtures. The feasibility of this methodology is also limited by the heat source, the base and the temperature used for the reaction. Under optimal conditions, the preparation of more complex polycyclic compounds via this novel tandem reaction should occur.
CHAPTER 4

4.1 Experimental

4.1.1 General

All reactions were performed under nitrogen atmosphere with flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All solvents were distilled prior to use; diethyl ether and THF over sodium and benzophenone; toluene and dichloromethane over calcium hydride. Reactions were monitored by thin layer chromatography analysis of aliquots using aluminum sheets pre-coated (0.2mm layer thickness) with silica gel 60 F254 (E. Merck). Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or p-anisaldehyde staining solution. Column chromatographies were performed with silica gel 60 (230-400 mesh, Merck). $^1$H and $^{13}$C NMR were measured at 500MHz and 125MHz with a Bruker AMX500 or at 300MHz and 75MHz on Bruker AMX300 with deuterated solvents. IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer and optical rotations were measured with a Perkins-Elmer model 241 polarimeter. The high-resolution mass spectra were recorded at The University of Ottawa Mass Spectrum Centre. Enantiomeric excesses were determined using a Waters HPLC 2690 equipped with a ChiralPak AS (4.6 X 250 mm) chiral column and a Waters photodiode array detector 996 at isocratic elution. Melting points were recorded on a Gallenkamp melting point machine apparatus P 1106G. X-ray crystallographs were performed on a Bruker AX SMART 1k CCD diffractometer.

4.1.2 Compounds Relative to Chapter 2

**Compound 40, 1-[3-(t-Butyl-diphenyl-silyloxy)-1-methylene-propyl]-6-isopropenyl-3-methyl-cyclohex-2-enol**

To a solution of $t$-butyl-(3-iodo-but-3-enyloxy)-diphenyl-silane (184.6 mg, 0.423 mmol) in Et$_2$O (4 mL) at $-90^\circ$C was added $t$-BuLi (1.12 mL, 0.846 mmol) and the mixture was stirred at $-90^\circ$C for 10 min. Ketone 39 (42.3
mg, 0.282 mmol) dissolved in Et₂O (5 mL) and cooled to –90°C was canulated into the solution of the lithiated compound and the mixture was slowly warmed to –40°C. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 40 (115.3 mg, 89%) as a colorless oil. All spectroscopic data were in accordance with that reported in the literature²⁷.

**Compound 41, 4-[2-(t-Butyl-diphenyl-silanyloxy)-ethyl]-6-methyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of alcohol 40 (22.3 mg, 0.0484 mmol) in toluene (15.2 mL) in a microwave cell was added DBU (72 μL, 0.484 mmol). The solution was degassed using argon and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (4% ethyl acetate in 96% hexanes) to give a colorless oil 41 (14.7 mg, 66%). ee determined using a ChiralPak AS column, eluent : 99.9/0.1 hexanes/i-PrOH, 0.6 mL/min, T_r(major) : 11.2 min, T_r(minor) : 12.4 min. All spectroscopic data were in accordance with that reported in the literature²⁷.

**Compound 43, 4-(2-Hydroxy-ethyl)-6-methyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of compound 41 (13.7 mg, 0.0297 mmol) in THF (2 mL) at 0°C was added TBAF (0.033 mL, 0.033 mmol). The solution was stirred for 75 min while slowly warming to room temperature. The mixture was filtered over silica and the residue was purified by flash chromatography (30% ethyl acetate in 70% hexanes) to give a colorless oil 43 (4.9 mg, 74%). ee determined using a ChiralPak AS column, eluent : 40/60 hexanes/i-PrOH, 0.75 mL/min, T_r(major) : 7.9 min, T_r(minor) : 5.9 min. All spectroscopic data were in accordance with that reported in the literature²⁷.
Compound 51, 1,6-Diisopropenyl-3-methyl-cyclohex-2-enol

To a solution of 2-bromopropene (120 µL, 1.33 mmol) in Et₂O (5 mL) at −90°C was added t-BuLi (1.95 mL, 2.66 mmol) and the mixture was stirred at −90°C for 45 min. Ketone 39 (94.1 mg, 0.63 mmol) dissolved in Et₂O (2 mL) and cooled to −90°C was cannulated into the solution of the lithiated compound and the mixture was warmed to −78°C. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (12% ethyl acetate in 88% hexanes) to give 51 (92.9 mg, 77%) as a colorless oil. IR (neat) 3500 (w), 3071 (w), 2930 (s), 1639 (m), 1449 (m), 1376 (m), 1081 (m), 958 (m), 898 (s), 558 (s); ¹H NMR (CDCl₃) δ 5.22 (m, 1H), 5.06 (m, 1H), 4.93 (m, 1H), 4.83 (m, 1H), 4.76 (m, 1H), 2.36 (dd, J = 2.8 Hz, 8.0 Hz, 1H), 2.03-1.99 (m, 2H), 1.97 (s, 1H), 1.96-1.88 (m, 1H), 1.74 (m, 3H), 1.71 (m, 3H), 1.69 (m, 3H), 1.57-1.53 (m, 1H); ¹³C NMR (CDCl₃) δ 150.2(C4), 147.4(C4), 138.5(C4), 126.6(CH), 112.8(CH₂), 110.2(CH₂), 73.7(C4), 47.0(CH), 30.9(CH₂), 24.7(CH₂), 24.5(CH₃), 23.4(CH₃), 20.0(CH₃); HRMS (EI) m/z calcd for C₁₃H₂₀O (M⁺) 192.1514, found 192.1515; [α]D₂⁰ +39.0° (c 1.00, CH₂Cl₂); ee determined using a ChiralPak AS column, eluent : 100/0 to 98/2 hexanes/i-PrOH, 1 mL/min, 10 min, T_r(major) : 5.7 min, T_r(minor) : 4.8 min.

Compound 52, 6-Isopropenyl-3-methyl-1-(1-phenyl-vinyl)-cyclohex-2-enol

To a solution of α-bromostyrene (155 µL, 1.20 mmol) in Et₂O (5 mL) at −90°C was added t-BuLi (1.80 mL, 2.40 mmol) and the mixture was stirred at −90°C for 45 min. Ketone 39 (100.5 mg, 0.67 mmol) dissolved in Et₂O (2 mL) and cooled to −90°C was cannulated into the solution of the lithiated compound and the mixture was warmed to −78°C. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give
52 (145.3 mg, 85%) as a colorless oil. IR (neat) 3500 (w), 3071 (w), 2931 (s), 2827 (m), 1636 (m), 1492 (m), 1442 (m), 1376 (m), 1177 (m); $^1$H NMR (CDCl$_3$) $\delta$ 7.42-7.38 (m, 2H), 7.30-7.19 (m, 3H), 5.63 (d, J = 1.6 Hz, 1H), 5.53 (s, 1H), 5.25 (d, J = 1.6 Hz, 1H), 4.91 (s, 1H), 4.71 (s, 1H), 2.47-2.42 (m, 1H), 2.08 (s, 1H), 2.03-1.97 (m, 2H), 1.94-1.83 (m, 1H), 1.79 (s, 3H), 1.63 (s, 3H), 1.58-1.49 (m, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 155.5(C4), 147.0(C4), 141.3(C4), 138.2(C4), 128.2(2CH), 128.1(CH), 127.8(2CH), 127.0(CH), 115.1(CH$_2$), 113.6(CH$_2$), 73.8(C4), 47.1(CH), 33.7(CH$_2$), 24.7(CH$_2$), 23.4(CH$_3$), 23.6(CH$_3$); HRMS (EI) m/z calcd for C$_{18}$H$_{22}$O (M$^+$) 254.1671, found 254.1626; [$\alpha$]$_D^{20}$ +131.0° (c 0.97 CH$_2$Cl$_2$).

**Compound 53, 4,6-Dimethyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of compound 51 (15.6 mg, 0.081 mmol) in toluene (18 mL) in a microwave cell was added DBU (120 $\mu$L, 0.81 mmol). The solution was degassed using argon and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give two diastereomers (dr = 15:1) as a colorless oil (9.3 mg, 60% for the major product). 53, major diastereomer, IR (neat) 3500 (w), 2923 (s), 2854 (m), 1649 (w), 1454 (m), (1379 (w), 938 (s); $^1$H NMR (CDCl$_3$) $\delta$ 5.68 (m, 1H), 4.88 (m, 1H), 4.63 (m, 1H), 2.34-2.27 (m, 1H), 2.12-1.97 (m, 4H), 1.79-1.49 (m, 4H), 1.69 (s, 3H), 1.39 (m, 1H), 1.23 (s, 1H), 0.96 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 149.6(C4), 138.8(C4), 124.4(CH), 107.7(CH$_2$), 71.2(C4), 48.1(CH), 39.8(CH), 35.9(CH$_2$), 32.5(CH$_2$), 30.7(CH$_2$), 23.8(CH$_3$), 20.5(CH$_2$), 14.5(CH$_3$); HRMS (EI) m/z calcd for C$_{13}$H$_{20}$O (M$^+$) 192.1514, found 192.1543; [$\alpha$]$_D$ = -157.5°, (c 1.22, CH$_2$Cl$_2$); ee determined using a ChiralPak AS column, eluent : 99.5/0.5 hexanes/i-PrOH, 1 mL/min, $T_{r$(major)$}$: 4.5 min, $T_{r$(minor)$}$: 5.2 min. Compound 55 (0.6 mg, 4% for the minor product). IR (neat) 3478 (b, w), 3078 (w), 2962 (s), 2931 (s), 2873 (m), 1648 (m), 1451 (m), 1378 (w), 947 (m); $^1$H NMR (CDCl$_3$) $\delta$ 5.31 (d, J = 1.2 Hz, 1H), 4.85 (d, J = 1.5 Hz, 1H), 4.59 (d, J = 1.5 Hz, 1H), 2.28-2.21 (m, 2H), 2.15-2.11 (m, 1H), 2.06-1.92 (m, 4H), 1.87-1.82 (m, 1H), 1.71-1.64 (m, 5H), 1.47-1.43 (m, 1H), 1.26-1.20
(m, 1H), 0.95 (d, J = 7.3 Hz, 2H); $^{13}$C NMR (CDCl$_3$) δ 150.0(C4), 138.1(C4), 127.4(CH), 107.4(CH$_2$), 73.3(C4), 41.3(CH), 38.5(CH), 30.8(CH$_2$), 30.6(CH$_2$), 29.6(CH$_2$), 23.4(CH$_3$), 20.3(CH$_2$), 14.9(CH$_3$); HRMS (EI) m/z calcd for C$_{13}$H$_{20}$O (M$^+$) 192.1514, found 192.1496; [α]$_D^{20}$ +403.4° (c 0.71, CH$_2$Cl$_2$).

**Compound 54, 6-Methyl-1-methylene-4-phenyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4-ol**

To a solution of compound 52 (14.5 mg, 0.057 mmol) in toluene (18 mL) in a microwave cell was added DBU (85 μL, 0.57 mmol). The solution was degassed using argon and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography 5% ethyl acetate in 95% hexanes) to give 54 (13.5 mg, 93%) as a colorless oil. IR (neat) 3500 (w), 3084 (w), 3026 (w), 2931 (s), 1650 (m), 1493 (m), 1089 (m), 942 (s), 701 (s); $^1$H NMR (CD$_3$)δ 7.54-7.46 (m, 2H), 7.29-7.25 (m, 2H), 7.19-7.17 (m, 1H), 5.33 (s, 1H), 4.97 (d, J = 0.8 Hz, 1H), 4.76 (d, J = 0.8 Hz, 1H), 2.57 (dd, J = 3.6 Hz, 12.6 Hz, 1H), 2.37-2.34 (m, 1H), 2.29-2.20 (m, 1H), 2.14-2.06 (m, 1H), 2.03-2.00 (m, 1H), 1.85-1.56 (m, 5H), 1.39 (s, 3H), 1.21 (s, 1H); $^{13}$C NMR (CD$_3$)δ 149.6(C4), 143.5(C4), 137.9(C4), 130.5(CH), 128.7(CH), 127.1(2CH), 127.0(2CH), 108.3(CH$_2$), 71.7(C4), 54.2(CH), 49.1(CH), 37.0(CH$_2$), 32.1(CH$_2$), 31.2(CH$_2$), 23.8(CH$_3$), 21.2(CH$_2$); HRMS (EI) m/z calcd for C$_{18}$H$_{22}$O (M$^+$) 254.1671, found 254.1670; [α]$_D^{20}$ -107.4° (c 0.89, CH$_2$Cl$_2$); ee determined using a ChiralPak AS column, eluent : 80/20 hexanes/i-PrOH, 1 mL/min, T$_{r$(major)}$: 3.4 min, T$_{r$(minor)}$: 4.7 min.

**Compound 57, 1a,7-Dimethyl-4-methylene-octahydro-1-oxa-cyclopropa-[a]-naphthalen-7a-ol**

To a solution of alcohol 53 (46.4 mg, 0.258 mmol) in DCM (4 mL) at room temperature was added a solution of VO(acac)$_2$ (1.0 mL, 0.010 mmol) and stirred for 5 min to produce a pink solution. t-BuOOH (43 μL, 0.31 mmol) was added to the mixture and it was stirred for 3 hrs to give a yellow solution. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The
mixture was extracted with ethyl acetate (3X) and the combined organic layers were washed with an aqueous solution of Na₂S₂O₃, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give 57 (38.7 mg, 76%) as a colorless oil. IR (neat) 3300 (w), 3085 (m), 2932 (s), 1652 (m), 1461 (m), 1380 (m), 891 (m); ¹H NMR (CDCl₃) δ 4.81 (d, J = 1.4 Hz, 1H), 4.52 (d, J = 1.4 Hz, 1H), 3.06 (s, 1H), 2.33-2.29 (m, 1H), 2.26 (s, 1H), 2.14-2.03 (m, 2H), 1.72-1.64 (m, 4H), 1.61-1.52 (m, 1H), 1.42-1.38 (m, 1H), 1.34 (s, 3H), 1.29-1.16 (m, 1H), 1.04 (d, J = 6.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 148.2(C4), 107.2(CH₂), 70.2(C4), 63.9(CH), 61.8(C4), 48.6(CH), 38.9(CH₃), 35.8(CH₂), 32.4(CH₂), 30.3(CH₂), 23.4(CH), 17.5(CH₂), 14.5(CH₃); HRMS (EI) m/z calcd for C₁₃H₂₀O₂ (M⁺) 208.1463, found 208.1474; [α]D²⁰ -103.5° (c 0.62, CH₂Cl₂).

**Compound 58, 2,8-Dimethyl-5-methylene-4,4a,5,6,7,8-hexahydro-1H-naphthalene-1,8a-diol**

To a solution of epoxide 57 (27.7 mg, 0.133 mmol) in benzene (5 mL) at 0°C was added DIBAL (0.55 mL, 0.798 mmol) dropwise. The mixture was heated to 80°C for 7 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 58 (11.2 mg, 40%) as a colorless oil. IR (neat) 3400 (w), 3085 (w), 2959 (s), 2924 (s), 2854 (m), 1645 (w), 1455 (w), 1024 (m); ¹H NMR (CDCl₃) δ 5.57 (m, 1H), 4.89 (d, J = 1.1 Hz, 1H), 4.87 (d, J=1.1 Hz, 1H), 3.90 (d, J = 8.6 Hz, 1H), 2.38-2.31 (m, 1H), 2.25 (d, J = 8.6 Hz, 1H), 2.17 (m, 1H), 2.14-2.04 (m, 1H), 1.93-1.83 (m, 1H), 1.79 (s, 1H), 1.74 (s, 3H), 1.67-1.48 (m, 3H), 1.40 (td, J = 4.1Hz, 13.2 Hz, 1H), 1.08 (d, J = 6.6 Hz, 3H); ¹³C NMR (CDCl₃) δ 148.6(C4), 134.4(C4), 123.1(CH), 109.1(CH₂), 75.4(CH), 73.5(C4), 46.4(CH), 43.0(CH), 36.4(CH₂), 32.7(CH₂), 23.7(CH₂), 19.8(CH₃), 16.6(CH₃); HRMS (EI) m/z calcd for C₁₃H₂₀O₂ (M⁺) 208.1463, found 208.1473.
**Compound 67, 3,7,10-Trimethyl-cyclodeca-2,6-dienone**

To a solution of alcohol 51 (67.1 mg, 0.349 mmol) in dimethoxyethane (10 mL) was added KHMDS (3.6 mL, 1.8 mmol). The mixture was heated at 85°C for 75 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give 67 (50.2 mg, 75%) as a colorless oil. IR (neat) 2966 (m), 2930 (s), 2866 (m), 1684 (s), 1637 (m), 1455 (m), 1081 (m), 1370 (w), 1081 (m), 1019 (m); ¹H NMR (CDCl₃) δ 6.06 (s, 1H), 5.01 (t, J = 7.4 Hz, 1H), 2.89-2.80 (m, 1H), 2.47-2.33 (m, 1H), 2.24-2.10 (m, 2H), 2.10-1.99 (m, 2H), 1.95-1.81 (m, 3H), 1.78 (s, 3H), 1.44 (s, 3H), 1.25-1.14 (m, 1H), 0.99 (d, J = 6.9 Hz, 2H); ¹³C NMR (CDCl₃) δ 207.6(C4), 145.0(C4), 138.5(C4), 128.4(CH), 124.5(CH), 46.7(CH), 40.2(CH₂), 32.7(CH₂), 29.6(CH₂), 24.4(CH₂), 24.0(CH₃), 18.7(CH₃), 14.7(CH₃); HRMS (EI) m/z calcd for C₁₃H₂₀O (M⁺) 192.1514, found 192.1509; ee determined by ChiralPak AS, eluent : 99.7/0.3 hexanes/i-PrOH, 0.8 mL/min, Tₑ₁ : 5.5 min, Tₑ₂ : 5.8 min.

