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**Development of the Tandem Oxy-Cope/Claisen/Ene Reaction:
Mechanistic Insights and Application Towards the Synthesis of
Wiedemannic Acid and LL-S491 β**

by

Effiette L. O. Sauer

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the
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Abstract

This thesis explores the tandem oxy-Cope/Claisen/ene reaction and its application towards the total synthesis of two natural products, wiedemannic acid and LL-S491 β . Drawing on earlier studies carried out on the oxy-Cope/ene rearrangement, the oxy-Cope/Claisen/ene reaction adds to the previous methodology by allowing for the formation of highly functionalized decalin cores bearing up to four contiguous stereocentres, including two adjacent quaternary carbons. The scaffolds accessed by this new tandem pericyclic cascade allow for an easy foray into the synthesis of numerous diterpenoid natural products.

The first part of this study focuses on the development of the oxy-Cope/Claisen/ene reaction with respect to both its scope and diastereoselectivity. A combination of experimental methods and theoretical studies allow for the origins of the observed diastereoselectivity to be unveiled. Through the use of judicious substituent selection and/or the addition of remote stereocentres for conformational control, the selectivity of this cascade reaction is effectively controlled.

Armed with a highly efficient and stereoselective method for the preparation of functionalized decalin cores, the second part of this study centres on the application of this method to total synthesis. The preparation of a wiedemannic acid analogue is successfully completed with four of its five adjoining stereocentres being effectively set during the key oxy-Cope/Claisen/ene reaction. Owing to a discrepancy in the reported structure of wiedemannic acid however, the synthesis of the natural product is not further pursued. Rather, a new target is chosen. Several innovative routes towards the synthesis of LL-S491 β are described, each relying on the key tandem reaction cascade to build the core of its pimarane skeleton.

Finally, the last section of this work addresses some of the novel chemistry discovered along the way including a unique ruthenium-mediated lactonization reaction and an enolate isomerization pathway during the oxy-Cope/ene reaction.

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Abbreviations

18-C-6	18-crown-6
acac	acetylacetonate
AIBN	2,2'-azobis(2-methyl)propionitrile
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl- <i>para</i> -cresol (butylated hydroxytoluene)
BINOL	(1,1')-binaphthalenyl-2,2'-diol
Bn	benzyl
Bu	butyl
cat.	catalytic or catalyst
Cy	cyclohexyl
DBB	di- <i>tert</i> -butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEG	diethylene glycol
DFT	density functional theory
DHP	3,4-dihydro-2 <i>H</i> -pyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	<i>N,N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide

DPS	<i>tert</i> -butyldiphenylsilyl
dr	diastereomeric ratio
E ⁺	electrophile
ee	enantiomeric excess
EI	electron impact
eq ^m	equilibrium
equiv	equivalent
Et	ethyl
GC	gas chromatography
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
Im	imidazole
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
L-selectride	lithium tri- <i>sec</i> -butylborohydride
MALDI	matrix-assisted laser desorption/ionization
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
MEG	monoethylene glycol
MOM	methoxymethyl
MOP	2-methoxypropane
mp	melting point
Ms	mesyl (methanesulfonyl)
MS	molecular sieves or mass spectrometry
MTPA	methoxy- α -(trifluoromethyl)phenylacetic acid
<i>n</i> BuLi	<i>n</i> -butyllithium
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NMM	<i>N</i> -methylmorpholine

NMO	4-methylmorpholine N-oxide
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu ⁻	nucleophile
OTf	trifluoromethylsulfonate
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonic acid
Pr	propyl
PTSA	<i>para</i> -toluenesulfonic acid
Py	pyridine
RCM	ring-closing metathesis
ROM	ring-opening metathesis
Rose-Bengal	2,4,5,7-tetraiodo-3',4',5',6'-tetrachlorofluorescein disodium salt
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
<i>t</i> BuLi	<i>tert</i> -butyllithium
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
TBS	<i>tert</i> -butyldimethylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethyl-1,2-ethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate

TPP	5,10,15,20-tetraphenylporphine
Tr	trityl (triphenylmethyl)
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet

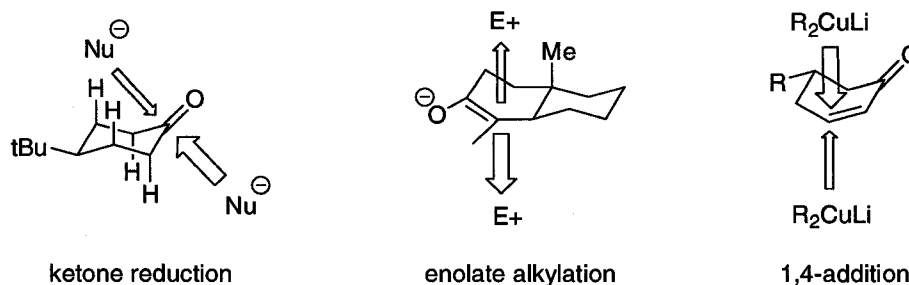
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Introduction

Conformational Preferences of Medium and Large Rings

The well-defined conformational preferences of cyclohexane derived ring systems has long been recognized as an efficient vehicle for carrying out stereoselective synthesis. From ketone reductions, to cuprate additions, to enolate chemistry, the predictable axial/equatorial arrangement of substituents in a six-membered ring routinely leads to high diastereoselectivity in these and other reactions (Figure 1.1).

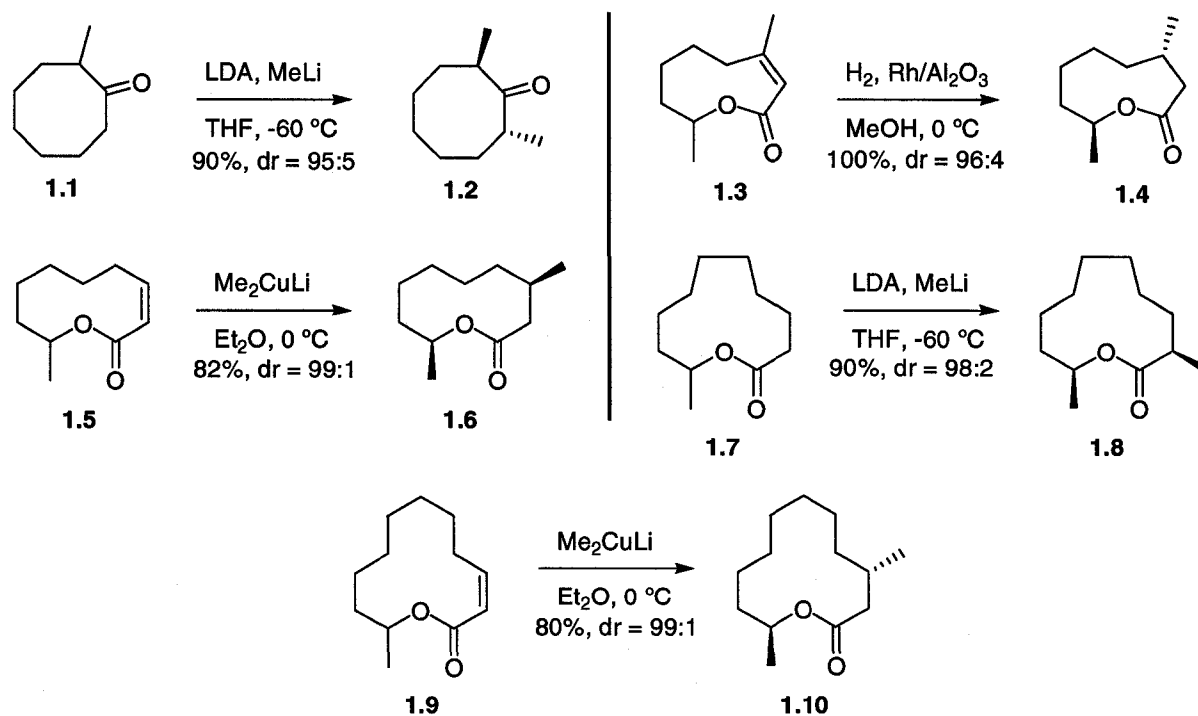
Figure 1.1 – Stereoselective reactions of the cyclohexane ring system



In contrast, medium and large-sized rings have often been falsely regarded as “floppy,” possessing numerous, poorly-defined conformations. Consequently, their potential use in asymmetric synthesis was, for many years, largely unexplored.¹ Pioneering work by Still and Galynker challenged this notion with their proposal that conformationally controlled stereoselection should also be feasible in larger ring sizes.² Drawing on dynamic NMR measurements, X-ray crystallography and semi-empirical molecular mechanics calculations, they argued that although macrocyclic compounds can adopt a number of stable conformations, only a few are sufficiently low in energy to be appreciably populated at ambient temperatures.

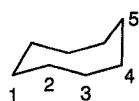
To test their theory, a series of mono-substituted 8- through 12-membered macrocyclic ketones and lactones were subjected to enolate alkylations, cuprate additions and hydrogenations (Scheme 1.1). In nearly all cases, the observed diastereoselectivities were greater than 95:5. In fact, several reactions exhibited greater stereoinduction than that reported for the analogous six-membered systems.

Scheme 1.1 – Stereoinduction in various sized macrocycles

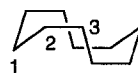


The resulting high levels of diastereoselectivity were concluded to be the result of conformational biases induced by the remote methyl substituents: just as a six-membered ring prefers to place its substituents equatorially, so too does a macrocycle. Interestingly, semi-empirical molecular mechanics calculations suggested that the energy associated with the axial placement of a methyl group varies substantially depending on where in the macrocycle it is located (Table 1.1). For example, the cost of axial substitution in the preferred chair-boat conformation of cyclooctane (**1.11**) varies from -0.3 kcal/mol to 6.1 kcal/mol, while that of the preferred boat-chair-boat conformation of cyclodecane (**1.12**) ranges from 0.0 to 9.2 kcal/mol. For comparison, the A-value³ for methyl substitution on cyclohexane is 1.74 kcal/mol. The magnitude of these calculated pseudo A-values was taken as confirmation that a single remote stereocentre could significantly limit the number of available conformations in medium and large-sized rings.

Table 1.1 – Pseudo A-values calculated for methyl substitution of various cycloalkanes



1.11
chair-boat



1.12
boat-chair-boat

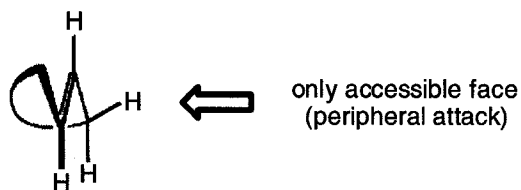
Methyl position	Pseudo A-values (kcal/mol) ^a	
	Cyclooctane	Cyclodecane
1	1.8	6.6
2	2.8	0.0
3	> 4.5	9.2
4	-0.3	---
5	6.1	---

^a Ground state energy difference between the axially and equatorially substituted cycloalkane.

A second factor used to rationalize the observed diastereoselectivity was the presence of sp^2 hybridized carbon atoms. Unlike in smaller rings, the sp^2 centres of larger rings prefer to lie orthogonal to the plane of the ring in order to minimize transannular interactions

(Figure 1.2). The result is a pronounced differentiation between the two faces of the π system, thus favouring peripheral attack by external reagents.

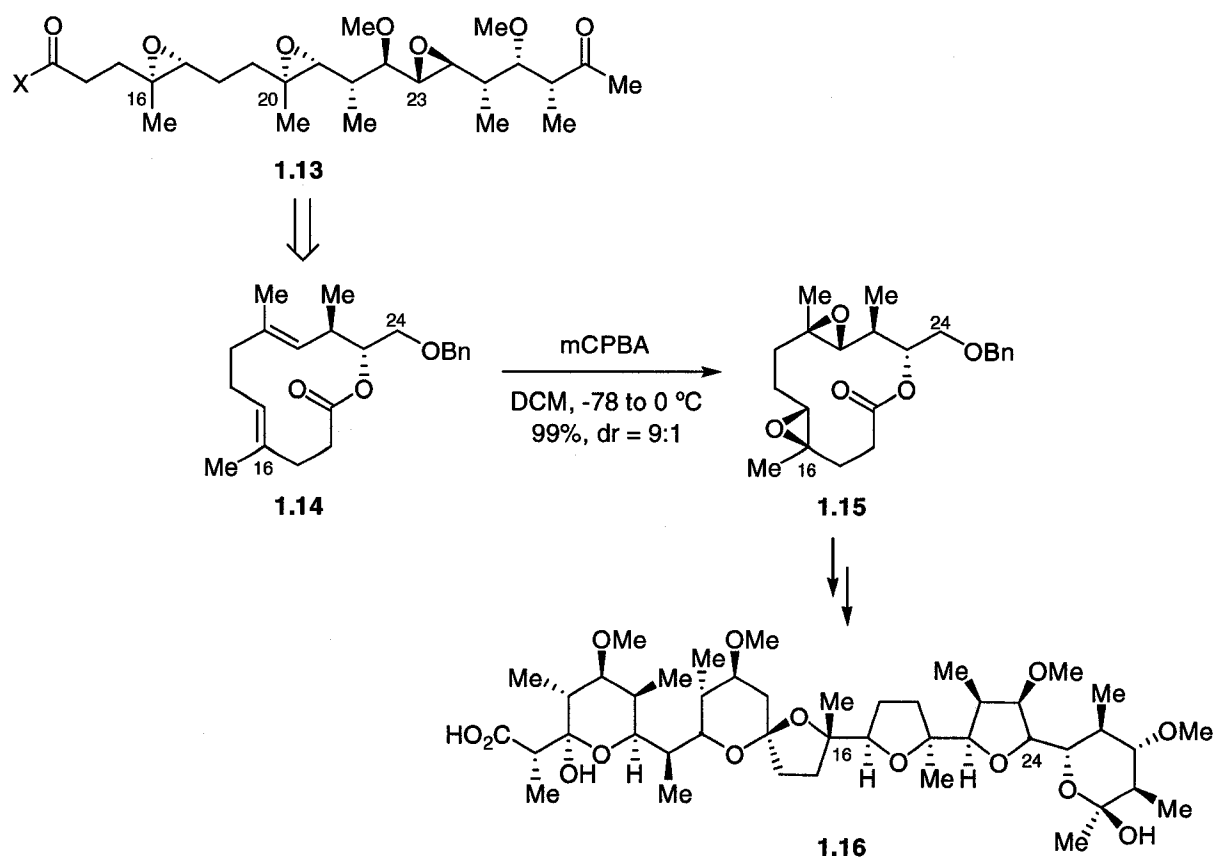
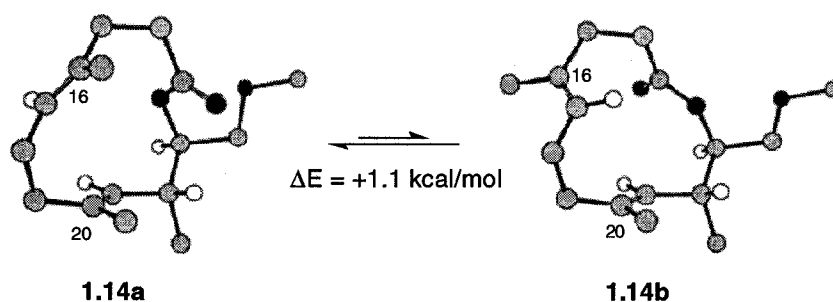
Figure 1.2 – Ground state conformation of cyclodecene: facial discrimination of the π -system



In the years following Still and Galynker's seminal publication, several groups went on to confirm that conformational control in the reactions of medium and large rings was indeed a widespread phenomenon. Larry Weiler, in particular, devoted significant effort to advancing this field through his studies on the diastereoselective reactions of 14- and 16-membered macrocycles.⁴ As a result of these and others' efforts, the use of substituted macrocycles as a scaffold for asymmetric synthesis has become a valuable tool in the synthesis of natural products. One notable example which highlights the utility of this strategy can be found in the total synthesis of antibiotic lonomycin A (**1.13**) by Evans et al.⁵

As a precursor for their key epoxide-opening cascade, a stereoselective synthesis of tri-epoxide **1.13** was required. The preparation of the C₁₆-C₁₇ epoxide was anticipated to be difficult owing to its relative isolation from the other stereogenic centres. To circumvent this potential problem, the acyclic structure was converted into a 12-membered lactone, **1.14**, in order to allow its conformational preferences to direct the epoxidation of the C₁₆-C₁₇ and C₂₀-C₂₁ olefins. Molecular mechanics calculations revealed **1.14a** to be the lowest energy conformer by 1.1 kcal/mol (Figure 1.5). Importantly, both double bonds had the correct face of the π -system exposed suggesting the reaction should proceed as desired. Indeed, treatment of **1.14** with *m*CPBA led to a 99% yield of bis-epoxide **1.15** as a 9:1 mixture of isomers. The minor isomer was the C₁₆-C₁₇ epimeric epoxide, presumably arising from attack of the minor conformer, **1.14b**.

Scheme 1.2 – Evans' synthesis of lonomycin A (1.15)

Figure 1.3 – Molecular mechanics minimization of macrocycle 1.14⁶

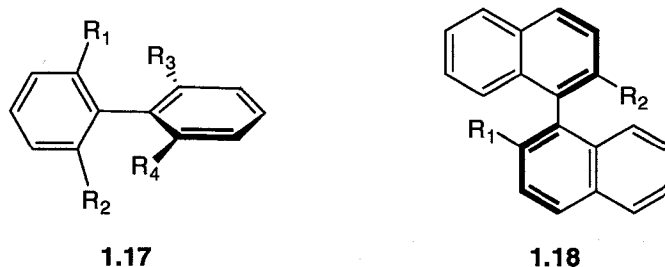
Atropisomerism and Planar Chirality

Integral to the success of the above approach is the existence of conformational preferences between freely interchanging conformers. By restricting the interconversion

between conformations, however, a contrasting situation arises where, in the extreme, individual conformations may become distinct, isolable species. This phenomenon is known as atropisomerism.

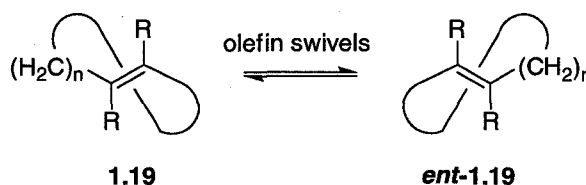
Defined as “stereoisomerism resulting from restricted rotation about single bonds where the rotational barrier is high enough to permit isolation of the isomeric species,”⁷ the term atropisomerism encompasses several classes of molecules. In its most common form, the restricted rotation about the C-C single bond of *ortho*-substituted biaryl systems gives rise to a chiral axis. Scaffolds such as **1.17** and **1.18** are especially prevalent as they form the basis of many widely used chiral ligands in asymmetric catalysis (Figure 1.4).

Figure 1.4 – Atropisomerism in biaryl systems



A less common form of atropisomerism can be found in (*E*)-cycloalkenes. When the transannular portion of an (*E*)-cycloalkene is sufficiently short, the transannular non-bonding interactions prohibit the olefin from rotating through the ring. Consequently, the olefin forms a chiral plane giving rise to stereoisomerism with respect to the remaining out of plane atoms (Figure 1.5). If additional stereocentres are present on the molecule, the resulting atropisomers are diastereomeric; in their absence, the isomers become enantiomeric.

Figure 1.5 – Atropisomerism in planar chiral (*E*)-cycloalkenes



The existence of such planar chiral⁸ molecules was first recognized by Blomquist in 1952.⁹ A decade passed, however, before Cope et al. successfully isolated and resolved the

first examples, (*E,Z*)-1,5-cyclooctadiene (**1.20**)¹⁰ and (*E*)-cyclooctene (**1.21**).¹¹ Racemic mixtures of these olefins were coordinated to platinum (II) chloride along with a chiral amine, (+)-1-phenyl-2-aminopropane. The resulting diastereomeric complexes were separated and the enantiopure olefins liberated by treatment with aqueous potassium cyanide. Both compounds gave rise to optically stable enantiomers.

Following this initial success, Cope went on to study the nine and ten-membered systems, **1.22** and **1.23**.¹² The addition of a carbon atom to the methylene bridge in (*E*)-cyclononene led to a significant reduction in its optical stability relative to (*E*)-cyclooctene: racemization at ambient temperature was rapid and low temperatures (-80 °C) were required for its resolution. The racemization of chiral (*E*)-cyclodecene was even more facile and all attempts to resolve these enantiomers led to racemic mixtures. Table 1.2 below summarizes these results, along with a comparison of the experimentally determined activation energies for racemization and the corresponding half-lives.

Table 1.2 – Properties of several (*E*)-cycloalkenes



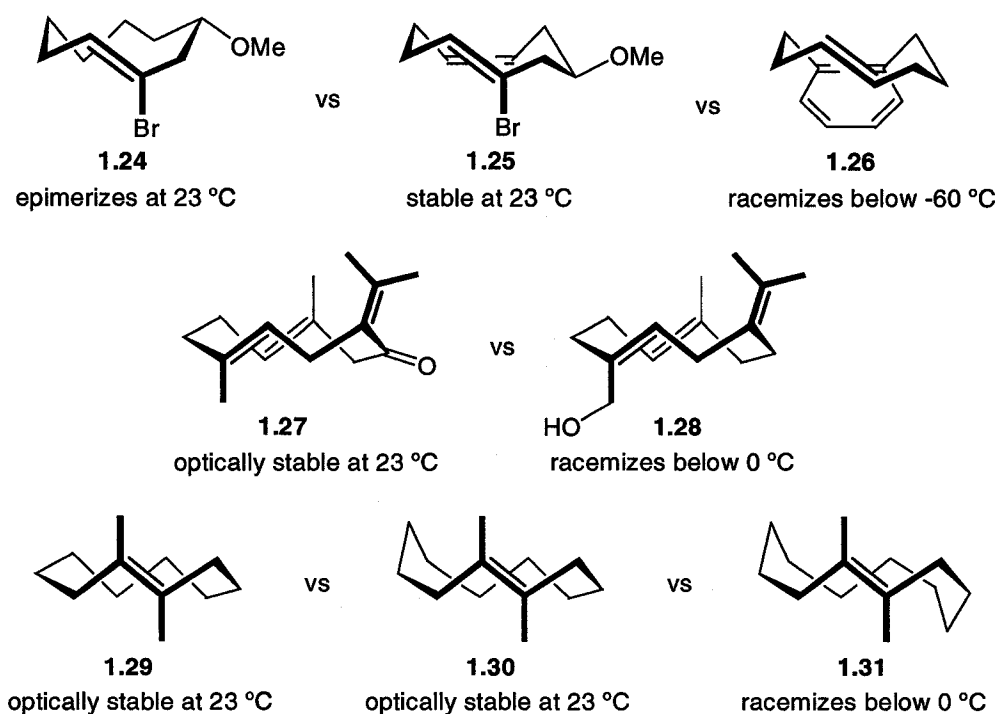
Species	Number of carbon atoms	Optically stable?	Barrier to racemization (kcal/mol)	Half-life at 23 °C ^c
1.20	8	Yes	n/a	n/a
1.21	8	Yes	35.6 ^a	10 ⁵ years
1.22	9	Yes, at -80 °C	20 ^b	10 seconds
1.23	10	No	10.7 ^c	10 ⁻⁴ seconds

^a See reference 13. ^b See reference 12. ^c Half-life of the enantiopure compound. See references 14 and 15

The above findings suggest that the occurrence of atropisomerism is dependent on the size of the cycloalkene ring. While this is partly true, further studies by Cope and others have revealed that adding substitution and/or unsaturation to the parent cycloalkene can dramatically influence whether the (*E*)-olefin is capable of passing through the ring (Figure 1.6). For example, the chiral plane of nine-membered cycloalkene **1.24** was found to epimerize at 23 °C giving rise to a mixture of diastereoisomers.^{16,17} The addition of a Z

double bond, however, led to an improvement in stability and **1.25** was isolated as a single diastereomer at ambient temperature.¹⁸ In contrast, the addition of unsaturation to compound **1.26** led to a decrease in optical stability relative to its parent compound, (*E*)-cyclononene (**1.22**): while neither was stable at ambient temperature, **1.22** did exhibit optical activity when isolated at sub-zero temperatures (see Table 1.2 above). A comparison of (*E,E*)-cyclodecadienes **1.27** and **1.28** reveals similar discrepancies: a partially resolved sample of **1.27** was reported to be optically stable at ambient temperatures for several months¹⁹ while the nearly identical compound, **1.28**, rapidly isomerized even at sub-zero temperatures.²⁰ This particular example highlights how seemingly subtle structural changes can greatly influence the free-rotation of the (*E*)-olefin. Finally, Marshall et al. prepared a series of 1,2-disubstituted (*E,E*)-cycloalkenes and found that both **1.29** and **1.30** were optically stable at ambient temperature while the 12-membered ring, **1.31**, readily racemized below 0 °C.²¹ The substitution of the vinylic protons for methyl groups increases the non-bonding transannular interactions that are incurred as the olefin passes through the ring, thus raising the activation energy for its racemization.

Figure 1.6 – Effect of substitution and unsaturation on atropisomerism of (*E*)-cycloalkenes

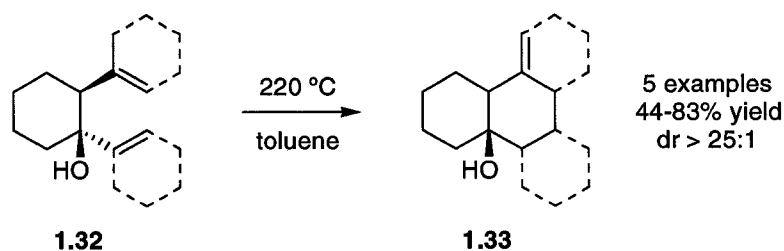


Alongside the identification and characterization of new planar chiral (*E*)-cycloalkenes, significant effort has been devoted to developing new methods for their asymmetric preparation.²² In addition, heterocyclic versions of these molecules have been prepared where one of the methylene groups has been replaced either by silicon,²³ oxygen²⁴ or nitrogen.²⁵ Beyond these developments, however, the chemistry of planar chiral cycloalkenes has remained primarily a curiosity. Given the well-defined arrangement of atoms imposed by their atropisomerism, it seems surprising that their use as synthetic intermediates in asymmetric synthesis has not been further exploited. Like Stille's use of macrocyclic conformations as an asymmetric scaffold, the transfer of planar chiral information should be a powerful means of affecting stereoselective transformations, even in molecules devoid of stereogenic centres. While this potential has been acknowledged,²⁶ only a few examples have been reported to date.²⁷

Remote Stereocontrol and Planar Chirality In the Oxy-Cope/Ene Reaction

Our own group's interest in the conformations of medium sized rings and their potential for planar chirality grew out of the tandem oxy-Cope/ene reaction published in 2000.²⁸ Barriault and Warrington reported a reliable and efficient means of generating polycyclic molecules in a stereocontrolled manner starting from simple 1,2-divinylcyclohexanols (Scheme 1.3).

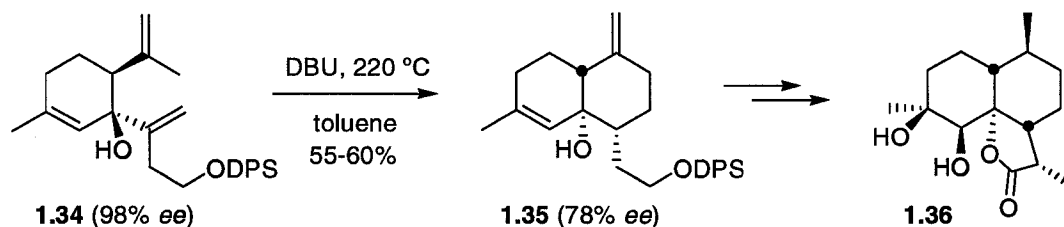
Scheme 1.3 – Warrington and Barriault's oxy-Cope/ene reaction



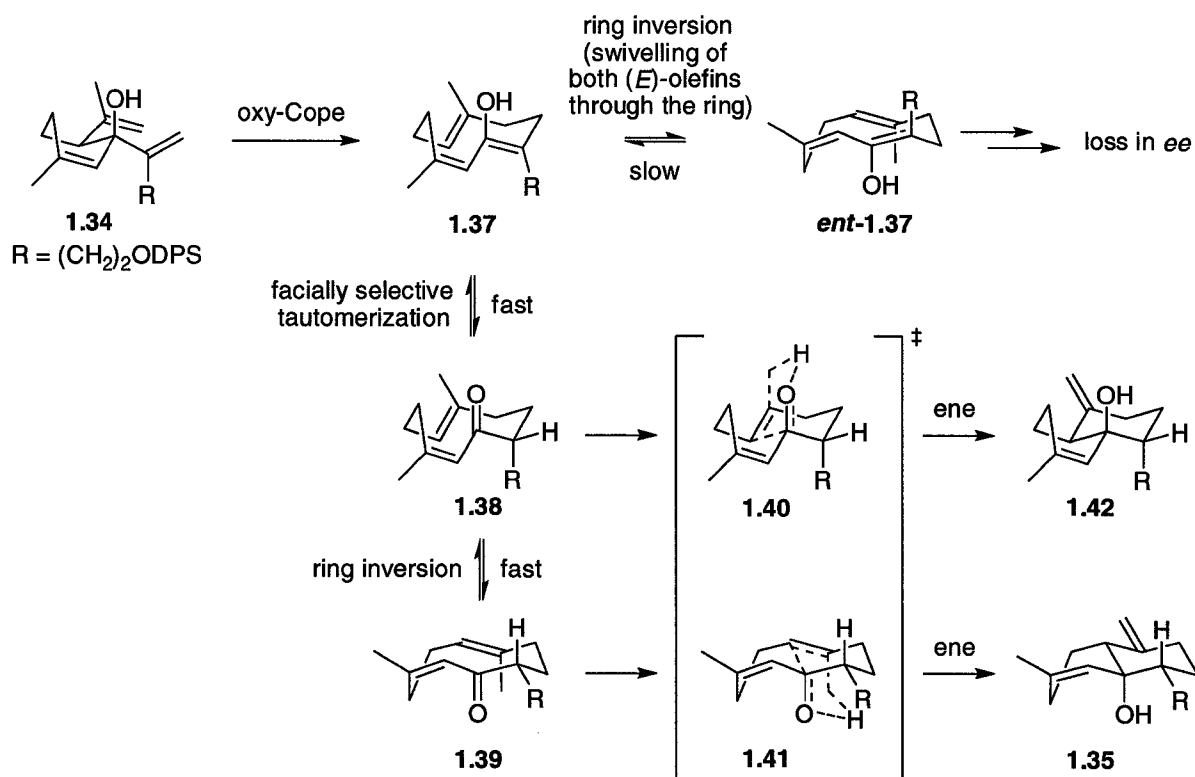
An application of this method was soon to follow and in 2001 Barriault and Deon reported the first total synthesis of (+)-arteannuin M, **1.36** (Scheme 1.4). The key oxy-

Cope/ene rearrangement effectively transformed **1.34** into **1.35** with excellent diastereoselectivity and partial preservation of chirality.

