Studies toward the Total Synthesis of (+)-Agelasimine A and its Analogs, and Development of the Tandem oxy-Cope/ene/Claisen Reaction
STUDIES TOWARD THE TOTAL SYNTHESIS OF (±)-AGELASIMINE A AND ITS ANALOGS, AND DEVELOPMENT OF THE TANDEM OXY-COPE/ENE/CLAISEN REACTION

By

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A Thesis Submitted to the School of Graduate Studies and Research In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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<td>BBN</td>
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ABSTRACT

The discovery and development of a novel tandem oxy-Cope/ene/Claisen reaction is described. The strategy allows for highly diastereoselective formation of trans-decalins having a quaternary carbon center at C9. Depending on the substitution pattern of the terminal olefin of the starting 1,2-divinylcyclohexanol an additional tertiary or quaternary carbon center can be introduced at C11.

The oxy-Cope/ene/Claisen reaction of 1,2-divinylcyclohexanol propargyl ethers provides decalines possessing an allene moiety.

An approach toward the total synthesis of (±)-agelasmine A, a clerodane-related diterpene isolated from orange sponge *Agelas mauritiana*, via the oxy-Cope/ene and the oxy-Cope/ene/Claisen reaction has been investigated.

The factors affecting the selectivity at C8 during the oxy-Cope/ene reaction have been studied in detail. Control over the selectivity at C8 can be achieved by either increasing the
energy difference between transition states of the ene-reaction or changing the electronic properties of the substituent α to the carbonyl.

\[
\begin{align*}
\text{OH} & \quad \overset{220 \, ^{\circ} \text{C, time}}{\text{toluene, Et,N}} \quad \begin{array}{c}
\text{OH} \\
\end{array} & \quad \begin{array}{c}
\text{OH} \\
\end{array} \\
\begin{array}{c}
R \\
\end{array} & \quad \begin{array}{c}
R \\
\end{array} & \quad \begin{array}{c}
R \\
\end{array} \\
\end{align*}
\]

\begin{align*}
\text{direct product-C}_1 & \quad + \quad \text{D}_1(\text{after ring inversion}) \\
R=\text{H}, \text{D}_1:\text{C}_1=3:1 \\
R=\text{SEt}, \text{D}_1:\text{C}_1=20:1
\end{align*}

The new approach toward formation of the quaternary carbon centers via an anionic oxy-Cope/alkylation reaction is also described. The anionic oxy-Cope reaction affords the macrocyclic enolate, which geometry is predetermined by the stereochemistry of the starting material and a chair-like transition state of the oxy-Cope reaction. The conformation of the macrocycle provides excellent means for controlling facial approach of the electrophile in the following alkylation step. Cleavage of the resulting macrocyclic ketone would afford a chiral ester bearing a quaternary carbon center α to a carbonyl.

\[
\begin{align*}
\text{Li} & \quad \begin{array}{c}
\text{RO} \\
\end{array} & \quad \begin{array}{c}
\text{RO} \\
\end{array} \\
\begin{array}{c}
R \\
\end{array} & \quad \begin{array}{c}
R \\
\end{array} & \quad \begin{array}{c}
R \\
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
& \quad \text{KHMD, DME, reflux} \\
\end{align*}
\]

\[
\begin{align*}
\text{E}^+ & \quad -78 \, ^{\circ} \text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{EtO} & \quad \begin{array}{c}
\text{C} \\
\end{array} & \quad \begin{array}{c}
\text{C} \\
\end{array} \\
\begin{array}{c}
\text{R} \\
\end{array} & \quad \begin{array}{c}
\text{E} \\
\end{array} \\
\end{align*}
\]
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ITHAKA

"As you set out for Ithaka
hope your road is a long one,
full of adventure, full of discovery.
Laistrygonians, Cyclops,
angry Poseidon - don't be afraid of them:
you'll never find things like that one on your way
as long as you keep your thoughts raised high,
as long as a rare excitement
stirs your spirit and your body.
Laistrygonians, Cyclops,
wild Poseidon - you won't encounter them
unless you bring them along inside your soul,
unless your soul sets them up in front of you.

Hope your road is a long one.
May there be many summer mornings when,
with what pleasure, what joy,
you enter harbours you're seeing for the first time;
may you stop at Phoenician trading stations
to buy fine things,
mother of pearl and coral, amber and ebony,
sensual perfumes of every kind -
as many sensual perfumes as you can;
and may you visit many Egyptian cities
to learn and go on learning from their scholars.

Keep Ithaka always in your mind.
Arriving there is what you're destined for.
But don't hurry the journey at all.
Better if it lasts for years,
so you're old by the time you reach the island,
wealthy with all you've gained on the way,
not expecting Ithaka to make you rich.

Ithaka gave you the marvellous journey.
Without her you wouldn't have set out.
She has nothing left to give you now.
And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
you'll have understood by then what these Ithakas mean."

Constantine P. Cavafy
"To my family........."
Chapter 1 Introduction

1.1 Clerodane diterpenes

Diterpenes possessing a carbon skeleton 1.1 as shown in Figure 1.1 belong to the clerodane family, which has been named after clerodin 1.2, an antifeedant isolated from Verbenaceae plants. More than a thousand compounds from this family have been isolated, mostly from higher plants, marine sponges and microorganisms. A distinct structural feature of the clerodanes is a presence of four contiguous chiral centers C5-C10-C9-C8 on the decalin core with a quaternary carbon center at C9 and a center at C4 usually sp² hybridized. There are four structural types of clerodanes (trans-trans, trans-cis, cis-cis, cis-trans), which are distinguished by the relationship between the stereocenters at the ring junction and the methyl groups at C8 and C9 as shown in Figure 1.2.

![Figure 1.1 Clerodane skeleton](image)

![Figure 1.2 Structural types of clerodanes](image)

The biosynthesis of clerodanes involves a rearrangement of labdane skeleton 1.4, which originates from geranylgeranyldiphosphate 1.3 as illustrated in Scheme 1.1. While concerted hydride and methyl group migration leads to trans-clerodanes, the stepwise process gives intermediate carbocation 1.5. The latter can undergo migration of the methyl to afford either cis or trans clerodanes. This intermediate can also react via other pathways such as elimination of the proton, or nucleophilic attack by water.

Scheme 1.1 Biosynthesis of clerodanes

A few compounds with the partially rearranged labdane skeleton, such as marine products ambiol B, agelasmine A and B and plant products chettaphanines have been isolated and

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characterized (Figure 1.3). This provides strong evidence for the proposed biosynthetic mechanism. There are also a number of compounds structurally related to clerodanes, such as dysidiolide (Figure 1.3), the marine sponge metabolite that exhibits significant anticancer activity.\(^5\) Many clerodanes exhibit antifeedant and insecticidal activities.\(^6\) In addition, cytotoxic,\(^7\) anti-peptic-ulcer,\(^8\) psychotropic\(^9\) and antimicrobial\(^10\) activity have also been reported.

\[
\begin{align*}
\text{chettaphanin I} & \quad \text{chettaphanin II} & \quad \text{ambiol B} & \quad \text{agelasimine A} & \quad \text{dysidiolide}
\end{align*}
\]

Figure 1.3 Various clerodane related diterpenes

1.2 Synthesis of clerodanes and related diterpenes

The major challenge in the synthesis of clerodanes is the stereoselective construction of four contiguous stereocenters C5-C10-C9-C8. Several synthetic strategies have been developed since early 1970’s. A recent comprehensive review by Tokorayama provides a detailed classification of these methods based on the sequence in which the four stereocenters are


installed.\textsuperscript{11} Although the presence of the quaternary center at C9 and the methyl group at C8 are characteristic of the clerodane skeleton, the C5 and C10 stereocenters are intrinsic to \textit{trans} and \textit{cis} decalin systems found in a vast number of polyterpenoids. Thus, it is not surprising that the methods employed in the synthesis of clerodanes are those traditionally applied for the construction of \textit{trans} and \textit{cis} decalins. Some of the classical synthetic approaches include Robinson and other aldol related annulations and inter- and intramolecular Diels-Alder reaction.\textsuperscript{12}

The Robinson annulation has been extensively exploited in the synthesis of terpenoids and steroids. It generally provides an unsaturated decalin, which can be further transformed to \textit{cis} or \textit{trans} decalin. The Wieland-Miescher (W-M) type diketones are readily available in racemic and enantiomerically pure forms via the Robinson annulation of the 2-methyl-1,3-cyclohexanedione and corresponding \textalpha,\textbeta-unsaturated ketone as shown in Scheme 1.2.

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme12.png}
\end{center}

\textbf{Scheme 1.2 Wieland-Miescher ketones}

W-M diketones are common starting materials for synthesis of diterpenes. Only the stereocenter at C5 is initially present. The remaining centers have to be introduced in a stepwise process. The synthesis usually begins by protecting the non-conjugated keto-group. Reduction of the alkene then follows, which, depending on the conditions, can afford either \textit{trans} (Birch reduction) or \textit{cis} (catalytic hydrogenation) ring junction, thus introducing the


stereocenter at C10 as shown in Scheme 1.3. When W-M ketone is applied to the synthesis of clerodanes, the quaternary carbon center at C9 is installed either by alkylation of the enolate generated in the Birch reduction or via a Claisen rearrangement. Finally, the methyl group at C8 is introduced via catalytic hydrogenation of the exocyclic methylene obtained either from the olefination of the ketone or via the Claisen rearrangement (Scheme 1.3).

1. Birch reduction/Alkylation

2. Birch reduction/Claisen

3. Cis-clerodanes

Scheme 1.3 Application of W-M diketones toward a synthesis of clerodanes

One of the first examples of using W-M ketone toward the synthesis of clerodanes was that of a clerodane related sesquiterpenoid, (±)-avoral, reported by Sarma et al. in 1982 as shown
in Scheme 1.4.\(^\text{13}\) (+)-Avarol belongs to the trans-cis clerodane structural type (see Figure 1.2), since it has a trans-decalin core and the methyl groups at C9 and C8 are cis to each other and to the C5 center at the ring junction. The synthesis began from the Birch reduction of 1.6 followed by the alkylation of the enolate generated in situ to afford decalin ketone 1.7 with the quaternary center at C9 and a trans-ring-junction as shown in Scheme 1.4. Wittig olefination of ketone 1.7 generated exo-cyclic double bond, which was then reduced using H\(_2\)/Pd/C to give 1.8 as a 5:6:1 mixture of epimers at C8 center. The total synthesis was competed in 8 steps starting from 1.6.

\[
\begin{align*}
&\text{1.6} \\
&\text{1.7} \\
&\text{1.8} \\
&\text{avarol}
\end{align*}
\]

a) Li-NH\(_3\)/THF, 2.5-dimethoxybenzylbromide, 75%; b) CH\(_2\)=PPPh\(_3\), DMSO, 80 °C, 40 h, 85%; c) H\(_2\). 10% Pd/C, EtOH, 75%; d) PCC, CH\(_2\)Cl\(_2\), 90%; e) MeLi, Et\(_2\)O, 90%; f) POCl\(_3\), Py, 95%; g) RhCl\(_3\), EtOH, 80%; h) n-BuSLi, HMPA, 80%.

**Scheme 1.4 Total synthesis of avarol**

In the total synthesis of (+)-annnonene the trans ring junction was first secured via the Birch reduction of acetal-protected W-M ketone 1.9 as shown in Scheme 1.5.\(^\text{14}\) Decalin 1.10 was then transformed to allyl enol ether 1.11. The thermally induced Claisen rearrangement of 1.11 afforded product 1.12 with a quaternary carbon center at C9 as a major diastereomer (dr


5.6:1). Further hydrogenation of the exo-cyclic methylene gave 1.13 as a 1:1 mixture of epimers at C8.

Scheme 1.5 Total synthesis of annonene

Methods employing cyclohexanones with both quaternary and tertiary centers installed prior annulation step can be an alternative to W-M diketones. Tokoroyama et al. developed a general method toward construction of cis and trans clerodanes using unsaturated decalin 1.14 as a common precursor (Scheme 1.6).15 Contrary to the W-M ketone, 1.14 already possessed stereocenters at C10, C9 and C8. The quaternary carbon center was introduced via conjugated addition of vinyl cuprate to cyclohexanone 1.15. Quenching the reaction with formaldehyde afforded ketone 1.16 in which all three stereocenters were present. The subsequent condensation reaction followed by decarboxylation and dehydration provided decalin 1.14. The enantioselective version of this approach was also developed.16

Scheme 1.6 Synthesis of Tokoroyama intermediate

The applicability of the strategy was demonstrated by a number of total syntheses. For example, Ohba et al. employed both racemic and chiral versions of the Tokoroyama method for the synthesis of agelasimine A (Scheme 1.7). As already mentioned before, biosynthetically agelasimine is a product of the partial rearrangement of the labdane skeleton in which cation 1.4 (see Scheme 1.1 in the beginning of the chapter) is quenched with water before the last migration of the methyl occurs. As a result, a tertiary alcohol is formed at the ring junction (C5), whereas geminal dimethyls at C4 are preserved. In order to install these two functionalities, decalin 1.14 was treated with potassium tert-butoxide to generate dienolate which was then alkylated to afford geminal dimethyls at C4. The carbonyl group was then reduced to the methylene using a Wolf-Kishner procedure. Epoxidation of the angular double bond followed by epoxide opening generated trans-decalin 1.17 with the tertiary alcohol at the ring junction.


Scheme 1.7 Total synthesis of agelasimine A

A slightly modified precursor 1.18 was used by Piers et al. in the synthesis of ambiol B, as shown in Scheme 1.8.\textsuperscript{19} In this case the tertiary alcohol at the ring junction (C5) was installed via intramolecular alkylation of the ketone with the vinyl lithium species.

Scheme 1.8 Total synthesis of ambiol B

Grossman et al. have recently reported the total synthesis of clerodane diterpene (±)-sacacararin using the double annulation strategy (Scheme 1.9).\textsuperscript{20} Double Michael addition of 1.19 and 3-butyln-2-one generated \textit{in situ} from 4-trimethylsilyl-3-butyln-2-one afforded

highly substituted cyclohexane 1.20 (dr=5:1). The latter possessed all four stereocenters required for the future C5-C10-C9-C8 network of the clerodane skeleton, although two quaternary centers had to be further desymmetrized. Thus, 1.20 was transformed via hydrolysis of the less hindered cyano group followed by Dieckmann condensation and enol etherification to trans-decalin 1.21. The synthesis of the natural product was completed in four additional steps.

\[ \text{Scheme 1.9 Total synthesis of (±)-sacarcarine} \]

Inter- and intramolecular Diels-Alder reactions have been successfully applied to the synthesis of both trans- and cis-diterpenes. Depending on the substitution pattern of the diene and dienophile, various functionalities can be introduced on the decalin ring including the quaternary carbon center at C9 and the methyl at C8 as depicted in Scheme 1.10. Type 1 Diels-Alder reactions afford decalins with sp\(^2\)-hybridized carbon at C5, which can be further transformed to trans- or cis-decalin. When cyclohexene is used as a dienophile (type 2), cis-decalins are obtained, which can be isomerized to provide the more stable trans-isomer. Intramolecular Diels-Alder reaction can provide both cis- and trans-decalins depending on geometry of the dienophile part of the molecule. In all cases controlling π-facial selectivity remains a significant challenge.
Barriault et al. have reported a highly diastereoselective synthesis of decalins using type 1 Diels-Alder reaction of dienes with tertiary and secondary alcohols as shown in Scheme 1.11. A temporary magnesium alkoxide tether was applied for controlling facial selectivity.

Scheme 1.11 Synthesis of decalines using hydroxy-directed Diels-Alder reaction

Remarkably, four out of seven reported total syntheses of clerodane related sesquiterpene dysidiolide utilized the Diels-Alder reaction for construction of the decalin core. Danishefsky et al. envisioned formation of the decalin framework via intermolecular Diels-Alder reaction (type 1, Scheme 1.10) using diene 1.22 and activated dienophile 1.23 as

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shown in Scheme 1.12.\textsuperscript{23} Endo addition of the dienophile occurred from the face anti to the large side chain to give adduct 1.24.

\begin{equation}
\text{OTBDPS} \quad \text{TBDPSO} \quad \text{dysidiolide}
\end{equation}

a) TMSOTf, CH\textsubscript{2}Cl\textsubscript{2}, -90 °C, 67%

Scheme 1.12 Diels-Alder reaction in Danishefsky's total synthesis of dysidiolide

Boukouvalas and co-workers performed an intermolecular Diels-Alder reaction using diene 1.25, which is similar to 1.22, and dienophile 1.26 to synthesize the decalin core of dysidiolide.\textsuperscript{24} In this case a 2.3:1 mixture of diastereomers was obtained (Scheme 1.13).

\begin{equation}
\text{TIPS} \quad \text{CHO} \quad \text{BnO} \quad \text{EtO}_2\text{C} \quad \text{BnO} \quad \text{EtO}_2\text{C}
\end{equation}

a) EtAlCl\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, -94 °C, 76%.

Scheme 1.13 Diels-Alder reaction in Boukouvalas total synthesis of dysidiolide

Yamada \textit{et al.} chose a slightly different approach toward the dysidiolide core by using the intramolecular Diels-Alder reaction of 1.27 as illustrated in Scheme 1.14.\textsuperscript{25} In this case, the facial attack was directed by the stereochemistry of the tethered dienophile moiety.


The total synthesis of (±) teucvive reported by Liu and co-workers demonstrates an application of type 2 Diels-Alder reaction (Scheme 1.10) to generating a core of the natural product (Scheme 1.15). The cycloaddition reaction using diene 1.28 and trans-2,4-pentadien-1-ol as a dienophile afforded a 11:1 diastereomeric mixture of decalines 1.30 and 1.29 respectively. Compound 1.30 was transformed to (±) teucvive in nine steps.

Scheme 1.14 Diels-Alder reaction in Yamada's total synthesis of dysidiolide

Fallis and co-workers have recently described an example of a type 3 (Scheme 1.10) intramolecular Diels-Alder reaction for the construction of cis-decalins. Cis-isopropylidene acetal group installed on the side chain was employed to restrict its flexibility and direct the facial attack of the dienophile as illustrated in Scheme 1.16.

Scheme 1.15 Total synthesis of (±)-teucvine

a) Dess-Martin periodinane, CH₂Cl₂, 21 °C, 60 h, or 40 °C, 4 h, 87%

Scheme 1.16 Construction of cis-decalines via a type 3 Diels-Alder reaction

1.3 Conclusion

To the best of our knowledge since the last reviews in the area of decalin synthesis no conceptually new methods have been developed. The classical methods briefly described in this chapter often require each stereogenic center of the target molecule to be separately installed. Moreover, the lack of selectivity at C9 and C8 centers is frequently encountered during the total synthesis of clerodane related diterpenes. In Chapter 2 we will demonstrate our novel tandem oxy-Cope/ene/Claisen strategy that has been developed to generate trans-
diterpenes possessing a quaternary carbon center at C9. We will also show the application of this strategy toward the synthesis of clerodane related diterpene (±)-agelasimine A and its analogs.
Chapter 2 Studies toward the total synthesis of (±)-agelasimine A and development of the oxy-Cope/ene/Claisen reaction

2.1 General Introduction

The rapid construction of complex polycyclic molecules in a highly stereoselective fashion remains a synthetic challenge. Processes, combining two or more reactions in one step, so called tandem reactions, can be an efficient solution to this problem.¹ Many tandem reactions reported in literature have found their application in a total synthesis of various natural products.²

In the past five years the main objective of the Barriault group has been the development of new tandem strategies for construction of multiple carbon-carbon bonds to generate in a few steps polycyclic terpene structures with high stereochemical complexity. The first methodology studied was a tandem oxy-Cope/transannular ene reaction. This reaction was originally observed by Sutherland as an undesired side reaction of an oxy-Cope rearrangement.³ Later, Paquette⁴ and Rajagopalan⁵ also reported that in some cases an anionic oxy-Cope reaction would give a side product resulting from an ene-reaction.

In our lab the tandem oxy-Cope/ene reaction has been developed as a strategy for the construction of trans-decalins with a tertiary alcohol at the ring junction. It has been shown by Warrington and Barriault that thermally induced rearrangement of trans-1,2-divinylcyclohexanols produces bi- and tricyclic structures 2.2 in a highly diastereoselective

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fashion as a result of two-step process as illustrated in Scheme 2.1. The trans stereochemistry of a decalin core of the product originates from a trans relationship of the vinyl groups on the cyclohexanol 2.1.

Scheme 2.1 Generation of bi- and tricyclic structures via oxy-Cope-ene reaction

The first step of this sequence is an oxy-Cope rearrangement generating 10-membered ring enol 2.3, which can rapidly tautomerize to give macrocyclic ketone 2.4. The ketone is properly aligned with a methyl group across the ring to undergo a transannular ene-reaction to yield 2.5 as illustrated in step 3 of Scheme 2.2.

Scheme 2.2 Mechanism of the tandem oxy-Cope/ene reaction

The applicability of this new methodology was first demonstrated in our lab by Dan Deon's total synthesis of (+)-Artemannium M, a natural product isolated from Artemisia annula L., where the tandem oxy-Cope/ene reaction was used to construct the core of the natural product as illustrated in Scheme 2.3. The simple procedure for the generation of 2.8 involved heating 1,2-divinylcyclohexanol 2.7 at 220 °C in toluene in the presence of DBU in a sealed tube. The product was obtained in good yield (55-60%), excellent diastereoselectivity

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(dr>25:1) and good enantioselectivity (ee=78%). The total synthesis was completed in only 9 steps with an overall yield of 14.1% starting from 2.6 available from (+)-limonene.

Scheme 2.3 Total synthesis of (+)-Arteannuin M from (+)-limonene

The next step in illustrating the synthetic versatility of the tandem oxy-Cope/ene methodology was demonstrating its use in the synthesis of a different family of diterpenes. Thus, the synthesis of (±)-agelasimine A was embarked upon.

2.2 Entry to the total synthesis of (±)-agelasimine A via the oxy-Cope/ene strategy

2.2.1 Introduction

Agelasimine A (Figure 2.1) is a novel nonquaternary adenine-related diterpene isolated from the orange sponge Agelas mauritiana by Fathi-Afshar and Allen in 1988.8 Its biological activities include cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca2+-channel antagonistic action and α1 adrenergic blockade.9 The structure of agelasimine A features a trans-decalin core with a tertiary alcohol at ring junction (C5 position). It bears four contiguous chiral centers C5-C10-C9-C8, including a quaternary carbon center at C9

and a tertiary center at C8, a feature characteristic of the clerodane family as well as a side chain attached to a modified adenine base. It also has geminal methyls at C4. The presence of four adjacent stereocenters, one of which is a quaternary carbon center, along with its interesting biological properties makes agelasimine an appealing synthetic target.

![Chemical structure of agelasimine A](image)

**Figure 2.1 Agelasimine A**

Ohba *et al.* have previously reported the total synthesis of agelasimine A in racemic and enantiomerically pure forms.\(^ {10}\) Their synthetic approach was to generate the bicyclic core via an aldol reaction, which took 11 steps to achieve (see Chapter 1, Scheme 1.7). Although efficient in accomplishing the goal, the strategy required each stereogenic center to be separately installed.

We have envisioned that our oxy-Cope/ene tandem strategy will generate *trans*-decalin core 2.10 of agelasimine A with three (C5, C10 and C8) chiral centers in only one step from 2.9 as depicted in Scheme 2.4.

![Scheme 2.4 Synthesis of a trans-decalin core of agelasimine A using the tandem oxy-Cope/ene reaction](image)

The two main challenges of the oxy-Cope/ene strategy that needed to be investigated were installation of a quaternary center at C9 and ensuring a syn relation of the methyl group at C8 to the tertiary alcohol at C5.

Before embarking on the synthesis of the natural product, model studies were performed on (±)-dihydroagelasimine A, an analog of agelasimine A without geminal methyls at C4 (Figure 2.2).

![Figure 2.2 Dihydroagelasimine A](image)

In order to generate the core of dihydroagelasimine A 2.12 via the tandem oxy-Cope/ene reaction we had to start from 1,2-divinylcyclohexanol 2.11 as shown in Scheme 2.5.

![Scheme 2.5 Tandem oxy-Cope/ene approach toward dihydroagelasimine A](image)

### 2.2.3 Results and Discussion

The synthesis of the substrate for the tandem oxy-Cope/ene step began by the alkylation of commercially available 1-chloro-2-cyclohexanone with the vinyl lithium species generated via metal-halogen exchange at −78 °C from trans-2-bromobutene to give chlorohydrin 2.13 in 76% yield (Scheme 2.6). Deprotonation of 2.13 with vinylmagnesium bromide induced
[1,2]-migration of the butene group followed by a nucleophilic attack on the resulting ketone to generate the desired tertiary alcohol 2.11 in 50% yield.

\[ \begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Cl} \\
\text{2.13} \\
b) \\
\text{2.11}
\end{array} \]

\text{a) trans-2-bromobutene, t-BuLi, -78 °C, 76%; b) vinylmagnesium bromide, reflux, THF, 50% over 2 steps}

Scheme 2.6 Synthesis of the starting material for the oxy-Cope/ene step

After heating in toluene at 220 °C 2.11 rearranged via the tandem oxy-Cope/ene mechanism previously described in Scheme 2.2 to give a core of dihydroagelasimine A, disappointingly as an inseparable 3.2:1 mixture of diastereomers at C8, 2.12 and 2.14 respectively (Scheme 2.7). The position of the methyl at C8 was assigned based on the NOESY and NOE difference data. When the methyl was \text{syn} to the alcohol (decaline 2.12), a strong correlation was observed between H_A and the protons of the methyl (Figure 2.3). On contrary, in the case of decaline 2.14, the NOE effect was observed for H_A and H_G. Unfortunately, we were not able to obtain the full network of NOE interactions for compound 2.14 since only few protons could be individually irradiated. The proton H_G in compound 2.14 was assigned based on its correlation with the methyl group observed in COSY experiment. Interestingly, heating the reaction in a sealed tube using a wax bath required 3 d for the reaction to go to completion whereas using the microwave oven reduced the reaction time to 1 h. Nevertheless, the results were identical; they demonstrated the capacity of oxy-Cope/ene reaction to generate a biterpene core in only 3 steps starting from commercially available 2-chlorocyclohexanone. They also revealed the first pitfall of our strategy, namely lack of selectivity at C8. (Detailed investigations on the selectivity at C8 will be presented in Chapter 3).
2.11 \[ \rightarrow \]

a) toluene, DBU, 220 °C, 70%, dr=3:2:1 in the µwave -1 h, in the sealed tube -3 d

Scheme 2.7 The tandem oxy-Cope reaction of 2.11

Figure 2.3 NOESY and NOE correlations for 2.12 and 2.14

Formation of the two diastereomers can be rationalized by the mechanism depicted in Scheme 2.8. The oxy-Cope rearrangement of 2.11 results, after tautomerization, in macrocyclic ketone 2.15. The ketone can then undergo either a ring inversion to conformer B followed by the ene-reaction generating compound 2.14 or proceed directly through the ene-reaction to give 2.12, which is the desired product (the methyl at C8 is equatorial and syn to the alcohol at C5).

Applying Curtin-Hammett principle to our model we may anticipate that the product ratio will be determined based exclusively on the difference in energies of transition states A" and B". Transition state A" (the methyl at C8 is equatorial) is expected to be lower in energy than transition state B", thus resulting in formation of desired product 2.12 as a major product.
Scheme 2.8 Proposed mechanism for the formation of the diastereomers

In spite of the low diastereoselectivity of the tandem oxy-Cope/ene reaction of 2.11 we then decided to continue the synthesis and attempt to install the next key feature – quaternary carbon center at C9. One would envision that cyclopropanation of the exo-cyclic double bond followed by reductive cleavage would provide the desired quaternary center (Scheme 2.9). Thus, the tertiary alcohols of inseparable 2.12 and 2.14 were protected with TMS group and subjected to various cyclopropanation conditions. Unfortunately, using ethyl diazoacetate in the presence of catalytic amounts of rhodium diacetate dimer, palladium acetate or copper salts as a catalyst led to the formation of complex mixtures and decomposition.
Scheme 2.9 Attempt to install the quaternary carbon center at C9 via cyclopropanation

It was obvious that a strategy toward dihydroagelasimine A needed revision, since in the course of the model studies two major problems were encountered, i.e. how to install a quaternary carbon center at C9 and how to control the selectivity at C8. On the other hand developing a new general method to install a quaternary center at C9 would provide an access to a variety of clerodanes possessing a quaternary carbon center at C9. Thus the original approach was abandoned and search for a new general method was undertaken.

2.3 Development of a tandem Oxy-Cope/ene/Claisen reaction

2.3.1 Introduction

Stereoselective synthesis of quaternary carbon centers remains a significant challenge to synthetic chemist. Although a vast number of methods have been reported, there is still a great need in developing general strategies toward construction of quaternary centers, in particular in diterpene synthesis.\(^\text{11}\)

We envisioned that adding a Claisen rearrangement step to a tandem oxy-Cope/ene sequence could provide an easy access to diterpenes with a quaternary carbon center at C9. Thus we proposed a new synthetic method based on a tandem oxy-Cope/ene/Claisen reaction sequence (Scheme 2.10).

Scheme 2.10 A proposed tandem oxy-Cope/ene/Claisen reaction

First, a thermal oxy-Cope reaction of 2.16 would produce, after tautomerization, macrocyclic ketone 2.17. The ketone would then undergo the tansannular ene-reaction to afford enol ether 2.18 properly set up to undergo the third tandem step, a Claisen rearrangement, to generate a desired quaternary carbon center at C9. A Claisen rearrangement would be expected to proceed via chair-like TS with the facial attack anti to the bridgehead alcohol. This would result in the formation of the aldehyde syn to the alcohol with potential for further hemiacetal formation.

2.3.2. Results and discussion

---

The simplest model studied was the rearrangement of allyl ether 2.21, easily prepared via etherification of diol 2.20 (Scheme 2.11). The diol was obtained in 62% yield (based on recovery of the starting material) via allylic oxidation of 2.19 with SeO₂. The etherification with allyl bromide afforded 2.21 in 73% yield. The latter was then dissolved in toluene and DBU (2 equiv) in the quartz cell equipped with a carboflon™. The solution was degassed with argon for 30 min, sealed and heated at 220 °C for 1 h in a CEM microwave. After 1 h there was no starting material present as indicated by TLC. Moreover, ¹H NMR (300 MHz) and GC-MS studies on the crude reaction mixture revealed the presence of only two diastereomeric (anomeric position) lactols 2.22. No peak corresponding to the free aldehyde was observed. This evidence confirmed our initial assumption about the Claisen rearrangement occurring anti to the bridgehead alcohol. In order to determine the precise diastereomeric ratio of the cascade process, the crude lactol mixture was oxidized with TPAP to give lactone 2.23 in 70% yield as a sole diastereomer (dr>25:1) according to ¹H NMR (300 MHz) and GC-MS of the crude. It is noteworthy that the initial experiment was performed on a rather small scale (20-50 mg) and showed great diastereoselectivity (dr>25:1). Interestingly, two years after the results were published the same reaction was performed on >1 g scale. To our dismay, formation of a side product, aldehyde 2.24 was observed in 9% yield.

¹⁴ Carboflon™ is a chemically inert fluoropolymer filled with carbon black, a strong microwave absorber. It transfers generated heat to non-polar solvents, which do not absorb microwaves, thus providing necessary energy for a reaction.
Scheme 2.11 Diastereoselective formation of the trans-decalin with a quaternary carbon center at C9

Formation of aldehyde 2.24 was attributed to the Claisen rearrangement occurring from the face syn to the bridgehead alcohol. The following rationalization has been proposed: An oxy-Cope/ene/Claisen reaction performed in the microwave in non-polar solvent such as toluene normally requires use of a carboflon™ as a heat conductor; that is assuming that substrate does not absorb microwaves itself. When an oxy-Cope/ene/reaction is carried on a scale of 20-50 mg, reaction concentration is extremely low (0.01-0.007 M), since 12-15 mL of toluene is always used due to the instrument design. Then microwaves are mostly absorbed by a carboflon™ transferring heat further to the reaction mixture. Even if a substrate partially absorbed microwaves, the excess energy would likely be dissipated in the surrounding solvent. However, scaling up (~1 g) significantly increases reaction concentration (up to 1 M). Now, the situation is changed dramatically. Extra energy received by molecules absorbing microwaves cannot be efficiently dissipated in the solvent; instead it is likely to be transferred to the neighboring molecules or used by original molecule-receptor. Thus energy supplied to these molecules is much higher than the energy, which can
be obtained by just heating at 220 °C. An excess of energy can be used by the molecules to populate higher energy conformational states, thus increasing a number of possible events that could occur in the course of the tandem reaction and during the Claisen rearrangement in particular. All this would eventually lead to general loss of selectivity for example allowing one of decaline rings to adopt boat-like conformation in which the Claisen attack syn to the alcohol is less hindered.

2.3.2.1 Synthesis of decalines with tertiary and quaternary carbon centers at C11

One could envision that, depending on the substitution pattern of allyl ether 2.16, additional tertiary or quaternary carbon centers could be introduced at C11, the center adjacent to C9 (Scheme 2.12).

Scheme 2.12 Installation of an asymmetric center at C11 via the oxy-Cope/ene/Claisen reaction

In order to investigate the scope of the oxy-Cope/ene/Claisen reaction allyl ethers with various degree of substitution at the terminal double bond were prepared via etherification of diol 2.20 with the corresponding allyl halides (Table 2-1). All allyl halides except for commercially available cinnamyl chloride 2.26e and 1-bromo-3-methyl-but-2-ene 2.26f (Scheme 12.4) were prepared from the corresponding alcohols via bromination with CBr₄/Ph₃P in CH₂Cl₂ (Scheme 2.13 and 2.14). Due to their instability on the silica gel allyl bromides were used in the etherification reaction without purification.
Ph\[\equiv\text{CH}]\text{OH} \quad \overset{\text{a)}\text{ Lindlar cat./H}_2, \text{ quinoline, hexanes, 67\%}; \text{ b)} \text{CBr}_4, \text{ Ph}_3\text{P, CH}_2\text{Cl}_2, 10 \text{ min, rt}; \text{ c)} \text{CBr}_4, \text{ Ph}_3\text{P, CH}_2\text{Cl}_2, 10 \text{ min, rt.}}{\longrightarrow} \quad \text{Ph}\[\equiv\text{CH}]\text{OH} \quad \overset{\text{b)}}{\longrightarrow} \quad \text{Ph}\[\equiv\text{CH}]\text{Br} \quad \overset{\text{2.25a}}{\longrightarrow} \quad \overset{\text{2.26a}}{\longrightarrow}

\text{2.25b}

\text{2.26b}

\text{a)} \text{(EtO)}_2\text{P(O)CH}_2\text{CO}_2\text{Et, NaH, THF, 0 \text{\degree} C}; \text{ b)} \text{DIBAL-H, THF, -78 \text{\degree} C, 67\% over 2 steps}; \text{ c)} \text{CBr}_4, \text{ Ph}_3\text{P, CH}_2\text{Cl}_2, 10 \text{ min, rt.}

\text{\textbf{Scheme 2.13} Synthesis of allyl bromides}

\text{a)} \text{(EtO)}_2\text{P(O)CH}_2\text{CO}_2\text{Et, NaH, THF, 0 \text{\degree} C, 62\%}; \text{ b)} \text{DIBAL-H, THF, -78 \text{\degree} C, 64\%}; \text{ c)} \text{CBr}_4, \text{ Ph}_3\text{P, CH}_2\text{Cl}_2, 10 \text{ min, rt.}

\text{Ph}\[\equiv\text{Cl}] \quad \overset{\text{2.26e}}{\longrightarrow} \quad \overset{\text{2.26f}}{\longrightarrow}

\text{available from Aldrich} \quad \text{available from Alfa}

\text{\textbf{Scheme 2.14} Synthesis of allyl bromides, contd.}

\textbf{Table 2-1 Preparation of substrates for the oxy-Cope/ene/Claisen reaction}

\begin{table}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Allyl bromide & R_1 & R_2 & R_3 & Product & Yield, \% \\
\hline
1 & \textbf{2.26b} & R_1, R_3 = -(\text{CH}_2)_4, R_2=\text{H} & 2.27 & 68 \\
\hline
2 & \textbf{2.26e} & Ph & H & H & \textbf{2.28} & 80 \\
\hline
\end{tabular}
\end{table}

44
Allyl ethers (2.27-2.29) were dissolved in toluene and 3-10 equiv of DBU in a quartz tube, degassed with argon for at least 30 min and irradiated at 220 °C for 1 h in a microwave reactor. In order to determine a diastereomeric ratio, the crude mixture of lactols was oxidized with TPAP. The results are summarized in the Table 2-2.

Table 2-2 Synthesis of decalines with tertiary centers at C11

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl ether</th>
<th>Product</th>
<th>Yield, %</th>
<th>Lactone</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.27</td>
<td><img src="image1" alt="Image" /></td>
<td>60</td>
<td>2.33a</td>
<td>25:1</td>
</tr>
<tr>
<td>2</td>
<td>2.28</td>
<td><img src="image2" alt="Image" /> and <img src="image3" alt="Image" /></td>
<td>90</td>
<td>2.34a and 2.35a</td>
<td>2:1</td>
</tr>
</tbody>
</table>
We were pleased to observe that irradiation of 2.27 (entry 1) produced a mixture of lactols 2.33, which upon oxidation gave the corresponding lactone 2.33a with tertiary center at C11 as a single diastereomer. The relative stereochemistry of the tertiary center (R configuration) was determined by X-ray crystallography (Appendix 1). Surprisingly, after heating allyl ether 2.29 in the microwave followed by oxidation of the crude reaction mixture with TPAP, a mixture of two diastereomeric lactones 2.34a and 2.35b was obtained in 2:1 ratio. Thus, replacing phenyl group for an alkyl chain resulted in loss of selectivity. Formation of two diastereomeric lactones 2.35a and 2.34a as a 1:1 mixture was also observed after the oxy-Cope/ene/Claisen reaction of 2.29 followed by TPAP oxidation of a crude mixture of lactols (entry 3). These observations can be rationalized by the mechanism shown in Scheme 2.15. First, the oxy-Cope rearrangement of 2.28 produces enol 2.36, which then rapidly tautomermizes to afford ketone 2.37. The latter is ready to undergo a tansannular-ene reaction. Assuming that the ene-reaction proceeds via chair-like transition state and therefore 10-membered ring macrocycle adopts chair-chair like conformation, two conformations, A\(^\#\) and B\(^\#\), are possible. The difference between A\(^\#\) and B\(^\#\) lies in which hydrogen is being abstracted in the course of the ene-reaction. When \(\text{H}_1\) is being abstracted (transition state A\(^\#\)), alkoxy group occupies a pseudo equatorial position, whereas abstraction of \(\text{H}_2\) (transition state B\(^\#\)) places the same alkoxy group in a pseudo axial position thus creating unfavorable 1,3-diaxial interactions with the macrocycle ring and raising the energy of
conformer B. This should make $A^*$ a dominant transition state and yield $E$ enol ether 2.38. Finally, the Claisen rearrangement proceeding via chair-like transition state gives lactol 2.34, which is, in fact, the major product of the tandem reaction. However if the energy difference between A and B were not significant, formation of both, $E$ (2.38) and $Z$ (2.39) enol ethers could be possible. In that case, both diastereomers 2.34 and 2.35 should be obtained.

Scheme 2.15 Proposed mechanism of the tandem oxy-Cope/ene/Claisen reaction

To determine which geometry results from the ene-reaction, the following experiment was performed. A primary alcohol in diol 2.20 was protected with Mel, therefore eliminating the possibility of the Claisen rearrangement. Resulting ether 2.40 was heated at 220 °C for 1 h to give only one isomer 2.41 according to $^1$H NMR (300 MHz) of the crude reaction mixture (Scheme 2.16). The $E$ geometry of the enol ether was confirmed by NOE experiment (For more details see Appendix 2, Table 9). The position of proton $H_A$ was unambiguously
assigned based on its chemical shift value (5.49 ppm, 500 MHz, C\textsubscript{6}D\textsubscript{6}). Upon irradiation of proton H\textsubscript{A} in NOE difference experiment, NOE was observed for a methyl group (2.5%) as well as a proton at 1.35-1.28 ppm (4.9%). In case of E-enol ether one would expect to see the correlation between H\textsubscript{A} and proton H\textsubscript{B}. Whereas for Z-enol ether a correlation between H\textsubscript{A} and H\textsubscript{C} would be detected. A multiplet at 3.12-3.07 ppm (\textsuperscript{1}H NMR, 500 MHz) was assigned as proton H\textsubscript{D}. Its chemical shift matched with the one expected for allylic proton and according to the HMOC data it 1.35-1.28 ppm neither in COSY nor NOE difference experiments. Described observations allowed us to assign a proton at 1.32 ppm as H\textsubscript{B} and therefore establish the geometry of the enol ether 2.41 as E. Exclusive formation of E enol ether supports our hypothesis of A\textsuperscript{#} being the only transition state for the ene-reaction, but does not explain loss of diastereoselectivity in entry 2 (Table 2-2).

Scheme 2.16 Formation of E enol ether
The use of DBU as a proton scavenger in the tandem oxy-Cope/ene/Claisen reaction originated from the oxy-Cope/ene project. Its presence led to higher yields and less degradation.\textsuperscript{16} Since DBU is quite a strong base (pK\textsubscript{protonated base} \sim 12), it could potentially abstract an acidic proton in the starting material or product at 220 °C. This could lead to loss of selectivity. In our system, the proton at C11 in 2.34 being next to the phenyl and vinyl groups might be acidic enough to be deprotonated with DBU upon formation of the lactol. Thus appearance of the second minor diastereomer could be attributed to epimerization

(Scheme 2.17). Intriguingly, changing from DBU to much weaker base Et$_3$N gave the same diastereomeric ratio of 2:1.

Scheme 2.17 Possible epimerization of the oxy-Cope/ene/Claisen product

In order to get a better insight into the real mechanism studies with deuterated allyl ether 2.42 were initiated. The rearrangement of 2.42 would result in lactol 2.43 featuring a deuterium atom at C11. If deuterium were to be removed from the tertiary center at C11 by a base, the reverse protonation would result in formation of the minor isomer 2.35 having now hydrogen instead of deuterium atom at C11 (Scheme 2.18). Therefore, the loss of deuterium would be observed and could be detected by $^1$H NMR due to the difference in their magnetogyric ratios (as a result the resonance frequency for $^1$H is always 6.6 times as large as that for $^2$H)

Scheme 2.18 Proposed studies with deuterated allyl ether

Deuterated allyl bromide 2.46 was first prepared from commercially available $\alpha$-deuterated benzaldehyde 2.44 using Horner-Wadsworth-Emmons protocol followed by DIBAL reduction and allylic bromination of the alcohol 2.45 (Scheme 2.19). It was used without purification in the etherification of diol 2.20 to give desired allyl ether 2.42 in 25% yield (not optimized). The allyl ether was heated in toluene with Et$_3$N (3 equiv) at 220 °C for 1 h in the
microwave to yield again a mixture of diastereomers 2.43 and 2.47 (Scheme 2.20). The crude mixture was further oxidized with TPAP to afford a 2:1 mixture of lactones 2.43a and 2.47a. However, no loss of deuterium was observed according to $^1$H NMR thereby ruling out a possible epimerization with a base.

\[
\begin{align*}
\text{Ph} & \quad \text{2.44} \quad \text{a), b)} \quad \text{Ph} \\
\text{D} \quad \text{2.45} \quad \text{c)} \quad \text{Ph} \\
\text{O} & \quad \text{2.46} \quad \text{d)} \\
\end{align*}
\]

a) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, 0 °C, b) DIBAL-H, THF, -78 °C, 25% over 2 steps; c) CBr$_4$, Ph$_3$P, CH$_2$Cl$_2$, 10 min, rt, use crude in the next step; d) 2.20, NaH, THF, 26%.