**Compound 70, 3,7-Dimethyl-10-phenyl-cyclodeca-2,6-dienone**

To a solution of alcohol 52 (29.9 mg, 0.118 mmol) in dimethoxyethane (2 mL) was added KHMDS (1.2 mL, 0.6 mmol). The mixture was heated at 85°C for 75 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give 70 (23.4 mg, 78%) as a colorless oil. IR (neat) 2968 (w), 2924 (m), 2852 (w), 1682 (s), 1635 (s), 1442 (m), 1109 (m), 1029 (m), 865 (m); ¹H NMR (CDCl₃) δ 7.28-7.15 (m, 5H), 6.04 (s, 1H), 5.18 (t, J = 6.2 Hz, 1H), 3.58 (dd, J = 2.0 Hz, 12.4 Hz, 1H), 3.07-2.94 (m, 1H), 2.75-2.59 (m, 1H), 2.34-2.22 (m, 1H), 2.20-2.12 (m, 1H), 2.07-1.97 (m, 1H), 1.96-1.80 (m, 2H), 1.78 (s, 3H), 1.69-1.60 (m, 1H), 1.56 (s, 3H); ¹³C NMR (CDCl₃)
δ 202.4(C4), 145.2(C4), 139.6(C4), 138.6(C4), 128.8(CH), 128.6(2CH), 127.9(2CH), 126.8(CH), 124.5(CH), 58.9(CH), 40.7(CH2), 32.9(CH2), 29.6(CH2), 24.5(CH2), 24.0(CH3), 14.8(CH3); HRMS (EI) m/z calc'd for C_{18}H_{22}O (M⁺) 254.1671, found 254.1675.

**Compound 71, 3,4-Diisopropenyl-3-methoxy-1-methyl-cyclohexene**

To a solution of alcohol 51 (20.6 mg, 0.107 mmol) in THF (1 mL) was added 18-crown-6 (107.6 mg, 0.407 mmol) and the mixture was stirred for 5 min. In another flask, KH (36.2 mg, 0.270 mmol) was washed with hexanes and dried under vacuum. The KH was dissolved in THF (3 mL) and cooled to 0°C. The solution containing the alcohol was added via canula to the KH solution at 0°C to produce a yellow mixture. After 15 min, dimethylsulfate (50 μL, 0.520 mmol) was added to the mixture and it was warmed to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (2% ethyl acetate in 98% hexanes) to give 71 (12.9 mg, 58%) as a colorless oil. IR (neat) 2955 (s), 2924 (s), 2854 (s), 1739 (w), 1463 (m), 1377 (w), 1264 (w), 801 (w), 722 (w); ¹H NMR (CDCl₃) δ 5.38 (s, 1H), 4.93 (d, J = 1.2 Hz, 1H), 4.88 (s, 1H), 4.73 (d, J = 1.2 Hz, 1H), 4.61 (s, 1H), 3.14 (s, 3H), 2.24-2.17 (m, 1H), 2.07-1.97 (m, 2H), 1.74 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H), 1.54-1.48 (m, 1H), 0.88-0.81 (m, 1H); ¹³C NMR (CDCl₃) δ 147.5(C4), 147.1(C4), 139.3(C4), 124.4(CH), 112.3(CH2), 112.1(CH2), 80.4(C4), 51.2(CH3), 50.1(CH), 30.8(CH2), 24.3(CH2), 23.6(CH3), 22.0(CH3), 19.7(CH3); [α]D²⁰ +93.1° (c 0.95, CH₂Cl₂); HRMS (EI) m/z calc'd for C_{14}H_{22}O (M⁺) 206.16706, found 206.16657.

**Compound 73, [6-Isopropenyl-3-methyl-1-(1-phenyl-vinyl)-cyclohex-2-enyloxy]-trimethyl-silane**

To a solution of alcohol 52 (22.5 mg, 0.088 mmol) in THF (2 mL) at room temperature was added KHMDS (0.20 mL, 0.100 mmol) and the mixture
was stirred for 10 min. TMSCl (1 drop) was added to the mixture and 90 min later, TMSCl (11 \( \mu \)L, 0.087 mmol) was added again. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (1% ethyl acetate in 99% hexanes) to give 73 (4.9 mg, 17%) as a colorless oil. \(^1\)H NMR (CD\(_2\)D\(_6\)) \( \delta \) 7.52-7.48 (m, 2H), 7.32-7.29 (m, 1H), 7.15-7.07 (m, 2H), 5.65 (m 1H), 5.63 (d, J = 2.2 Hz, 1H), 5.32 (d, J = 2.2 Hz, 1H), 4.93 (m, 1H), 4.77 (m, 1H), 2.43 (dd, J = 2.5 Hz, 12.8 Hz, 1H), 2.14-1.97 (m, 1H), 1.91 (s, 3H), 1.74-1.62 (m, 2H), 1.61 (s, 1H), 1.47 (s, 3H), 0.17 (s, 9H).

Compound 77, 6-Methyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol

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\text{To a solution of ketone 39 (34.2 mg, 0.228 mmol) in Et}_2\text{O (3.5 mL) at -78°C was added vinyl magnesiumbromide (0.44 mL, 0.23 mmol) and the mixture was warmed up slowly to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X), dried over MgSO}_4\text{, filtered and concentrated. The residue was purified by flash chromatography (very rapidly, 20% ethyl acetate in 80% hexanes) to give a colorless oil 68. The oil was dissolved in toluene (18 mL) in a microwave cell and DBU (340 \( \mu \)L, 2.28 mmol) was added to the mixture. The solution was degassed using argon and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (8% ethyl acetate in 92% hexanes) to give 77 (4.9 mg, 12%) as a colorless oil. IR (neat) 3500 (w), 3077 (w), 2929 (s), 2855 (m), 1649 (m), 1435 (m), 1378 (w), 941 (s), 886 (m); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 5.40 (q, J = 1.5 Hz, 1H), 4.89 (dd, J = 1.5 Hz, 3.2 Hz, 1H), 4.64 (dd, J = 1.5 Hz, 3.2 Hz, 1H), 2.38-2.31 (m, 1H), 2.08-1.95 (m, 4H), 1.78-1.70 (m, 2H), 1.67 (d, J = 0.6 Hz, 3H), 1.66-1.61 (m, 1H), 1.54 (d, J = 10.1 Hz, 2H), 1.47 (dd, J = 5.0 Hz, 7.0 Hz, 1H), 0.90-0.81 (m, 1H); \(^13\)C NMR (CDCl\(_3\)) \( \delta \) 149.5(C4), 138.1(C4), 127.7(CH), 107.9(CH\(_2\)), 69.8(C4), 47.7(CH), 38.3(CH\(_2\)), 36.1(CH\(_2\)), 30.9(CH\(_2\)), 23.4(CH\(_3\)), 23.3(CH\(_3\)), 20.3(CH\(_2\)); HRMS (EI) m/z calcd for C\(_{12}\)H\(_{18}\)O (M\(^+\)) 178.13576, found}
178.13841; ee determined using a ChiralPak AS column, eluent: 99/1 hexanes/i-PrOH, 1 mL/min, \( T_{r1} \): 6.2 min, \( T_{r2} \): 6.9 min.

**Compound 88, 1-(1-Iodo-vinyl)-naphthalene**

![Chemical structure](image)

To a solution of 1-B-iodo-9-BBN (2.0 mL, 2.0 mmol, 1.0M in hexanes) in DCM (30 mL) cooled to 0°C was added a solution of 1-ethynyl-naphthalene (249.4 mg, 1.64 mmol) in DCM (5 mL) via canula. The mixture was stirred for 15 hrs at room temperature. Acetic acid (2.0 mL) was added to the solution and the mixture was stirred for 1 hr. A solution of NaOH 2N (30 mL) was then slowly added to the mixture, followed by the addition of \( \text{H}_2\text{O}_2 \) 30% in water (4.0 mL) and the mixture was stirred for 30 min. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were washed with water, a saturated aqueous solution of NaHCO\(_3\) and a saturated aqueous solution of Na\(_2\)SO\(_4\). The organic phase was dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (0.5% ethyl acetate in 99.5% hexanes) to give 88 (294.0 mg, 69%) as a colorless oil. IR (neat) 3052 (w), 2923 (w), 1622 (w), 1507 (w), 1170 (w), 906 (m), 800 (m), 775 (s), 600 (m); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 8.25 (dd, \( J = 0.5 \) Hz, 8.4 Hz, 1H), 7.90 (dd, \( J = 0.5 \) Hz, 8.2 Hz, 1H), 7.85 (d, \( J = 8.2 \) Hz, 1H), 7.66-7.60 (m, 1H), 7.57-7.51 (m, 2H), 7.43 (dd, \( J = 7.3 \) Hz, 8.1 Hz, 1H), 6.40 (dd, \( J = 0.4 \) Hz, 1.2 Hz, 1H), 6.36 (dd, \( J = 0.4 \) Hz, 1.2 Hz, 1H); \(^13\)C NMR (CDCl\(_3\)) \( \delta \) 141.4(C4), 133.5(C4), 131.0(CH\(_2\)), 129.7(C4), 128.8(CH), 128.1(CH), 126.3(CH), 126.1(CH), 125.6(CH), 125.3(CH), 125.1(CH), 102.3(C4); HRMS (EI) m/z calcd for C\(_{12}\)H\(_9\)I (M\(^+\)) 279.97490, found 279.97571.

**Compound 91, 6-Isopropenyl-3-methyl-1-(1-trifluoromethyl-vinyl)-cyclohex-2-enol**

![Chemical structure](image)

To a solution of 2-bromo-3,3,3-trifluoro-propene (190.2 mg, 1.09 mmol) in Et\(_2\)O (1.2 mL) at -105°C was added, in 4 aliquots, n-BuLi (0.43 mL, 1.087 mmol, dissolved in 0.6 ml Et\(_2\)O) immediately thereafter a solution of ketone 39 dissolved in Et\(_2\)O (0.4 mL) was added via canula and the mixture was stirred at -105°C for 120 min. The solution was slowly warmed up to room temperature and
quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 91 (100.3 mg, 41%) as a colorless oil. IR (neat) 3619 (w), 3500 (m), 3071 (w), 2936 (s), 2833 (m), 1638 (m), 1322 (s), 1166 (s), 1127 (s), 1069 (s), 952 (s); ¹H NMR (CDCl₃) δ 5.83 (d, J = 1.1 Hz, 1H), 5.73 (dd, J = 1.4 Hz, 2.9 Hz, 1H), 5.37 (s, 1H), 4.96 (t, J = 1.4 Hz, 1H), 4.77 (d, J = 0.9 Hz, 1H), 2.51 (dd, 2.9 Hz, 12.3 Hz, 1H), 2.16 (s, 1H), 2.10-1.99 (m, 2H), 1.95-1.87 (m, 1H), 1.73 (s, 3H), 1.70 (s, 3H), 1.62 (m, 1H); ¹³C NMR (CDCl₃) δ 146.1(C4), 144.0(C4, JCF = 25 Hz), 138.9(C4), 125.0(CH), 123.5(C4, JCF = 273 Hz), 120.7(CH₂, JCF = 6 Hz), 114.1(CH₂), 72.1(C4), 48.7(CH), 30.4(CH₂), 24.4(CH₂), 24.0(CH₃), 23.4(CH₃); HRMS (EI) m/z calcd for C₁₂H₁₄F₂O ([M-CH₃]⁺) 231.09967, found 231.0933; [α]D³⁰ +35.1° (c 1.42, CH₂Cl₂).

**Compound 92, 1-(1-Ethoxy-vinyl)-6-isopropenyl-3-methyl-cyclohex-2-enol**

![Chemical structure of Compound 92](image)

To a solution of ethyl vinyl ether (200 µL, 2.09 mmol) in THF (0.1 mL) at −78°C was added t-BuLi (0.66 mL, 1.05 mmol) and the mixture was stirred at −78°C for 30 min. The solution was warmed rapidly to 0°C and it was stirred for 5 min. Ketone 39 (35.2 mg, 0.234 mmol) dissolved in THF (1 mL) cooled to 0°C was added via canula into the solution of the lithiated compound and the solution was stirred at 0°C for 15 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 92 (42.8 mg, 82%) as a colorless oil (dr = 5:1). IR (neat) 3500 (m), 3077 (w), 2976 (s), 2833 (m), 1622 (s), 1446 (s), 1376 (s), 1270 (s), 1089 (s), 811 (s); ¹H NMR (CDCl₃) δ 5.30 (d, J = 1.0 Hz, 1H), 4.91 (m, 1H), 4.73 (m, 1H), 4.27 (dd, J = 0.8 Hz, 2.1 Hz, 1H), 3.98 (d, J = 2.1 Hz, 1H), 3.66 (q, J = 7.0 Hz, 2H), 2.53 (dd, J = 2.8 Hz, 12.9 Hz, 1H), 2.32 (s, 1H), 2.04-1.97 (m, 2H), 1.96-1.85 (m, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.52-1.47 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃) δ 166.7(C4), 147.5(C4), 138.8(C4), 125.8(CH), 112.3(CH2), 80.0(CH2), 71.8(C4), 62.9(CH₂), 47.7(CH), 30.8(CH₂), 85
24.5(CH₃), 24.3(CH₂), 23.5(CH₃), 14.4(CH₃); HRMS (EI) m/z calcd for C₁₄H₂₂O₂ (M⁺) 222.16198, found 222.15992.

**Compound 93, 6-Isopropenyl-3-methyl-1-(1-naphthalen-1-yl-vinyl)-cyclohex-2-enol**

![Structure of Compound 93](image)

To a solution of 1-(1-iodo-vinyl)-naphthalene 88 (66.0 mg, 0.253 mmol) in Et₂O (4 mL) at -78°C was added t-BuLi (0.31 mL, 0.507 mmol) and the mixture was stirred at -78°C for 10 min. Ketone 39 (30.1 mg, 0.200 mmol) dissolved in THF (1 mL) and cooled to -78°C was added via canula into the solution of the lithiated compound and the mixture was slowly warmed up. The reaction was quenched at -60°C with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give 93 (40.1 mg, 65%) as a colorless oil. IR (neat) 3500 (w), 3045 (w), 2929 (m), 1637 (w), 1448 (w), 1376 (w), 779 (s); ¹H NMR (CDCl₃) δ 8.15-8.12 (m, 1H), 7.82-7.78 (m, 1H), 7.76-7.73 (m, 1H), 7.47-7.36 (m, 4H), 5.76 (d, J = 1.6 Hz, 1H), 5.65 (s, 1H), 5.23 (d, J = 1.6 Hz, 1H), 4.92 (s, 1H), 4.85 (s, 1H), 2.63-2.59 (m, 1H), 2.07-1.83 (m, 4H), 1.76-1.70 (m, 7H); ¹³C NMR (CDCl₃) δ 152.5(C4), 146.6(C4), 138.8(C4), 137.2(C4), 133.7(C4), 132.9(C4), 128.3(CH), 128.0(CH), 127.3(CH), 127.1(CH), 125.7(CH), 125.4(CH), 125.3(CH), 124.6(CH), 118.2(CH₂), 113.7(CH₂), 75.5(C4), 48.6(CH), 29.6(CH₂), 24.8(CH₂), 24.1(CH₂), 23.4(CH₃); HRMS (EI) m/z calcd for C₂₂H₂₄O (M⁺) 304.18271, found 304.18105; [α]D²⁰ -41.3° (c 1.0, CH₂Cl₂).