Scheme 1.4 – Application of the oxy-Cope/ene reaction to the synthesis of (+)-arteannium M



The observed stereoselectivity was rationalized according to Figure 1.7 below. Following the oxy-Cope rearrangement of **1.34**, enol **1.37** is generated which is devoid of all stereocentres. Owing to the two (*E*)-olefins, however, the molecule remains chiral by virtue of its two chiral planes. Thus, inversion of both double bonds through the ring gives rise to its enantiomer, *ent*-**1.37**, and the corresponding enantiomeric products. Alternatively, enol **1.37** can tautomerize to give ketone **1.38**. Since the back face of the enol is shielded by the ring, this process should be highly stereoselective. Thus, to the extent that tautomerization out-competes the ring inversion, the transformation of **1.34** to **1.38** can be seen as an effective transfer of planar chirality to a stereogenic centre. Having removed one double bond from the molecule, ketone **1.38** is now considerably more flexible and inversion of the remaining (*E*)-olefin competes with the carbonyl ene reaction. The stereogenic centre, however, appears to impose a conformational preference favouring its equatorial placement and thus giving rise exclusively to isomer **1.35**.

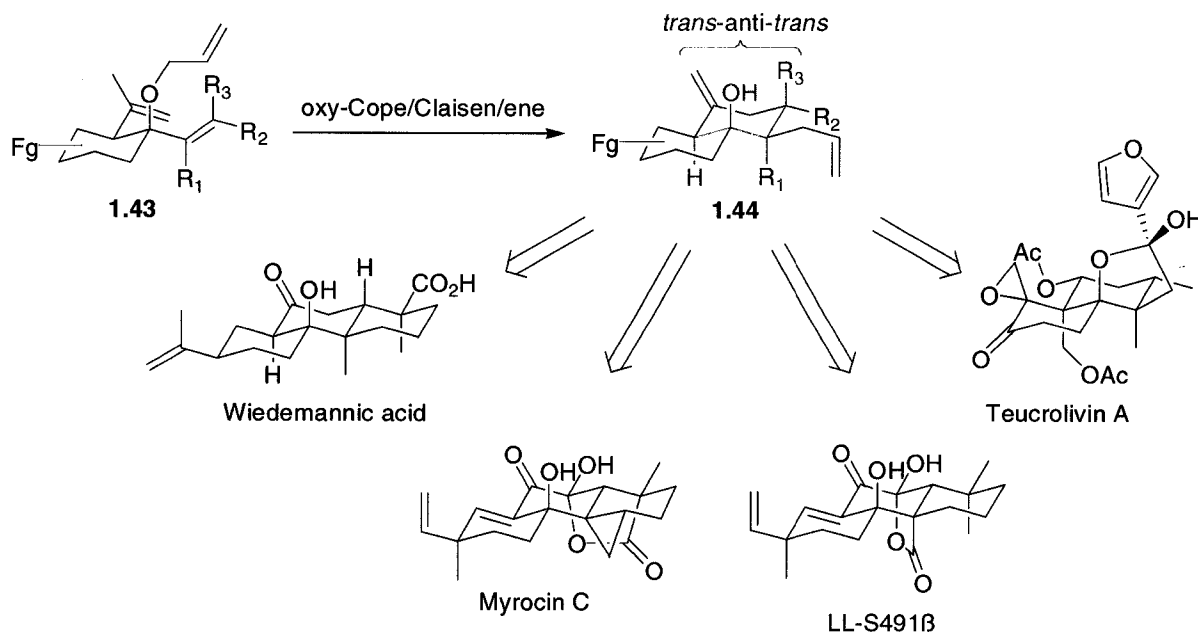
Figure 1.7 – Diastereoselectivity and enantioselectivity in the oxy-Cope/ene reaction of **1.34**

Exchanging Tautomerization for a Claisen Rearrangement

Encouraged by the success of the oxy-Cope/ene reaction, we set out to explore whether this methodology could be extended to include the formation of decalin cores bearing an all-carbon quaternary stereocentre. Given the challenge associated with the stereoselective synthesis of quaternary carbon centres,²⁹ such a development could prove to be a significant advancement. Revisiting the above reaction mechanism, it was envisioned that by replacing the proton of enol intermediate **1.37** with an allyl moiety, the stereoselective tautomerization might be transformed into a stereoselective Claisen rearrangement. The resulting oxy-Cope/Claisen/ene cascade would thus be capable of transforming starting materials of type **1.43** into decalin cores of type **1.44** (Figure 1.8). Notably, the substitution pattern on such scaffolds lends itself well to generate the *trans-anti-trans* stereochemistry found in many diterpenoid natural products. Consequently, the successful development of this method could

open the door for numerous total syntheses, including that of wiedemannic acid,³⁰ myrocin C,³¹ LL-S491 β ³² and teucrolivin A.³³

Figure 1.8 – Proposed oxy-Cope/Claisen/ene reaction and its applications



Thesis Goals and Outline

From the initial idea stated above, the following objectives were laid out:

- 1) Establish the feasibility of the oxy-Cope/Claisen/ene reaction.
- 2) Evaluate the reaction's scope.
- 3) Rationalize the stereoselectivity of the process with respect to the atropisomerism and/or conformational preferences of the macrocyclic intermediates.
- 4) Apply the reaction to the total synthesis of a natural product.

Chapter 2 addresses our efforts to establish the tandem oxy-Cope/Claisen/ene reaction as a viable process and to understand the observed diastereoselectivities. Chapters 3 and 4, respectively, summarize our work towards the total synthesis of natural products

wiedemannic acid and LL-S491 β . Chapter 5 highlights some emerging results which were borne from the previous three chapters' work: a novel lactonization reaction mediated by Grubbs' first generation catalyst, as well as an alternative interpretation of several key oxy-Cope/ene results. Finally, Chapter 6 offers a brief summary while Chapter 7 provides detailed experimental procedures and characterization for all new compounds.

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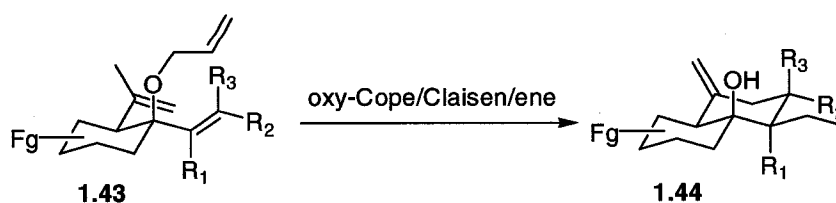
2

The Oxy-Cope/Claisen/Ene Reaction

Introduction to the Oxy-Cope/Claisen/Ene Reaction

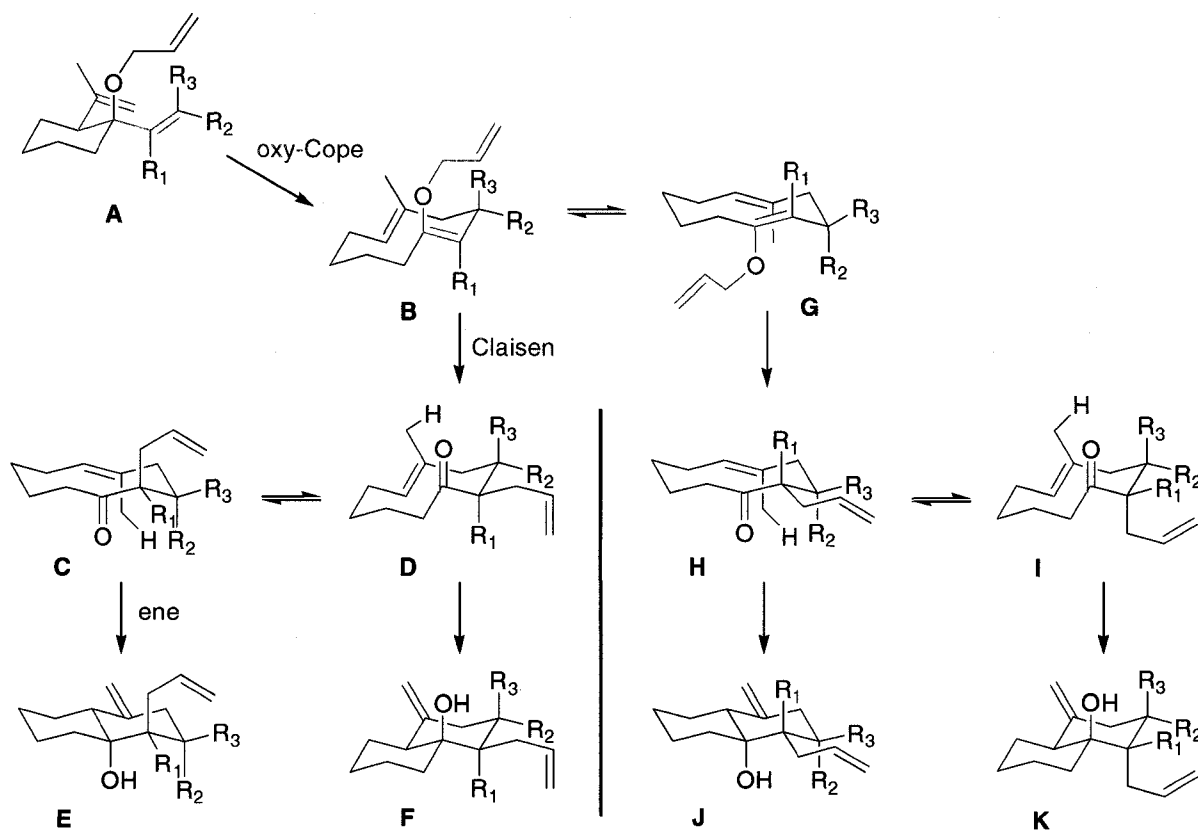
With the envisioned oxy-Cope/Claisen/ene reaction, it was hoped that highly functionalized decalin ring systems of type **1.44** could be rapidly generated from relatively simple, easy to make substrates of type **1.43** (Figure 2.1). Of particular interest was the potential for creating up to four contiguous stereocentres, including as many as three quaternary carbon centres, depending on the substitution of R_1 , R_2 and R_3 . Given the prevalence of such *trans*-decalin frameworks in terpenoid natural products, the potential applications for such a method could be far-reaching.

Figure 2.1 – Proposed oxy-Cope/Claisen/ene reaction



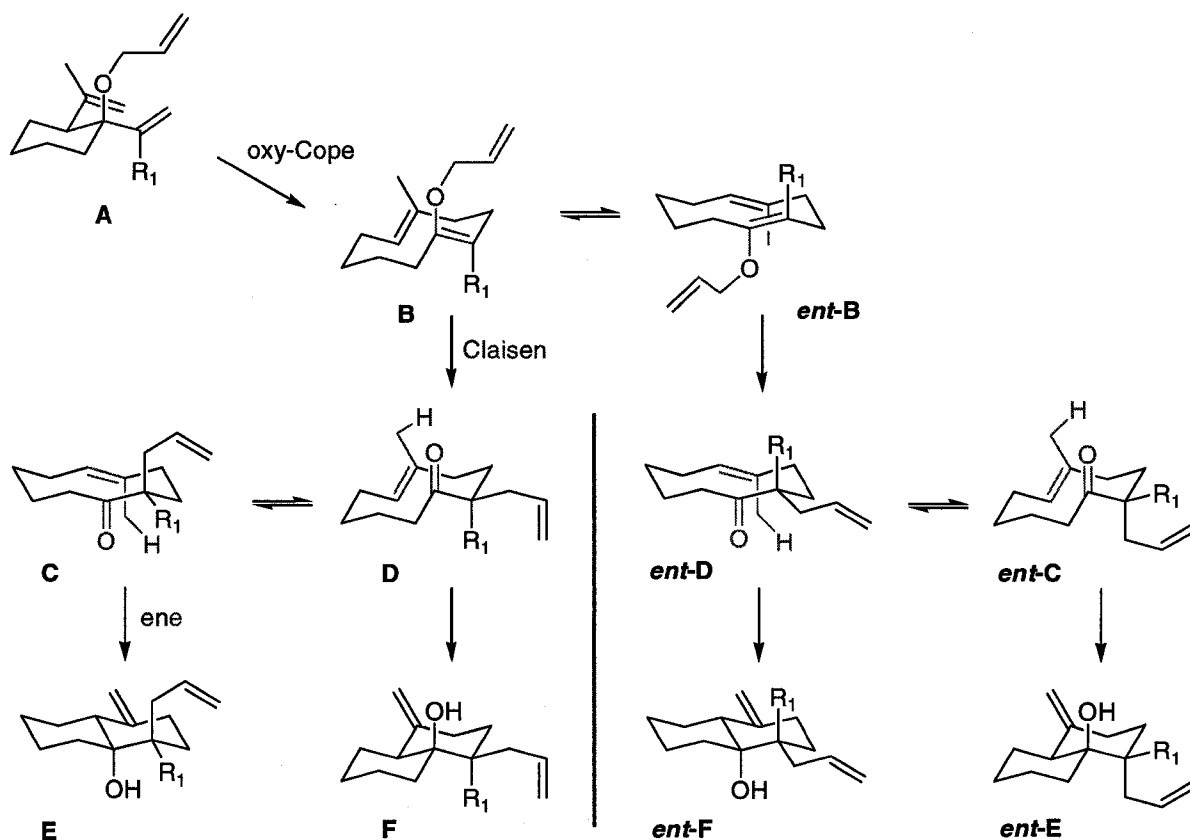
Of central importance to the future application of the proposed tandem sequence would be the ability to control the diastereoselectivity of the newly forming stereocentres. An analysis of the reaction mechanism (Figure 2.2) reveals several points of potential concern: After the oxy-cope rearrangement of **A**, 10-membered enol ether **B** is produced which can either undergo the desired Claisen rearrangement to give **D**, or a ring inversion¹ to give its atropisomer, **G**.² In contrast to the tautomerization process of the oxy-Cope/ene reaction (see Chapter 1, Figure 1.7), the Claisen rearrangement is expected to have an appreciably sized activation energy. Consequently, the possible competition between these two processes, and the resulting formation of intermediate **H**, must be considered. Ketones **D** and **H** are both poised to undergo a transannular carbonyl ene reaction to give diastereomeric products **F** and **J**. Prior to the carbonyl ene reaction, however, **D** and **H** could each undergo a second ring inversion³ to give intermediates **C** and **I**, which, in turn would yield products **E** and **K** respectively. As a result of these multiple ring inversions, four diastereomeric products are possible from the reaction of **A**.

Figure 2.2 – Mechanism of the oxy-Cope/Claisen/ene reaction



It is worth noting that for substrates bearing substitution only at R_1 , a simplified version of the reaction mechanism can be presented (Figure 2.3). Following the oxy-Cope rearrangement of **A** ($R_2 = R_3 = H$), intermediate **B** is generated. Unlike in the previous mechanism, intermediate **B** is now devoid of any stereocentres. Consequently, an inversion of the two (*E*)-olefins gives its enantiomer,⁴ **ent-B**, which goes on to generate enantiomeric products **ent-E** and **ent-F**. Provided then, that achiral substrates are used, the right-hand side of the reaction mechanism becomes redundant and can ultimately be ignored.

Figure 2.3 – Simplified mechanism for substrates bearing substitution only at R_1

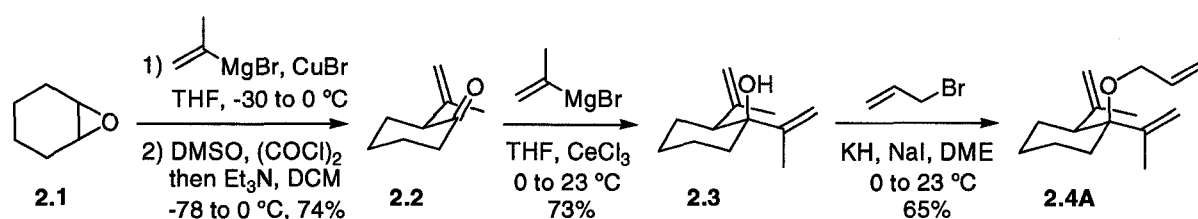


Appreciating the importance of diastereoselectivity to the success of our proposed tandem reaction, we turned our attention to the preparation of substrates with which to evaluate the oxy-Cope/Claisen/ene reaction.

Investigating the Scope of the Oxy-Cope/Claisen/Ene Reaction

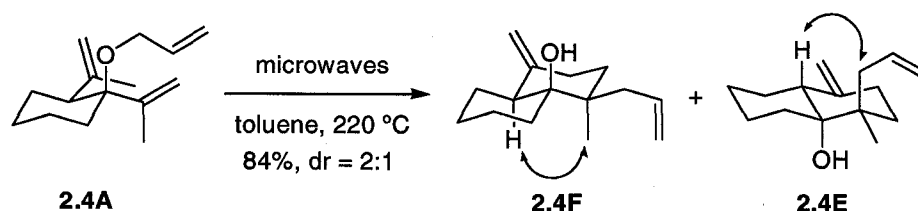
To test the viability of our proposed tandem reaction, compound **2.4A** was chosen as the initial substrate (Scheme 2.1). Starting from cyclohexane oxide (**2.1**), an epoxide opening in the presence of copper (I) bromide, followed by a Swern oxidation,⁵ gave ketone **2.2** in 74% yield for the two steps. Treatment with a second equivalent of isopropenylmagnesium bromide in the presence of anhydrous cerium (III) chloride gave **2.3** in 73% yield. Finally, allylation with allyl bromide, potassium hydride and a catalytic amount of sodium iodide in DME gave the desired tandem reaction precursor in 65% yield. It should be noted that no reaction was observed using the allylation conditions optimized previously in our laboratory for similarly hindered substrates (NaH, NaI, THF/DMF 4:1).⁶

Scheme 2.1 – Preparation of the initial test substrate, **2.4A**

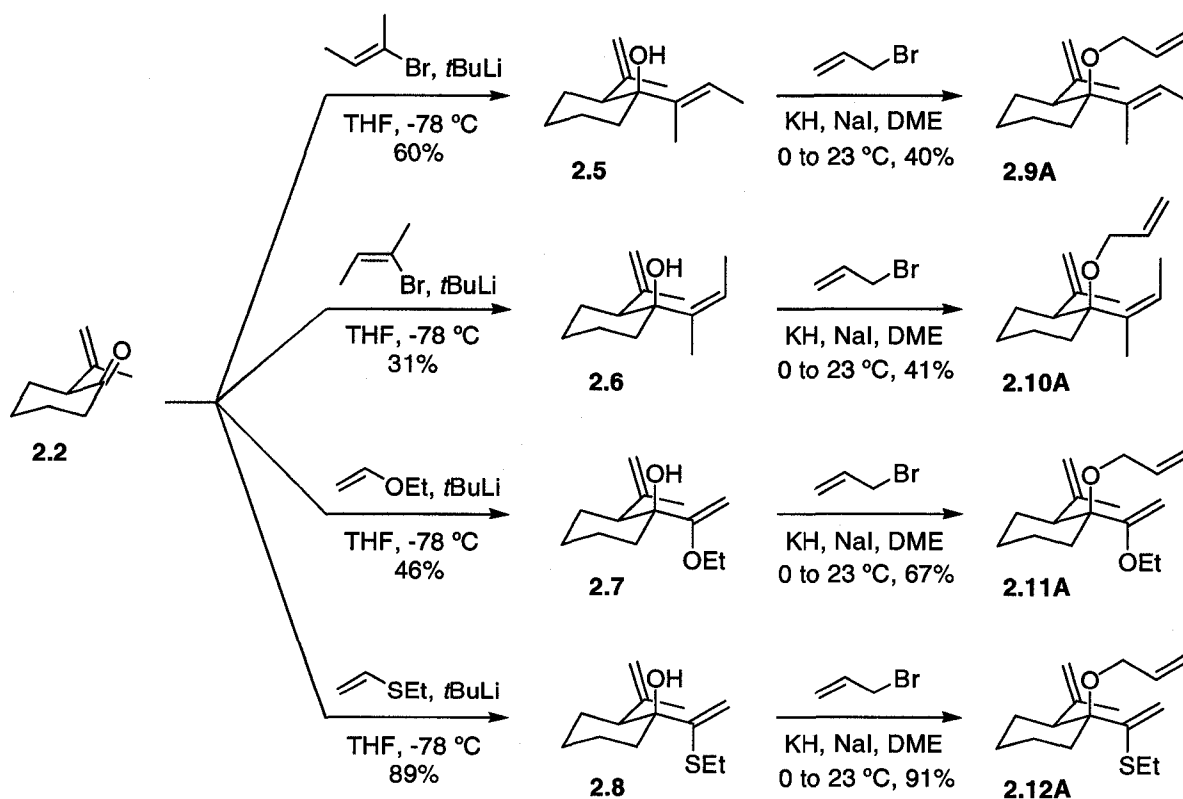


Noting the advantageous use of microwaves⁷ for inducing the oxy-Cope/ene reaction,⁸ as well as the required temperature of 220 °C for initiating the tandem cascade,⁶ we adopted a similar set of conditions for our initial test reaction. The addition of DBU, however, was omitted since its use in suppressing the retro-ene reaction was no longer needed given the introduction of the allyl group to our substrate.⁹ To our delight, heating **2.4A** in toluene at 220 °C in a microwave oven for 1 hour afforded cleanly the desired oxy-Cope/Claisen/ene product in 84% yield, albeit as a 2:1 mixture of diastereomers (Scheme 2.1). An NOE correlation of 2.7% between the methyl group and the axial proton of the ring junction allowed us to assign the major isomer as **2.4F**. Likewise, the minor isomer showed strong NOESY cross-peaks between the allylic methylene protons and the axial proton of the ring junction, thus confirming its structure to be that of **2.4E**. (Further details regarding the assignment of relative stereochemistry for these compounds, as well as all subsequent oxy-Cope/Claisen/ene products can be found in Chapter 7).

Scheme 2.2 – Products of the first oxy-Cope/Claisen/ene reaction; NOE correlations

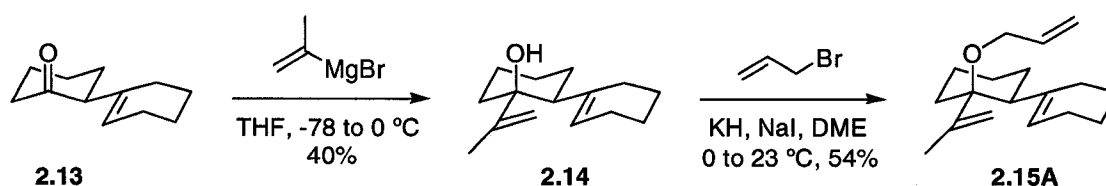


Having confirmed that the oxy-Cope/Claisen/ene reaction was indeed feasible, we set out to examine its scope and to further evaluate its diastereoselectivity. To this end, a variety of new substrates were prepared from ketone **2.2** (Scheme 2.3). Alkylation with the appropriate vinyllithium reagents gave tertiary alcohols **2.5-2.8** in modest to good yields. Subsequent allylation with allyl bromide, potassium hydride and sodium iodide in DME gave substrates **2.9A-2.12A** with yields ranging from 40-91%.

Scheme 2.3 – Preparation of additional substrates from ketone **2.2**

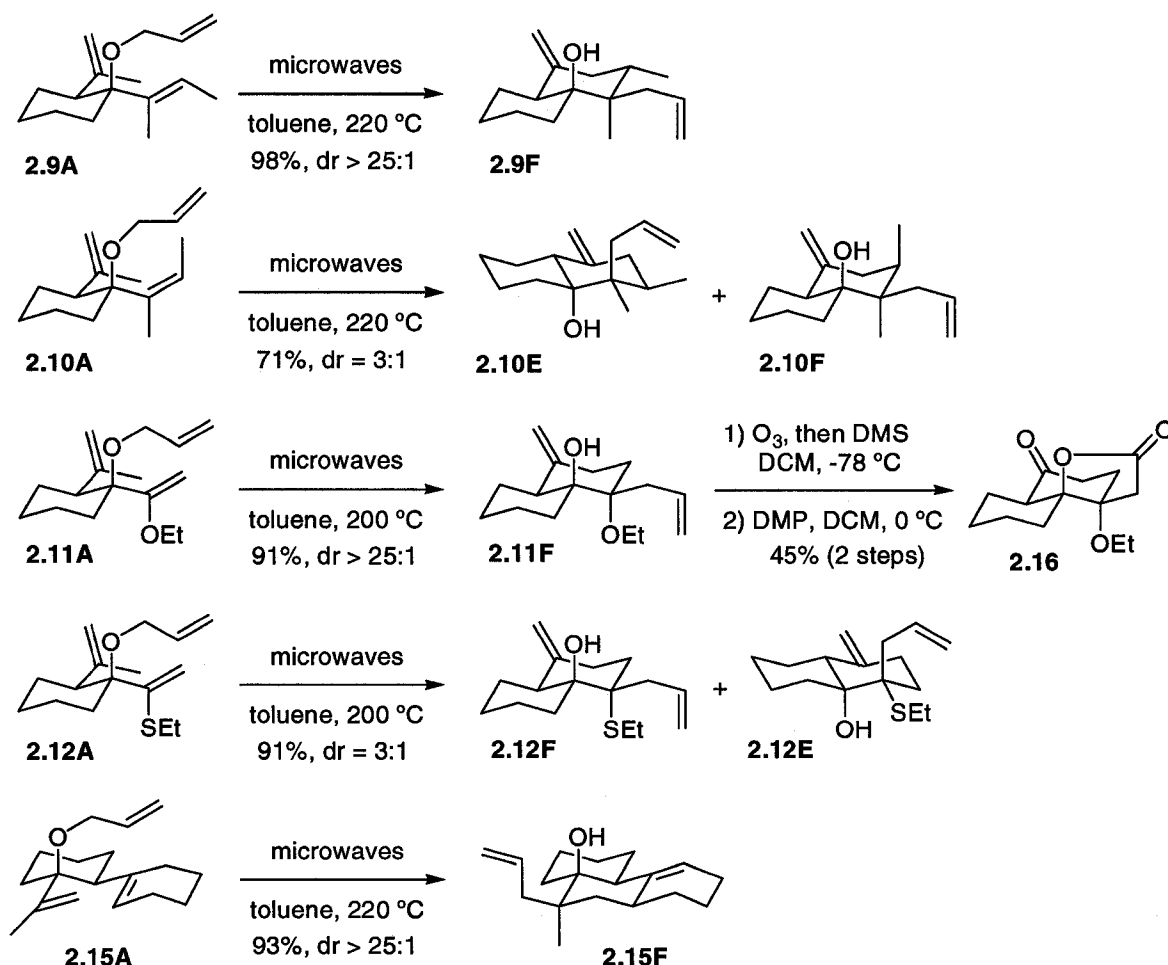
From commercially available **2.13**, substrate **2.15A** was also prepared wherein the isopropenyl group was replaced by a cyclohexene ring (Scheme 2.4).

Scheme 2.4 – Replacing an isopropenyl group with cyclohexenyl moiety



Subjecting substrates **2.9A-2.12A** and **2.15A** to microwave irradiation for 1 hour at either 200¹⁰ or 220 °C once again afforded the desired products (Scheme 2.5). With the exception of **2.11F**, the resulting stereochemistry was successfully assigned by 2D NMR. The assignment of **2.11F**, however, required a chemical proof. Ozonolysis followed by oxidation using Dess-Martin periodinane gave lactone **2.16** in 45% yield. The cyclization of the aldehyde with the tertiary alcohol confirmed the equatorial placement of the allyl group.

Scheme 2.5 – Investigating substituent effects on the outcome of the tandem reaction

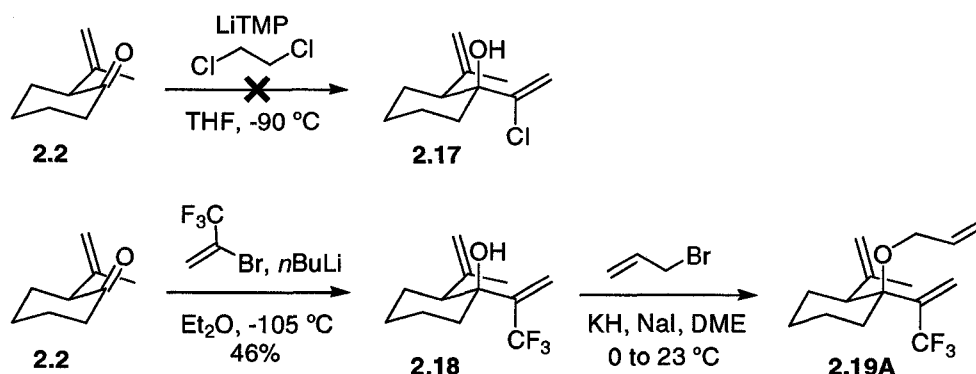


The yields for these reactions were generally excellent with four of the five substrates yielding more than 90%. More importantly, the diastereomeric ratio of all five reactions was higher than that of the originally tested compound, **2.4A**. In fact, substrates **2.9A**, **2.11A** and **2.15A** all gave a single detectable diastereomer. This is particularly noteworthy for the reaction of **2.9A** where three additional isomers could have been formed. Likewise, the reaction of **2.10A** could also have given rise to four products; while not as selective as **2.9A**, only two of the four possible products were nonetheless observed (**2.10E** and **2.10F**, in a 3:1 ratio).