Scheme 2.19 Preparation of deuterated allyl bromide

\[
\begin{align*}
\text{Ph} & \quad \text{2.42} \quad \text{a)} \\
\text{O} & \quad \text{2.43 and 2.47} \quad \text{b)} \\
\text{OH} & \quad \text{2.43a} \quad 2:1 \\
\text{OH} & \quad \text{2.47a} \\
\end{align*}
\]

a) 1 h, 220 °C, μwaves, Et$_3$N; b) ms, TPAP, NMO, CH$_2$Cl$_2$, 44% over 2 steps.

Scheme 2.20 The tandem oxy-Cope/ene/Claisen rearrangement of deuterated allyl ether

Interestingly, performing oxy-Cope/ene/Claisen reaction on 2.28 at different temperatures clearly demonstrated that diastereomeric outcome of the reaction is temperature dependent (Table 2-3).

Table 2-3 Temperature dependence of the oxy-Cope/ene/Claisen rearrangement of 2.28
<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temperature, °C</th>
<th>Yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr (2.34a : 2.35a)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>220</td>
<td>44</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>220</td>
<td>N/A</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>200</td>
<td>40</td>
<td>11:1</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>180</td>
<td>55</td>
<td>13:1</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>160</td>
<td>Trace</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield of the lactone mixture over 2 steps.<sup>b</sup> Diastereomeric ratios were determined by 300 MHz <sup>1</sup>H NMR of a crude mixture of lactones. We have originally reported that the oxy-Cope/ene/Claisen rearrangement of 2.28 at 220 °C occurs with a high diastereoselectivity (dr>25:1), however, this result has been found irreproducible.

At 220 °C the diastereoselectivity of the tandem reaction remained poor regardless of the presence of the base (entries 1 and 2). However, decreasing the reaction temperature to 200 °C gave a ratio of 11:1 (entry 3) thereby significantly improving the selectivity. The further progress in diastereoselectivity (now 13:1 ratio) was achieved when the temperature was lowered to 180 °C (entry 4). Finally, at 160 °C no reaction or only trace of the product was observed after prolonged heating in the microwave, thereby outlining a temperature barrier for the oxy-Cope reaction. This temperature dependant behaviour suggests that there is a competing pathway for the Claisen reaction at 220 °C. The Claisen rearrangement can occur via chair-like transition state A to afford lactol 2.34 (major product) or through higher energy boat-like transition state B resulting in the formation of minor isomer 2.35 (Scheme 2.21).
Scheme 2.21 Two possible transition states for the Claisen rearrangement step in the tandem reaction of 2.28

Encouraged by our success in generation of decalines with a tertiary center at C11, we then investigated the synthesis of decalines with a quaternary carbon center at C11.

To our satisfaction, when allyl ether 2.30 was subjected to standard reaction conditions (toluene, DBU, 220 °C, microwave, 1 h) desired lactol 2.48 bearing two adjacent quaternary carbon centers at C11 and C9 was isolated (dr>25:1, determined after reduction with LiAlH₄) in 76% yield (Scheme 2.22). Interestingly, E enol ether 2.49 (E/Z > 98%) was also formed as a side product in 15% yield. (Assignment of the geometry of enol ether 2.49 was done using the same arguments as for compound 2.41). Prolonged exposure of 2.49 to heat resulted in degradation products.
Scheme 2.22 Formation of decaline with two adjacent quaternary carbon centers

The next step was to attempt a synthesis of decalines with an asymmetric quaternary center. Contrary to expectations, heating allyl ether 2.31 in the microwave afforded a 1,3 shift product 2.50 as a single diastereomer at C9 (dr>25:1)\(^{17}\) (Scheme 2.23). Moreover, partial isomerization of the double bond was observed (\(E/Z=9:1\))

\[
\begin{align*}
\text{2.31} & \xrightarrow{\text{a)} DBU, toluene, 220 ^\circ C, 1 \text{ h, microwaves}} \rightarrow \begin{align*}
\text{2.50} & \quad \text{Observed} \\
\text{2.50a} & \quad \text{Not observed}
\end{align*} \\
\text{2.50} & \xrightarrow{\text{b)} TPAP, NMO, ms, CH}_2\text{Cl}_2, 51\% \text{ over 2 steps.}
\end{align*}
\]

a) DBU, toluene, 220 °C, 1 h, microwave; b) TPAP, NMO, ms, CH\(_2\)Cl\(_2\), 51% over 2 steps.

Scheme 2.23 Formation of 1,3-shift product

\(^{17}\) Diastereomeric ratio was determined after the oxidation of lactol to corresponding lactone 2.50a
Later on Julie Frand (MSc student in our lab) demonstrated that irradiation of allyl ether 2.51 gave similar results (Scheme 2.24).\(^{18}\) Heating of this substrate in the microwave resulted in the formation of 1,3 shift product 2.52 \( (E/Z = 56:44) \) in 34% yield. As in the case of irradiation of allyl ether 2.30 in which formation of enol ether was observed (Scheme 2.22), enol ether 2.53 was also isolated in 51% yield. Remarkably, irradiations of 2.54 afforded 1,3 shift product 2.55 and dimer 2.56 in 24% and 20% yield respectively.

![Scheme 2.24 Results of Julie Farand](attachment://Scheme-2.24.png)

**Scheme 2.24 Results of Julie Farand**

Isomerization of the double bond as well as formation of the dimer points to a possibility of radical mechanism involved in the tandem process. Thus formation of an oxaallyl-allyl radical pair A in the course of the Claisen rearrangement was postulated (Scheme 2.25). This mechanism is also supported by literature examples.\(^{19}\) Gajewski has previously demonstrated that the chair-like transition state for the Claisen rearrangement resembles the oxaallyl-allyl radical pair, particularly, in the presence of radical stabilizing substituents. In our case, phenyl groups can act as radical stabilizers. Thereby formation of the oxaallyl-allyl radical pair can lead via consequent recombination to 3,3-, 1,3- or dimer products. Sterically demanding substituents increase the activation energy of the Claisen rearrangement, favoring the alternative 1,3 shift.

---


Scheme 2.25 Claisen rearrangement proceeding via an oxaallyl-allyl radical pair

According to the Curtin-Hammett principle and assuming that allyl ethers 2.31 (Scheme 2.26) and 2.51 generate the oxaallyl–allyl radical pairs B₁ and B₂, if isomerization equilibrium of the allyl components C₁ and C₂ is fast, allyl ether should form products 2.50 and 2.52 with identical E/Z ratio. The difference in ratios demonstrates that the recombination rate of the radical pair competes with the allyl radical isomerization rate.

An attempt to generate a decalin with asymmetric quaternary carbon centers at C9 and C11 from allyl ether 2.32 was not successful (Scheme 2.27). Formation of a complex mixture of products was observed. E enol ether 2.59 was isolated in 55% yield along with a mixture of desired 3,3-product (2.57) and 1,3-shift product (2.58) in 10% yield. A mixture of 2.57 and 2.58 was reduced by LiAlH₄ to afford diols 2.60 and 2.61 in a 1:1.4 ratio. Their structures were tentatively assigned based on spectroscopic data of the mixture, since we were unable to isolate individual compounds.
2.3.2.2 Propargyl ether series

The new tandem oxy-Cope/ene/Claisen reaction gave excellent results in case of propargyl ether series. Ethers 2.63, 2.64, and 2.65 were prepared from the corresponding propargyl bromides 2.62a-c (Scheme 2.28) and heated in the microwave under standard conditions (toluene, DBU, 1h, 220 °C or 210 °C) (Table 2-4).
Scheme 2.28 Preparation of propargyl ethers

Table 2-4 Oxy-Cope/ene/Claisen reaction of propargyl ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Temp., °C</th>
<th>Time, min</th>
<th>Product</th>
<th>Yield, %a</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.63</td>
<td>H</td>
<td>220</td>
<td>60</td>
<td>2.66(A)</td>
<td>98</td>
<td>25:1</td>
</tr>
<tr>
<td>2</td>
<td>2.64</td>
<td>Me</td>
<td>210</td>
<td>50</td>
<td>2.67(A)</td>
<td>68</td>
<td>25:1</td>
</tr>
<tr>
<td>3</td>
<td>2.65</td>
<td>CH₂OBn</td>
<td>220</td>
<td>60</td>
<td>2.68(B)</td>
<td>81</td>
<td>25:1</td>
</tr>
</tbody>
</table>

a Isolated yields. b Diastereomeric ratios were determined after TPAP oxidation to the corresponding lactones

Depending on the substituents on the propargyl group, either compound A or B was isolated. In the case of R being electron-donating group such as H or CH₃ (entries 1 and 2) only formation of allene A was observed in 98% and 68% yields and great diastereomeric ratios.
When R was an electron-withdrawing group such as CH₂OBn (entry 3) tetracyclic acetal B was obtained in 81% yield as a single diastereomer (dr>25:1). Formation of tetracyclic acetal B can be explained via attack of the lactol hydroxyl group on the allene (Scheme 2.29). Interestingly, only one isomer is formed since lactol C is not able to cyclize to acetal D due to geometrical reason. Thereby, the equilibrium is completely shifted toward lactol A.

Scheme 2.29 Mechanism of formation of tetracyclic acetal B

2.3.3. Conclusion.

The tandem oxy-Cope/ene/Claisen reaction is a powerful method to generate trans-decalines with a quaternary carbon center at C9. It can be used to install a tertiary and quaternary carbon center at C11. However, restrictions apply: 1) Sterically demanding substituents on the double bond increase the activation energy of the Claisen rearrangement, therefore favoring the alternative 1,3 shift. 2) Claisen rearrangement can pass through a boat-like transition state at high internal temperatures, thereby resulting in loss of diastereoselectivity.
2.4 Application of the oxy-Cope/ene/Claisen reaction to the synthesis of (\pm)-dihydroagelasimine A

We have previously demonstrated (Section 2.3.2) that the oxy-Cope/ene/Claisen reaction can generate decaline 2.22 with a quaternary carbon center at C9 in only one step from allyl ether 2.21 as illustrated on Scheme 2.30.

\[ \text{2.21} \xrightarrow{\text{a) DBU, toluene, \text{\textmu}waves, 220^\circ C, 75\%}} \text{2.22} \]

**Scheme 2.30** Formation of decaline 2.22 with a quaternary carbon center at C9

With this new powerful tool we returned to the total synthesis of dihydroagelasimine A. The first challenge was to establish whether introduction of substitution at C-8 would have any impact on diastereoselectivity of the oxy-Cope/ene/Claisen reaction (Scheme 2.31).

\[ \text{2.69} \xrightarrow{\text{\textmu}waves} \text{2.69a} \xrightarrow{\text{OH}} \text{dihydroagelasimine A} \]

**Scheme 2.31** Application of the tandem oxy-Cope/ene/Claisen reaction to the synthesis of dihydroagelasimine A

In order to synthesize precursor 2.69 for the tandem reaction several synthetic approaches were investigated. It was envisioned that the large allyl ether side chain could be prepared separately and then attached to a cyclohexane core.

Synthesis of the side chain began with hydrostannylation of 2-butyne-1-ol 2.70 in the presence of palladium (0) catalyst in toluene to afford desired regioisomer 2.71 as a major
product in 70% yield (Scheme 2.32).\textsuperscript{20} Tin-iodine exchange in CH\textsubscript{2}Cl\textsubscript{2} produced unstable vinyl iodide 2.72 in 89%.\textsuperscript{21} The latter was deprotonated with NaH, followed by addition of freshly distilled allyl bromide and refluxed for 3 h to give allylated product 2.74 in 50-70% yield.\textsuperscript{22}

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\text{OH}};
\node (b) at (1,0) {\text{SnBu}_3};
\node (c) at (2,0) {\text{OH}};
\node (d) at (3,0) {\text{O}};
\node (e) at (0,-0.5) {\text{2.70}};
\node (f) at (1,-0.5) {\text{2.71a}};
\node (g) at (2,-0.5) {\text{2.72}};
\node (h) at (3,-0.5) {\text{2.73}};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);

\node (i) at (1.5,-1) {\text{Bu}_3\text{Sn}};
\node (j) at (1.5,-1.5) {\text{2.71b}};

\node (k) at (1.5,-2) {\text{a) Pd(Ph}_3\text{), n-Bu}_3\text{SnH, toluene, 70\% of 2.71a and 10\% of 2.71b; b) CH}_2\text{Cl}_2, I_2, 89\%; c) NaH, THF, 70 \%}};

\end{tikzpicture}
\end{center}

a) Pd(Ph\textsubscript{3}), n-Bu\textsubscript{3}SnH, toluene, 70\% of 2.71a and 10\% of 2.71b; b) CH\textsubscript{2}Cl\textsubscript{2}, I\textsubscript{2}, 89\%; c) NaH, THF, 70 \%.

Scheme 2.32 Synthesis of the side chain

The 1,2-rearrangement method was first considered for attaching the side chain to a cyclohexane core (as described in Section 2.2.3, Scheme 2.6). Alkylation of commercial 1-chloro-2-cyclohexanone with the vinyl lithium species (generated via metal-halogen exchange of 2.73 with t-BuLi at −100 °C for 1 h) gave chlorohydrine 2.74 (Scheme 2.33). It was then deprotonated with excess of vinylmagnesium bromide (3 equiv) to induce [1,2]-rearrangement followed by alkylation. Unfortunately this procedure was inefficient, since a mixture of the intermediate ketone 2.75 and vinyl alcohol 2.69 was always isolated. Thus the strategy was slightly modified. Only 1 equiv of vinylmagnesium bromide was added to chlorohydrine 2.74 affording ketone 2.75 after 1 h of reflux in THF. The product was isolated, purified and treated with vinylmagnesium bromide at rt. The reaction went to completion giving a mixture diastereomers 2.69 and 2.76 in 56\% and 12\% yields.

\textsuperscript{21} Decomposition was evident when 2.73 was stored in the freezer for more than two days.
\textsuperscript{22} The iodide was found to be quite volatile and difficult to handle, but stored for more than six months without degradation.
respectively. Formation of diastereomers can be attributed to attack of vinyl anion from both faces of the ketone with preferred mode of attack being anti to the large side chain. Attempts to increase selectivity by decreasing reaction temperature to –78 °C, 0 °C or 10 °C were not successful, giving mainly starting material.

\[
\text{a) } \text{2.73, t-BuLi, Et}_2\text{O, -90 °C, 45%; b) vinylmagnesium bromide, THF, reflux, 2 h, 68%; c) vinylmagnesium bromide, THF, rt, 56% of 2.70 and 12% of 2.76.}
\]

Scheme 2.33 Synthesis of allyl ether 2.69
Due to the low yield of the overall process (17% yield over 3 steps) other coupling strategies were also explored, such as Stille or Negishi coupling with iodoenone 2.77 followed by reduction of the conjugated double bond (Scheme 2.34).

\[
\text{Scheme 2.34 Proposed synthesis of 2.69 via metal catalyzed coupling reaction}
\]

Unfortunately, Negishi coupling with protected bromo-enone 2.78 resulted in only 26% yield of coupling product 2.79 and was not reproducible. While Stille coupling worked well
with simple vinyl stannanes and several examples were reported in our lab,\textsuperscript{23} the presence of extra functionalities on the vinyl stannane compound seemed to decrease its reactivity dramatically resulting in no reaction.

\[
\begin{align*}
\text{2.78} & \xrightarrow[\text{a)]{2 \text{ equiv of } t\text{-BuLi, THF then } ZnBr}_2 \text{ then 2.73 and } Pd(PPh}_3)_4}\text{, 26%}.
\end{align*}
\]

\text{Scheme 2.35 Approach using Negishi coupling}

Finally, the epoxide opening strategy was undertaken. A three-step sequence starting from cyclohexene oxide opening with vinyl cuprate generated from vinyl iodide 2.73, followed by oxidation of the alcohol and vinylmagnesium bromide addition to the ketone was expected to afford desired substrate 2.69 (Scheme 2.36).

\[
\begin{align*}
\text{a) } & 2.73, t\text{-BuLi, Et}_2\text{O, Cu (I) catalyst; b) [O], c) vinylmagnesium bromide, THF, rt.}
\end{align*}
\]

\text{Scheme 2.36 Epoxide-opening strategy}

A number of protocols employing cuprates of different order were investigated. Unfortunately, formation of the desired product was never observed. Since most of the conditions required prolonged stirring at \(-40\) to \(-20\) °C, \(\beta\)-elimination could likely be an alternative reaction pathway.\textsuperscript{24}

Since all our attempts to optimize the strategy were unsuccessful, we returned to the original approach for generating 2.69. The latter was subjected to the oxy-Cope/ene/Claisen reaction

\textsuperscript{23} Thomas, J.D.O.; MSc Thesis, University of Ottawa, 2002.

in the microwave (Scheme 2.37). After heating at 220 °C for 1 h all starting material was consumed according to TLC. The ^1H NMR spectrum of the crude reaction mixture was quite complex, indicating a presence of more than two products. Also, a peak at 9 ppm characteristic to an aldehyde was observed. Purification by flash chromatography led to the isolation of two products, the less polar being indeed an inseparable 15:1 mixture of aldehydes 2.80 and 2.81 (47% yield). The more polar spot (41% yield) was found to be a mixture of four lactols 2.82a-b, which upon oxidation with TPAP afforded a 2:1 mixture of lactone 2.83 and 2.84 (Scheme 2.38). Relative stereochemistry of aldehyde 2.80 was assigned based on a NOESY correlation.

Scheme 2.37 The oxy-Cope/ene/Claisen reaction of 2.69

Scheme 2.38 TPAP oxidation of lactols 2.82a and 2.82b

In order to rationalize complete loss of selectivity with the addition of the methyl group at C8 a stepwise mechanism of the tandem oxy-Cope/ene/Claisen reaction was thoroughly investigated. As illustrated in Scheme 2.39, the oxy-Cope reaction of 2.69 generates enol
2.85, which then tautomerizes to afford macrocyclic ketone 2.86. In the latter the equatorial position of methyl at C8 is inherited from the original cis-geometry of the vinyl group in the starting material. Ketone 2.86 can either directly proceed to the ene-reaction or first undergo a ring inversion to conformer B followed by the ene-reaction. Two transition states should be considered for each of the ene-reactions depending on the proton being abstracted.\(^{25}\)

Abstraction of H\(_1\) (transition states A\(_1^*\) and B\(_1^*\)) should lead to formation of E-enol ethers 2.87 and 2.88 respectively. When H\(_2\) is being abstracted (transition states A\(_2^*\) and B\(_2^*\)), Z-enol ethers 2.89 and 2.90 should be generated. In transition state A\(_1^*\), the alkoxy group occupies a lower energy pseudo equatorial position, whereas in transition state A\(_2^*\) the alkoxy group is pseudo axial and develops 1,3-diaxial interactions with the macrocycle ring. However, in A\(_1^*\), there is a destabilizing syn pentane interaction between the methyl at C8 and the alkoxy group. Thus, the difference in energy between transition state A\(_1^*\) and transition state A\(_2^*\) becomes less significant and formation of both E and Z enol ethers is expected. It will not affect, however, the outcome of the subsequent Claisen rearrangement since there is no chiral center at C11 present in the final product. Transition state B\(_1^*\) does not exhibit a syn pentane interaction between the methyl at C8 and the alkoxy group and should be favored over B\(_2^*\), resulting in E-enol ether 2.88. The successive Claisen rearrangement can occur from the face either anti or syn to the alcohol. Since only a trace of aldehyde 2.81 (Scheme 2.37) was detected, it can be concluded that the Claisen rearrangement for enol ethers 2.87 and 2.89 occurs almost exclusively from the face anti to the alcohol to avoid steric repulsions, affording lactol 2.82a (Scheme 2.40). In case of enol ether 2.88 one has to discriminate between attacks anti to the alcohol or anti to the axial.

\(^{25}\) Again, we assume that Curtin-Hammet principle applies to this case, i.e. a product ration is only dependant on the difference in energies of the corresponding transition states.
methyl at C8 with no real preference for either two, since both transition states should have similar energies. This results in formation of both lactol 2.82b and aldehyde 2.80.

Scheme 2.39 Proposed mechanism for the oxy-Cope/ene/Claisen reaction of 2.69. The oxy-Cope/ene part
Scheme 2.40 Proposed mechanism for the oxy-Cope/ene/Claisen reaction of 2.69. The Claisen part

2.5 Conclusion

Unfortunately, selectivity of the ene-reaction and the Claisen rearrangement step are both affected by the presence of substituent at C8. Ross MacLean (MSc student in our lab) obtained similar results in the course of his attempts toward the total synthesis of natural product Rosane, when substrate containing the allyl group at C8 was employed.\textsuperscript{26} Significant effort was also made in our lab to install the functionality at C8 after the oxy-Cope/ene/Claisen reaction, however without major success.

A different approach was taken in the course of our studies. It was proposed that control over the macrocycle ring inversion could be gained by installing extra substituents on the ring,

\textsuperscript{26} MacLean, P.R.; MSc Thesis, University of Ottawa, 2003.
thus changing the steric component. This led to the new model studies, which are described in Chapter 3.
Chapter 3 Control of the selectivity at C8

3.1 Background

As we demonstrated in Chapter 2, the loss of selectivity at C8 during both oxy-Cope/ene and oxy-Cope/ene/Claisen tandem reactions originates from the ene-reaction step, in which the starting material, 10-membered ring ketone, can adopt a number of conformations. The reactivity of the system in which many conformers exist in equilibrium is directly related to their conformations. Thus both reaction rates and product ratios may depend on the ratio of the conformers in their ground states as well as the conformation of the corresponding transition states. The general kinetic scheme (Figure 3.1) is applied to describe a system with several reactive conformers.¹

\[ \begin{align*}
D & \xrightleftharpoons[k_d]{k_j} B \xrightleftharpoons[k_2]{k_1} A \xrightarrow[k_c]{\cdot} C
\end{align*} \]

Three situations that should be considered are listed below:

1. \( k_1, k_2 \gg k_d \) and \( k_c \) - Curtin-Hammett principle²

\[ \frac{[C]}{[D]} = e^{\Delta G^\ddagger / RT} \text{ or } \Delta G^\ddagger = RT \ln \frac{[C]}{[D]} \]

2. \( k_c, k_d \gg k_1 \) and \( k_2 - B/A \) ratio remains constant during the reaction

\[ D/C \text{ ratio reflects } B/A \text{ ratio} \]

3. \( k_c, k_d \sim k_1 \) and \( k_2 - \) equilibrium is not maintained, complex kinetics

Figure 3.1 General kinetic scheme for two reactants in equilibrium

Returning to the oxy-Cope/ene reaction and concentrating on the ene-step, we should take into account that conformer A, which is a direct result of the chair-like transition state of the

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oxy-Cope reaction, can undergo a ring inversion prior the ene reaction to give more than one stable conformer as shown in Scheme 3.1.

![Scheme 3.1 Preliminary analysis of the oxy-Cope/ene reaction](image)

To simplify matters we should again consider the case when the rate constants for the ring inversion are much higher than the reaction rates of the ene-reactions of all possible conformers. Thus we can apply Curtin-Hammett principle (case 1, Figure 3.1) and rationalize the product ratio based solely on the energies of the transition states in going from the macrocycle ketone conformers to the ene-products.³

10-membered ring macrocycles can adopt more than two conformations, with the most stable one being a boat-chair-boat (BCB) conformation not a chair-chair-chair (CCC) conformation (Figure 3.2).⁴

![Figure 3.2 The most stable conformation for a saturated 10-membered macrocycle](image)

However, not all conformations of the macrocycle can give the ene-products for two reasons. First, the methyl group on the double bond and the ketone group and have to align for further proton abstraction. Second, the ene-reaction has to proceed via chair-like transition state. Therefore due to geometrical constraints, only a few of the possible

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conformers can reach the transition state of the ene-reaction. AM1 semi-empirical calculations that we have performed using Spartan software show that the energy of the transition state for the ene-reaction is minimized when the macrocyclic ketone is in CCC conformation. Now we can assume that conformers A and B are the only reactive conformers out of all possible ones (Scheme 3.2). Thus conformer A will convert to product C via transition state $A^*$ whereas conformer B will give product D via transition state $B^*$. As we previously demonstrated (see Scheme 2.7, Chapter 2), the experimental C/D ratio was 3.2:1 (at 220 °C). This ratio is consistent with 1.14 kcal/mol energy difference between transition state $A^*$ (lower in energy) and transition state $B^*$ at the reaction temperature of 493 K (220 °C).

Scheme 3.2 Conformational and kinetic analysis of the ene reaction of macrocycle conformers A and B
To increase the C/D ratio at a particular temperature one would have to increase the energy difference between $A^*$ and $B^*$. For example, to get a ratio of 10:1 at 493 K, the $\Delta G^*$ would have to be ~2.5 kcal/mol.
W.C. Still et al. previously demonstrated by studying medium- and large-ring organic molecules that conformational properties of macrocycles determine the stereochemical outcome of their chemical reactions. This is directly related to the fact that macrocycles are most likely to adopt a conformation in which all transannular nonbonding repulsions are minimized. As already mentioned above, in the case of saturated 10-membered rings BCB conformation is the most stable one. Moreover, the pseudo A-values for a substituent on the macrocycle depend not only on the size of a given substituent but also on which site of the macrocycle this substituent is located. For some sites the energy difference between pseudo equatorial and pseudo axial substitution is so high, that the latter becomes forbidden. Most importantly, W.C. Still has shown that in some cases having a single remote substituent on the macrocycle can provide an effective control over asymmetric induction in the course of a reaction. For example, alkylation of macrocyclic enolate 3.1 under kinetic conditions gave macrocycle 3.2 as a single diastereomer (dr>99:1) (Scheme 3.2), which was in agreement with results of molecular mechanics calculations. The latter demonstrated that BCB was the most stable conformation of the 10-membered enolate and axial substitution was preferred for the methyl at C9 position. Thus, formation of only cis-isomer was observed after nucleophilic attack.

![Scheme 3.3 Control over asymmetric induction by a single substituent on a 10-membered macrocycle](image)

Based on our kinetic and conformational analysis of the ene-reaction step in the oxy-Cope/ene sequence discussed above (Scheme 3.2), we proposed installing a remote chirality on the macrocyclic ketone to improve the ratio of the ene-products and therefore increasing selectivity at C8. When choosing a proper substituent for the remote stereochemical control, we had to consider its further applicability in the total synthesis of agelasimine. Two factors were taken into account: 1. In the total synthesis of (±)-agelasimine it was necessary to install geminal dimethyls at C4 (Figure 3.3). At the time neither oxy-Cope/ene nor oxy-Cope/ene/Claisen reactions had been performed in our lab with this functionality present on the substrate. Thus its impact on the selectivity outcome of the tandem processes remained unknown and required further investigation. 2. Extra substituents, if they were not present on the natural product, would have to be easily removable after the oxy-Cope/ene step.

![Image of agelasimine A and dihydroagelasimine A](image)

**Figure 3.3 Agelasimine A and dihydroagelasimine A**

Based on the above-mentioned criteria an “ideal substrate” for our model studies on the oxy-Cope/ene reaction was designed. As shown in Figure 3.4 this substrate contained geminal dimethyls and axial alkoxy group, which could be removed later in the synthesis.

![Image of ideal substrate](image)

**Figure 3.4 Ideal substrate for the model studies on the selectivity at C8 in the oxy-Cope/ene reaction**
In addition, the geometry of the butenyl group was changed to trans (compare to the cis geometry in the original model).

As illustrated in Scheme 3.4, the oxy-Cope reaction of 1,2-divinylcyclohexanol 3.3 followed by tautomerization would generate macrocyclic ketone 3.4. Once again, assuming that relative stabilities of the conformational isomers of the macrocycle do not contribute to a product ratio (Curtin-Hammett principle), we would only have to account for stabilities of the conformers relevant to the transition state of the ene-reaction.

Scheme 3.4 Proposed mechanism of the oxy-Cope/ene reaction of 3.3
In this regard, two conformers C" and D" should be considered. In conformer C" the methyl at C8 as well as the alkoxy group at C2 occupy axial positions creating unfavorable 1,3-diaxial interactions with hydrogen at C10 and one of the geminal methyls. Inversion of macrocycle 3.4 will lead to transition state D" in which the methyl and the alkoxy are in equatorial positions, thus making it preferred over C". The ene-reaction would then produce D as a major product, with the methyl at C8 syn to the bridgehead alcohol exactly as in the natural product. It was expected that the presence of an alkoxy group on the macrocycle would increase ΔG" (ΔG" = ΔG"c - ΔG"d) so that only product D is formed.
3.2 Results and Discussion

In planning the synthesis of substrate for model studies, 1,4 addition to conjugated ketone 3.7 was chosen to install the butenyl moiety. The synthesis of ketone 3.6 from 5,5-dimethyl-cyclohexanedione 3.5 was previously reported in the literature. This procedure was further optimized and allowed for convenient generation of up to 10 g of 3.6. The latter was protected with TMSCl to afford ketone 3.7 in good yield.

![Chemical Structure](image)

a) (MeO)2CH, MeOH, H2SO4, 93%; b) Mn(OAc)3, benzene, reflux, 48h, 91%; c) LiAlH4, reflux, Et2O, 70%; d) TMSCl, imidazole, THF, 82%.

Scheme 3.5 Synthesis of the starting material 3.7 for the model studies

A convenient protocol was established for the 1,4 conjugate addition on ketone 3.7. The vinyl lithium species generated from cis-2-bromo-but-2-ene via metal-halogen exchange with t-BuLi in deoxygenated Et2O at −78 °C was canulated to a suspension of copper (I) cyanide (0.5 equiv) inEt2O to give the corresponding cuprate reagent(Scheme 3.5). Addition of 3.7 to the cuprate solution at −78 °C followed by NH4OH/NaCl work up provided 3.8 in yields varying from 80 to 98% depending on the reaction scale. Ketone 3.8 was then reduced with L-selectride to afford axial alcohol 3.9 in 60% yield, resulting from an equatorial attack of the reducing agent on the carbonyl group. The free alcohol was deprotonated with KH and trapped with methyl iodide followed by removal of TMS group from the second alcohol to give 3.10 in 85% yield over two steps. Alcohol 3.10 was oxidized with TPAP to ketone 3.11, thus placing us only one step away from desired compound 3.3. Unfortunately, all our

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attempts to alkylate ketone 3.11 with vinylmagnesium bromide were unsuccessful, probably due to the axial substituents hindering approach to the carbonyl. Surprisingly, when vinylmagnesium bromide was replaced with a smaller nucleophile, lithium TMS-acetylene, only syn-product 3.12 was obtained. The relative stereochemistry of 3.12 was assigned from the NOE experiment, as illustrated in Figure 3.5. (For more details see Appendix 2, Table 1)

![Chemical structures and reaction schemes](image)

a) cis-2-bromo-but-2-ene, t-BuLi, Et₂O, CuCN, -78 °C, 91%; b) L-selectride, THF, -78 °C, 60%; c) Mel, KH, THF; d) TBAF, THF, 85% over 2 steps; e) TPAP, NMO, CH₂Cl₂, ms, 80%.

![Chemical structures and reaction schemes](image)

a) TMS-acetylene, n-BuLi, THF, -78 °C; b) TBAF, THF, 88% over 2 steps

Scheme 3.6 Synthesis of the precursor for model studies

![Chemical structures and reaction schemes](image)

Figure 3.5 NOE correlations for 3.12

It was not obvious what would be the stereochemical outcome of the oxy-Cope/ene reaction of 3.12. Assuming that the oxy-Cope rearrangement would proceed via half chair-like
transition state one would expect to obtain macrocyclic ketone 3.13 with a Z double bond (the bond which participates in the ene-reaction) as illustrated in Scheme 3.7. This ketone could give rise to two cis-decaline diastereomers 3.14 and 3.15 formed via two different transition states A and B. If the Curtin-Hammett principle applied, the energy difference between these transition states would determine the ratio of the products 3.14 and 3.15.

Scheme 3.7 Expected outcome of the oxy-Cope/ene reaction of 3.12

To establish what the stereochemistry of the oxy-Cope/ene products would be, substrate 3.12 was dissolved in toluene followed by addition of Et3N (3 equiv). The resulting solution was deoxygenated with argon, sealed and heated in the microwave. Remarkably, the reaction required higher temperature (230 °C) and longer time (2 h) to proceed than in the case of trans-1,2-divynylcyclohexanoles (compare to 200-220 °C, 1h). The 1H NMR spectrum of the crude reaction mixture showed a 1.5:1 mixture of diastereomers and starting material (<5%) was also detected by GC. Interestingly, using DBU (12 equiv) instead of Et3N improved the yield and suppressed product decomposition. Separation by flash chromatography afforded two products 3.16 and 3.17 in 27% and 10% yields respectively (2.7:1 ratio) (Scheme 3.8).
Partial loss of one of the products was attributed to its instability on the silica gel; basifying silica gel with Et$_3$N did not improve the yield. Contrary to our expectations, the diastereomers 3.16 and 3.17 were found to be trans-decalines. The relative stereochemistry was assigned based on 2D NMR data including COSY, NOESY and HMQC (Figure 3.6, see also Appendix 2, Table 2 and 3).

![Diagram](image)

Scheme 3.8 Oxy-Cope/ene reaction of 3.12

![Diagram](image)

Figure 3.6 Some NOE correlations for 3.16 and 3.17

Our original prediction of cis-decaline formation was based on the assumption that the oxy-Cope rearrangement of 3.12 occurs via the half-chair-like transition state. However, closer examination of this transition state indicates that there is a strong interaction between one of the methyls of the butenyl moiety and the cyclohexane ring as depicted in Scheme 3.9. Alternatively, the oxy-Cope reaction can pass through a twist-boat-like transition state to give macrocyclic ketone 3.18 with an $E$ double bond (the bond further participating in the ene-reaction). Two diastereomers 3.16 and 3.17 are formed as a result of the ene-reaction occurring via transition state A and B respectively. The ratio of 1.5:1 indicates that there is no sufficient energy difference between the two transition states (1.5:1 ratio corresponds to a $\Delta G^*$ of 0.4 kcal/mol when calculated for 503 K)
Scheme 3.9 Proposed mechanism of the tandem oxy-Cope/ene reaction of 3.12

To investigate if the ratio can be improved by simply changing the size of the protecting group on the alcohol, the original procedure was slightly modified to prepare divinyl alcohol 3.22 having its secondary alcohol protected with a large TIPS group (Scheme 3.10).

When subjected to the same experimental conditions (toluene, 10 equiv of DBU, 230 °C, 2 h) in the microwave both substrates rearranged to give 2:1 ratio of diastereomers (Scheme 3.11).\(^7\) Multiple purification of the mixture containing TIPS protected diastereomers afforded 3.23 contaminated with non-polar impurities in 33% yield and a mixture of 3.23 and 3.24 in 40% yield. Compound 3.23 was treated with TBAF to give diol 3.25, which was easily purified by flash chromatography. Full stereochemical assignment of 3.25 was achieved based on 2D NMR data (See Appendix 2, Table 4). Unfortunately, we were unable to isolate 3.24 from the mixture. Thus the stereochemistry of this product was assigned by analogy with methyl-protected compound 3.17. It appears that the size of the substituent on the oxygen does not affect the ratio. However this preliminary conclusion can only be made for the case of cis-1,2-vinyl alkynyl cyclohexanols.

\(^7\) Ratios were determined by GC and \(^1\)H NMR of the crude reaction mixture

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Scheme 3.10 Preparation of 3.22

Scheme 3.11 The oxy-Cope/ene reaction of 3.22

Since we were unable to prepare trans-1,2-divinylcyclohexanol while having geminal methyls on the ring, we decided to study the influence of a remote alkoxy group on the oxy-Cope/ene reaction using more simple substrates. During her summer project Nathalie Goulet prepared and tested three compounds (3.26-3.28) having either an axial or an equatorial benzyloxy group or a different geometry of the butenyl group as shown in Scheme 3.12. In all cases the oxy-Cope/ene reaction produced mixtures of products. The highest ratio (5:1)
was observed in the case of 3.27. The diastereoselectivity of these reactions can also be rationalized using the Curtin-Hammett principle.

![Chemical reaction diagrams]

Scheme 3.12 Natalie Goulet results

We can therefore conclude that the remote alkoxy substituent at C2 does not provide adequate energy difference between macrocycle conformations of the ene-reaction transition states such that only one product is formed.

3.3 Influence of the electronic factors on the selectivity at C8

Our previous attempts to control the selectivity of the ene-reaction step in the tandem oxy-Cope/ene sequence were based exclusively on altering the steric factors of the system. A different approach was chosen based on the results obtained by Effiette Sauer during her
studies on an oxy-Cope/Claisen/ene reaction. She observed that heating allyl ether 3.29 at 200 °C for 1 h in the microwave gave a 2.5:1 mixture of diastereomers 3.30a and 3.30b, whereas heating 3.31 under the same conditions provided decaline 3.32 as a single product as depicted in Scheme 3.13.

![Scheme 3.13 Oxy-Cope/Claisen/ene reaction](image)

The reaction mechanism is shown in Scheme 3.14. The oxy-Cope reaction of the allyl ether gives 10-membered ring enol ether, which then undergoes the Claisen rearrangement to generate macrocyclic ketone A. Assuming that conformer A is in rapid equilibrium with conformer B, two products C and D can be obtained from the ene-reaction in a ratio dependant only on the energy difference between transition states from A to C and B to D. The 2.5:1 ratio, observed in the case of 3.29 (R=Me), corresponds to 0.86 kcal energy difference (calculated for 473K, 200 °C) between transition states C" and D". The value seems to be reasonable since in C" the allyl group occupies equatorial position and the methyl group is axial, whereas in D" it is a reverse. However, it is unlikely that changing from the methyl group to the ethoxy (smaller A value then the methyl: AMe=1.74 kcal/mol, AOE=0.65 kcal/mol) would raise the energy difference between C" and D" up to 3.14 kcal/mol, the value accounting for the 25:1 ratio. This ratio cannot be explained using the Curtin-Hammett principle. One could rationalize the high selectivity assuming that the ene-

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reaction is competing with equilibrium between A and B. Then the ratio of the products should reflect the A/B ratio (case 2, Figure 3.1). Since B is not initially present in the reaction mixture, A can convert to the ene-product before undergoing a ring-inversion to B, thus forming C exclusively. The ethoxy-group does not change the steric factors but contributes to the rate enhancement of the ene-reaction. This is supported by the fact, that the electron withdrawing groups α to the carbonyl accelerate ene-reactions.⁹

Scheme 3.14 Proposed mechanism for the Oxy-Cope/Claisen/ene reaction

As we learnt from the observations made by Effiette Sauer, the presence of ethoxy group α to the carbonyl accelerates the ene-reaction thus eliminating the macrocycle inversion and formation of the second diastereomer. We then envisioned that the oxy-Cope/ene reaction of 1,2-divinylcyclohexanol 3.33 in the microwave would result in exclusive formation of decaline 3.34, in which the methyl group at C8 would be equatorial and syn to the bridgehead alcohol as illustrated in Scheme 3.15. Substrate 3.33 was prepared in 49% yield

via alkylation of ketone 3.35 with vinyl lithium species 3.36 in THF as shown in Scheme 3.16.

![Relevant chemical structures](image)

**Scheme 3.15 Proposed outcome for the oxy-Cope/ene reaction of 3.33**

![Relevant chemical structures](image)

**Scheme 3.16 Preparation of 3.33**

Heating 3.33 in toluene with Et₃N (3 equiv) at 210 °C for 2 h gave only starting material. The temperature was increased to 220 °C, however, after heating for 2 h the oxy-Cope/ene reaction did not go to completion. ¹H NMR of the crude reaction mixture indicated the presence of desired decaline 3.34 as a single diastereomer along with decomposition products and the starting material. In agreement with earlier observations, using DBU instead of Et₃N eliminated decomposition, although it did not affect the rate of the reaction as shown in Scheme 3.17. Heating 3.33 in toluene in the presence of DBU for 2 h at 223 °C afforded the desired product 3.34, an unknown side product and a starting material in a 1:1:3 ratios (detected by ¹H NMR). Purification by flash chromatography allowed for separation of 3.34 in 18% yield and an inseparable mixture of the starting material and the side product in 70% yield. The relative stereochemistry of 3.34 was assigned based on the 2-D NMR experiments (Figure 3.7). The first evidence of the axial position of the ethoxy substituent
was given by two small J values (2.3 Hz) of the adjacent proton H₄. Strong correlation between H₅ and the protons of the methyl group was observed from NOESY experiment.

![Chemical structure](image)

Scheme 3.17 Oxy-Cope/ene reaction of 3.33

The side product 3.37 was believed to be a result of the retro-ene reaction of the starting material (Scheme 3.18).

![Chemical structure](image)

Scheme 3.18 Explanation of formation of the side product

![Chemical structure](image)

Figure 3.7 NOE correlations for 3.34

Jeff Warrington and Daniel Deon (Barriault’s laboratory) have previously reported formation of retro-ene products when substrates with an electron rich double bond attached to the tertiary alcohol were used for the oxy-Cope/ene reaction.¹⁰ ¹¹ Their observation can be applied to our case since oxy-Cope/ene substrate 3.33 has an electron rich vinyl ether group.

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The mixture of the starting material and the retro-ene product was resubmitted to heating in the microwave at 230 °C. After prolonged exposure (6 h, 230 °C) all starting material reacted. Unfortunately, we mostly observed degradation and only traces of the desired product were isolated (<1 mg). It was also possible to isolate retro-ene product 3.37 (<1 mg) and prove its structure by $^1$H-NMR (300 MHz).

We were pleased to find out that the oxy-Cope/ene reaction of 3.33 led to formation of the single decaline. Interestingly, it appeared to be a much more energetically demanding process than in the case of the substrate without the ethoxy group. Paquette et al. have recently demonstrated that the presence of ether substituent on the 1,5-diene decreases the reactivity of the oxy-Cope reaction.$^{12}$ Thus, in the case of the tandem oxy-Cope/ene sequence, the ethoxy group plays a dual role by increasing the activation energy of the oxy-Cope step due to the electron donation to the double bond and decreasing the activation energy of the following ene-reaction because of its electron-withdrawing properties. Although the low yield of the oxy-Cope/ene reaction of 3.33 and the formation of the side product make its application in the total synthesis impractical, the results demonstrate that exceptionally high selectivity can be achieved during the ene-reaction of the macrocyclic ketone by changing the electronic nature of the substituent α to the carbonyl.

Also, the oxy-Cope/ene/Claisen reaction was attempted with a substrate having the ethoxy group on the double bond. Unfortunately, after heating 3.38 at 230 °C for 4 h only degradation was observed (Scheme 3.19).