**Compound 94, 6-Isopropenyl-1-[1-(4-methoxy-phenyl)-vinyl]-3-methyl-cyclohex-2-enol**

![Structure of Compound 94](image)

To a solution of 1-(1-iodo-vinyl)-4-methoxy-benzene (120.0 mg, 0.461 mmol) in Et₂O (4.0 mL) at -78°C was added t-BuLi (1.00 mL, 0.922 mmol) and the mixture was stirred at -78°C for 15 min. Ketone 39 (70.0 mg, 0.461 mmol) dissolved in Et₂O (1.5 mL) and cooled to -78°C was
added via canula into the solution of the lithiated compound and the mixture was stirred at –78°C for 20 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give 94 (70.1 mg, 53%) as a colorless oil. IR (neat) 3500 (w), 3080 (w), 2931 (m), 2837 (w), 1608 (m), 1509 (s), 1246 (s), 1178 (m), 1035 (m), 836 (m); ¹H NMR (CDCl₃) δ 7.32 (m, 2H), 6.78 (m, 2H), 5.55 (d, J = 1.6 Hz, 1H), 5.50 (d, J = 1.0 Hz, 1H), 5.18 (d, J = 1.6 Hz, 1H), 4.89 (t, J = 1.6 Hz, 1H), 4.69 (d, J = 1.0 Hz, 1H), 3.77 (s, 3H), 2.44 (dd, J = 3.0 Hz, 12.3 Hz, 1H), 2.08 (s, 1H), 2.02-1.84 (m, 3H), 1.78 (s, 3H), 1.62 (s, 3H), 1.56-1.47 (m, 1H); ¹³C NMR (CDCl₃) δ 158.6(C4), 154.8(C4), 147.0(C4), 138.1(C4), 133.6(C4), 129.3(2CH), 128.1(CH), 113.9(CH₂), 113.4(CH₂), 113.1(2CH), 73.8(C4), 55.1(CH), 47.1(CH₃), 30.7(CH₂), 24.7(CH₂), 24.3(CH₃), 23.5(CH₃); HRMS (EI) m/z calcd for C₁₉H₂₄O₂ (M⁺) 284.17763, found 284.17582.

**Compound 95, 6-Methyl-1-methylene-4-trifluoromethyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of compound 91 (20.9 mg, 0.0849 mmol) in toluene (18 mL) in a microwave cell was added TMEDA (128 µL, 0.849 mmol). The solution was degassed using N₂ and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (7% ethyl acetate in 93% hexanes) to give 95 (15.1 mg, 72%) as a colorless oil as the major product (dr = 8.5:1). IR (neat) 3500 (w), 3090 (w), 2928 (s), 2859 (m), 1733 (w), 1653 (w), 1266 (m), 1143 (m), 1118 (s), 946 (m); ¹H NMR (CDCl₃) δ 5.87 (t, J = 1.5 Hz, 1H), 4.95 (d, J = 1.5 Hz, 1H), 4.72 (d, J = 1.5 Hz, 1H), 2.45 (m, 1H), 2.27-2.19 (m, 1H), 2.14 (td, J = 4.8 Hz, 13.5 Hz, 1H), 2.05-1.97 (m, 4H), 1.84 (qd, J = 4.6 Hz, 13.2 Hz, 1H), 1.77-1.68 (m, 5H), 1.54 (s, 1H); ¹³C NMR (CDCl₃) δ 147.2(C4), 140.1(C4), 127.3(C4, J_CF = 280 Hz), 123.5(CH, J_CF = 2.5 Hz), 109.1(CH₂), 69.9(C4), 50.0(CH, J_CF = 22.9 Hz), 47.9(CH), 34.4(CH₂), 30.4(CH₂), 23.9(CH₃), 23.4(CH₂, J_CF = 3.6 Hz), 20.2(CH₂); HRMS (EI) m/z calcd for C₁₃H₁₁F₃O (M⁺) 246.12315, found
246.12338; [α]D \textsuperscript{20} -251.8° (c 0.71, CH₂Cl₂); ee determined by ChiralPak AS, eluent: 99/1 hexanes/i-PrOH, 1 mL/min, \textit{T}_{r(\text{major})}: 5.9 min, \textit{T}_{r(\text{minor})}: 7.2 min. Compound 95b was obtained as the minor product (1.7 mg, 8%). \textsuperscript{1}H NMR (CDCl₃) δ 5.53 (m, 1H), 4.96 (dd, \textit{J} = 1.6 Hz, 3.1 Hz, 1H), 4.70 (dd, \textit{J} = 1.5 Hz, 3.1 Hz, 1H), 2.49-2.41 (m, 2H), 2.37-2.02 (m, 4H), 1.77 (s, 1H), 1.69-1.61 (m, 1H), 1.51 (s, 1H).

**Compound 96, 4-Ethoxy-6-methyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of compound 92 (18.8 mg, 0.0846 mmol) in toluene (18.0 mL) in a microwave cell was added DBU (125 μL, 0.837 mmol). The solution was degassed using N₂ and it was heated in a microwave oven for 180 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 96 (4.9 mg, 26%) as a colorless oil as the major product (dr = 2.3:1). IR (neat) 3500 (w), 2932 (m), 1723 (m), 1613 (w), 1515 (m), 1249 (s); \textsuperscript{1}H NMR (CDCl₃) δ 5.38 (m, 1H), 4.88 (dd, \textit{J} = 1.6 Hz, 3.2 Hz, 1H), 4.62 (dd, \textit{J} = 1.6 Hz, 3.1 Hz, 1H), 3.64-3.54 (m, 1H), 3.50-3.40 (m, 1H), 3.31 (t, \textit{J} = 2.5 Hz, 1H), 2.49 (t, \textit{J} = 7.6 Hz, 1H), 2.32 (m, 1H), 2.16-2.02 (m, 3H), 1.92-1.84 (m, 1H), 1.76 (dq, \textit{J} = 2.6 Hz, 13.8 Hz, 1H), 1.71-1.65 (m, 5H), 1.52 (s, 1H), 1.15 (t, \textit{J} = 7.0 Hz, 3H); \textsuperscript{13}C NMR (CDCl₃) δ 149.7(C4), 139.1(C4), 126.5(CH), 107.6(CH₂), 79.7(CH), 72.2(C4), 64.8(CH₂), 41.6(CH), 30.7(CH₂), 30.4(CH₂), 26.6(CH₃), 23.6(CH₃), 20.0(CH₂), 15.6(CH₃); HRMS (EI) m/z calcd for C₁₄H₂₂O₂ (M⁺) 222.16198, found 222.15982; [α]D \textsuperscript{20} +171.8° (c 0.51, CH₂Cl₂); ee determined using a ChiralPak AS column, eluent: 99.8/0.2 hexanes/i-PrOH, 1 mL/min, \textit{T}_{r(\text{major})}: 8.1 min, \textit{T}_{r(\text{minor})}: 7.5 min. Compound 101, minor product (2.1 mg, 11%). IR (neat) 3400 (m), 2929 (s), 2866 (m), 1448 (m), 1376 (s), 1121 (s), 1094 (s), 947 (m); \textsuperscript{1}H NMR (CDCl₃) δ 5.82 (dd, \textit{J} = 1.7 Hz, 4.9 Hz, 1H), 4.88 (dd, \textit{J} = 1.5 Hz, 3.1 Hz, 1H), 4.68 (dd, \textit{J} = 1.5 Hz, 3.1 Hz, 1H), 3.74-3.64 (m, 1H), 3.49-3.39 (m, 1H), 3.15 (dd, \textit{J} = 4.6 Hz, 11.3 Hz, 1H), 2.40-2.28 (m, 1H), 2.08-1.96 (m, 3H), 1.93-1.74 (m, 3H), 1.73-1.65 (m, 5H), 1.21 (t, \textit{J} = 7.0 Hz, 3H), 0.91-0.73 (m, 1H); \textsuperscript{13}C NMR (CDCl₃) δ 147.8(C4), 138.1(C4),
124.0(CH), 107.9(CH), 81.7(CH), 71.4(C4), 65.2(CH2), 45.4(CH), 33.4(CH2), 30.7(CH2), 27.8(CH2), 23.6(CH3), 19.9(CH2), 15.6(CH3); HRMS (EI) m/z calcd for C14H22O2 (M+) 222.16198, found 222.16102; [α]D 20 ~ -50.6° (c 0.35, CH2Cl2).

**Compound 97, 7-Methyl-4-methylene-2,3,4,4a,5,6-hexahydro-1H-[1,1']-binaphthalenyl-8a-ol**

To a solution of compound 93 (19.4 mg, 0.0636 mmol) in toluene (20.0 mL) in a microwave cell was added DBU (95 µL, 0.636 mmol). The solution was degassed using N2 and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (12% ethyl acetate in 88% hexanes) to give 97 (14.8 mg, 76%) as a colorless oil. IR (neat) 3500 (w), 3045 (w), 2928 (s), 2854 (m), 1648 (w), 1087 (w), 940 (m), 780 (s); 1H NMR (CD6) δ 8.11-8.07 (m, 2H), 7.75-7.70 (m, 1H), 7.66-7.60 (m, 1H), 7.45-7.28 (m, 3H), 5.17 (s, 1H), 4.99 (s, 1H), 4.78 (s, 1H), 3.63 (d, J = 12.1 Hz, 1H), 2.40-2.31 (m, 2H), 2.22-2.15 (m, 2H), 1.81-1.61 (m, 3H), 1.46-1.25 (m, 2H), 1.18 (s, 3H), 0.97-0.88 (m, 1H); 13C NMR (CD6) δ 149.6(C4), 139.4(C4), 138.0(C4), 134.8(C4), 133.9(C4), 129.9(CH), 127.6(CH), 127.5(CH), 127.3(CH), 126.3(CH), 126.2(CH), 125.6(CH), 124.3(CH), 108.4(CH2), 72.2(C4), 49.6(CH), 46.7(CH), 37.3(CH2), 32.2(CH2), 31.2(CH2), 23.5(CH3), 21.3(CH2); HRMS (EI) m/z calcd for C22H24O (M+) 304.18271, found 304.18094; [α]D 20 ~ -163.0° (c 1.26, CH2Cl2); ee determined using a ChiralPak AS column, eluent: 99/1 hexanes/i-PrOH, 0.4 mL/min, T[major]: 12.8 min, T [minor]: 13.5 min.

**Compound 98, 4-(4-Methoxy-phenyl)-6-methyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of compound 94 (30.8 mg, 0.108 mmol) in toluene (18.0 mL) in a microwave cell was added DBU (160 µL, 1.08 mmol). The solution was degassed using N2 and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (9% ethyl acetate in 91% hexanes) to give 98 (25.9 mg, 84%) as a
colorless oil. IR (neat) 3500 (m), 3080 (w), 2931 (s), 2831 (m), 1611 (m), 1513 (s), 1441 (m), 1246 (s), 1179 (m), 1036 (m); $^1$H NMR (CDCl$_3$) $\delta$ 7.25 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 5.10 (d, $J = 1.4$ Hz, 1H), 4.96 (d, $J = 1.4$ Hz, 1H), 4.72 (d, $J = 1.3$ Hz, 1H), 3.78 (s, 3H), 2.61 (dd, $J = 4.0$ Hz, 12.7 Hz, 1H), 2.48-2.42 (m, 1H), 2.27-2.10 (m, 2H), 2.07-1.97 (m, 3H), 1.82-1.71 (m, 3H), 1.57 (s, 3H), 1.41 (s, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 158.1(C4), 149.3(C4), 138.7(C4), 134.4(C4), 130.5(CH), 125.4(2CH), 113.3(2CH), 107.9(CH$_2$), 71.3(C4), 55.1(CH), 52.2(CH), 48.2(CH$_3$), 36.1(CH$_2$), 31.3(CH$_2$), 30.6(CH$_2$), 23.5(CH$_3$), 20.5(CH$_2$); HRMS (El) m/z calcd for C$_{15}$H$_{22}$O$_2$ (M$^+$) 284.17763, found 284.17592; ee attempted to be determined using a ChiralPak AS column, eluent : 99.5/0.5 hexanes/i-PrOH, 1 mL/min, $T_r$: 9.1 min for both enantiomers.

**Compound 102, 2-Isopropenyl-5,5-dimethyl-cyclohexanone**

Cul (268.0 mg, 1.41 mmol) was dissolved in Et$_2$O (20 mL) and cooled to -10°C. MeLi (1.76 mL, 2.81 mmol) was added to the previous solution until the yellow color of the solution disappeared. A solution of ketone 39 (102.2 mg, 0.680 mmol) in Et$_2$O (5 mL) was added to the methylcuprate solution (still at -10°C) and the mixture was warmed slowly to room temperature. The reaction was quenched 45 min later with an aqueous solution of NH$_4$Cl/NH$_4$OH (pH = 8) saturated with sodium chloride and it was stirred for 60 min. The aqueous phase was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 102 (93.6 mg, 83%) as a colorless oil. IR (neat) 3071 (w), 2961 (s), 2871 (m), 1712 (s), 1648 (w), 1454 (m), 1371 (m), 881 (m); $^1$H NMR (CDCl$_3$) $\delta$ 4.92 (t, $J = 1.4$ Hz, 1H), 4.72 (s, 1H), 2.91 (dd, $J = 7.2$ Hz, 9.9 Hz, 1H), 2.20 (d, $J = 13.2$ Hz, 1H), 2.13 (dd, $J = 1.5$ Hz, 13.2 Hz, 1H), 2.03-1.89 (m, 2H), 1.73 (s, 3H), 1.70-1.61 (m, 2H), 1.03 (s, 3H), 0.89 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 210.8(C4), 143.3(C4), 112.8(CH$_2$), 57.3(CH), 54.9(CH$_2$), 37.8(CH$_2$), 36.7(C4), 31.2(CH$_3$), 27.5(CH$_2$), 25.8(CH$_3$), 21.2(CH$_3$); HRMS (El) m/z calcd for C$_{11}$H$_{18}$O (M$^+$) 166.13576, found 166.13562; $[\alpha]_D^{20}$ -30.2$^\circ$ (c 2.61, CH$_2$Cl$_2$).
Compound 103, 1,2-Diisopropenyl-5,5-dimethyl-cyclohexanol

To a solution of 2-bromopropene (15 µL, 0.144 mmol) in Et₂O (3 mL) at −78°C was added t-BuLi (0.20 mL, 0.288 mmol) and the mixture was stirred at −78°C for 15 min. Ketone 102 (20.4 mg, 0.123 mmol) dissolved in Et₂O (1 mL) and cooled to −78°C was added via canula into the solution of the lithiated compound and the mixture was stirred at −78°C for 60 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (3% ethyl acetate in 97% hexanes) to give 103 (16.2 mg, 63%) as a colorless oil. IR (neat) 3500 (w), 3084 (w), 2949 (s), 2865 (m), 1635 (m), 1448 (m), 1364 (m), 888 (m); ¹H NMR (CDCl₃) δ 4.97 (m, 1H), 4.87 (t, J = 1.3 Hz, 1H), 4.77 (t, J = 1.3 Hz, 1H), 4.76 (s, 1H), 2.23 (dd, J = 3.4 Hz, 12.7 Hz, 1H), 1.94 (dq, J = 3.1 Hz, 13.1 Hz, 1H), 1.83 (d, J = 2.0 Hz, 1H), 1.77 (t, J = 0.6 Hz, 3H), 1.70 (t, J = 0.6 Hz, 3H), 1.57-1.43 (m, 2H), 1.40-1.30 (m, 2H), 1.26-1.16 (m, 1H), 1.12 (s, 3H), 0.88 (s, 3H); ¹³C NMR (CDCl₃) δ 151.5(C4), 148.3(C4), 111.9(CH₂), 110.1(CH₂), 76.2(C4), 49.4(CH), 47.4(CH₂), 39.6(CH₂), 34.4(CH₃), 30.4(C4), 26.6(CH₃), 25.1(CH₃), 24.6(CH₂), 20.4(CH₃); HRMS (EI) m/z calcd for C₁₄H₂₄O (M⁺) 208.18272, found 208.1807; [α]D²⁰ -2.63° (c 0.70, CH₂Cl₂).