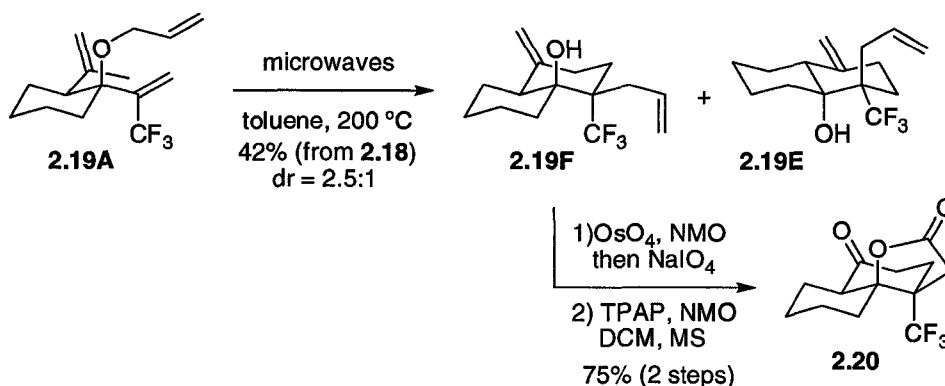
The excellent selectivity observed for ethoxy substituted **2.11A** was an unexpected, but welcomed, surprise. In contrast to the 2:1 mixture of isomers observed for the analogous substrate, methyl substituted **2.4A** (see Scheme 2.2 above), the reaction of **2.11A** gave only a single observable diastereomer. Such a dramatic change in selectivity prompted us to consider that an electronic effect might be at play. When the ethoxy group was changed to an ethyl sulfide (**2.12A**), the reaction gave a 3:1 mixture of products, **2.12F** and **2.12E**. This ratio is similar to that obtained for **2.4A**. That sulfur's electronegativity is nearly identical to that of carbon further supports the existence of an electronic influence on the reaction's mechanism.¹¹ Moreover, a steric argument can be ruled out on the grounds that the A-values of -OEt and -SMe (value for -SEt not known) are virtually the same at 0.95¹² and 1.04¹³ kcal/mol respectively. In comparison, the A-value of a methyl group is 1.74 kcal/mol.¹³ Thus, sterics would predict that the ethoxy and ethyl sulfide substrates, **2.11A** and **2.12A**, should give similar product ratios.

Interested in further probing the electronic influence of the R₁ substituent, the synthesis of chloro- and trifluoromethyl-substituted substrates was attempted (Scheme 2.6). Introduction of the chloro-substituted vinyl group was unsuccessful and the in situ preparation of 1-chloro-vinyl lithium from 1,2-dichloroethane and LiTMP,¹⁴ followed by alkylation onto ketone **2.2**, gave no detectable reaction. Preparation of the trifluoromethyl-substituted substrate was more successful and the alkylation of ketone **2.2** gave compound **2.19** in 46% yield. The allylation step also proceeded well, however, the increased volatility of the product prevented its complete isolation from the petroleum ether used in purification. Consequently, a dilute solution of **2.19** (~ 1.9 M) was used in the subsequent step.

Scheme 2.6 – Preparation of chloro- and trifluoromethyl- substituted substrates



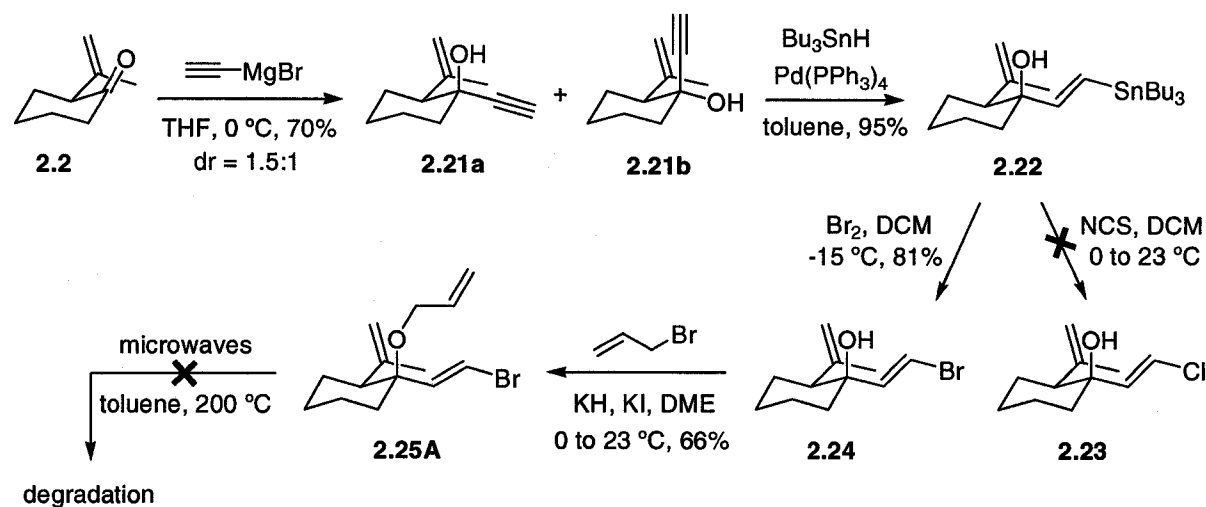
Treating trifluoromethyl-substituted **2.19A** with microwave radiation at 200 °C gave a 42% combined yield of products **2.19F** and **2.19E** as a 2.5:1 mixture (Scheme 2.7). To be sure of our stereochemical assignment, the major isomer was subjected to an oxidative cleavage of the double bonds followed by TPAP oxidation of the resulting lactol to give **2.20** in 75% yield over the two steps. The cyclization with the tertiary alcohol proved the *cis* relationship between it and the allyl substituent, leaving the trifluoromethyl group to occupy the axial position. This observed preference for the trifluoromethyl group to be axial despite its increased steric bulk¹⁵ further hints at an electronic influence on the reaction's selectivity.

Scheme 2.7 – Tandem reaction of trifluoromethyl-substituted **2.19A**

Exploring the effect of an electron withdrawing group at R₂ was also attempted (Scheme 2.8). Preparation of bromo-substituted **2.25A** began by treating ketone **2.2** with ethynylmagnesium bromide to give alcohols **2.21a** and **2.21b** in 70% yield as a 1.5:1 mixture of separable isomers. Hydrostannylation of **2.21a** proceeded well giving a 95% yield of **2.22**,

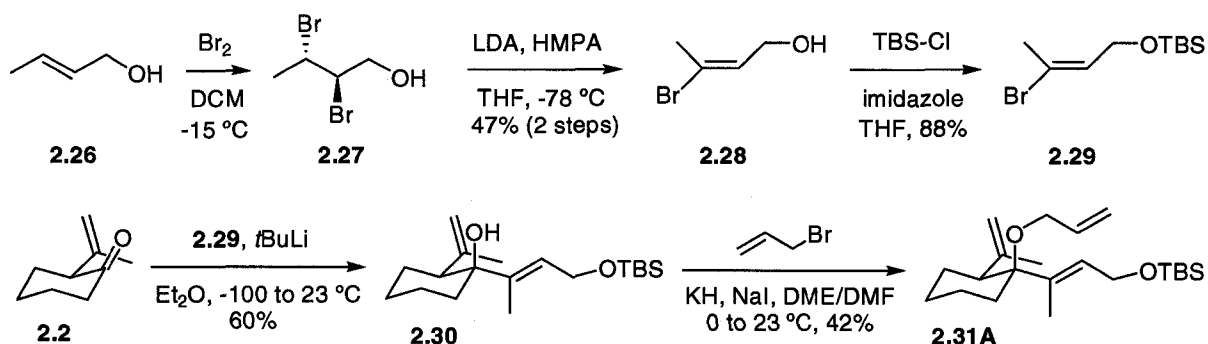
which was subsequently brominated to give **2.24** in 81% yield. Chlorination with *N*-chlorosuccinimide was also attempted, however, no reaction was observed. Finally, treatment of **2.24** with allyl bromide and potassium hydride gave the desired substrate, **2.25A**, in 66% yield. Unfortunately, heating **2.25A** in the microwave to 200 °C led to complete degradation of the substrate with no identifiable products being isolable from the reaction mixture.

Scheme 2.8 – Introducing an electron withdrawing group at R₂



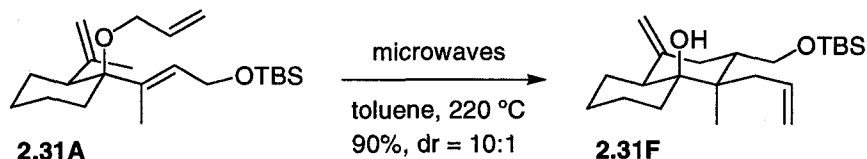
Having achieved no further success with our investigation into electronic effects, we turned our attention to introducing additional functionality to our tandem substrates. With our present examples so far limited to alkyl, ether, sulfide and trifluoromethyl substituents, it was clear that more versatile functional groups would be needed in order to apply this chemistry to natural product synthesis. Accordingly, the preparation of a vinyl halide **2.29** was pursued such that the protected alcohol could serve as a handle for future manipulations (Scheme 2.9). Following the literature procedure of Lee and Rho,¹⁶ crotyl alcohol (**2.26**) was treated with bromine to give dibrominated **2.27** which was then eliminated by LDA to give vinyl bromide **2.28** in 47% yield for the two steps. Protection with TBS-Cl gave the desired compound, **2.29**, in 88% yield. Lithium-halogen exchange followed by the addition of ketone **2.2** gave **2.30** in 60% yield. Finally, allylation of the tertiary alcohol gave a 42% yield of the functionalized tandem reaction precursor, **2.31A**.

Scheme 2.9 – Introducing additional functionality



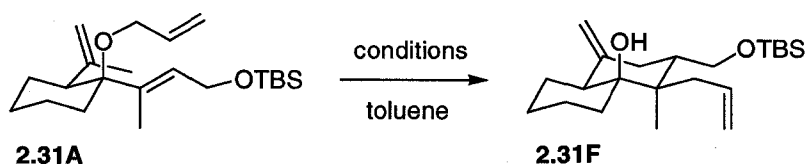
Subjecting **2.31A** to the usual reaction conditions at 220 °C gave the desired product in 90% yield as a 10:1 mixture of diastereomers (Scheme 2.10). The major product was identified as **2.31F**, however, difficulty separating the two isomers made it impossible to get a sufficiently pure sample of the minor isomer for characterization. While the successful tolerance of the TBS-protected alcohol was gratifying, the presence of a second product was disappointing. Based on the result of **2.9A**, which also had *cis* R₁ and R₂ substituents, we had expected to have a single diastereomer.

Scheme 2.10 – Tolerance of a TBS-protected alcohol



Up until this point, the oxy-Cope/Claisen/ene reactions had been run following the originally optimized procedure for the oxy-Cope/ene reaction (microwave irradiation at 220 °C for one hour). While the more sensitive substrates **2.11A** and **2.12A** had been successfully run at 200 °C, no direct effort to optimize the reaction conditions had yet been attempted. In light of the unexpected 10:1 ratio of products observed with substrate **2.31A**, we decided to use this substrate to investigate the effects of both the temperature and the heat source on the reaction's diastereoselectivity. These results are summarized in Table 2.1 below.

Table 2.1 – Effect of temperature and heat source on the reaction's diastereoselectivity



Entry	Heat source	Temp (°C)	Time (hours)	Product ratio
1	microwave	220	1	10 : 1
2	microwave	200	1	16 : 1
3	microwave	180	1	17 : 1
4	microwave	160	1	incomplete
5	sealed tube ^a	220	20	17 : 1
6	sealed tube ^a	180	18	21 : 1
7	sealed tube ^a	160	18	incomplete

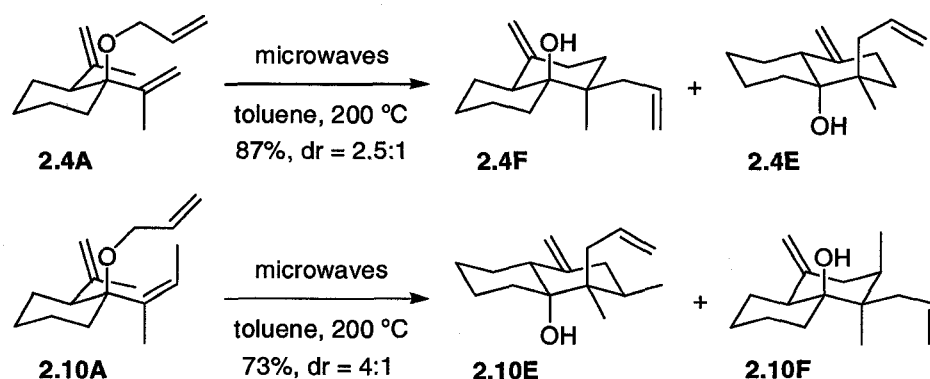
^a Reactions were run in a sealed tube immersed in a wax bath heated to the indicated temperature.

Unlike the oxy-Cope/ene reaction, which had required a temperature of 220 °C, the oxy-Cope/Claisen/ene of **2.31A** proceeded well even at 180 °C (entries 3 and 6). Lowering the temperature further to 160 °C, however, led to a sluggish reaction both under microwave and sealed tube conditions (entries 4 and 7). Not surprisingly, the diastereomeric ratio improved upon lowering the temperature with the most dramatic increase in dr occurring when the microwave temperature was dropped from 220 °C to 200 °C (entries 1 and 2). Reactions occurring in the sealed tubes took substantially longer to go to completion and, by TLC, considerable degradation was evident. Comparing their diastereoselectivity to those of the microwave reactions, however, revealed an improved product ratio. This unanticipated finding could be explained by a discrepancy between the recorded and actual temperatures in the microwave vessel. Since the reactions are run in toluene, a relatively non-polar solvent, insufficient microwave energy is absorbed by the system to heat the reaction to the desired temperature. To overcome this, microwave-absorbing carboflonsTM (Teflon doped with graphite) are added to the reaction vessel. When the carboflonsTM heat up, they transfer heat by passive diffusion to the bulk solvent, the temperature of which is measured by a fiber optic probe. Since the temperature at the surface of the carboflon is not measured directly, and the reaction is not stirred, it is likely that the temperature in the reaction mixture is not

uniform and that “hot spots” exist. Alternatively, reactions could be taking place at the surface of the carboflon where the temperature is likely much higher. Reactions occurring at these higher temperatures can be expected to give decreased selectivity making the overall diastereoselectivity of the microwave reactions lower than the corresponding sealed tube reactions. From the results in Table 2.1, it could be suggested that future reactions ought to be run using conventional heating at 180 °C. Weighing the longer reaction times against the improved selectivity, however, it was decided that microwave irradiation at 200 °C would be the optimal conditions. (Heating to 180 °C did not offer sufficient improvement in the selectivity to warrant the risk of having unreacted starting material with other, perhaps less reactive substrates).

With a newly optimized reaction temperature, the reactions of substrates **2.4A** and **2.10A** were repeated in the hopes of improving their selectivity (Scheme 2.11). Indeed, lowering the temperature by 20 °C gave rise to improved diastereomeric ratios, however, the increases were less dramatic than that observed with **2.31A**. Substrate **2.4A** went from giving a 2:1 ratio of isomers to a 2.5:1 ratio while substrate **2.10A** had its ratio improved from 3:1 to 4:1.

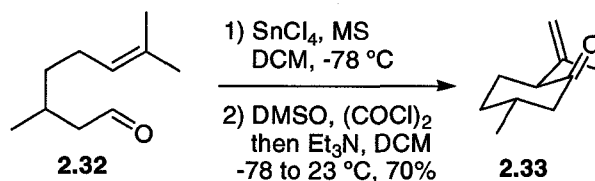
Scheme 2.11 – Repeating reactions at a lower temperature



While the increased selectivity brought on by lowering the reaction temperature was rewarding, we hoped that further improvements could be made by the addition of a remote stereocentre along the backbone of the cyclohexyl ring. As suggested by the findings of Still and Galynker,¹⁷ an appropriately placed equatorial substituent could be enough to bias the conformational preferences of the 10-membered ring intermediates and ensure the formation

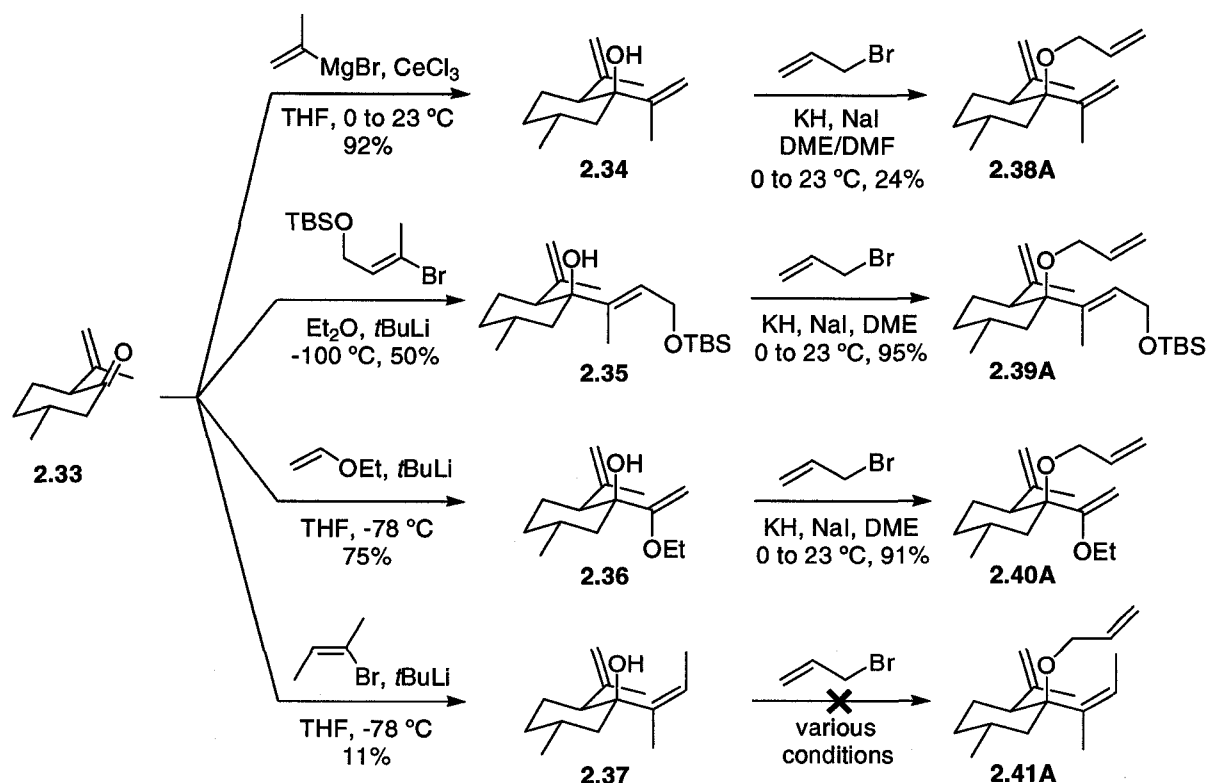
of a single isomer. To test this idea, substrates derived from isopulegone (**2.33**) were targeted (Scheme 2.12).

Scheme 2.12 – Synthesis of isopulegone from citronellal



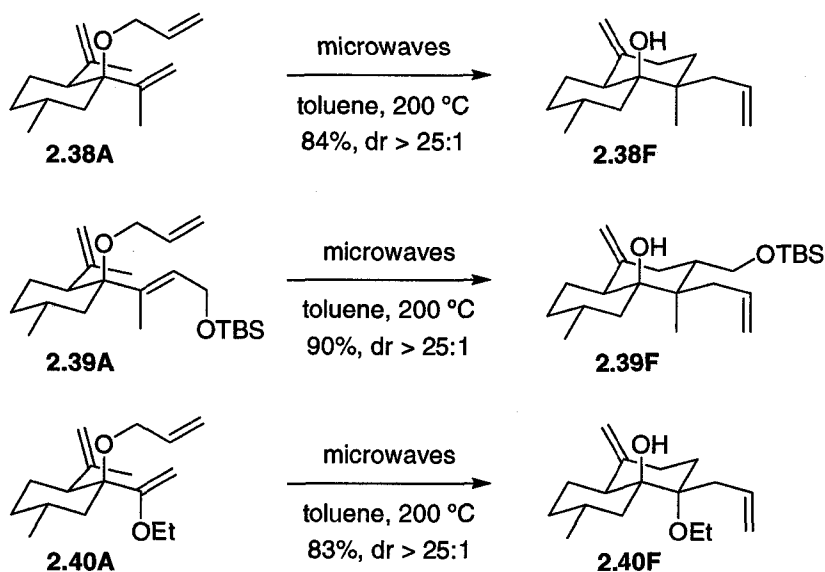
Following procedures used for the previously prepared substrates, isopulegone was alkylated with various vinyl lithium species to give substrates **2.34-2.37**. Alkylation of the tertiary alcohols proceeded well for substrates **2.36** and **2.37**, however, the reaction of **2.34** gave a meager 24% yield of **2.38A** while the alkylation of **2.37** afforded nothing but unreacted starting material (Scheme 2.13).

Scheme 2.13 – Introduction of an equatorial methyl group for remote stereocontrol



Substrates **2.38A**-**2.40A** were heated in the microwave to 200 °C and their products isolated. In all cases, only a single diastereomer was found to be present (Scheme 2.14). For substrate **2.38A**, this selectivity is especially notable given that the analogous substrate, **2.4A**, had given a 2.5:1 ratio of products under identical reaction conditions. These results clearly demonstrate that a single equatorial substituent can be sufficient to control the diastereoselectivity of these tandem reactions. For future applications in synthesis, such knowledge could prove useful when designing novel oxy-Cope/Claisen/ene substrates.

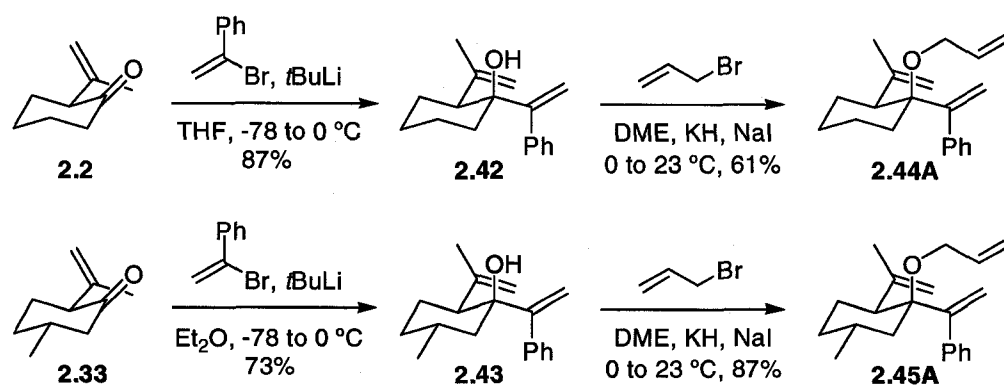
Scheme 2.14 – Effect of an equatorial methyl group on the diastereoselectivity of the reaction



While the above results showed remarkable potential for controlling the diastereoselectivity of the tandem reaction, we wondered how effective this approach would be if the R_1 substituent was increased in size. Of the products isolated thus far, the allyl group of the quaternary carbon has always preferred to be equatorial rather than the R_1 substituent. If R_1 was changed to a bulkier phenyl group, however, this preference might change. If so, it would be worth knowing whether the presence of a remote equatorial methyl group would continue to be sufficient to override such competing preferences.

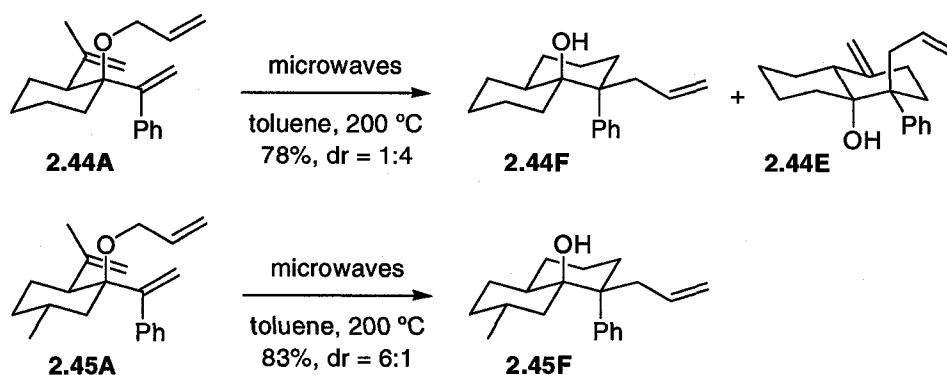
To answer this question, substrates **2.44A** and **2.45A** were targeted. Alkylation of ketones **2.2** and **2.33** with the vinyllithium of α -bromo-styrene proceeded well giving **2.42** and **2.43** in 87% and 73% yield, respectively (Scheme 2.15). Subsequent allylation of the tertiary alcohols gave the tandem reaction precursors in 61% and 87% yield.

Scheme 2.15 – Preparation of simple phenyl-substituted substrates



Reacting phenyl substituted **2.44A** in the microwave at 200 °C for 1 hour afforded the oxy-Cope/Claisen/ene product in 78% yield as a 1:4 mixture of isomers (Scheme 2.16). Assignment of the relative stereochemistry revealed **2.44E** to be the major product. This change in preference for the **E** isomer was not surprising given its equatorial placement of the bulky phenyl substituent. Conversely, **2.45A** reacted under identical reaction conditions to give **2.45F** as the major product as a 6:1 mixture with an unidentified second isomer. While the presence of the equatorial methyl group was not sufficient to completely override the inherent preference for the equatorial phenyl group, it was, nonetheless, able to induce a more than 4-fold increase in the formation of the **F** isomer.

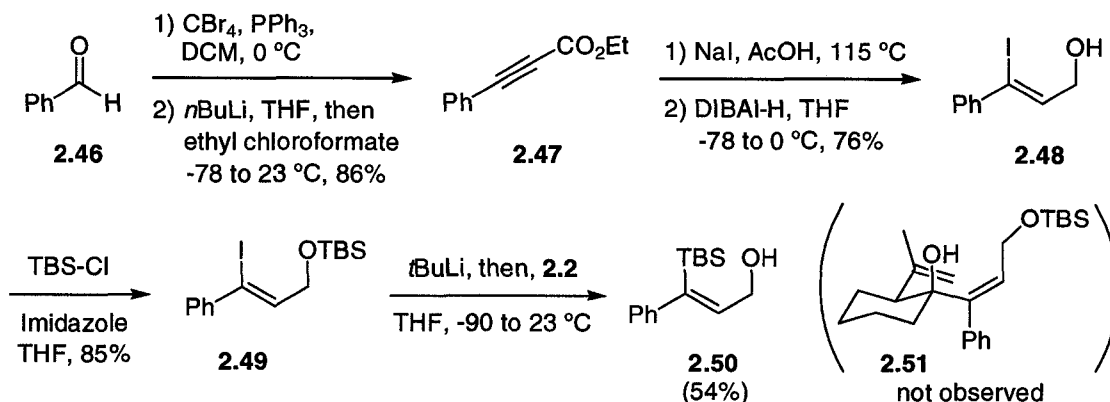
Scheme 2.16 – Oxy-Cope/Claisen/ene of simple phenyl-substituted substrates



Alongside the above efforts, substrates based on vinyl iodide **2.48** were also targeted (Scheme 2.17). A Corey-Fuchs¹⁸ reaction of benzaldehyde (**2.46**) and subsequent trapping of the alkynyllithium with ethyl chloroformate gave **2.47** in 86% yield for the two steps (note: **2.47** is also commercially available). Michael addition of sodium iodide followed by

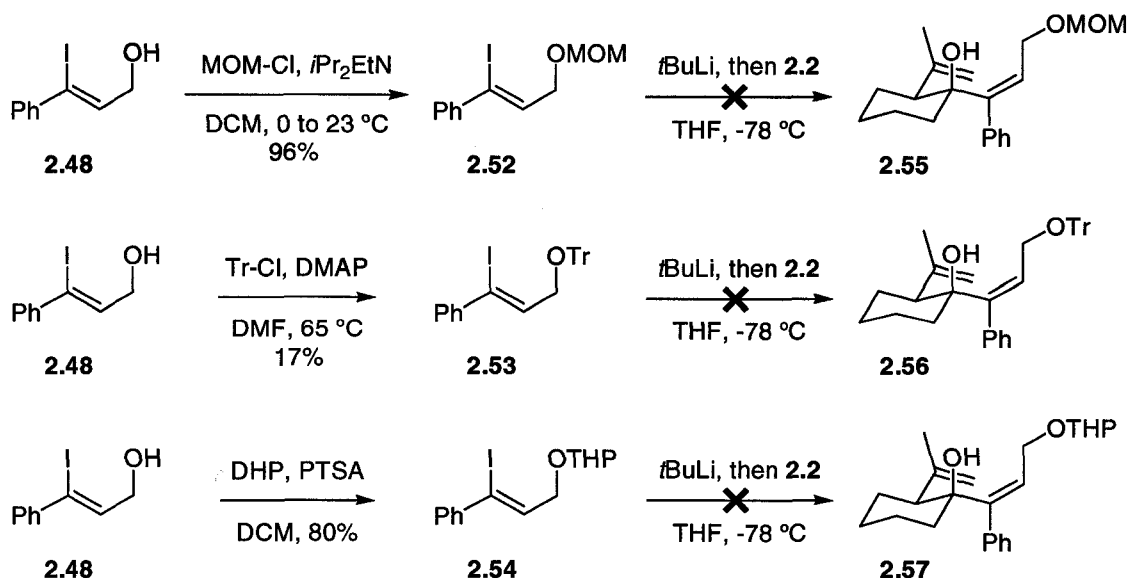
reduction with DIBAL-H gave **2.48** in 76% yield. Given the established tolerance of the tandem reaction for the TBS protecting group, alcohol **2.48** was protected with TBS-Cl in 85% yield to give **2.49**. Alkylation of ketone **2.2** with the vinyl lithium of **2.49**, however, gave primarily unreacted starting material together with a 54% yield of vinyl silane **2.50**.