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Scheme 3.19 Attempted oxy-Cope/ene/Claisen reaction of 3.38

3.4 Control of the selectivity at C8 by adding substituent at C6 of the macrocyclic ketone

We have noticed before that the presence of a phenyl group on 1,5-diene systems significantly accelerates an anionic oxy-Cope reaction (see Chapter 5). We then decided to investigate how a replacement of the ethoxy by the phenyl group would affect the course of the thermal oxy-Cope/ene reaction and how it would change electronic and steric factors contributing to the selectivity of the ene-step. It was also interesting to make a comparison with a case where the ethoxy group is replaced by a methyl. 1,2-divinylcyclohexanols 3.39 and 3.40 were prepared via alkylation of ketone 3.35 with a corresponding vinyl lithium species (Scheme 3.20).

Scheme 3.20 Preparation of 1,2-divinylcyclohexanols 3.39 and 3.40

The substrates were heated in the microwave to afford the oxy-Cope/ene products. The results are shown in Table 3.1.
Table 3-1 Oxy-Cope/ene reaction of the substrates with a substituent at C6 obtained from ketone 3.35

![Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Time, h</th>
<th>Product $^d$</th>
<th>dr (D$_1$ : C$_1$) $^b$</th>
<th>Yield, % $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.11$^a$</td>
<td>H</td>
<td>1</td>
<td>2.12(C$_1$) and 2.14(D$_1$)</td>
<td>1:3</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>3.39</td>
<td>Me</td>
<td>2</td>
<td>3.41(C$_1$) and 3.42(D$_1$)$^e$</td>
<td>3.4:1</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>3.40</td>
<td>Ph</td>
<td>1</td>
<td>3.43(D$_1$)</td>
<td>&gt;25:1</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$ Preparation and the oxy-Cope/ene reaction of this substrate was discussed in Chapter 2. $^b$ Diastereomeric ratios were determined by 300 MHz $^1$H NMR and GC of the crude reaction mixtures. $^c$ Combined isolated yields. $^d$ Relative stereochemistry was assigned based on 2D NMR (see Appendix). $^e$ Relative stereochemistry of 3.42 was assigned based on the proposed mechanism of the reaction.

As we have already seen before in Chapter 2, in the case of R=H (entry 1) the oxy-Cope/ene reaction (1 h, 220 °C) affords a 3:1 mixture of 2.12(C$_1$) and 2.14(D$_1$). Interestingly, the replacement of H by a methyl group (entry 2) gave a mixture of 3.42(D$_1$) and 3.41(C$_1$) in a 3.4:1 ratio respectively. Remarkably, the exclusive formation of product 3.43(D$_1$) (93% yield) was observed in entry 3 (R=Ph).

To complete our investigation, ketone 3.45 was prepared from 2-chloro-1-cyclohexanone in two steps in 51% overall yield as illustrated in Scheme 3.20. The ketone was alkylated with three different vinyl lithium species to give trans-1,2-divinylcyclohexanols 3.46, 3.47 and 3.48 in 56%, 72% and 40% yields respectively (Scheme 3.21). In the case of R=SEt, formation of cis-1,2-divinylcyclohexanol was also detected by $^1$H NMR.
Scheme 3.21 Preparation of ketone 3.45

Scheme 3.22 Synthesis of substrates for the oxy-Cope/ene reaction via alkylation of ketone 3.45

Substrates (3.46-3.48) were heated in the microwave oven to give the corresponding oxy-Cope/ene products. The results are summarized in Table 3-2.

Table 3-2 Oxy-Cope/ene reaction of the substrates with a substituent at C6 obtained from ketone 3.45

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Time, h</th>
<th>Product</th>
<th>dr (D2 : C2)</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.46</td>
<td>H</td>
<td>1</td>
<td>3.49 (C2) and 3.50 (D2)</td>
<td>3:1</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>3.47</td>
<td>Ph</td>
<td>3</td>
<td>3.51 (D2)</td>
<td>&gt;25:1</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>3.48</td>
<td>SET</td>
<td>3</td>
<td>3.52 (D2)</td>
<td>20:1</td>
<td>81</td>
</tr>
</tbody>
</table>

* Diastereomeric ratios were determined by 300 MHz 'H NMR and CG of the crude reaction mixtures. * Isolated yields.

Interestingly, the oxy-Cope/ene reaction of 3.47 (R=Ph, entry 2) required heating for 3 h at 220 °C. Product 3.51(D2) was obtained in good yield (64%) and excellent diastereoselectivity. A similar result was obtained in the case of R=SET (entry 3). Heating 3.48 for 3 h at 220 °C afforded product 3.52(D2) in 81% yield (dr=20:1).
The oxy-Cope/ene reaction of 3.46 (R=H, entry 1) resulted in formation of a 3:1 mixture of products 3.49 (C₂) and 3.50 (D₂). After comparing product 3.50(D₂) in Table 3-2 to product 2.12(C₁) in Table 3-1 it becomes obvious that they are identical with the exception of being enantiomers. The same conclusion applies to product 3.49(C₂) from Table 3-2 and product 2.14(D₁) from Table 3-1. Moreover, the ratio of D₁/C₁ obtained in entry 1 of Table 3-1 and the ratio of C₂/D₂ obtained in entry 1 of Table 3-2 are identical. This important observation provides an experimental justification to the use of the Curtin-Hammett principle in explaining the mechanism of the oxy-Cope/ene reaction. Detailed rationalization to this observation is provided below.

As shown on the right-hand side of Scheme 3.22, the oxy-Cope rearrangement of 3.46 gives directly macrocyclic ketone A₂. This ketone is a mirror image of ketone B₁ (the left-hand side of the Scheme) obtained via a ring inversion of macrocycle A₁. A₂ can either react to give the ene-product C₂ (via transition state C''₂), which is a mirror image of product D₁, or undergo ring inversion to afford B₂ (mirror image of A₁). The ene-reaction of B₂ generates D₂ (a mirror image of C₁) via transition state D''₂. Therefore identical products (with the exception that they are enantiomers) can be obtained from both right- and left-hand side reactions. The ene-product generated prior to the ring inversion on the left-hand side corresponds to the ene-product obtained after the ring inversion on the right-hand side. If we again assume that macrocyclic conformers A₂ and B₂ and A₁ and B₁ are in rapid equilibrium and the rates of the ene-reactions of all the conformers are at least 10 times slower (Curtin-Hammett principle), then the ratio of the products is determined based only on \( \Delta G'' = \Delta G''_{C₁} - \Delta G''_{D₁} \), which equals \( \Delta G'' = \Delta G''_{D₂} - \Delta G''_{C₂} \). Therefore the ratio of the products on the right-hand side should be exactly the same as the ratio of the products on the left-hand side.
Scheme 3.23 Proposed mechanism for the oxy-Cope/ene reaction of 2.12 and 3.36

Returning to the results obtained in entries 2 and 3 of both tables, we can now rationalize the observed ratios based only on the energy differences of the transition states of the ene-reaction. As illustrated in Scheme 2.23, the oxy-Cope rearrangement of 1,2-divinylcyclohexanol affords macrocyclic ketone $A_1$. The latter can either undergo the ene-reaction via transition state $C^1$ to give product $C_1$ or undergo ring inversion followed by the ene-reaction via transition state $D^1$ to generate product $D_1$.

Scheme 3.24 Proposed mechanism of the oxy-Cope/ene reaction of 3.39 and 3.40

When $R$=Me (entry 2, Table 3-1), in transition state $C^1$, the methyl at C8 occupies equatorial position and the methyl at C6 is axial. Inversion of the macrocycle $A_1$ to $B_1$ will give
transition state $D^\#_1$ in which the methyl at C8 is now axial and the methyl at C6 becomes equatorial. The observed 3:1 ratio of $D_1/C_1$ corresponds to 1.1 kcal/mol (calculated for 493 K or 220 °C) difference between $\Delta G^\#_{C_1}$ and $\Delta G^\#_{D_1}$. This value indicates that the methyl at the position C8 contributes less to the stability of the transition state than the methyl at the position C6. It can be easily explained by the fact that in $C^\#_1$, the equatorial methyl at C8 develops pseudo-guache interactions with the methyl participating in the ene-reaction. Thus the energy of the equatorial methyl becomes closer to the energy of the methyl at C8 in axial position (transition state $D^\#_1$). When the phenyl group replaces the methyl at C6 (entry 3, table 3-1), the $D_1/C_1$ ratio becomes greater than 25:1, which corresponds to the greater than 3.08 kcal/mol (calculated for 483 K or 210 °C) energy difference between $C^\#_1$ and $D^\#_1$. This increase of the energy difference between transition states can be attributed to the much larger size of the phenyl group compared to the methyl group. (The A value of a phenyl group is 2.8 kcal/mol; the A value of a methyl is 1.74 kcal/mol).

Scheme 3.24 illustrates the mechanism of the oxy-Cope/ene reaction responsible for the formation of the products $C_2$ and $D_2$ (Table 3-2, entries 2 and 3). Again, the oxy-Cope reaction of 3.47 or 3.48 generates macrocyclic ketone $A_2$, which is either converted to ene-product $C_2$ via transition state $C^\#_2$, or undergoes the ring inversion to $B_2$, followed by the ene-reaction via transition state $D^\#_2$ to give $D_2$. The ratio of greater than 25:1 in entry 2 ($R=\text{Ph}$) and 20:1 in entry 1 ($R=\text{SEt}$) suggest that in both cases the energy difference between $C^\#_2$ and $D^\#_2$ is greater than 3.14 kcal/mol and 2.92 kcal/mol (calculated for 493 K or 220 °C) respectively. Examination of transition state $C^\#_2$ reveals strong 1,3 diaxial interactions between R group at C6 and the methyl at C8, explaining the large energy difference between $D^\#_2$ and $C^\#_2$. 

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Scheme 3.25 Explanation of diastereoselective outcome of the oxy-Cope/ene reaction of 3.47 and 3.48

AM1 semi-empirical calculations using Spartan software were performed to estimate the energy differences between transition states of the ene-reactions in the case of R=Me (entry 1, Table 3-2). As shown in Figure 3.7, $\Delta G^\#$ between $C_1^#$ and $D_1^#$ was found to be 1.7 kcal/mol, which would give the 5.7:1 ratio of the products (calculated for 493 K or 220 °C). This result was consistent with the experimentally obtained 3:1 ratio.

![Chemical Structures](image)

$\Delta G^\# = 1.7$ kcal/mol

Figure 3.8 Results of AM1 semi-empirical calculation for $\Delta G^\#$ between $D_1^#$ and $C_1^#$

3.5 Conclusion

We have found that introducing substituents of different nature on the macrocycle at C6 ($\alpha$ to the carbonyl) can control the selectivity of the ene-reaction step of the oxy-Cope/ene sequence and therefore selectivity at C8. It has been demonstrated that having an electron-withdrawing substituent (OEt) $\alpha$ to the carbonyl accelerates the ene-reaction, thus making the impact of the macrocycle ring inversion on the selectivity of the ene-reaction negligible. We have also shown that in the case where the ring inversion is much faster than the ene-
reaction (i.e. the Curtin-Hammett principle applies), excellent selectivity can be achieved by increasing the energy difference between transition states of the ene-reaction.

These results open a new perspective for the application of the oxy-Cope/ene and eventually the oxy-Cope/ene/Claisen strategy in the total synthesis of agelasimine A and other diterpenes having a substituent at C8.

3.6. Future perspectives

As previously demonstrated, while having ethoxy group next to a tertiary alcohol on a 1,5 diene system accelerated the ene-reaction. It also increased the activation energy of the oxy-Cope step, resulting in low yield of the oxy-Cope/ene sequence. To overcome this disadvantage a new approach has recently been proposed as shown in Scheme 3.26. The oxy-Cope/ene reaction of 3.53 is expected to give only one isomer, since the macrocyclic ketone generated in the course of the oxy-Cope step possesses an electron-withdrawing (alkoxy) group α to a carbonyl. However, this alkoxy group is not a part of a 1,5-diene system of 3.53, therefore its presence should not affect the rate of the oxy-Cope rearrangement. Importantly, the group can further be transformed to the geminal dimethyls, which are present on the natural product.

![Scheme 3.26 New approach to agelasimine A](image)

*Scheme 3.26 New approach to agelasimine A*
Another strategy that needs to be explored is illustrated in Scheme 3.27. As we already know the oxy-Cope/ene reaction of 3.48 gives decaline 3.52 in which the methyl at C8 and the tertiary alcohol are syn to each other. One could envision that removal of SEt would give a core of dihydroagelasimine with the methyl at C8 in the right position. Similarly, the oxy-Cope/ene/Claisen reaction of 3.54 should generate compound 3.55, which has not only the methyl at C8 but also the quaternary carbon center at C9 with the desired stereochemistry.

Scheme 3.27 New approach to dihydroagelasimine A
Chapter 4 Synthesis of (±)-agelasimine A analogues

4.1 Introduction

A natural product with known biological activity is often altered by introducing new and modifying existing functional groups.\(^1\) This is done in the hopes of improving the biological activity and providing information about structure-activity relationship. A highly active analogue may also be obtained from a biosynthetic precursor, for example, taxotere\(^2\), which is the structurally related to taxol\(^3\). In some situations however the desired chemical modifications cannot be achieved. In addition, the biosynthetic precursor may not be readily available for technical or stability reasons.

Danishefsky et al. have introduced the concept of diverted total synthesis, where desired structural modifications are incorporated into advanced intermediates.\(^2\) The goal of this approach is to prepare analogues, which are less structurally complex than the natural product, but have similar or improved biological activity. This new strategy is currently being implemented for the discovery of new biologically active molecules.\(^3\)

As discussed in Chapter 2 agelasimine A is a natural product that exhibits significant in vitro cytotoxicity against L1210 leukemia cells (ED\(_{50}=2.1\) nM) and acts as a smooth muscle relaxant.\(^4\) As we have previously demonstrated, the core of agelasimine A, lactol 4.1, without geminal dimethyls at C4 and the methyl group at C8 can be generated via our new tandem oxy-Cope/ene/Claisen strategy in only 6 steps starting from commercially available cyclohexene oxide (Scheme 4.1). We were interested in determining whether the presence of

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\(^1\) For the recent review see: Tietze, L.F.; Bell, H.P.; Chandrasekhar, S. Angew. Chem., Int. Ed. 2003, 42, 3996 and references therein.


geminal dimethyls or the methyl at C8 and the length of the side chain contribute to these activities. We have envisioned that analogues A-F can be synthesized from a common intermediate, lactol 4.1, as illustrated in Scheme 4.2.

a) isopropenylmagnesium bromide, THF, CuBr-DMS, -40 °C; b) Swern oxidation, 90% over 2 steps; c) vinylmagnesium bromide, THF, 60%; d) SeO₂, t-BuOOH, CH₂Cl₂, 62% based on the recovery of the starting material; e) allyl bromide, NaH, THF, 70%; f) toluene, Et₃N, 220 °C, 1 h, microwave, 80%.

Scheme 4-1 Synthesis of the core of (±)-agelasimine A

Scheme 4-2 Proposed analogues of (±)-agelasimine A

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4.2 Studies toward analogue A

The synthesis of analogue A was initially attempted. The installation of the side chain began by a Wolf-Kischner reduction of the lactol 4.1 as shown in Scheme 4.3. Heating 4.1 in diethyleneglycol in the presence of K₂CO₃ and NH₂NH₂·H₂O at 150 °C for 12 h afforded inseparable 15:1 mixture of desired product 4.2 and side-product 4.3 with a reduced allyl group in 50-55% combined yield. Ozonolysis of the allyl group followed by LiAlH₄ reduction provided diol 4.4 in 82% yield over two steps and allowed for separation of compound 4.3. Tosylation of diol 4.4 using freshly recrystallized TsCl, Et₃N and catalytic amount of DMAP in CH₂Cl₂ gave mono-tosylate 4.5 in 90% yield. It was envisioned that the SN₂ displacement of the tosyl group with vinyl cuprate generated from vinyl bromide 4.7 would install the rest of the carbon side chain. Vinyl bromide 4.7 was prepared in three steps starting from crotyl alcohol (Scheme 4.4).\(^5\) Attempts to perform the SN₂ reaction using substrate 4.5 with unprotected tertiary alcohol were unsuccessful.

\(^5\) Vinyl bromide 4.6 was prepared according to procedure reported by: Corey, E.J.; Bock, M.G.; Kozikowski, A.P.; Rama Rao, A.V.; Floyd, D.; Lipshutz, B. Tetrahedron Lett. 1978, 19, 1051.
a) NH$_2$NH$_2$·H$_2$O, K$_2$CO$_3$, diethylene glycol, 50-55%, 15:1; b) O$_3$, CH$_2$Cl$_2$, -78 °C, DMS c) LiAlH$_4$, THF, rt, 82% over 2 steps; d) TsCl, CH$_2$Cl$_2$, Et$_3$N, DMAP, 90%; e) 4,6, Cul, t-BuLi, Et$_2$O or THF, no reaction.

Scheme 4-3 First attempt toward analogue A

a) Br$_2$, CHCl$_3$; b) LDA, HMPA, THF, -78 °C, 37% over 2 steps; c) TBDPS, THF, imidazole, 87%.

Scheme 4-4 Synthesis of vinyl bromide 4.7

Treating diol 4.4 with 4 equiv of TMSCl and 2.2 equiv of KHMDS in THF at -78 °C followed by a basic work up and deprotection of the primary alcohol using K$_2$CO$_3$ in MeOH afforded compound 4.8 with protected tertiary alcohol in 81% (Scheme 4.5). The monoprotected diol was treated with TsCl to give 4.9 in 65% yield. The SN$_2$ displacement of the tosyl group using the mixed cuprate was attempted. Unfortunately, no desired product was observed.

We then proposed to perform SN$_2$ displacement using a substrate with a better leaving group (e.g. bromide or iodide). Iodide 4.10 was prepared from 4.9 in 67% yield (Scheme 4.5). However, no reaction was observed upon addition of the iodide to the vinyl cuprate solution.

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Scheme 4-5 Attempts to extend the side chain

Installation of the side chain using Suzuki coupling conditions, developed by Ohba et al. in the course of their synthesis of agelasamine A, was also attempted as shown in Scheme 4.6. In order to prepare substrate 4.14 for the Suzuki coupling it was necessary to transform the allyl chain into the vinyl group. The isomerization of the double bond of 4.2 using ruthenium catalyst gave an inseparable 15:1 mixture of 4.11 and 4.2 in 92% yield. We expected that ozonolysis of 4.11 followed by reductive work up and the Wittig reaction would result in formation of 4.14. Unexpectedly, the ozonolysis gave a mixture of acid 4.12 and aldehyde 4.13 in 43% and 32% yields respectively. Changing the ozonolysis conditions did not suppress acid formation. Attempts to obtain 4.14 via Wittig olefination of 4.13 were unsuccessful, probably due to the presence of a free tertiary alcohol on the substrate.

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Scheme 4-6 Attempt to install the side chain using the Suzuki coupling

We then envisioned that the cross-coupling metathesis of decaline 4.2 and a corresponding alkene would give product 4.16. The latter was expected to generate aldehyde 4.17 upon oxidation followed by migration of the double bond as shown in Scheme 4.7.

Scheme 4-7 Installation of the side chain using cross-coupling metathesis

However, an attempt to perform the cross coupling resulted only in dimerization of decaline 4.2. The dimerization can be attributed to the difference in the degree of substitution of two coupling partners.

4.3. Studies toward analogue B

The synthesis of analogue B was carried parallel to the synthesis of A. It began with the Suzuki cross coupling between decaline 4.2 and vinyl bromide 4.7 (Scheme 4.8).

Hydroboration of 4.2 with 9-BBN in THF under refluxing conditions afforded the corresponding 9-alkyl-9-BBN derivative, which was then added to a solution of 4.7,
Pd(dppf)Cl$_2$, AsPh$_3$, Cs$_2$CO$_3$ and H$_2$O in DMF. After stirring the reaction mixture at rt for 3-5 h the expected coupling product 4.18 was obtained in 50-65% yields. The removal of TBDPS group with TBAF gave alcohol 4.19 in 70-80% yields. At this stage, all attempts to brominate the resulting primary alcohol in a presence of a free tertiary alcohol with either CBr$_4$/Ph$_3$P or PBr$_3$ and to use crude allyl bromide in a consequent coupling with 3-methyl adenine$^9$ in DMA of DMF failed. Protection of the tertiary alcohol was then undertaken. We were unable to install the TMS group using the method employed in the synthesis of analogue A (TMSCl, KHMDS, THF, -78 °C).

\[ \text{Scheme 4-8 Attempted synthesis of analogue B using the Suzuki cross coupling} \]

### 4.4 Conclusion and future perspectives

Unfortunately, due to the time constraint we were unable to complete the analogue syntheses. We have established, however, that protection of the tertiary alcohol is required prior the modification of the side chain and coupling with 3-methyladenine. A modified

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approach toward analogues A and B is illustrated in Schemes 4.9 and 4.10 respectively. The synthesis of the analogues will be continued in the nearest future.

**Scheme 4-9 Modified approach toward analogue A**

![Scheme 4-9]

**Scheme 4-10 Modified approach toward analogue A**

![Scheme 4-10]
Chapter 5 Anionic oxy-Cope reaction – a new approach toward generation of quaternary carbon centers

5.1 Background

Alkylation of tetrasubstituted enolates is a method commonly used to generate quaternary carbon centers α to a carbonyl. Formation of the enolate in a stereoselective fashion and control of the facial selectivity of the consequent electrophilic attack are two major challenges associated with this strategy. A majority of the methods reported in literature combine traditional approaches to enolate formation (removal of acidic proton α to a carbonyl with a base) with a use of a chiral auxiliary.\(^1\) Although presence of a chiral auxiliary allows for efficient diastereoselective and enantioselective induction, removal of chiral auxiliary can pose a problem. In many cases harsh conditions are required resulting in low yields.

We have envisioned that the anionic oxy-Cope reaction of 1,2 divinylcyclohexanols 5.1 and 5.6 could be used as a new approach toward construction of quaternary carbon centers based on a stereoselective enolate formation/electrophilic addition as illustrated in Schemes 5.1 and 5.2. The anionic oxy-Cope reaction of 5.1 will generate 10-membered ring $E$-enolate 5.2. The geometry of this enolate is predetermined by a stereochemistry of the starting material and a chair-like transition state of the oxy-Cope reaction. The conformation of the macrocyclic enolate provides excellent means for controlling facial approach of the electrophile, since one face of the π-system is severely hindered by the ring.\(^2\) Trapping the

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macrocyclic enolate with a source of a carbon electrophile under conditions favoring C-alkylation should result in formation of macrocyclic ketone 5.4 bearing a quaternary carbon center α to the carbonyl. It was previously shown that the anionic oxy-Cope reaction of enantiomerically pure 5.1 (when R=Ph) results in complete racemization.3 This is because macrocyclic enolate 5.2 generated from the anionic oxy-Cope reaction does not have any chiral centers as shown in Scheme 5.1, but instead possesses so-called planar chirality.4 Chiral plane can be described as a planar arrangement of at least four centers (atoms) with a fifth center outside of this plane. Therefore information about chirality is coded in the conformation of the macrocycle (conformation is treated as a topographic property of the macrocycle).5 The ring inversion of the enolate 5.2 gives its mirror image, macrocycle 5.3. If the barrier of inversion is low and the alkylation is the rate-determining step, then the mixture of enantiomers 5.4 and 5.5 is obtained in the end of the reaction.


Scheme 5.1 Proposed formation of quaternary centers via an oxy-Cope/alkylation reaction

However, the racemization cannot occur when the oxy-Cope reaction is performed with substrates having two substituents on the vinyl group next to the alcohol (Scheme 5.2). In this case the anionic oxy-Cope reaction of 5.6 will generate macrocyclic enolate 5.7 with a chiral center on the ring. Inversion of this enolate will give diastereomeric enolate 5.8, which is not a mirror image of 5.7. Trapping 5.7 with an electrophile should generate macrocyclic ketone 5.9 having a quaternary carbon center adjacent to a tertiary center. One can envision that cleavage of the macrocycle will provide ketoester 5.10, which can be used as a building block in a synthesis of natural and non-natural products.

Scheme 5.2 Anionic oxy-Cope/alkylation reaction of 5.6

It was shown in our laboratory by Danny Gauvreau that treating 1,2-divinylcyclohexanol 5.11 with 5 equiv of KHMDS in DME followed by 1.5 h reflux initiated the anionic oxy-
Cope reaction (Scheme 3).\textsuperscript{3} Quenching the reaction with MeI at -78 °C afforded 10-membered ring ketone 5.12 bearing two contiguous chiral centers including the quaternary carbon center $\alpha$ to the carbonyl (determined by 1H NMR of the reaction mixture) (Scheme 5.3). Ozonolysis of the crude reaction mixture followed by hydrogenation and diazomethane treatment resulted in formation of ketoester 5.13 as a single diastereomer in 13% yield starting from the 1,2-divinylcyclohexanol. Encouraged by the excellent diastereoselectivity of the quaternary carbon center formation in the oxy-Cope/alkylation sequence we then proceeded to explore a scope of the new methodology.

![Scheme 5.3](image)

\textbf{Scheme 5.3 Results of Danny Gauvreau}

5.2 Results and Discussion

5.2.1 Preparation of 1,2-divinylcyclohexanols

The substrates 5.15 for the anionic oxy-Cope reaction can be easily obtained in either racemic or enantiomerically pure forms by alkylation of isopiperitenone 5.14 as shown in Scheme 5.4. The procedure used in our lab to prepare optically active ketone 5.14 involves oxidation of (+) or (-)-limonene with CrO$_3$·2Py complex. Although the oxidation provides a rapid access to the enantiomerically pure substrate, it is a low yielding process (the isolated yields are 10-13%). Furthermore, at least 5.5 equiv of CrO$_3$·2Py is required for oxidation to occur. In order to prepare (±)-isopiperitenone a 1:1 mixture of (+)- and (-)-limonene is prepared and oxidized.
Scheme 5.4 Preparation of the substrates for the anionic oxy-Cope reaction

A different approach to the synthesis of (±)-isopiperitenone 5.14 was chosen in the course of our studies. It was found in literature that the Diels-Alder reaction of diene 5.16 with methylvinyl ketone, followed by the Wittig reaction and Jones oxidation affords the desired ketone 5.14 in 56-64% overall yield as depicted in Scheme 5.5. This procedure is also effective on larger scale, e.g. 3-5 g (Compare to oxidation of limonene, where to obtain 5 g of the product one has to use 500 g of CrO₃·2Py).

Scheme 5.5 Synthesis of 5.14 using a Diels-Alder strategy

A number of racemic and enantiomerically pure 1,2-divinycyclohexanols were synthesized by the alkylation of 5.14 with the corresponding lithium species generated in situ via metal-halogen exchange from the vinyl halides as shown in Scheme 5.6.

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6 For preparation of this diene see: South, M.S.; Liebeskind, L.S. J. Org. Chem. 1982, 47, 3815.
Scheme 5.6 Preparation of 1,2-divinylcyclohexanols via alkylation of 5.14

Vinyl halides that were not commercially available were prepared from the alkynes as illustrated in Scheme 5.7. All vinyl halides were found to be light sensitive and could not be stored in the freezer longer than for a few days. Interestingly, attempts to prepare vinyl iodide 5.23 using the same procedure\(^8\) as for 5.24 gave a mixture of \(E\) and \(Z\) isomers. Instead, a two-step procedure involving hydrostannylation\(^9\) followed by the tin-iodine exchange was employed. Using vinyl-stannane 5.22 directly to generate vinyl lithium species for alkylation of ketone 5.14 gave a mixture of products.

![Image](image.png)

a) \(\text{Bu}_3\text{SnH}, \text{PdCl}_2(\text{PPh}_3)_2, 53\%\); b) \(\text{I}_2, \text{CH}_2\text{Cl}_2, 63\%\)

Scheme 5.7 Synthesis of vinyl iodides


5.2.2 Generation of quaternary centers

The anionic oxy-Cope reaction of (+)-5.11 was attempted using reaction conditions (5 equiv of KHMDS, DME, 1.5 h of reflux, addition of MeI at −78 °C), which were previously established by Danny Gauvreau for the same substrate in its racemic form. To our disappointment the result was found irreproducible. Attempts to modify reaction conditions by varying a solvent, reaction temperature and electrophile were unsuccessful.

In order to ensure that lack of consistency in our results was not due to a quality of reagents, we performed the anionic oxy-Cope/alkylation reaction on 1,2-divinylcyclohexanol 5.19.\textsuperscript{10}

When subjected to the same conditions (5 equiv of KHMDS, DME, reflux) 5.19 reacted smoothly after 40 min according to TLC. The reaction mixture was then cooled to −78 °C followed by addition of freshly distilled EtI, stirred for 2 h at −78 °C and quenched. Purification by flash chromatography afforded desired macrocyclic ketone 5.25 with quaternary carbon center α to the carbonyl in 98% yield (Scheme 5.8).

\[
\begin{align*}
\text{5.19} & \quad \xrightarrow{\text{a), b)}} \quad \text{5.25} \\
\text{a) KHMDS (5 equiv), DME, 85 °C, 2h; b) quench with EtI at -78 °C, 98%}
\end{align*}
\]

Scheme 5.8 Anionic oxy-Cope /alkylation reaction of 5.19

Having demonstrated that the anionic oxy-Cope/alkylation reaction works well in case of 5.19 we then investigated the reaction of 1,2-divinylcyclohexanols 5.20 and 5.21 (Scheme 5.9).

\textsuperscript{10} It was previously reported by Danny Gauvreau that the anionic oxy-Cope of 5.19 occurs smoothly giving the corresponding macrocyclic ketone in 78% yield.
Scheme 5.9 Attempted anionic oxy-Cope/alkylation reaction of substrates (+)-5.20 and (+)-5.21

After refluxing for 1 h in DME the anionic oxy-Cope reaction of (+)-5.21 gave only the starting material, prolonged periods of heating led to complete decomposition. This result is consistent with that of substrate (+)-5.11 having the propyl group at C1 position of the 1,5-diene. All attempts to initiate the anionic oxy-Cope reaction of 5.21 (entry 2) using different conditions, i.e. base, solvent, reaction time and temperature were unsuccessful.

Based on our results, it appears that adding a second substituent on the vinyl group decreases the rate of the oxy-Cope reaction. Moreover, when the substrate possesses an alkyl group is at C1 position of the 1,5-diene system (cases of 5.11 and 5.21), the oxy-Cope reaction does not occur.

As previously discussed, racemization of the enolate generated in the course of the anionic oxy-Cope reaction of 1,2-divinylcyclohexanols 5.1 and 5.6 (Schemes 5.1 and 5.2) can be avoided if a chiral center is present. In the case of compounds (+)-5.11, (+)-5.20 and 5.21 this chiral center originates from a substituent at C1 of the 1,5-diene fragment. However, the presence of a substituent at C1 decreases the reactivity of these substrates. Thus we proposed to implement a substrate for the anionic oxy-Cope reaction in which a chiral center is present prior the enolate formation but is not a part of 1,5-diene moiety.
Ketone 5.26 is readily available in two steps from citronellal in 42% yield (Scheme 5.10). Alkylation of the ketone should afford 1,2-divinylcyclohexanols 5.27, the anionic oxy-Cope reaction of which will generate macrocyclic enolate 5.28 having a chiral center. If the enolate ring inversion occurs, it will give diastereomeric macrocycle. However, no racemization is possible in this case via the ring inversion. The next step was to investigate whether the anionic oxy-Cope/alkylation reaction of 5.27 can be used to generate a quaternary carbon center. In order to establish the reaction conditions all studies were done using racemic material.

\[
\begin{align*}
\text{(±)- citronellal} & \quad \overset{a), b)}{\longrightarrow} \quad 5.26 \\
5.28 & \quad \overset{\text{c)} \quad \text{Br}}{\longrightarrow} \quad 5.27 \quad \text{OH} \\
 & \quad \overset{d)}{\longrightarrow} \\
\end{align*}
\]

a) SnCl\(_4\), CH\(_2\)Cl\(_2\), -78 °C, 70%; b) Jones reagent, Et\(_2\)O, 60%. c) t-BuLi, Et\(_2\)O or THF, -90 or -78 °C; d) KHMDS, DME, reflux, then quench with E\(^+\) at -78 °C.

Scheme 5.10 New substrate for the anionic oxy-Cope/alkylation reaction prepared from citronellal
Initially, (±)-1,2-divinylcyclohexanol 5.29 was prepared via alkylation of ketone 5.26 with \(\alpha\)-lithium styrene (obtained from \(\alpha\)-bromostyrene via metal halogen exchange) in 73% yield (Scheme 5.11).

\[\text{References:}
\]
Scheme 5.11 Preparation of 5.29
The 1,2-divinylcyclohexanol was treated with 5 equiv of KHMDS in DME at 25 °C and heated to 90 °C. Monitoring the reaction by TLC indicated that after 15 min the starting material was consumed. Cooling the reaction mixture to −78 °C and stirring for 2 h after adding EtI afforded macrocycle 5.31 as a single diastereomer in 64% yield (dr>25:1, detected by 1H NMR). However, double alkylated product 5.32 was also isolated in 20% yield (Scheme 5.12). Formation of the side product was explained by the deprotonation of generated ketone 5.31 with excess of KHMDS followed by a second alkylation with EtI. An attempt to decrease the reaction time led to the isolation of the oxy-Cope product, macrocyclic ketone 5.30. Christiane Grise (honors project) has been able to improve the ratio of the monoalkylated to the double alkylated product from 2.5:1 to 5.7:1 by decreasing the amount of base and EtI. However, the yield of 2.31 decreased to 48%. Further optimization of the reaction yield is currently under investigation. Relative stereochemistry of 5.31 and 5.32 was tentatively assigned based on the proposed mechanism of the reaction (see Scheme 5.13). We expect to obtain a solid proof of the relative stereochemistry of the quaternary center once the conditions for the macrocycle cleavage are established and cyclic 6-membered derivative can be prepared.
Scheme 5.12 Anionic oxy-Cope/alkylation reaction of 5.29

Our result demonstrated that high diastereoselectivity in formation of the quaternary carbon center could be achieved by using a remote chiral center. This is rationalized by the mechanism depicted in Scheme 5.13. The anionic oxy-Cope rearrangement of 5.29 generates macrocyclic enolate A. The enolate can then either undergo ring inversion to macrocycle B followed by the alkylation with EtI to give product D or proceed directly to the alkylation step to afford C. Assuming that the Curtin-Hemmett principle applies to this case, we can determine the product ratio based solely on the energy difference between transition states C° (from A to C) and D° (from B to D). Transition state C° has the methyl group pseudo-equatorial, whereas in transition state D° this methyl is in the pseudo-axial position, thereby developing steric interactions with the ring. Thus transition state C° should be lower in energy than D° favoring formation of product C. The observed C/D ratio of 25:1 corresponds to a 1.3 kcal/mol (calculated for 195 K = -78 °C) energy difference between transition states C° and D°.
Scheme 5.13 Proposed mechanism for the anionic oxy-Cope/alkylation reaction of 5.29

In order to investigate how the replacement of the phenyl group with an alkyl substituent affects the reactivity of the anionic oxy-Cope reaction, 1,2-divinylcyclohexanol 5.33 was prepared and subjected to the established anionic oxy-Cope/alkylation conditions (Scheme 5.14). Unfortunately, no reaction was observed. The attempts to modify the reaction conditions (base, solvent, reaction temperature) were unsuccessful. Further work needs to be done on determining the reaction conditions suitable for the substrates with alkyl substituents on the vinyl moiety.

\[
\begin{align*}
5.26 & \quad \xrightarrow{a)} \quad 5.33 \quad \xrightarrow{b)} \quad E \\
\end{align*}
\]

a) isopropenyl magnesium bromide, CeCl₃, THF, 0 °C to rt, 92% b) KHMS, DME, reflux then E⁺.

Scheme 5.14 Studies on 1,2-divinylcyclohexanol 2.53

5.3 Future perspectives

Starting from enantiomerically pure citronellal would lead to formation of enantiomerically pure macrocyclic ketone 5.31 with the quaternary carbon center α to the carbonyl. Cleavage
of the macrocycle would afford a chiral ester 5.35 as illustrated in Scheme 5.15. The preliminary results obtained by Christiane Grise show that this could be achieved via formation of methyl enolate 5.34 followed by the ozonolysis and reductive work up. The hydrolysis of the ester would provide chiral acid 5.36.

Scheme 5.15 Preparation of a chiral acid with a quaternary carbon center

Once the anionic oxy-Cope/alkylation reaction and the macrocyclic cleavage conditions are optimized, the method could be extended to a number of carbon as well as oxygen and nitrogen electrophiles as shown in Scheme 5.16. The use of nitrogen electrophile could potentially lead to a formation of chiral amino acids.

Scheme 5.16 Future perspectives
Chapter 6 Experimental

6.1 General

All reactions were carried out under dry N₂ or argon atmospheres in flame-dried glassware or sealed tubes equipped with a magnetic bar and a rubber septum, unless otherwise indicated. THF, Et₂O and DME were freshly distilled from sodium/benzophenone. Toluene, CH₂Cl₂ and Et₃N were freshly distilled from CaH₂. The other commercially available reagents were used without purification, unless otherwise indicated.

Reactions were monitored by TLC analysis of aliquots using aluminum and glass sheets pre-coated (0.2 and 0.25 mm layer thickness respectively) with silica gel 60 F₂₅₄ (E. Merck). Flash chromatography was carried out on Silicycle silica gel (0.35-0.75 mm, 60 Å pore size). TLC plates were viewed under UV light and stained with p-anisaldehyde or phosphomolybdic acid staining solution. GC (Agilent 6890 Series) was equipped with a crosslinked 5% PH ME siloxane column (30m × 0.32 mm, 0.25 μm film). ¹H spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 500 MHz spectrometers, ¹³C NMR spectra were recorded at 75 MHz and 125 MHz. IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer. HRMS spectra were obtained on a Kratos Analytical Concept instrument. Melting points were recorded on a Gallenkamp Melting Point Apparatus P 1106G. X-ray crystallographs were performed on a Bruker AX SMART 1k CCD diffractometer.

Microwave reactions were conducted in a CEM Model ESP-1500 Plus oven equipped with a pressure monitoring device and an EST-300 Plus fibre optic temperature probe. All experiments were performed in a quartz tube previously washed with an aqueous 2-propanol/NaOH solution.
Trans-2-bromo-butene (IUPAC nomenclature) and cis-2-bromo-butene (IUPAC nomenclature) were purchased from Aldrich under the names of cis-2-bromo-butene and trans-2-bromo-butene respectively.

6.2 Experimental for Chapter 2

6.2.1 General procedures

A. Tandem oxy-Cope/ene/Claisen reaction in the microwave: A solution of an allyl ether (0.10 mmol) in 12-15 mL of toluene in a quartz tube (previously washed with an aqueous 2-propanol/NaOH solution) equipped with a carboflon™ was added freshly distilled DBU¹ (0.50-1.00 mmol). The resulting solution was deoxygenated with argon for 0.5 h, sealed and heated in the CEM microwave at 220 °C for 1 h. The reaction was then cooled to rt. The solution was transferred to a round-bottom flask and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (20 % EtOAc in hexanes) afforded a corresponding lactol.

B. Oxidation with TPAP: To a solution of a lactol (0.10 mmol) in CH₂Cl₂ (1 mL) were added molecular sieves (4Å, 50 mg per 0.10 mmol), NMO (0.15 mmol) and TPAP. Resulting black mixture was left stirring for 4-6 h, and then it was filtered through a short pad of silica gel. The silica gel was rinsed with 50 mL of 10 % MeOH in EtOAc solution. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10 % EtOAc in hexanes) on silica gel to yield a corresponding lactone.

C. Preparation of allyl bromides: To a solution of an allyl alcohol (1.0 mmol) in 10 mL of CH₂Cl₂ was added CBr₄ (1.25 mmol). To a resulting mixture was transferred by cannula a solution of Ph₃P (1.50 mmol) in 5 mL of CH₂Cl₂. After stirring for 10 min the reaction

¹ In the later studies DBU was replaced with Et₃N (3-5 equiv)
mixture was concentrated under reduced pressure and diluted with 50 mL of hexanes to induce a precipitation of triphenylphosphine oxide. The precipitate was filtered through Celite and the filtrate was concentrated under reduced pressure. The last two steps were repeated two more times to ensure that most of triphenylphosphine oxide was removed. The residue containing allyl bromide was used in the allylation of diol 2.20 without further purification.

6.2.2 Spectroscopic data

2-Chloro-1-(1-methyl-propenyl)-cyclohexanol (2.13)

![Chemical Structure]

To a solution of a trans-2 bromo-2-butene (0.15 mL, 1.50 mmol) in Et₂O (5 mL) at −78 °C was added t-BuLi (1.65 mL, 1.7 M in pentane, 2.80 mmol). The mixture was stirred for 2 h at −78 °C. Then a solution of 1-chloro-cyclohexan-2-one (132 mg, 1.00 mmol) in Et₂O (2 mL) was transferred by cannula to the lithiated compound at −78 °C. The reaction was completed in 20 min after addition of the ketone. It was quenched with H₂O and extracted with Et₂O 3 x 10 mL. The combined organic extracts were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (7% EtOAc in hexanes) gave chloroalcohol 2.13 (143 mg, 76%) as a yellowish oil. IR (cm⁻¹, neat) 3570 (m), 3482 (bm), 2939 (s), 2850 (m), 1447 (m), 988 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.74-5.67 (m, 1H), 4.35-4.15 (m, 1H), 2.07-1.93 (m, 3H), 1.79-1.52 (m, 10H), 1.51-1.38 (m, 1H), 1.34-1.18 (m, 1H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 134.0 (C₄), 119.0 (CH), 76.8 (C₄), 66.4 (CH), 36.6 (CH₂), 32.7 (CH₂), 26.7 (CH₂), 21.0 (CH₂), 13.7 (CH₃), 12.8 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₀H₁₇OCl 188.0968, found 188.0953.
2-(1-Methyl-propenyl)-1-vinyl-cyclohexanol (2.11)

To a solution of chloroalcohol 2.13 (62 mg, 0.33 mmol) in THF (5 mL) at rt was added vinylmagnesium bromide (0.66 mL, 1.5 M in THF, 0.99 mmol). The reaction mixture was refluxed for 3 h. It was then cooled to rt and quenched with a saturated aqueous solution of NH₄Cl. The mixture was extracted with Et₂O 3 x 15 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (8% EtOAc in hexanes) to afford product 2.11 (34.5 mg, 58%) as a yellow oil. IR (cm⁻¹, neat) 3549 (m), 3479 (m), 2933 (s), 2859 (m), 1640 (w), 1447 (m), 970 (m), 915 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.86 (dd, J = 10.7 Hz, J = 17.2 Hz, 1H), 5.24 (q, J = 6.2 Hz, 1H), 5.10 (dd, J = 1.5 Hz, J = 17.2 Hz, 1H), 4.91 (dd, J = 1.4 Hz, J = 10.7 Hz, 1H), 2.00 (dd, J = 3.2 Hz, J = 12.6 Hz, 1H), 1.80-1.35 (m, 14H), 1.28-1.13 (m, 1H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 147.2 (CH), 138.5 (C₄), 120.5 (CH), 110.6 (CH₂), 73.5 (C₄), 54.3 (CH), 38.3 (CH₂), 27.4 (CH₃), 26.7 (CH₂), 21.7 (CH), 19.6 (CH₃), 13.8 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₂H₂₀O 180.1514, found 180.1503.