Compound 104, 2-Isopropenyl-5,5-dimethyl-1-(1-phenyl-vinyl)-cyclohexanol

To a solution of α-bromostyrene (35 µL, 0.254 mmol) in Et₂O (4 mL) at −78°C was added t-BuLi (0.30 mL, 0.508 mmol) and the mixture was stirred at −78°C for 10 min. Ketone 102 (21.1 mg, 0.127 mmol) dissolved in Et₂O (1.5 mL) and cooled to −78°C was added via canula into the solution of the metalated compound. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (7% ethyl acetate in 93% hexanes) to give 104 (35.2 mg, 100%) as a colorless oil. IR (neat) 3600 (w), 3080 (m), 2950 (s), 1636 (m), 1492 (m), 1364 (m), 1028 (m), 903 (s), 702 (s); ¹H NMR (CDCl₃) δ 7.29-7.22 (m, 5H),
5.33 (d, J = 1.2 Hz, 1H), 5.04 (d, J = 1.2 Hz, 1H), 4.91 (m, 1H), 4.85 (m, 1H), 2.35 (dd, J = 3.4 Hz, 12.7 Hz, 1H), 1.99 (dq, J = 3.4 Hz, 13.6 Hz, 1H), 1.81 (m, 3H), 1.67 (d, J = 1.1 Hz, 1H), 1.61 (dd, J = 2.2 Hz, 14.4 Hz, 1H), 1.55 (d, J = 14.4 Hz, 1H), 1.50-1.41 (m, 2H), 1.27-1.21 (m, 1H), 1.12 (s, 3H), 0.85 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 157.7(C4), 148.2(C4), 141.8(C4), 128.7(C2H), 127.7(C2H), 126.9(CH), 114.4(CH$_2$), 113.1(CH$_2$), 77.2(C4), 52.2(CH$_2$), 51.7(CH), 39.7(CH$_2$), 34.4(CH$_3$), 30.9(C4), 26.8(CH$_3$), 25.4(CH$_2$), 24.9(CH$_3$); HRMS (EI) m/z calcd for C$_{15}$H$_{26}$O (M$^+$) 270.19837, found 270.20729; [α]$_D^{20}$ -40.3° (c 3.94, CH$_2$Cl$_2$).

**Compound 105, 1-[3-(t-Butyl-diphenyl-silanyloxy)-1-methylene-propyl]-2-isopropenyl-5,5-dimethyl-cyclohexanol**

To a solution of t-Butyl-(3-iodo-but-3-enyloxy)-diphenyl-silane (154.1 mmol, 0.353 mmol) in Et$_2$O (5 mL) at −90°C was added t-BuLi (0.45 mL, 0.706 mmol) and the mixture was stirred at −90°C for 10 min. Ketone 102 (29.4 mg, 0.177 mmol) dissolved in Et$_2$O (1.5 mL) and cooled to −90°C was added via canula into the solution of the lithiated compound. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash chromatography (3% ethyl acetate in 97% hexanes) to give 105 (73.7 mg, 87%) as a colorless oil. IR (neat) 3541 (w), 3400 (w), 3072 (m), 2950 (s), 2859 (m), 1634 (w), 1473 (m), 1428 (m), 1363 (m), 1112 (s), 702 (s); $^1$H NMR (CDCl$_3$) δ 7.69-7.63 (m, 4H), 7.45-7.35 (m, 6H), 5.07 (s, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 4.72 (s, 1H), 3.85-3.68 (m, 2H), 2.46-2.36 (m, 1H), 2.28-2.18 (m, 1H), 2.14 (dd, J = 3.2 Hz, 12.8 Hz, 1H), 2.09 (s, 1H), 1.95 (dq, J = 2.8 Hz, 12.8 Hz, 1H), 1.68 (s, 3H), 1.49-1.44 (m, 2H), 1.40-1.17 (m, 3H), 1.12 (s, 3H), 1.06 (s, 9H), 0.86 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 153.1(C4), 148.1(C4), 135.5(4CH), 133.6(2C4), 129.6(2CH), 127.6(4CH), 112.1(CH$_2$), 109.8(CH$_2$), 76.4(C4), 64.5(CH$_2$), 50.8(CH), 48.2(CH$_2$), 39.6(CH$_2$), 35.2(CH$_2$), 34.4(CH$_3$), 30.5(C4), 26.9(3CH$_3$), 26.7(CH$_3$), 24.8(CH$_2$), 24.6(CH$_2$), 19.1(C4); HRMS (EI) m/z calcd for C$_{31}$H$_{46}$O$_2$Si (M$^+$) 476.31106, found 476.3111; [α]$_D^{20}$ +2.4° (c 1.04, CH$_2$Cl$_2$).
Compound 106, 4,6,6-Trimethyl-1-methylene-octahydro-naphthalen-4a-ol

To a solution of compound 103 (14.3 mg, 0.0686 mmol) in toluene (21.6 mL) in a microwave cell was added DBU (100 μL, 0.686 mmol). The solution was degassed using N₂ and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (2% ethyl acetate in 98% hexanes) to give 106 (9.8 mg, 69%) as a colorless oil. IR (neat) 3500 (w), 3077 (w), 2931 (s), 2869 (m), 1645 (w), 1455 (m), 999 (w), 894 (m), 532 (m); ¹H NMR (CDCl₃) δ 4.87 (d, J = 1.5 Hz, 1H), 4.68 (d, J = 1.5 Hz, 1H), 2.26-2.23 (m, 1H), 2.09-1.98 (dt, J = 4.9 Hz, 12.6 Hz, 1H), 1.88-1.83 (m, 1H), 1.77-1.63 (m, 2H), 1.59-1.50 (m, 2H), 1.50-1.36 (m, 2H), 1.36-1.15 (m, 4H), 1.05 (s, 3H), 0.88 (s, 3H), 0.83 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃) δ 150.1(C4), 108.4(CH₂), 74.2(C4), 50.3(CH), 47.3(CH₂), 42.4(CH), 39.1(CH₂), 36.2(CH₂), 34.4(CH₃), 32.5(CH₂), 30.6(C4), 26.9(CH₃), 20.8(CH₂), 14.5(CH₃); HRMS (EI) m/z calcd for C₁₄H₂₄O (M⁺) 208.18272, found 208.18347; [α]D²⁰ -17.5° (c 0.39, CH₂Cl₂). ee attempted to be determined using a ChiralPak AS column, eluent: 100% hexanes, 1 mL/min, Tᵣ: 4.7 min for both enantiomers.

Compound 107, 6,6-Dimethyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol

To a solution of compound 104 (8.8 mg, 0.0325 mmol) in toluene (18.0 mL) in a microwave cell was added TMEDA (49 μL, 0.325 mmol). The solution was degassed using N₂ and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (4% ethyl acetate in 96% hexanes) to give 107 (8.8 mg, 100%) as a white solid. IR (neat) 3550 (w), 3090 (w), 2930 (s), 2899 (m), 1645 (w), 1453 (m), 1363 (w), 955 (m), 898 (m), 701 (m); ¹H NMR (CDCl₃) δ 7.30-7.17 (m, 5H), 4.96 (d, J = 1.5 Hz, 1H), 4.78 (d, J = 1.5 Hz, 1H), 2.54 (dd, J = 3.8 Hz, 9.6 Hz, 1H), 2.46-2.40 (m, 1H), 2.19 (dt, J = 4.9 Hz, 13.2 Hz, 1H), 2.04-1.90 (m, 2H), 1.83-1.69 (m, 2H), 1.50-1.44 (m, 2H), 1.33 (s, 1H), 1.27-1.17 (m, 1H), 1.10 (d, J = 14.4 Hz, 1H), 1.04 (dd, J = 1.8 Hz, 14.4 Hz, 1H), 0.93 (s, 3H), 0.77 (s, 3H); ¹³C NMR (CDCl₃) δ 149.7(C4), 142.4(C4),
129.1(CH), 128.0(2CH), 126.3(2CH), 108.8(CH₂), 74.3(C₄), 55.5(CH), 50.6(CH),
48.7(CH₂), 39.1(CH₂), 36.4(CH₂), 34.2(CH₃), 31.0(CH₂), 30.6(C₄), 26.7(CH₃),
20.9(CH₂); HRMS (EI) m/z calc'd for C₁₉H₂₆O (M⁺) 270.19837, found 270.19718;
melting point : 80.1-82.6°C; [α]D⁰⁻ -42.1° (c 0.50, CH₂Cl₂); ee determined using a
ChiralPak AS column, eluent : 99.9/0.1 hexanes/i-PrOH, 1 mL/min, Tᵣ(major) : 5.6 min,
Tᵣ(minor) : 5.2 min.

**Compound 108, 4-(2-Hydroxy-ethyl)-6,6-dimethyl-1-methylene-octahydro-
naphthalen-4a-ol**

To a solution of compound 108b (18.9 mg, 0.0396 mmol) in THF (1.5
mL) cooled to 0°C was added a solution of TBAF solution (0.05 mL,
0.05 mmol). The mixture was stirred at 0°C for 90 min and it was passed through a pad
of silica. The residue was purified by flash chromatography (40% ethyl acetate in 60%
hexanes) to give 108 (9.5 mg, 100%) as a white solid. IR (neat) 3400 (m), 2932 (s), 2864
(m), 1647 (w), 1456 (w), 1028 (m), 955 (m), 498 (m); ¹H NMR (CDCl₃) 8 4.90 (dd, J =
1.6 Hz, 3.2 Hz, 1H), 4.71 (dd, J = 1.6 Hz, 2.8 Hz, 1H), 3.71-3.67 (m, 1H), 3.54 (m, 1H),
2.71 (s, 1H), 2.34 (dq, J = 2.4 Hz, 12.9 Hz, 1H), 2.08-2.02 (m, 1H), 1.95 (dd, J = 2.3 Hz,
14.2 Hz, 1H), 1.94-1.90 (m, 1H), 1.79-1.72 (m, 1H), 1.70-1.56 (m, 3H), 1.55 (s, 3H),
1.54-1.47 (m, 1H), 1.47-1.39 (m, 1H), 1.24-1.17 (m, 1H), 1.06 (d, J = 13.7 Hz, 1H), 1.05
(s, 3H), 0.89 (s, 3H); ¹³C NMR (CDCl₃) 8 149.8(C₄), 108.9(CH₂), 74.4(C₄), 59.7(CH₂),
50.5(CH), 47.0(CH₂), 45.4(CH), 38.9(CH₂), 36.2(CH₂), 34.4(CH₃), 32.1(CH₂), 30.6(C₄),
28.9(CH₂), 26.9(CH₃), 20.9(CH₂); HRMS (EI) m/z calc'd for C₁₉H₂₆O₂ (M⁺) 238.19328,
found 238.19519; melting point : 96.1-100.0°C; [α]D⁰⁻ -26.5° (c 0.717, CH₂Cl₂); ee
determined using a ChiralPak AS column, eluent : 85/15 hexanes/i-PrOH, 1 mL/min,
Tᵣ(major) : 6.4 min, Tᵣ(minor) : 5.1 min.

**Compound 108b, 4-[2-(t-Butyl-diphenyl-silyl-xyloxy)-ethyl]-6,6-dimethyl-1-
methylene-octahydro-naphthalen-4a-ol**

To a solution of compound 105 (20.8 mg, 0.0436 mmol) in toluene
(13.7 mL) in a microwave cell was added DBU (65 µL, 0.436 mmol).
The solution was degassed using N₂ and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (4% ethyl acetate in 96% hexanes) to give 108b (19.2 mg, 92%) as a colorless oil. IR (neat) 3500 (w), 3071 (w), 2931 (s), 2858 (s), 1646 (w), 1472 (m), 1428 (m), 1112 (s), 1089 (s), 702 (s); ¹H NMR (CDCl₃) δ 7.66-7.63 (m, 4H), 7.43-7.32 (m, 6H), 4.84 (d, J = 1.3 Hz, 1H), 4.66 (d, J = 1.3 Hz, 1H), 3.75-3.57 (m, 2H), 2.27-2.21 (m, 1H), 1.99-1.85 (m, 2H), 1.81-1.58 (m, 4H), 1.55 (s, 3H), 1.51-1.35 (m, 3H), 1.30-1.11 (m, 5H), 1.03 (s, 9H), 0.87 (s, 3H); ¹³C NMR (CDCl₃) δ 150.1(C4), 135.6(C4H), 134.0(2C4), 129.6(2CH), 127.6(C4H), 108.2(2CH₂), 74.6(C4), 62.4(CH₂), 50.5(CH), 47.2(CH₂), 44.3(CH₃), 39.0(CH₂), 36.1(CH₂), 34.4(CH), 31.7(CH₂), 30.6(C4), 29.5(CH₂), 27.0(CH₃), 26.9(3CH₃), 20.9(CH₂), 19.2(C4); HRMS (EI) m/z calcd for C₂₇H₅₅O₂Si ([M – iBu⁺) 419.24063, found 419.2395.

**Compound 109, 1-Ethynyl-6-isopropenyl-3-methyl-cyclohex-2-enol**

To a solution of ketone 39 (119.2 mg, 0.794 mmol) in Et₂O (8.0 mL) at 0°C was added ethynylimagnesium chloride (2.55 mL, 1.28 mmol). The mixture was slowly warmed to room temperature and stirred for 6 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (7% ethyl acetate in 93% hexanes) to give 109 (122.6 mg, 88%) as a colorless oil inseparable mixture of diastereomers (dr = 5:1). IR (neat) 3500 (w), 3305 (m), 2969 (m), 2933 (m), 2831 (w), 1638 (m), 1447 (m), 1376 (m), 1071 (s), 951 (s), 895 (m); ¹H NMR (CDCl₃) δ 5.60 (d, J = 1.0 Hz, 1H), 5.06 (m, 1H), 4.88 (d, J = 0.8 Hz, 1H), 2.45 (d, J = 0.8 Hz, 1H), 2.36 (dd, J = 2.7 Hz, 10.3 Hz), 2.33 (s, 1H), 2.08-1.95 (m, 5H), 1.92-1.76 (m, 1H), 1.71 (s, 3H), 1.64-1.52 (m, 1H); ¹³C NMR (CDCl₃) δ 146.6(C4), 138.8(C4), 124.3(CH), 113.9(CH₂), 88.2(C4), 71.4(CH), 65.2(C4), 50.5(CH), 30.7(CH₂), 25.3(CH₃), 23.4(CH₂), 23.3(CH₃); HRMS (EI) m/z calcd for C₁₁H₁₁O ([M-CH₃⁺) 161.09664, found 161.09629; [α]₂⁰ +91.8° (c 1.88, CH₂Cl₂); ee determined using a ChiralPak AS column, eluent: 99/1 hexanes/i-PrOH, 1 mL/min, Tₑ(major): 7.2 min, Tₑ(minor): 6.6 min..
Compound 110, 3-Allyloxy-3-ethynyl-4-isopropenyl-1-methyl-cyclohexene

To a solution of alkyne 109 (105.6 mg, 0.60 mmol) in THF/DMF (4.5/1.5 mL) at 0°C was added allyl bromide (210 μL, 2.43 mmol) followed by addition of NaH 60% in oil (34.5 mg, 0.863 mmol). The mixture was slowly warmed to room temperature and stirred for 15 hrs. Allyl bromide (100 μL, 1.16 mmol) and NaH (15.0 mg, 0.375 mmol) were added again and the reaction was quenched 5 hrs later with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (7% ethyl acetate in 93% hexanes) to give 110 (85.9 mg, 86%) as a colorless oil. IR (neat) 3297 (m), 3071 (w), 2936 (m), 2859 (m), 1667 (w), 1641 (m), 1448 (m), 1061 (s); ¹H NMR (CDCl₃) δ 5.94-5.82 (m, 1H), 5.64 (s, 1H), 5.23 (d, J = 17.3 Hz, 1H), 5.05 (d, J = 10.4 Hz, 1H), 4.91 (s, 2H), 4.17 (dd, J = 3.5 Hz, 12.4 Hz, 1H), 4.05 (dd, J = 2.2 Hz, 4.4 Hz, 1H), 2.47 (s, 1H), 2.37 (d, J = 10.4 Hz, 1H), 2.02 (m, 3H), 1.86 (s, 3S), 1.70 (s, 3H), 1.65-1.55 (m, 1H); ¹³C NMR (CDCl₃) δ 145.6(C4), 139.1(C4), 135.6(CH), 123.5(CH), 115.2(CH₂), 113.9(CH₂), 85.6(C4), 73.3(CH), 72.7(C4), 65.0(CH₂), 51.1(CH), 30.6(CH₂), 23.5(CH₃), 22.9(CH₂), 22.2(CH₃); [α]D²⁰ +122.2° (c 1.12, CH₂Cl₂); HRMS (EI) m/z calcd for C₁₄H₁₇O ([M-CH₃]⁺) 201.12794, found 201.12779.