Scheme 2.17 – First attempt at preparing trans-substituted phenyl substrates



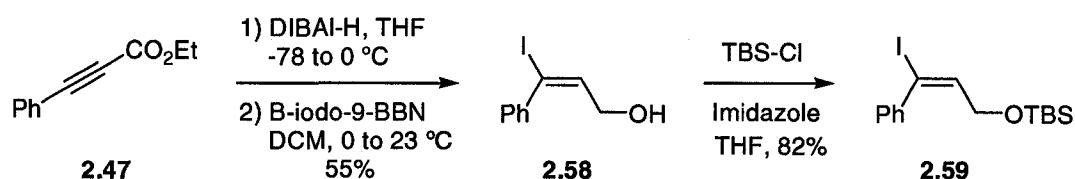
In light of the apparent retro-Brook rearrangement¹⁹ of the vinyl lithium species, a series of non silyl-based protecting groups was investigated: THP, MOM and Trityl protected substrates **2.52-2.54** were prepared from alcohol **2.48** (Scheme 2.18). In all cases, however, treatment with *tert*-butyllithium, followed by ketone **2.2** failed to give any of the desired alkylated species. Rather, unreacted ketone was recovered.

Scheme 2.18 – Alternative protecting groups for the trans-substituted phenyl substrates



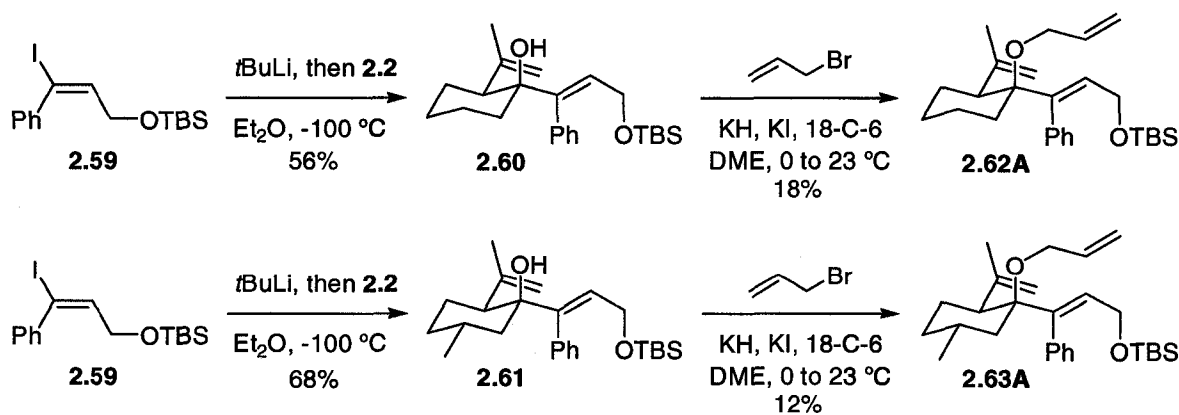
Given the lack of reactivity observed with the lithium species of substrates **2.52-2.54**, we decided to change the geometry of the double bond from *Z* to *E* in order to reduce some of the steric hindrance around the carbanion. Accordingly, *cis*-substituted vinyl iodide **2.59** was targeted (Scheme 2.19). From **2.47**, reduction to the primary alcohol followed by treatment with B-iodo-9-BBN gave **2.58** in 55% yield for the two steps. Subsequent protection with TBS-Cl gave **2.59** in 82% yield.

Scheme 2.19 – Synthesis of *cis*-substituted phenyl vinyl iodide **2.59**



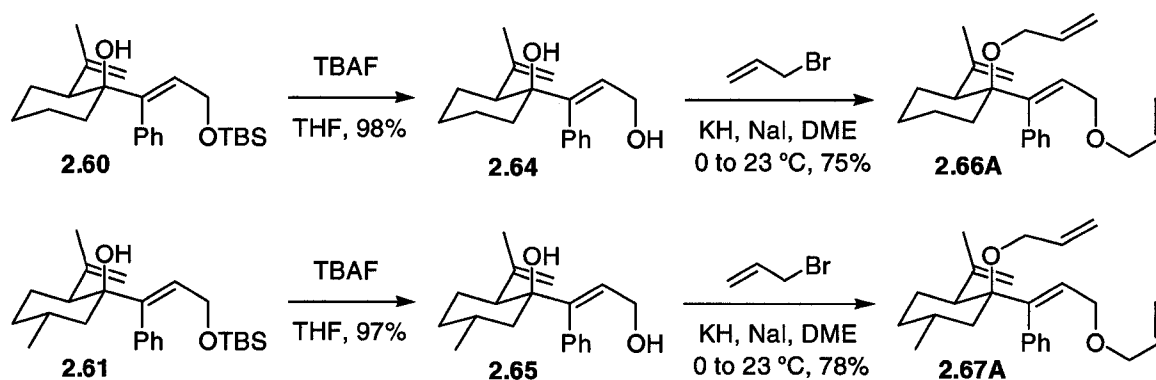
Alkylation onto ketones **2.2** and **2.33** with the vinyl lithium species of **2.59** proceeded well with **2.60** and **2.61** being isolated in 56% and 68% yield, respectively (Scheme 2.20). Allylation of the tertiary alcohols, however, proved difficult and substrates **2.62A** and **2.63A** were obtained with yields of just 18% and 12%. In addition to these low yields, both products were contaminated with an unidentified substance, which, despite several attempts at purification, could not be removed. With only a small amount of impure material available, the tandem oxy-Cope/Claisen/ene reactions of these substrates was not further pursued.

Scheme 2.20 – Preparation of *cis*-substituted phenyl substrates



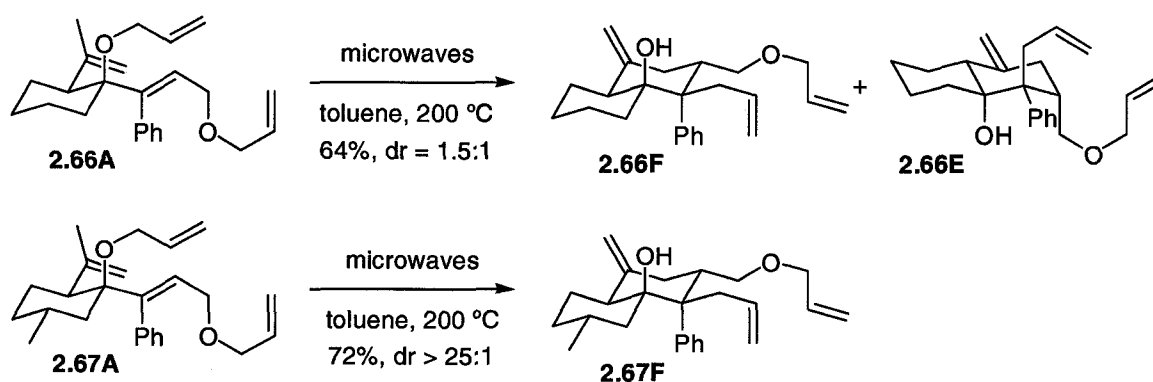
Having noticed a general trend that the allylation step of these tertiary alcohols was dependent on the “greasiness” of the substrate, it was thought that perhaps removal of the TBS group would facilitate the reaction. To test this theory, substrates **2.60** and **2.61** were deprotected with TBAF and the resulting diols were allylated with excess allyl bromide (Scheme 2.21). In contrast to the TBS-protected substrates, the allylation of these compounds proceeded well giving bis-allylated **2.66A** and **2.67A** in 75% and 78% yield, respectively.

Scheme 2.21 – Preparation of bis-allylated, phenyl-substituted substrates



The results of the tandem oxy-Cope/Claisen/ene reaction of compounds **2.66A** and **2.67A** are shown in Scheme 2.22 below. Substrate **2.66A** gave a 1.5:1 mixture of isomers favouring **2.66F**. It is notable that while the *cis*-substitution of the alkyl groups for these substrates is analogous to that of the highly selective compounds **2.9A** and **2.31A**, the increased steric bulk of the phenyl group has a detrimental effect on the diastereoselectivity of the reaction. In contrast, the reaction of compound **2.67A** gave a single detectable isomer, **2.67F**, once again highlighting the ability of a remote stereocentre to control the stereoselectivity of the tandem oxy-Cope/Claisen/ene reaction.

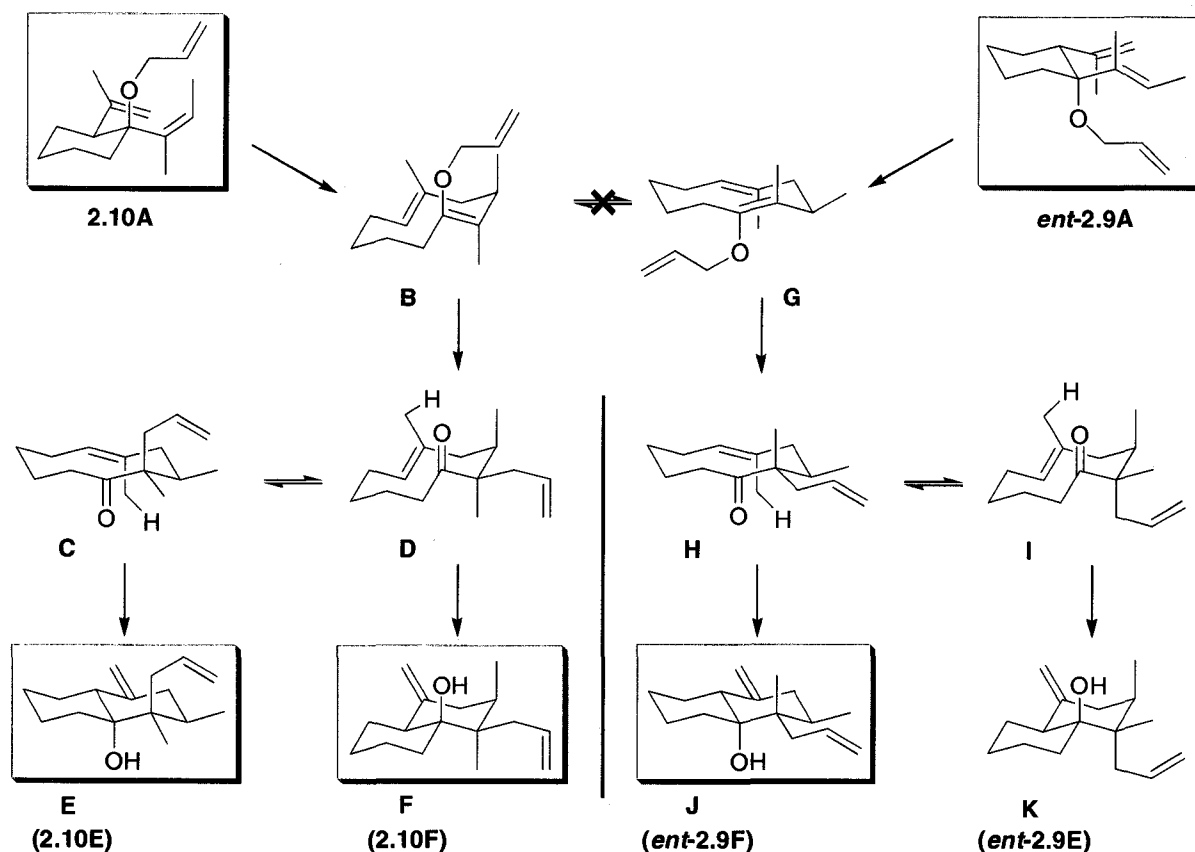
Scheme 2.22 – Tandem reactions of phenyl substituted substrates



Investigating the Origin of Diastereoselectivity

With more than a dozen examples of successful tandem oxy-Cope/Claisen/ene reactions, our attention was turned to understanding the factors controlling the diastereoselectivity of this reaction cascade. Immediately apparent from the observed product distributions was an overwhelming preference for the **E** and **F** isomers: of the ten substrates which could have produced four products (i.e. substrates with either R_2 or $R_3 \neq H$), none gave rise to products corresponding to the **J** and **K** isomers (though substrates **2.31A** and **2.67A** did yield minor products, the stereochemistry of which was never determined). This observation led to the hypothesis that the ring inversion between intermediates **B** and **G** does not compete with the Claisen rearrangement of **B** to **D** (Figure 2.2).

Further evidence to support this claim can be found by taking a more detailed look at the reaction of substrates **2.9A** and **2.10A**. If one takes the enantiomer of **2.9A**, *ent*-**2.9A**, it becomes apparent that these substrates feed into the same reaction mechanism (Figure 2.4). If interconversion of intermediates **B** and **G** was occurring, substrates **2.9A** and **2.10A** should give rise to the same products. Treating **2.10A** in the microwave at 200 °C for 1 hour, however, gives a mixture of **E** (**2.10E**) and **F** (**2.10F**), while the reaction of *ent*-**2.9A** gives isomer **J** (*ent*-**2.9F**). That these substrates give entirely different product distributions is clear evidence that the ring inversion converting **B** and **G** is not occurring for these substrates.

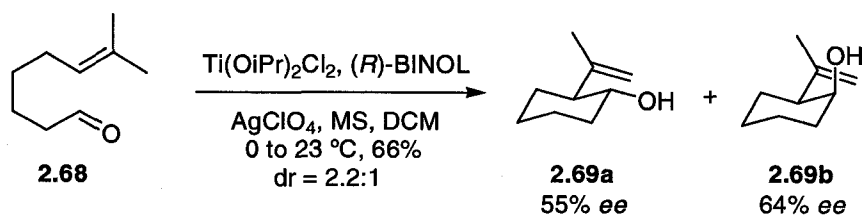
Figure 2.4 – Converging mechanisms for substrates **2.9A** and **2.10A**

While the above analysis lends strong support for a high energy ring inversion of **B** to **G** for substrates **2.9A** and **2.10A**, generalizing to the remaining substrates, particularly to those bearing substitution only at R_1 , is difficult. Recall that when $R_2 = R_3 = H$, intermediate **B** bears no chiral centres and the two halves of the reaction mechanism become enantiomeric (see Figure 2.3 above). Since all of the substrates tested have been racemic, the existence of an equilibrium between **B** and **ent-B** has been undetectable. In order to determine whether the ring inversion was occurring for such mono-substituted substrates ($R_1 \neq H$, $R_2 = R_3 = H$), the use of enantioenriched compounds was envisioned such that any interconversion between **B** and **ent-B** would be easily detectable as a loss of enantiomeric excess in the final products.

The synthesis of chiral substrates would require access to a chiral version of ketone **2.2**. Mikami et al. reported the use of a Ti-BINOL complex capable of inducing a chiral carbonyl ene reaction of **2.68** to give alcohols **2.69a** and **2.69b** in 55% and 64% *ee*, respectively (Scheme 2.23).²⁰ Oxidation of these alcohols would afford a chiral version of

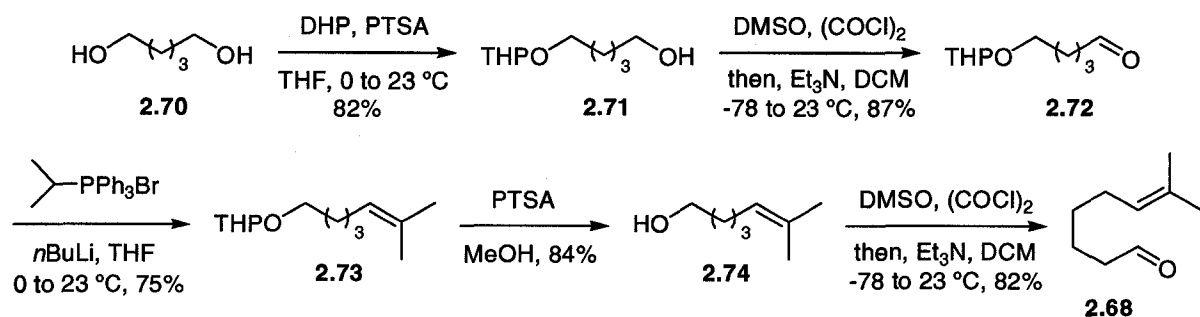
ketone **2.68**. Since we were only interested in detecting changes in *ee* during the reaction, enantiopure substrates would not be required and Mikami's protocol would be sufficient for our purposes.

Scheme 2.23 – Mikami's chiral carbonyl ene reaction



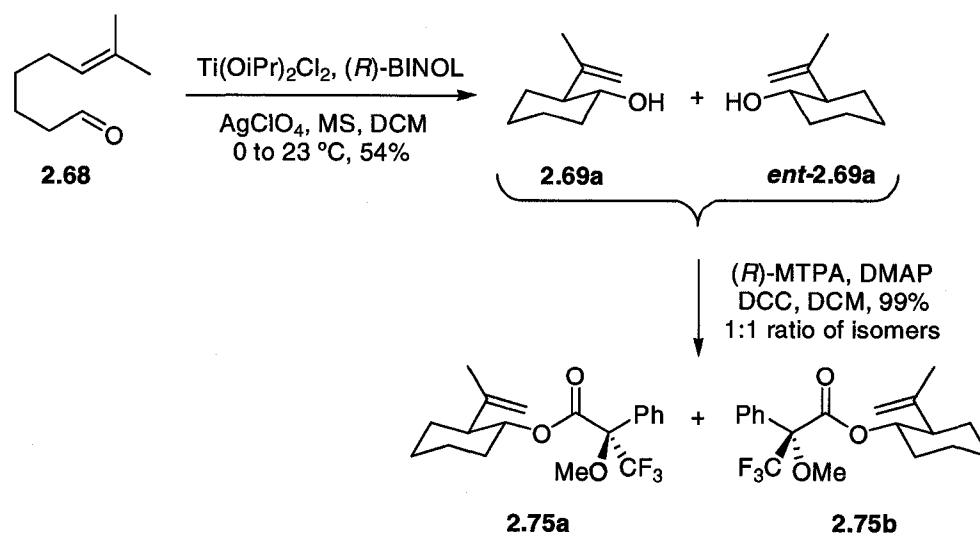
Preparation of **2.68** following Sakane's literature procedure²¹ was originally undertaken by honor's student Jennifer Racine, and later scaled up by myself (Scheme 2.24). Mono-protection of 1,6-hexanediol (**2.70**) with a THP group followed by a Swern oxidation gave aldehyde **2.72** in good yield. A Wittig reaction with commercially available isopropyltriphenylphosphonium bromide and subsequent removal of the THP protecting group gave alcohol **2.74**. Finally, a second Swern oxidation yielded the desired carbonyl ene reaction precursor, **2.68**.

Scheme 2.24 – Preparation of the chiral ene reaction precursor

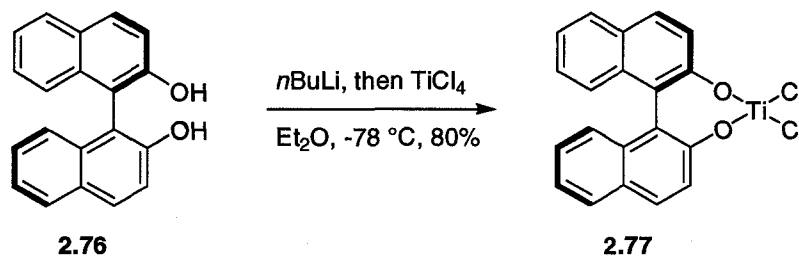


Treatment of **2.68** with Mikami's originally reported conditions gave **2.69a** in 54% yield (**2.69b** was formed, but not isolated). Unfortunately, conversion to the known Mosher's ester^{20b} using $(+)\alpha$ -methoxy- α -(trifluoromethyl)phenylacetic acid, DMAP and DCC gave **2.75a** and **2.75b** in a 1:1 ratio, indicating an *ee* of 0% for the carbonyl ene product **2.69a** (result by Jennifer Racine).

Scheme 2.25 – First attempt at the chiral ene reaction (result by Jennifer Racine)

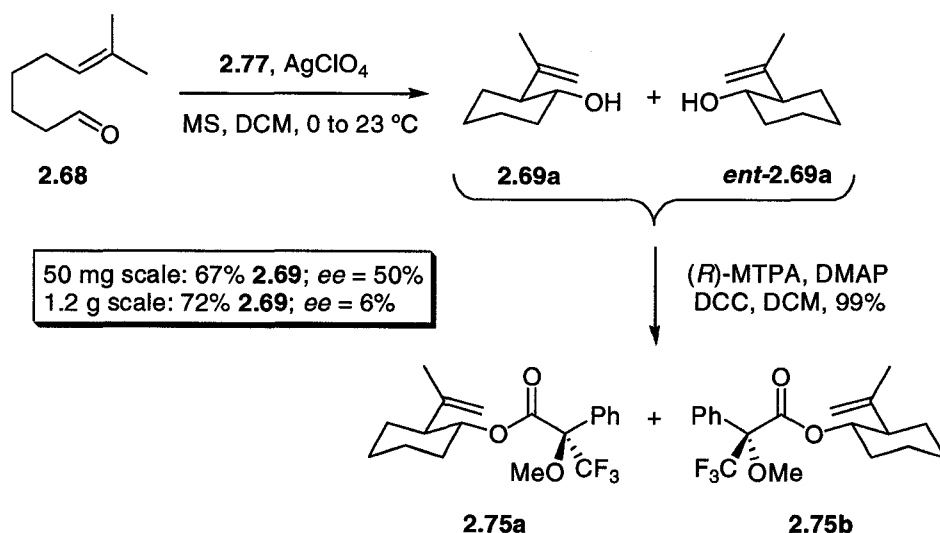


The lack of chiral induction during the reaction of **2.68** suggested that the in situ formation of the Ti-BINOL complex was incomplete leaving unreacted $\text{Ti}(\text{iOPr})_2\text{Cl}_2$ to catalyze the achiral reaction. To avoid this problem, catalyst **2.77** was prepared directly following the procedure reported by Reetz et al (Scheme 2.26).²² Treatment of (*R*)-BINOL (**2.76**) with *n*-butyllithium followed by TiCl_4 gave **2.77** as an orange solid in 80% yield.

Scheme 2.26 – Preparation of Ti-BINOL complex **2.77**

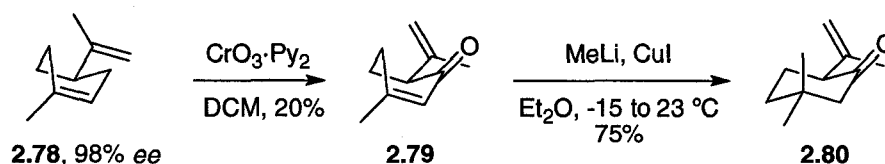
Repeating the carbonyl ene reaction of **2.68** in the presence of preformed catalyst **2.77**, AgClO_4 and 4Å molecular sieves gave **2.69a** in 67% yield (Scheme 2.27). Following quantitative conversion to the MTPA esters, a diastereomeric ratio of 3:1 was observed, corresponding to an *ee* of 50% for the parent alcohol, **2.69a**. Upon scaling up the reaction, however, (including preparation of a new batch of catalyst) the *ee* of **2.69a** was found to be a mere 6%.

Scheme 2.27 – Chiral ene reaction with pre-formed catalyst 2.77



In light of the difficulties encountered with *reliably* preparing **2.69a** in suitable *ee*, a new route to the chiral substrates was investigated. It was known from previous work in our laboratory that ketone **2.80** was readily accessible from limonene (**2.78**) in 98% *ee* (Scheme 2.28).²³ Although the allylic oxidation with Collins' CrO₃·Py₂ complex²⁴ was low-yielding, the steps were reliable and multi-gram quantities of **2.80** could be easily prepared.

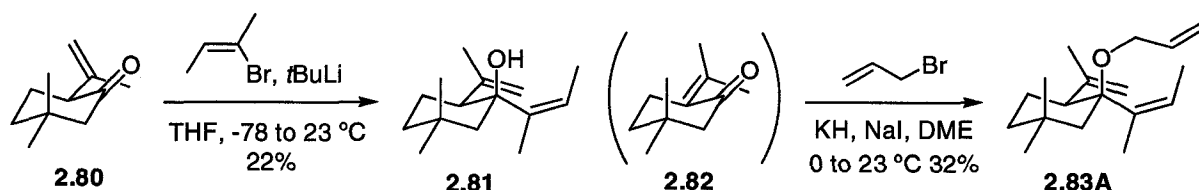
Scheme 2.28 – Preparation of chiral ketone 2.80 from limonene



As the addition of the *gem*-dimethyl group does not create any new stereocentres, substrates derived from **2.80** would still give rise to enantiomeric intermediates **B** and *ent*-**B**. Before adopting this new scaffold for our chiral substrates, however, we wanted to be sure that the *gem*-dimethyl group would not interfere with the relative kinetics of the reaction. To this end, substrate **2.83A** was prepared. If the *gem*-dimethyl group influenced the reaction outcome, **2.83A** would likely give a different product ratio than that obtained with the analogous substrate, **2.10A**.

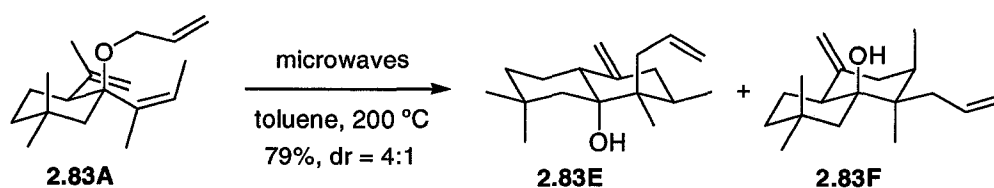
Alkylation of **2.80** with the lithium species of (Z)-2-bromo-2-butene gave **2.81** in 22% yield, along with **2.82** in 42% yield (Scheme 2.29). The undesired side product could likely have been avoided with the use of an organocerium reagent, however, for our purposes, sufficient quantities of **2.81** were obtained and the reaction was never repeated. Allylation of **2.81** gave **2.83A** in 32% yield along with recovered starting material.

Scheme 2.29 – Preparation of **2.83A** for testing the influence of the *gem*-dimethyl group

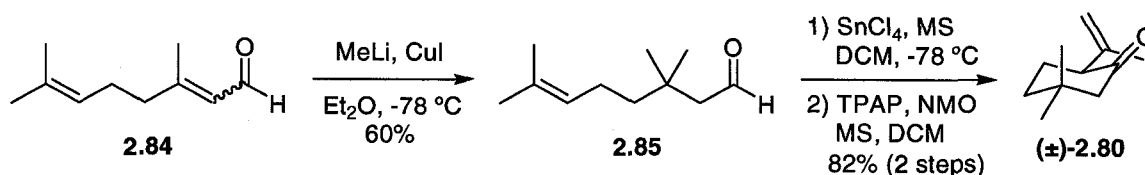


The oxy-Cope/Claisen/ene reaction of **2.83A** proceeded smoothly and the desired product was obtained in 79% yield as a 4:1 mixture of isomers **2.83E** and **2.83F** (Scheme 2.30). Notably, this diastereomeric ratio was identical to that obtained with **2.10A**, indicating that the presence of the *gem*-dimethyl group does not interfere with the relative kinetics of the reaction to any appreciable extent.

Scheme 2.30 – Testing the influence of the *gem*-dimethyl group

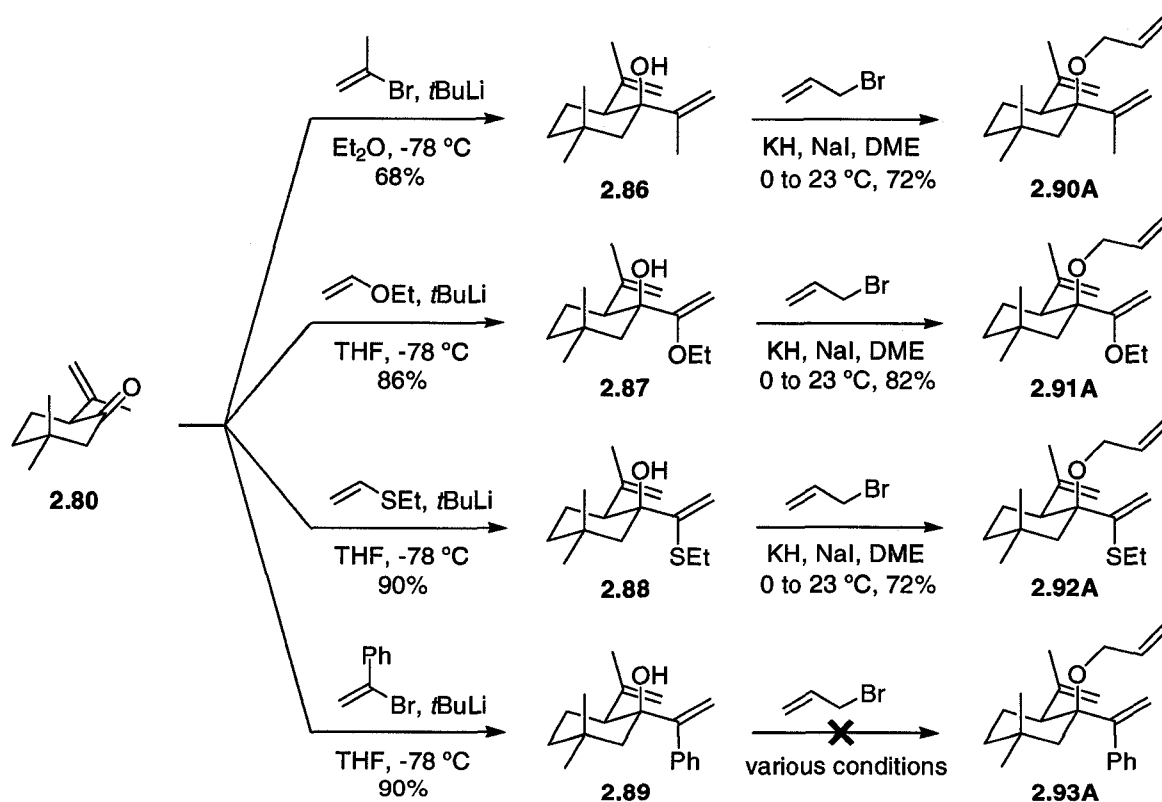


Having assured ourselves that this new substrate class would be a suitable model for probing the ring inversion of **B** to *ent*-**B**, we turned our attention to the preparation of the desired chiral substrates. In order to develop HPLC/GC conditions for measuring the *ee* of the oxy-Cope/Claisen/ene products, racemic versions of these substrates were also required. To avoid the low-yielding allylic oxidation of **2.78** to **2.79**, however, an alternative route was employed. From citral (**2.84**), a cuprate addition of methyllithium gave **2.85** in 60% yield (Scheme 2.31). A subsequent Lewis-acid induced carbonyl ene reaction followed by a TPAP oxidation thus gave racemic **2.80** in 82% yield for the two steps.