2-Methyl-1-methylene-octahydro-naphthalen-4a-ols (2.12 and 2.14)

The microwave induced oxy-Cope/ene reaction (procedure A) of 2.11 (30 mg, 0.17 mmol) afforded an inseparable 3.2:1 mixture of diastereomers 2.12 and 2.14 respectively (21 mg, 70%). The ratio was determined from ¹H NMR spectrum by integrating the proton at 4.09 ppm and calibrating the integral for one. Reagents and quantities: DBU (0.13 mL, 0.84 mmol), toluene (12 mL). ¹H NMR (300 MHz, CDCl₃), δ ppm 4.09 (dd, J = 1.6
Hz, $J = 1.6$ Hz, 1H, 2.14), 4.84 (bs, 1H, 2.12), 4.70 (bs, 1H, 2.12), 4.57 (dd, $J = 1.9$ Hz, $J = 1.9$ Hz, 1H, 2.14), 2.58 (q, $J = 6.7$ Hz, 1H, 2.14), 2.22 (m, 1H, 2.14), 2.03-1.20 (m, 28H, 212 and 2.14), 1.09 (d, $J = 7.0$ Hz, 3H, 2.14), 1.05 (d, $J = 6.6$ Hz, 3H, 2.12); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 154.7, 154.1, 108.7, 106.0, 72.4, 72.3, 50.4, 44.3, 40.3, 39.0, 38.9, 38.8, 35.0, 33.1, 29.2, 26.4, 26.3, 24.5, 24.2, 21.7, 21.6, 19.1, 18.7.

![Z-3-Phenyl-prop-2-en-1-ol (2.25a)](image)

To a solution of 3-phenyl-prop-2-yne-1-ol (315 mg, 2.38 mmol) in 10 mL of hexanes was added Lindlar catalyst (32 mg, 10% w/w), followed by addition of quinoline (0.03 mL). The mixture was stirred under H$_2$ (1 atm) for 20 h at rt. The mixture was concentrated and purified by flash chromatography on silica gel (40% EtOAc in hexanes) to give allyl alcohol 2.25a (210 mg, 67%). The spectroscopic data was in accord with that reported by Charette et al.$^2$

![Z-1-bromo-3-phenyl-prop-2-en (2.26a)](image)

Bromination of allyl alcohol 2.25a (180 mg, 1.34 mmol) according to procedure C afforded 2.26a as a yellow oil. Crude oil was used for the etherification of diol 2.20 without purification. Reagents and quantities: CBr$_4$ (556 mg, 1.68 mmol), Ph$_3$P (527 mg, 2.01 mmol), CH$_2$Cl$_2$ (10 mL).

![2-Cyclohexylidene-ethanol (2.25b)](image)

1. To a suspension of NaH (1.44 g, 0.036 mol, 60% in oil) in 50 mL of

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THF at 0 °C was added dropwise triethylphosphonoacetate (4 mL, 0.020 mol). The mixture was stirred for 40 min at 0 °C, then cyclohexanone (1.1 mL, 0.010 mmol) was added dropwise. The reaction was stirred overnight at rt and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. Resulting crude oil was used in the next step without further purification.

2. To a solution of ester (1.680 g, 0.010 mol) in 100 mL of THF at −78 °C was added dropwise a solution of DIBAL-H (20 mL, 1.5 M in toluene, 0.030 mol). The contents were stirred for 2 hours at −78 °C and then slowly transferred by cannula to a stirred mixture of hexanes/Et₂O/saturated aqueous solution of tartaric acid (1:1:1) at 0 °C. The resulting emulsion was stirred for 2.5 h and diluted with H₂O and Et₂O. The aqueous phase was extracted with Et₂O 5 x 100 mL. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (30% EtOAc in hexanes) afforded 2.25b (916 mg, 73% over 2 steps) as a clear oil. The spectroscopic data was in accord with that reported by Sabol et al.³

(2-Bromo-ethyldiene)-cyclohexane (2.26b)

Bromination of allyl alcohol 2.25b (916 mg, 7.27 mmol) according to procedure C afforded 2.27b as a yellow oil. Crude oil was used for the etherification of diol 2.20 without purification. Reagents and quantities: CBr₄ (3.000 g, 9.09 mmol), Ph₃P (2.860 g, 10.91 mmol), CH₂Cl₂ (50 mL).

Cyclohex-1-enyl-methanol (2.25c)

1. To a solution of cyclohexanone tosyl hydrazone (9.580 g, 0.036 mol) in freshly distilled TMEDA (50 mL) at −78 °C was added n-BuLi (57 mL, 2.5 M in pentane, 0.14 mmol). After stirring for 2 h at −78 °C the mixture was warmed to rt and stirred for 3 h followed by addition of freshly distilled DMF (3.5 mL, 45.00 mmol). The resulting mixture was then stirred for 1 h at rt and quenched with H₂O. The aqueous phase was extracted with Et₂O 5 x 50 mL. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (15% Et₂O in hexanes) afforded aldehyde (3.00 g, 75%) as a yellow oil.

2. To a solution of cyclohex-1-enecarbaldehyde (3.000 g, 0.027 mol) in 200 mL of THF at −78 °C was added dropwise a solution of DIBAL-H (27 mL, 1.5 M in toluene, 0.041 mol). The contents were stirred for 2 hours at −78 °C and then slowly transferred by cannula to a stirred mixture of hexanes/Et₂O/saturated aqueous solution of tartaric acid (1:1:1) at 0 °C. The resulting emulsion was stirred for 2.5 h and diluted with H₂O and Et₂O. The aqueous phase was extracted with Et₂O 5 x 200 mL. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (40% EtOAc in hexanes) afforded 2.25c (1.235 g, 42%) as a clear oil. The spectroscopic data was in accord with that reported in literature.⁴

1-Bromomethyl-cyclohexene (2.26c)

Bromination of allyl alcohol 2.25c (877 mg, 7.80 mmol) according to

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procedure C afforded 2.26c as an orange oil. Crude oil was used for the etherification of diol 2.20 without purification. Reagents and quantities: CBr₄ (3.237 g, 9.75 mmol), Ph₃P (3.068 g, 11.70 mmol), CH₂Cl₂ (50 mL).

3-Phenyl-but-2-en-1-ol (2.25d)

1. To a suspension of NaH (1.152 g, 0.029 mol, 60% in oil) in 50 mL of THF at 0 °C was added dropwise triethylphosphonoacetate (3.2 mL, 0.016 mol). The mixture was stirred for 40 min at 0 °C, then acetophenone (1.0 mL, 0.008 mol) was added dropwise. The reaction was stirred overnight at rt and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 50 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15 % EtOAc in hexanes) afforded ethyl (E)-3-phenylbut-2-enoate (940 mg, 62%).

2. To a solution of ethyl (E)-3-phenylbut-2-enoate (335 mg, 0.010 mol) in 100 mL of THF at −78 °C was added dropwise a solution of DIBAL-H (20 mL, 1.5 M in toluene, 0.030 mol). The contents were stirred for 2 hours at −78 °C and then slowly transferred by cannula to a stirred mixture of hexanes/Et₂O/saturated aqueous solution of tartaric acid (1:1:1) at 0 °C. The resulting emulsion was stirred for 2.5 h and diluted with H₂O and Et₂O. The aqueous phase was extracted with Et₂O 5 x 100 mL. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (30% EtOAc in hexanes) afforded 2.25d (165 mg, 64%) as a clear oil. The spectroscopic data was in accord with that reported in literature.²
(1-Bromo-3-phenyl-but-2-ene) (2.26d)

Bromination of allyl alcohol 2.25d (304 mg, 2.08 mmol) according to procedure C afforded 2.26d as a yellow oil. Crude oil was used for the etherification of diol 2.20 without purification. Reagents and quantities: CBr₄ (864 mg, 2.60 mmol), Ph₃P (818 mg, 3.12 mmol), CH₂Cl₂ (20 mL).

1-bromo-4-O-Benzyl-2-butyne (2.62c)

1. To a solution of but-2-yne-1,4-diol (5.00 g, 58.00 mmol) in 50 mL of THF was added NaH (232 mg, 5.80 mmol, 60% in oil) 0 °C. The resulting mixture was stirred for 5 min followed by addition of freshly distilled benzyl bromide (0.69 mL, 5.80 mmol). The reaction mixture was stirred for 4 h at rt and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 50 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (30% EtOAc in hexanes) afforded 1-O-benzyl-2-butyne-1,4-diol (728 mg, 71%) as a yellow oil. The spectroscopic data were in accord with those reported in literature.⁵

2. Bromination of 1-O-benzyl-2-butyne-1,4-diol (364 mg, 2.07 mmol) according to procedure C afforded 2.62c as a yellow oil. Crude oil was used for the etherification of diol 2.20 without purification. Reagents and quantities: CBr₄ (857 mg, 2.59 mmol), Ph₃P (814 mg, 3.11 mmol), CH₂Cl₂ (20 mL).

2-(1-Hydroxymethyl-vinyl)-1-vinyl-cyclohexanol (2.20)

To a solution of 1,2-divinylcyclohexanol 2.19 (6.53 g, 0.04 mol) in 300 mL of CH₂Cl₂ was added SeO₂ (1.99 g, 0.02 mol) and t-BuOOH (18.5 mL, 70% in H₂O, 0.16 mol). The mixture was stirred for 24 h and diluted with CH₂Cl₂ (300 mL). The combined organic fractions were washed with H₂O 1 x 400 mL, a saturated aqueous solution of NaHCO₃ 2 x 500 mL, H₂O 1 x 400 mL and brine x 400 mL, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes then 40% EtOAc in hexanes) afforded diol 2.20 (3.308 g, 47% or 62% based on the recovery of 2.19) as a white solid. IR (cm⁻¹, neat) 3310 (br), 3201 (br), 3073 (m), 3010 (m), 2978 (m), 2934 (s), 2855 (s), 1638 (m), 1448 (m); ¹H NMR (300 MHz, CDCl₃), δppm 5.83 (dd, J =10.7 Hz, J =17.2 Hz, 1 H), 5.14 (d, J =17.2 Hz, 1H), 5.03 (s, 1H), 4.96 (d, J =10.7 Hz, 1H), 4.86 (s, 1H), 4.03 (d, JᵧAB =12.5, 1H), 3.90 (d, JᵧBA =12.5 Hz, 1H), 3.46 (bs, 2H), 2.21 (dd, J =3.1 Hz, J =12.8 Hz, 1H), 1.92-1.19 (m, 8H); ¹³C NMR (75 MHz, CDCl₃), δppm 149.8 (C₄), 146.4 (CH), 116.7 (CH₂), 111.7 (CH₂), 73.3 (C₄), 65.1 (CH₂), 52.4 (CH), 38.7 (CH₂), 27.2 (CH₂), 26.4 (CH₂), 21.5 (CH₂); HRMS (EI), m/z (M⁺-H₂O) calculated for C₁₁H₁₆O 164.1247, found 164.1223; mp = 77.9-80.1 °C.

2-(1-Allyloxyethyl-vinyl)-1-vinyl-cyclohexanol (2.21)

To a suspension of NaH (1.590 g, 0.039 mol, 60% in oil) in THF (180 mL) was transferred by cannula a solution of diol 2.20 (3.308 g, 0.018 mol) in 10 mL of THF at 0 °C. The resulting mixture was stirred for 5 min followed by addition of freshly distilled allyl bromide (1.9 mL, 0.022 mol). The reaction was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase
was extracted with Et₂O 3 x 150 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether 2.21 (2.713 g, 68%) as a yellowish oil. Note: diallylated product (1.033 g, 22%) was also isolated as a yellowish oil. IR (cm⁻¹, neat) 3411 (m), 3083 (w), 2932 (s), 2855 (m), 1640 (w), 1445 (m), 1413 (m), 1067 (s), 974 (m), 916 (s); ¹H NMR (500 MHz, CDCl₃), δppm 5.91-5.81 (m, 2H), 5.26 (dddd, J = 1.7 Hz, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.19-5.15 (m, 2H), 5.06-5.05 (m, 1H), 4.97 (d, J = 1.9 Hz, 1H), 4.94 (dd, J = 1.0 Hz, J = 10.6 Hz, 1H), 4.03-3.96 (m, 2H), 3.86 (dddd, JAX = 1.4 Hz, JAY = 1.4 Hz, JAM = 5.8 Hz, JAB = 12.7 Hz, 1H), 3.73-3.70 (m, 1H), 3.57 (d, J = 2.3 Hz, 1H), 2.25 (dd, J = 3.4 Hz, J = 12.8 Hz, 1H), 1.85 (dddd, J = 3.6 Hz, J = 12.9 Hz, J = 16.4 Hz, 1H), 1.80-1.65 (m, 2H), 1.62 -0.59 (m, 1H), 1.53-1.48 (m, 1H), 1.43-1.37 (m, 2H), 1.31-1.23 (m, 1H); ¹³C NMR (75 MHz, CDCl₃), δppm 146.5 (CH), 146.2 (C4), 133.9 (CH), 118.0 (CH₂), 117.5 (CH₂), 111.0 (CH₂), 72.6 (C4), 72.2 (CH₂), 70.9 (CH₂), 65.8 (CH₂), 52.0 (CH), 38.4 (CH₂), 26.8 (CH₂), 26.2 (CH₂); HRMS (EI), m/z (M⁺-H₂O) calculated for C₁₄H₁₉O 204.1514; found 204.1504.

7-Allyl-11-oxa-tricyclo[5.3.2.0₁,₆]dodecan-12-ol (2.22), mixture of anomers

1. The microwave induced oxy-Cope/ene/Claisen rearrangement (procedure A) of 2.21 (80 mg, 0.36 mmol) afforded 2.22 (60 mg, 75%) as a white solid. Reagents and quantities: DBU (0.11 mL, 7.20 mmol), toluene (12 mL). 2. The microwave reaction (procedure A) of 2.21 (2.713 g, 0.012 mol) in the presence of Et₃N (0.16 mL, 0.001 mol) in 15 mL of toluene gave lactol 2.22 (2.164 g, 80%) and aldehyde 2.24 (0.248 g, 9%).
$^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.84-5.68 (m, 1H), 5.32 (s) and 5.08-4.98 (m) give 1H, 3.46-3.42 (m) and 3.37-3.22 (m) give 1H, 2.31 (dd, $J = 7.4$ Hz, $J = 14.0$ Hz, 1H), 2.23-2.08 (m, 1H), 2.05-1.97 (m, 1H), 1.88-0.81 (m, 16H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 136.0, 135.3, 117.4, 104.5, 102.2, 84.1, 82.7, 50.8, 50.4, 49.4, 48.9, 39.6, 39.0, 37.1, 35.8, 34.9, 34.5, 31.5, 25.3, 24.9, 24.2, 23.9, 21.9, 19.8.

1-Allyl-4a-hydroxy-decahydro-naphthalene-1-carbaldehyde (2.24)

IR (cm$^{-1}$, neat) 3523 (bm), 2931 (s), 2854 (m), 1719 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 9.15 (d, $J = 1.1$ Hz, 1H), 5.92 (m, 1H), 5.18-5.12 (m, 1H), 5.06-5.02 (m, 1H); 3.09-3.01 (m, 1H), 2.65-2.58 (m, 1H), 1.82-1.62 (m, 3H), 1.49-0.89 (m, 12 H), 0.25 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 205.5 (C$_4$), 136.6 (CH), 117.3 (CH$_2$), 70.2 (C$_4$), 52.3 (C$_4$), 44.9 (CH), 42.2 (CH$_2$), 40.4 (CH$_2$), 31.9 (CH$_2$), 29.1(CH$_2$), 26.9 (CH$_2$), 23.0 (CH$_2$), 21.7 (CH$_2$), 16.3 (CH$_2$); HRMS (EI), m/z (M$^+$- H$^+$) calculated for C$_{14}$H$_{21}$O$_2$ 221.1541, found 221.1537.

7-Allyl-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-one (2.23)

The oxidation (procedure B) of lactol 2.22 (28 mg, 0.13 mmol) gave lactone 2.23 (20 mg, 70%) as a white solid. Reagents and quantities: molecular sieves (65 mg), TPAP (2 mg, 5% mol), NMO (22 mg, 0.20 mmol). IR (cm$^{-1}$, neat) 2932 (s), 2859 (w), 1767 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.79-5.65 (m, 1H), 5.12-5.06 (m, 2H), 2.36-2.24 (m, 2H), 2.02-1.99 (m, 1H), 1.79-0.81 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 180.7 (C$_4$), 133.5 (CH), 118.7 (CH$_2$), 83.5 (C$_4$), 52.6 (C$_4$), 49.6 (CH), 36.0 (CH$_2$), 35.3 (CH$_2$), 33.6
(CH$_2$), 32.3 (CH$_2$), 24.7 (CH$_2$), 24.2 (CH$_2$), 21.2 (CH$_2$), 19.8 (CH$_2$); HRMS (EI), m/z (M$^+$) calculated for C$_{14}$H$_{20}$O$_2$ 220.1463; found 220.1485; mp = 35.6-38.8 °C.

2-[1-(Cyclohex-1-enylmethoxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.27) 

To a suspension of NaH (50 mg, 1.25 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (103 mg, 0.56 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of solution of allyl bromide 2.26c (200 mg, 1.13 mmol) in 1 mL of THF. The reaction was left stirring overnight at rt. It was quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous phase was extracted with Et$_2$O 3 x 20 mL. The combined organic extracts were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford product 2.27 (106 mg, 68%) as a yellow oil. IR (cm$^{-1}$, neat) 3403 (m), 2929 (s), 2856 (s), 1638 (w), 1443 (m), 1055 (m), 915 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.8 (dd, $J = 10.6$ Hz, $J = 17.2$ Hz, 1H), 5.65-5.64 (m, 1H), 5.17 (dd, $J = 1.7$Hz, $J = 17.1$ Hz, 1H), 5.05-5.04 (m, 1H), 4.94 (dd, $J = 1.7$ Hz, $J = 10.6$ Hz, 1H), 4.95-4.95 (m, 1H), 3.98-3.62 (m, 5H), 2.26 (dd, $J = 3.2$ Hz, $J = 12.8$ Hz, 1H), 2.03-1.16 (m, 16H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 146.9 (C4), 146.6 (CH), 134.5 (C4), 125.9 (CH), 118.5 (CH$_2$), 113.2 (CH$_2$), 75.3 (CH$_2$), 72.9 (C4), 71.9 (CH$_2$), 52.5 (CH), 38.6 (CH$_2$), 27.1 (CH$_2$), 25.6 (CH$_2$), 26.4 (CH$_2$), 25.4 (CH$_2$), 22.8 (CH$_2$), 22.7 (CH$_2$), 21.6 (CH$_2$); HRMS (EI), m/z (M$^+$ - H$_2$O) calculated for C$_{18}$H$_{26}$O 258.1983, found 258.19927.
7-(2-Methylene-cyclohexyl)-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-ol (2.33), (mixture of anomers)
The microwave induced oxy-Cope/ene/Claisen rearrangement (procedure A) of 2.27 (50 mg, 0.18 mmol) gave lactol 2.33 (30 mg, 60%) as a white solid. Reagents and quantities: DBU (0.27 mL, 1.80 mmol), toluene (12 mL). $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.55 (d, $J = 3.0$ Hz) and 5.12 (d, $J = 4.1$ Hz) give 1H, 4.82 (s) and 4.80 (s) give 1H, 4.64 (s) and 4.71 (s) give 1H, 2.50-2.40 (m, 2H), 2.27-1.04 (m, 23H).

7-(2-Methylene-cyclohexyl)-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-one (2.33a)
The oxidation (procedure B) of lactol 2.33 (30 mg, 0.11 mmol) afforded lactone 2.33a (19 mg, 63%) as a white solid. Reagents and quantities: molecular sieves (55 mg), TPAP (2 mg, 5% mol), NMO (20 mg, 0.17 mmol). IR (cm$^{-1}$, neat) 2930 (s), 2855 (m), 1766 (s), 1648 (w), 1445 (w); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 4.88 (s, 1H), 4.73 (s, 1H), 2.37-2.25 (m, 2H), 2.11-1.02 (m, 24H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 179.5 (C$_4$), 148.9 (C$_4$), 107.7 (CH$_2$), 82.5(C$_4$), 56.4 (C$_4$), 52.3 (CH), 48.1 (CH), 39.9 (CH$_2$), 36.8 (CH$_2$), 33.8 (CH$_2$), 33.5 (CH$_2$), 31.8 (CH$_2$), 29.7 (CH$_2$), 28.1 (CH$_2$), 25.9 (CH$_2$), 24.5 (CH$_2$), 22.2 (CH$_2$), 21.3 (CH$_2$); HRMS (EI), m/z (M$^+$) calculated for C$_{16}$H$_{26}$O$_2$ 274.1933, found 274.1915; mp = 98.0-101.2 $^\circ$C.

2-[1-(E-3-Phenyl-allyloxy)methyl]-1-vinyl-cyclohexanol (2.28)
To a suspension of NaH (90 mg, 2.20 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (100 mg, 0.55 mol) in 1
mL of THF at rt. The resulting mixture was stirred for 5 min followed by addition of cinnamyl chloride 2.26e (0.15 mL, 1.10 mmol) and NaI (8 mg, 0.06 mmol). The reaction mixture was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether 2.28 (132 mg, 80%) as a yellow oil. IR (cm⁻¹, neat) 3403 (m), 2931 (s), 2854 (m), 1618 (s), 1447 (s); ¹H NMR (300 MHz, CDCl₃), δppm 7.38-7.20 (m, 5H), 6.58 (d, J = 16.6 Hz, 1H), 6.34 (ddd, J_MA = 6.1 Hz, J_MB = 6.1 Hz, J = 16.6 Hz 1H), 5.86 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.20 (dd, J = 1.8 Hz, J = 17.2 Hz, 1H), 5.10 (bs, 1H), 5.01 (d, J = 1.9 Hz, 1H), 4.97 (dd, J = 1.8 Hz, J = 10.6 Hz, 1H), 4.16 (ddd, J_AM = 6.0 Hz, J_AX = 1.4 Hz, J_AB = 12.6 Hz, 1H), 4.09-4.01 (m, 2H), 3.77 (d, J_AB = 12.0 Hz, 1H), 3.61 (s, 1H), 2.26 (dd, J = 3.2 Hz, J = 12.0 Hz, 1H), 1.94-1.19 (m, 8H). ¹³C NMR (75 MHz, CDCl₃), δppm 147.0 (C4), 146.5 (CH), 137.2 (C4), 132.9 (CH), 128.5 (CH) x 2, 127.7 (CH), 126.5 (CH) x 2, 125.13 (CH), 118.1 (CH₂), 111.1 (CH₂), 73.0 (C4), 72.0 (CH₂), 70.5 (CH₂), 51.9 (CH), 38.3 (CH₂), 26.8 (CH₂), 26.1 (CH₂), 21.2 (CH₂); HRMS (EI), m/z (M⁺-C₅H₁₀O) calculated for C₁₁H₁₆O 164.1201; found 164.1199.

![Chemical Structure](image)

**7-(1-Phenyl-allyl)-1,1-oxatricyclo[5.3.2.0²⁶]dodecaden-12-ol (2.34) (mixture of anomers)**

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of allyl ether 2.28 (80 mg, 0.27 mmol) afforded 2.34 (50 mg, 63%) as a white solid and 2.35 (22 mg, 28%) as a white solid. Reagents and quantities: DBU (0.3 mL, 1.80 mmol), toluene (12 mL). ¹H NMR (300 MHz, CDCl₃), δppm 7.36-7.24 (m, 5H), 6.47-6.42 (m) and 6.38-6.14
(m) give 1H, 5.51 (d, J = 4.5 Hz) and 5.25 (d, J = 3.0 Hz, 1H), 5.13-4.93 (m, 2H), 4.11 (d, J = 7.1 Hz) and 3.62 (d, J = 9.3 Hz) give 1H, 3.34 (d, J = 4.6 Hz) and 3.30 (d, J = 3.3 Hz) give 1H, 2.50-0.81 (m, 15H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 142.1, 141.8, 140.0, 139.8, 130.8, 129.6, 128.5, 128.3, 127.9, 126.6, 117.3, 115.9, 104.0, 101.8, 84.3, 82.7, 54.8, 53.0, 51.3, 51.2, 49.3, 49.1, 39.7, 38.8, 35.2, 34.9, 31.0, 29.2, 25.3, 25.2, 25.1, 23.7, 21.8, 21.8, 20.1, 20.0

7-(1-Phenyl-allyl)-11-oxa-tricyclo[5.3.2.0$^{14}$]dodecan-12-one (2.34a)

The oxidation (procedure B) of lactol 2.34 (25 mg, 0.08 mmol) afforded lactone 2.34a (20 mg, 80%) as a white solid. Reagents and quantities: molecular sieves (42 mg), TPAP (2 mg, 5% mol), NMO (15 mg, 0.12 mmol). IR (cm$^{-1}$, neat) 3077 (w), 3022 (w), 2932 (m), 2858 (w), 1764 (s), 1634 (w), 1596 (w), 1448 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 6.71-6.61 (m, 1H), 5.13 (d, J = 9.9 Hz, 1H), 4.64 (d, J = 17.3 Hz, 1H), 3.79-3.78 (d, J = 4.7 Hz, 1H), 2.19-2.12 (m, 1H), 2.02-0.79 (m, 19H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 179.0 (C$_4$), 140.7 (C$_4$), 139.6 (CH), 130.5 (CH), 130.5 (CH), 128.6 (CH), 128.6 (CH), 127.0 (CH), 117.3 (CH$_2$), 82.9 (C$_4$), 56.2 (C$_4$), 51.3 (CH), 50.0 (CH), 36.3 (CH$_2$), 33.9 (CH$_2$), 30.0 (CH$_2$), 24.6 (CH$_2$), 24.3 (CH$_2$), 21.1 (CH$_2$), 20.4 (CH$_2$); HRMS (EI), m/z (M$^+$) calculated for C$_{20}$H$_{24}$O$_2$ 296.1776, found 296.1778.

2-[1-(Z-3-Phenyl-allyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.29)

To a suspension of NaH (50 mg, 1.25 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (103 mg, 0.57 mol) in 1 mL of THF at rt. The resulting mixture was stirred for 5 min followed by addition of allyl
bromide 2.26a (263 mg, 1.34 mmol). The reaction mixture was stirred for 3 h at rt and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded allyl ether 2.29 (97 mg, 60%) as a yellow oil. IR (cm⁻¹, neat) 3407 (bm), 3084 (w), 3027 (w), 2931 (s), 2855 (s), 1782 (w), 1733 (w), 1447 (m), 1071 (s); ¹H NMR (300 MHz, CDCl₃), δppm 7.35-7.15 (m, 5H), 6.60 (d, J = 11.8 Hz, 1H), 5.91-5.77 (m, 2H), 5.15 (dd, J = 1.3 Hz, J = 17.2 Hz, 1H), 5.02 (s, 1H), 4.95 (s, 1H), 4.89 (dd, J = 1.2 Hz, J = 10.7 Hz, 1H), 4.30-4.24 (m, 1H), 4.19-4.08 (m, 1H), 4.02 (d, JAB = 11.6 Hz, 1H), 3.72 (d, JBA = 11.7 Hz, 1H), 3.60 (d, J = 2.0 Hz, 1H), 2.25 (dd, J = 3.1 Hz, J = 12.9 Hz, 1H), 1.91-1.19 (m, 8H); ¹³C NMR (75 MHz, CDCl₃), δppm 146.8 (CH), 146.4 (C₄), 136.9 (C₄), 132.3 (CH), 129.1 (CH) x 2, 128.6 (CH) x 2, 128.5 (CH), 127.6 (CH), 118.5 (CH₂), 111.4 (CH₂), 73.0 (C₄), 72.8 (CH₂), 67.1 (CH₂), 52.2 (CH), 38.7 (CH₂), 27.1 (CH₂), 26.5 (CH₂), 21.6 (CH₂); HRMS (EI), m/z (M⁺) calculated for C₂₀H₂₆O₂ 298.1933, observed degradation.

7-(1-Phenyl-allyl)-1,1-oxatricyclo[5.3.2.0¹⁴]dodecadecan-12-ol
(2.35) (mixture of anomers)

¹H NMR (300 MHz, CDCl₃), δppm 7.37-7.12 (m, 5H), 6.35-6.17 (m, 1H), 5.54 (d, J = 4.7 Hz) and 4.78 (d, J = 3.4 Hz) give 1H, 5.14-5.04 (m, 2H), 4.07 (d, J = 9.1 Hz) and 3.59 (d, J = 8.5 Hz) give 1H, 2.77 (d, J = 3.5 Hz, 1H), 2.15-1.00 (m, 15H); ¹³C NMR (75 MHz, CDCl₃), δppm 142.7, 141.8, 138.7, 138.0, 131.0, 129.7, 128.5, 128.0, 126.9, 126.3, 117.5, 117.3, 103.3, 101.7, 84.2, 82.1, 54.7, 53.0, 51.3, 49.4, 48.2, 39.8, 38.9, 35.1, 35.0, 29.3, 27.1, 25.4, 25.2, 24.4, 23.0, 22.0, 21.9, 19.8, 19.7.
7-(1-Phenyl-allyl)-11-oxa-tricyclo[5.3.2.01,6]dodecan-12-one (2.35a)

The oxidation (procedure B) of lactol 2.35 (20 mg, 0.07 mmol) afforded lactone 2.35a (18 mg, 90%) as a white solid. Reagents and quantities: molecular sieves (34 mg), TPAP (1 mg, 5% mol), NMO (12 mg, 0.11 mmol). IR (cm\(^{-1}\), neat) 2934 (s), 2861 (m), 1767 (s), 1634 (w), 1602 (w), 1446 (m); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta\) ppm 7.33-7.20 (m, 5H), 6.21 (ddd, \(J = 7.2\) Hz, \(J = 10.4\) Hz, \(J = 17.3\) Hz, 1H), 5.05-5.00 (m, 1H), 4.92-4.85 (m, 1H), 3.78 (d, \(J = 7.1\) Hz, 1H), 2.09-1.95 (m, 3H), 1.74-1.11 (m, 12H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)), \(\delta\) ppm 179.1 (C\(_4\)), 140.2 (C\(_4\)), 139.3(CH), 130.6 (CH) x 2, 128.5 (CH) x 2, 127.1 (CH), 116.9 (CH\(_2\)), 82.7 (C\(_4\)), 56.7 (C\(_4\)), 53.0 (CH), 51.4 (CH), 36.2 (CH\(_2\)), 34.0 (CH\(_2\)), 32.3 (CH\(_2\)), 26.9 (CH\(_2\)), 24.6 (CH\(_2\)), 21.3 (CH\(_2\)), 19.8 (CH\(_2\)); HRMS (EI), m/z (M⁺) calculated for C\(_{20}\)H\(_{24}\)O\(_2\) 296.1776, found 296.1782.

2-[1-(3-Methyl-but-2-enyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.30)

To a suspension of NaH (48 mg, 1.21 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (100 mg, 0.55 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of 1-bromo-3-methyl-but-2-ene (0.127 mL, 1.10 mmol). The reaction was refluxed for 2 h. The mixture was then cooled to rt and quenched with a saturated aqueous solution of NH\(_4\)Cl. The aqueous phase was extracted with Et\(_2\)O 3 x 20 mL. The combined organic extracts were dried over MgSO\(_4\), concentrated under reduced pressure. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded product 2.30 (100 mg, 73%) as a yellow oil. IR (cm\(^{-1}\), neat) 3727 (w),
3399 (m), 2931 (s), 2857 (m), 1675 (w), 1638 (w), 1445 (w), 1063 (m), 974 (w); \( ^1H \) NMR (300 MHz, CDCl\(_3\)), \( \delta_{ppm} \) 5.82 (dd, \( J = 10.6 \) Hz, \( J = 17.2 \) Hz, 1H), 5.32-5.26 (m, 1H), 5.13 (dd, \( J = 1.7 \) Hz, \( J = 17.2 \) Hz, 1H), 5.04-5.04 (m, 1H), 4.95-4.91 (m, 2H), 3.99-3.82 (m, 4H), 3.68 (d, \( J = 11.5 \) Hz, 1H), 2.26 (dd, \( J = 3.3 \) Hz, \( J = 12.9 \) Hz, 1H), 1.86-1.22 (m, 14H); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)), \( \delta_{ppm} \) 146.9 (C4), 146.6 (C4), 137.8 (C4), 120.6 (CH), 118.5 (CH\(_2\)), 111.3 (CH\(_2\)), 72.9 (CH\(_2\)), 72.2 (C4), 67.0 (CH\(_2\)), 52.5 (CH\(_2\)), 38.6 (CH\(_2\)), 27.0 (CH\(_2\)), 26.5 (CH\(_2\)), 26.1 (CH\(_3\)), 21.6 (CH\(_2\)), 18.5 (CH\(_3\)); HRMS (EI), \( m/z \) (M\(^+\)) calculated for C\(_{16}\)H\(_{26}\)O\(_2\), observed degradation.

![Chemical Structure](image)

7-(1,1-Dimethyl-allyl)-11-oxa-tricyclo[5.3.2.0\(^{1,6}\)]dodecan-12-ol (2.48) (mixture of anomers)

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of 2.30 (100 mg, 0.40 mmol) at 200 °C gave lactol 2.48 (76 mg, 76%) as a clear oil and enol ether 2.49 (15 mg, 15%) as a clear oil. Reagents and quantities: DBU (0.3 mL, 2.00 mmol), toluene (12 mL). Purification by flash chromatography on silica gel (10% EtOAc in hexanes, then 20% EtOAc in hexanes) \( ^1H \) NMR (300 MHz, CDCl\(_3\)), \( \delta_{ppm} \) 6.12 (dd, \( J = 10.6 \) Hz, \( J = 18.2 \) Hz, 1H), 5.82 (d, \( J = 5.0 \) Hz, 1H), 4.94-4.91 (m, 1H), 4.87-4.86 (m, 1H), 3.86 (d, \( J = 5.0 \) Hz, 1H), 2.26-2.02 (m, 2H), 1.81-0.83 (m, 19H); \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)), \( \delta_{ppm} \) 148.2, 110.7, 110.0, 103.2, 101.0, 83.3, 82.3, 77.8, 77.6, 77.4, 77.0, 53.7, 50.8, 49.6, 40.8, 40.5, 39.8, 39.7, 35.9, 35.7, 33.4, 32.0, 29.0, 28.1, 25.8, 25.7, 25.5, 25.0, 23.0, 22.1, 21.8, 20.4, 14.5.
1-(3-Methyl-but-2-enyloxymethylene)-octahydro-naphthalen-4-ol (2.49)

IR (cm\(^{-1}\), neat) 3547 (w), 3474 (w), 2928 (s), 2857 (m), 1672 (m), 1446 (m), 1154 (s), 1088 (w); \(^1\)HMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 5.69 (s, 1H), 5.35-5.27 (m, 1H), 4.35 (d, \(J = 6.9\) Hz, 2H) 2.87-2.82 (m, 1H), 1.95-1.89 (m, 1H), 1.75-1.20 (m, 20H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 139.9 (CH), 136.8 (C\(_4\)), 121.6 (CH), 118.8 (C\(_4\)), 70.8 (C\(_4\)), 68.4 (CH\(_2\)), 47.4 (CH), 40.5 (CH\(_2\)), 38.8 (CH\(_2\)), 26.7 (CH\(_2\)), 26.6 (CH\(_2\)), 25.7 (CH\(_3\)), 23.9 (CH\(_2\)), 23.1 (CH\(_2\)), 21.8 (CH\(_2\)), 18.0 (CH\(_3\)); HRMS (EI), m/z (M\(^+\)-C\(_5\)H\(_{10}\)O) calculated for C\(_{11}\)H\(_{16}\)O 164.1201; found 164.1175.

1-(1,1-Dimethyl-allyl)-1-hydroxymethyl-octahydro-naphthalen-4-ol (2.48a)

To a solution of lactol 2.48 (38 mg, 0.15 mmol) in 2 mL of THF was carefully added LiAlH\(_4\) (11 mg, 0.30 mmol) at -78 °C. After 10 min a dry-ice/isopropanol bath was removed and the mixture was stirred at 0 °C for 5 h. It was quenched by a dropwise addition of 2 mL of 1.0 M aqueous solution of sodium tartrate. The resulting emulsion was stirred for 10 h until it became almost clear and the phases separated. The aqueous phase was extracted with EtOAc 5 x 5 mL. The combined fractions were dried over MgSO\(_4\) and concentrated under reduced pressure. Purification by flash chromatography (40 % EtOAc in hexanes) on silica gel afforded diol 2.48a (30 mg, 79%) as a white solid. IR (cm\(^{-1}\), neat) 3226 (s), 2970 (m), 2930 (s), 2846 (m), 1632 (w), 1449 (m), 1410 (m), 1055 (s); \(^1\)HMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 6.01 (dd, \(J = 10.6\) Hz, \(J = 17.7\), 1H), 4.92-4.87 (m, 2H), 3.89 (d, \(J = 1.1\) Hz, 1H), 3.58 (d, \(J = 11.1\) Hz, 1H), 3.28-3.23 (m, 2H), 2.01-1.16 (m, 15H), 1.01 (s, 3H),
0.99 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 147.5 (CH), 111.2 (CH$_2$), 71.5 (C4), 65.8 (CH$_2$), 47.8 (CH), 44.6 (C4), 43.8 (C4), 42.3 (CH$_2$), 40.5 (CH$_2$), 32.0 (CH$_2$), 27.5 (CH$_2$), 25.8 (CH$_3$), 24.3 (CH$_2$), 24.3 (CH$_3$), 22.0 (CH$_2$), 20.2 (CH$_2$); HRMS (EI), m/z (M$^+ \cdot$ H$_2$O) calculated for C$_{16}$H$_{26}$O 234.1984, found 234.1947; mp = 140.0-143.0 °C.

2-[1-(3-Phenyl-but-2-enoxy)methyl]-1-vinyl-cyclohexanol
(2.31)

To a suspension of NaH (45 mg, 1.14 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (94 mg, 0.52 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of allyl bromide 2.26b (220 mg, 1.04 mmol) in 3 mL of THF. The reaction was stirred overnight and quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous phase was extracted with Et$_2$O 3 x 20 mL. The combined organic extracts were dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford product 2.31 (119 mg, 73%) as a yellow oil. IR (cm$^{-1}$, neat) 3560 (w), 3399 (m), 3081 (w), 3058 (w), 3027 (w), 2979 (w), 2931 (s), 2857 (s), 1639 (m), 1598 (w), 1576 (w), 1494 (m), 1445 (m), 1402 (m), 1381 (m), 1285 (w), 1270 (w), 1049 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 7.41-7.26 (m, 5H), 5.90-5.82 (m, 2H), 5.20 (dd, $J = 1.7$ Hz, $J = 17.2$ Hz, 1H), 5.11-5.10 (m, 1H), 5.01-4.98 (m, 1H), 4.97 (dd, $J = 1.7$ Hz, $J = 10.6$ Hz, 1H), 4.20 (ddd, $J_{AX} = 0.8$ Hz, $J_{AM} = 6.3$ Hz, $J_{AB} = 12.3$ Hz, 1H), 4.13-4.06 (m, 2H), 3.77 (dd, $J_{AX} = 0.5$ Hz, $J_{AB} = 11.6$ Hz, 1H), 3.71 (d, $J = 2.3$ Hz, 1H), 2.30 (dd, $J = 3.3$ Hz, $J = 12.7$ Hz, 1H), 2.05-2.04 (m, 3H), 1.92-1.25 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 146.9 (CH), 146.6 (C4), 143.1 (C4), 139.1 (C4), 128.6 (CH) x 2, 127.6 (CH), 126.2 (CH) x 2,
123.8 (CH), 118.6 (CH$_2$), 113.9 (CH$_2$), 72.9 (C$_4$), 72.5 (CH$_2$), 67.4 (CH$_2$), 52.4 (CH), 38.7 (CH$_2$), 27.2 (CH$_2$), 26.6 (CH$_2$), 21.6 (CH$_2$), 16.6 (CH$_3$); HRMS (EI), m/z (M$^+$-H$_2$O) calculated 294.2029 for (C$_{21}$H$_{26}$O), found 294.1998.

![Image of 7-(3-Phenyl-but-2-etyl)-11-oxa-tricyclo[5.3.2.0$_1$6]dodecan-12-ol](image)

(2.50) (mixture of the anomers)

The microwave reaction (procedure A) of 2.31 (71 mg, 0.38 mmol) afforded lactol 2.50. Reagents and quantities: DBU (0.3 mL, 2.00 mmol), toluene (15 mL). The crude lactol was oxidized to lactone 2.50a without further purification.

![Image of 7-(3-Phenyl-but-2-etyl)-11-oxa-tricyclo[5.3.2.0$_1$6]dodecan-12-one](image)

mixture E/Z (89:11) (2.50a)

The oxidation (procedure B) of lactol 2.50 (43 mg, 0.14 mmol) afforded lactone 2.50a (22 mg, 51%) as a yellowish oil. Reagents and quantities: molecular sieves (69 mg), TPAP (3 mg, 5% mol), NMO (24 mg, 0.21 mmol). IR (cm$^{-1}$, neat) 2922 (m), 2858 (w), 1769 (s), 1692 (m), 1641 (m), 1538 (m), 1447 (m), 1093 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 7.59-7.22 (m, 5H), 5.67-5.66 (m, 1H), 2.51 (dd, $J = 8.0$ Hz, $J = 15.5$ Hz, 1H), 2.40 (dd, $J = 15.5$ Hz, $J = 6.5$ Hz, 1H), 2.05-2.01 (m, 4H), 1.86-0.80 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 180.9 (C$_4$), 144.2 (C$_4$), 138.2 (C$_4$), 128.6 (CH) x 2, 127.3 (CH), 126.1 (CH), 126.1 (CH), 122.7 (CH), 83.6 (C$_4$), 53.5 (C$_4$), 49.5 (CH), 36.0 (CH$_2$), 33.6 (CH$_2$), 32.5 (CH$_2$), 30.2 (CH$_2$), 24.8 (CH$_2$), 24.2 (CH$_2$), 21.2 (CH$_2$), 19.9 (CH$_2$), 16.7 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{21}$H$_{26}$O$_2$ 310.1933, found 310.1926.
2-[1-(2-Cyclohexylidene-ethoxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.32)

To a suspension of NaH (56 mg, 1.28 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (115 mg, 0.63 mmol) in 2 mL of THF at rt. The resulting mixture was stirred for 3 min followed by addition of allyl bromide 2.26b solution (438 mg, 2.32 mmol) in THF (3 mL). The solution was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc in hexanes) afforded 2.32 (128 mg, 70%) as a yellowish oil. IR (cm⁻¹, neat) 3395 (bm), 2930 (s), 2854 (m), 1668 (w), 1637 (w), 1445 (m); ¹H NMR (300 MHz, CDCl₃), δppm 5.63 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.26-5.20 (m, 1H), 5.16 (dd, J = 1.7 Hz, J = 17.2 Hz, 1H), 5.04-5.03 (m, 1H), 4.94-4.93 (m, 1H), 4.91 (dd, J = 1.7 Hz, J = 10.7 Hz, 1H), 4.00-3.65 (m, 5H), 2.26 (dd, J = 3.3 Hz, J = 12.8 Hz, 1H), 2.13-2.08 (m, 4H), 1.86-1.21 (m, 14H); ¹³C NMR (75 MHz, CDCl₃), δppm 147 (C₄), 146.7 (CH), 145.8 (C₄), 118.4 (CH₂), 117.2 (CH), 113.0 (CH₂), 72.9 (C₄), 72.0 (CH₂), 66.1 (CH₂), 52.5 (CH), 38.7 (CH₂), 37.4 (CH₂), 29.4 (CH₂), 28.8 (CH₂), 28.1 (CH₂), 27.0 (CH₂), 27.0 (CH₂), 26.6 (CH₂), 21.6 (CH₂); HRMS (EI), m/z (M⁺-H₂O) calculated for C₁₉H₂₈O 272.2140, found 272.2152.