Compound 111, 3-Allyloxy-4-isopropenyl-1-methyl-3-vinyl-cyclohexene

To a solution of alkyne 110 (39.4 mg, 0.182 mmol) in benzene (2 mL) at room temperature was added one drop of quinoline. A little quantity of Lindlar’s catalyst was added to the mixture and the solution was put under H₂ atmosphere. A small amount of Lindlar’s catalyst was added until the reduction of the alkyne began (apparition of a blue spot with higher Rₜ on TLC). The mixture was then stirred for 6 hrs under H₂ atmosphere. The solution was finally filtered through silica and the crude mixture was used for the next reaction without other purification. ¹H NMR (CDCl₃) δ 5.93-5.81 (m, 1H), 5.51 (d, J = 1.3 Hz, 1H), 5.25-5.18 (m, 1H), 5.14-5.00 (m,
3H), 4.80 (m, 1H), 4.67 (m, 1H), 3.86 (m, 1H), 2.21-1.98 (m, 4H), 1.81 (t, J = 0.7 Hz, 3H), 1.73 (s, 3H), 1.53-1.41 (m, 1H), 1.30-1.17 (m, 1H), 0.86 (t, J = 3.4 Hz, 1H).

**Compound 112, 4-Allyl-6-methyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of alcohol 111 (crude, assumed 0.182 mmol) in toluene (18 mL) in a microwave cell was added DBU (270 µL, 1.82 mmol). The solution was degassed using N₂ and it was heated in a microwave oven for 60 min at 200°C. The solution was concentrated and the residue was purified by flash chromatography (7% ethyl acetate in 93% hexanes) to give 112 (7.8 mg, 20% for 2 steps) as a colorless oil. IR (neat) 3500 (w), 3077 (w), 2932 (s), 2867 (m), 1650 (m), 1440 (m), 1380 (w), 1172 (w), 942 (s); ¹H NMR (CDCl₃) δ 5.83-5.74 (m, 2H), 5.01 (dq, J = 1.9 Hz, 17.0 Hz, 1H), 4.97 (m, 1H), 4.89 (dd, J = 1.5 Hz, 3.1 Hz, 1H), 4.64 (dd, J = 1.5 Hz, 2.9 Hz, 1H), 2.56 (m, 1H), 2.33 (dq, J = 2.3 Hz, 13.0 Hz, 1H), 2.03 (m, 3H), 1.97-1.90 (m, 1H), 1.86-1.81 (m, 1H), 1.76-1.63 (m, 5H), 1.55 (s, 1H), 1.52-1.46 (m, 1H), 1.34-1.24 (m, 2H); ¹³C NMR (CDCl₃) δ 149.5(C4), 139.1(C4), 138.2(CH₂), 124.2(CH₂), 115.5(CH), 107.7(CH), 71.5(C4), 48.4(CH), 44.9(CH), 35.8(CH₂), 33.7(CH₂), 30.7(CH₂), 29.6(CH₂), 23.8(CH₃), 20.5(CH₂); HRMS (EI) m/z calcd for C₁₃H₂₂O (M⁺) 218.16706, found 218.17295; ee determined by ChiralPak AS, eluent : 99/1 hexanes/PrOH, 1 mL/min, Tᵣ₁ : 4.9 min, Tᵣ₂ : 5.7 min.

**Compound 122, 6-Isopropenyl-3-methyl-1-(1-phenyl-pent-1-ethyl)-cyclohex-2-enol**

To a solution of (1-iodo-pent-1-ethyl)-benzene (182.3 mg, 0.670 mmol) in Et₂O (5.0 mL) at -78°C was added t-BuLi (0.77 mL, 1.34 mmol) and the mixture was stirred at -78°C for 10 minutes. Ketone 39 (81.0 mg, 0.540 mmol) dissolved in Et₂O (2.0 mL) and cooled to -78°C was added via canula into the solution of the lithiated compound and the mixture was stirred at -78°C for 20 min. The reaction was quenched at -78°C with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue
was purified by flash chromatography (4% ethyl acetate in 96% hexanes) to give 122 (96.7 mg, 60%) as a colorless oil, mixture of diastereomers (dr = 5:1). IR (neat) 3528 (w), 3078 (w), 2959 (s), 2930 (s), 2871 (m), 1636 (w), 1442 (m), 1376 (m), 1079 (m), 703 (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.33-7.20 (m, 3H), 7.18-7.13 (m, 2H), 5.89 (t, J = 7.4 Hz, 1H), 5.45 (s, 1H), 4.95 (t, J = 2.0 Hz, 1H), 4.85 (s, 1H), 2.32-2.26 (m, 1H), 2.08-1.93 (m, 1H), 1.87-1.71 (m, 7H), 1.68 (s, 3H), 1.59-1.52 (m, 1H), 1.35-1.28 (q, J = 7.3 Hz, 2H), 0.97-0.88 (m, 1H), 0.79 (t, J = 7.3 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 147.0(C4), 145.9(C4), 139.3(C4), 137.2(C4), 130.1(2CH), 129.2(CH), 128.2(CH), 127.4(2CH), 126.3(CH), 113.7(CH2), 74.3(C4), 47.8(CH3), 31.2(CH2), 30.1(CH2), 24.9(CH2), 24.6(CH), 23.4(CH3), 22.9(CH2), 13.8(CH3).

**Compound 126, 4-Acetyl-2-methyl-2-phenyl-heptanoic acid methyl ester**

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

To a solution of alcohol 122 (96.7 mg, 0.326 mmol) in dimethoxyethane (6 mL) was added KHMDS (325 mg, 1.63 mmol). The mixture was heated to 85°C for 5 hrs. The mixture was cooled to \(-78^\circ\text{C}\) and MeI (200 \text{uL}, 3.2 mmol) was added. The solution was allowed to warm to room temperature and stirred for 15 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give a yellow oil. The oil (77.9 mg) was dissolved in DCM (5 mL) and cooled to \(-78^\circ\text{C}\) and ozone was bubbled in the solution until a grey coloration persisted (15 min). The solution was warmed to room temperature while a stream of N\(_2\) was bubbled in the solution and it was stirred for 10 min. The solution was cooled to \(0^\circ\text{C}\) and Pd on charcoal (50 mg) was added to the mixture. The mixture was put under 1 atmosphere of H\(_2\) at room temperature and it was stirred for 20 hrs. The mixture was filtered through a pad of celite. The residue was purified by flash chromatography (20% ethyl acetate in 80% hexanes) to give 126 (11.3 mg, 12.5% for 3 steps) as a colorless oil. IR (neat) 3058 (w), 2992 (m), 2962 (m) 2878 (w), 1722 (s), 1362 (m), 1229 (s), 1182 (m); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.44-7.40 (m, 2H), 7.32-7.17 (m, 3H), 3.61 (s, 3H), 3.23-3.19 (m, 1H), 2.07 (d, J = 5.3
Hz, 2H), 1.83 (s, 3H), 1.47 (s, 3H), 1.35-1.14 (m, 4H), 0.87 (t, \( J = 6.8 \text{ Hz} \), 3H); \(^{13}\text{C NMR (CDCl}_3\)) \( \delta \) 207.6(C4), 175.8(C4), 141.8(C4), 128.4(2CH), 127.1(CH), 126.9(2CH), 53.9(C4), 52.1(CH3), 45.6(CH2), 39.7(CH), 36.4(CH2), 29.9(CH3), 21.5(CH2), 16.3(CH3), 14.4(CH3); HRMS (EI) m/z calcld for \( \text{C}_17\text{H}_{26}\text{O}_3 \) (M\(^+\)) 276.17255, found 276.16854.

4.1.3 Compounds Relative to Chapter 3

**Compound 142, 1-Ethynyl-2-(1-hydroxymethyl-vinyl)-cyclohexanol**

![Chemical Structure](image)

To a solution of ketone 141 (1.50 g, 10.8 mmol) in ether (100 mL) at 0°C was added dropwise ethynylmagnesium bromide (26 mL, 13 mmol). The mixture was warmed to room temperature and allowed to stir for 3 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give a mixture of diastereomer (dr = 1.5:1) as a yellow oil. The oil (450 mg) was dissolved in DCM (40 mL) at room temperature and SeO\(_2\) (0.205 g, 1.85 mmol) was added to the mixture, followed by \( t\)-BuOOH (2.0 mL, 14.5 mmol). After 48 hrs, SeO\(_2\) (0.201 g, 1.81 mmol) was added and 24 hrs later, \( t\)-BuOOH (1.0 mL, 7.3 mmol) was added. The reaction was quenched 48 hrs later with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the organic layers were combined and were washed with Na\(_2\)CO\(_3\), water and a saturated solution of sodium chloride. The combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (12% ethyl acetate in 88% hexanes) to give 142 (296.0 mg, 15% for 2 steps), the major diastereomer, as a white solid. IR (neat) 3200 (w), 2927 (m), 2847 (w), 1654 (w), 1264 (m), 1129 (m), 1071 (w), 1048 (s), 971 (m); \(^1\text{H NMR (CDCl}_3\)) \( \delta \) 5.17 (s, 1H), 5.06 (s, 1H), 4.41 (s, 1H), 4.13 (s, 1H), 2.87 (s, 1H), 2.41 (s, 1H), 2.34 (dd, \( J = 3.4 \text{ Hz}, 12.9 \text{ Hz}, 1\text{H} \)), 2.14-2.06 (m, 1H), 1.87-1.24 (m, 3H), 1.50-
1.17 (m, 4H); $^{13}$C NMR (CDCl$_3$) δ 148.5(C4), 117.4(CH$_2$), 88.5(C4), 71.8(C4), 67.6(CH), 64.8(CH$_2$), 52.4(CH), 39.5(CH$_2$), 26.0(CH$_2$), 25.6(CH$_2$), 20.4(CH$_2$); HRMS (EI) m/z calcd for C$_{11}$H$_{14}$O ([M-H$_2$O]$^+$) 162.10447, found 162.1050; mp 85.6-87.1°C.

Compound 162, the minor diastereomer, was also obtained as a white solid (197.0 mg, 10% for 2 steps). IR (neat) 3300 (m), 2934 (s), 2859 (m), 1651 (w), 1445 (w), 1124 (w), 1064 (m), 1004 (w), 906 (w); $^1$H NMR (CDCl$_3$) δ 5.25 (d, J = 0.9 Hz, 1H), 5.19 (s, 1H), 4.36 (s, 1H), 4.18 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 12.4 Hz, 1H), 3.18 (s, 1H), 2.49 (s, 1H), 2.18-2.05 (m, 2H), 1.77-1.47 (m, 6H), 1.32-1.13 (m, 1H); $^{13}$C NMR (CDCl$_3$) δ 148.2(C4), 116.0(CH$_2$), 85.2(C4), 74.7(CH), 72.0(C4), 67.4(CH$_2$), 51.7(CH), 41.3(CH$_2$), 30.0(CH$_2$), 25.7(CH$_2$), 23.7(CH$_2$); HRMS (EI) m/z calcd for C$_{11}$H$_{16}$O$_2$ (M$^+$) 180.11503, found 180.11467.

**Compound 142b, 2-(1-Allyloxyethyl-vinyl)-1-ethynyl-cyclohexanol**

To a solution of diol 142 (96.8 mg, 0.537 mmol) in a mixture of TFH/DMF (5/1.7 mL) was added sodium hydride 60% in oil (23.0 mg, 0.575 mmol) at 0°C. After 10 min, allyl bromide (55 μL, 0.636 mmol) was added to the mixture. The solution was stirred at 0°C for 1 hr. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash chromatography (30% diethyl ether in 70% hexanes) to give 142b (99.8 mg, 84%) as a colorless oil. IR (neat) 3306 (s), 3300 (m), 3079 (m), 2936 (s), 2857 (s), 1644 (m), 1446 (m), 1351 (m), 1144 (m), 1070 (s), 977 (s), 922 (s), 648 (m); $^1$H NMR (CDCl$_3$) δ 5.92-5.79 (m, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.17-5.13 (m, 3H), 4.48 (s, 1H), 4.11-4.06 (m, 2H), 3.91-3.78 (m, 2H), 2.35-2.27 (m, 2H), 2.10-2.04 (m, 1H), 1.83-1.50 (m, 4H), 1.48-1.13 (m, 3H); $^{13}$C NMR (CDCl$_3$) δ 144.8(C4), 133.6(CH), 119.6(CH$_2$), 117.7(CH$_2$), 88.5(C4), 71.5(CH$_2$), 71.2(C4), 70.4(CH$_2$), 67.3(CH), 52.9(CH), 39.4(CH$_2$), 25.7(2CH$_2$), 20.3(CH$_2$); HRMS (EI) m/z calcd for C$_{11}$H$_{14}$O ([M-C$_3$H$_6$O]$^+$) 162.10447, found 162.1061.
**Compound 143, 1-Allyloxy-2-(1-allyloxyethyl-vinyl)-1-ethynyl-cyclohexane**

To a solution of diol 142 (36.7 mg, 0.204 mmol) in a mixture of TFH/DMF (3/1 mL) was added allyl bromide (150 µL, 1.22 mmol). After 5 min, sodium hydride 60% in oil (34.0 mg, 0.85 mmol) was added slowly to the mixture and it was stirred for 1 hr. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were washed over MgSO_4_, filtered and concentrated. The residue was purified by flash chromatography (8% ethyl acetate in 92% hexanes) to give 143 (52.8 mg, 100%) as a colorless oil. IR (neat) 3304 (m), 3081 (w), 2936 (s), 2857 (s), 1646 (w), 1447 (m), 1139 (m), 1095 (m), 1060 (m), 919 (m); ^1_H NMR (CDCl_3) δ 5.97-5.83 (m, 2H), 5.31-5.27 (m, 1H), 5.25-5.21 (m, 1H), 5.19-5.17 (m, 2H), 5.15-5.06 (m, 2H), 4.16-4.09 (m, 2H), 4.05-3.86 (m, 4H), 2.40 (s, 1H), 2.28 (dd, J = 3.5 Hz, 12.7 Hz, 1H), 2.24-2.20 (m, 1H), 1.84 (dd, J = 9.1 Hz, 12.7 Hz, 1H), 1.74-1.63 (m, 1H), 1.53-1.19 (m, 5H); ^13_C NMR (CDCl_3) δ 146.4(C4), 135.3(CH), 135.0(CH), 116.5(CH_2), 115.2(CH_2), 113.9(CH_2), 84.9(C4), 73.8(C4), 73.8(CH), 73.2(CH_2), 70.8(CH_2), 64.1(CH_2), 51.0(CH), 35.4(CH_2), 27.0(CH_2), 25.8(CH_2), 20.4(CH_2); HRMS (EI) m/z calcld for C_{14}H_{19}O_2 ([M-C_3H_5]^+) 219.13851, found 219.13953.

**Compound 144, 7,10-Diallyl-11-oxa-tricyclo[5.3.2.0^1,6]dodec-9-en-12-ol**

To a solution of compound 143 (32.1 mg, 0.123 mmol) in toluene (18 mL) in a microwave cell was added DBU (50 µL, 0.34 mmol).

The solution was degassed using argon and it was heated in a microwave oven for 60 min at 210°C. The solution was concentrated and the residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 144 and 144b (mixture of diastereomers, 20.2 mg, 63% for mixture) as a colorless oil. 144, major diastereomer, IR (neat) 3400 (m), 3075 (m), 3003 (m), 2932 (s), 2859 (m), 1640 (m), 1439 (m), 1101 (m), 990 (s), 912 (s), 812 (m); ^1_H NMR (CDCl_3) δ 5.87-5.68 (m, 2H), 5.40-5.38 (m, 1H), 5.22 (d, J = 8.7 Hz, 1H), 5.09-4.94 (m, 4H), 3.02 (d, J = 8.7 Hz, 1H),
2.89-2.60 (m, 2H), 2.32-2.01 (m, 4H), 2.00-1.90 (m, 2H), 1.84-1.02 (m, 7H); $^{13}$C NMR (CDCl$_3$) δ 144.9(C4), 137.0(CH), 134.7(CH), 123.5(CH), 117.4(CH$_2$), 116.1(CH$_2$), 105.7(CH), 80.4(C4), 49.0(C4), 48.9(CH), 37.3(CH$_2$), 35.7(CH$_2$), 32.7(CH$_2$), 29.4(CH$_2$), 24.4(CH$_2$), 23.9(CH$_2$), 21.0(CH$_2$); HRMS (EI) calcd for C$_{17}$H$_{22}$O ([M-H$_2$O]$^+$) 242.17489, found 242.17061. 144b, minor diastereomer, IR (neat) 3400 (m), 3075 (m), 3003 (m), 2932 (s), 2859 (m), 1640 (m), 1439 (m), 1101 (m), 990 (s), 912 (s), 812 (m); $^1$H NMR (CDCl$_3$) δ 5.87-5.68 (m, 2H), 5.29-5.24 (m, 1H), 5.22 (d, J = 8.7 Hz, 1H), 5.09-4.94 (m, 4H), 3.36 (d, J = 4.6 Hz, 1H), 2.89-2.60 (m, 2H), 2.32-2.01 (m, 4H), 2.00-1.90 (m, 2H), 1.84-1.02 (m, 7H); $^{13}$C NMR (CDCl$_3$) δ 143.6(C4), 137.2(CH), 135.4(CH), 122.4(CH), 117.3(CH$_2$), 115.9(CH$_2$), 104.1(CH), 80.6(C4), 49.0(CH), 46.3(C4), 38.1(CH$_2$), 35.4(CH$_2$), 32.7(CH$_2$), 29.2(CH$_2$), 24.6(CH$_2$), 23.8(CH$_2$), 21.1(CH$_2$); HRMS (EI) m/z calcd for C$_{17}$H$_{22}$O ([M-H$_2$O]$^+$) 242.17489, found 242.17061.