Scheme 2.31 – Preparation of racemic ketone **2.80**

From ketone **2.80**, synthesis of both the enantioenriched tandem precursors and their racemic equivalents was initiated (Scheme 2.32). Alkylation with various vinyl lithium species gave alcohols **2.86–2.89** in yields ranging from 68% to 90%. Allylation of the tertiary alcohols also proceeded well with the exception of phenyl-substituted substrate **2.89** which failed to react despite several attempted reaction conditions.

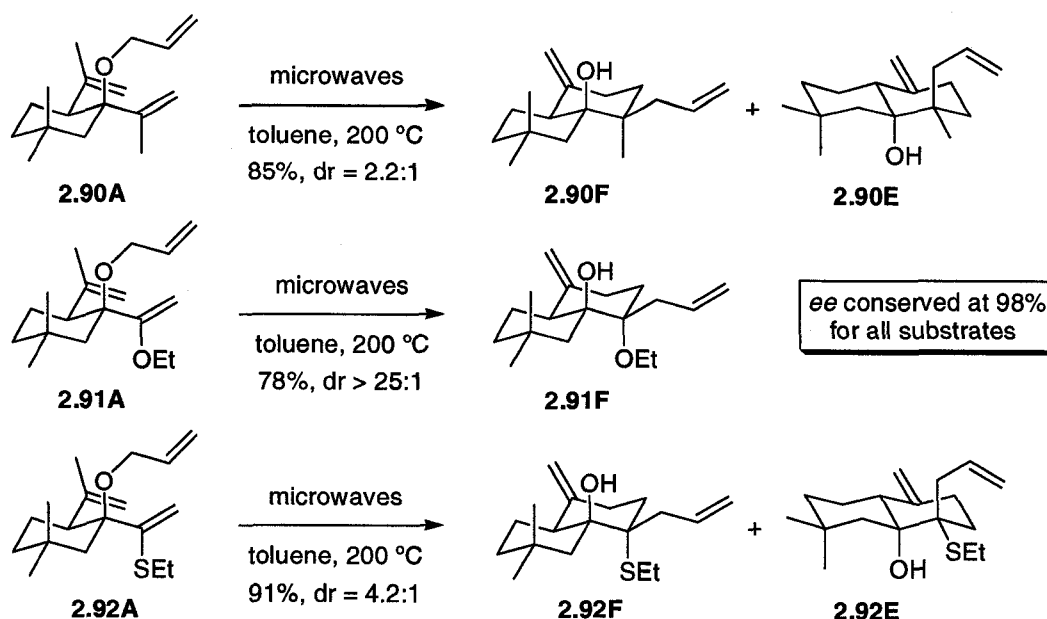
Scheme 2.32 – Preparation of chiral tandem precursors



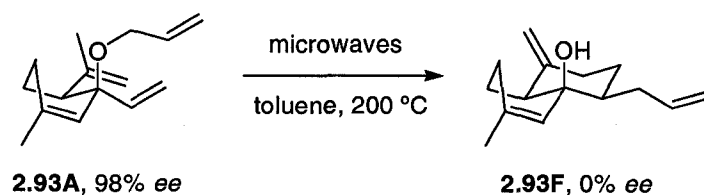
Subjecting both the chiral and racemic versions of substrates **2.90A–2.92A** to microwave irradiation at 200 °C yielded the desired products in 85%, 78% and 91% yield respectively (Scheme 2.33). In all cases, the enantiopurity of the products was completely

conserved at 98% as determined by chiral GC analysis. These results confirm that the interconversion of **B** and *ent*-**B** does not compete with the Claisen rearrangement of **B** to **D** for those substrates bearing substitution only at R₁. Moreover, it should be pointed out that the observed diastereoselectivities closely reflect those obtained previously for the analogous substrate series, **2.4A**, **2.11A**, and **2.12A**, further confirming that the *gem*-dimethyl group does not interfere with the relative kinetics of the process.

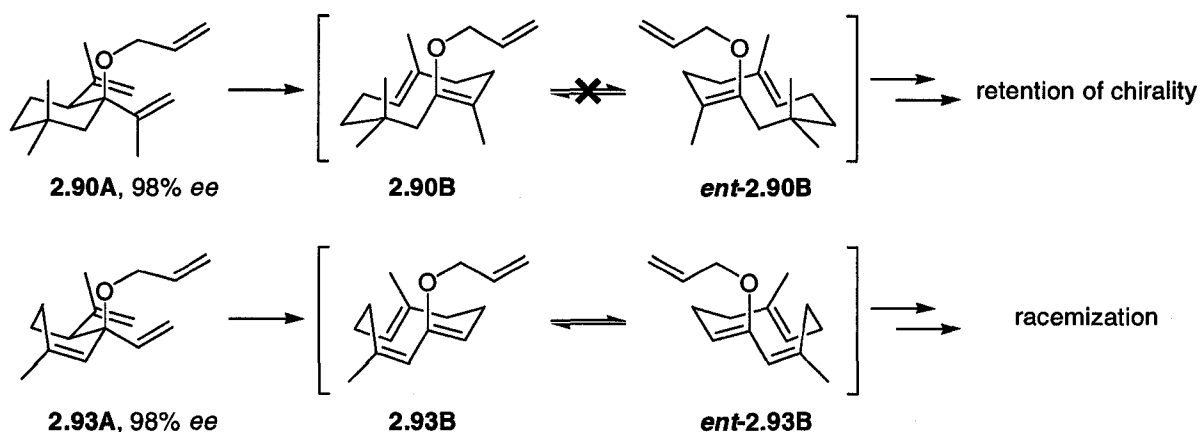
Scheme 2.33 – Oxy-Cope/Claisen/ene of chiral substrates; conservation of *ee*



The results of this chiral study, together with the previously discussed results obtained with *cis*- and *trans*- methyl substituted **2.9A** and **2.10A** (Figure 2.4), suggest that for a wide range of substrates, the ring inversion of **B** to **G** (or *ent*-**B**) is a high energy process which is unable to compete with the Claisen rearrangement. Importantly, this translates into a higher degree of diastereoselectivity such that two out of the four possible products are inaccessible (**J/ent-F** and **K/ent-E**). It could be tempting, based on the above studies, to suggest that these relative kinetics are always true. However, a result by former graduate student Danny Gauvreau²⁵ has shown this not to be the case (Scheme 2.34): Chiral substrate **2.93A** (*ee* = 98%) was subjected to microwave irradiation at 200 °C for one hour. The product of the resulting oxy-Cope/Claisen/ene reaction, **2.93F**, was isolated in its racemic form indicating that the inversion between **B** and *ent*-**B** readily occurs for this substrate.

Scheme 2.34 – Conflicting result by Danny Gauvreau: racemization of **2.93A**

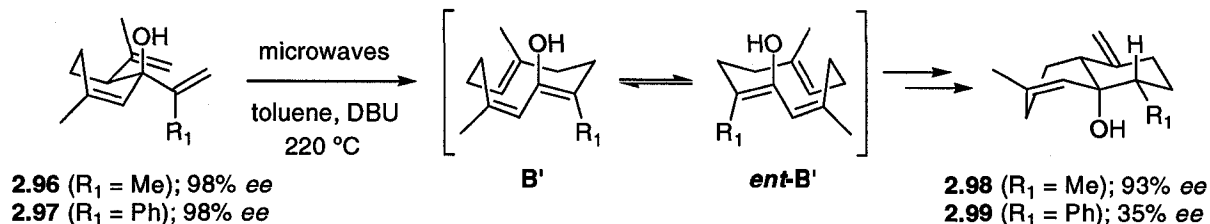
The seemingly obvious explanation for these conflicting results is the degree of olefin substitution found on the enol ether intermediates: the oxy-Cope product of **2.90A** bears a tetrasubstituted enol ether olefin while that of **2.93A** is trisubstituted (Figure 2.5). Based on the findings of Marshall et al. (See Chapter 1, Figure 1.6), inversion of the tetrasubstituted olefin should be the higher energy process suggesting that its presence is what prevents the racemization of **2.90A**.

Figure 2.5 – Tri- versus tetra- substituted enol ether intermediates **B**

The assertion that a tetrasubstituted olefin in intermediate **B** prevents the ring inversion from occurring appears, at first, to be a viable hypothesis. Results obtained during the study of the oxy-Cope/ene reaction, however, have strongly suggested that the ring inversion of a tetrasubstituted olefin is possible. Prompted by the observed loss of chirality during the synthesis of (+)-arteannium M (see Chapter 1, Scheme 1.4 and Figure 1.7), Danny Gauvreau went on to demonstrate the generality of this phenomenon. Substrates **2.96** and **2.97** (*ee* = 98%) were subjected to microwave irradiation and the *ee* of the products analyzed. Oxy-Cope/ene product **2.98** ($R_1 = \text{Me}$) was isolated in 93% *ee* while **2.99** ($R_1 = \text{Ph}$) was found to have an *ee* of just 35%.²⁶ The observed partial racemization was rationalized by a facile ring

inversion of the 10-membered enol intermediate, **B'**, which, incidentally, requires the rotation of a tetrasubstituted olefin through the ring.

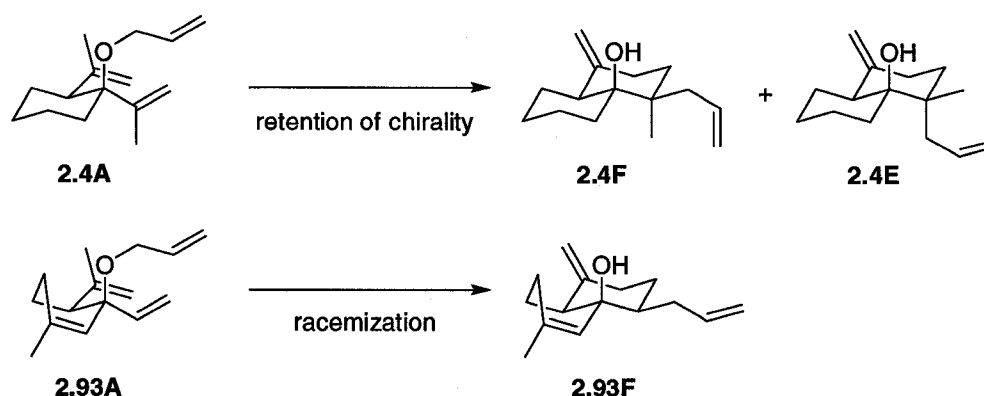
Scheme 2.35 – Ring inversion during the oxy-Cope/ene reaction (results by Danny Gauvreau)



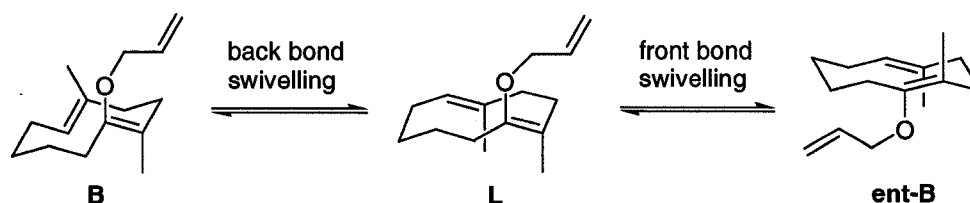
While the above observations suggest that the ring inversion of a tetrasubstituted olefin through a 10-membered ring is possible, they provide no information regarding the energy for such a process. In fact, a scan of the literature reveals no attempt to determine the associated activation energy, either experimentally²⁷ or theoretically.²⁸ In order to advance the scope of our oxy-Cope/Claisen/ene reaction, it would be beneficial to know the relative energies for the Claisen rearrangement of **B** to **D** compared to the ring inversion of **B** to **G** (or **B** to **ent-B**) for substrates both with and without substitution at R_1 . Such information would allow us to determine how reliably the ring inversion, and consequently, the formation of additional diastereomers, could be avoided. To this end, computational methods were pursued in order to map out the potential energy surface for the tandem reactions.

Compound **2.4A** was chosen to be representative of those substrates bearing substitution at R_1 (Figure 2.6). Although direct experimental evidence for a lack of interconversion between **B** and **ent-B** is available only for the analogous *gem*-dimethyl substituted **2.90A**, structure **2.4A** was chosen in order to simplify conformational searches and reduce computational time. For comparison, substrate **2.93A** (which does undergo the ring inversion) was also modeled in order to assess the energetic cost associated with the inversion of a tri- versus tetrasubstituted olefin.

Figure 2.6 – Representative tandem reactions to be modeled



Of particular importance to the theoretical examination of this tandem reaction sequence are the ring inversion transition state energies. Up until this point, the interconversion between **B** and *ent*-**B** has been represented as a concerted process. It must be acknowledged, however, that the ring inversion is in fact a multi-step step process with each double bond rotating through the ring separately. Thus, for substrate **2.4A**, the inversion of **B** to *ent*-**B** goes through partially inverted enol ether **L** (Figure 2.7). (Alternatively, the front double bond could rotate first giving rise to intermediate *ent*-**L**. This process is enantiomeric to that depicted in Figure 2.7, however, and was therefore not considered).

Figure 2.7 – Stepwise mechanism for the inversion of **B** to *ent*-**B**

Gas-phase relative free energies at 473 K (200 °C) were obtained for intermediates **B**, **L**, and **D**, as well as the Claisen and ring inversion transition states for substrates **2.4A** and **2.93A**. All energies and geometry optimizations were obtained from the Jaguar 6.0 program²⁹ using Kohn-Sham DFT³⁰ at the B3LYP level of theory³¹ with a 6-311G** basis set. All of the reported energies include unscaled zero point energy corrections. Frequency calculations were performed on all stationary points to confirm that minimum energy structures had no imaginary frequencies and that the transition states had a single imaginary

frequency. For the transition state structures, the eigenvector of the imaginary frequency was examined to evaluate if the mode could effectively bring the 'reactant' to the 'product'. In addition, intrinsic reaction coordinate (IRC) calculations were performed for the ring inversion transition states **B-L[‡]** and **L-ent-B[‡]** for substrates **2.4A** and **2.93A**.

Due to conformational flexibility in the 10-membered ring and allyl substituent, comprehensive conformer searches were carried out according to the following procedure. First, a conformational search was performed at the semi-empirical PM3³² level of theory using the default Monte Carlo based conformational search engine of the Spartan 2002 molecular modeling package.³³ Of the 700-1200 structures sampled (the exact number varied depending on the number of rotatable bonds involved), the ten lowest-energy, distinct conformers obtained were then re-optimized at the B3LYP/6-31G** level, the lowest energy of which was further optimized at the B3LYP/6-311G** level.

Transition states were obtained by the following protocol. Transition states for the **B-L[‡]** and **L-ent-B[‡]** structures were first found with a simplified model wherein the -OCH₂CHCH₂ group was replaced by an -OMe group at the B3LYP/6-31G** level. Once a transition state was found and confirmed to have a single imaginary frequency, a Monte Carlo based conformational search was performed on the structure with the coordinates of the two olefins frozen. In this way the conformations of the backbone ring were sampled to search for other possible ring conformations that might lead to a lower energy inversion barrier. The lowest-energy, distinct structure obtained from the 500-600 conformers scanned was used as a starting point for another transition state search at the semi-empirical PM3 level. The -OMe group of the resulting lowest-energy transition state was replaced with an -OCH₂CHCH₂ group and a Monte Carlo based conformational search was performed on the allyl group (all other coordinates were frozen). The five lowest-energy, distinct structures from the 1200-1700 conformers scanned were then used as starting structures for transition state searches at the B3LYP/6-31G** level of theory. The lowest energy transition state structure located from the conformer search was then finally optimized at the B3LYP/6-311G** level. In some cases, several transition state structures were located that were within 2 kcal/mol energy of one another. However, the differences in these structures involved small conformational changes of peripheral groups (typically the allyl moiety), rather than a different core mechanism.

Finally, it is to be noted that the potential energy surface for these systems is complicated in that they possess many shallow local minima and the pathways between **B** and *ent*-**B** likely include several lower energy processes relating to the interconversion of different conformers. Such processes, however, can reasonably be assumed to be significantly lower in energy than the respective ring inversion transition state energies. Accordingly, our attention was focused on the rate limiting steps for these processes, **B-L**[‡] and **L-ent-B**[‡], and the lowest energy conformers for intermediates **B**, **L** and *ent*-**B**. The results of these calculations are summarized in Table 2.2 and Figures 2.8 and 2.9 below.

Table 2.2 – Relative free energies for substrates **2.4A** and **2.93A**, zeroed to **B**

Species (2.4A)	ΔG^a (kcal/mol)	Species (2.93A)	ΔG^a (kcal/mol)
D	-18.8	D	-25.5
B-D [‡]	24.1	B-D [‡]	24.3
B	0.0	B	0.0
B-L [‡]	17.3	B-L [‡]	19.4
L	2.6	L	3.3
L-ent-B [‡]	163.2	L-ent-B [‡]	18.1
<i>ent</i> - B	0.0	<i>ent</i> - B	0.0

^a Gas-phase relative free energy at 473 K calculated at the B3LYP/6-311G** level.

The calculated energy profiles for substrates **2.4A** and **2.93A** showed similar relative energies for the ground-state intermediates **B**, **D** and **L**, as well as for the transition states of the Claisen rearrangement (**B-D**[‡]) and the first step of the ring inversion (**B-L**[‡]). Not surprisingly, the second step of the ring inversion revealed a significant difference in the activation energy for the rotation of the tetra- and trisubstituted olefins: in the case of **2.4A**, the tetrasubstituted olefin forces a methyl group to pass through the ring (compared to a hydrogen for substrate **2.93A**) at an added cost of ~ 145 kcal/mol.

Figure 2.8 – Free energy profile for **2.4A**, zeroed to **B** (no ring inversion observed)

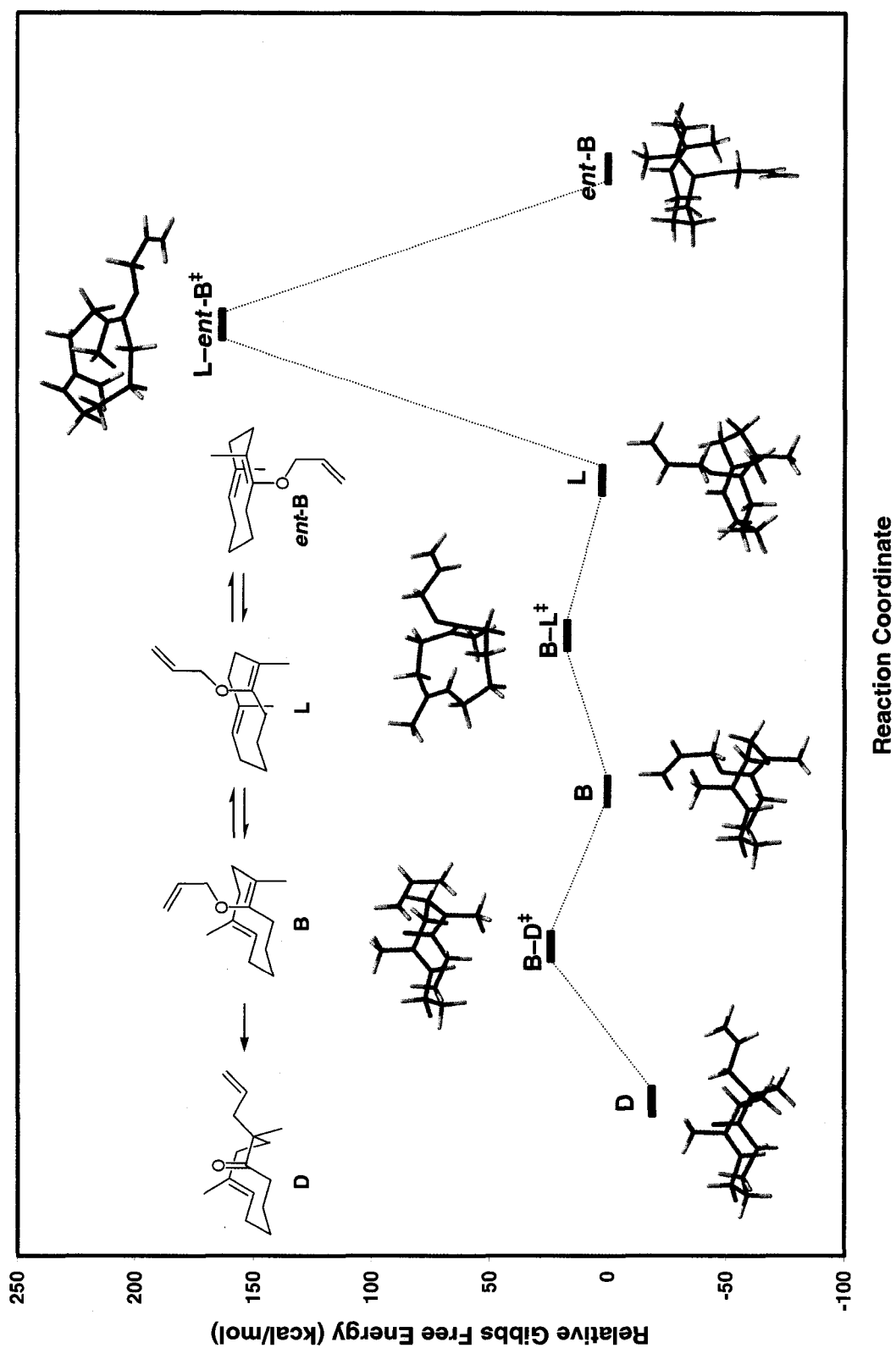
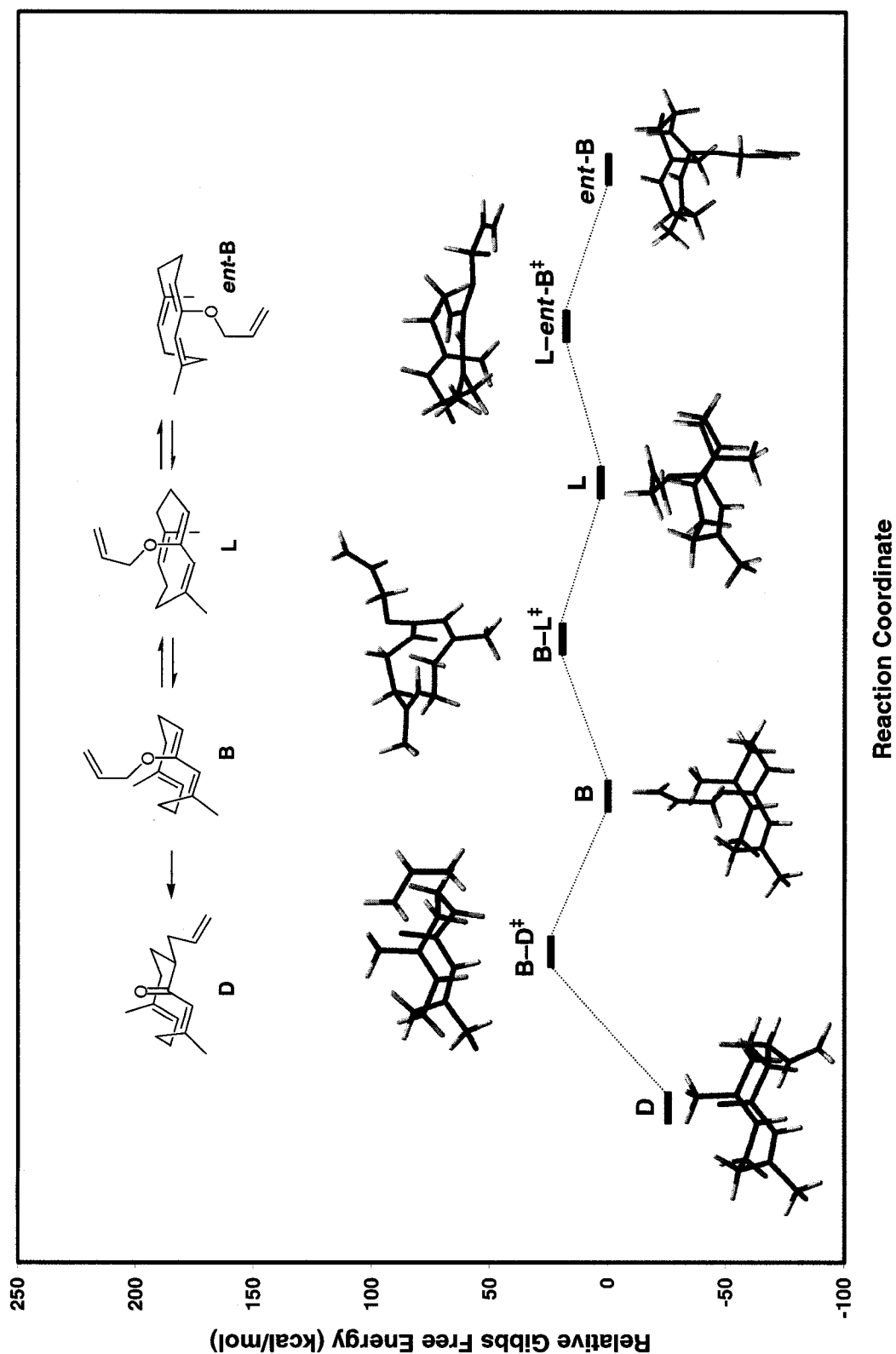


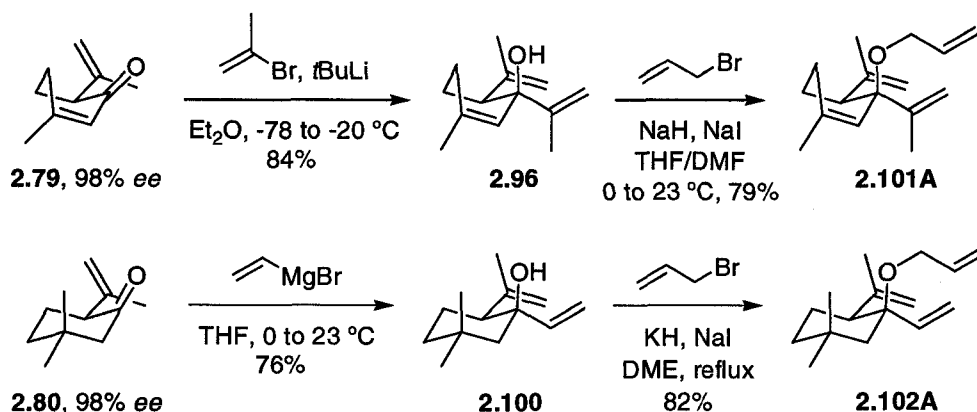
Figure 2.9 – Free energy profile for 2.93A, zeroed to **B** (ring inversion observed)

While the existence of a high energy barrier for this ring inversion was anticipated, its magnitude was not. To the best of our knowledge, this represents the first attempt to determine the activation energy for the inversion of an (*E*)-tetrasubstituted olefin through a 10-membered ring. In light of the energetic cost associated with this process, it becomes clear that *the Claisen rearrangement should be highly favoured over the ring inversion for any substrates bearing substitution at R₁*, thus preserving the diastereoselectivity of the process.

Given the significant activation energy for the ring inversion of the tetrasubstituted olefin, the feasibility of such a process occurring in the oxy-Cope/ene reaction becomes questionable (Scheme 2.35). Accordingly, an investigation into an alternative mechanism for the loss of chirality during this reaction was initiated. The preliminary results of these studies are presented in Chapter 5.

To confirm the validity of our findings, substrates **2.101A** and **2.102A** were prepared in both their chiral and racemic forms from ketones **2.79** and **2.80** (Scheme 2.36). The additional R₁ methyl group in **2.101A** was expected to give an oxy-Cope/Claisen/ene reaction which proceeded with retention of chirality. Conversely, the removal of R₁ substitution from **2.102A** was expected to cause racemization during the tandem reaction.

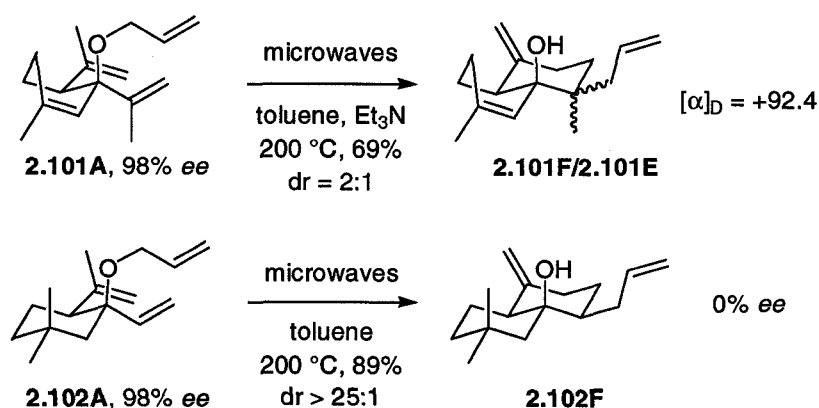
Scheme 2.36 – Preparation of substrates to prove the role of R₁ substitution



Subjecting **2.101A** to microwave irradiation under standard conditions initially gave a complex mixture of products. Repeating the reaction in the presence of 10 equivalents of triethylamine proved beneficial and a 2:1 mixture of inseparable isomers **2.101F** and **2.101E** was isolated in 69% yield (Scheme 2.37). Unfortunately, the products of the reaction were

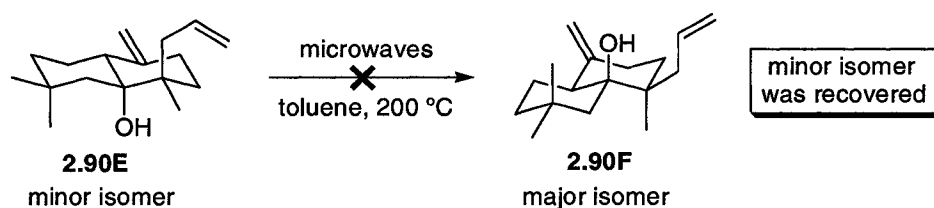
unstable making their characterization difficult (**2.101F** was assumed to be the major isomer based on analogy to previous substrates, but no direct evidence was obtained). Moreover, their instability prevented the development of GC conditions making a measurement of their *ee* impossible. An $[\alpha]_D$ of +92.4 for the freshly prepared material did confirm that the products were not racemic, however, a leak in *ee* could not be ruled out. The reaction of **2.102A** was more straightforward and the expected product, **2.102F**, was isolated as a single isomer in 89% yield. More importantly, it was found to be completely racemic, as predicted by the tri-substitution of its enol ether intermediate, **2.102B**.