1-(2-Cyclohexylidene-ethoxymethylene)-octahydro-naphthalen-4a-ol (2.59)

¹H NMR (300 MHz, CDCl₃), δppm 5.69 (s, 1H), 5.26 (tdd, J = 1.1 Hz,
$J = 1.1 \text{ Hz}, J = 7.1 \text{ Hz}, 1 \text{H}$, 4.21 (d, $J = 7.0 \text{ Hz}, 2 \text{H}$), 2.86-2.82 (m, 1H), 2.18-2.10 (m, 4H), 1.94-1.89 (m, 1H), 1.77-1.16 (m, 20H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 146.1 (C$_4$), 139.8 (CH), 118.3 (C$_4$), 117.4 (CH), 71.3 (CH), 67.9 (CH$_2$), 47.5 (CH), 40.3 (CH$_2$), 38.4 (CH$_2$), 37.4 (CH$_2$), 29.5 (CH$_2$), 28.8 (CH$_2$), 28.1 (CH$_2$), 27.0 (CH$_2$), 26.5 (CH$_2$), 26.4 (CH$_2$), 23.7 (CH$_2$), 22.92 (CH$_2$), 21.7 (CH$_2$).

2-(1-Prop-2-ynyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.63)

To a suspension of NaH (48 mg, 1.14 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (100 mg, 0.55 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of propargyl bromide 2.62a (0.92 mL, 0.82 mmol) and NaI (8 mg, 0.05 mmol). The reaction was refluxed for 5 h, cooled to rt and quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous phase was extracted with Et$_2$O 3 x 20 mL. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product 2.63 (85 mg, 70%) as a yellow oil. IR (cm$^{-1}$, neat) 3425 (m), 3084(w), 2930 (s), 2858 (m), 1782 (w), 1640 (w), 1447 (m), 1068 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 5.83 (dd, $J = 10.6 \text{ Hz}, J = 17.2 \text{ Hz}, 1 \text{H}$), 5.16 (dd, $J = 2.0 \text{ Hz}, J = 10.6 \text{ Hz}, 1 \text{H}$), 5.19-5.10 (m, 1H), 5.02-5.01 (m, 1H), 4.94 (dd, $J = 10.6 \text{ Hz}, J = 2.0 \text{ Hz}, 1 \text{H}$), 4.14-3.98 (m, 3H), 3.84 (dd, $J = 3.3 \text{ Hz}, J = 12.9 \text{ Hz}, 1 \text{H}$), 2.96 (s, 1H), 2.41 (dd, $J = 2.4 \text{ Hz}, J = 2.4 \text{ Hz}, 1 \text{H}$), 2.24 (dd, $J = 3.3 \text{ Hz}, J = 12.9 \text{ Hz}, 1 \text{H}$), 1.89-1.19 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 146.7 (C$_4$), 146.0 (CH), 118.3 (CH$_2$), 111.1 (CH$_2$), 79.5 (C$_4$), 75.2 (C$_4$), 73.0 (C$_4$), 72.2 (CH$_2$), 57.1 (CH$_2$), 51.4 (CH), 38.6 (CH$_2$), 27.2 (CH$_2$), 26.5
(CH₂), 21.5 (CH₂); HRMS (EI), m/z (M⁺-C₃H₄O) calculated for C₁₁H₁₆O 164.1201, found 164.1195.

7-Propa-1,2-dienyl-11-oxa-tricyclo[5.3.2.0₁⁶]dodecan-12-ol (2.66)
(mixture of anomers)

The microwave reaction (procedure A) of 2.63 (42 mg, 0.18 mmol) afforded lactol 2.66 (41 mg, 98%) as a clear oil. Reagents and quantities: DBU (0.15 mL, 1.00 mmol), toluene (12 mL). ¹H NMR (300 MHz, CDCl₃), δ ppm 5.53-5.49 (m, 1H), 5.13-5.05 (m, 1H), 4.74 (dd, J = 3.9 Hz, J = 6.6 Hz, 2H), 3.56 (d, J = 5.2 Hz) and 3.42 (d, J = 5.2 Hz) give 1H, 2.33-2.15 (m, 1H), 2.09-0.80 (m, 14H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 208.5, 208.4, 102.8, 102.2, 91.8, 91.5, 84.5, 82.8, 77.8, 77.59, 77.4, 77.0, 76.9, 76.7, 52.9, 51.6, 50.3, 49.5, 39.4, 38.9, 34.8, 34.3, 34.3, 32.9, 25.3, 25.0, 24.4, 21.9, 20.0, 19.8.

7-Propa-1,2-dienyl-11-oxa-tricyclo[5.3.2.0₁⁶]dodecan-12-one
(2.66a)

The oxidation (procedure B) of lactol 2.67 (40 mg, 0.18 mmol) afforded lactone 2.66a (31 mg, 78%) as a yellowish oil. Reagents and quantities: molecular sieves (91 mg), TPAP (3 mg), NMO (32 mg, 0.27 mmol). IR (cm⁻¹, neat) 2934 (s), 2859 (m), 1956 (w), 1772 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.32 (dd, J = 6.8 Hz, J = 6.8 Hz, 1H), 4.89-4.78 (m, 2H), 2.04-1.98 (m, 1H), 1.92-0.83 (m, 14 H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 209.3 (C₄), 179.1 (C₄), 89.4 (CH), 83.8 (C₄), 78.0 (CH₂), 53.3 (C₄), 51.7 (CH), 35.9 (CH₂), 33.5 (CH₂), 33.2 (CH₂), 25.5 (CH₂), 24.2 (CH₂), 21.1 (CH₂), 19.8 (CH₂); HRMS (EI), m/z (M⁺) calculated for C₁₄H₁₈O₂ 218.1307, found 218.1316.
2-(1-But-2-ynyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.64)

To a suspension of NaH (50 mg, 1.25 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (100 mg, 0.55 mmol) at rt. The resulting mixture was stirred for 3 min followed by adding solution of 1-bromo-2-butyne 2.62b (110 mg, 0.83 mmol). The reaction was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product 2.64 (105 mg, 82%) as a yellow oil. IR (cm⁻¹, neat) 3423 (m), 3082 (w), 2931 (s), 2856 (m), 1780 (w), 1639 (w); ¹H NMR (300 MHz, CDCl₃, δppm 5.84 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.18 (dd, J = 1.6 Hz, J = 17.2 Hz, 1H), 5.10-5.09 (m, 1H), 5.00-4.99 (m, 1H), 4.95 (dd, J = 1.6 Hz, J = 10.6 Hz, 1H), 4.11-3.79 (m, 4H), 3.18 (d, J = 2.2 Hz, 1H), 2.2 (dd, J = 3.3 Hz, J = 12.9 Hz, 1H), 1.83 (dd, J = 2.3 Hz, J = 2.3 Hz, 3H), 1.81-1.22 (m, 8H); ¹³C NMR (75 MHz, CDCl₃, δppm 146.8 (C₄), 146.2 (CH), 118.3 (CH₂), 111.4 (CH₂), 83.3 (C₄), 74.9 (C₄), 73.0 (C₄), 72.0 (CH₂), 57.8 (CH₂), 51.6 (CH), 38.6 (CH₂), 27.2 (CH₂), 26.5 (CH₂), 21.6 (CH₂), 4.0 (CH₃); HRMS (EI), m/z (M⁺-C₄H₆O) calculated 164.1200 for C₁₁H₁₆O, found 164.1192.

7-(1-Methyl-propa-1,2-dienyl)-11-oxa-tricyclo[5.3.2.0¹⁶]dodecan-12-ol (2.67)

The microwave reaction (procedure A) of 2.64 (40 mg, 0.17 mmol) afforded lactol 2.67 (27 mg, 68%) as a clear oil. Reagents and quantities: DBU (0.20 mL,
1.34 mmol), toluene (12 mL). IR (cm⁻¹, neat) 3393 (m), 2931 (s), 2857 (m), 1963 (w), 1445 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.59 (d, J = 5.0 Hz, 1H), 4.68-4.59 (m, 2H), 3.06 (d, J = 5.6 Hz, 1H), 2.33-2.20 (m, 1H), 1.83-1.07 (m, 17H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 206.4 (C₄), 102.6 (CH), 98.7 (C₄), 82.4 (C₄), 75.1 (CH₂), 52.5 (C₄), 50.7 (CH), 38.9 (CH₂), 34.8 (CH₂), 31.3 (CH₂), 29.9(CH₂), 24.8 (CH₂), 21.9 (CH₂), 20.1 (CH₂), 16.1 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₅H₂₂O₂ 234.1619, found 234.1605.

1.7-(1-Methyl-propa-1,2-diencyl)-11-oxatricyclo[5.3.2.01,6]dodecan-12-one (2.67a)

The oxidation (procedure B) of lactol 2.67 (27 mg, 0.12 mmol) afforded lactone 2.67a (22 mg, 81%) as a yellow oil. Reagents and quantities: molecular sieves (58 mg), TPAP (2 mg, 5% mol), NMO (20 mg, 0.18 mmol). IR (cm⁻¹, neat) 2931 (s), 2858 (m), 1958 (w), 1771 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 4.78- 4.63 (m, 2H), 2.02-1.97 (m, 1H), 1.86-0.80 (m, 17H) ¹³C NMR (75 MHz, CDCl₃), δ ppm 207.8 (C₄), 177.3 (C₄), 95.8 (C₄), 82.6 (C₄), 76.0 (CH₂), 56.4 (C₄), 50.7 (CH), 36.1 (CH₂), 33.6 (CH₂), 32.8 (CH₂), 25.5 (CH₂), 24.3 (CH₂), 21.2 (CH₂), 20.0 (CH₂), 16.6 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₅H₂₀O₂ 232.1463, found 232.1452.

2-[1-(4-Benzoxo-2-ynyloxymethyl)-vinyl]-1-vinylcyclohexanol (2.65)

To a suspension of NaH (53 mg, 1.33 mmol, 60% in oil) in THF (10 mL) was transferred by cannula a solution of diol 2.20 (110 mg, 0.60 mmol) at rt. The resulting mixture was stirred for 3 min followed by addition of allyl bromide 2.62c (217 mg,
0.91 mmol) solution in 2 mL of THF. The reaction was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic extracts were dried over MgSO₄, MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product 2:65 (167 mg, 81%) as a yellow oil. IR (cm⁻¹, neat) 3567(w), 3444(m), 3084(w), 3065(w), 3030(w), 3005(w), 2932 (s), 2855 (s), 1950 (w), 1828 (w), 1639 (w), 1496 (w), 1445 (m), 1387 (m), 1349 (s), 1120 (s), 918 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 7.35-7.24 (m, 5H), 5.85 (dd, J = 17.2 Hz, J = 10.6 Hz, 1H), 5.18 (dd, J = 17.2 Hz, J = 1.6 Hz, 1H), 5.12-5.11 (m, 1H), 5.03-5.02 (m, 1H), 4.96 (dd, J = 1.6 Hz, J = 10.6 Hz, 1H), 4.58 (s, 2H), 4.17-4.11 (m, 4H), 4.08 (dd, J = 0.1 Hz, J = 12.2 Hz, 1H), 3.84 (dd, J = 0.5 Hz, J = 12.1 Hz, 1H), 3.03-3.02 (m, 1H), 2.25 (dd, J = 3.3 Hz, J = 12.8 Hz, 1H), 1.87-1.23 (m, 8H), ¹³C NMR (75 MHz, CDCl₃), δ ppm 146.7 (CH), 146.1 (C₄), 137.7 (C₄), 128.8 (4 CH), 128.3 (CH), 118.3 (CH₂), 114.7 (CH₂), 83.1 (C₄), 82.4 (C₄), 73.0 (C₄), 73.02 (C₄), 72.3 (CH₂), 72.0 (CH₂), 57.7 (CH₂), 57.5 (CH₂), 51.5 (CH), 38.7 (CH₂), 27.3 (CH₂), 26.5 (CH₂), 21.6 (CH₂); HRMS (EI), m/z (M⁺ - C₁₁H₁₂O₂) calculated 164.1201; found 164.1413.

![Tetracyclic acetal (2.68)](image)

**Tetracyclic acetal (2.68)**

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of 2.65 (102 mg, 0.45 mmol) afforded acetal 2.68 (83 mg, 81%) as a white solid. Reagents and quantities: DBU (0.30 mL, 2.00 mmol), toluene (15 mL). IR (cm⁻¹, neat) 2924 (s), 2857 (m), 1679 (m), 1599 (w), 1448 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 7.36-7.26 (m, 5H), 5.73 (s, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 3.99 (d, J = 11.8 Hz, 1H), 3.90 (d, J = 11.8 Hz, 1H), 1.95-1.90 (m, 1H), 1.77 (s, 3H), 1.71-
0.83 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 152.4 (C$_4$), 139.0 (C$_4$), 128.7 (CH) x 2, 127.9 (CH) x 3, 112.8 (CH), 108.5 (C$_4$), 89.4 (C$_4$), 72.1 (CH$_2$), 64.6 (CH$_2$), 61.5 (C$_4$), 50.9 (CH), 39.2 (CH$_2$), 33.9 (CH$_2$), 31.4 (CH$_2$), 25.3 (CH$_2$), 24.3 (CH$_2$), 21.6 (CH$_2$), 19.7 (CH$_2$), 12.0 (CH$_3$); HRMS (EI), m/z ($M^+\cdot$C$_7$H$_8$O ) calculated for C$_{15}$H$_{20}$O$_2$ 232.1462, found 232.1443; mp = 72.6-74.9 °C.

2-(1-Methoxymethyl-vinyl)-1-vinyl-cyclohexanol (2.40)

To a suspension of NaH (21 mg, 0.53 mmol, 60% in oil) in 5 mL of THF was transferred by cannula a solution of diol 2.20 (43 mg, 0.24 mmol) in 0.5 mL of THF at 0 °C. The resulting mixture was stirred for 5 min followed by addition of freshly distilled MeI (0.02 mL, 0.36 mmol). The reaction mixture was stirred overnight and quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous phase was extracted with Et$_2$O 3 x 10 mL. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded methyl ether 2.40 (20 mg, 43%) as a yellowish oil. Note: dimethylated product was also detected by GCMS. $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.84 (dd, $J = 10.7$ Hz, $J = 17.2$ Hz, 1H), 5.17 (dd, $J = 1.7$ Hz, $J = 17.2$ Hz, 1H), 5.06-5.05 (m, 1H), 4.98 (s, 1H), 4.96 (dd, $J = 10.7$ Hz, $J = 1.7$ Hz, 1H), 4.00 (dd, $J = 1.0$ Hz, $J = 11.6$ Hz, 1H), 3.64 (d, $J = 2.3$ Hz, 1H), 3.61 (dd, $J = 0.6$ Hz, $J = 11.6$ Hz, 1H), 3.28 (s, 3H), 2.26 (dd, $J = 3.3$ Hz, $J = 11.3$ Hz, 1H), 1.92-1.20 (m, 8H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 146.9 (CH), 146.3 (C$_4$), 118.6 (CH$_2$), 111.4 (CH$_2$), 75.0 (CH$_2$), 72.9 (C$_4$), 58.1 (CH), 52.4 (CH$_3$), 38.7 (CH$_2$), 27.1 (CH$_2$), 26.5 (CH$_2$), 21.6 (CH$_2$); GC/MS, m/z ($M^+\cdot$H$_2$O) calculated for C$_{12}$H$_{18}$O 178, found 178.
1-Methoxymethylene-octahyronaphthalen-4a-ol (2.41)

The microwave reaction of 2.40 (procedure A) at 210 °C (20 mg, 0.10 mmol) afforded enol ether 2.41 (14 mg, 70%) as a yellow oil.

Reagents and quantities: DBU (0.20 mL, 1.3 mmol), toluene (12 mL), flash chromatography on silica gel (15% EtOAc in hexanes). IR (cm⁻¹, neat) 3559 (w), 3478 (w), 2928 (s), 2852 (m), 1680 (w); ¹H NMR (300 MHz, CDCl₃), δppm 5.52 (d, J = 1.5 Hz, 1H), 3.20-3.13 (m, 1H), 3.18 (s, 3H), 1.93-1.15 (m, 15H); ¹³C NMR (75 MHz, CDCl₃), δppm 141.5 (CH), 118.3 (C₄), 70.8 (C₄), 59.1 (CH₃), 47.5 (CH), 40.4 (CH₂), 38.8 (CH₂), 26.6 (CH₂), 26.4 (CH₂), 23.8 (CH₂), 23.0 (CH₂), 21.8 (CH₂); GC/MS, m/z (M⁺) calculated for C₁₂H₂O₂ 196.15, found 196.00.

3-Deutero-(E)-3-phenyl-prop-2-en-1-ol (2.45)

1. To a suspension of NaH (708 mg, 17.77 mmol, 60% in oil) in 20 mL of THF at 0 °C was added dropwise triethylphosphonoacetate (1.95 mL, 9.84 mmol). The mixture was stirred for 40 min at 0 °C, then α-deuterobezaldehyde (0.5 mL, 4.92 mmol) was added dropwise. The reaction was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 50 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. Resulting crude oil was used in the next step without further purification.

2. To a solution of ethyl 3-deutero-(E)-3-phenylprop-2-enoate (575 mg, 4.92 mmol) in 40 mL of THF at −78 °C was added dropwise a solution of DIBAL-H (9.80 mL, 1.5 M in toluene 14.76 mmol). The contents were stirred for 2 hours at −78 °C and then slowly
transferred by cannula to a stirred mixture of hexanes/Et₂O/saturated aqueous solution of tartaric acid (1:1:1). The resulting emulsion was stirred for 2.5 h and diluted with H₂O and Et₂O. The aqueous phase was extracted with Et₂O 5 x 30 mL. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (40% EtOAc in hexanes) afforded allyl alcohol 2.45 (163.5 mg, 25% over 2 steps) as a yellowish solid. IR (cm⁻¹, neat) 3332 (bs), 3080 (w), 3058 (w), 3032 (m), 2918 (m), 2861 (m), 1708 (w), 1642 (w), 1598 (w), 1576 (w), 1493 (s); H NMR (300 MHz, CDCl₃), δ (ppm) 7.39-7.19 (m, 5H), 6.38-6.33 (m, 1H), 4.32 (d, J = 5.8 Hz, 2H); C NMR (75 MHz, CDCl₃), δ (ppm) 136.9 (C₄), 128.7 (CH) x 3, 128.7 (CH), 128.1 (CH), 126.8 (CH) x 2, 64.1 (CH₂); HRMS (EI), m/z (M⁺) calculated for C₉H₅DO 135.0793, found 135.0788.

1-Bromo-3-deutero-(E)-3-phenyl-prop-2-ene (2.46)

To a solution of allyl alcohol 2.45 (163 mg, 1.22 mmol) in 10 mL of CH₂Cl₂ was added CBr₄ (506 mg, 1.53 mmol) followed by a cannulation of a solution of PPh₃ (480 mg, 1.83 mmol) in 2 mL of CH₂Cl₂. The mixture was stirred for 10 min and then concentrated under reduced pressure. The rest of the solvent was removed with a vacuum pump. The crude solidifying oil was used for the etherification of diol 2.20 without further purification.

2-[1-(3-Deutero-E-3-Phenyl-allyloxymethyl)-vinyl]-1-vinyl-cyclohexanol (2.42)

To a suspension of NaH (90 mg, 2.20 mmol, 60% in oil) in 10 mL of THF
was slowly transferred by cannula a solution of diol 2.20 (100 mg, 0.55 mmol) in 1 mL of THF. The mixture was stirred for 5 min followed by addition of a solution of allyl bromide (240 mg, 1.22 mmol) in 5 mL of THF and NaI (8 mg, 0.06 mmol). The reaction was stirred overnight and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford 2.42 (43 mg, 26%) as a yellow oil. IR (cm⁻¹, neat) 3401 (s), 3084 (w), 3059 (w), 3023 (w), 2932 (s), 2855 (s), 1779 (w), 1642 (w), 1494 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 7.43-7.20 (m, 5H), 6.26-6.22 (m, 1H), 5.86 (dd, J = 10.6 Hz, J = 17.2 Hz, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 4.97 (d, J = 10.7 Hz, 1H), 4.16 (dd, J₆ₓ₇ = 6.2 Hz, J₆₇ = 12.6 Hz, 1H), 4.04 (dd, J₇ₓ₈ = 8.1 Hz, J₇₈ = 12.6 Hz, 1H), 4.05 (d, J₇₈ = 12.5 Hz, 1H), 3.78 (d, J₈₉ = 12.0 Hz, 1H), 3.64 (s, 1H), 2.28 (dd, J = 3.0 Hz, J = 12.7 Hz, 1H), 1.94-1.20 (m, 8H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 146.9 (CH), 146.5 (C₆), 136.8 (C₄), 128.9 (CH) x 3, 128.2 (CH), 126.9 (CH) x 2, 125.4 (CH), 118.6 (CH₂), 11.5 (CH₂), 73.0 (C₄), 72.4 (CH₂), 70.9 (CH₂), 52.3 (CH), 38.7 (CH₂), 27.2 (CH₂), 26.5 (CH₂), 21.6 (CH₂); HRMS (EI), m/z (M⁺) calculated for C₂₀H₂₅DO₂ 299.1995, observed degradation.

2.43 (anomeric mixture) and 2.47 (anomeric mixture)

The microwave induced oxy-Cope/ene/Claisen reaction (procedure A) of allyl ether 2.42 (15 mg, 0.05 mmol) afforded a mixture of lactols 2.43 and 2.47. Reagents and quantities: Et₃N (0.03 mL, 0.21 mmol), toluene (11 mL). The crude mixture of lactols was used in the oxidation with TPAP without further purification.
Mixture of lactones (2.43a and 2.47a)

The oxidation (procedure B) of the crude mixture of lactols 2.43 and 2.47 (15 mg, 0.05 mmol) afforded a 2:1 mixture of lactones 2.43a and 2.47a respectively (6.6 mg, 44% over 2 steps) as a white solid. Reagents and quantities: molecular sieves (25 mg), TPAP (1 mg, 5% mol), NMO (9 mg, 0.18 mmol). $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 6.66 (dd, $J = 10.5$ Hz; $J = 17.2$ Hz, 1H, 2.43a), 6.20 (dd, $J = 10.6$ Hz, $J = 17.4$ Hz, 1H, 2.47a), 5.13 (dd, $J = 1.6$ Hz; $J = 10.5$ Hz, 1H, 2.43a), 5.03 (dd, $J = 1.5$ Hz, $J = 10.3$ Hz, 1H, 2.47a), 4.89 (dd, $J = 1.6$ Hz, $J = 17.1$ Hz, 1H, 2.47a), 4.65 (dd, $J = 1.6$ Hz; $J = 17.3$ Hz, 1H, 2.43a), 2.18-0.81 (m, 40H, 2.43a and 2.47a); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 179.8, 140.7, 140.2, 139.6, 139.3, 130.5, 130.4, 128.6, 128.5, 127.1, 127.0, 117.3, 116.9, 82.9, 82.7, 56.6, 56.2, 56.1, 51.3, 36.3, 36.2, 34.0, 33.9, 32.2, 30.1, 30.0, 26.8, 24.6, 24.6, 24.3, 21.3, 21.1, 20.4, 19.8.

2-Tributylstannanyl-but-2-en-1-ol (2.71a)

To a solution of Pd(PPh$_3$)$_4$ (323 mg, 0.28 mmol) in 10 mL of toluene was added but-2-yne-1-ol 2.70 (1.07 mL, 14.00 mmol) and stirred for 2 min at rt. Bu$_3$SnH (4.2 mL, 15.20 mmol) was then added dropwise. After an abrupt change of reaction color additional 0.1 equivalent of Bu$_3$SnH (0.38 mL, 1.40 mmol) was introduced into the mixture. The solution was stirred for 10 min and concentrated under reduced pressure. Crude oil was initially passed through a short pad of silica gel in order remove Pd catalyst. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded 2.71a (3.537 g, 70%) as
a clear oil, regioisomer 2.71b was also isolated (0.500 g, 10%). The spectroscopic data was in accord with that reported in literature.\(^6\)

\[
\text{1-Allyloxy-2-iodo-but-2-ene (2.73)}
\]

1. Preparation of 2-iodo-but-2-en-1-ol (2.72)

To a solution of 2.71a (2.000 g, 5.54 mmol) in 40 mL of CH\(_2\)Cl\(_2\) was added in portions \(\text{I}_2\) (1.56 g, 6.09 mmol). After addition was completed and an iodine color maintained, reaction mixture was stirred for 10 min and quenched with a saturated aqueous solution of Na\(_2\)SO\(_3\). The aqueous phase was extracted with CH\(_2\)Cl\(_2\) 3 x 50 mL. The combined organic extracts were dried over MgSO\(_4\) and concentrated under atmospheric pressure. Purification by flash chromatography on silica gel (20% Et\(_2\)O in pentane) afforded 2.72 (890 mg, 81%) as a yellow oil. Caution: vinyl iodide is volatile and light sensitive!!!

2. To a suspension of NaH (277 mg, 6.95 mmol, 60% in oil) in THF (10mL) at rt was transferred by cannula a solution of 2-iodo-but-2-en-1-ol 2.72 (1.146 g, 5.79 mmol) in THF (5 mL). The mixture was stirred for 3 min. Allyl bromide (0.5 mL, 6.37 mmol) was then added and the solution was refluxed for 3h. The reaction was then cooled to rt and quenched with a saturated aqueous solution of NH\(_4\)Cl followed by extraction with Et\(_2\)O 3 x 15 mL. The combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. Caution: resulting iodide is volatile!!! Purification by flash chromatography on silica gel (5% Et\(_2\)O in petroleum ether) afforded 2.73 (910 mg, 66% yield) as a yellow oil. IR (cm\(^{-1}\), neat) 3079 (w), 2924 (s), 2854 (s), 1646 (w), 1633 (w), 1456 (m); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 6.46 (qt, \(J = 7.2\) Hz, \(J = 0.9\) Hz, 1H), 5.92 (dddd, \(J = 5.7\) Hz, \(J = 5.7\) Hz,

$J = 10.4 \text{ Hz, } J = 17.2 \text{ Hz, } 1\text{H)}, 5.32-5.25 \text{ (m, } 1\text{H)}, 5.22-5.17 \text{ (m, } 1\text{H)}, 4.12 \text{ (s, } 2\text{H)}, 3.95 \text{ (ddd, } J = 1.4 \text{ Hz, } J = 1.4 \text{ Hz, } J = 5.7 \text{ Hz, } 2\text{H)}, 1.71 \text{ (d, } J = 7.2 \text{ Hz, } 3\text{H}); ^{13}\text{C NMR (75 MHz, CDCl}_3\text{), } \delta_{\text{ppm}} 140.1 \text{ (CH), 134.8 (CH), 118.1 (CH}_2\text{), 99.1 (C}_4\text{), 71.0 (CH}_2\text{), 70.7 (CH}_2\text{), 17.3 (CH}_3\text{); HRMS (EI), m/z (M^+) calculated for C}_{7}\text{H}_{11}\text{O}_{1237.9855, \text{ found 237.9878.}}$

![1-(1-Allyloxy)methyl-propenyl]-2-chloro-cyclohexanol (2.74)](image)

To a solution of vinyl iodide 2.73 (540 mg, 2.27 mmol) in Et$_2$O (10 mL) at $-100 \degree \text{C}$ was added a solution of t-BuLi (2.45 mL, 1.7 M in pentane, 12.49 mmol). The reaction mixture was stirred for 1 h at $-100 \degree \text{C}$. Then a solution of 1-chloro-2-cyclohexanone (100 mg, 0.78 mmol) in Et$_2$O (1 mL) was cooled to $-100 \degree \text{C}$ and transferred by cannula to the lithiated compound. The solution was allowed to warm to $-60 \degree \text{C}$, then cooled to $-100 \degree \text{C}$ and quenched with H$_2$O. The aqueous layer was extracted with Et$_2$O 3 x 20 mL. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (12% EtOAc in hexanes) to afford product 2.74 (83 mg, 45%) as a colorless oil. IR (cm$^{-1}$, neat) 3495 (br), 3079 (w), 2938 (s), 2860 (s), 1647 (w), 1447 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 5.97-5.84 (m, 2H), 5.30-5.23 (m, 1H), 5.19-5.14 (m, 1H), 4.23 (dd, $J = 6.2$ Hz, $J = 10.2$ Hz, 1H), 4.15 (d, $J_{AB} = 11.5$ Hz, 1H), 4.07 (d, $J_{BA} = 11.5$ Hz, 1H), 4.02-3.89 (m, 2H), 2.78 (d, $J = 1.8$ Hz, 1H), 2.10-1.95 (m, 2H), 1.82-1.49 (m, 7H), 1.47-1.41 (m, 1H), 1.35-1.20 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 140.7(C$_4$), 135.0 (CH), 125.6 (CH), 117.6 (CH$_2$), 76.6 (C$_4$), 71.3 (CH$_2$), 67.4 (CH), 65.0 (CH$_2$), 39.2 (CH$_2$), 33.0 (CH$_2$), 25.6 (CH$_2$), 21.1 (CH$_2$), 13.9 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{13}$H$_{21}$O$_2$Cl 244.1230, found 244.1230.
2-(1-Allyloxymethyl-vinyl)-cyclohexanone (2.75)

To a solution of chlorohydrine 2.74 (83 mg, 0.34 mmol) in THF (6 mL) at rt was added vinylmagnesium bromide (0.38 mL, 0.9 M in THF, 0.34 mmol). The solution was refluxed for 2 h, cooled to rt and quenched with a saturated aqueous solution of NH₄Cl. The mixture was extracted with Et₂O 3 x 10 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to afford ketone 2.75 (48 mg, 68%) as a colorless oil. IR (cm⁻¹, neat) 3084 (w), 2950 (m), 2864 (m), 1707 (s), 1639 (w), 1453 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.94-5.81 (m, 1H), 5.44 (q, J = 6.9 Hz, 1H), 5.26-5.12 (m, 2H), 4.05 (d, JAB = 11.4 Hz, 1H), 3.95-3.83 (m, 3H), 3.17 (dd, J = 4.7 Hz, J = 11.7 Hz, 1H), 2.43-2.27 (m, 2H), 2.08-1.96 (m, 2H), 1.92-1.63 (m, 7H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 212.3 (C₄), 135.3 (C₄), 135.2 (CH), 126.2 (CH), 117.4 (CH₂), 71.4 (CH₂), 67.1 (CH₂), 56.2 (CH), 42.3 (CH₂), 32.4 (CH₂), 28.1 (CH₂), 25.7 (CH₂), 13.9 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₃H₂₀O₂ 208.1464, found 208.1443.

2-(1-Allyloxymethyl-vinyl)-1-vinyl-cyclohexanol (2.69)

Procedure A (from chlorohydrine 2.74)

To a solution of 2.74 (61.7 mg, 0.33 mmol) in THF (5 mL) at rt was added vinylmagnesium bromide (0.65 mL, 1.5 M in THF, 0.99 mmol). The reaction mixture was refluxed for 3 h, cooled to rt and quenched with a saturated aqueous solution of NH₄Cl. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by
flash chromatography on silica gel (8% EtOAc in hexanes) to afford product 2. 69 (34.5 mg, 58%) as a clear oil.

Procedure B (from ketone 2.75)

To a solution of 2.75 (25 mg, 0.12 mmol) in THF (2 mL) at 0 °C was added a solution of vinylmagnesium bromide (0.27 mL, 0.9 M in THF, 0.24 mmol). The solution was stirred for 1.5 h at 0 °C and quenched with a saturated aqueous solution of NH₄Cl. The mixture was extracted with Et₂O 3 x 5 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded desired product 2.69 (16 mg, 56%) as a clear oil. Syn isomer (3.4 mg, 12%) was also isolated as a clear oil. IR (cm⁻¹, neat) 3411 (br), 3083 (w), 2932 (s), 2856 (m), 1642 (w), 1445 (m), 1401 (m), 1171 (w), 1057 (s), 975 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.95 (m, 2H), 5.52 (q, J = 6.7 Hz, 1H), 5.30-5.11 (m, 3H), 4.90 (dd, J = 1.8 Hz, J = 10.7 Hz, 1H), 4.14-3.95 (m, 3H), 3.89-3.78 (m, 2H), 2.20 (dd, J = 2.9 Hz, J = 12.5 Hz, 1H), 1.94-1.19 (m, 8H), 1.65 (d, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 147.5 (CH), 136.6 (C₄), 134.3 (CH), 129.8 (CH), 117.9 (CH₂), 111.0 (CH₂), 73.4 (C₄), 72.1 (CH), 64.5 (CH₂), 55.3 (CH), 38.9 (CH₂), 27.0 (CH₂), 26.8 (CH₂), 21.8 (CH₂), 13.9 (CH₃); HRMS (EI), m/z (M⁺-H₂O) calculated for C₁₅H₂₂O 218.1672, found 218.1706.

[Diagrams of 7-Allyl-8-methyl-11-oxa-tricyclo[5.3.2.0¹⁴]dodecan-12-ols (2.82a) (anomic mixture) and (2.82b) (anomic mixture)]
The microwave reaction (procedure A) of 2.69 (13 mg, 0.06 mmol) gave a mixture of lactols 2.82a and 2.82b (6.1 mg, 47%) and (76 mg, 76%) as a clear oil and 15:1 mixture of aldehydes 2.80 and 2.81 (5.4 mg, 41%) as a clear oil. Reagents and quantities: Et$_3$N (0.03 mL, 0.18 mmol), toluene (12 mL). In order to determine the diastereomeric ratio the mixture of lactols was oxidized with TPAP to corresponding lactones 3.83 and 3.84.

1-Allyl-4a-hydroxy-2-methyl-decahydro-naphthalene-1-carbaldehyde (2.80)

IR (cm$^{-1}$, neat) 3511 (bm), 3077 (w), 2929 (s), 2861 (m), 2712 (w), 1713 (s), 1640 (w); $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ ppm 9.46 (s, 1H), 6.00-5.86 (m, 1H), 5.12-5.03 (m, 2H), 2.96 (dd, $J = 8.4$ Hz, $J = 14.7$ Hz, 1H), 2.54 (dd, $J = 6.8$ Hz, $J = 14.8$ Hz, 1H), 2.21-2.09 (m, 2H), 1.88 (dd, $J = 2.5$ Hz, $J = 11.8$ Hz, 1H), 1.82-1.19 (m, 12H), 0.91 (d, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ ppm 207.7 (C$_4$), 135.8 (CH), 118.1 (CH$_2$), 71.4 (C$_4$), 53.8 (C$_4$), 42.3 (CH$_2$), 40.2 (CH), 35.2 (CH$_2$), 34.2 (CH$_2$), 31.4 (CH), 27.1 (CH$_2$), 23.9 (CH$_2$), 23.7 (CH$_2$), 22.1 (CH$_2$), 15.4 (CH$_3$); HRMS (EI), m/z (M$^+$-H$_2$O) calculated for C$_{15}$H$_{22}$O 218.1671, found 218.1681.

Mixture of lactones 2.83 and 2.84

The oxidation (procedure B) of a mixture of lactols 2.82a and 2.82b (6.1 mg, 0.03 mmol) afforded a 2.2:1 mixture of lactones 2.83 and 2.84 (4 mg, 68%) as a white solid. Reagents and quantities: molecular sieves (13 mg), TPAP (1 mg, 10% mol), NMO (5 mg, 0.05 mmol). $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ ppm 6.11-6.14 (m, 1H, 2.83), 5.73-5.59 (m, 1H, 2.84), 5.20-
5.02 (m, 4H, 2.83 and 2.84), 2.59-2.48 (m, 1H, 2.84), 2.46-2.38 (m, 1H, 2.83), 2.24-2.16 (m, 1H, 2.84), 2.73-0.83 (m, 39H, 2.83 and 2.84); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ ppm 181.6, 179.1, 134.9, 133.2, 118.8, 117.5, 83.8, 83.2, 55.8, 55.1, 49.5, 45.0, 36.6, 34.9, 34.1, 33.7, 33.5, 32.8, 31.1, 30.1, 29.4, 27.0, 25.2, 25.0, 24.6, 24.4, 24.2, 21.2, 16.6, 13.9.

6.3. Spectroscopic data for Chapter 3

3-Methoxy-5,5-dimethyl-cyclohex-2-eneone was prepared according to procedure reported in literature$^7$: to a solution of 5,5-dimethyl-cyclohexane-1,3-dione (2.000 g, 0.014 mol) in 78 mL of MeOH was added 1 mL of concentrated H$_2$SO$_4$. The mixture was refluxed for 2 h, and concentrated under reduced pressure. To the concentrate was added a saturated aqueous solution of NaHCO$_3$ until pH=8. The mixture was extracted with CH$_2$Cl$_2$ 3 x 100 mL. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (45% EtOAc in hexanes) gave 3-methoxy-5,5-dimethyl-cyclohex-2-eneone (1.960 g, 93%) as a yellow solid.

4-methoxy-6,6-dimethyl-2-oxo-cyclohex-3-enyl acetate$^8$

A suspension of Mn(OAc)$_3$:2H$_2$O (12.86 g, 0.048 mol) in 200 mL of benzene was refluxed using a Dean-Stark trap for 2 h. The mixture was cooled to rt, followed by addition of 3-methoxy-5,5-dimethyl-cyclohex-2-eneone (1.84 g, 0.012 mol). The resulting suspension was refluxed (Dean-Stark trap) for 2 d, cooled and diluted with EtOAc (200 mL). The aqueous phase was extracted with EtOAc 2 x 200 mL.


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The combined organic extracts were washed with 1 N HCl x 400 mL, a saturated aqueous solution of NaHCO₃ x 400 mL and with brine x 400 mL, dried over MgSO₄ and concentrated under reduced pressure. Purification on flash chromatography (30% EtOAc in hexanes) afforded 4-methoxy-6,6-dimethyl-2-oxo-cyclohex-3-enyl acetate (2.33 g, 91%) as a yellow oil.

4-Hydroxy-5,5-dimethyl-cyclohex-2-enone (3.6)

To a suspension of LiAlH₄ (6.00 g, 0.154 mol) in 300 mL of Et₂O at rt was transferred by cannula a solution of 4-methoxy-6,6-dimethyl-2-oxo-cyclohex-3-enyl acetate (16.49 g, 0.077 mol) in 20 mL of Et₂O. The mixture was stirred at rt for 30 min and then refluxed for 3 h. The reaction was cooled to 0 °C and quenched by a dropwise addition of H₂O (100 mL) (H₂O must be added very carefully) followed by addition of a 10% aqueous solution of H₂SO₄. The suspension was stirred for 3 h at rt. The aqueous phase was extracted with EtOAc 3 x 300 mL. The combined organic fractions were washed with a saturated aqueous solution of NaHCO₃ and brine, dried over MgSO₄ and concentrated under reduced pressure. The crude oil (7.58 g) was used for protection with TMSCl without further purification. The spectroscopic data was in accord with that reported in literature.⁸

5,5-Dimethyl-4-trimethylsilyl oxy-cyclohex-2-enone (3.7)

To a solution of crude ketone 3.6 (0.054 mol, 7.58 g) in 200 mL of THF was added imidazole (0.065 mL, 4.66 g) followed by addition of TMSCl (8.2 mL, 0.065 mol). Formation of a white precipitate was observed almost immediately. The mixture was stirred for 2 h at rt, then the reaction was quenched by addition of a
saturated aqueous solution of NaCl. The aqueous phase was extracted three times with EtOAc 3 x 200 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded product 3.7 (9.387 g, 82 %) as yellow crystals. IR (cm⁻¹, neat) 3045 (w), 2961 (s), 2904 (m), 2978 (m), 2827 (w), 1680 (s), 1461 (m), 888 (s), 837 (s); 
¹H NMR (300 MHz, CDCl₃), δ ppm 6.59 (dd, J = 2.4 Hz, J = 10.2 Hz, 1H), 5.91 (ddd, J = 1.1 Hz, J = 1.1 Hz, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.2 Hz, J = 2.2 Hz, 1H), 2.33 (dd, Jₓᵧ = 1.1 Hz, Jᵧₓ = 16.2 Hz, 1H), 2.21 (dd, Jₓₓ = 0.5 Hz, Jᵧᵧ = 16.2 Hz, 1H), 1.01 (s, 3H), 0.91 (s, 3H), 0.15 (s, 9H); 
¹³C NMR (75 MHz, CDCl₃), δppm 199.6 (C₄), 152.4 (CH), 128.8 (CH), 75.0 (CH), 50.7 (CH₂), 40.3 (C₄), 28.1 (CH₃), 20.5 (CH₃), 0.5 (CH₃) x 3; HRMS (EI), m/z (M⁺) calculated for C₁₁H₂₀O₂Si 212.1283, observed degradation, no M⁺ detected.

![Structural formula](image)

3,3-Dimethyl-5-(1-methyl-propenyl)-4-trimethylsilyloxy-cyclohexanone (3.8)

The reaction was preformed under argon. Et₂O was degassed with argon for at least 0.5 h.

**Procedure for a scale up:** To a −78 °C solution of 2-cis-bromobutene (2.7 mL, 0.03 mol) in 60 mL of Et₂O was added a solution of i-BuLi (31 mL, 1.64 M in pentane, 50.84 mmol) over 10 min under argon. The resulting solution was stirred for 2 h at −78 °C. A separate flame-dried flask was charged with copper (I) cyanide (1.209 g, 13.49 mmol) and dried with a heat-gun under vacuum for approximately 40 sec. The flask was then filled with argon (Caution: copper cyanide is a fine powder, letting argon in the evacuated flask should be done slowly and with a lot of care, otherwise all the powder ends up on the septum and the
flask joint). Then 60 mL of Et₂O was added to the flask with the copper salt and the resulting suspension was cooled to −78 °C. A solution of vinyl lithium at −78 °C was transferred by cannula into the copper cyanide and the mixture was stirred for 10 min at −78 °C. The dry-ice bath was removed and the reaction mixture was stirred for additional 10 min, during which time it became slightly yellow. Solution was then cooled to −78 °C and a solution of ketone 3.7 (1.500 g, 6.70 mmol) in 5 mL of Et₂O was transferred by cannula into the flask under argon. The mixture was stirred for additional 30 min at −78 °C and then quenched with a solution of NH₄OH/NaCl (prepared by mixing an aqueous solution of NaOH with a saturated aqueous solution of NH₄Cl until pH 8-9) at −78 °C. The bath was then removed and the mixture was left stirring for 1 h. The product was extracted with EtOAc 3 x 200 mL. The combined organic fractions were washed with a saturated aqueous solution of NaCl, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded product 3.8 (1.760 g, 98%) as a yellow oil.