**Compound 145, 5,8-Diallyl-8-hydroxymethyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol**

To a solution of lactol 144 (20.2 mg, 0.077 mmol) in THF (2 mL) at room temperature was added LiAlH$_4$ (10 mg). The mixture was stirred for 2 hrs and then cooled to 0°C. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in 80% hexanes) to give 145 (20.2 mg, 100%) as a white solid, from which a X-ray was obtained (see on figure 32, page 68).

**Compound 152, 2-(1-allyloxymethyl-vinyl)-1-ethynyl-1-prop-2-ynyloxy-cyclohexane**

To a solution of alcohol 142b (99.8 mg, 0.453 mmol) in a mixture of TFH/DMF (3/1 mL) was added sodium hydride 60% in oil (23.0 mg, 0.575 mmol) at room temperature. After 10 min, propargyl bromide (200 µL, 1.79 mmol, 80% in toluene) was added to the mixture. After 3 hrs, sodium
hydride (11.5 mg, 0.288 mmol) and propargyl bromide (100 μL, 0.90 mmol) were added. The mixture was stirred for 3 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (8% diethyl ether in 92% hexanes) to give 152 (106.0 mg, 91%) as a colorless oil; IR (neat) 3303 (m), 2931 (s), 2856 (m), 1646 (w), 1447 (w), 1258 (w), 1139 (m), 1094 (s), 1060 (s), 919 (m); ¹H NMR (CDCl₃) δ 5.27-5.12 (m, 1H), 5.96-5.77 (m, 1H), 5.18 (s, 2H), 5.14-5.11 (m, 1H), 4.29-4.09 (m, 3H), 3.99-3.93 (m, 3H), 2.46 (s, 1H), 3.46 (t, J = 2.4 Hz, 1H), 2.29-2.17 (m, 2H), 1.89-1.64 (m, 2H), 1.60-1.42 (m, 4H), 1.32-1.26 (m, 1H); ¹³C NMR (CDCl₃) δ 146.1(C4), 135.0(CH), 116.5(CH₂), 114.2(CH₂), 84.0(C4), 80.7(C4), 75.1(C4), 74.9(CH), 73.2(CH), 73.1(CH₂), 70.7(CH₂), 51.9(CH), 50.8(CH₂), 35.7(CH₂), 26.9(CH₂), 25.7(CH₂), 20.4(CH₂); HRMS (EI) m/z calcd for C₁₇H₂₂O₂ ([M-C₃H₃]⁺) 217.1620, found 217.1203.

**Compound 153, 7-Allyl-10-propa-1,2-dietyl-11-oxa-tricyclo[5.3.2.01,6]dodec-9-en-12-ol**

To a solution of compound 152 (29.9 mg, 0.116 mmol) in toluene (18 mL) in a microwave cell was added triethylamine (200 μL, 1.43 mmol). The solution was degassed using N₂ and the solution was heated in a microwave oven for 60 min at 150°C. The solution was concentrated and the residue was purified by flash chromatography (15% ethyl acetate in 85% hexanes) to give 153 and 153b (mixture of diastereomers, 9.0 mg, 30% for the mixture) as a colorless oil. 153 major diastereomer, ¹H NMR (CDCl₃) δ 5.85-5.64 (m, 3H), 5.11-5.03 (m, 2H), 4.88 (s, 1H), 4.86 (s, 1H), 2.69-2.64 (m, 1H), 2.48-2.08 (m, 4H), 2.02-1.95 (m, 1H), 1.81-1.67 (m, 2H), 1.67-1.54 (m, 2H), 1.53-1.31 (m, 3H), 1.23-1.03 (m, 2H); ¹³C NMR (CDCl₃) δ 209.6(C4), 140.1(C4), 134.6(CH), 125.7(CH), 117.6(CH₂), 105.7(CH), 89.2(CH), 80.0(C4), 76.6(CH₂), 49.1(CH), 48.9(C4), 37.3(CH₂), 33.0(CH₂), 30.6(CH₂), 24.2(CH₂), 23.9(CH₂), 21.1(CH₂). 153b minor diastereomer, ¹H NMR (CDCl₃) δ 5.85-5.64 (m, 3H), 5.26 (s, 1H), 5.23 (s, 1H), 5.11-5.03 (m, 2H), 2.69-2.64 (m, 1H), 2.48-2.08 (m, 4H), 2.02-1.95 (m, 1H), 1.81-1.67 (m, 2H), 1.67-1.54 (m, 2H), 1.53-1.31 (m, 3H), 1.23-1.03 (m,
2H); \(^{13}C\) NMR (CDCl\(_3\)) \(\delta\) 209.6(C4), 139.0(C4), 135.1(CH), 124.6(CH), 117.6(CH\(_2\)), 104.3(CH), 89.2(CH), 80.3(C4), 76.6(CH\(_2\)), 48.9(C4), 46.4(CH), 38.4(CH\(_2\)), 35.3(CH\(_2\)), 30.3(CH\(_2\)), 24.5(CH\(_2\)), 23.9(CH\(_2\)), 21.2(CH\(_2\)).

**Compound 154, 2-(1-Hydroxymethyl-vinyl)-1-[3-(4-methoxy-benzylxyo)-prop-1-ylnyl]-cyclohexanol**

To a solution of compound 154b (338.6 mg) in DCM (11 mL) at room temperature was added SeO\(_2\) (60.2 mg, 0.538 mmol), followed by \(t\)-BuOOH (0.60 mL, 4.32 mmol). After 24 hrs, \(t\)-BuOOH (0.30 mL, 2.16 mmol) was added. The reaction was quenched 48 hrs later with a saturated aqueous solution of ammonium chloride, extracted with ethyl acetate (3X). The combined organic layers were washed with an aqueous solution of Na\(_2\)CO\(_3\), water and a saturated aqueous solution of sodium chloride. The organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (35% ethyl acetate in 65% hexanes) to give 154 (234.2 mg, 66%) as a colorless oil. IR (neat) 3300 (w), 2934 (s), 2855 (m), 1612 (w), 1514 (s), 1172 (m), 1072 (m), 975 (w); \(^1H\) NMR (CDCl\(_3\)) \(\delta\) 7.26-7.22 (m, 2H), 6.88-6.83 (m, 2H), 5.17-5.16 (m, 1H), 5.07-5.06 (m, 1H), 4.47 (s, 2H), 4.12 (s, 2H), 3.78 (s, 3H), 2.36 (dd, \(J = 3.4\) Hz, 12.8 Hz, 1H), 2.12-2.02 (m, 1H), 1.87-1.64 (m, 4H), 1.62-1.38 (m, 3H), 1.31-1.21 (m, 2H); \(^{13}C\) NMR (CDCl\(_3\)) \(\delta\) 159.5(C4), 149.1(C4), 129.7(2CH), 129.4(C4), 116.9(CH\(_2\)), 113.8(2CH), 91.2(C4), 79.5(C4), 71.0(CH\(_2\)), 67.7(C4), 65.0(CH\(_2\)), 57.0(CH\(_2\)), 55.2(CH), 52.4(CH\(_3\)), 39.7(CH\(_2\)), 26.2(CH\(_2\)), 25.7(CH\(_2\)), 20.5(CH\(_2\)).

**Compound 154b, 2-Isopropenyl-1-[3-(4-methoxy-benzylxyo)-prop-1-ylnyl]-cyclohexanol**

A solution of dry CeCl\(_3\) (255.0 mg, 1.03 mmol) in THF (4 mL) was stirred for 6 hrs at room temperature to produce a milky solution. The ketone 141 (49.2 mg, 0.356 mmol) dissolved in THF (2 mL) was added to the mixture via canula and it was stirred for 6 hrs. The mixture was cooled to -78°C and a solution of propargyl alcohol protected with a \(p\)-methoxybenzyl (191.9 mg,
1.089 mmol) in THF (2 mL) at -78°C pretreated with n-BuLi (0.506 mL, 1.089 mmol) and cooled to -78°C was added via canula. The mixture was stirred at -78°C for 15 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in 85% hexanes) to give 154b (43.7 mg, 39%) as a colorless oil. IR (neat) 3500 (w), 2935 (s), 2855 (m), 1612 (w), 1513 (m), 1249 (s), 1172 (w), 1073 (m). ¹H NMR (CDCl₃) δ 7.27-7.22 (m, 2H), 6.88-6.83 (m, 2H), 4.99-4.97 (m, 1H), 4.84-4.83 (m, 1H), 4.48 (s, 2H), 4.13 (s, 2H), 3.78 (s, 3H), 2.23-2.11 (m, 3H), 1.97 (s, 3H), 1.75-1.39 (m, 7H), 7.26-7.22 (m, 2H). ¹³C NMR (CDCl₃) δ 159.7(C4), 148.2(C4), 129.7(CH), 129.5(C4), 113.8(CH), 112.4(CH₂), 91.2(C4), 79.1(C4), 71.0(CH₂), 67.2(C4), 57.0(CH₂), 55.3(CH), 52.5(CH₃), 39.8(CH₂), 26.7(CH₂), 25.8(CH₃), 25.7(CH₂), 20.5(CH₂). HRMS (EI) m/z calcd for C₂₀H₂₆O₃ ([M]⁺) 314.1882, found 314.1878.

**Compound 154c**, 2-(1-Allyloxymethyl-vinyl)-1-[3-(4-methoxy-benzyl)-prop-1-ynyl]-cyclohexanol

To a solution of diol 157 (127.9 mg, 0.387 mmol) in a mixture of TFH/DMF (3/1 mL) was added sodium hydride 60% in oil (16.3 mg, 0.408 mmol) at 0°C. After 10 min, allyl bromide (35 μL, 0.405 mmol) was added to the mixture. The solution was stirred for 1 hr while warming to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (20% ethyl acetate in 80% hexanes) to give 154c (123.0 mg, 86%) as a colorless oil. IR (neat) 3400 (w), 3080 (w), 2934 (s), 2854 (m), 1613 (m), 1514 (s), 1249 (s), 1172 (m), 1072 (s); ¹H NMR (CDCl₃) δ 7.24 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.94-5.81 (m, 1H), 5.30-5.23 (m, 1H), 5.19-5.15 (m, 3H), 4.51-4.48 (m, 3H), 4.16-4.08 (m, 4H), 3.94-3.82 (m, 2H), 3.77 (s, 3H), 2.40 (dd, J = 3.3 Hz, 12.8 Hz, 1H), 2.14-2.07 (m, 1H), 1.88-1.71 (m, 3H), 1.67-1.63 (m, 1H), 1.53-1.24 (m, 3H); ¹³C NMR (CDCl₃) δ 159.2(C4), 145.2(C4), 133.7(CH), 129.7(2CH), 129.6(C4),
119.6(\(\text{CH}_2\)), 117.7(\(\text{CH}_2\)), 113.7(\(2\text{CH}_2\)), 91.3(\(\text{C}_4\)), 79.3(\(\text{C}_4\)), 71.6(\(\text{CH}_2\)), 70.7(\(\text{CH}_2\)), 70.5(\(\text{CH}_2\)), 67.6(\(\text{C}_4\)), 57.0(\(\text{CH}_2\)), 55.2(\(\text{CH}_3\)), 53.1(\(\text{CH}\)), 39.6(\(\text{CH}_2\)), 25.8(\(\text{CH}_2\)), 25.8(\(\text{CH}_2\)), 20.5(\(\text{CH}_2\)).

**Compound 155**, 1-{3-[1-Allyloxy-2-(1-allyloxyethyl-vinyl)-cyclohexyl]-prop-2-nyloxyxmethyl}-4-methoxy-benzene

To a solution of diol 154 (98.3 mg, 0.298 mmol) in a mixture of TFH/DMF (6/2 mL) was added allyl bromide (210 \(\mu\text{L}\), 1.71 mmol).

After 5 min, sodium hydride 60% in oil (52.3 mg, 1.31 mmol) was slowly added to the previous solution and it was stirred for 1 hr. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (12% diethyl ether in 88% hexanes) to give 155 (101.3 mg, 83%) as a colorless oil.

IR (neat) 2928 (s), 2855 (s), 1613 (m), 1460 (w), 1250 (m), 1079 (m), 918 (w); \(^1\text{H}\) NMR (CDCl\(_3\)) \(\delta\) 7.25 (d, \(J = 8.6 \text{ Hz}\), 2H), 6.86 (d, \(J = 8.6 \text{ Hz}\), 2H), 5.99-5.83 (m, 2H), 5.32-5.22 (m, 2H), 5.20 (s, 2H), 5.15-5.08 (m, 2H), 4.48 (s, 2H), 4.18-4.11 (m, 2H), 4.13 (s, 2H), 4.09-3.89 (m, 4H), 3.78 (s, 3H), 2.32 (dd, \(J = 3.4 \text{ Hz}, 12.8 \text{ Hz}\), 1H), 2.24-2.18 (m, 1H), 1.95-1.81 (m, 1H), 1.74-1.70 (m, 1H), 1.53-1.41 (m, 4H), 1.37-1.19 (m, 1H); \(^1\text{C}\) NMR (CDCl\(_3\)) \(\delta\) 159.3(\(\text{C}_4\)), 146.7(\(\text{C}_4\)), 135.4(\(\text{CH}\)), 135.0(\(\text{CH}\)), 129.7(\(2\text{CH}\)), 129.4(\(\text{C}_4\)), 116.4(\(\text{CH}_2\)), 115.1(\(\text{CH}_2\)), 113.7(\(2\text{CH}_2\)), 113.6(\(\text{CH}_2\)), 87.7(\(\text{C}_4\)), 81.8(\(\text{C}_4\)), 74.0(\(\text{C}_4\)), 73.0(\(\text{CH}_2\)), 70.8(\(\text{CH}_2\)), 70.7(\(\text{CH}_2\)), 64.1(\(\text{CH}_2\)), 56.8(\(\text{CH}_2\)), 55.2(\(\text{CH}\)), 51.4(\(\text{CH}_3\)), 35.4(\(\text{CH}_2\)), 27.0(\(\text{CH}_2\)), 25.8(\(\text{CH}_2\)), 20.4(\(\text{CH}_2\)); HRMS (EI) m/z calcd for C\(_{26}\)H\(_{34}\)O\(_4\) ([M-\(\text{C}_3\text{H}_3\)]\(^+\)) 369.2457, found 369.2144.

**Compound 156**, 7,10-Diallyl-9-(4-methoxy-benzoylomethyl)-11-oxa-tricyclo-[5.3.2.0\(_1\)\(_6\)]dodec-9-en-12-ol

To a solution of compound 155 (31.0 mg, 0.076 mmol) in toluene (18 mL) in a microwave cell was added triethylamine (120 \(\mu\text{L}\), 0.86 mmol). The solution was degassed using N\(_2\) and the solution was
heated in a microwave oven for 60 min at 165°C. The solution was concentrated and the residue was purified by flash chromatography (25% ethyl acetate in 75% hexanes) to give 156 (3.5 mg, 11%) as a colorless oil. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.27-7.20 (m, 2H), 6.89-6.84 (m, 2H), 5.85-5.69 (m, 2H), 5.27-4.89 (m, 5H), 4.45-4.31 (m, 2H), 3.99-3.88 (m, 1H), 3.79 (s, 3H), 3.74 (d, \(J = 11.0\) Hz, 1H), 2.96-2.81 (m, 2H), 2.46-2.03 (m, 6H), 1.75-1.26 (m, 8H).