Scheme 2.37 – Proving the role of R_1 substitution in controlling the first ring inversion



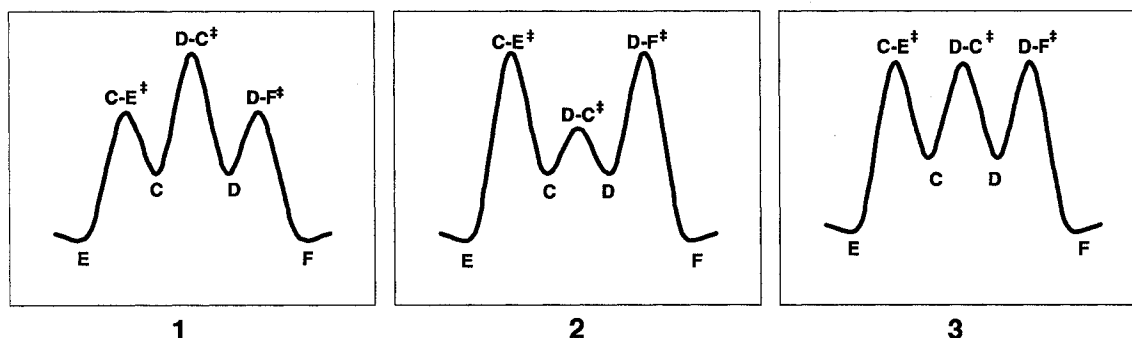
Having successfully modeled the first half of the reaction mechanism, we turned our attention to understanding the origin of diastereoselectivity in the transannular carbonyl ene portion of the reaction cascade. From the relative stereochemistry of the final products, it could be tempting to suggest that the reaction is under thermodynamic control since, in all cases, the major products are those which maximize the number of equatorially-placed bulky substituents. Studies by Danny Gauvreau on the oxy-Cope/ene reaction, however, demonstrated that the carbonyl ene reaction was irreversible. To confirm that this was also the case for the oxy-Cope/Claisen/ene reaction, minor isomer **2.90E** was resubjected to the reaction conditions for 1 hour (Scheme 2.38). Analysis of the crude material by ^1H NMR showed no peaks corresponding to the major isomer, **2.90F**.

Scheme 2.38 – Proof that the oxy-Cope/Claisen/ene reaction is irreversible



In the absence of thermodynamic control, three distinct kinetic profiles remain (Figure 2.10). In the first figure, a high energy barrier exists for the ring inversion of **D** to **C** preventing the formation of product **E**. In the second figure, a rapid equilibrium establishes between intermediates **C** and **D** and the relative transition state energies for the two ene reactions ($\text{D-F}^\ddagger$ and $\text{C-E}^\ddagger$) govern the product ratios (i.e. Curtin-Hammett³⁴ conditions). Finally, the third figure depicts a more complicated scenario where the ring inversion and ene transition states have similar energies. Since **D** is the intermediate formed directly after the Claisen rearrangement, one could expect such a potential energy surface to favour the formation of **F**. There is also, of course, the possibility that our reaction profile lies somewhere in-between these three extremes, or that different substrates have different kinetic profiles. Nonetheless, a discussion of these scenarios provides a good starting point for analysis.

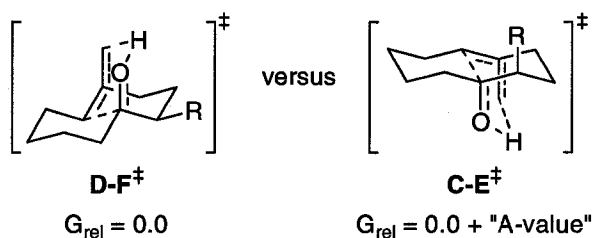
Figure 2.10 – Possible kinetic profiles for the ene reaction



The potential energy surface in the first figure can be ruled out on the basis that several substrates were shown to give rise to the **E** isomer. The second and third figures, however, are more difficult to distinguish. To begin, let us consider the second energy profile, depicting Curtin-Hammett control.

As previously noted, the major isomers obtained correspond to those conformers which maximize the equatorial placement of the bulkier substituents. While such a product distribution is typically attributed to thermodynamic control, it is also possible that the preferential formation of equatorial substituted products is a result of kinetic control under Curtin-Hammett conditions: in the same manner that products bearing equatorial substitution are lower in energy than their axial counterparts, so too the absolute energy of a transition state which places substituents in an equatorial position should be lower in energy than an equivalent transition state bearing axial substituents. A simplified representation of the transannular carbonyl ene transition states **D-F[‡]** and **C-E[‡]** is shown in Figure 2.11 below. The absolute energy of **D-F[‡]** should be lower than that of **C-E[‡]** by an amount approximately equal to the A-value for the substituent R.

Figure 2.11 – Effect of an equatorial versus an axial substituent of the ene transition state



If the above hypothesis is correct, it should be possible to estimate the relative energies of **D-F[‡]** and **C-E[‡]** for a given substrate simply by summing the A-values of the axial substituents at each transition state. Moreover, the difference of these energies should predict the observed product ratio using Equation 1 below.

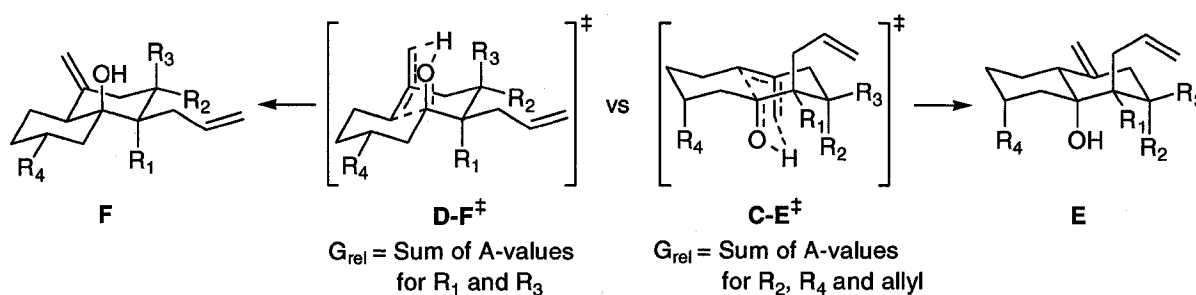
$$[F]/[E] = \exp[(\Delta G_{\text{C-E}^{\ddagger}} - \Delta G_{\text{D-F}^{\ddagger}})/RT] \quad (1)$$

The relative energies of **D-F[‡]** and **C-E[‡]** were estimated for twelve substrates, and the calculated energy difference between these transition states ($\Delta\Delta G^{\ddagger}_{\text{calc'd}}$) was compared with the observed energy difference ($\Delta\Delta G^{\ddagger}_{\text{exp't}}$, extrapolated from the observed product ratios using equation 1). Likewise, the calculated and observed product ratios were also compared. These results are summarized in Table 2.3 below. In all cases but one, the major isomer was correctly predicted by this method (CF₃ substituted **2.18A** was wrongly predicted to favour

the E isomer, entry 6). Beyond predicting the major product, however, the accuracy of the calculated ratios varied from good (entries 3, 5, 10-11) to poor (entries 2, 4, 6 and 8).³⁵ Several possible sources of error must be acknowledged: 1) Approximated A-values were used for the ethyl sulfide (an A-value for *methyl* sulfide was used instead), allyl and –CH₂OTBS substituents (both approximated by an ethyl group). 2) We have assumed that the backbone of the 10-membered ring adopts a chair-chair-chair conformation and that the ene reaction proceeds via a chair-like transition state. It is possible that one or both of the transition states proceeds via a different conformation. 3) The transition states involve partially formed bonds so the A-values could be expected to *overestimate* the steric interactions of a partially formed 6-membered ring. 4) On the other hand, A-values do not account for the developing 1,3-diaxial interactions at the transition states as a result of having R₃ (D–F[‡]) or R₂ and R₄ (C–E[‡]) in an axial position. Consequently, the A-values of these substituents may *underestimate* the steric interactions. 5) A-values are inherently steric parameters which would not account for any electronic influence that a substituent might have. 6) The reaction may not be under Curtin-Hammett control!

In light of the numerous sources of potential error in our approximation, it is impossible to evaluate whether the poorly predicted product ratios are a symptom of our method or an indication that Curtin-Hammett control is not in effect. Consequently, we were forced to consider an alternative kinetic profile.

Table 2.3 – Estimated ene transition state energies and product ratios from A-values



Entry	S.M.	R ₁	R ₂	R ₃	R ₄	$\Delta\Delta G^\ddagger$ calc'd ^a (kcal/mol)	$\Delta\Delta G^\ddagger$ exp't ^b (kcal/mol)	F/E calc'd	F/E exp't
1	2.4A	Me	H	H	H	0.1	0.9	1.1	2.5
2	2.9A	Me	Me	H	H	1.8	3.0	6.4	25.0
3	2.10A	Me	H	Me	H	-1.7	-1.3	0.2	0.3
4	2.11A	OEt	H	H	H	0.8	3.0	2.5	> 25
5	2.12A	SEt	H	H	H	0.8	1.0	2.3	3.0
6	2.18A	CF ₃	H	H	H	-0.3	0.9	0.8	2.5
7	2.31A	Me	CH ₂ OTBS	H	H	1.8	2.6	6.7	16.0
8	2.38A	Me	H	H	Me	1.8	3.0	6.4	> 25
9	2.39A	Me	CH ₂ OTBS	H	Me	3.6	3.0	38.2	> 25
10	2.40A	OEt	H	H	Me	2.6	3.0	14.0	> 25
11	2.62A	Ph	CH ₂ OTBS	H	H	0.8	0.3	2.3	1.4
12	2.63A	Ph	CH ₂ OTBS	H	Me	2.5	3.0	13.2	> 25

^a $\Delta\Delta G^\ddagger = G_{C-E^\ddagger} - G_{D-F^\ddagger} = (\text{sum of A-values for } R_2, R_4 \text{ and allyl}) - (\text{sum of A-values for } R_1 \text{ and } R_3)$ where the following A-values were used: Me (1.74), OEt (0.95), SEt (1.04, approximated as SMe), Ph (3.0), CF₃ (2.1), CH₂OTBS and CH₂CHCH₂ (1.79, approximated as CH₂CH₃).^{12,13} ^b Calculated from the observed product ratios using Equation 1 with T = 473 K.

The third scheme in Figure 2.10 above depicts a scenario where the ring inversion and ene reactions have similar transition state energies. The kinetics for such a system would be quite complicated and a detailed analysis is not possible from the available data. It is, however, reasonable to assume that such an energy profile should favour the **F** isomer given that intermediate **D** is the initially formed product of the Claisen rearrangement. Indeed, with the exception of **2.10A**, all substrates have been observed to favour the **F** isomer.

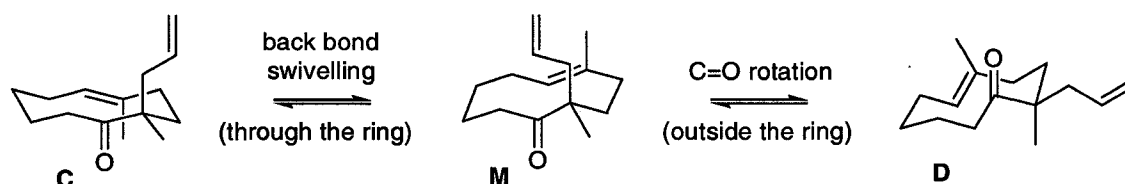
While this model may explain the preferential formation of the **F** isomer, it is more difficult to rationalize the dramatic changes in selectivity which were observed by seemingly subtle changes to the substitution at R₁-R₄. An exception to this are the ethoxy and CF₃

substituted substrates, **2.11A** and **2.18A**: It is known in the literature that electron-withdrawing groups alpha to the enophile can accelerate an ene reaction.³⁶ It could thus be argued that the ethoxy and CF₃ groups lower the energy of the ene reaction relative to the ring inversion giving rise to preferential formation of the **F** isomer.

To help decipher between these two conflicting models, we once again turned to computational methods. In particular, an energy profile comparing the two transannular carbonyl ene reactions with the ring inversion was required. Substrate **2.4A** was initially chosen to model these processes. Before beginning the calculations, however, a more detailed look at the ring inversion was again needed.

As for the ring inversion of **B** to *ent*-**B**, conversion of **D** to **C** is acknowledged to be a multi-step process. Figure 2.12 below illustrates the distinct steps. Unlike intermediates **B** and *ent*-**B**, the inversion of **D** requires a single (*E*)-olefin to rotate through the ring; the carbonyl is capable of rotating outside the ring. As the latter process is presumably low in energy, the rate limiting step for the interconversion of **C** and **D** is expected to be the transformation of **M** to **C**. Consequently, our attention was focused on obtaining the activation energy for this step.

Figure 2.12 – Multi-step ring inversion from **D** to **C**



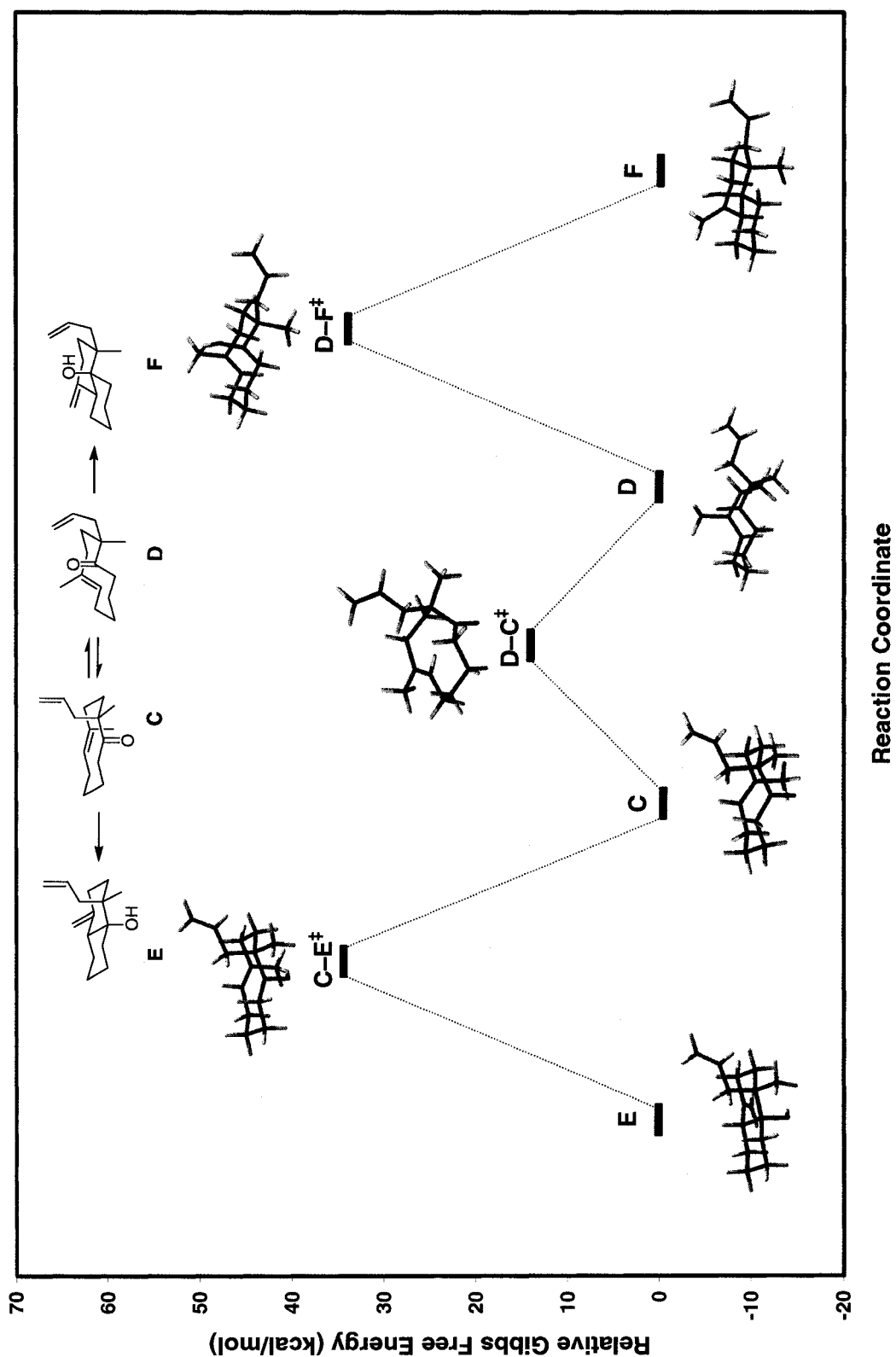
Gas-phase relative free energies at 473 K (200 °C) were calculated for the relevant intermediates and transition states for substrate **2.4A** according to the procedures described above. These results are summarized in Table 2.4 and Figure 2.13 below.

Table 2.4 – Relative free energies for the carbonyl ene reaction of 2.4A, zeroed to **D**

Species (2.4A)	ΔG^a (kcal/mol)
F	-0.2
D-F[‡]	33.8
D	0.0
D-C[‡]	14.0
C	-0.5
C-E[‡]	34.4
E	0.1

^a Gas-phase relative free energies at 473 K calculated at the B3LYP/6-311G** level of theory.

It is to be noted that the calculations erroneously predict that intermediates **C** and **D** are thermoneutral with respect to the products, **E** and **F**. These energetics suggest that intermediates **C** and **D** should be isolatable, though experimentally, we know this to be false. The B3LYP exchange-correlation functional has been shown to underestimate the exothermicity of converting a π bond to a σ bond.³⁷ This could explain the above discrepancy between the calculations and the experimental observations. For our purposes, however, we were interested in the relative energies of the transition states, **D-F[‡]** and **C-E[‡]**, rather than the thermodynamics of the corresponding reactions. Consequently, no significant effort to correct the problem was made. (The matter could likely be resolved by moving to a purely ab initio method, however, such an approach would require significantly more computational resources. We did note, however, that calculations using the PBE exchange-correlation functional gave somewhat improved thermodynamics: intermediates **C** and **D** were found to be 2.2 and 2.7 kcal/mol higher in energy, respectively, than **F**, and **E** was calculated to be 0.2 kcal/mol less stable than **F**).

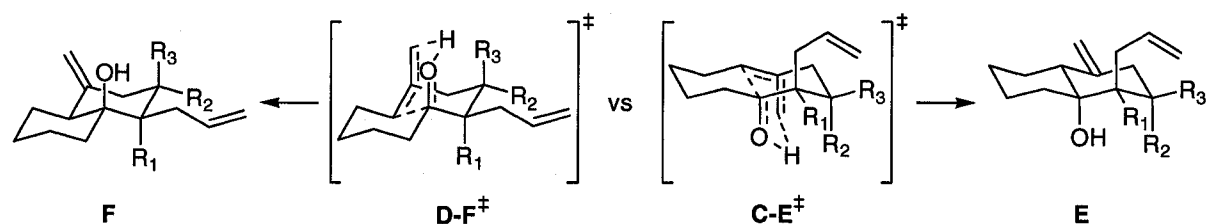
Figure 2.13 – Free energy profile for the carbonyl ene reaction of **2.4A**, zeroed to **D**

The barrier to ring inversion for the conversion of **D** to **C** was found to be 14 kcal/mol, about 5 kcal/mol lower than the comparable process of **B** to **L** (Figure 2.8). This is likely due to the increase in flexibility for intermediate **D** as a result of having only one double bond present in the ring. In contrast, the transannular carbonyl ene transition states **D-F[‡]** and **C-E[‡]** were found to be substantially higher in energy at 33.8 and 34.4 kcal/mol, respectively. This finding clearly indicates that a rapid interconversion between **C** and **D** is occurring and that Curtin-Hammett conditions are likely resulting.

For Curtin-Hammett to apply, two conditions must be met: the reaction must be irreversible and the ring inversion rate constant must be at least an order of magnitude greater than that of the Claisen rearrangement ($k_{\text{inversion}} \geq 10k_{\text{ene}}$).³⁸ The irreversibility of the reaction has already been proven (Scheme 2.38). Although we lack kinetic data, the ~ 20 kcal/mol difference in energy between the inversion and ene transition states suggests that the second condition is also met. If we therefore assume Curtin-Hammett conditions are in effect, we should be able to predict the product ratio from the calculated transition state energies for the two ene reactions using Equation 1 above. Indeed, the calculated values predict a 1.8:1 ratio of products, in close agreement with the observed 2.5:1 ratio for substrate **2.4A**.³⁹

On the assumption that the relative energetics for the ring inversion and ene transition states would not differ substantially between substrates, we speculated that Curtin-Hammett conditions were likely a general phenomenon for this ene reaction. To confirm this, the calculated product ratios of other substrates would need to be successfully fit to their experimental data. Accordingly, we began modeling the two competing carbonyl ene transition states for a selection of our previously tested compounds. These results are summarized in Table 2.5 below.

Table 2.5 – Comparison of calculated product ratios based on Curtin-Hammett control



Entry	S.M.	R ₁	R ₂	R ₃	$\Delta\Delta G^\ddagger$ calc'd ^a (kcal/mol)	$\Delta\Delta G^\ddagger$ exp't ^b (kcal/mol)	F/E calc'd	F/E exp't
1	2.4A	Me	H	H	0.6	0.9	1.8	2.5
2	2.9A	Me	Me	H	3.9	> 3.0	62.1	> 25
3	2.10A	Me	H	Me	-2.1	-1.3	0.1	0.25
4	2.11A	OEt	H	H	9.2	> 3.0	1.7x10 ⁴	> 25
5	2.12A	SEt	H	H	2.0	1.0	8.1	3.0
6	2.18A	CF ₃	H	H	2.2	0.9	10.5	2.5

^a Calculated difference in gas-phase free energies at 473 K for the ene transition states D-F[‡] and C-E[‡].

^b Calculated from the observed product ratios using Equation 1 with T = 473 K.

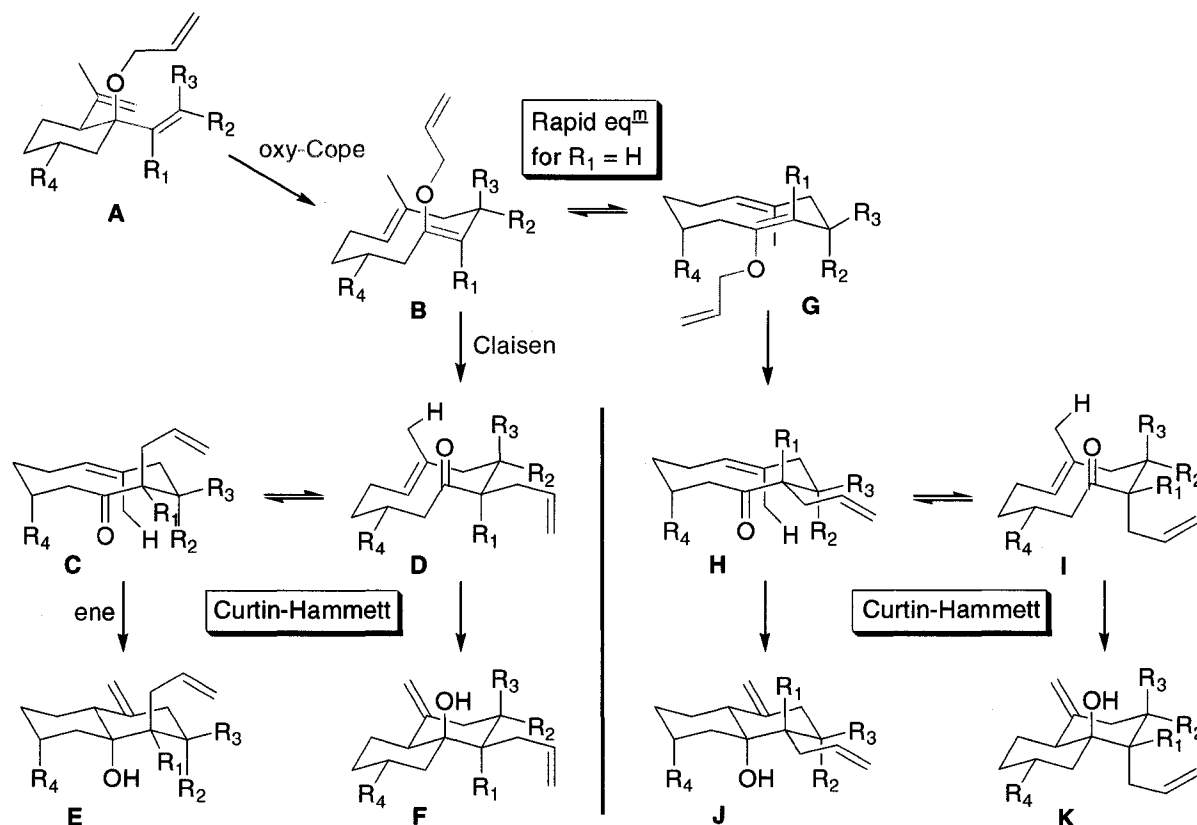
In the first five examples, the predicted ratios closely mirror the observed product ratios with less than a 1 kcal/mol difference in energy between the predicted and experimentally determined $\Delta\Delta G^\ddagger$ values. Notably, substrates **2.9A** and **2.11A** (entries 2 and 4) are now accurately predicted to give exclusively the **F** isomer. (Recall that our earlier approximation of Curtin-Hammett control had poorly modeled these substrates; see Table 2.3 above). The calculated transition state energies for CF₃ substituted **2.18A** also now predict the preferential formation of **2.18F**, although, the extent to which this isomer is favoured is somewhat exaggerated (entry 6).

It is worth noting that the above calculations support the previously suggested electronic influence of the R₁ substituent on the reaction's energy profile. In particular, for the ethoxy substituted substrate, the D-F[‡] transition state is significantly lower in energy than that of C-E[‡]. The nature of this effect, however, remains uncertain. According to the polar Felkin-Anh model,⁴⁰ the preferred conformation at the transition state should maximize the interaction between the C-R₁ σ* and C=O π* orbitals thus would wrongly predicting the preferential formation of isomer **E** via the C-E[‡] transition state. Alternatively, the Cornforth

model⁴¹ correctly predicts that the $D-F^\ddagger$ transition state should be favoured owing to the minimization of its carbonyl and $C-R_1$ dipoles. In an attempt to confirm this theory, we repeated the reaction of **2.11A** in a more polar solvent, DMF. As it is known that dipole moments are stabilized by polar solvents,⁴² we expected to see a decrease in selectivity for the formation of **2.11F**. In fact, no change was observed and a greater than 25:1 ratio was once again noted. Given that solvent effects for isopolar reactions are often small,⁴³ it remains unclear whether this result should be taken as evidence against the Cornforth model. No further efforts to elucidate this matter have been made.

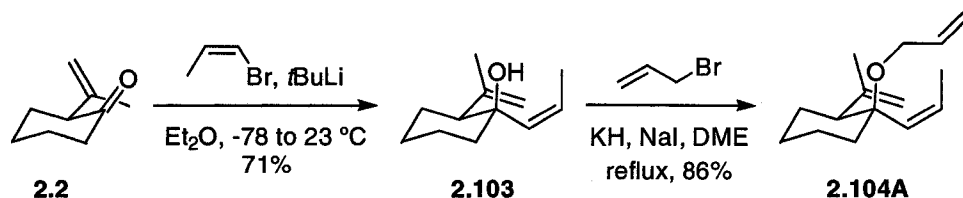
The generally good correlation between the observed and predicted product ratios, along with the energy profile for **2.4A** (Figure 2.13), strongly suggest that Curtin-Hammett conditions are in effect for the transannular carbonyl ene portion of the oxy-Cope/Claisen/ene reaction. Taken together with the results of the Claisen rearrangement and the first ring inversion, a new mechanistic picture for the tandem reaction emerges. Figure 2.14 summarizes these results.

Figure 2.14 – Updated mechanism for the oxy-Cope/Claisen/ene reaction

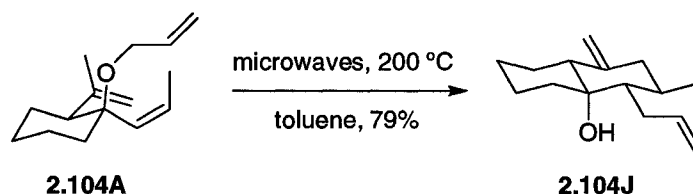


Beyond simply explaining the results obtained, the above mechanism provides a means of predicting the reaction outcome for new substrates. This was demonstrated above with the reaction of substrates **2.101A** and **2.102A** and their respective conservation and loss of chirality during the tandem sequence (Scheme 2.37). While the retention of chirality could certainly be an important issue when applying this reaction to total synthesis, other applications of our mechanistic findings might also prove useful. For instance, the judicious choice of substituents should allow one to gain access to the previously unobserved isomers **J** and **K**. Up until now, the inversion of **B** has always given rise to its enantiomer and subsequent product racemization. If, however, additional substitution were present on a molecule with $R_1 = H$, inversion of **B** would give rise to a diastereomeric intermediate, **G**, which, in turn could yield products **J** and **K**. To test this theory, substrate **2.104A** was prepared from ketone **2.2** (Scheme 2.39). Alkylation with the vinyl lithium of (*Z*)-1-bromopropene gave tertiary alcohol **2.103** in 71% yield. Subsequent allylation gave the desired tandem reaction precursor, **2.104A**, in 86% yield.