The yields varied from 80 to 98% depending on the scale of the reaction.

In order to perform this reaction on a small scale for each step of cuprate formation the time is reduced to 2-3 min of stirring. Formation of vinyl lithium species takes around 2 h at −78 °C. IR (neat, cm⁻¹) 2955 (s), 2872 (m), 1725 (s), 1474 (m); ¹H NMR (300 MHz, CDCl₃), δppm 5.34-5.32 (m, 1H), 3.70 (d, J = 10.3 Hz, 1H), 3.10 (ddd, J = 4.6 Hz, J = 10.3 Hz, J = 13.5 Hz, 1H), 2.41-2.28 (m, 2H), 2.12-2.06 (m, 2H), 1.65—1.64 (m, 3H), 1.54 (dq, J = 1.4 Hz, J = 6.8 Hz, 3H), 1.00 (s, 3H), 0.88 (s, 3H), 0.06 (s, 9H); ¹³C NMR (75 MHz, CDCl₃), δppm 210.7 (C₄), 133.5 (C₄), 124.4 (CH), 78.3 (CH), 53.5 (CH₂), 43.8 (CH₂), 41.5 (CH), 40.0
(C₄), 30.2 (CH₃), 19.5 (CH₃), 18.8 (CH₃), 13.1 (CH₃), 0.83 (CH₃) x 3; HRMS (EI), m/z (M⁺) calculated for C₁₅H₂₈O₂Si 268.1859, found 268.1862.

3,3-Dimethyl-5-(1-methyl-propenyl)-4-trimethylsilyloxy-cyclohexanol (3.9)

To a solution of ketone 3.8 (854 mg, 3.18 mmol) in 30 mL of THF was added L-selectride (6.4 mL, 1.0 M in THF, 6.36 mmol) at -78 °C. The mixture was stirred for 1.5 h at -78 °C and then quenched with a saturated aqueous solution of NH₄Cl. The dry-ice bath was removed and the mixture was left stirring for 2 h at rt. The aqueous phase was extracted with EtOAc 4 x 50 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc in hexanes) on silica gel afforded alcohol 3.9 (515 mg, 60%) as a white solid. IR (neat, cm⁻¹) 3377 (bs), 2964 (s), 2919 (s), 2868 (m), 1438 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.32-5.25 (m, 1H), 4.07 (bs, 1H), 3.27 (d, J = 10.4 Hz, 1H), 3.14 (ddd, J = 4.5 Hz, J = 10.8 Hz, J = 10.8 Hz, 1H), 1.69-1.52 (m, 9H), 1.38 (dd, J = 3.4 Hz, J = 14.7 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 3H), 0.1 (s, 9H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 135.7 (C₄), 123.0 (CH), 80.4 (CH), 67.5 (CH), 45.5 (CH₂), 37.3 (CH₂), 36.8 (CH), 35.4 (CH), 31.9 (CH₃), 22.4 (CH₃), 19.8 (CH₃), 13.6 (CH₃), 1.2 (CH₃) x 3; HRMS (EI), m/z (M⁺) calculated for C₁₅H₃₀O₂Si 270.2015, found 270.2020; mp 66.6-67.2 °C.
[4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexyloxy]-trimethyl-silane (3.10a)

Potassium hydride (190 mg, 35 wt% in mineral oil, 3.33 mmol) was first purified from oil by washing with dry hexanes three times and drying under vacuum. To its suspension in 10 mL of THF was transferred by cannula a solution of alcohol 3.9 (300 mg, 1.11 mmol) in 2 mL of THF at rt, followed by addition of Mel (0.11 mL, 1.67 mmol) freshly distilled from CaH₂. The reaction was completed after 15 min. It was then quenched with a saturated aqueous solution of NH₄Cl, followed by extraction with EtOAc 3 x 15 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. The crude oil was used in the next step without further purification.

4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexanol (3.10)

To a solution of crude 3.10a (235 mg, 1.11 mmol) in 20 mL of THF was added TBAF (2.2 mL, 1.0 M in THF, 2.22 mmol) at rt. The reaction was completed after 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to afford 3.10 (199 mg, 85% yield over 2 steps) as a clear oil. IR (neat, cm⁻¹) 3487 (bm), 2967 (s), 2909 (s), 2864 (s), 2829 (m), 1461 (m), 1367 (m), 1095 (s); ¹H NMR (300 MHz, CDCl₃), δppm 5.31-5.45 (m, 1H), 3.47-3.43 (m, 1H), 3.27 (s, 3H), 3.18 (d, J = 10.7 Hz, 1H), 3.03 (ddd, J = 3.3 Hz, J = 10.7 Hz, J = 12.2 Hz, 1H), 1.86 (ddd, J = 2.7 Hz, J = 2.7 Hz, J = 14.8 Hz, 1H), 1.74 (ddd, J = 3.0 Hz, J = 6.1 Hz, J = 14.1 Hz, 1H), 1.63-1.62 (m, 6H), 1.56-1.46 (m, 2H), 1.21 (dd, J = 3.4 Hz, J = 14.8 Hz, 1H), 1.09 (s, 3H), 0.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), δppm 135.6 (C₄), 124.4
(CH), 78.0 (CH), 76.2 (CH), 56.2 (CH), 41.3 (CH$_2$), 35.8 (CH$_3$), 35.8 (C$_4$), 33.8 (CH$_2$), 30.9 (CH$_3$), 20.6 (CH$_3$), 19.0 (CH$_3$), 13.5 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{13}$H$_{24}$O$_2$ 212.1776, found 212.1774.

![4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexanone](image)

(3.11)

To a solution of alcohol 3.10 (0.80 mmol, 169 mg) in 8 mL of CH$_2$Cl$_2$ was added 4Å molecular sieves (400 mg, 500 mg per 1 mmol), NMO (140 mg, 1.20 mmol) and TPAP (14 mg, 0.04 mmol). The resulting black mixture was stirred for 3 h at rt, then it was filtered through a short pad of silica gel. The silica gel pad was rinsed with 100 mL of 10 % MeOH in EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10 % EtOAc in hexanes) on silica gel to yield product 3.11 (148 mg, 88%) as a clear oil. IR (neat, cm$^{-1}$) 2961 (m), 2934 (m), 2876 (m), 2823 (w), 1709 (s), 1466 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ ppm 5.45 (m, 1H), 4.07 (dd, $J = 5.2$ Hz, $J = 13.6$ Hz, 1H), 3.67-3.64 (m, 1H), 3.38 (s, 3H), 2.17-2.07 (m, 2H), 2.02-1.92 (m, 1H), 1.70-1.63 (m, 4H), 1.49 (dq, $J = 1.5$ Hz, $J = 6.8$ Hz, 3H), 1.23 (s, 3H), 1.03 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ ppm 215.0 (C$_4$), 133.4 (C$_4$), 122.7 (CH), 75.3 (CH), 56.4 (CH), 45.5 (C$_4$), 43.2 (CH$_2$), 42.4 (CH$_3$), 35.4 (CH$_3$), 28.6 (CH$_3$), 26.7 (CH$_3$), 20.8 (CH$_3$), 13.5 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{13}$H$_{22}$O$_2$ 210.1620, found 210.1611.

![4-Methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-1-trimethylsilyllysyl-ethyl-cyclohexanol](image)

(3.12a)

To a solution of trimethylsilyl acetylene (0.40 mL, 2.82 mmol) in 7...
mL of THF at \(-78^\circ C\) was added \(n\)-BuLi (1.04 mL, 2.0 M in pentane, 2.11 mmol). After stirring for 20 min at \(-78^\circ C\) a solution of ketone 3.11 (148 mg, 0.70 mmol) in 1 mL of THF was transferred by cannula into the flask. The reaction mixture was stirred for additional 30 min and quenched with a saturated aqueous solution of \(NH_4Cl\) at \(-78^\circ C\), warmed to rt and extracted with \(Et_2O\) 3 x 10 mL. The combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. The resulting crude oil was used in the next step without further purification.

1-Ethynyl-4-methoxy-2,2-dimethyl-6-(1-methyl-propenyl)-cyclohexanol (3.12)

To a solution of crude 3.12a (165 mg, 0.70 mmol) in 7 mL of THF was added TBAF (1.1 mL, 1.0 M in THF, 1.1 mmol). The mixture was stirred for 15 min, then concentrated under reduced pressure and purified by flash chromatography on silica gel (15% EtOAc in hexanes) to afford product 3.12 (144 mg, 87% over 2 steps) as a white solid.

IR (cm\(^{-1}\), neat) 3547 (bm), 3304 (m), 2973 (s), 2926 (s), 2824 (m), 2361 (w), 1734 (w), 1457 (m), 1092 (s); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 5.60-5.57 (m, 1H), 3.51-3.49 (m, 1H), 3.39 (dd, \(J = 2.9\) Hz, \(J = 13.1\) Hz, 1H), 3.27 (s, 3H), 2.45 (s, 1H), 2.35 (s, 1H), 2.06 (ddd, \(J = 3.3\) Hz, \(J = 14.1\) Hz, 1H), 1.86-1.74 (m, 5H), 1.65-1.57 (m, 4H), 1.24 (s, 3H), 1.10 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 134.8 (C\(_4\)), 126.0 (CH), 86.4 (C\(_4\)), 76.2 (C\(_4\)), 76.1 (CH), 75.5 (C\(_4\)), 56.2 (CH), 39.7 (CH\(_2\)), 39.5 (C\(_4\)), 37.3 (CH\(_3\)), 32.7 (CH\(_2\)), 27.1 (CH\(_3\)), 22.1 (CH\(_3\)), 21.5 (CH\(_3\)), 14.2 (CH\(_3\)): HRMS (EI), m/z (M\(^+\) - CH\(_3\)) calculated for C\(_{14}\)H\(_{21}\)O\(_2\) 221.1541, found 221.1540; mp = 59.6-62.6 \(^\circ C\).
2-Methoxy-4,4,7-trimethyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.16)

To a solution of alcohol 3.12 (13 mg, 0.06 mmol) in toluene (12 mL) in a microwave cell was added DBU (0.1 mL, 0.67 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 230 °C. Reaction was monitored by CG. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford two products 3.16 (3.5 mg, 27%) as a white solid and 3.17 (1.3 mg, 10%) as a clear oil. IR (neat, cm\(^{-1}\)) 3430 (bm), 2961 (s), 2887 (m), 1463 (m), 1079 (s); \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)), \(\delta_{ppm}\) 5.77 (dd, \(J = 3.0 \text{ Hz}, J = 9.9 \text{ Hz}, 1\text{H}\)), 5.36 (dd, \(J = 2.0 \text{ Hz}, J = 9.8 \text{ Hz}, 1\text{H}\)), 4.72-4.70 (m, 2H), 3.36-3.23 (m, 1H), 3.23 (s, 3H), 2.54-2.52 (m, 1H), 2.34-2.29 (m, 1H), 2.05 (dd, \(J = 12.2 \text{ Hz}, J = 12.2 \text{ Hz}, 1\text{H}\)), 1.91-1.84 (m, 2H), 1.67-1.62 (m, 1H), 1.17 (s, 3H), 1.0 (s, 1H), 0.90 (d, \(J = 7.1 \text{ Hz}, 3\text{H}\)), 0.84 (s, 3H); \(^13\)C NMR (75 MHz, C\(_6\)D\(_6\)), \(\delta_{ppm}\) 151.3 (C\(_4\)), 135.6 (CH), 130.5 (CH), 106.6 (CH\(_2\)), 76.3 (CH), 74.3 (C\(_4\)), 55.6 (CH\(_3\)), 43.6 (CH), 41.6 (CH\(_2\)), 38.1 (CH\(_2\)), 38.1 (C\(_4\)), 30.0 (CH\(_2\)), 25.0 (CH\(_3\)), 24.3 (CH\(_3\)), 17.4 (CH\(_3\)); HRMS (EI), m/z (M\(^+\)) calculated for C\(_{15}\)H\(_{24}\)O\(_2\) 236.1776, found 236.1772.

2-Methoxy-4,4,7-trimethyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.17)

IR (neat, cm\(^{-1}\)) 3485 (bm), 2921 (s), 2872(m), 1455 (m), 1087 (s); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)), \(\delta_{ppm}\) 5.95 (d, \(J = 10.2 \text{ Hz}, 1\text{H}\)), 5.62 (dd, \(J = 4.3 \text{ Hz}, J = 9.9 \text{ Hz}, 1\text{H}\)), 4.94 (bs, 1H), 4.81 (dd, \(J = 1.5 \text{ Hz}, J = 1.6 \text{ Hz}, 1\text{H}\)), 3.53 (dddd, \(J = 2.1 \text{ Hz}, J = 2.1 \text{ Hz}, J = 4.0 \text{ Hz}, J = 4 \text{ Hz}, 1\text{H}\)), 3.29-3.26 (m, 1H), 3.19 (s, 3H), 2.75-2.70 (m, 1H), 2.01 (ddd, \(J = 2.1 \text{ Hz}, J = 2.1 \text{ Hz}, J = 4.0 \text{ Hz}, J = 4 \text{ Hz}, 1\text{H}\)).
= 3.7 Hz, J = 13.4 Hz, J = 13.4 Hz, 1H), 1.95-1.87 (m, 2H), 1.70 (ddd, J = 2.3 Hz, J = 2.3 Hz, J = 14.4 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.17 (s, 1H), 1.12 (d, J = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, C$_6$D$_6$), $\delta$ppm 152.3 (C$_4$), 134.5 (CH), 130.2 (CH), 108.7 (CH$_2$), 76.6 (CH), 74.9 (C$_4$), 55.7 (CH$_3$), 40.2 (CH), 37.6 (CH$_2$), 37.0 (C$_4$), 34.4 (CH), 27.8 (CH$_2$), 25.6 (CH$_3$), 25.3 (CH$_3$), 21.1 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{13}$H$_{24}$O$_2$ 236.1776, found 236.1766.

2,2-Dimethyl-6-(1-methyl-propenyl)-cyclohexane-1,4-diol (3.19)

To a solution of 3.9 (309 mg, 1.14 mmol) in 15 mL of THF was added TBAF (1.26 mL, 1.0 M in THF, 1.26 mmol). The mixture was stirred overnight and concentrated under reduced pressure. Purification by flash chromatography on silica gel (60% EtOAc in hexanes) afforded diol 3.19 (226 mg, 100%) as a white solid. IR (neat, cm$^{-1}$) 3432 (bs), 2921 (s), 2872 (s), 1453 (m), 1059 (s), 1024 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta$ppm 5.51-5.47 (m, 1H), 4.12-4.10 (m, 1H), 3.22-3.11 (m, 2H), 1.70-1.40 (m, 11H), 1.44 (s, 1H), 1.17 (s, 3H), 1.00 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ppm 135.4 (C$_4$), 124.6 (CH), 78.0 (CH), 67.5 (CH), 45.7 (CH$_2$), 36.8 (CH$_2$), 35.6 (C$_4$), 35.4 (CH), 30.9 (CH$_3$), 21.6 (CH$_3$), 19.1 (CH$_3$), 13.5 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{15}$H$_{22}$O$_2$ 198.1620, found 198.1584.

2,2-Dimethyl-6-(1-methyl-propenyl)-4-triisopropylsilanyloxy-cyclohexanol (3.20)$^9$

To a solution of diol 3.19 (128 mg, 0.65 mmol) in CH$_2$Cl$_2$ (8 mL) at –

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$^9$ Nathalie Goulet (summer student) assisted in preparation of this compound
78 °C was added 2,6-lutidine (0.60 mL, 5.18 mmol) followed by addition of TIPSOTf (0.69 mL, 2.56 mmol). The solution was stirred for 1 h and quenched with a saturated aqueous solution of NaHCO₃ at −78 °C. The mixture was extracted with CH₂Cl₂ 3 x 10 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes, then 15% EtOAc in hexanes) afforded product 3.20 contaminated with TIPSOH. Alcohol 3.20 was oxidized to ketone 3.21 without further purification.

![2,2-Dimethyl-6-(1-methyl-propenyl)-4-triisopropylsilanyloxy-cyclohexanone (3.21)](image)

To a solution of alcohol 3.20 (206 mg, 0.58 mmol) in CH₂Cl₂ (1 mL) was added 4Å molecular sieves (291 mg, 500 mg per 1 mmol), NMO (103 mg, 0.87 mmol) and TPAP (45 mg, 2% mol). The resulting black mixture was stirred for 14 h, then it was filtered through a short pad of silica gel. The silica gel was rinsed with 100 mL of 10% CH₃OH in EtOAc solution. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to yield ketone 3.21 (134 mg, 65%) as a white solid. IR (neat, cm⁻¹) 2927 (s), 2867 (s), 1711 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.44-5.37 (m, 1H), 4.36-4.82 (m, 2H), 2.77 (m, 3H), 1.74 (dd, J = 3.4 Hz, J = 14.2 Hz, 1H), 1.65-1.63 (m, 3H), 1.50 (dq, J = 1.5 Hz, J = 6.8 Hz, 3H), 1.41 (s, 3H), 1.10-1.05 (m, 21H), 1.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 215.4 (C₄), 133.7 (C₄), 122.4 (CH), 67.3 (CH), 47.8 (CH₂), 45.7 (C₄), 41.9 (CH), 40.1 (CH₂), 29.5 (CH₃), 26.9 (CH₃), 20.8 (CH₃), 18.5 (CH₃) x 6, 13.4 (CH₃), 12.6 (CH) x 3; HRMS (EI), m/z (M⁺) calculated for C₂₃H₄₄O₂Si 352.2798, found 352.2789.
1-Ethynyl-2,2-dimethyl-6-(1-methyl-propenyl)-4-triisopropylsilanyloxy-cyclohexanol (3.22)

1. To a solution of trimethylsilyl acetylene (0.18 mL, 1.24 mmol) in THF (5 mL) at −78 °C was added \( n \)-BuLi (0.36 mL, 2.6 M in pentane, 0.93 mmol). After stirring for 20 min at −78 °C a solution of ketone 3.21 (110 mg, 0.31 mmol) in THF (1 mL) was transferred by cannula and the reaction mixture was stirred for additional 30 min. It was then quenched with a saturated aqueous solution of \( \text{NH}_4\text{Cl} \) at −78 °C, warmed up to rt and extracted with \( \text{Et}_2\text{O} \) 3 x 10 mL. The combined organic extracts were dried over MgSO\(_4\) and concentrated under reduced pressure. The resulting crude oil was used in the next step without further purification.

2. To a solution of unpurified product from part 1 (139 mg, 0.31 mmol) in THF (5 mL) was added a solution of TBAF (0.34 mL, 1.0 M in THF, 0.34 mmol). The mixture was stirred for 15 min, then concentrated under reduced pressure and purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford 3.22 (69 mg, 58% over 2 steps) as a white solid.

IR (neat, cm\(^{-1}\)) 3563 (w), 3314 (m), 2947 (s), 2869 (s), 1466 (m); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \( \delta\text{ppm} \) 5.59 (q, \( J = 6.5 \) Hz, 1H), 4.18-4.17 (m, 1H), 3.58 (dd, \( J = 2.6 \) Hz, \( J = 12.9 \) Hz, 1H), 2.44 (s, 1H), 2.33 (s, 1H), 2.15 (ddd, \( J = 2.9 \) Hz, \( J = 13.4 \) Hz, \( J = 13.4 \) Hz, 1H), 1.85 (s, 3H), 1.74-1.58 (m, 6H), 1.32 (s, 3H), 1.09 (s, 3H), 1.04 (s, 21H); \(^13\)C NMR (75 MHz, CDCl\(_3\)), \( \delta\text{ppm} \) 135.1 (C\(_4\)), 126.3 (CH), 86.5 (C\(_4\)), 76.1 (C\(_4\)), 75.4 (CH), 67.8 (CH), 44.7 (CH\(_2\)), 39.6 (C\(_4\)), 37.4 (CH), 37.3 (CH\(_2\)), 27.6 (CH\(_3\)), 23.2 (CH\(_3\)), 21.4 (CH\(_3\)), 18.5 (CH\(_3\)) x 6, 13.9 (CH\(_3\)), 12.6 (CH\(_3\)) x 3; HRMS (EI), m/z (M\(^+\)) calculated for C\(_{23}\)H\(_{42}\)O\(_2\)Si 378.2954, found 378.2933; mp = 58.0-59.8 °C.
\[
\text{4,4,7-Trimethyl-8-methylene-2-}
\text{triisopropylsilanyloxy-1,3,4,7,8,8a-}
\text{hexahydro-2H-naphthalen-4a-ols (3.23) and}
\text{(3.24)}
\]

To a solution of alcohol 3.22 (30 mg, 0.08 mmol) in toluene (12 mL) in a microwave cell
was added DBU (0.12 mL, 0.70 mmol). The solution was degassed using argon for 30 min
and heated in the microwave oven for 2 h at 230 °C. Reaction was monitored by CG. The
solvent was then removed under reduced pressure and the residue was purified by flash
chromatography on silica gel (5% EtOAc in hexanes) to afford 3.23 (10 mg, 33%)
contaminated with non-polar impurities and a mixture of 3.23 and 3.24 (12 mg, 40%).
Compound 3.23 was treated with TBAF to afford diol 3.25, which was easily purified.

\[
\text{4,4,7-Trimethyl-8-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalene-}
\text{2,4a-diol (3.25)}
\]

To a solution of decaline 3.24 (10 mg, 0.03 mmol) in 0.5 mL of THF was
added TBAF (0.03 mL, 1.0 M in THF, 0.03 mmol). The mixture was stirred overnight and
concentrated under reduced pressure. Purification by flash chromatography on silica gel
(pure hexanes to remove non-polar impurities then 50% EtOAc in hexanes) afforded diol
3.25 (3 mg, 60%) as a white solid. IR (neat, cm\(^{-1}\)) 3335 (s), 3258 (s), 2949 (s), 2921 (s), 2865
(s), 1469 (m), 1092 (s); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta_{\text{ppm}}\) 5.84 (dd, \(J = 2.9\) Hz, \(J = 9.7\) Hz,
1H), 5.45 (dd, \(J = 2.0\) Hz, \(J = 9.7\) Hz, 1H), 4.84 (s, 1H), 4.79 (b, 1H), 3.78-3.72 (m, 1H),
2.60-2.58 (m, 1H), 2.40-2.37 (m, 1H), 1.94 (dd, \(J = 12.0\) Hz, \(J = 12.0\) Hz, 1H), 1.82 (ddd, \(J =
12.3\) Hz, \(J = 12.3\) Hz, \(J = 12.3\) Hz, 1H), 1.74-1.72 (m, 1H), 1.50-1.37 (m, 3H), 1.23 (s,
3H), 1.00 (d, J = 7.0 Hz, 3 H), 0.90 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 151.3 (C\(_4\)), 135.6 (CH), 130.4 (CH), 106.5 (CH\(_2\)), 74.0 (C\(_4\)), 67.1 (CH), 45.1 (CH), 43.7 (CH), 38.3 (C\(_4\)), 38.0 (CH\(_2\)), 33.8 (CH\(_2\)), 24.9 (CH\(_3\)), 24.0 (CH\(_3\)), 17.4 (CH\(_3\)); HRMS (EI), m/z (M\(^+\)) calculated for C\(_{14}\)H\(_{22}\)O\(_2\) 222.1620, found 222.1610.

\[\text{2-(1-Methyl-propenyl)-cyclohexanone (3.35)}\]

To solution of chloroalcohol 2.13 (196 mg, 1.04 mmol) in THF (10 mL) at rt was added vinylvagnesium bromide (1.16 mL, 0.9 M in THF, 1.04 mmol). The solution was refluxed for 50 min, cooled to rt and quenched with a saturated aqueous solution of NH\(_4\)Cl. The mixture was extracted with Et\(_2\)O 3 x 30 mL. The combined organic layers were dried over MgSO\(_4\) and concentrated under reduced pressure. The residue was purified by flash chromatography (8% EtOAc in hexanes) to afford product (128 mg, 81%) as a yellow oil. IR (cm\(^{-1}\), neat) 2934 (m), 2862 (m), 1710 (s), 1448 (m); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 5.23-5.15 (m, 1H), 2.90 (dd, J = 5.3 Hz, J = 11.6 Hz, 1H), 2.41-2.20 (m, 2H), 2.05-1.56 (m, 12H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 212.2 (C\(_4\)), 134.3 (C\(_4\)), 121.8 (CH), 60.6 (CH), 42.6 (CH\(_2\)), 32.6 (CH\(_2\)), 27.9 (CH\(_2\)), 25.4 (CH\(_2\)), 15.0 (CH\(_3\)), 13.8 (CH\(_3\)); HRMS (EI), m/z (M\(^+\)) calculated for C\(_{10}\)H\(_{16}\)O\(_4\) 152.1201, found 152.1189.

\[\text{1-(1-Ethoxy-vinyl)-2-(1-methyl-propenyl)-cyclohexanol (3.33)}\]

To a mixture of THF (0.1 mL) and ethyl vinyl ether (0.38 mL, 3.94 mmol) at \(-78^\circ\) C was added dropwise (over 5 min) a solution of \(\text{t-BuLi (1.16 mL, 1.7 M in pentane, 1.97 mmol)}\). The solution was stirred for 5 min at \(-78^\circ\) C. It was then warmed to 0 \({}^\circ\) C (a dry-ice/isopropanol bath was replaced with an ice bath), stirred for 45 min at 0 \({}^\circ\) C and re-cooled.
to −78 °C. Ketone 3.35 (30 mg, 0.20 mmol) was dissolved in THF (1 mL) and transferred by cannula to the solution of the lithiated compound at −78 °C. The reaction mixture was stirred for 40 min and quenched with H₂O at −78 °C. The mixture was extracted with Et₂O 3 x 5 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to give product (20 mg, 45%) as a colorless oil. IR (cm⁻¹, neat) 3541 (m, sharp), 2978 (m), 2931 (s), 2859 (m), 1654 (m), 1608 (m); ¹H NMR (300 MHz, C₆D₆), δ ppm 5.28 (q, J = 6.4 Hz, 1H), 4.49-4.48 (m, 1H), 3.84 (s, 1H), 3.44-3.29 (m, 2H), 2.60 (dd, J = 3.4 Hz, J = 13.2 Hz, 1H), 2.08-1.77 (m, 5H), 1.72-1.65 (m, 1H), 1.65 (s, 3H), 1.59-1.44 (m, 5H), 1.37-1.17 (m, 1H), 1.05 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆), δ ppm 168.7 (C₄), 139.0 (C₄), 120.0 (CH), 79.3 (CH₂), 74.2 (C₄), 62.7 (CH₂), 51.1 (CH), 37.1 (CH₂), 27.6 (CH₂), 26.7 (CH₂), 21.8 (CH₂), 17.9 (CH₃), 14.6 (CH₃), 13.6 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₄H₂₄O₂ 224.1776, found 224.1760.

4-Ethoxy-2-methyl-1-methylene-octahydro-naphthalen-4a-ol (3.34)

[Chemical structure image]

To a solution of alcohol 3.33 (27 mg, 0.12 mmol) in toluene (10 mL) in a microwave cell was added DBU (0.18 mL, 1.20 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 223 °C. Reaction was monitored by 300 MHz ¹H NMR. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 3.34 (4.8 mg, 18%) as a yellowish oil and an inseparable 3:1 mixture of the starting material and retro-ene product 3.37 (20 mg). IR (cm⁻¹, neat) 3564 (bm), 2929 (s), 2864 (s), 1639 (m), 1448 (m), 1094 (s); ¹H NMR (300 MHz, C₆D₆), δ ppm 4.80 (s, 1H), 4.70
(s, 1H), 3.40-3.35 (m, 1H), 3.15-3.09 (m, 1H), 3.00 (dd, J = 2.5 Hz, J = 2.5 Hz, 1H), 2.52-2.43 (m, 1H), 2.09-2.04 (m, 1H), 1.81-1.16 (m, 11H), 1.05 (t, J = 6.9 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆), δppm 154.6 (C₄), 106.0 (CH₂), 81.8 (CH), 74.4 (CH), 65.1 (CH₂), 44.8 (CH), 36.2 (CH₂), 33.8 (CH₂), 32.5 (CH), 26.1 (CH₂), 24.4 (CH₂), 21.7 (CH₂), 18.3 (CH₃), 15.9 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₄H₂₄O₂ 224.1776, found 224.1758.

2-Ethoxy-9-methyl-undeca-1,8-dien-3-one (3.37)

¹H NMR (500 MHz, C₆D₆), δppm 5.45 (d, J = 2.0 Hz, 1H), 5.24-5.20 (m, 1H), 4.09 (d, J = 2.0 Hz, 1H), 3.34 (q, J = 7.0 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.11-2.04 (m, 4H), 1.74 (s, 3H), 1.45-1.40 (m, 4H), 1.08 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H).

2-(1-Allyloxymethyl-propenyl)-1-(1-ethoxy-vinyl)-cyclohexanol (3.38)

To a mixture of ethyl vinyl ether (0.21 mL, 2.20 mmol) in THF (0.05 mL) at −78 °C was added dropwise (over 5 min) a solution of t-BuLi (0.65 mL, 1.7 M in pentane, 1.10 mmol). The solution was stirred for 5 min at −78 °C. The mixture was warmed to 0 °C (a dry-ice/isopropanol bath was replaced with an ice bath), stirred for 45 min at 0 °C and re-cooled to −78 °C. Ketone 3.33 (23 mg, 0.11 mmol) was dissolved in THF (1 mL) and transferred by cannula to the solution of the lithiated compound at −78 °C. The reaction mixture was stirred for 40 min and quenched with H₂O at −78 °C. The mixture was extracted with Et₂O 3 x 5 mL. The combined organic layers were
dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes) on silica gel to give desired product 3.38 (10 mg, 32%) as a colorless oil. IR (cm⁻¹, neat) 3401 (m), 2981 (m), 2927 (s), 2857 (m), 1652 (m), 1612 (m), 1447 (m), 1067 (s); ¹H NMR (300 MHz, C₆D₆), δppm 5.84-5.72 (m, 1H), 5.62 (q, J = 7.0 Hz, 1H), 5.23-5.18 (m, 1H), 5.03-4.99 (m, 1H), 4.75-4.75 (m, 1H), 4.54 (s, 1H), 3.97-3.94 (m, 2H), 3.82 (dddd, Jₓₓ = 1.6 Hz, Jₐᵧ = 1.6 Hz, Jₐₐ = 5.1 Hz, Jⱼⱼ = 12.9 Hz, 1H), 3.72 (dd, Jⱼⱼ = 11.2 Hz, 1H), 3.64 (dddd, Jₓₓ = 1.4 Hz, Jₐᵧ = 1.14 Hz, Jₐₐ = 5.5 Hz, Jⱼⱼ = 12.8 Hz, 1H), 3.54-3.34 (m, 2H), 2.96 (dd, J = 3.0 Hz, 12.9 Hz, 1H), 2.16-1.98 (m, 4H), 1.81-1.77 (m, 1H), 1.57-1.27 (m, 6H), 1.10 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆), δppm 169.3 (C₄), 136.9 (C₄), 134.7 (CH), 127.8 (CH), 116.9 (CH₂), 79.9 (CH₂), 75.0 (C₄), 71.0 (CH₂), 64.4 (CH₂), 62.7 (CH₂), 57.2 (CH), 37.4 (CH₂), 27.1 (CH₂), 26.9 (CH₂), 22.0 (CH₂), 14.8 (CH₃), 13.7 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₇H₂₆O₃ 280.2038, found 280.2060.

![Chemical Structure](image)

1-Isopropenyl-2-(1-methyl-propenyl)-cyclohexanol (3.39)

To a solution of 2-bromopropene (0.09 mL, 1.05 mmol) in THF (5 mL) at −78 °C was added dropwise a solution of t-BuLi (1.16 mL, 1.7 M in pentane, 1.95 mmol). The resulting mixture was stirred for 1 h at −78 °C. Then a solution of ketone 3.35 (40 mg, 0.26 mmol) in THF (0.5 mL) was transferred by cannula. The mixture was stirred for 1 h at −78 °C and quenched with H₂O. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic fractions were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) afforded product 3.39 (44 mg, 86%) as a yellow oil. IR (cm⁻¹, neat)
3545 (m), 2931 (s), 2850 (s), 1441 (m); $^1$H NMR (300 MHz, C$_6$D$_6$), $\delta_{ppm}$ 5.27-5.21 (m, 1H), 5.10-5.09 (m, 1H), 4.80-4.79 (m, 1H), 2.12 (dd, $J = 3.3$ Hz, $J = 12.7$ Hz, 1H), 1.92-1.65 (m, 8H), 1.58-1.33 (m, 9H), 0.99 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 151.8 (C$_4$), 139.0 (C$_4$), 120.1 (CH), 109.5 (CH$_2$), 76.2 (C$_4$), 52.3 (CH), 37.7 (CH$_2$), 27.9 (CH$_2$), 26.8 (CH$_2$), 21.8 (CH$_2$), 20.1 (CH$_3$), 16.7 (CH$_3$), 13.5 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{13}$H$_{22}$O 194.1671, found 194.1659.

2-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (3.41)

To a solution of alcohol 3.39 (44 mg, 0.23 mmol) in toluene (12 mL) in a microwave cell was added Et$_3$N (0.16 mL, 1.15 mmol). The resulting solution was degassed using argon for 30 min and heated in the microwave oven for 2 h at 220 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 3.41 (22 mg, 50%) as a clear oil and an inseparable mixture of 3.41 and 3.42 (12 mg, 27%). IR (cm$^{-1}$, neat) 3571 (m), 2931 (s), 2853 (s), 1460 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 4.89-4.89 (m, 1H), 4.58 (dd, $J = 1.8$ Hz, $J = 1.8$ Hz, 1H), 2.59-2.51 (m, 1H), 2.20-2.14 (m, 1H), 1.98-1.91 (m, 1H), 1.80-1.65 (m, 2H), 1.60-1.41 (m, 5H), 1.35-1.06 (m, 7H), 0.81(d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 154.4 (C$_4$), 108.9 (CH$_2$), 73.8 (C$_4$), 44.6 (CH), 39.1 (CH), 38.7 (CH$_2$), 36.3 (CH), 35.6 (CH$_2$), 26.2 (CH$_2$), 24.5 (CH$_2$), 21.9 (CH$_2$), 19.9 (CH$_3$), 14.8 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{13}$H$_{22}$O 194.1671, found 194.1676.

2-(1-Methyl-propenyl)-1-(1-phenyl-vinyl)-cyclohexanol (3.40)

To a solution of α-bromostyrene (0.34 mL, 2.63 mmol) in Et$_2$O (10 mL)
at -90 °C was added dropwise a solution of t-BuLi (2.9 mL, 1.7 M in pentane, 4.93 mmol). The resulting solution was stirred for 1 h 20 min at -90 °C (a reaction flask was covered with aluminum foil to protect it from light). Then a solution of ketone 3.35 (100 mg, 0.67 mmol) in Et₂O (1 mL) was transferred by cannula and the mixture was warmed to -60 °C. The solution was cooled to -90 °C and quenched with H₂O. The aqueous phase was extracted with Et₂O 3 x 20 mL. The combined organic fractions were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes then 5 % EtOAc in hexanes) afforded product 3.40 (138 mg, 82%) as a yellow oil. IR (cm⁻¹, neat) 3564 (bm), 3080 (m), 3054 (m), 3021 (m), 2932 (s), 2858 (m), 1949 (w), 1877 (w), 1816 (w), 1598 (w), 1573 (w), 1492 (m), 1443 (m), 980 (m), 775 (m), 702 (s); ¹H NMR (300 MHz, C₆D₆), δppm 7.30-7.27 (m, 2H), 7.18-7.06 (m, 3H), 5.39-5.33 (m, 2H), 5.02 (d, J = 1.7 Hz, 1H), 2.25 (dd, J = 3.4 Hz, J = 12.6 Hz, 1H), 1.96 (ddd, J = 3.5 Hz, J = 13.0 Hz, J = 16.5 Hz, 1H), 1.73-1.72 (m, 3H), 1.70-1.31 (m, 10H), 1.22 (s, 1H); ¹³C NMR (75 MHz, C₆D₆), δppm 157.8 (C₄), 142.5 (C₄), 138.7 (C₄), 129.2 (CH) x 2, 127.8 (CH) x 2, 127.1 (CH), 121.5 (CH), 114.1 (CH₂), 76.8 (C₄), 53.8 (CH), 40.9 (CH₂), 28.5 (CH₂), 26.5 (CH₂), 21.9 (CH₂), 16.4 (CH₃), 13.5 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₈H₂₄O 256.1827, found 256.1827.

![2-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (3.43)](image)

To a solution of alcohol 3.40 (70 mg, 0.27 mmol) in toluene (12 mL) in a microwave cell was added Et₃N (0.19 mL, 1.35 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 1 h at 210 °C. The solvent was removed under reduced pressure and the residue was purified by flash
chromatography on silica gel (5% EtOAc in hexanes) to afford 3.43 (65 mg, 93%) as a clear oil. IR (cm\(^{-1}\), neat) 3555 (m), 3083 (m), 3060 (m), 3025 (m), 2931 (s), 2894 (m), 2858 (m), 1937 (w), 1861 (w), 1801 (w), 1641 (m), 1494 (m), 1452 (m); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 7.30-7.15 (m, 5H), 4.89-4.87 (m, 1H), 4.61 (dd, \(J = 1.9\) Hz, \(J = 1.9\) Hz, 1H), 2.67 (dd, \(J = 3.7\) Hz, \(J = 13.6\) Hz, 1H), 2.53-2.44 (m, 1H), 2.24-2.14 (m, 2H), 1.67-1.36 (m, 6H), 1.29-1.11 (m, 3H), 1.08 (d, \(J = 7.2\) Hz, 3H), 1.03-0.92 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 153.9 (C\(_4\)), 142.6 (C\(_4\)), 128.3 (CH) x 2, 126.8 (CH) x 2, 126.8 (CH), 109.3 (CH\(_2\)), 73.9 (C\(_4\)), 49.3 (CH), 45.0 (CH), 39.1 (CH), 37.2 (CH\(_2\)), 36.9 (CH\(_2\)), 26.2 (CH\(_2\)), 24.5 (CH\(_2\)), 21.7 (CH\(_2\)), 19.8 (CH\(_3\)); HRMS (El), m/z (M\(^+\)) calculated for C\(_{18}\)H\(_{24}\)O 256.1827, found 256.1846.

\[\text{2-Chloro-1-(1-methyl-propenyl)-cyclohexanol (3.44)}\]

To a solution of cis -2 bromo-2-butene (0.46 mL, 4.55 mmol) in Et\(_2\)O (20 mL) at \(-78^\circ\)C was added t-BuLi (4.70 mL, 1.8 M in pentane, 8.48 mmol). The mixture was stirred for 2 h at \(-78^\circ\)C. A solution of 1-chloro-cyclohexan-2-one (400 mg, 3.03 mmol) in Et\(_2\)O (2 mL) was then transferred by cannula to the lithiated compound at \(-78^\circ\)C. The reaction was completed in 20 min after addition of the ketone. The mixture was quenched with H\(_2\)O and extracted with Et\(_2\)O 3 x 20 mL. The combined organic extracts were dried over MgSO\(_4\), and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc in hexanes) gave product (330 mg, 58%) as a colorless oil. IR (cm\(^{-1}\), neat) 3576 (s), 2969 (s), 2941 (s), 2864 (s), 2736 (w), 1446 (s), 1069 (s), 987 (s); \(^1\)H NMR (300 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 5.37-5.30 (m, 1H), 4.19 (dd, \(J = 4.9\) Hz, \(J = 11.6\) Hz, 1H), 2.19-2.17 (m, 1H), 2.07-1.89 (m, 3H), 1.82-1.79 (m, 3H), 1.71-1.39 (m, 7H), 1.32-1.21 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)), \(\delta_{ppm}\) 139.7 (C\(_4\)), 123.9 (CH), 77.1 (C\(_4\)), 67.9 (CH), 35.7
(CH$_2$), 32.3 (CH$_2$), 26.5 (CH$_2$), 22.7 (CH$_3$), 20.6 (CH$_2$), 15.3 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{10}$H$_{17}$OCl 188.0968, found 188.0953.

2-(1-Methyl-propenyl)-cyclohexanone (3.45)

To a solution of chloroalcohol 3.44 (50 mg, 0.27 mmol) in THF (3 mL) at rt was added vinylmagnesium bromide (0.3 mL, 0.9 M in THF, 0.27 mmol). The solution was refluxed for 1 h, cooled to rt and quenched with a saturated aqueous solution of NH$_4$Cl. The mixture was extracted with Et$_2$O 3 x 10 mL. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) on silica gel to afford ketone 3.45 (25 mg, 62%) as a yellow oil. Note: the compound is volatile. IR (cm$^{-1}$, neat) 2935 (s), 2863 (m), 1710 (s), 1449 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.44-5.37 (m, 1H), 3.34 (dd, $J = 5.6$ Hz, $J = 11.6$ Hz, 1H), 2.46-2.40 (m, 1H), 2.35-2.21 (m, 1H), 2.11-2.02 (m, 1H), 1.98-1.64 (m, 8H), 1.49-1.46 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 210.8 (C$_4$), 133.9 (C$_4$), 122.5 (CH), 52.1 (CH), 42.6 (CH$_2$), 32.0 (CH$_2$), 27.4 (CH$_2$), 25.6 (CH$_2$), 21.1 (CH$_3$), 13.6 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{10}$H$_{16}$O 152.1201, found 152.1194.

2-(1-Methyl-propenyl)-1-vinyl-cyclohexanol (3.46)

To a solution of ketone 3.45 (50 mg, 0.33 mmol) in 5 mL of THF was added vinylmagnesium bromide (1.50 mL, 0.9 M in THF, 1.35 mmol) at 0°C. The solution was stirred for 3 h at rt and then quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous phase was extracted with Et$_2$O 3 x 5 mL. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography
on silica gel (8% EtOAc in hexanes) afforded product 3.46 (28.6 mg, 48%, dr=20:1) as a clear oil. Note: due to a high volatility of the compound the solvent could not be removed completely. IR (cm$^{-1}$, neat) 3489 (bm), 2932 (s), 2859 (s), 1448 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 5.88 (dd, $J = 10.8$ Hz, $J = 17.3$ Hz, 1H), 5.26-5.12 (m, 2H), 4.95 (dd, $J = 1.3$ Hz, $J = 10.8$ Hz, 1H), 2.47 (dd, $J = 3.2$ Hz, 12.7 Hz, 1H), 1.93-1.45 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 145.9 (CH), 138.0 (C$_4$), 120.9 (CH), 111.0 (CH$_2$), 75.4 (C$_4$), 46.1 (CH), 39.7 (CH$_2$), 26.6 (CH$_2$), 26.5 (CH$_2$), 22.3 (CH$_2$), 21.8 (CH$_3$), 13.9 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{12}$H$_{20}$O 180.1514, found 180.1533.