**Compound 157, 1-[3-[2-(1-Allyloxymethyl-vinyl)-1-prop-2-nyloxy-cyclohexyl]-prop-2-nyloxy-methyl]-4-methoxy-benzene**

To a solution of alcohol 154c (118.0 mg, 0.319 mmol) in a mixture of TFH/DMF (3/1 mL) was added sodium hydride 60% in oil (25.0 mg, 0.637 mmol) at room temperature. After 10 min, propargyl bromide (110 \(\mu\)L, 0.955 mmol, 80% in toluene) was added to the mixture. After 3 hrs, sodium hydride (12.5 mg, 0.319 mmol) and propargyl bromide (55 \(\mu\)L, 0.478 mmol) were added. The mixture was stirred for 3 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography (12% ethyl acetate in 88% hexanes) to give 157 (97.1 mg, 75%) as a colorless oil. IR (neat) 3293 (w), 2926 (m), 2854 (m), 1612 (w), 1513 (m), 1456 (w), 1249 (s), 1171 (m), 1066 (s); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.25 (d, \(J = 8.1\) Hz, 2H), 6.86 (d, \(J = 8.1\) Hz, 2H), 5.96-5.83 (m, 1H), 5.28-5.11 (m, 4H), 4.48 (s, 2H), 4.48-4.16 (m, 5H), 4.13-3.94 (m, 3H), 3.78 (s, 3H), 2.36-2.20 (m, 3H), 1.91-1.70 (m, 2H), 1.66-1.43 (m, 5H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 159.3(C4), 146.4(C4), 135.0(CH), 129.8(2CH), 129.4(C4), 116.4(CH\(_2\)), 113.9(CH\(_2\)), 113.7(2CH\(_2\)), 86.8(C4), 82.9(C4), 80.9(C4), 75.4(C4), 73.2(CH), 72.9(CH\(_2\)), 70.9(CH\(_2\)), 70.8(CH\(_2\)), 56.8(CH\(_2\)), 55.2(CH\(_3\)), 51.9(CH\(_2\)), 51.2(CH\(_2\)), 35.7(CH\(_2\)), 26.9(CH\(_2\)), 25.8(CH\(_2\)), 20.5(CH\(_2\)).
Compound 158, [3-[2-(1-Allyloxymethyl-vinyl)-1-ethynyl-cyclohexyloxy]-propenyl]-benzene

To a solution of alcohol 142b (103.5 mg, 0.280 mmol) in a mixture of THF/DMF (6/2 mL) was added sodium hydride 60% in oil (36.4 mg, 0.927 mmol) at room temperature. After 10 min, cinnamyl chloride (190 μL, 1.364 mmol) and flame dried sodium iodide (202.2 mg, 1.349 mmol) were added to the mixture. The solution was stirred for 3 hrs at room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO4, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 158 (130.8 mg, 92%) as a colorless oil. IR (neat) 3301 (m), 3080 (w), 2933 (s), 2855 (s), 1639 (m), 1448 (m), 1139 (m), 1099 (s); 1H NMR (CDCl3) δ 7.39-7.36 (m, 2H), 7.33-7.26 (m, 2H), 7.24-7.19 (m, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.29 (dt, J = 5.4 Hz, 15.9 Hz, 1H), 5.98-5.86 (m, 1H), 5.29-5.23 (m, 3H), 5.13 (dd, J = 0.7 Hz, 10.4 Hz, 1H), 4.35-4.28 (m, 1H), 4.20-4.01 (m, 3H), 3.97 (d, J = 5.5 Hz, 2H), 2.45 (s, 1H), 2.35-2.23 (m, 2H), 1.96-1.82 (m, 1H), 1.76-1.72 (m, 1H), 1.55-1.45 (m, 5H); 13C NMR (CDCl3) δ 146.5(C4), 137.0(C4), 135.1(CH), 130.8(CH), 128.5(2CH), 127.9(CH), 126.9(CH), 126.3(2CH), 116.5(CH2), 114.0(CH2), 85.0(C4), 74.0(C4), 74.0(CH), 73.2(CH2), 70.8(CH2), 64.0(CH2), 50.9(CH), 35.5(CH2), 27.1(CH2), 25.8(CH2), 20.4(CH2); HRMS (EI) m/z calcd for C23H28O2 ([M+C3H3]⁺) 295.2089, found 295.1621.

Compound 159, 2-(1-Hydroxymethyl-vinyl)-1-(4-phenyl-but-3-en-1-ynyl)-cyclohexanol

The oil 159b (322.0 mg) was dissolved in DCM (15 mL) at room temperature and SeO2 (0.070 mg, 0.605 mmol) was added to the mixture, followed by t-BuOOH (0.67 mL, 4.84 mmol). After 24 hrs, t-BuOOH (0.34 mL, 2.42 mmol) was added. The reaction was quenched 48 hrs later with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X). The combined organic layers were washed with
Na₂CO₃, water and a saturated aqueous solution of sodium chloride. The combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (50% diethyl ether in 50% hexanes) to give 159 (134.6 mg, 39%) as a colorless oil. IR (neat) 3400 (m), 2927 (s), 2857 (m), 1443 (m), 1071 (w), 1048 (m), 970 (m), 952 (m), 747 (s); ¹H NMR (CDCl₃) δ 7.68-7.26 (m, 5H), 6.85 (d, J = 16.3 Hz, 1H), 6.13 (d, J = 16.3 Hz, 1H), 5.22 (s, 1H), 5.11 (s, 1H), 4.20 (s, 2H), 3.83 (s, 1H), 2.41 (dd, J = 3.3 Hz, 12.9 Hz, 1H), 2.16-1.21 (m, 9H); ¹³C NMR (CDCl₃) δ 149.3(C4), 141.1(CH), 136.1(C4), 128.7(2CH), 128.5(CH), 126.2(2CH), 116.6(CH₂), 107.7(CH), 96.1(C4), 83.0(C4), 68.1(C4), 65.5(CH₂), 52.1(CH), 39.7(CH₂), 26.3(CH₂), 25.8(CH₂), 20.6(CH₂); HRMS (EI) m/z calcd for C₁₉H₂₂O₂ (M⁺) 282.16198, found 282.16385.

**Compound 159b, 2-Isopropenyl-1-(4-phenyl-but-3-en-1-ynyl)-cyclohexanol**

To a solution of (4,4-Dibromo-buta-1,3-dienyl)-benzene (1.506 g, 5.23 mmol) in THF (40 mL) at -78°C was added n-BuLi (3.85 mL, 9.57 mmol) and the solution was stirred for 60 min at -78°C. The mixture was warmed to -25°C and stirred for 30 min. After cooling to -78°C, ketone 141 (655.6 mg, 4.75 mmol) dissolved in diethyl ether (5 mL) and cooled to -78°C was added to the lithiated solution via canula. The mixture was stirred for 60 min at -78°C. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in 90% hexanes) to give 159b (322.0 mg, 25%) as a yellow oil. IR (neat) 3554 (m), 3400 (m), 2942 (s), 2859 (m), 1642 (m), 1442 (s), 1371 (m), 1281 (m), 1172 (m), 972 (s), 747 (s); ¹H NMR (CDCl₃) δ 7.37-7.22 (m, 5H), 6.88 (d, J = 16.3 Hz, 1H), 6.18 (d, J = 16.3 Hz, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 2.28 (s, 1H), 2.25-2.17 (m, 1H), 2.02 (s, 3H), 1.77-1.18 (m, 8H); ¹³C NMR (CDCl₃) δ 148.3(C4), 141.0(CH), 136.1(C4), 128.6(2CH), 128.5(CH), 126.1(2CH), 112.3(CH₂), 107.7(CH), 96.3(C4), 82.4(C4), 67.4(C4), 52.6(CH), 39.6(CH₂), 26.7(CH₂), 26.0(CH₃), 25.7(CH₂), 20.6(CH₂); HRMS (EI) m/z calcd for C₁₉H₂₂O (M⁺) 266.16706, found 266.16713.
Compound 159c, 2-(1-Allyloxymethyl-vinyl)-1-(4-phenyl-but-3-en-1-ynyl)-cyclohexanol

To a solution of diol 159 (69.8 mg, 0.247 mmol) in a mixture of TFH/DMF (3/1 mL) was added sodium hydride 60% in oil (10.6 mg, 0.265 mmol) at 0°C. After 10 min, allyl bromide (25 μL, 0.289 mmol) was added to the mixture. The solution was stirred at 0°C for 60 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (12% ethyl acetate in 88% hexanes) to give 159c (70.0 mg, 88%) as a colorless oil. IR (neat) 3400 (s), 2931 (m), 2856 (w), 1635 (s), 1067 (w), 925 (w), 748 (w); ¹H NMR (CDCl₃) δ 7.35-7.21 (m, 5H), 6.84 (d, J = 16.3 Hz, 1H), 6.14 (d, J = 16.3 Hz, 1H), 5.98-5.85 (m, 1H), 5.32-5.26 (m, 1H), 5.20-5.17 (m, 3H), 4.42 (d, J = 1.3 Hz, 1H), 4.21-4.11 (m, 2H), 3.95-3.86 (m, 2H), 2.43 (dd, J = 3.4 Hz, 12.8 Hz, 1H), 2.18-2.14 (m, 1H), 1.91-1.62 (m, 4H), 1.56-1.41 (m, 2H), 1.35-1.19 (m, 1H); ¹³C NMR (CDCl₃) δ 145.3(C4), 140.6(CH), 136.3(C4), 133.8(CH), 128.6(2CH), 128.4(CH), 126.1(2CH), 119.3(CH₂), 117.7(CH₂), 108.0(CH), 96.5(C4), 82.7(C4), 71.8(CH₂), 70.4(CH₂), 68.0(C4), 53.0(CH), 39.5(CH₂), 25.9(CH₂), 25.8(CH₂), 20.6(CH₂); HRMS (EI) m/z calcd for C₂₂H₃₆O₂ ([M-H₂O]⁺) 304.1933, found 304.1839.

Compound 160, [4-[2-(1-Allyloxymethyl-vinyl)-1-prop-2-nyloxy-cyclohexyl]-but-1-en-3-ynyl]-benzene

To a solution of alcohol 159c (69.0 mg, 0.214 mmol) in a mixture of TFH/DMF (3/1 mL) was added sodium hydride 60% in oil (17.0 mg, 0.428 mmol) at room temperature. After 10 min, propargyl bromide (75 μL, 0.671 mmol, 80% in toluene) was added to the mixture. After 3 hrs, sodium hydride (8.5 mg, 0.214 mmol) and propargyl bromide (40 μL, 0.358 mmol) were added to the mixture. The solution was stirred for 3 hrs. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was
extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (8% ethyl acetate in 92% hexanes) to give 160 (41.5 mg, 54%) as a colorless oil. IR (neat) 3297 (m), 3032 (w), 2933 (s), 2856 (m), 1736 (w), 1448 (m), 1177 (w), 1091 (s), 1062 (s); ¹H NMR (CDCl₃) δ 7.36-7.24 (m, 5H), 6.87 (d, J = 16.3 Hz, 1H), 6.14 (d, J = 16.3 Hz, 1H), 5.99-5.86 (m, 1H), 5.30-5.22 (m, 3H), 5.16-5.12 (m, 1H), 4.33-4.16 (m, 3H), 4.05-3.97 (m, 3H), 2.38-2.22 (m, 3H), 1.94-1.80 (m, 1H), 1.76-1.68 (m, 1H), 1.65-1.46 (m, 4H), 1.35-1.22 (m, 1H); ¹³C NMR (CDCl₃) δ 146.3(C4), 141.5(CH), 136.2(C4), 135.1(CH), 128.7(2CH), 128.6(CH), 126.2(2CH), 116.5(CH₂), 114.2(CH₂), 107.5(CH), 91.8(C4), 85.9(C4), 81.4(C4), 75.8(C4), 73.3(CH₂), 73.1(CH), 70.8(CH₂), 52.0(CH₂), 50.8(CH), 35.9(CH₂), 27.0(CH₂), 25.8(CH₂), 20.6(CH₂).

**Compound 161, 7- Allyl-10-propa-1,2-dienyl-11-oxa-tricyclo[5.3.2.01,6]dodec-9-en-12-one**

To a solution of lactol 153 (9.0 mg, 0.0348 mmol) in DCM (1.5 mL) at room temperature were added molecular sieves 4 Å (25 mg), TPAP (~1 mg) and NMO (6.2 mg, 0.0529 mmol). After 2 hrs, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography (15% ethyl acetate in 85% hexanes) to give 161 (8.9 mg, 100%) as a colorless oil. IR (neat) 2928 (s), 2856 (m), 1940 (w), 1770 (s), 1639 (w), 1124 (w), 924 (m); ¹H NMR (CDCl₃) δ 5.82-5.77 (m, 1H), 5.77-5.68 (m, 2H), 5.18-5.15 (m, 1H), 5.12 (s, 1H), 4.92-4.89 (m, 2H), 2.53-2.47 (m, 1H), 2.43-2.31 (m, 2H), 2.21-2.02 (m, 2H), 1.89-1.83 (m, 1H), 1.75-1.65 (m, 2H), 1.57-1.52 (m, 1H), 1.48-1.35 (m, 1H), 1.23-1.09 (m, 3H); ¹³C NMR (CDCl₃) δ 209.6(C4), 180.6(C4), 137.2(C4), 132.8(CH), 126.5(CH), 119.2(CH₂), 88.7(CH), 81.3(C4), 77.1(CH₂), 50.6(C4), 46.7(CH), 35.0(CH₂), 33.9(CH₂), 29.8(CH₂), 24.6(CH₂), 23.3(CH₂), 20.5(CH₂); HRMS (EI) m/z calcd for C₁₇H₂₀O₂ (M⁺) 256.1463, found 256.1475.
Compound 163, 1-Ethynyl-1-methoxy-2-(1-methoxymethyl-vinyl)-cyclohexane

To a solution of diol 142 (51.0 mg, 0.283 mmol) in a mixture of TFH/DMF (6/2mL) was added methyl iodide (0.17 mL, 2.8 mmol). After 5 min, sodium hydride 60% in oil (40.0 mg, 1.4 mmol) was slowly added to the mixture and it was stirred for 60 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (8% ethyl acetate in 92% hexanes) to give 163 (24.4 mg, 41%) as a colorless oil. IR (neat) 3307 (w), 2932 (s), 2857 (m), 2827 (w), 1448 (w), 1191 (w), 1091 (s), 938 (w), 906 (w). ¹H NMR (CDCl₃) δ 5.17 (s, 1H), 5.14 (s, 1H), 4.02 (d, J = 12.6 Hz, 1H), 3.88 (d, J = 12.6 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.51 (s, 1H), 2.26-2.22 (m, 1H), 2.16 (dd, J = 2.9 Hz, 12.0 Hz, 1H), 1.78-1.48 (m, 5H), 1.34-1.20 (m, 2H). ¹³C NMR (CDCl₃) δ 147.3(C4), 113.0(CH₂), 82.0(C4), 79.3(C4), 77.6(CH₂), 76.9(CH), 57.7(CH₃), 50.8(CH₃), 48.7(CH), 36.8(CH₂), 30.0(CH₂), 25.9(CH₂), 23.4(CH₂). HRMS (EI) m/z calcd for C₁₂H₁₇O₁ ([M-OCH₃]⁺) 177.12794, found 177.12732.

Compound 164, 1-Ethynyl-1-methoxy-2-(1-methoxymethyl-vinyl)-cyclohexane

To a solution of diol 162 (207.0 mg, 1.149 mmol) in a mixture of TFH/DMF (9/3 mL) was added methyl iodide (1.0 mL, 11.1 mmol). After 5 min, sodium hydride 60% in oil (40.0 mg, 5.75 mmol) was slowly added to the mixture and it was stirred for 60 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (5% ethyl acetate in 95% hexanes) to give 164 (205.1 mg, 86%) as a colorless oil. IR (neat) 3303 (w), 2933 (s), 2857 (m), 1648 (w), 1191 (w), 1091 (s), 938 (w), 906 (w); ¹H NMR (CDCl₃) δ 5.16 (d, J = 1.3 Hz, 1H), 5.13 (s, 1H), 4.01 (d, J = 12.6 Hz, 1H), 3.87 (d, J = 12.6 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 2.51 (s, 1H), 2.26-2.21 (m, 1H), 2.15 (dd, J = 3.2 Hz, 12.1 Hz, 1H), 1.78-1.46 (m, 5H), 1.36-1.13 (m, 2H); ¹³C NMR (CDCl₃) δ 147.3(C4), 113.0(CH₂), 112
82.0(C4), 79.3(C4), 77.5(CH2), 76.9(CH), 57.7(CH3), 50.8(CH3), 48.6(CH), 36.8(CH2),
30.0(CH2), 25.9(CH2), 23.4(CH2); HRMS (EI) m/z calcd for C_{12}H_{17}O_{2} ([M-CH_]^{+})
193.12286, found 193.1219.