Scheme 2.39 – Preparation of a new substrate for the formation of the **J** isomer



Given the lack of substitution at R_1 , a rapid equilibrium between intermediates **B** and **G** is predicted to establish.⁴⁴ A qualitative look at the two available Claisen transition states suggests that the equatorial placement of the R_3 methyl group should lower the absolute energy of the **G-H**[‡] transition state over that of **B-D**[‡]. Likewise, a similar evaluation of the two carbonyl ene transition states, **H-J**[‡] and **I-K**[‡], predicts that **J** should be the major product. Indeed, subjecting **2.104A** to microwaves at 200 °C for 4 hours yielded **2.104J** as the solely detectable diastereomer in 79% yield (Scheme 2.40). Notably, this is the first example of the tandem oxy-Cope/Claisen/ene reaction giving rise to this isomer.⁴⁵

Scheme 2.40 – Selective formation of the previously undetected **J** isomer

Conclusions

The tandem oxy-Cope/Claisen/ene reaction has been shown to be a powerful method for the stereoselective formation of contiguous stereogenic centres along a *trans*-decalin framework. A variety of substrates were found to successfully undergo the pericyclic cascade with high yields and with moderate to excellent diastereoselectivities. Fundamental to the utility of this reaction, however, is the ability to accurately predict and control its product distributions. Such a requirement can only be met by a clear understanding of the reaction mechanism. To this end, a detailed investigation into the factors governing the observed diastereoselectivity was undertaken. Through the use of enantioenriched substrates as a mechanistic probe and DFT calculations for the modeling of key intermediates and transition states, several key insights into the origins of diastereoselectivity were made. Most notably, the occurrence of the first ring inversion from **B** to **G** (or *ent*-**B**) was found to be dependent on whether a tri- or tetrasubstituted double bond was present in the enol ether intermediate. As a result, controlling the substitution at R₁ allows one to control the preservation of planar chirality in the intermediates and ultimately determine whether products **J** and **K** are accessible. Finally, the transannular carbonyl ene reaction was found to be under Curtin-Hammett control such that the interconversion between intermediates **C** and **D** is fast and the relative transition state energies for the two ene reactions control the final product distribution. With these findings in hand, several new substrates were prepared and their reaction outcomes successfully predicted. For cases where mixtures were unavoidable, the addition of a remote stereocentre along the backbone of the ring was found to be an effective means of biasing the conformational preferences of the 10-membered ring intermediates and ensuring the formation of a single isomer.

Having established the viability of the tandem oxy-Cope/Claisen/ene reaction, our attention was turned to the application of this method in total synthesis. The following two chapters will address these efforts.

References

- ¹ By the term “ring inversion,” we mean the rotation of both (*E*)-olefins through the ring.
- ² Strictly speaking, the term “atropisomer” refers to conformers which are isolatable as separate chemical entities (See Chapter 1). As **B** and **G** are intermediates in the reaction which are not isolated, their classification as atropisomers remains speculative at this point.
- ³ In this case, a “ring inversion” entails the rotation of the remaining (*E*)-olefin through the ring as well as a 180° rotation of the carbonyl.
- ⁴ **B** and *ent*-**B** are enantiomeric by virtue of planar chirality. For details, see Chapter 1 and references cited therein.
- ⁵ Swern, D.; Mancuso, A. J. *Synthesis* **1981**, 165.
- ⁶ Warrington, J. M. Ph.D Thesis, University of Ottawa, Ottawa, Canada, 2005.
- ⁷ For reviews on the use of microwaves in organic synthesis, see: (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1995**, 1213. (b) Majetich, G.; Hichs, R. J. *J. Microwave Power and Electromagnetic Energy* **1995**, 30, 27. (c) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, 57, 9199. (d) Lidström, P.; Tierny, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, 57, 9225. (d) Loupé, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.
- ⁸ Deon, D. H. M.Sc Thesis, University of Ottawa, Ottawa, Canada, 2001.
- ⁹ Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, 3, 1925.
- ¹⁰ Substrates **2.11A** and **2.12A** were found to be unstable; to minimize their decomposition, their reactions were run at 200 °C rather than the usual 220 °C.
- ¹¹ From the Pauling electronegativity scale, carbon’s electronegativity is 2.55 while sulfur’s is 2.58.
- ¹² Hirsch, J. A. *Topics in Stereochemistry* **1967**, 3, 199.

- ¹³ Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, 696.
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- ²⁷ The closest systems to ours for which the ring inversion activation energies have been determined experimentally are (a) (*E*)-cyclodecene-1,2,4,4,9,9-d₆: Binsch, G.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157. (b) (*E*)-1,2-dimethylcycloalkenes of ring size 12, 13 and 14: Marshall, J. A.; Audia, V. H.; Jenson, T. M.; Guida, W. C. *Tetrahedron* **1986**, *42*, 1703.
- ²⁸ Theoretical studies into the ring inversion mechanism have been reported for related systems. See, (a) (*E,E*)-cyclodecadiene: Yavari, I.; Hosseini-Tabatabaei, M. R.; Nori-Sharhg, D.; Jabbari, A. *J. Mol. Struct. (THEOCHEM)* **2001**, *574*, 9. (b) (*E,Z*)-cyclononadiene: Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Chem. Eur. J.* **2002**, *8*, 1833. (c) (*E*)-1,2-dimethylcycloalkenes of ring size 12, 13 and 14: see reference 27b.

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- ³⁵ The categorization of calculated $\Delta\Delta G^\ddagger$ values was based on the following criteria: a difference between the calculated and experimentally determined $\Delta\Delta G^\ddagger$ of less than 0.5 kcal/mol was designated as a good approximation while a difference of greater than 1.0 kcal/mol was taken to be a poor approximation.
- ³⁶ (a) Snider B. B. In *Comprehensive Organic Synthesis, Combining C-C π bond*; Paquette, L. A., Ed.; Pergamon Press: Oxford, **1991**; Vol. 5; Chapter 1.1. (b) Snider B. B. In *Comprehensive Organic Synthesis, addition to C-X π bond*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, **1991**; Vol. 2; Chapter 2.1.
- ³⁷ Check, C. E.; Gilbert, T. M. *J. Org. Chem.* **2005**, *70*, 9828.
- ³⁸ Seeman, J. I., Farone, W. A. *J. Org. Chem.*, **1978**, *43*, 1854.
- ³⁹ Molecular mechanics calculations have been used to model the ene reaction of related cyclodecenone systems. In both cases, the authors similarly concluded that the product selectivity was determined by the relative energy of the transition states rather than the population of the ground state conformers. See: (a) Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, *18*, 1623. (b) Došen-Mićović, J; Lorenc, L.; Mihailović, M. L. *Tetrahedron* **1990**, 3659.

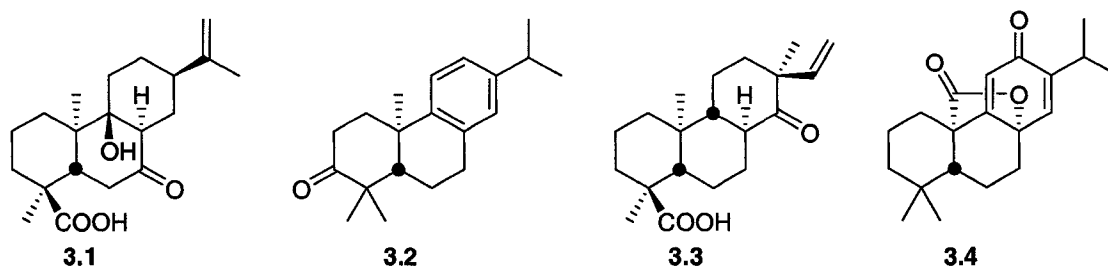
- ⁴⁰ (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron* **1968**, *18*, 2199. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2005. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
- ⁴¹ (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. For a modified version, see: (b) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920.
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- ⁴³ See reference 42, pages 187-199 and references cited therein.
- ⁴⁴ The equilibrium between **B** and **G** can be assumed to be rapid relative to the rate of the Claisen rearrangements based on the fact that full racemization was observed for substrates **2.93A** and **2.102A**; if the rate of interconversion between **B** and *ent*-**B** had been slow for these substrates, a leak in *ee* would have been observed rather than racemization.
- ⁴⁵ It must be acknowledged that a boat-like transition state for the oxy-Cope rearrangement would also give access to products **J** and **K** and cannot, at this point, be ruled out.

3

Towards the Synthesis of Wiedemannic Acid

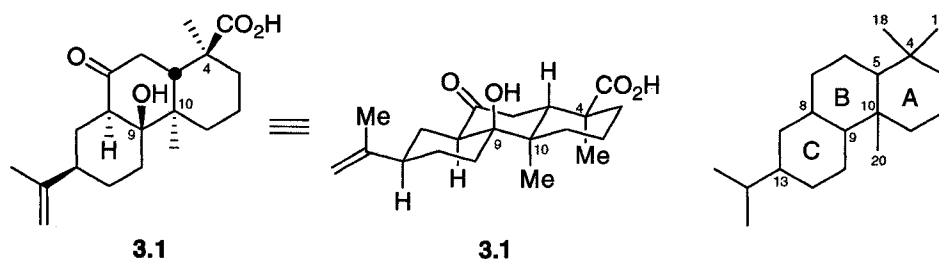
Introduction to Wiedemannic Acid

Located at the junction of three principal phytogeographic regions (Mediterranean, Irano-Turanian and Euro-Siberian), the country of Turkey is home to a uniquely rich and diverse population of flora.¹ As of the year 2000, more than 11,000 species had been identified in the region.² In light of such biodiversity, it is not surprising that there exists significant interest in identifying the chemical constituents of the region's vegetation.³ In particular, species belonging to the genus *Salvia* (family: Labiatae) have attracted great interest owing to their common employment in traditional medicinal practices in Turkey. One such species, *Salvia wiedemannii*, has been the focus of the Ulubelen and Snyder research groups. From the aerial parts of this plant, four new diterpenoids have been isolated (Figure 3.1): wiedemannic acid (**3.1**),⁴ 3-oxoabieta-8,11,13-triene (**3.2**),⁴ 4-oxopimaric acid (**3.3**),⁵ and 8-hydroxy-12-oxoabieta-9,13-dien-20-oic acid 8,20-lactone (**3.4**).⁶

Figure 3.1 – Diterpenoids isolated from *Salvia wiedemannii*

While no biological activity has been reported to date for any of the above compounds, several structural features present in wiedemannic acid (**3.1**) make it an interesting synthetic target. As a member of the abietane family of diterpenoids, its *trans-anti-trans* ring junction is commonly found in terpenoid natural products. Moreover, its five contiguous stereocentres, including three quaternary carbon centres (C4, C9 and C10), add considerable molecular complexity (Figure 3.2). Of central importance to its synthesis, and that of related diterpenoids, would be the ability to efficiently generate these stereocentres in a controlled manner.

Figure 3.2 – Abietane diterpenoid wiedemannic acid

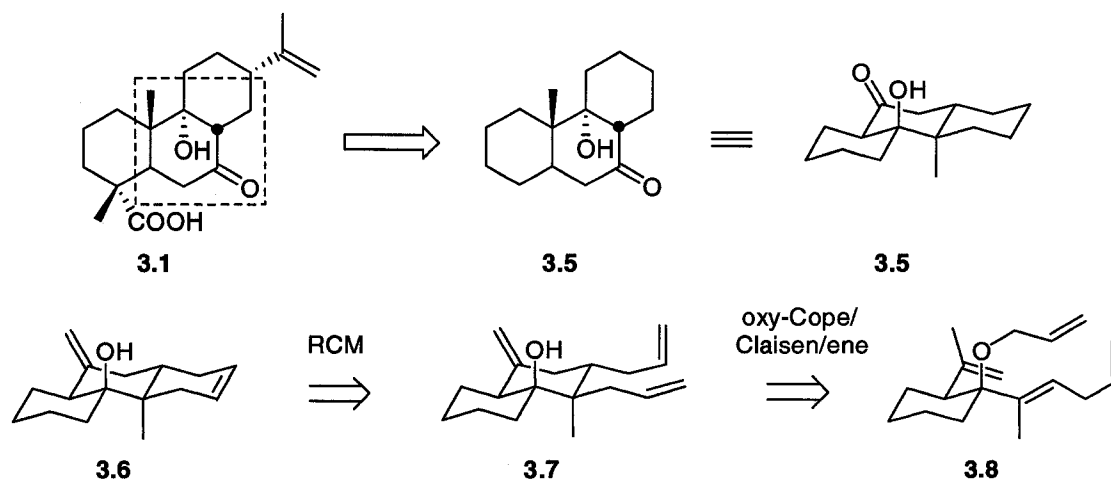


An Oxy-Cope/Claisen/Ene Approach to the Synthesis of Wiedemannic Acid

Having developed the tandem oxy-Cope/Claisen/ene reaction into an efficient means of generating functionalized decalins with good stereocontrol, it seemed obvious that the synthesis of wiedemannic acid would be an excellent means of showcasing the success of this new method. Accordingly, we set out to complete the first total synthesis of this natural product.

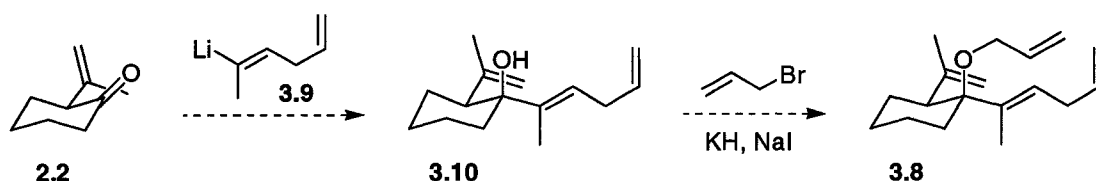
A simplification of the core of wiedemannic acid reveals a *trans*-decalin (**3.5**) which could easily be prepared by our tandem methodology (Figure 3.3). As a model for such an approach, it was envisioned that the oxy-Cope/Claisen/ene reaction of **3.8**, followed by a ring closing metathesis of **3.7** would be an expeditious route to the tricyclic core of wiedemannic acid (**3.6**).

Figure 3.3 – A tandem oxy-Cope/Claisen/ene approach to the core of wiedemannic acid



To begin our synthesis of the wiedemannic acid core, we first investigated the preparation of tandem precursor **3.8**. Beginning from ketone **2.2**, the first step would require alkylation with a vinyl lithium species such as **3.9** (Scheme 3.1).

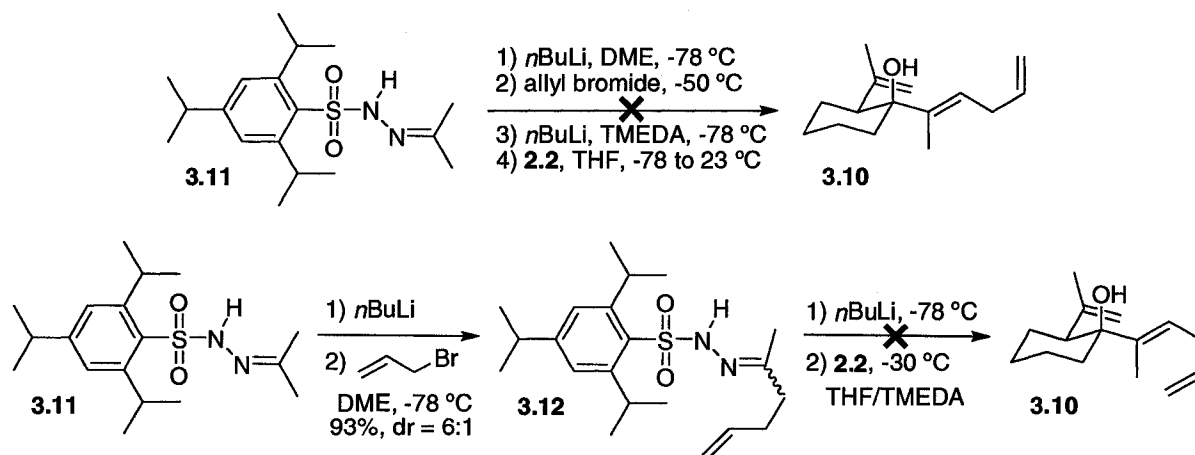
Scheme 3.1 – Proposed synthesis of tandem precursor **3.8**



Initially, the in situ generation of **3.9** was attempted via a Shapiro reaction⁷ of **3.11**. When this failed to give any reaction, a stepwise approach was taken instead. Preparation of **3.12** proceeded smoothly giving a 6:1 mixture of regioisomers in 93% yield. Treatment of **3.12** with *n*-butyllithium followed by ketone **2.2**, however, gave none of the desired product. Rather, recovered starting material was isolated, together as an inseparable mixture with a

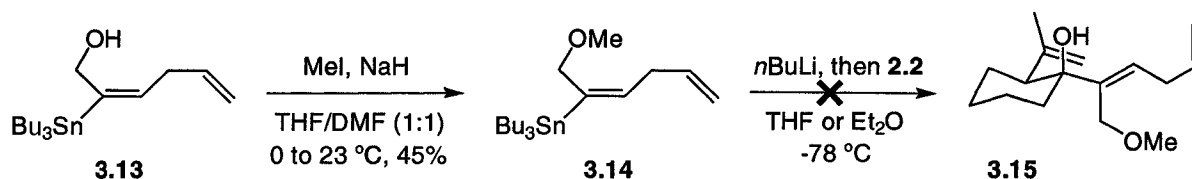
second, strongly UV active compound, presumed to be the isomerized ketone, pulegone (Scheme 3.2).

Scheme 3.2 – Shapiro reaction for the generation of vinyl lithium 3.9



As part of a related project in our laboratory, former graduate student Peter Ross MacLean had prepared vinyl stannane **3.13**⁸ which he generously made available. While the primary alcohol was not required for our model study, its presence seemed unlikely to be detrimental. Capping the alcohol with a methyl group was thus carried out, followed by sequential treatment with *n*-butyllithium and ketone **2.2**. Unfortunately, no reaction was observed.

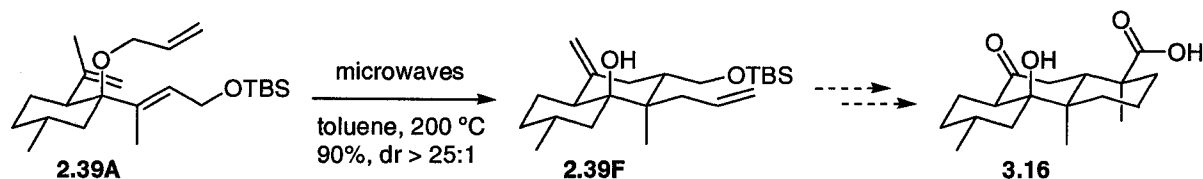
Scheme 3.3 – Alkylation from a vinyl stannane



Given the difficulties experienced with forming adducts **3.10** and **3.15**, it was decided that the terminal olefin needed to form the A-ring of our model would be introduced after the tandem reaction. Such a modification was particularly attractive given that decalin **2.39F** was known to be available as a single diastereomer in 90% yield from the oxy-Cope/Claisen/ene reaction of **2.39A**. From this compound, installation of the requisite vinyl group was expected to be trivial. Moreover, the presence of the primary alcohol would provide a handle

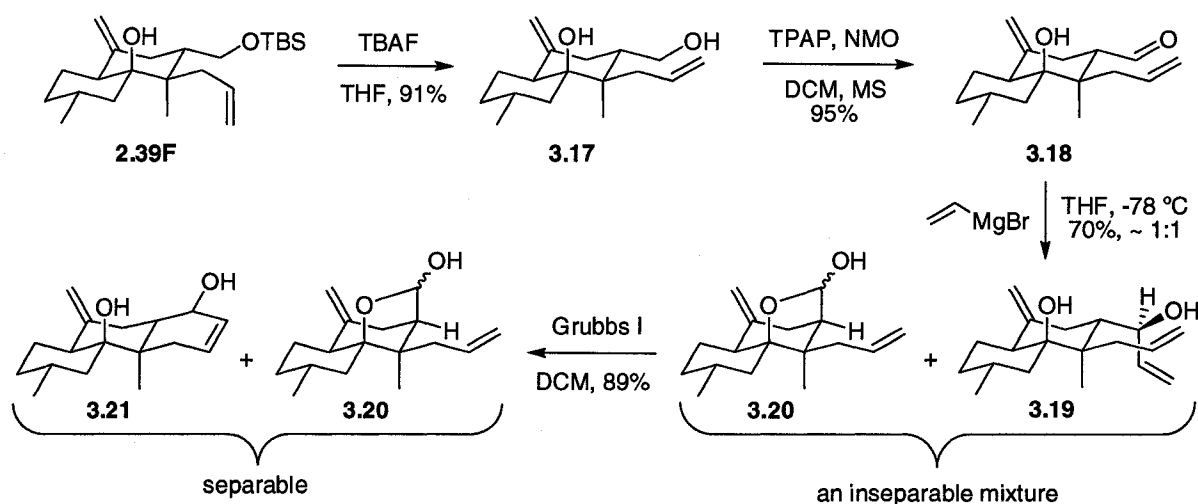
for installing the C4 quaternary carbon present in the natural product. Consequently, a more in depth model study was envisioned and the preparation of wiedemannic acid analogue **3.16** was targeted.

Scheme 3.4 – Improved model study for the synthesis of wiedemannic acid: analogue 3.16



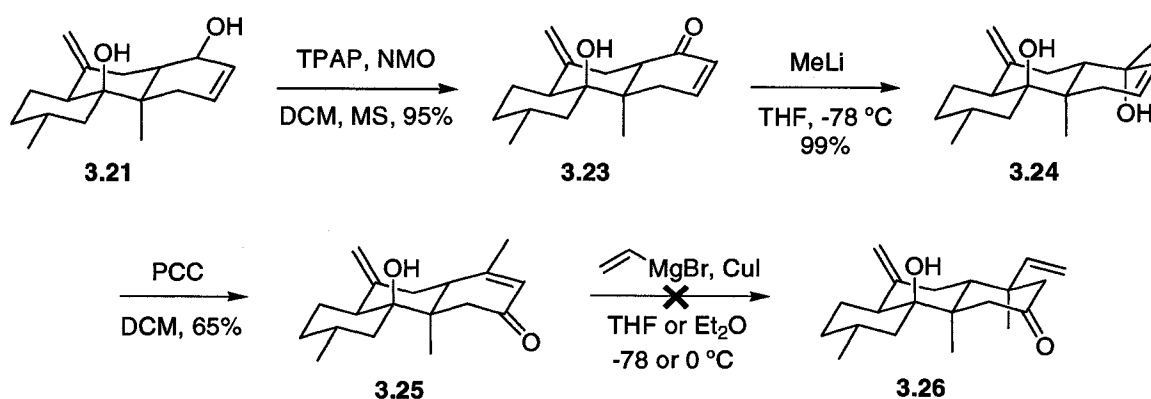
The transformation of **2.39F** to analogue **3.16** began with removal of the TBS protecting group with TBAF to afford diol **3.17** in 91% yield. Oxidation with TPAP gave aldehyde **3.18** in 95% yield. From here, installation of the vinyl group was attempted by reacting **3.18** with vinylmagnesium bromide. The result was a complicated mixture of inseparable products. From the ^1H NMR, three new olefinic peaks gave us reason to believe that **3.19** had been formed, however, a substantial amount of side product precluded its full characterization at the time. Fortunately, treating the mixture with Grubbs' first generation catalyst⁹ gave the desired ring closed product in 89% yield (with respect to **3.19**) which, more importantly, was now isolable from the unreacted side product, lactol **3.20** (identity was proven by subsequent oxidation to the lactone, **3.22**. Result not shown). Although the stereochemistry of **3.21** was inconsequential given the upcoming oxidation, it was interesting to note that only a single isomer of the alcohol was observed implying that the Grignard attack on **3.18** had been highly selective for the Felkin-Ahn product, **3.19** (Scheme 3.5).

Scheme 3.5 – Initial route for the formation of the A-ring: problematic lactol formation



While the formation of lactol **3.20** would ultimately need to be eliminated from the alkylation of **3.18**, our immediate attention was first turned to the further functionalization of the A-ring using the small amount of **3.21** which had been prepared (Scheme 3.6). Oxidation of the allylic alcohol followed by treatment with methyllithium gave **3.24** as a single diastereomer. Next, a 1,3-allylic oxidative transposition of the tertiary alcohol using PCC¹⁰ gave enone **3.25** in 65% yield. From here, completion of the remaining quaternary carbon centre was envisioned to proceed via a 1,4-addition to give **3.26**. Unfortunately, only two attempts could be made with the material available, neither of which was successful.

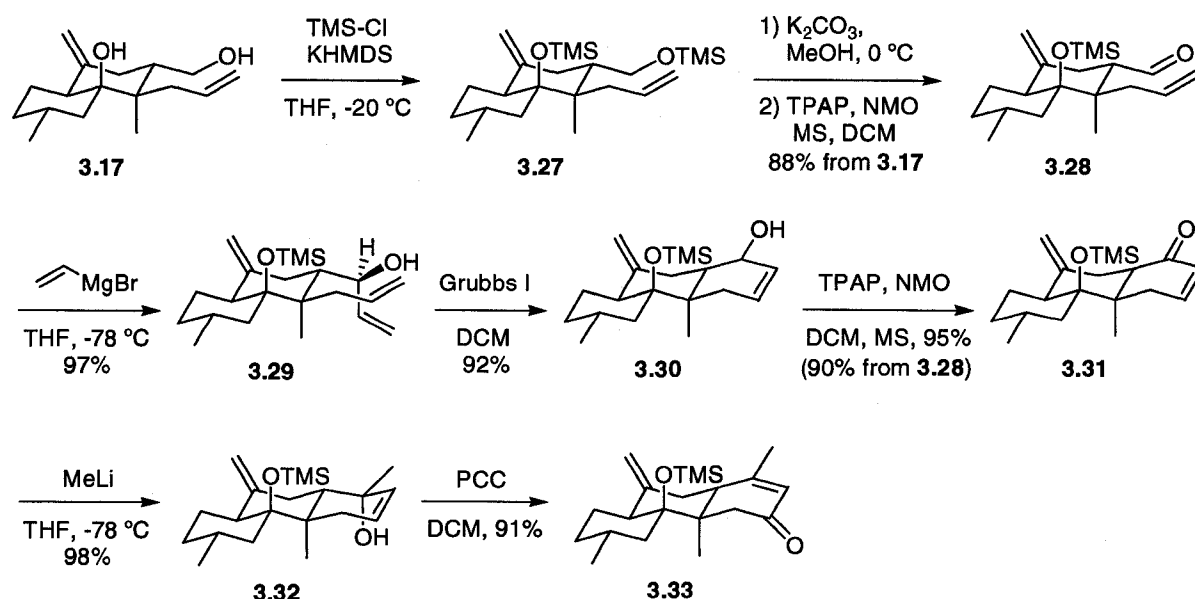
Scheme 3.6 – Functionalization of the A-ring



Before further investigation of the proposed cuprate addition could proceed, we needed to prepare more substrate. This, in turn, meant revisiting the problematic Grignard addition

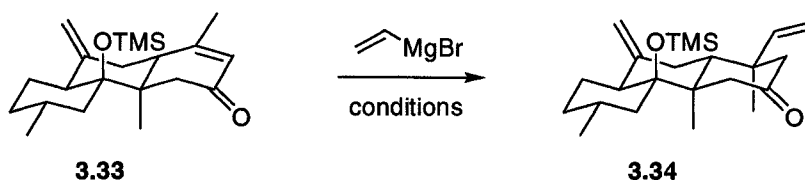
of **3.18** to **3.19** (Scheme 3.5 above). Since the formation of the lactol side product was a result of epimerization alpha to the aldehyde followed by cyclization with the free alcohol, protection of the tertiary alcohol seemed like a possible solution. Accordingly, **3.17** was treated with excess TMS-Cl to afford bis-protected **3.27** (Scheme 3.7). Selective removal of the more labile primary silyl ether with potassium carbonate in methanol, followed by a TPAP oxidation of the crude material gave aldehyde **3.28**. The entire three step sequence could be carried out without isolation of the intermediates in an overall yield of 88%. With **3.28** in hand, we were ready to test the alkylation with vinylmagnesium bromide. To our delight, **3.29** was now obtained as a single isomer in 97% yield with no trace of epimerization. Having successfully optimized this step, we could now follow the remainder of the previously developed route with our new TMS-protected substrate. Ring closing metathesis by Grubbs' first generation catalyst gave **3.30** which was subsequently oxidized with TPAP to give **3.31**. It should be noted that while these intermediates were originally purified between steps, it was later found that their isolation was unnecessary. In fact, unpurified **3.28** could be treated with Grubbs' catalyst, followed by sequential addition of TPAP and NMO to the reaction mixture to give **3.31** in 90% yield from **3.28** as a two-step procedure. Finally, alkylation of **3.31** with methyllithium afforded **3.32** in 98% yield, which, upon treatment with PCC gave the desired enone, **3.33**, in an improved yield of 91% (compared to 65% with **3.24**).

Scheme 3.7 – Improved route for the formation of the A-ring



As suggested by our initial attempts at converting **3.25** into **3.26** (see Scheme 3.6 above), the installation of the all carbon quaternary centre by cuprate addition onto **3.33** turned out to be nontrivial (Table 3.1). Treatment of TMS-protected **3.33** with vinylmagnesium bromide in the presence of CuI gave a mere 12% yield of the desired product, **3.34** (entry 1). Numerous changes to the reaction conditions were attempted in order to improve the reaction yield: switching the solvent from THF to Et₂O, using HMPA as a co-solvent, adding BF₃·OEt₂¹¹ or TMS-Cl¹² to the reaction, replacing CuI with either CuBr·DMS or CuCN. In no case could the yield be improved *until the source of the CuI was changed*. The CuI originally used had been purified by precipitation from a saturated solution of NaI. Precipitation from a saturated KI solution,¹³ on the other hand, yielded a CuI source which now reliably gave 80% yield for the same reaction (entry 10).