2-(1-Methyl-propenyl)-1-(1-phenyl-vinyl)-cyclohexanol (3.47)

To a solution of α-bromostyrene (0.17 mL, 1.32 mmol) in Et$_2$O (5 mL) at −90 °C was added dropwise a solution of t-BuLi (1.45 mL, 1.7 M in pentane, 2.47 mmol). The resulting mixture was stirred for 1 h 20 min at −90 °C (a reaction flask was covered with aluminum foil to protect it from light). Then a solution of ketone 3.45 (50 mg, 0.33 mmol) in Et$_2$O (1 mL) was transferred by cannula and the mixture was warmed to −60 °C. The solution was re-cooled to −90 °C and quenched with H$_2$O. The aqueous phase was extracted with Et$_2$O 3 x 10 mL. The combined organic fractions were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexane then 5 % EtOAc in hexanes) afforded product 3.47 (61 mg, 72%) as a yellow oil. IR (cm$^{-1}$, neat) 3594 (bm), 3981 (w), 3053 (w), 3029 (w), 2929 (s), 2857 (s), 1949 (w), 1892 (w), 1828 (w), 1749 (w), 1690 (w), 1625 (w), 1598 (w), 1573 (w); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 7.30 (m, 2H), 7.12-7.08 (m, 3H), 5.42 (d, $J = 1.8$ Hz, 1H), 5.25-5.18 (m, 1H), 4.98 (d, $J = 1.8$ Hz, 1H), 2.64 (dd, $J = 3.5$ Hz, J
= 12.7 Hz, 1H), 2.03-1.86 (m, 4H), 1.73-1.52 (m, 3H), 1.47-1.25 (m, 6H), 1.15-1.03 (m, 1H), 1.00 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 157.7 (C$_4$), 142.1 (C$_4$), 140.1 (C$_4$), 129.6 (CH) x 2, 127.8 (CH) x 2, 127.2 (CH), 120.7 (CH), 113.7 (CH$_2$), 77.0 (C$_4$), 44.9 (CH), 41.0 (CH$_2$), 27.7 (CH$_2$), 26.4 (CH$_2$), 22.7 (CH$_3$), 21.8 (CH$_2$), 13.5 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{18}$H$_{24}$O 256.1827, found 256.1831.

![Chemical Structure](image)

2-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (3.51)

To a solution of alcohol 3.47 (25 mg, 0.08 mmol) in toluene (12 mL) in a microwave cell was added Et$_3$N (0.06 mL, 0.40 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 3 h at 220 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 3.51 (16 mg, 643%) as a yellowish oil. IR (cm$^{-1}$, neat) 3553 (m), 3087 (m), 3060 (m), 3026 (m), 2931 (s), 2855 (s), 1945 (w), 1876 (w), 1802 (w), 1727 (w), 1643 (m), 1494 (m), 982 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{\text{ppm}}$ 7.25-7.11 (m, 5H), 4.84 (d, $J= 1.1$ Hz, 1H), 4.71 (s, 1H), 2.37 (dd, $J = 4.7$ Hz, $J = 12.1$ Hz, 1H), 1.96-1.86 (m, 1H), 1.82-1.77 (m, 1H), 1.68-1.39 (m, 7H), 1.29-1.21 (m, 1H), 1.15-1.05 (m, 2H), 1.01-0.91 (m, 4H); $^{13}$C NMR (75 MHz, C$_6$D$_6$), $\delta_{\text{ppm}}$ 153.9 (C$_4$), 142.8 (C$_4$), 128.2 (CH) x 2, 128.0 (CH) x 2, 126.6 (CH), 106.2 (CH$_2$), 73.3 (C$_4$), 55.2 (CH), 50.6 (CH), 40.7 (CH$_2$), 38.7 (CH), 37.1 (CH$_2$), 26.2 (CH$_2$), 24.8 (CH$_2$), 21.7 (CH$_2$), 18.3 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{18}$H$_{24}$O 256.1827, found 256.1818.
1-(1-Ethylsulfanyl-vinyl)-2-(1-methyl-propenyl)-cyclohexanol (3.48)

To a mixture of THF (0.17 mL) and ethylsulfanylethene (0.67 mL, 6.60 mmol) at −78 °C was added dropwise (over 5 min) a solution of t-BuLi (1.90 mL, 1.7 M in pentane, 3.30 mmol). The solution was stirred for 5 min at −78 °C. It was then warmed to 0 °C (a dry-ice/isopropanol bath was replaced with an ice bath), stirred for 45 min at 0 °C and re-cooled to −78 °C. Ketone 3.45 (50 mg, 0.33 mmol) was dissolved in THF (0.5 mL) and transferred by cannula to a solution of the lithiated compound at −78 °C. The reaction mixture was stirred for 40 min and quenched with H₂O at −78 °C. The mixture was extracted with Et₂O 3 x 5 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) on silica gel pretreated with Et₃N to give product 3.48 (27 mg, 34%) as a colorless oil and a 2:1 mixture of 3.48 and the syn-diastereomer (6.6 mg, 8%). IR (cm⁻¹, neat) 3496 (bm), 2930 (s), 2858 (s), 1598 (m), 1448 (m); ¹H NMR (500 MHz, C₆D₆), δppm 5.56 (s, 1H), 5.41-5.37 (m, 1H), 4.79 (s, 1H), 3.08 (dd, J = 3.4 Hz, J = 12.7 Hz, 1H), 2.55-2.44 (m, 2H), 2.17-2.04 (m, 4H), 1.82-1.67 (m, 5H), 1.57-1.40 (m, 3H), 1.39-1.31 (m, 3H), 1.14 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆), δppm 153.7 (C₆), 138.5 (C₄), 120.9 (CH), 104.4 (CH₂), 78.0 (C₄), 45.2 (CH), 40.4 (CH₂), 27.3 (CH₂), 26.5 (CH₂), 26.4 (CH₂), 22.3 (CH₃), 21.9 (CH₂), 13.8 (CH₃), 13.0 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₄H₂₄OS 240.1548, found 240.1537.
4-Ethylsulfanyl-2-methyl-1-methylene-octahydro-naphthalen-4a-ol (3.52)

To a solution of alcohol 3.48 (13 mg, 0.05 mmol) in toluene (12 mL) in a microwave cell was added Et₃N (0.03 mL, 0.22 mmol). The solution was degassed using argon for 30 min and heated in the microwave oven for 3 h at 220 °C. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to afford 3.43 (11 mg, 81%) as a clear oil. IR (cm⁻¹, neat) 3524 (bm), 2931 (s), 2854 (s), 1644 (m), 1449 (m); ¹H NMR (500 MHz, C₆D₆), δ ppm 4.77 (s, 1H), 4.69 (s, 1H), 2.54-2.50 (m, 1H), 2.41-2.29 (m, 3H), 1.93 (ddd, J = 4.0 Hz, J = 4.0 Hz, J = 13.0 Hz, 1H), 1.84-1.79 (m, 1H), 1.74-1.57 (m, 4H), 1.54-1.45 (m, 3H), 1.25 (s, 1H), 1.13-1.08 (m, 4H), 0.99-0.92 (m, 4H); ¹³C NMR (75 MHz, C₆D₆), δ ppm 152.6 (C₄), 105.8 (CH₂), 74.2 (C₄), 55.4 (CH), 50.4 (CH), 41.6 (CH₂), 38.7 (CH), 37.5 (CH₂), 26.3 (CH₂), 26.2 (CH₂), 24.9 (CH₂), 21.8 (CH₂), 18.0 (CH₃), 15.5 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₄H₂₄OS 240.1548, found 240.1534.

6.4. Spectroscopic data for Chapter 4

1- Allyl-1-methyl-octahydro-naphthalen-4a-ol (4.2)

To a solution of lactol 4.1 (720 mg, 3.24 mmol) in 32 mL of diethylene glycol was added K₂CO₃ (3.58 g, 25.92 mmol) followed by addition of NH₂NH₂·H₂O (0.786 mL, 16.2 mmol). The flask was then equipped with a condenser and immersed into a wax bath preheated to 150 °C. The reaction mixture was left stirring for 12 h at 150 °C. Then it was cooled to rt and poured into an Erlenmeyer flask containing 320 mL of distilled H₂O. The resulting milky solution was extracted five times with Et₂O. The
combined organic extracts were concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) yielded deoxygenated product 4.2 (387 mg, 57 % yield) as a clear oil.

The yields vary from 43% to 57%. In some cases reduction of a double bond was observed as a side reaction, resulting in an inseparable mixture of 4.2 and 4.3, with the ratios ranging from 4:1 to 15:1. IR (cm⁻¹, neat) 3490 (brm), 3073 (m), 3000 (m), 2930 (s), 2865 (s), 2850 (s), 1637 (m), 1446 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.84-5.72 (m, 1H), 5.02-4.93 (m, 2H), 2.03-1.72 (m, 4H), 1.59-1.02 (m, 12H), 0.95 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 135.6 (CH), 117.3 (CH₂), 71.9 (C₄), 49.2 (CH), 47.8 (CH₂), 42.2 (CH₂), 41.1 (CH₂), 38.3 (CH₂), 36.3 (C₄), 27.1 (CH₂), 22.1 (CH₂), 21.7 (CH₃), 21.2 (CH₂), 15.5 (CH₂); HRMS (EI), m/z (M⁺-H₂O) calculated for C₁₄H₂₂ 190.1722, found 190.1720.

1-(2-Hydroxy-ethyl)-1-methyl-octahydro-naphthalen-4a-ol (4.4)

A. Ozonolysis: A solution of 4.2 (190 mg, 0.91 mmol) in 10 mL of CH₂Cl₂ in a round-bottom flask was saturated with oxygen at rt. The contents were then cooled to −78 °C and bubbled with ozone. After 15 min the color of the reaction turned gray-blue and bubbling was discontinued, followed by immediate addition of DMS (0.25 mL, 4.57 mmol) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, warmed to rt and stirred for 0.5 h. The solution was concentrated under reduced pressure and used for the reduction without further purification.

B. LiAlH₄ Reduction: To a solution of a crude oil from part A in 10 mL of THF was carefully added LiAlH₄ (78 mg, 2.74 mmol) at −78 °C. After 10 min the dry-ice/isopropanol bath was removed and the mixture was left stirring at rt overnight. It was quenched by a
dropwise addition of 10 mL of a 1.0 M aqueous solution of sodium tartrate. The resulting emulsion was left stirring for 10 h until it became almost clear and the phases separated. The aqueous phase was extracted with EtOAc 5 x 20 mL. The combined fractions were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (40 % EtOAc in hexanes) on silica gel afforded product 4.4 (158 mg, 82% yield over 2 steps) as a white solid. IR (cm⁻¹, neat) 3606 (w), 3382 (bs), 2930 (s), 2850 (s), 2668 (w), 1448 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 3.65 (t, J = 8.1 Hz, 2H), 1.86-1.70 (m, 2H), 1.63-1.16 (m, 16H), 1.02-0.98 (m, 4H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 71.8 (C₄), 59.6 (CH₂), 50.3 (CH), 46.2 (CH₂), 42.3 (CH₂), 41.0 (CH₂), 38.8 (CH₂), 35.5 (C₄), 27.3 (CH₂), 22.0 (CH₂), 21.9 (CH₂), 20.6 (CH₃), 18.2(CH₂); HRMS (EI), m/z (M⁺) calculated for C₁₁H₂₄O₂ 212.1777, found 212.1797; mp=114.7-116.1 °C

2-(1-Methyl-4a-trimethylsilyloxy-decahydro-naphthalen-1-yl)-ethanol (4.8)

To a solution of crude 4.4 (66 mg, 0.31 mmol) in 5 mL of THF at -78 °C was added TMSCl (0.16 mL, 1.24 mmol) freshly distilled over CaH₂, followed by addition of solid KHMDS (155 mg, 0.78 mmol). The resulting solution was stirred for 3 h during which time it slightly warmed up (to -50 °C). The reaction was monitored by TLC and quenched with a saturated aqueous solution of NaHCO₃ when no starting material and only trace of mono-protected product were observed. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. The resulting yellowish oil was dissolved in 3 mL of MeOH, followed by addition of K₂CO₃ (47 mg, 0.34 mmol). The mixture was stirred for 10-15 min,
quenched with brine and extracted with CH$_2$Cl$_2$ 3 x 10 mL. Purification by flash chromatography on silica gel (40 % EtOAc in hexanes) afforded product 4.8 (33 mg, 37% over 4 steps) as a clear oil. IR (cm$^{-1}$, neat) 3526 (bm), 2936 (s), 2853 (m), 1514 (w), 1447 (m), 1057 (s), 1032 (s), 836 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 3.63 (t, $J = 7.9$ Hz, 2H), 1.85-1.09 (m, 19H), 0.91 (s,$^3$H), 0.10 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 75.8 (C$_4$), 59.6 (CH$_2$), 52.2 (CH), 46.5 (CH$_2$), 41.5 (CH$_2$), 40.6 (CH$_2$), 38.9 (CH$_2$), 35.5 (C$_4$), 27.6 (CH$_2$), 22.4 (CH$_2$), 21.9 (CH$_3$), 20.8 (CH$_2$), 18.5 (CH$_2$), 2.9 (CH$_3$) x 3; HRMS (EI), m/z (M$^+$) calculated for C$_{16}$H$_{32}$O$_2$Si 284.2172, found 284.2177.

![Toluene-4-sulfonic acid 2-(4a-hydroxy-1-methyl-decahydro-naphthalen-1-yl)-ethyl ester (4.5)](image)

To a mixture of diol 4.4 (20 mg, 0.09 mmol), Et$_3$N (0.04mL, 0.28 mmol) and DMAP (2 mg, 10% mol) in 1 mL of CH$_2$Cl$_2$ was added TsCl (27 mg, 0.14 mmol), freshly recrystallized from benzene. The resulting solution was stirred at rt for 2 h and quenched with a saturated aqueous solution of NaHCO$_3$. The aqueous phase was extracted with CH$_2$Cl$_2$ 3 x 5 mL. The combined organic fractions were dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexanes) on silica gel afforded product 4.5 (31 mg, 90% yield) as a clear oil. IR (cm$^{-1}$, neat) 3551 (w), 2929 (s), 2854 (m), 1721 (s), 1598 (w), 1451 (w), 948 (s), 815 (m), 665 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 7.77 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J =8.1$ Hz, 2H), 4.04 (t, $J = 7.4$ Hz, 2H), 2.43 (s, 3H), 2.39-0.98 (m, 17H), 0.92 (s, 3H), 0.92-0.87 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 145.1 (C$_4$), 133.5 (C$_4$), 130.2 (CH) x 2, 128.3 (CH) x 2, 71.7 (C$_4$), 68.1 (CH$_2$), 51.4 (CH), 42.3 (CH$_2$), 41.9 (CH$_2$), 40.9 (CH$_2$), 38.5 (CH$_2$), 35.5 (C$_4$), 27.1 (CH$_2$), 22.0 (CH$_2$),
21.9 (CH₃), 21.9 (CH₂), 21.8 (CH₃), 18.0 (CH₂) HRMS (EI), m/z (M⁺) calculated for C₂₀H₃₀O₄S 366.1865, found 366.1877.

**Toluene-4-sulfonic acid 2-(1-methyl-4a-trimethylsilyloxy-decahydro-naphthalen-1-yl)-ethyl ester (4.9)**

To a solution of 4.8 (16 mg, 0.06 mmol) and pyridine (0.02 mL, 0.17 mmol) in 1 mL of CH₂Cl₂ was added TsCl (16 mg, 0.09 mmol) at rt. The mixture was stirred for 2 h, followed by addition of more pyridine (0.02 mL, 0.17 mmol) and TsCl (16 mg, 0.09 mmol). After 5 h the reaction was quenched with a saturated aqueous solution of NaHCO₃. It was extracted with CH₂Cl₂ 3 x 5 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. Flash chromatography on silica gel (15% EtOAc in hexanes) yielded product 4.9 (10 mg, 65%) as a clear oil. IR (cm⁻¹, neat) 2935 (s), 2858 (m), 1917 (w), 1729 (w), 1596 (w), 1447 (m), 1059 (s), 1033 (s), 952 (s), 906 (m), 837 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 7.77 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.02 (t, J = 7.5 Hz, 2H), 2.43 (s, 3H), 1.74-0.99 (m, 15H), 0.92-0.85 (m, 4H), 0.71 (dd, J = 2.7 Hz, J = 11.9 Hz, 1H), 0.08 (s, 9H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 145.0 (C₄), 133.6 (C₄), 130.2 (CH) x 2, 128.3 (CH) x 2, 75.6 (C₄), 68.3 (CH₂), 51.4 (CH), 41.7 (CH₂), 41.4 (CH₂), 40.4 (CH₂), 38.6 (CH₂), 35.5 (C₄), 27.4 (CH₂), 22.2 (CH₂), 22.0 (CH₃), 21.8 (CH₂), 20.6 (CH₃), 18.3 (CH₂), 2.9 (CH₃) x 3; HRMS (EI), m/z (M⁺) calculated for C₂₃H₃₈O₄Si 438.2260, found 438.2271.

**1-Methyl-1-propenyl-octahydro-naphthalen-4a-ol (4.11)**

To a solution of 4.2 (130 mg, 0.63 mmol) in 6 mL of toluene in a sealed
tube was added RuCl₂(PPh₃)₂ (45 mg, 0.06 mmol) and diisopropylethylamine (0.82 ml, 5.04 mmol). The sealed tube was immersed into a preheated to 145 °C wax bath and stirred for 18.5 h. It was then concentrated and purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give an inseparable 20:1 mixture of 4.11 and 4.2 (120 mg, 92% yield) as a white solid.

¹H NMR is the only way to monitor a reaction progress since TLC results and retention times of product and starting material (CG) coincide. IR (cm⁻¹, neat) 3473 (m), 3026 (w), 2997 (w), 2977 (s), 2848 (m), 1445 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.32-5.13 (m, 2H), 1.88-1.12 (m, 19H), 1.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 144.1 (CH), 121.2 (CH), 71.6 (C₄), 50.6 (CH), 42.3 (CH₂), 41.0 (CH₂), 40.9 (CH₂), 39.1 (C₄), 27.3 (CH₂), 22.7 (CH₂), 22.2 (CH₂), 18.6 (CH₃), 18.3 (CH₂), 18.2 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₄H₂₄O 208.1827, found 208.1804.

![4a-Hydroxy-1-methyl-decahydro-naphthalene-1-carbaldehyde](image)

(4.13)

A solution of 4.11 (20 mg, 0.10 mmol) in 2 mL of CH₂Cl₂ in a round-bottom flask was saturated with oxygen at rt. The contents were then cooled to −78 °C and bubbled with ozone. After 10 min a flow of ozone was discontinued, followed by bubbling of argon for 10 min and addition of DMS (0.04 mL, 0.48 mmol) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, warmed to rt and stirred for 0.5 h under argon. The solution was concentrated under reduced pressure and purified by flash chromatography on silica gel (20 % EtOAc in hexanes) to afford aldehyde 4.13 (6.1 mg, 32%) as a clear oil and acid 4.14 (8.7 mg, 43%) as a white solid. IR (cm⁻¹, neat) 3529 (m), 2930 (s), 2853 (s), 2965
(w), 1719 (s), 1448 (m), 951 (s); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 9.25 (s, 1H), 1.95-1.06 (m, 19H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 207.2 (C$_4$), 70.7 (C$_4$), 49.8 (C$_4$), 44.8 (CH), 42.0 (CH$_2$), 40.4 (CH$_2$), 33.3 (CH$_2$), 26.8 (CH$_2$), 24.2 (CH$_2$), 21.9 (CH$_2$), 16.9 (CH$_2$), 14.5 (CH$_3$); HRMS (EI), m/z calculated for C$_{12}$H$_{20}$O$_2$ 196.1443, found 196.1458.

\[
\text{4a-Hydroxy-1-methyl-decahydro-naphthalene-1-carboxylic acid (4.12)}
\]

IR (cm$^{-1}$, neat) 3422 (bm), 2930 (s), 2856 (m), 1694 (s), 1445 (m), 1166 (m), 948 (m); $^1$H NMR (300 MHz, CDCl$_3$), $\delta_{ppm}$ 1.91-1.64 (m, 5H), 1.58-1.22 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta_{ppm}$ 185.6 (C$_4$), 71.3 (C$_4$), 47.0 (C$_4$), 46.9 (CH), 42.1 (CH$_2$), 40.4 (CH$_2$), 37.7 (CH$_2$), 26.9 (CH$_2$), 24.4 (CH$_2$), 21.9 (CH$_2$), 17.7 (CH$_2$), 16.4 (CH$_3$); HRMS (EI), m/z calculated for C$_{12}$H$_{20}$O$_3$ 212.1412, found 212.1417; mp = 137-140 °C.

\[
\text{E-3-Bromo-but-2-en-1-ol (4.6)}
\]

1. To a solution of crotyl alcohol (2 mL, 0.023 mol) in 115 mL of CHCl$_3$ at $-10$ °C (acetone-ice bath) was added dropwise Br$_2$ (1.17 mL, 0.023 mol). After stirring for 1.5 h the reaction was quenched with a saturated aqueous solution of Na$_2$SO$_3$. The aqueous phase was extracted with CH$_2$Cl$_2$ 3 x 10 mL. The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The brominated crotyl alcohol was used in the next step without purification.

2. To a solution of DIPA (8.38 mL, 0.06 mol) in 80 mL of THF at $-78$ °C was added dropwise n-BuLi (20 mL, 1.7 M in pentane, 0.05 mol) followed by addition of HMPA (2 mL, 0.01 mol), freshly distilled twice over CaH$_2$. A solution of the brominated crotyl alcohol
(4.64 g, 0.02 mol) in 20 mL of THF was then added to the reaction mixture with a syringe pump over 1.5 h. After stirring for additional 1 h the reaction was quenched with H₂O at -78 °C. The aqueous phase was extracted with EtOAc 4 x 100 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded 4.6 (1.27 g, 37% over 2 steps) as a yellow oil. The spectroscopic data was in accord with that reported in literature.¹⁰

\[
\text{E-(3-Bromo-but-2-enyloxy)-tert-butyl-diphenyl-silane (4.7)}
\]

To a solution of 4.6 (131 mg, 0.87 mmol) in 5 mL of THF was added imidazole (178 mg, 2.62 mmol) followed by addition of TBDPSCI (0.34 mL, 1.31 mmol). Formation of white precipitate was immediately observed. The mixture was stirred for 1 h at rt and quenched with brine. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) gave 4.7 (294 mg, 87 %) as a yellowish oil.¹¹

\[
\text{1-[6-(tert-Butyl-diphenyl-silyl oxy)-4-methyl-hex-4-}
\text{enyl]-1-methyl-octahydro-naphthalen-4a-ol (4.19)}
\]

This reaction was performed using procedure developed by Ohba et al.¹² To a solution of 9-BBN-dimer (35 mg, 0.02)


0.14 mmol) in 0.3 mL of THF was added dropwise a solution of 4.2 (20 mg, 0.10 mmol) in 0.12 mL of THF and the mixture was refluxed for 1 h 20 min. In a separate flask were placed Cs₂CO₃ (56 mg, 0.17 mmol), 10% mol of Pd(dpdpf)Cl₂¹³ (7 mg), 10% mol of Ph₃As (3 mg), vinyl bromide 4.7 (52 mg, 0.13 mmol), DMF (0.24 mL) and H₂O (0.02 mL, 12 equiv mol). To this mixture was transferred by cannula the THF solution of the borane at rt. Resulting red suspension was stirred for 3 h and poured into H₂O (1 mL). The aqueous phase was extracted with Et₂O 3 x 3 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded product 4.19 (236 mg, 48%) as a clear oil. Yields varied from 48% to 65%. IR (cm⁻¹, neat) 3578 (w), 3490 (w), 3071 (w), 3049 (w), 2997 (w), 2932 (s), 1960 (w), 1897 (w), 1822 (w), 1669 (w), 1589 (w), 1472 (m), 1462 (m), 1428 (m); ¹H NMR (300 MHz, CDCl₃), δppm 7.69-7.66 (m, 4H), 7.43-7.33 (m, 6H), 5.34 (t, J = 6.3 Hz, 1H), 4.20 (d, J = 6.3 Hz, 2H), 1.91-1.86 (m, 2H), 1.83-1.73 (m, 2H), 1.58-1.03 (m, 21H), 1.03 (s, 9H), 0.93 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), δppm 137.7 (C₄), 136.0 (CH) x 4, 134.4 (C₄) x 2, 129.7 (CH) x 4, 127.9 (CH) x 2, 124.3 (CH), 72.0 (C₄), 61.5 (CH₂), 49.7 (CH), 43.1 (CH₂), 42.3 (CH₂), 41.1 (CH₂), 40.6 (CH₂), 38.2 (CH₂), 35.6 (C₄), 27.3 (CH₂), 27.2 (CH₃) x 3, 22.1 (CH₂), 21.8 (CH₂), 21.3 (CH₂), 21.1 (CH), 19.6 (C₄), 18.3 (CH₂), 16.6 (CH₃); HRMS (EI), m/z (M⁺-C₄H₉) calculated for C₃₀H₄₁O₂Si 461.2876, found 461.2849.

1-(6-Hydroxy-4-methyl-hex-4-enyl)-1-methyl-octahydro-naphthalen-4a-ol (4.20)

To a solution of 4.19 (202 mg, 0.39 mmol) in 5 mL of THF was added TBAF (0.39 mmol, 1.0 M solution in THF, 0.39 mL). The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. Flash chromatography on silica gel (50% EtOAc in hexanes) afforded 4.20 (77 mg, 82%) as a clear oil, which eventually solidified in the freezer. IR (cm⁻¹, neat) 3380 (bs), 2933 (s), 2865 (s), 2848 (s), 1447 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 5.52 (t, J = 6.7 Hz, 1H), 4.10 (d, J = 6.7 Hz, 2H), 1.90 (t, J = 7.5 Hz, 2H), 1.85-1.71 (m, 2H), 1.61 (s, 3H), 1.61-0.94 (m, 19H), 0.89 (s, 3H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 40.2 (C₄), 123.7 (CH), 72.0 (C₄), 59.7 (CH₂), 49.4 (CH), 43.2 (CH₂), 42.3 (CH₂), 41.0 (CH₂), 40.7 (CH₂), 38.1 (CH₂), 35.7 (C₄), 27.3 (CH₂), 22.1 (CH₂), 21.8 (CH₂), 21.5 (CH₂), 21.2 (CH₃), 18.26 (CH₂), 16.6 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₈H₃₂O₂ 280.2402, found 280.2386.

[1-(2-Iodo-ethyl)-1-methyl-octahydro-naphthalen-4a-yloxy]-trimethyl-silane (4.10)

To a solution of 4.9 (27 mg, 0.07 mmol) in acetone (2 mL) was added NaI (131 mg, 0.88 mmol). The mixture was stirred for 3 d. The white precipitate was then removed by filtering through celite. The obtained filtrate was concentrated under reduced pressure. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded 4.10 (32 mg, 67%) as a yellowish oil. IR (cm⁻¹, neat) 2935 (s), 2851 (m), 1446 (m), 1260 (m), 1059 (s), 1029 (s), 836 (s); ¹H NMR (300 MHz, CDCl₃), δ ppm 3.18-3.02 (m, 2H), 1.93-1.10 (m, 16H), 0.89-0.81 (m, 4H), 0.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 75.3
(C₄), 51.0 (CH), 49.0 (CH₂), 41.1 (CH₂), 40.1 (CH₂), 38.7 (C₄), 37.5 (CH₂), 27.2 (CH₂), 21.9 (CH₂), 21.5 (CH₂), 19.8 (CH₃), 17.9 (CH₂), 2.5 (CH₃) x 3, 2.1 (CH₂); HRMS (EI), m/z (M⁺) calculated for C₁₆H₃₁OSil 394.1189, found 394.1174.

6.5. Spectroscopic data for Chapter 5

![Diagram of Tributyl-(1-phenyl-propenyl)-stannane (5.22)]

**Tributyl-(1-phenyl-propenyl)-stannane (5.22)**

Vinyl stannane 5.22 was prepared according to a procedure reported in literature.¹⁴

To a suspension of PdCl₂(PPh₃)₂ (56 mg, 0.08 mmol) in 12 mL of THF was added 1-phenyl-1-propyne (0.50 mL, 3.90 mmol). The mixture was stirred for 2 min followed by dropwise addition of Bu₃SnH (0.11 mL, 4.68 mmol) upon which the color of reaction mixture changed from green to dark brown. The solution was stirred for 10 min and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pure hexanes) afforded tributyl-(1-phenyl-propenyl)-stannane 5.22 (848 mg, 53%) as a yellowish oil. The spectroscopic data was in accord with that reported in the original paper.

![Diagram of (1-Iodo-propenyl)-benzene (5.23)]

**(1-Iodo-propenyl)-benzene (5.23)**

To a solution of vinyl stannane 5.22 (640 mg, 1.57 mmol) in 10 mL of CH₂Cl₂ was added in portions I₂ (164 mg, 1.57 mmol). The mixture was stirred for 10 min and quenched with a saturated aqueous solution of NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ 2 x 20 mL. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure (Note: the compound is light and temperature sensitive, the flask must be protected from light). Purification by flash chromatography on

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silica gel (pure hexanes) afforded vinyl iodide 2.23 (242 mg, 63%). The spectroscopic data was in accord with that reported in the literature.\textsuperscript{15}

\[
\text{1-Iodo-1-phenyl-1-pentene (5.24)}
\]

Vinyl iodide 5.24 was prepared using a procedure reported by Suzuki \textit{et al.}\textsuperscript{16}

To a solution of B-I-9-BBN (7.5 mL, 1 M in CH\textsubscript{2}Cl\textsubscript{2}, 7.50 mmol) in 60 mL of CH\textsubscript{2}Cl\textsubscript{2} at 0 °C was added dropwise 1-phenyl-1-pentyne (1 mL, 0.06 mmol). The mixture was warmed to rt over 15 h. The reaction was quenched with 7.5 mL of AcOH and stirred for 1 h, then a 3 N aqueous solution of NaOH (90 mL) and a 30% aqueous solution of H\textsubscript{2}O\textsubscript{2} were slowly added at 0 °C. The emulsion was stirred for 30 min at 0 °C. The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} 3 x 60 mL. The combined organic extracts were washed with H\textsubscript{2}O, a saturated aqueous solution of NaHCO\textsubscript{3} and again H\textsubscript{2}O, dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded vinyl iodide 5.24 (1.398 g, 83%) as a yellow oil.

\[
\text{1-(4-Methyl-2-trimethylsilanyloxy-cyclohex-3-enyl)-ethanone (5.17)}
\]

To a solution of diene 5.16 (4.22 g, 0.027 mol) in 3 mL of toluene was added methyl vinyl ketone (2.5 mL, 0.030 mol) previously dried over CaCl\textsubscript{2} and distilled under reduced pressure. The mixture was refluxed for 26 h, cooled to rt and concentrated under reduced pressure. Purification by flash chromatography on silica gel


pretreated with Et$_3$N (10% EtOAc in hexanes) afforded product 5.17 (4.48 g, 76%) as a yellow oil. The spectroscopic data was in accord with that reported in literature.$^{17}$

(6-Isopropenyl-3-methyl-cyclohex-2-enyloxy)-trimethyl-silane (5.18)

To a suspension of Ph$_3$P$^+$CH$_3$I (18.85 g, 0.047 mol) in 60 mL at $-78 \, ^\circ$C was added dropwise $n$-BuLi (11.2 mL, 2.6 M in pentane, 0.030 mol). The reaction was stirred for 1 h at $-78 \, ^\circ$C, then a dry-ice bath was removed and the mixture was stirred for 40 min at rt. The suspension was cooled to $-78 \, ^\circ$C and a solution of 5.17 (2.61 g, 0.012 mol) in 5 mL of THF was transferred by cannula and stirred for 30 min at $-78 \, ^\circ$C. The bath was removed and the mixture was stirred overnight. The reaction was quenched with a 1:1 mixture of Et$_2$O/H$_2$O (300 mL). The aqueous fraction was extracted with Et$_2$O x 100 mL. The combined organic extracts were diluted with hexanes, filtered through a pad of Celite and concentrated under reduced pressure. The crude mixture was used for the oxidation without further purification.

6-Isopropenyl-3-methyl-cyclohex-2-enone (5.14)

To a solution of crude 5.18 (2.64 g, 0.012 mol) in 50 mL of Et$_2$O at 0 $^\circ$C was added dropwise Jones reagent (8 mL, 2.16 M, 0.018 mmol). The mixture was stirred at room temperature for 2 h and quenched with H$_2$O. The aqueous layer was extracted with Et$_2$O 3 x 100 mL. The combined organic layers were washed with a 5 % aqueous solution of KOH x 50 mL and brine x 50 mL, dried with MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography (10 % EtOAc in hexanes)

$^{17}$Friedrick, D.; Bohlmann, F. Tetrahedron 1988, 44, 13697.
afforded 5.14 (1.48 g, 71%) as a yellow oil. The spectroscopic data was in accord with that reported in literature.\textsuperscript{17}

\begin{center}
\textbf{6-Isopropenyl-3-methyl-1-(1-phenyl-vinyl)-cyclohex-2-enol (5.19)}
\end{center}

To a solution of $\alpha$-bromostyrene (0.16 mL, 1.20 mmol) in 5 mL of Et\textsubscript{2}O at $-90$ °C was added a solution of $t$-BuLi (1.80 mL, 1.3 M in pentane, 2.40 mmol). The mixture was stirred for 45 min at $-90$ °C. A solution of ketone 5.14 (100 mg, 0.67 mmol) in 2 mL of Et\textsubscript{2}O was transferred by cannula and the mixture was warmed to $-78$ °C. The reaction was quenched with a saturated aqueous solution of NH\textsubscript{4}Cl. The aqueous phase was extracted with EtOAc 3 x 10 mL. The combined organic extracts were dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The spectroscopic data was identical to that previously reported in our lab.

\begin{center}
\textbf{(+)-6-Isopropenyl-3-methyl-1-(1-methyl-propenyl)-cyclohex-2-enol (5.20)}
\end{center}

To a solution of cis-2-bromobutene (0.34 mL, 3.34 mmol) in Et\textsubscript{2}O (17 mL) at $-78$ °C was added dropwise a solution of $t$-BuLi (3.73 mL, 1.7 M in pentane, 6.35 mmol). The mixture was stirred for 2 h at $-78$ °C, then a solution of ketone (+)-5.14 (250 mg, 1.67 mmol) in Et\textsubscript{2}O (2 mL) was transferred by cannula to the solution of the lithiated compound. The resulting mixture was stirred for 15 min followed by quenching with H\textsubscript{2}O at $-78$ °C. The mixture was extracted with Et\textsubscript{2}O 3 x 20 mL. The combined organic layers were dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in hexanes) on silica gel pretreated with Et\textsubscript{3}N to give product 5.20 (278 mg, 81%) as a yellowish oil. IR (cm\textsuperscript{-1}, neat) 3546 (bm), 3086 (w), 2969 (s), 2931
6-Isopropenyl-3-methyl-1-(1-phenyl-propenyl)-cyclohex-2-enol (5.21)

To a solution of E-1-iodo-1-phenyl-1-propene 2.23 (242 mg, 0.99 mmol) in 
Et₂O (5 mL) at −90 °C was added dropwise a solution of i-BuLi (1.02 mL, 
1.7 M in pentane, 1.74 mmol). The resulting solution was stirred for 1 h at −90 °C (a reaction 
flask was covered with aluminum foil to protect it from light). Then a solution of ketone 
5.14 (37 mg, 0.25 mmol) in Et₂O (1 mL) at −90 °C was transferred by cannula and the 
mixture was gradually warmed to −60 °C. The solution was cooled to −90 °C and quenched 
with H₂O. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic 
fractions were washed with brine, dried over MgSO₄ and concentrated under reduced 
pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) 
afforded product 5.21 (40 mg, 61%) as a yellow oil. IR (cm⁻¹, neat) 3524 (m), 2307 (m), 
3053 (m), 2929 (s), 2859 (s), 1950 (w), 1885 (w), 1808 (w), 1667 (w), 1636 (m), 1599 (w), 
1492 (m), 1440 (s), 1075 (s); ¹H NMR (300 MHz, C₆D₆), δppm 7.31-7.29 (m, 2H), 7.21-7.15 
(m, 2H), 7.11-7.02 (m, 1H), 6.22 (q, J = 6.9 Hz, 1H), 5.51 (bs, 1H), 4.98-4.96 (m, 2H), 2.35 
(dd, J = 2.9 Hz, J = 11.8 Hz, 1H), 1.86-1.73 (m, 4H), 1.68-1.42 (m, 10H); ¹³C NMR (75
MHz, C₆D₆), δ ppm 147.3 (C₄), 147.3 (C₄), 139.9 (C₄), 136.7 (C₄), 130.7 (CH) x 2, 129.6 (CH), 127.8 (CH) x 2, 126.8 (CH), 122.6 (CH), 113.5 (CH₂), 75.3 (C₄), 48.6 (CH), 30.4 (CH₂), 25.3 (CH₂), 23.9 (CH₃), 23.5 (CH₃), 15.1 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₉H₂₄O 268.1827, found 268.1824.

10-Ethyl-3,7-dimethyl-10-phenyl-cyclodeca-2,6-dienone (5.25)

To a solution of alcohol 5.19 (15 mg, 0.06 mmol) in DME (2 mL) was transferred by cannula a solution of KHMDS (59 mg, 0.30 mmol) in DME (1 mL) at rt. The resulting yellow solution was heated (oil bath, 90 °C) for 40 min. During the reflux, the reaction color changed to red-orange. The solution was then cooled to −78 °C (Note: the condenser was left on the flask) followed by addition of EtI (0.02 mL, 0.30 mmol) freshly distilled form CaH₂. The solution was stirred for 2 h at −78 °C and quenched with a saturated aqueous solution of NH₄Cl at −78 °C. The mixture was extracted with Et₂O 3 x 5 mL. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to give ketone 5.25 (16.4 mg, 98%) as a yellow oil. IR (cm⁻¹, neat) 3055 (w), 3020 (w), 2965 (s), 2935 (s), 2872 (m), 1677 (s), 1619 (s), 1493 (w), 1444 (m); ¹H NMR (300 MHz, CDCl₃), δ ppm 7.32-7.17 (m, 5H), 5.65 (s, 1H), 4.87 (m, 1H), 3.30 (ddd, J = 4.5 Hz, J = 12.3 Hz, J = 12.3 Hz, 1H), 2.38-1.76 (m, 9H), 1.69 (s, 3H), 1.45 (s, 3H), 0.48 (t, J = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃), δ ppm 206.5 (C₄), 149.5 (C₄), 142.7 (C₄), 139.2 (C₄), 128.8 (CH) x 2, 127.2 (CH) x 2, 126.9 (CH) x 2, 126.3 (CH), 58.0 (C₄), 35.0 (CH₂), 30.8 (CH₂), 30.3 (CH₂), 26.6 (CH₂), 26.1 (CH₂), 25.9 (CH₃), 16.2 (CH₃), 7.6 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₂₀H₂₆O 282.1984, found 282.1987.

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2-isopropenyl-5-methyl-cyclohexanone (5.26)

1. To a suspension of (±)-citronelal (2.94 g, 13.80 mmol) and dried molecular sieves (3.2 mm, 1.38 g) in 150 mL of CH₂Cl₂ was added dropwise a solution of SnCl₄ (1.38 mL, 1 M in CH₂Cl₂, 1.38 mmol). The mixture was stirred for 1 h at -78 °C and quenched with a saturated aqueous solution of NH₄Cl. The resulting emulsion was stirred for 1 h at rt. The aqueous phase was extracted with CH₂Cl₂ 4 x 200 mL. Purification by flash chromatography on silica gel (15% EtOAc in hexanes) afforded a mixture of axial and equatorial alcohols (1.48 g, 70% combined yield).

2. To a solution of a diastereomeric mixture of alcohols from part 1 (5.20 g, 33.7 mmol) in 100 mL of Et₂O at 0 °C was added dropwise Jones reagent (23.0 mL, 3.0 M, 67.4 mmol). The reaction was stirred at room temperature for 5 min, then 3.0 mL of Jones reagent (8.9 mmol) were added. The mixture was stirred at rt for 3 hours and quenched with H₂O. The aqueous layer was extracted with Et₂O 3 x 150 mL. The combined organic layers were washed with a 5% aqueous solution of KOH x 70 mL and brine, dried with MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (5 to 10 % EtOAc in hexanes) afforded 5.26 (2.58 g, 50%, a yellow oil) as a single diastereomer. The spectroscopic data was identical to that reported in literature.¹⁸

2-Isopropenyl-5-methyl-1-(1-phenyl-vinyl)-cyclohexanol (5.29)

To a solution of α-bromostyrene (0.34 mL, 2.64 mmol) in Et₂O (10 mL) at -90 °C was added dropwise a solution of t-BuLi (2.5 mL, 1.7 M in pentane, 4.21 mmol). The resulting mixture was stirred for 1 h 20 min at -90 °C (a reaction

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flask was covered with aluminum foil to protect it from light). A solution of ketone 5.29 (100 mg, 0.66 mmol) in Et₂O (1 mL) was transferred by cannula and the mixture was warmed to −60 °C. The solution was then cooled to −90 °C and quenched with H₂O. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic fractions were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (5 % EtOAc in hexanes) afforded product 5.30 (122.5 mg, 73%) as a yellow oil. IR (cm⁻¹, neat) 3561 (bm), 3476 (bm), 3079 (w), 2984 (s), 2924 (s), 2867 (w), 2843 (w), 1636 (m), 1597 (w), 1571 (w), 1491 (m), 1454 (m), 1441 (m); ¹H NMR (300 MHz, C₆D₆), δ ppm 7.35-7.32 (m, 2H), 7.17-7.05 (m, 3H), 5.34 (d, J = 1.6 Hz, 1H), 5.03 (d, J = 1.6 Hz, 1H), 4.93-4.91 (m, 2H), 2.25 (dd, J = 3.5 Hz, J = 12.9 Hz, 1H), 2.00-1.69 (m, 5H), 1.64-1.44 (m, 3H), 1.32-1.23 (m, 2H), 0.80-0.66 (m, 1H), 0.76 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆), δ ppm 157.4 (C₄), 148.4 (C₄), 142.4 (C₄), 129.3 (CH) x 2, 127.6 (CH) x 2, 127.3 (CH), 114.3 (CH₂), 113.5 (CH₂), 76.8 (C₄), 51.5 (CH), 49.4 (CH₂), 35.1 (CH₂), 28.8 (CH₂), 27.8 (CH₃), 23.9 (CH₃), 22.5 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₈H₂₄O 256.1827, found 256.1831.