**Compound 165, 1-Methoxy-6-(1-methoxymethyl-buta-1,3-dienyl)-cyclohexene**

To a solution of compound 163 (21.4 mg, 0.103 mmol) in toluene (18
mL) in a microwave cell was added DBU (120 µL, 0.82 mmol). The
solution was degassed using argon and it was heated in a microwave
oven for 60 min at 220°C. The solution was concentrated and the residue was purified by
flash chromatography (2% ethyl acetate in 49% hexanes and 49% DCM) to give 165
(14.2 mg, 66%) as a colorless oil. $^1$H NMR (Acetone-d$_6$) δ 6.54 (dd, J = 10.3 Hz, 10.6
Hz, 16.7 Hz, 1H), 5.77 (m, 1H), 5.40 (d, J = 10.6 Hz, 1H), 4.96 (dd, J = 0.7 Hz, 2.3 Hz,
16.7 Hz, 1H), 4.74 (ddd, J = 0.7 Hz, 2.3 Hz, 10.3 Hz, 1H), 3.70-3.64 (m, 1H), 3.55-3.50
(m, 2H), 3.52 (s, 3H), 3.15 (s, 3H), 2.06-1.95 (m, 2H), 1.82-1.67 (m, 3H), 1.60-1.43 (m,
1H). $^{13}$C NMR (CDCl$_3$) δ 161.5 (C4), 134.5(C4), 132.4(CH), 127.5(CH), 111.4(CH$_2$),
101.3(CH), 75.3(CH$_2$), 57.9(CH$_3$), 54.6(CH$_3$), 37.1(CH), 27.8(CH$_2$), 24.9(CH$_2$),
21.2(CH$_2$).

**Compound 166, 6-(1-Methoxy-buta-1,3-dienyl)-1-methoxymethyl-cyclohexene**

To a solution of compound 164 (31.6 mg, 0.152 mmol) in toluene (18
mL) in a microwave cell was added Et$_3$N (120 µL, 0.86 mmol). The
solution was degassed using argon and it was heated in a microwave
oven for 60 min at 220°C. The solution was concentrated and the residue was purified by
flash chromatography (1.5% ethyl acetate in 98.5% benzene, twice) to give 166 (9.1 mg,
29%) as a colorless oil. IR (neat) 3054 (w), 2934 (s), 2870 (s), 2834 (m), 1638 (s), 1451
(m), 1142 (m), 1105 (m), 885 (m); $^1$H NMR (C$_6$D$_6$) δ 6.71 (td, J = 16.6 Hz, 10.2 Hz, 1H),
5.87 (s, 1H), 5.32 (d, J = 10.6 Hz, 1H), 5.11 (dd, J = 2.0 Hz, 16.6 Hz, 1H), 4.93 (dd, J =
2.0 Hz, 10.2 Hz, 1H), 3.22-3.11 (m, 2H), 3.13 (s, 3H), 3.10 (s, 3H), 2.69-2.40 (m, 1H),
2.01-1.78 (m, 3H), 1.77-1.62 (m, 1H), 1.61-1.29 (m, 2H); $^{13}$C NMR (CDCl$_3$)
δ 161.9(C4), 135.0(C4), 133.0(CH), 126.7(CH), 111.4(CH₂), 101.9(CH), 75.6(CH₂), 57.6(CH₃), 54.1(CH₃), 37.4(CH), 28.3(CH₂), 25.2(CH₂), 21.6(CH₂); LRMS (EI) m/z calcd for C₁₃H₂₀O₂ (M⁺) 208.3, found 208.

Compound 167, 1-Ethynyl-1-methoxy-2-(1-methoxymethyl-vinyl)-cyclohexane

To a solution of alkyne 164 (49.4 mg, 0.237 mmol) in Et₂O at −78°C was added n-BuLi (0.13 mL, 0.284 mmol). The mixture was stirred at −78°C for 15 min. The reaction was quenched with D₂O (1 mL, 50 mmol) was −78°C then warm to room temperature. The mixture was extracted with ethyl acetate (3X) and the combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in 85% hexanes) to give 167 (45.7 mg, 92%) as a colorless oil. IR (neat) 2985 (w), 2935 (s), 2859 (m), 2826 (w), 1460 (w), 1448 (m), 1191 (w), 1090 (s), 906 (w); ¹H NMR (CDCl₃) δ 5.17 (dd, J = 1.5 Hz, 3.0 Hz, 1H), 5.14 (dd, J = 0.7 Hz, 1.5 Hz, 1H), 4.01 (d, J = 12.6 Hz, 1H), 3.90-3.87 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 2.65-2.22 (m, 1H), 2.15 (dd, J = 3.1 Hz, 12.4 Hz, 1H), 1.75-1.67 (m, 3H), 1.63-1.50 (m, 2H), 1.33-1.17 (m, 2H); ¹³C NMR (CDCl₃) δ 147.3(C4), 112.9(CH₂), 81.6(C4), 79.3(C4), 77.5(CH₂), 76.5(CD), 57.7(CH₃), 50.8(CH₃), 48.7(CH), 36.9(CH₂), 30.0(CH₂), 25.9(CH₂), 23.4(CH₂); HRMS (EI) m/z calcd for C₁₂H₁₆O₃ ([M-OCH₃]⁺) 178.13412, found 178.1301.

Compound 168, 6-(1-Methoxy-3-deutero-buta-1,3-dienyl)-1-methoxymethyl-cyclohexene

To a solution of compound 167 (32.5 mg, 0.155 mmol) in toluene (18 mL) in a microwave cell was added DBU (120 µL, 0.82 mmol). The solution was degassed using argon and it was heated in a microwave oven for 60 min at 220°C. The solution was concentrated and the residue was purified by flash chromatography (4% ethyl acetate in 96% benzene) to give 168 (12.4 mg, 38%) as a colorless oil. IR (neat) 3060 (w), 2932 (s), 2869 (m), 1637 (s), 1451 (m), 1210 (s), 1142 (m), 1105 (m), 883 (m); ¹H NMR (CDCl₃) δ 5.87 (m, 1H), 5.32 (s, 1H), 5.11 (d, J = 2.1
Hz, 1H), 4.93 (s, 1H), 3.22-3.11 (m, 2H), 3.13 (s, 3H), 3.10 (s, 3H), 2.69-2.40 (m, 1H), 2.01-1.78 (m, 3H), 1.77-1.62 (m, 1H), 1.61-1.29 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ 161.9(C4), 135.1(C4), 133.0(CD), 126.7(CH), 111.4(CH$_2$), 101.8(CH), 75.6(CH$_2$), 57.6(CH$_3$), 54.1(CH$_3$), 37.4(CH), 28.3(CH$_2$), 25.2(CH$_2$), 21.6(CH$_2$); LRMS (EI) m/z calcd for C$_{13}$H$_{19}$DO$_2$ (M$^+$) 209.2, found 209.
CLAIMS TO ORIGINAL RESEARCH

1. Explained the enantioselectivity of a tandem oxy-Cope/ene reaction due to the rigidity of an intermediate enol atropisomer and due to the rates of the different processes involved in the cascade reaction (tautomerization and ene reaction).

2. Discovered a novel approach for the formation of quaternary centers using an anionic oxy-Cope quench with different electrophiles.

3. Studied the novel tandem oxa-Cope/Claisen/ene/Claisen reaction.

PRESENTATION OF ORIGINAL RESEARCH


REFERENCES

32. Special thanks to Colette Boucher from Boehringer Ingelheim for the determination of the appropriate chiral column for the separation of the enantiomers


APPENDIX
Current Data Parameters
NAME  chd_349
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date_  20010219
Time  9.18
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PRBD  5 mm NMR 1H/1
PULPROG  zg30
TD  30720
SOLVENT  CDCl3
NS  16
DS  0
SMH  5081.301 Hz
FIDRES  0.105407 Hz
AQ  3.0228990 sec
RG  128
DN  98.400 usec
DE  6.00 usec
TE  300.0 K
D1  1.00000000 sec

*********** CHANNEL f1 ***********
NUC1  1H
P1  9.50 usec
PL1  -3.00 dB
SF01  300.1315877 MHz

F2 - Processing parameters
SI  69536
SF  300.1300000 Mhz
MDM  EM
SSB  0
LB  0.10 Hz
GB  0
PC  1.00

1D NMR plot parameters
CX  20.00 cm
CY  10.00 cm
FIP  8.000 ppm
F1  2401.04 Hz
F2P  0.000 ppm
F2  0.00 Hz
PPMCM  0.00000 ppm/cm
HZCM  120.0520 Hz/cm
Current Data Parameters
NAME     dga-337
EXPN     1
PROCNO   1

F2 - Acquisition Parameters
Date     20020626
Time     10.44
INSTRUM  av300
PROBHD   5 mm ONP 1H/1
PULPROP  zg30
TD       30720
SOLVENT  CDC13
NS       16
DS       0
SWH      5081.301 Hz
FIDRES   0.16546 Hz
A0       3.0226980 sec
RG       256
Dw       98.400 usec
DE       6.00 usec
TE       300.0 K
D1       1.00000000 sec

********** CHANNEL f1 **********
NUC1     1H
P1       20.00 usec
P1t      -3.00 dB
SF01     300.1314977 MHz

F2 - Processing parameters
S1       65536
SF       300.1300001 MHz
MCM      EM
SSB      0
LB       0.10 Hz
GB       0
PC       1.00

1D NMR plot parameters
CX       20.00 cm
CY       10.00 cm
F1P      10.000 ppm
F1       3001.30 Hz
F2P      0.000 ppm
F2       0.00 Hz
PPMCM    0.500000 ppm/cm
HZCM     150.06500 Hz/cm
Current Data Parameters

NAME  dga-360
EXPNO  1
PRCOND  1

F2 - Acquisition Parameters
Date_  20020801
Time  9.03
INSTI  av300
PRBD  5 mm GNP 1H/1
PULPROG  zg30
TD  30730
SOLVENT  CDCl3
NS  16
DS  0
SWH  5001.301 Hz
FIORES  0.165407 Hz
AQ  3.0229980 sec
RG  143.7
DM  98.400 usec
DE  6.00 usec
TE  3.00 sec
DI  1.00000000 sec

************ CHANNEL f1 ************
NUCI  1H
P1  8.00 usec
PL1  -3.00 dB
SFO1  300.1319477 MHz

F2 - Processing parameters
SI  0.9538
SF  300.1299999 MHz
WDW  EM
SSB  0
LB  0.10 Hz
GB  0
PC  1.00

1D NMR plot parameters
CX  20.00 cm
CY  10.00 cm
F1P  10.000 ppm
F1  3001.30 Hz
F2P  0.000 ppm
F2  0.00 Hz
PPCH  0.50000 ppm/cm
HZCH  150.05650 Hz/cm
Current Data Parameters
NAME     dga-bia
EXPN0    2
PROCNO   1

F2 - Acquisition Parameters
Date      20020820
Time      14.35
INSTRAUM  6 ¥ 300
PROBD   5 cm UNP 1H/1
PULPROG   2 ¥ 30
TD      30720
SOLVENT  CDCl3
NS      64
DS      0
SWH     5081.301 Hz
FIDRES   0.165407 Hz
AG       3.0225685 sec
RG      574.7
DW      98.450 usec
DE      6.00 usec
TE      300.0 K
DT      1.0000000 sec

---------------- CHANNEL 1 ----------------
NUC1     H
P1      8.00 usec
P2      -3.00 dB
SF01    300.1315477 MHz

F2 - Processing parameters
SI      65536
SF       300.1300000 MHz
MWN     EM
SSB     0
LB      0.10 Hz
GB      0
PC      1.00

1D NMR plot parameters
CA      20.00 cm
CY      10.00 cm
F1P    10.000 ppm
F1      3001 30 Hz
F2P    0.000 ppm
F2      0.00 Hz
PPNCHM  0.50000 ppm/cm
Hz/cm   150.06500 Hz/cm
### Current Data Parameters

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
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<td>NAME</td>
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<td>PROCNO</td>
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</tbody>
</table>

### F2 - Acquisition Parameters

- **Date**: 20021126
- **Time**: 8.56
- **INSTROM**: av300
- **PROBD**: 5mm QNP 1H/13C
- **PULPROG**: 2q30
- **TD**: 30720
- **SOLVENT**: CC13
- **N**: 16
- **DS**: 0
- **SNH**: 5081.301 Hz
- **FIDRES**: 0.165407 Hz
- **AG**: 3.0228980 sec
- **DG**: 80.6
- **DN**: 99.400 usec
- **DE**: 6.00 usec
- **TE**: 300.0 K
- **DT**: 1.00000000 sec

#### CHANNEL f1

- **NUC1**: 1H
- **P1**: 9.75 usec
- **PL1**: -3.00 dB
- **SF01**: 300.1319477 MHz

### F2 - Processing parameters

- **SI**: 65536
- **SF**: 300.1300000 MHz
- **WDW**: EM
- **SSB**: 0
- **LB**: 0.10 Hz
- **GB**: 0
- **PC**: 1.00

### 1D NMR plot parameters

- **EX**: 20.00 cm
- **CY**: 10.00 cm
- **F1P**: 10000 ppm
- **F1**: 3001.30 Hz
- **F2P**: 0.000 ppm
- **F2**: 0.00 Hz
- **PPM/W**: 0.500000 ppm/cm
- **Hz/W**: 150.06500 Hz/cm
Current Data Parameters
NAME dga-217
EXPRO 1
PROCON 1

F2 - Acquisition Parameters
Date_ 20020320
Time 20.40
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG 2g30
TO 30720
SOLVENT CDCl3
NS 32
DS 0
SNH 5001.301 Hz
T1RES 0.155407 Hz
AG 3.0235680 sec
AG 322.5
DM 98.400 usec
dE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

--------------- CHANNEL f1 ---------------
NUC1 1H
P1 16.00 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 05536
SF 300.1300000 MHz
WOW EM
SSB 0
LB 0.15 Hz
GB 0
PC 1 D0

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 10.000 ppm
F1 3001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPCHM 0.50000 ppm/cm
HZCM 150.06500 Hz/cm
Current Data Parameters
NAME ppm-diol
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20011018
Time 15:26
INSTRUM av300
PROBHDI 5 mm NPH 1H/1
PULPROG zg30
TD 30720
SOLVENT CDCl3
NS 48
DS 0
SHH 5081.301 Hz
FIDRES 0.165407 Hz
AQ 3.028900 sec
RG 265
DW 98.400 usec
DE 6.00 usec
TE 300.0 K
DI 1.00000000 sec

************ CHANNEL f1 ************
Nuc1 1H
P1 11.00 usec
PL1 -3.00 dB
SF01 300.1319477 MHz

F2 - Processing parameters
SI 60536
SF 300.1300000 MHz
WDM EM
SSB 0
LB 0.10 Hz
SC 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 10.00 cm
F1P 10.000 ppm
F1 3001.30 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCH 0.50000 ppm/cm
H2OCH 150.00500 Hz/cm
Current Data Parameters
NAME      dga-183a
EXPIANO   1
PROCNO    1

F2 - Acquisition Parameters
Date_     20020130
Time      17.11
INSTRUM   av300
PROBDIO   5 mm DNP 1H/1
PULPROG   2930
TD         30720
SOLVENT   CDCl3
NS         16
DS         0
SNR       5081.301 Hz
FIDRES    0.165467 Hz
A9        3.0238980 sec
RG         203.2
DW        98.400 usec
DE         6.00 usec
TE         300.0 Hz
DI        1.00000000 sec

************ CHANNEL f1 ************
Nuc1      1H
P1        11.00 usec
PB1       -3.00 dB
SF01      300,1319477 MHz

F2 - Processing parameters
SI         69536
SF         300,1299997 MHz
MOD       EM
SSB        0
LB         0.10 Hz
GB         0
PC         1.00

1D NMR plot parameters
C1        20.00 cm
C2        10.00 cm
F1P       10.0000 ppm
F1        3001.30 Hz
F2P       0.0000 ppm
F2        0.00 Hz
PPMCH     0.500000 ppm/cm
HZOM      150.06500 Hz/cm