![5,9-Dimethyl-2-phenyl-cyclodec-5-enone (5.30)](image)

5,9-Dimethyl-2-phenyl-cyclodec-5-enone (5.30)

Compound 5.30 was isolated as a side product during the studies on the oxy-Cope/alkylation reaction of alcohol 5.29. IR (cm⁻¹, neat) 2947 (m), 2928 (m), 1692 (s), 1595 (w), 1492 (m), 1454 (m), 1433 (m), 1418 (m), 1096 (m); ¹H NMR (300 MHz, C₆D₆), δ ppm 7.28-7.26 (m, 2H), 7.23-7.01 (m, 3H), 5.03-5.00 (m, 1H), 3.29-3.25 (m, 1H), 2.85 (ddd, J = 3.4 Hz, J = 12.8 Hz, J = 16.3 Hz, 1H), 2.32-2.23 (m, 1H), 2.19-2.01 (m, 2H), 1.97-1.77 (m, 4H), 1.61-1.49 (m, 5H), 1.07-0.84 (m, 1H), 0.64 (d, J = 7.0 Hz, 3H); ¹³C NMR (75
MHz, C₆D₆), δppm 205.7 (C₄), 141.0 (C₄), 138.6 (C₄), 129.0 (CH) x 2, 128.4 (CH) x 2, 127.1 (CH), 126.6 (CH), 61.4 (CH), 52.3 (CH₂), 41.4 (CH₂), 38.3 (CH₂), 35.6 (CH₂), 28.9 (CH), 27.9 (CH₂), 24.8 (CH₃), 16.3 (CH₃); HRMS (EI), m/z (M⁺) calculated for C₁₈H₂₄O 256.1827, observed degradation, no M⁺ detected.

2-Ethyl-5,9-dimethyl-2-phenyl-cyclodec-5-enone (5.31)

To a solution of alcohol 5.29 (157 mg, 0.61 mmol) in DME (5 mL) was transferred by cannula a solution of KHMDS (245 mg, 1.22 mmol) in DME (5 mL) at rt. The resulting yellow solution was heated in the oil bath at 90 °C for 15 min. During the reflux, the reaction color changed to orange. The reaction flask was then cooled to –78 °C followed by addition of EtI (0.06 mL, 0.73 mmol) freshly distilled from CaH₂. The solution was stirred for 2 hours at –78 °C and quenched with H₂O at –78 °C. The aqueous phase was extracted with Et₂O 3 x 10 mL. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give 5.31 (83 mg, 48 %) as a yellow oil, dialkylated compound 5.32 (9.1 mg, 5%) as a yellow oil and their 1:1 mixture (16.2 mg) in combined yield of 62 %. IR (cm⁻¹, neat) 3085 (w), 3059 (w), 3024 (w), 2952 (s), 2929 (s), 2867 (m), 1954 (w), 1866 (w), 1801 (w), 1696 (s), 1598 (w), 1498 (w), 1445 (m); ¹H NMR (300 MHz, C₆D₆), δppm 7.23-7.20 (m, 2H), 7.14-7.11 (m, 2H), 7.05-7.01 (m, 1H), 5.12-5.10 (m, 1H), 2.98-2.85 (m, 2H), 2.27-1.81 (m, 8H), 1.62-1.60 (m, 4H), 1.15-0.88 (m, 2H), 0.78 (d, J = 7.1 Hz, 3H), 0.57 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, C₆D₆), δppm 208.8 (C₄), 144.7 (C₄), 137.7 (C₄), 128.4 (CH) x 2, 128.0 (CH) x 2, 127.0 (CH), 126.4 (CH), 57.0 (C₄), 47.8 (CH₂), 38.2 (CH₂), 35.8 (CH₂), 33.0 (CH₂), 28.0 (CH), 27.9 (CH₂), 25.2
(CH$_3$), 25.2 (CH$_2$), 16.5 (CH$_3$), 8.2 (CH$_3$); HRMS (EI), m/z (M$^+$) calculated for C$_{20}$H$_{28}$O$_2$ 284.2140, observed degradation, no M$^+$ detected.

2,10-Diethyl-5,9-dimethyl-2-phenyl-cyclodec-5-enone (5.32)

IR (cm$^{-1}$, neat) 3093 (w), 3056 (w), 3020 (w), 2970 (s), 2936 (s), 2880 (m), 2859 (m), 1941 (w), 1877 (w), 1838 (w), 1806 (w), 1690 (s), 1598 (w), 1580 (w), 1498 (w), 1475 (m), 1445 (m); $^1$H NMR (300 MHz, CD$_2$Cl$_2$), $\delta$ ppm 7.56-7.54 (m, 2H), 7.15-7.12 (m, 2H), 7.04-6.97 (m, 1H), 5.33-5.28 (m, 1H), 3.16-3.02 (m, 1H), 2.74-2.65 (m, 1H), 2.42-2.02 (m, 6H), 1.93-1.83 (m, 1H), 1.75-1.61 (m, 4H), 1.55-1.47 (m, 1H), 1.55-1.47 (m, 1H), 1.44-1.26 (m, 2H), 1.25-1.11 (m, 1H), 0.86-0.77 (m, 6H), 0.19 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ ppm 211.9 (C$_4$), 142.5 (C$_4$), 138.8 (C$_4$), 128.2 (CH) x 2, 128.1 (CH) x 2, 126.3 (CH), 125.8 (CH), 56.9 (C$_4$), 53.2 (CH), 36.8 (CH$_2$), 36.1 (CH$_2$), 32.0 (CH), 29.9 (CH$_3$), 23.0 (CH$_2$), 22.0 (CH$_2$), 21.0 (CH$_2$), 18.7 (CH$_2$), 17.1 (CH$_3$), 14.5 (CH$_3$), 8.7 (CH$_3$); HRMS (EI), m/z (M$^+$) degradation observed, no M$^+$ detected.

1,2-Diisopropenyl-5-methyl-cyclohexanol (5.33)

Anhydrous CeCl$_3$ (210 mg, 0.85 mmol) was suspended in 4 mL THF and stirred for 1 h. A solution of ketone 5.26 in 1 mL of THF pre-cooled to 0 °C was transferred by cannula into the suspension and cooled to 0 °C. Isopropenyl magnesium bromide (4 mL, 2.0 M solution in THF, 2.00 mmol) was added slowly and the reaction was allowed to warm to rt. After 3 h the reaction was quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous phase was extracted with EtOAc 3 x 5 mL. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography
(2% EtOAc in hexanes) on silica gel afforded compound 5.33 (76 mg, 92 %) as a colorless oil. The spectroscopic data was identical to that previously reported in our lab.\textsuperscript{19}

CLAIMS TO ORIGINAL RESEARCH

1. Solved two major challenges encountered during the synthesis of (±)-agelasimine A: formation of the quaternary center at C9 and control of the selectivity at C8.

2. Developed the novel highly diastereoselective tandem oxy-Cope/ene/Claisen reaction as a general method for construction of trans-decalines with a quaternary center at C9.

3. Studied in detail the scope and limitations of the new tandem process.

4. Investigated the effect of substituents on the diastereoselectivity of the oxy-Cope/ene reaction.

5. Developed a new approach toward the quaternary centers via the anionic oxy-Cope/alkylation reaction.

PUBLICATIONS AND PRESENTATIONS


Appendix 1

X-Ray Data
Table 1. Crystal data and structure refinement for lb005.

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                          b = 9.296(3) Å  
                          c = 16.278(5) Å  
                          alpha = 90 deg.  
                          beta = 101.88(2) deg.  
                          gamma = 90 deg. |
| Volume              | 1583.5(8) Å³ |
| Z, Calculated density | 4, 1.243 Mg/m³ |
| Absorption coefficient | 0.078 mm⁻¹ |
| F(000)              | 640 |
| Crystal size        | 0.1 x 0.1 x 0.1 mm |
| Theta range for data collection | 2.10 to 23.25 deg. |
| Limiting indices    | -10<=h<=11, 0<=k<=10, 0<=l<=18 |
| Reflections collected / unique | 4486 / 2142 [R(int) = 0.0472] |
| Completeness to theta = 23.25 | 94.3 % |
| Absorption correction | None |
| Refinement method   | Full-matrix least-squares on F² |
| Data / restraints / parameters | 2142 / 0 / 199 |
| Goodness-of-fit on F² | 1.010 |
| Final R indices [I>2sigma(I)] | R1 = 0.0482, wR2 = 0.0979 |
| R indices (all data) | R1 = 0.0975, wR2 = 0.1112 |
| Largest diff. peak and hole | 0.165 and -0.223 eÅ⁻³ |
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for 1b005. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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Table 3. Bond lengths [Å] and angles [deg] for lb005.

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å^2 x 10^{-3}) for 1b005. The anisotropic displacement factor exponent takes the form: 
\[ -2 \pi^2 [ h^2 a^*^2 U11 + \ldots + 2 h k a^* b^* U12 ] \]

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Table 5. Hydrogen coordinates (x \times 10^{-4}) and isotropic displacement parameters (\AA^2 \times 10^{-3}) for lb005.

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Table 6. Torsion angles [deg] for 1b005.

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C(13)-C(12)-C(20)-C(15)  51.5(4)
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Symmetry transformations used to generate equivalent atoms:
Table 1. Crystal data and structure refinement for 1b006.

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<td>b = 10.9953(8) Å   beta = 100.36(2) deg</td>
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<td>Reflections collected / unique</td>
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<tr>
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Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^{-3}$) for 1b006. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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Table 3. Bond lengths [Å] and angles [deg] for lb006.

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O(2) - C(18) - C(10)  127.8(3)
O(1) - C(18) - C(10)  107.6(3)

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å^2 x 10^-3) for 1b006. The anisotropic displacement factor exponent takes the form:
\[-2 \pi^2 \left( \sum_{i,j} a_{ij} U_{ij} \right) \]

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<td>C(1) - C(6) - C(10) - C(11)</td>
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<tr>
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<td></td>
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<tr>
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<td>C(5) - C(6) - C(10) - C(18)</td>
<td>-42.5 (3)</td>
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<tr>
<td>C(9) - C(10) - C(11) - C(16)</td>
<td>59.7 (3)</td>
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<td></td>
</tr>
<tr>
<td>C(6) - C(10) - C(11) - C(16)</td>
<td>-69.2 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(18) - C(10) - C(11) - C(16)</td>
<td>174.7 (3)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C(9) - C(10) - C(11) - C(12)</td>
<td>-171.1 (2)</td>
<td></td>
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<tr>
<td>C(6) - C(10) - C(11) - C(12)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>C(18) - C(10) - C(11) - C(12)</td>
<td>-56.2 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(16) - C(11) - C(12) - C(13)</td>
<td>-62.8 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(10) - C(11) - C(12) - C(13)</td>
<td>163.2 (3)</td>
<td></td>
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</tr>
<tr>
<td>C(11) - C(12) - C(13) - C(14)</td>
<td>59.7 (3)</td>
<td></td>
<td></td>
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<tr>
<td>C(12) - C(13) - C(14) - C(15)</td>
<td>-54.5 (4)</td>
<td></td>
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</tr>
<tr>
<td>C(13) - C(14) - C(15) - C(16)</td>
<td>54.5 (4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C(14) - C(15) - C(16) - C(17)</td>
<td>117.3 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(14) - C(15) - C(16) - C(11)</td>
<td>-59.0 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(12) - C(11) - C(16) - C(17)</td>
<td>-113.8 (4)</td>
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<td></td>
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<tr>
<td>C(10) - C(11) - C(16) - C(17)</td>
<td>20.6 (5)</td>
<td></td>
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<tr>
<td>C(12) - C(11) - C(16) - C(15)</td>
<td>62.4 (3)</td>
<td></td>
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<tr>
<td>C(10) - C(11) - C(16) - C(15)</td>
<td>-163.3 (3)</td>
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<td>C(5) - O(1) - C(18) - O(2)</td>
<td>-173.9 (3)</td>
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<td>C(5) - O(1) - C(18) - C(10)</td>
<td>2.2 (3)</td>
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<td></td>
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<td>C(9) - C(10) - C(18) - O(2)</td>
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<td>C(6) - C(10) - C(18) - O(2)</td>
<td>-157.1 (3)</td>
<td></td>
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<tr>
<td>C(11) - C(10) - C(18) - O(2)</td>
<td>-27.1 (4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C(9) - C(10) - C(18) - O(1)</td>
<td>-87.1 (3)</td>
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<td>C(6) - C(10) - C(18) - O(1)</td>
<td>27.0 (3)</td>
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<tr>
<td>C(11) - C(10) - C(18) - O(1)</td>
<td>157.0 (2)</td>
<td></td>
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</tr>
</tbody>
</table>
Appendix 2

2D and NOE NMR Data
Table 1 2D and NOE NMR data for 3.12

<table>
<thead>
<tr>
<th>Irradiated proton</th>
<th>Correlation, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>H (1.6), L (2.4)</td>
</tr>
<tr>
<td>B</td>
<td>G (^a) (1.4), H (4.2), M (4.8)</td>
</tr>
</tbody>
</table>

\(^a\) Chemical shift of a hydroxy proton (G) was determined by addition of D\(_2\)O

<table>
<thead>
<tr>
<th>Proton</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>F, I</td>
</tr>
<tr>
<td>C</td>
<td>F, I, J, K</td>
</tr>
<tr>
<td>A</td>
<td>L, H</td>
</tr>
<tr>
<td>F</td>
<td>I, B, C</td>
</tr>
<tr>
<td>I</td>
<td>F, J, C</td>
</tr>
<tr>
<td>J</td>
<td>K, I, C</td>
</tr>
<tr>
<td>K</td>
<td>I, C</td>
</tr>
<tr>
<td>M</td>
<td>N</td>
</tr>
<tr>
<td>H</td>
<td>L, A</td>
</tr>
<tr>
<td>L</td>
<td>A, H</td>
</tr>
</tbody>
</table>
Table 2 2D and NOE NMR data for 3.16 (Chapter 3, Scheme 3.8)

<table>
<thead>
<tr>
<th>Irradiated proton</th>
<th>Correlation, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>D (8.5), N (5.3)</td>
</tr>
<tr>
<td>F</td>
<td>E (0.7)</td>
</tr>
<tr>
<td>N</td>
<td>G (2.6), C (2.4), B (1.5)</td>
</tr>
<tr>
<td>B</td>
<td>A (6.5), G (3.4)</td>
</tr>
<tr>
<td>A</td>
<td>B (4.6), M (5.6), O (2.6)</td>
</tr>
<tr>
<td>E</td>
<td>F (2.3), H (4.1), K (3.2), L (3.2), O (3.0)</td>
</tr>
<tr>
<td>H</td>
<td>G (4.5), E (4.1), K (2.6), O (5.4)</td>
</tr>
<tr>
<td>G</td>
<td>B (2.8), H (5.0), N (5.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(^{13})C</th>
<th>Proton correlation</th>
<th>Proton</th>
<th>COSY data</th>
</tr>
</thead>
<tbody>
<tr>
<td>106.6</td>
<td>C, D</td>
<td>A</td>
<td>B, G</td>
</tr>
<tr>
<td>55.6 (CH₃)</td>
<td>F</td>
<td>B</td>
<td>A, G</td>
</tr>
<tr>
<td>41.6</td>
<td>I, L</td>
<td>C and D</td>
<td>G, H</td>
</tr>
<tr>
<td>30.0</td>
<td>J, K</td>
<td>I</td>
<td>L, E, O</td>
</tr>
<tr>
<td>25.0 (CH₃)</td>
<td>M</td>
<td>E</td>
<td>I, L, J, K</td>
</tr>
<tr>
<td>24.2 (CH₃)</td>
<td>O</td>
<td>G</td>
<td>N, C, D, A, B</td>
</tr>
<tr>
<td>17.4 (CH₃)</td>
<td>N</td>
<td>H</td>
<td>J, K, C, D</td>
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</tbody>
</table>
Table 3 2D and NOE data for 3.17 (Chapter 3, Scheme 3.8)

<table>
<thead>
<tr>
<th>Irradiated proton</th>
<th>Correlation, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H (1.7), F (1.0), B (0.5)</td>
</tr>
<tr>
<td>H</td>
<td>B (3.6), C (3.4), O (4.5)</td>
</tr>
<tr>
<td>G</td>
<td>E (1.1), K (0.8), L (0.5), M (0.4)</td>
</tr>
<tr>
<td>F</td>
<td>K (2.0), M (5.7), O (3.2)</td>
</tr>
<tr>
<td>E</td>
<td>G (2.5), K (2.0), I (3.5), J (6.0)</td>
</tr>
<tr>
<td>D</td>
<td>C (12.7), I (3.7), K (3.0)</td>
</tr>
<tr>
<td>C</td>
<td>D (13.8), H (3.5)</td>
</tr>
<tr>
<td>B</td>
<td>A (4.3), H (3.2), O (1.9)</td>
</tr>
<tr>
<td>A</td>
<td>B (3.9), M (2.3), N (5.2)</td>
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COSY

<table>
<thead>
<tr>
<th>Proton</th>
<th>Correlation</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>B</td>
<td>A, H</td>
</tr>
<tr>
<td>C</td>
<td>D, F</td>
</tr>
<tr>
<td>D</td>
<td>C, F</td>
</tr>
<tr>
<td>E</td>
<td>I, J, K, L</td>
</tr>
<tr>
<td>F</td>
<td>C, D, I, K</td>
</tr>
<tr>
<td>H</td>
<td>O, B</td>
</tr>
<tr>
<td>I</td>
<td>K, E, F</td>
</tr>
<tr>
<td>J</td>
<td>L, M, E</td>
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Table 4 2D and NOE NMR data for 3.25 (Chapter 3, Scheme 3.11)

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<tbody>
<tr>
<td>Proton</td>
<td>Observed correlation</td>
</tr>
<tr>
<td>F</td>
<td>E, G, H</td>
</tr>
<tr>
<td>E</td>
<td>F, C</td>
</tr>
<tr>
<td>B</td>
<td>C, A</td>
</tr>
<tr>
<td>A</td>
<td>L, M, B</td>
</tr>
<tr>
<td>D</td>
<td>N, C</td>
</tr>
<tr>
<td>N</td>
<td>K, M, G, D</td>
</tr>
<tr>
<td>I</td>
<td>H, J</td>
</tr>
<tr>
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NOE difference data

<table>
<thead>
<tr>
<th>Irradiated proton</th>
<th>Correlation, (%)</th>
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</thead>
<tbody>
<tr>
<td>E</td>
<td>F (4.6), D (2.4), C (2.3)</td>
</tr>
<tr>
<td>D</td>
<td>E (1.6), B (0.4), N (3.5), C (4.4)</td>
</tr>
<tr>
<td>N</td>
<td>D (3.9), M (1.8), G (5.6), K (3.4)</td>
</tr>
<tr>
<td>K</td>
<td>N (2.9), M (2.4), J (2.0), G (2.5)</td>
</tr>
<tr>
<td>C</td>
<td>D (1.6), B (1.5), E (1.0)</td>
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Table 5 COSY and NOE NMR data for 3.42 (Chapter 3, Table 3-1)

![Chemical structure diagram]

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<th>NOE difference data</th>
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<tbody>
<tr>
<td>Irradiated proton</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>A</td>
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<table>
<thead>
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<th>COSY</th>
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<tbody>
<tr>
<td>Proton</td>
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<tr>
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<tr>
<td>O</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
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Table 6 NOE data for 3.43 (Chapter 3, Table 3-1)

![Chemical structure diagram]

<table>
<thead>
<tr>
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<th>Correlation, (%)</th>
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<tbody>
<tr>
<td>D</td>
<td>A (5.6), F (4.0), G (2.6), J (4.0)</td>
</tr>
<tr>
<td>C</td>
<td>E (5.5), J (3.9), F (3.0), phenyl protons (5.9)</td>
</tr>
<tr>
<td>A</td>
<td>B (2.9), D (4.5)</td>
</tr>
<tr>
<td>B</td>
<td>A (13.8), I (6.3)</td>
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</table>

<table>
<thead>
<tr>
<th>HMQC</th>
<th>Proton correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.3 (CH)</td>
<td>C</td>
</tr>
<tr>
<td>45.0 (CH)</td>
<td>E</td>
</tr>
<tr>
<td>39.1 (CH)</td>
<td>D</td>
</tr>
<tr>
<td>37.2 (CH₂)</td>
<td>F+G</td>
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Table 7 COSY and NOE NMR data for 3.51 (Chapter 3, Table 3-2)

![Chemical structure with NOE data points]

<table>
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<th>Irradiated proton</th>
<th>Correlation, (%)</th>
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</thead>
<tbody>
<tr>
<td>D</td>
<td>C (3.5), E (1.8), F (3.7)</td>
</tr>
<tr>
<td>B</td>
<td>A (13.8), I (6.7)</td>
</tr>
<tr>
<td>A</td>
<td>B (11.3), F (4.8)</td>
</tr>
<tr>
<td>D</td>
<td>E (1.8), C (3.5), F (3.7)</td>
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<tr>
<td>E</td>
<td>C (5.3), I (3.3)</td>
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**COSY**

<table>
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<th>Proton</th>
<th>Observed correlation</th>
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<tbody>
<tr>
<td>A</td>
<td>E (small)</td>
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<tr>
<td>B</td>
<td>E</td>
</tr>
<tr>
<td>D</td>
<td>F, G, K</td>
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<tr>
<td>C</td>
<td>G, K</td>
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Table 8 COSY and NOE NMR data for 3.52 (Chapter 3, Table 32)

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<th>(B)</th>
<th>(C)</th>
<th>(D)</th>
<th>(E)</th>
<th>(I)</th>
<th>(J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradiated proton</td>
<td></td>
<td></td>
<td>(A) (12.0), K (3.8), L (2.6)</td>
<td>(G) (3.6), E (2.6), C (3.9), Q (2.5)</td>
<td>(F) (14.0), G (2.9), C (2.0)</td>
<td>(M) (1.3), N (2.0), O (2.0), H (1.0), J (17.0)</td>
<td>(I) (8.0), G (5.0)</td>
</tr>
<tr>
<td>Correlation, (%)</td>
<td>B (11.0), C (5.1)</td>
<td>A (12.0), K (3.8), L (2.6)</td>
<td>(A) (5.0), F (7.0), E (6.0), D (5.3)</td>
<td>(G) (3.6), E (2.6), C (3.9), Q (2.5)</td>
<td>(F) (14.0), G (2.9), C (2.0)</td>
<td>(M) (1.3), N (2.0), O (2.0), H (1.0), J (17.0)</td>
<td>(I) (8.0), G (5.0)</td>
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\(a\) Me group was irradiated together with proton \(H_j\)

---

<table>
<thead>
<tr>
<th>COSY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>G</td>
</tr>
<tr>
<td>E</td>
</tr>
<tr>
<td>D</td>
</tr>
</tbody>
</table>
Table 9 NOE difference, COSY and HMQC data for 2.41 (See Chapter 2)

Chemical Shift for some protons, (500 MHz, C₆D₆), δppm:

Hₐ 5.49 (d, J = 1.5 Hz), Hₖ 1.28-1.35 (m), H₇ 1.52-1.48 (m), Hₚ 3.12-3.07 (m)

<table>
<thead>
<tr>
<th>Irradiated proton</th>
<th>Correlation, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B (4.9), Me (2.5)</td>
</tr>
<tr>
<td>Me and D together</td>
<td>A (1.0), C (1.8)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HMQC data</th>
<th>COSY data</th>
</tr>
</thead>
<tbody>
<tr>
<td>13C (125 MHz, C₆D₆)</td>
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<td>------------</td>
<td>-------------------</td>
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<tr>
<td>141.8</td>
<td>A (CH)</td>
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<tr>
<td>118.7</td>
<td>C₄</td>
</tr>
<tr>
<td>71.1</td>
<td>C₄</td>
</tr>
<tr>
<td>59.4</td>
<td>CH₃ at 3.15 ppm</td>
</tr>
<tr>
<td>47.5</td>
<td>CH</td>
</tr>
<tr>
<td>47.5</td>
<td>CH₂</td>
</tr>
<tr>
<td>40.8</td>
<td>CH₂</td>
</tr>
<tr>
<td>26.9</td>
<td>C and D</td>
</tr>
<tr>
<td>26.7</td>
<td>CH₂</td>
</tr>
<tr>
<td>24.1</td>
<td>CH₂</td>
</tr>
<tr>
<td>23.3</td>
<td>CH₂</td>
</tr>
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<td>22.1</td>
<td>CH₂</td>
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</table>
Appendix 3

$^1$H NMR Spectra
Current Data Parameters
NAME irina_B-67-p
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_  20040511
Time  14:34
INSTRUM av300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD  30720
SOLVENT CDCl3
NS  13
DS  0
SWM  5081.301 Hz
FIDRES  0.165407 Hz
AQ  3.023992 sec
RG  181
DW  98.400 usec
DE  6.000 usec
TE  300.0 K
DI  1.00000000 sec

********** CHANNEL f1 **********
NUC1  1H
Pt  10.500 usec
P1  -3.00 dB
SF01  300.1319477 MHz

F2 - Processing parameters
SI  65536
SF  300.1300000 MHz
MDW  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  7.556 ppm
F1  2276.40 Hz
F2P  0.145 ppm
F2  43.50 Hz
PPNMCH  0.37067 ppm/cm
H2CMH  111.24892 Hz/cm
Current Data Parameters
NAME     irina_7-140
EXPRD    1
PROCESS   1

F2 - Acquisition Parameters
Date_     20031120
Time      12.02
INSTRUM   av300
PROBD     5 mm DNP 1H/1
PULPROG   zg30
TD        30720
SOLVENT   CDCl3
MS        16
DS        0
SNH       5081.301 Hz
FIDRES    0.165407 Hz
AQ        3.028000 sec
RG        203.2
DW        90.000 usec
DE        6.00 usec
TE        300.0 K
DI        1.0000000 sec

********** CHANNEL f1 ************
NUCl      1H
P1        10.50 usec
PL1       -3.00 dB
SF01      300.1319477 MHz

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

1D NMR plot parameters
CX        0.00 cm
CY        10.00 cm
F1P       8.000 ppm
F1        2401.04 Hz
F2P       0.000 ppm
F2        0.00 Hz
PRMCM     0.40000 ppm/cm
HZCM      120.05200 Hz/cm
Current Data Parameters
NAME  irina_16
EXPAND  1
PROCD  1

F2 - Acquisition Parameters
Date_  2001046
Time  18 31
INSTRUM  av300
PROBHD  5 mm GNP TH/1
PULPROG  zg30
TD  30720
SOLVENT  CDC13
NS  16
DS  0
SHM  5081.301 Hz
FIDRES  0.165407 Hz
AD  3.0225800 sec
RG  724 1
OW  98.400 usec
DE  6.00 usec
TE  300.0 K
DI  1.00000000 sec

*********** CHANNEL f1 ***********
NUC1  1H
P1  9.50 usec
PL1  -3.00 dB
SF01  300.1319477 MHz

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

1D NMR plot parameters
CX  20.00 cm
CY  10.00 cm
FP  10.000 ppm
F1  300.130 Hz
FP  0.500 ppm
F2  150.96 Hz
RPMCH  0.47500 ppm/cm
HzCM  142.56175 Hz/cm
Current Data Parameters
NAME: irina lact
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20010716
Time: 14:37
INSTRUM: av300
PROBD: 5 mm QNP 1H/1
PULPROG: zg30
TD: 30720
SOLVENT: CDCl3
NS: 16
DS: 0
SW: 5081.301 Hz
FIDRES: 0.165407 Hz
AQ: 3.0228980 sec
M: 812.7
DW: 98.400 usec
DE: 6.00 usec
TE: 300.0 K
DT: 1.00000000 sec

********** CHANNEL 11 **********
NUCI: 1H
P1: 9.50 usec
PL1: -3.00 dB
SF: 300.1319477 MHz

F2 - Processing parameters
ST: 65536
SF: 300.1300000 MHz
MDF: 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: 14.955 ppm
F1: 4488.35 Hz
F2P: -1.976 ppm
F2: -592.8 Hz
PPMCH: 0.84652 ppm/cm
HZCM: 254.06503 Hz/cm
Current Data Parameters
NAME
EXPNO
PROCNO
F2 - Acquisition Parameters
Date
Time
INSTRM
PHD
PULPROG
TO
SOLVENT
NS
G5
SMN
FIGRES
AG
RG
DW
DE
TE
T1
F2 - Processing Parameters
SI
SF
NDM
SSB
LB
GB
PC
1D NMR plot parameters
CX
CY
F1P
F1
F2P
F2
PPMCH
HzCM
Current Data Parameters
NAME  irina_488
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date  2001/08/17
Time  17:21
INSTRUM  av300
PROBID  5 mm QNP 1H/1
PULPROG  ZG30
TD  30720
SOLVENT  CDCl3
VG  16
DS  0
SWM  5081.301 Hz
F1RES  0.165407 Hz
AQ  3 0229860 sec
RG  228.1
TW  98.440 usec
DE  6.00 usec
TE  300.0 K
DI  1 00000000 sec

************ CHANNEL f1 ************
NUC1  1H
P1  9.50 usec
PL1  3.00 dB
SF01  300.1319477 MHz

F2 - Processing parameters
SI  65536
SF  300 1300000 MHz
NDM  EM
SSB  0
LB  0.10 Hz
GB  0
PC  1.00

10 NMR plot parameters
CXT  20.00 cm
CY  10.00 cm
CF  8.000 ppm
FT  2401.00 Hz
FT  0.000 ppm
FT  0.00 Hz
PANCM  0.40000 ppm/cm
ZCM  120.05200 Hz/cm
Current Data Parameters
NAME   irin3_methyl
EXPNO  3
PROCND 4

F2 - Acquisition Parameters
Date_  20020107
Time  15.36
INSTRUM AV300
PROBD  5 mm GNP 1H/1
PULPROG zg30
TD  30720
SOLVENT CDCl3
NS5  16
DS1  0
SWH  5081.301 Hz
FIDRES  0.165407 Hz
AQ  3.028860 sec
AQG  405.4
DM  98.400 usec
DE  6.00 usec
TE  300.0 K
DT  1.00x00000 sec

********** CHANNEL 1 **********
NUC1  1H
PI  11.00 usec
PL1  -3.00 dB
SPD1  300.1319477 MHz

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

1D NMR plot parameters
CX  20.00 cm
CY  30.00 cm
F1P  8.000 ppm
F1  2401.04 Hz
F2P  0.000 ppm
F2  0.00 Hz
PRMCM  0.40000 ppm/cm
HZCM  120.05200 Hz/cm
Current Data Parameters
NAME: irina_methox
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20020131
Time: 13.00
INSTRM: av300
PROBH: 5 mm QNP 1H/1
PULPROG: zg30
TD: 30720
SOLVENT: C6D6
NS: 16
DS: 0
SMH: 5081.301 Hz
FIDRES: 0.165407 Hz
AQ: 3.0220980 sec
R: 574.7
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: 65536
SF: 300.130000 MHz
WID: 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: 8000 ppm
F1: 2401.04 Hz
F2P: 0.000 ppm
F2: 0.00 Hz
PPWCM: 0.40000 ppm/cm
HZCM: 120.05200 Hz/cm
Current Data Parameters
NAME    iriha_7-63
EXPN    1
PROCNO  1

F2 - Acquisition Parameters
Date_   20030628
Time    12:52
INSTRUM av300
PROBD   5 mm QNP 1H/1
PULPROG zg30
TD      30720
SOLVENT CDC13
NS      16
DS*     0
SNR     5081.30 Hz
FIDRES  0.165407 Hz
AQ      3.0728680 sec
RQ      151.3
DW      98.4000 usec
DE      6.00 usec
TE      300.0 K
DT      1.000000000 sec

*************** CHANNEL f1 ***************
NUC1    1H
P1      10.50 usec
PL1     3.00 db
SF01    300.131947 MHz

F2 - Processing parameters
SI      688886
SF      300.130000 MHz
WDM     EM
SSB     0
LB      0.10 Hz
GB      0
PC      1.00

ID NMR plot parameters
CXX     20.00 cm
CY      10.00 cm
F1P     8.000 ppm
F1      2401.04 Hz
F1P     0.000 ppm
F2      0.00 Hz
DPMCM   0.40000 ppm/cm
-2CM    120.05200 Hz/cm
Current Data Parameters
NAME       ng_7
EXPNO      1
PROCNO     1

F2 - Acquisition Parameters
Date       20930513
Time       17.13
INSTRUM    a300
RSBOH      5 mm GNP
PULPROG    zg30
TD          30720
SOLVENT    CCl13
MS         16
DS         0
SWH        5081.301 Hz
FTOFRES    0.165407 Hz
AQ          3.0228990 sec
RS          287.4
DW         96.400 usec
DE          6.00 usec
TE        300.0 K
DI     1.00000000 sec

************ CHANNEL f1 ************
NUC1       1H
P1          10.50 usec
PL1         -3.00 dB
SF01      300.1319477 MHz

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

ID NMR plot parameters
CX          20.00 cm
CY          10.00 cm
F1P       7.843 ppm
F1     2353.81 Hz
F2P        0.216 ppm
F2     64.88 Hz
PPMCM     0.38132 ppm/cm
HZCM      114.44675 Hz/cm
Current Data Parameters
NAME  irina_B-97-1
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date_  20040510
Time  18:01
INSTRUM  NMR-5001
PROBHD  5 mm BBI 1H-BB
PULPROG  zg30
TD  65536
SOLVENT  Acetone
NS  1
DS  0
SNH  7440.476 Hz
FIDRES  0.113533 Hz
AG  4.4046594 sec
RG  25.4
C0W  67.200 ussec
DE  6.00 ussec
TE  300.0 K
DI  0.00000000 sec

====== CHANNEL f1 ======
NUC1  1H
P1  10.50 ussec
PL1  3.00 dB
SF01  500.1321766 MHz

F2 - Processing parameters
SI  65536
SF  500.130049 MHz
NON  EM
SSB  0
LB  0.00 Hz
GB  0
PC  1.00

1D NMR plot parameters
CX  20.00 cm
CY  10.00 cm
F1P  8.000 ppm
F1  4001.04 Hz
F2P  0.000 ppm
F2  0.00 Hz
PPNCN  0.400000 ppm/cm
HZCN  200.05200 Hz/cm
Current Data Parameters
NAME: irina_8-45
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20040211
Time: 22:10
INSTRUM: AV300
PRDB: 5 mm QNP 1H/1
PULPROG: zg30
TD: 30720
SOLVENT: CDCl3
NS: 16
DG: 0
SWH: 5081.301 Hz
FIDRES: 0.165407 Hz
AG: 3.0226980 sec
RG: 143.7
DW: 98.400 usec
DE: 6.00 usec
TE: 300.0 K
DI: 1.00000000 sec

========== CHANNEL f1 ==========
NUC1: 1H
P1: 10.50 usec
PL1: -3.00 dB
SF01: 300.1319477 MHz

F2 - Processing parameters
SI: 65536
SF: 300.1300000 MHz
WOW: 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: 7.523 ppm
F1: 2257.89 Hz
F2P: 0.997 ppm
F2: 299.95 Hz
PPMCM: 0.32630 ppm/cm
Hzcm: 97.93180 Hz/cm
compound is very volatile
Current Data Parameters
NAME: irina_B-86
EXPG: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20040329
Time: 16.53
INSTRUM: AV500/406
PROBNO: 5 mm BB1, 1H-9B
PULPROG: zg30
TD: 65536
SOLVENT: Acetone
HS: 32
DS: 0
SMN: 7440.476 Hz
FIDRES: 0.113533 Hz
AQ: 4.4040694 sec
RG: 1149
DM: 67200 usec
DE: 6.00 usec
TE: 300.0 K
DI: 0.01000000 sec

********* CHANNEL 1 *********
NUC1: 1H
P1: 10.50 usec
PL1: 3.00 dB
SF01: 500.1327766 MHz

F2 - Processing parameters
SI: 65536
SF: 500.1300626 MHz
MDM: EH
SSB: 0
LB: 0.00 Hz
DB: 0
PC: 1.00

1D NMR plot parameters
CX: 20.00 cm
CY: 10.00 cm
FP1: 8.000 ppm
F1: 4001.04 Hz
FP2: 0.000 ppm
F2: 0.00 Hz
PPMCM: 0.40000 ppm/cm
HZCM: 200.05203 Hz/cm
Current Data Parameters
NAME: irina_J-149
EXPPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 2003/11/26
Time: 12:49
INSTRUM: av300
PROBHD: 5 mm QNP
PULPROG: zg30
TO: 30720
SOLVENT: CDCl3
NR: 16
DS: 0
SWH: 400 Hz
FIDRES: 0.15625 Hz
AQ: 3.02 MSW sec
RG: 8
DN: 98 400 usec
DE: 6.00 usec
TE: 300.0 K
DI: 1.00000000 sec

CHANNEL: f1
MUC1: 1H
P1: 10.50 usec
PL1: -3.00 dB
SF(1): 300 1319.477 MHz

F2 - Processing parameters
SI: 65536
SF: 300 1300000 MHz
MDW: EM
SSB: 0
LB: 0.10 Hz
GB: 0
FC: 1.00

1D NMR plot parameters
CX: 20.00 cm
CY: 10.00 cm
F1P: 0.000 ppm
F1: 7701.04 Hz
F2P: 0.000 ppm
F2: 0.00 Hz
PPM/cm: 0.40000 ppm/cm
HZCM: 120 05200 Hz/cm
13C with proton decoupling

Current Data Parameters
NAME: irina_7-174
EXPNO: 3
PROCNO: 1

F2 - Acquisition Parameters
Date: 2003/12/15
Time: 17:53
INSTRUM: o-200
FRQPROG: 5 mm DNP 1H/1
PULPROG: zgpg30
TD: 0.3268
SOLVENT: CDCl3
NS: 52
DS: 0
SNP: 17085.611 Hz
FIDRES: 0.5848 Hz
AQ: 0.01170 sec
NB: 1024.5
DM: 27.800 ussec
DE: 5.70 ussec
TE: 30.00 us K
DI: 1.00000000 sec
d1: 0.03000000 sec
d2: 0.00000000 sec

********** CHANNEL f1 **********
NUC1: 13C
P1: 5.00 ussec
PL1: -6.00 dB
SF01: 75.4752 MHz

********** CHANNEL f2 **********
CPDp[6]: 65536
NUC2: 1H
CPSq[2]: 70.00 ussec
PL2: -3.00 dB
PL12: 14.48 dB
PL13: 15.63 dB
SF02: 300.1314860 MHz

F2 - Processing parameters
SI: 65536
SF: 75.46772 MHz
WDC: 5.0
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

1D NMR plot parameters
CX: 20.00 cm
CY: 10.00 cm
F1P: 220.000 ppm
F1: 16602.90 Hz
F2P: 0.000 ppm
F2: 0.00 Hz
PPMCH: 11.000000 ppm/cm
HzCH: 83.0394 Hz/cm
13C with proton decoupling

Current Data Parameters
NAME  irina_7-17429
EXPNO  2
PROCNO  1

F2 - Acquisition Parameters
Date_  20031215
Time  21:24
INSTRUM

PROBES  5 mm NMR 1H/1
PULPROG  2pgg30
TD  32768
SOLVENT CDC13
NS  83
DS  0
SNR  17995.61 Hz

FTRES  0.548977 Hz
AQ  0.9110004 sec
RG  2890.3
DW  27.800 usec
DE  6.000 usec
tE  300.0 K
D1  1.00000000 sec
d1t  0.03000000 sec
d12  0.00002000 sec

-------- CHANNEL 11  --------
NUC1  13C
P1  5.00 usec
PL1  -6.00 dB
SF01  75.4728653 MHz

-------- CHANNEL 12  -------
CTRL2  wait:16
NUC2  1H
PCDQ2  70.00 usec
PL2  -3.00 dB
PL12  13.40 dB
PL13  15.63 dB
SF02  300.134860 MHz

F2 - Processing parameters
SI  69536
SF  75.4677190 MHz
WSM  EN
SSB  0
LB  1.00 Hz
GB  0
DC  1.40

1D NMR plot parameters
CX  0.00 cm
CY  0.00 cm
FP1  2200000 ppm
F1  16602.90 Hz
F2P  0.000 ppm
F2  0.00 Hz
PPMCM  11 00000 ppm/cm
HzCM  830.14490 Hz/cm
Current Data Parameters
NAME  irina_7 159
EXPNO  1
PROCNO  1

$^2$ - Acquisition Parameters
Date  2003.42
Time  14:47
INSTRUM  a300
PULPROG:  5 mm UND  UND
PULPROG  100
TD  30720
SOLVENT  CDCl3
$^4$  16
S2  0
SWX  50001.001 Hz
TINGS  0.105947 Hz
AQ  1.0288840 sec
AG  16
DM  98.400 us
DC  0.0000 us
DC  300.0 K
T1  1.00000000 sec

-------------- CHANNEL 1 --------------
NUC1  1H
P1  10.500 us
E1  3.0000 us
SF01  300.012877 MHz

$^2$ - Processing parameters
F1  695 Hz
SF  300.130000 MHz
WON  8
LB  0 Hz
GB  0
PC  1

$^2$ NMR plot parameters
CH  20.00 cm
CV  30.00 cm
F1P  8000 ppm
F1  2401.04 Hz
F2P  0.000 ppm
F2  0.000 Hz
WFM  400000 ppm/cm
AGCM  120.05200 Hz/cm
Current Data Parameters
NAME       irina_7-46
EXPIRE    1
PROCEDURE  1

F2 - Acquisition Parameters
Date       20030710
Time        18:27
INSTRUM  11.0000
PROBHD  5 mm GNP  1H/1
PULPROG  zg30
TD          30720
SOLVENT  CDC13
NSW       16
DS        0
SWM       5081.301 Hz
CTURES  0.165407 Hz
AD       3.0228980 sec
BG          456.1
DM       98.400 usec
DE         6.00 usec
TE         300.0 K
DT     1.0000000 sec

********** CHANNEL 1 **********
NUC1       1H
P1        10.50 usec
PB        -3.00 dB
SF01   300.1319477 MHz

F2 - Processing parameters
SI         695536
SF       300.1300000 MHz
MOE       EN
S5B       0
LB        0.10 Hz
GB        0
RC        1.00

1D NMR oplot parameters
CX        20.00 cm
CY        10.00 cm
F1P      7.756 ppm
F1        2382.27 Hz
F2P       -0.937 ppm
F2     -291.25 Hz
RPMCM    0.43733 ppm/cm
HZCM   130.47655 Hz/cm
Current Data Parameters
NAME  irina_7-68-2nd
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date  20030802
Time  12:46
INSTURM  15v300
PRDBO  5 mm GNP 1H/1
PLPORG  z930
TD  30.720
SOLVENT  CDCl3
NSC  16
DS  0
SNR  5081.301 Hz
FIDRES  0.165407 Hz
AQ  3.0229850 sec
AG  512
DW  98.400 usec
DE  6.00 usec
TE  300.0 K
DI  1.00000000 sec

************** CHANNEL f1 **************
NUCL  1H
PI  10.50 usec
PL1  -3.00 dB
SFO1  300.131947 MHz

F2 - Processing parameters
SI  65536
SF  300.130000 MHz
WDM  EM
SSB  0
LB  0.10 Hz
GB  0
PC  1.00

1D NMR plot parameters
CX  20.00 cm
CY  50.00 cm
F1P  7.724 ppm
F1  2321.12 Hz
F2P  -0.024 ppm
F2  -7.20 Hz
PPMCM  0.38789 ppm/cm
HZCM  116.41597 Hz/cm