Table 3.1 – Installation of the quaternary carbon centre by cuprate addition

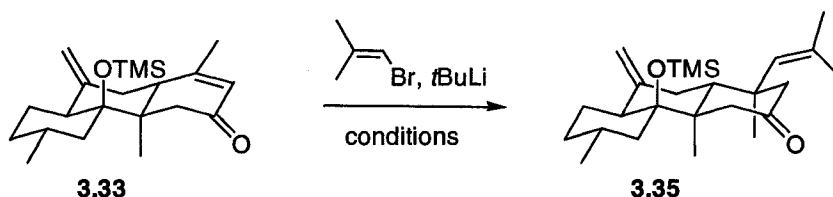


Entry	Solvent	Reagents	Temp (°C) ^a	Results
1	THF	CuI	-78 to -10 to -78 to 0	12% 3.30
2	Et ₂ O	CuI	-78 to -10 to -78 to 0	no reaction
3	THF, HMPA	CuBr·DMS, TMS-Cl	-78 to 0	no reaction
4	THF	CuBr·DMS, TMS-Cl	-78 to 0	no reaction
5	THF	CuBr·DMS	-78 to 0 to -78 to 0	no reaction
6	THF	CuBr·DMS	-30 to 0	no reaction
7	THF	CuCN	-78 to 0 to -78 to 0	no reaction
8	Et ₂ O	CuCN	-78 to 0 to -78 to 0	no reaction
9	THF	CuI, BF ₃ ·OEt ₂	-78 to 0	no reaction
10	THF	CuI ^b	-78 to -10 to -78 to 0	80% 3.34
11	THF	CuI ^b , BF ₃ ·OEt ₂	-78 to -10 to -78 to 0	23% 3.34
13	THF	CuI	-78 to -10 to -78 to 0	no reaction
14	Et ₂ O	CuI	-78 to -10 to -78 to 0	no reaction

^a For those entries with four temperatures listed: Grignard and copper source were combined at the first temperature, warmed to the second temperature for 5 minutes, cooled to the third temperature prior to adding substrate, and finally allowed to warm gradually to the fourth temperature. ^b CuI purified from a saturated solution of KI, rather than NaI.

Prior to this discovery, the generation of an organocuprate from a vinyl lithium was also attempted. Since vinyl lithium itself can be difficult to work with, the vinyl lithium derived from transmetalation of 1-bromo-2-methyl-propene was used instead. Oxidative cleavage of the double bond later in the synthesis would make the additional methyl groups inconsequential. Nonetheless, the conversion of **3.33** to **3.35** also failed to give any detectable reaction (Table 3.2).

Table 3.2 – Attempt to add an organocuprate derived from 1-lithio-2-methyl-propene

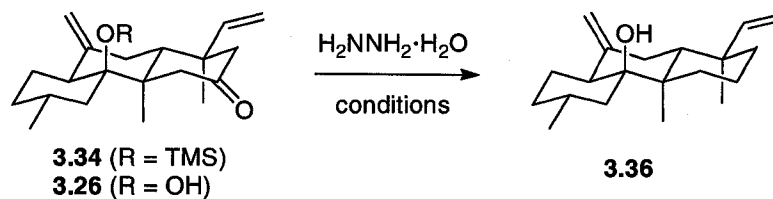


Entry	Solvent	Reagents	Results
1	Et ₂ O	CuCN	no reaction
2	THF	CuCN	no reaction
3	Et ₂ O	CuI, BF ₃ ·OEt ₂	no reaction
4	THF	CuI, BF ₃ ·OEt ₂	no reaction

Having successfully used the enone functionality to install our final quaternary stereocentre, the remaining ketone would need to be removed. While many methods exist for deoxygenation, a Wolff-Kishner reduction¹⁴ was considered first since it could be carried out on the ketone directly in one step. Moreover, its strongly basic conditions were expected to simultaneously remove the silyl protecting group. Indeed, heating **3.34** with excess hydrazine hydrate and potassium carbonate in diethylene glycol gave **3.36**, albeit in only 20% yield (entry 1, Table 3.3). No other identifiable material was isolated from the reaction mixture and an insoluble residue around the outside of the flask suggested polymerization of either the reagents or the substrate. Attempts to optimize this reaction included lowering the reaction temperature, changing the base and reducing the amount of reagents added. In addition, monoethylene glycol was tried as a solvent and deprotected substrate **3.26** (obtained by TBAF deprotection of **3.34** in 97% yield. Reaction not shown) was tested. Although in some cases good to excellent yields could be obtained, the reaction suffered

from irreproducible yields (see entries 2 and 12). As a result, a more reliable means of deoxygenating **3.34** was pursued.

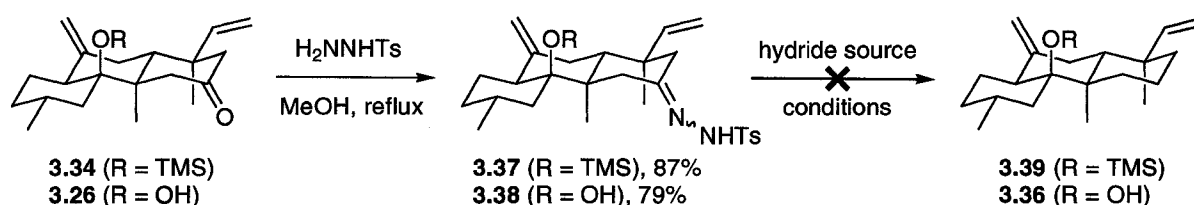
Table 3.3 – Optimization of the Wolff-Kishner reduction



Entry	R	H ₂ NNH ₂ (equiv)	Base (equiv)	Solvent	Temp (°C)	Result
1	TMS	100	K ₂ CO ₃ (35)	DEG	160 to 200	20% + decomposition
2	TMS	100	K ₂ CO ₃ (35)	DEG	160	24-68% 3.36
3	TMS	100	K ₂ CO ₃ (35)	DEG	75 to 120	decomposition
4	TMS	100	K ₂ CO ₃ (35)	DEG	160	<5% by crude NMR
5	TMS	50	K ₂ CO ₃ (15)	DEG	160	<5% by crude NMR
6	TMS	10	K ₂ CO ₃ (15)	DEG	160	34% 3.36
7	TMS	1	K ₂ CO ₃ (8)	DEG	160	decomposition
8	TMS	100	KOH (20)	DEG	160 to 200	decomposition
9	TMS	100	KOH (3)	DEG	75 to 120	decomposition
10	TMS	100	K ₂ CO ₃ (15)	MEG	160	decomposition
11	TMS	50	K ₂ CO ₃ (15)	MEG	160	decomposition
12	H	7	K ₂ CO ₃ (15)	DEG	160	8-79% 3.36
13	H	7	K ₂ CO ₃ (15)	MEG	160	decomposition
14	H	7	KOH (5)	DEG	160	decomposition

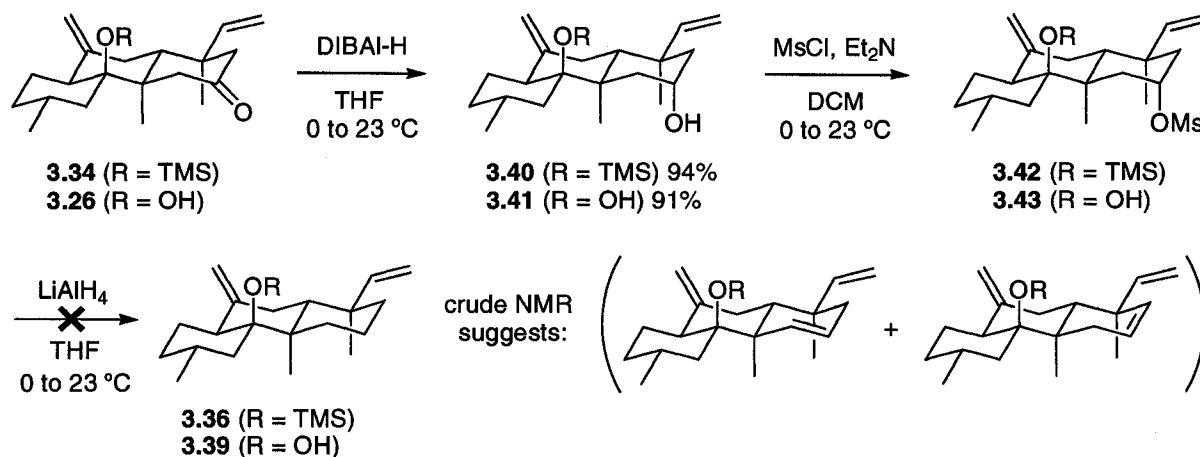
A two-step reduction of a tosylhydrazone was investigated next. Preparation of hydrazones **3.37** and **3.38** proceeded smoothly by treating **3.34** and **3.26** with *para*-toluenesulfonylhydrazide in refluxing methanol (Scheme 3.8). In both cases, the products were isolated as a 1:1 mixture of regioisomers. Reduction of the hydrazones was attempted using a variety of reducing agents (NaBH₄, NaBH₃CN, LiAlH₄, and DIBAL-H)¹⁵ under various reaction conditions (MeOH, DCM, DCE, and THF at temperatures ranging from 23 to 85 °C). Milder reaction conditions led to only trace amounts (< 5%) of the desired products being formed while harsher conditions led to complex mixtures from which no discernable material could be isolated.

Scheme 3.8 – Preparation and attempted reduction of tosylhydrazones

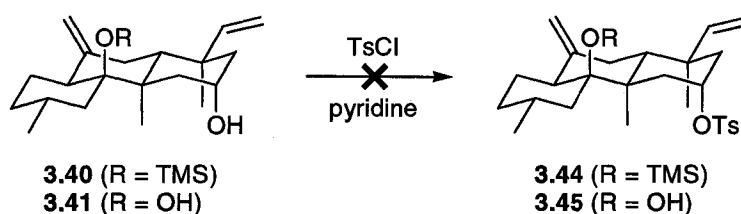


Since deoxygenation at the carbonyl oxidation state was proving to be difficult, deoxygenation via the secondary alcohol was considered. Accordingly, reduction of **3.34** and **3.26** with DIBAL-H gave alcohols **3.40** and **3.41** in 94% and 91% yield respectively (Scheme 3.9). Conversion to the corresponding mesylates afforded **3.42** and **3.43**, however, their instability precluded their purification. Treatment of the crude mesylates with LiAlH_4 gave a complex mixture of products. New olefinic peaks in the crude NMR suggested competing elimination reactions, perhaps by triethylamine leftover from the previous step. To avoid such possible contamination, the use of a more robust tosylate was considered since it would likely tolerate purification. Unfortunately, attempts at forming both **3.44** and **3.45** gave only unreacted starting material, likely owing to the steric hindrance imposed by the two axial methyl groups flanking the secondary alcohol (Scheme 3.10).

Scheme 3.9 – Attempted deoxygenation via a mesylate

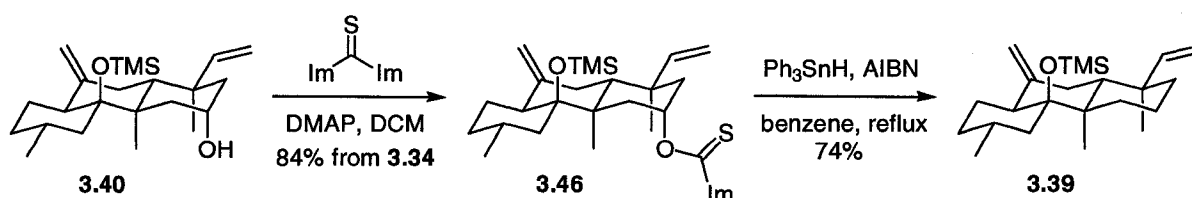


Scheme 3.10 – Attempted preparation of tosylated substrates for deoxygenation



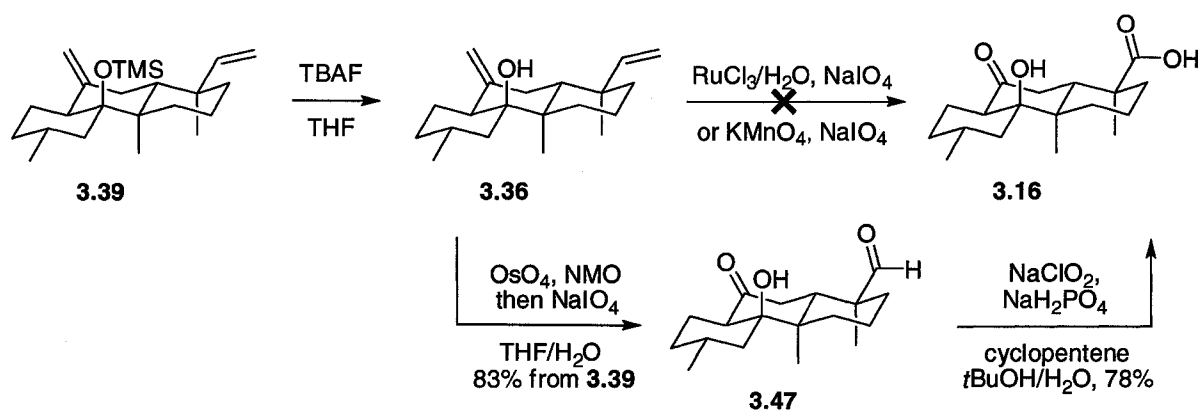
After numerous failed attempts at deoxygenating our substrate, success finally came with a Barton-McCombie reduction (Scheme 3.11).¹⁶ Treatment of unpurified **3.40** with thiocarbonyldiimidazole and DMAP gave **3.46** in 84% yield over two steps. Subsequent radical deoxygenation with triphenyltin hydride and AIBN in refluxing benzene successfully gave the desired product, **3.39** in 74% yield. Although this method required several additional steps compared to the originally envisioned Wolff-Kishner reduction, the relatively high yields, and more importantly, their reliability, more than made up for the lengthier procedure.

Scheme 3.11 – Barton-McCombie radical deoxygenation



At this point, all that remained for the synthesis of analogue **3.16** was to remove the silyl protecting group and oxidatively cleave the two double bonds. While deprotection with TBAF proceeded smoothly, direct cleavage of the double bonds to give carboxylic acid **3.16** led to a complex mixtures of products (Scheme 3.12). Fortunately, a two step procedure via a Pinnick oxidation¹⁷ of aldehyde **3.47** gave the desired product in 78% yield.

Scheme 3.12 – Completion of the wiedemannic acid analogue



To confirm the stereochemistry of our final product, a single crystal X-ray analysis of its methyl ester, **3.48**, was obtained following treatment of the acid with diazomethane (Scheme 3.13 and Figure 3.4).

Scheme 3.13 – Preparation of methyl ester 3.48

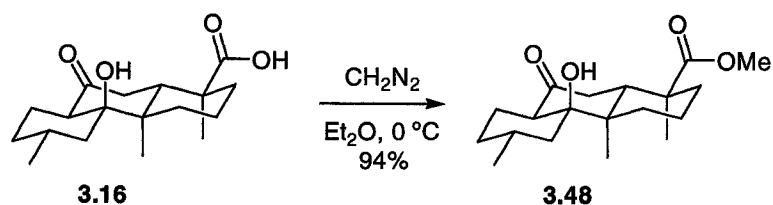
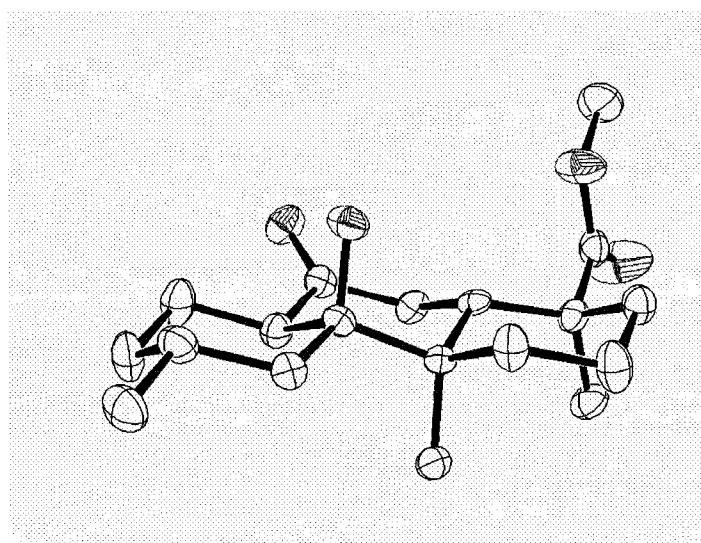
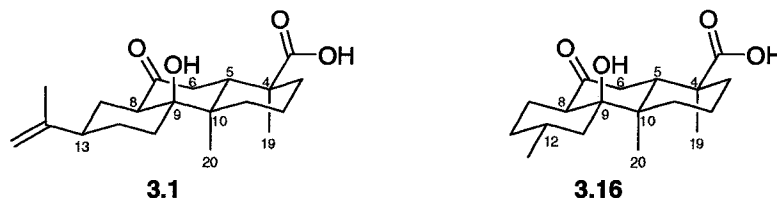


Figure 3.4 – ORTEP plot of methyl ester 3.48



With analogue **3.16** in hand, we proceeded to compare its spectral data to that of wiedemannic acid, **3.1**.⁴ To our surprise, significant differences were noted in both the chemical shifts and coupling constants of the ^1H and ^{13}C NMR spectra. In particular, significant variation at C5, C6, and C8 was observed (Table 3.4).

Table 3.4 – Selected ^1H and ^{13}C data in CDCl_3 for wiedemannic acid, **3.1**, and analogue **3.16**



Atom	^{13}C NMR of 3.1 (ppm)	^{13}C NMR of 3.16 (ppm)	^1H NMR of 3.1 (ppm)	^1H NMR of 3.16 (ppm)
5	52.2	41.8	1.08 (dd, $J = 8, 4$ Hz)	2.92 (dd, $J = 13.8, 3.0$ Hz)
6	37.0	41.1	2.27 ax. (dd, $J = 14, 8$ Hz) 1.90 eq. (dd, $J = 14, 4$ Hz)	2.33 ax. (dd, $J = 14.4, 13.4$ Hz) 2.09 eq. (dd, $J = 14.4, 3.2$ Hz)
8	52.6	52.1	3.49 (dd, $J = 12, 6$ Hz)	2.34 (dd, $J = 11.2, 3.8$ Hz)

On the assumption that neither the equatorial methyl group at C12 nor the isopropenyl group at C13 should appreciably influence the chemical shift of atoms in the A and B rings (C1-C10, C19 and C20), the discrepancies in the spectral data forced us to conclude that the proposed structure of wiedemannic acid was incorrect. In light of this finding, the synthesis of the reported structure was not pursued.

Despite not completing the synthesis of wiedemannic acid, the successful preparation of analogue **3.16** in 18 linear steps from isopulegone and with an overall yield of 8.8% successfully highlights the synthetic utility of the tandem oxy-Cope/Claisen/ene reaction. By setting the relative stereochemistry at C5, C8, C9 and C10, our cascade reaction allowed rapid access to the reported core of wiedemannic acid. From this success, the groundwork was laid for the application of this new method to a more challenging natural product, that of LL-S491 β .

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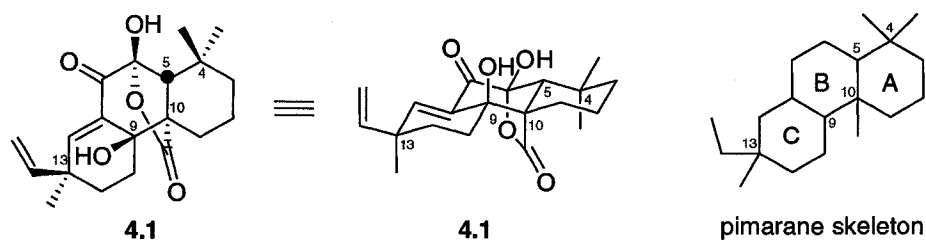
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4

Towards the Synthesis of LL-S491 β Introduction to LL-S491 β

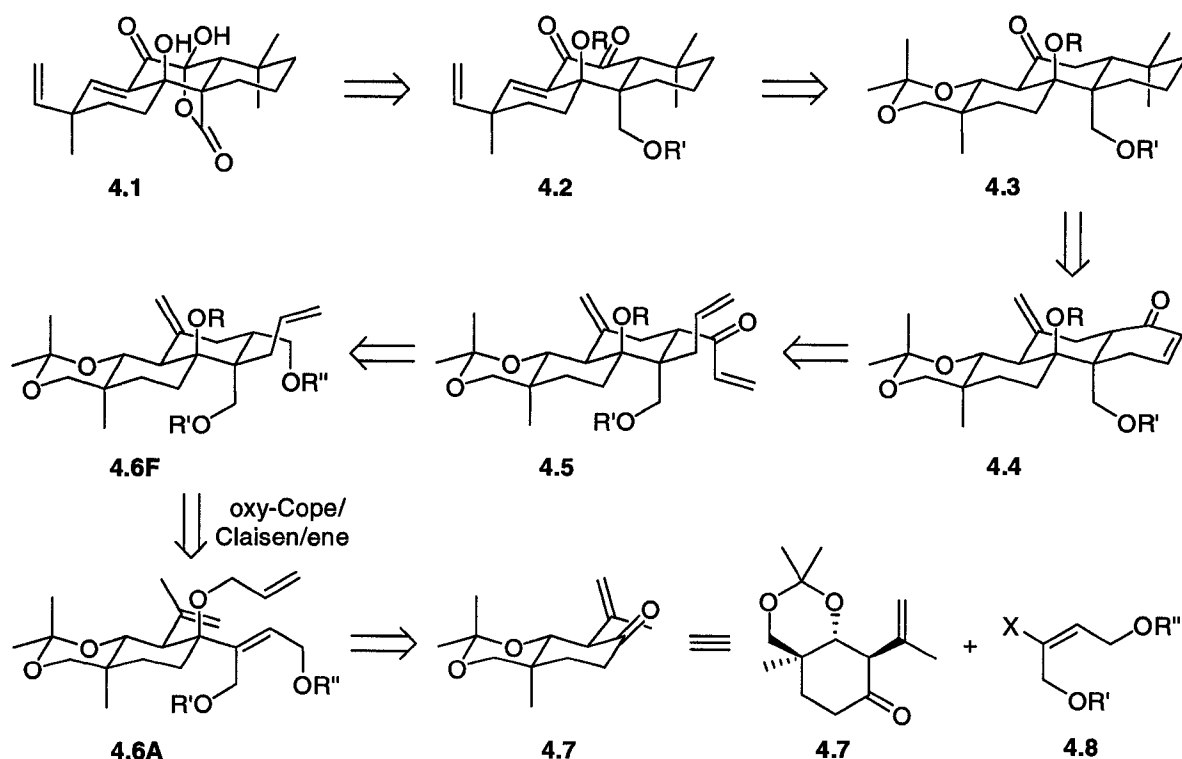
LL-S491 β (**4.1**) is a pimarane diterpene first isolated in 1971 from the fermentation of *Aspergillus chevalieri* (Figure 4.1).¹ This fungal metabolite was found to exhibit antibacterial activity against gram-positive organisms as well as antiprotozoal activity against *Tetrahymena pyriformis*. Despite its potentially interesting biological profile, no attempts to synthesize this molecule have yet been reported in the literature.

Figure 4.1 – Pimarane diterpene LL-S491 β



Like wiedemannic acid (**3.1**), the synthesis of LL-S491 β (**4.1**) would require the controlled formation of the C9 tertiary alcohol as well as the all-carbon quaternary carbon

stereocentre at C10. A retrosynthetic analysis shows that these features could easily be introduced by a tandem oxy-Cope/Claisen/ene strategy (Figure 4.2). Disconnection at the hemi-acetal of LL-S491 β with reduction of the carboxylic acid gives intermediate **4.2**. An α -oxidation of **4.3** could introduce the diketone functionality while the α,β -unsaturation could be generated via an elimination of a β -secondary alcohol. From **4.3**, a strategy similar to that employed in the synthesis of wiedemannic acid analogue **3.16** could be used to introduce the *gem*-dimethyl group from enone **4.4** and convert the exocyclic double bond to the desired ketone. Likewise, enone **4.4** could be prepared via an olefin metathesis reaction of **4.5**, which could itself be prepared from **4.6F**. Finally, **4.6F** is the expected product of an oxy-Cope/Claisen/ene reaction of **4.6A**. Note that the conformational preferences imposed by the acetal should ensure that the desired **F** isomer is the major product (see Chapter 2 for a more detailed discussion). Thus, to build our tandem reaction precursor, ketone **4.7** would need to be alkylated with the corresponding vinyl lithium of halide **4.8**.

Figure 4.2 – Retrosynthesis of LL-S491 β 

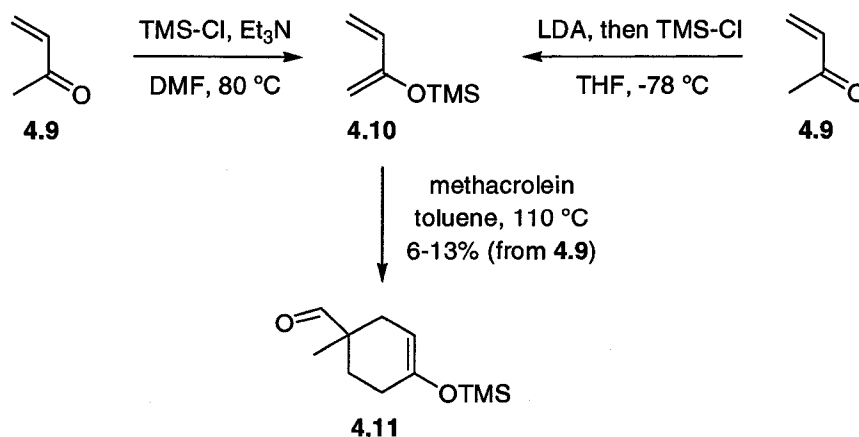
While much of the proposed chemistry is reminiscent of our earlier efforts to synthesize wiedemannic acid, several new challenges are present. Of particular note is the

high degree of functionalization found on **4.6A**. The successful transformation of **4.6A** to **4.6F** would be a testament to the robustness of our oxy-Cope/Claisen/ene method. In addition, the synthesis of **4.7** requires the formation of an all-carbon quaternary stereocentre. Finally, **4.8** will need to have orthogonal protecting groups in order to allow differentiation of the two primary alcohols later in the synthesis. While the preparation of such vinyl halides was not expected to be difficult, alkylation of their corresponding vinyl lithium species had the potential to suffer from an unwanted elimination of OR' to give an allene decomposition product.² Anticipating that the introduction of the quaternary carbon would likely be the greater challenge, our attention was first directed to the preparation of **4.7**.

Introducing the All-Carbon Quaternary Stereocentre

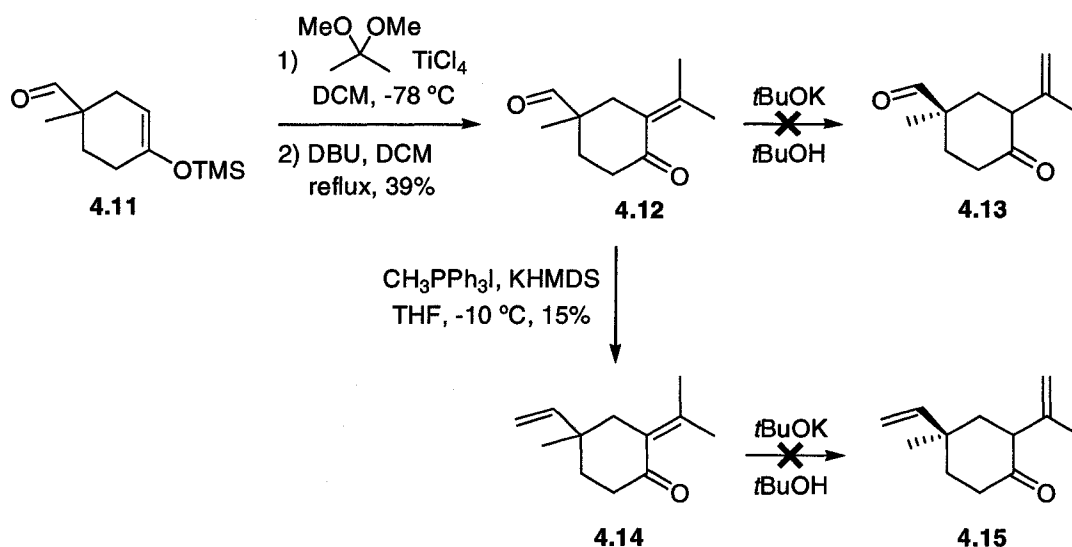
The introduction of the all-carbon quaternary stereocentre to the tandem precursor was originally envisioned to proceed via a Diels-Alder reaction between **4.10** and methacrolein (Scheme 4.1). The generation of silyl enol ether **4.10**³ from ethyl vinyl ketone (**4.9**) proceeded well, however its purification proved to be a challenge owing both to the compound's high volatility and its tendency to polymerize. Consequently, the diene was reacted in its crude form with methacrolein to give the known Diels-Alder adduct **4.11** in yields ranging from 6 to 13%. Despite these low yields, sufficient quantities of material were made available for subsequent transformations.

Scheme 4.1 – First approach to the quaternary carbon centre



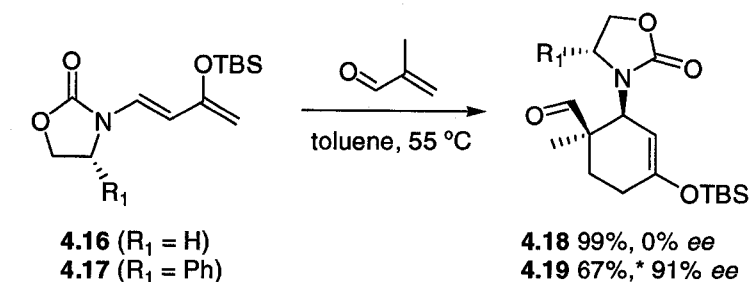
To install the isopropenyl group, **4.11** was treated with 2,2-dimethoxypropane in the presence of TiCl_4 to give a mixture of aldol products (Scheme 4.2). The crude material was then further reacted with DBU to give the dehydrated adduct **4.12** in 39% yield for the two steps.⁴ From **4.12**, it was hoped that a deconjugation with $t\text{BuOK}$ ⁵ would afford the requisite compound, **4.13**. Rather, a complex mixture of products was obtained from which none of the desired product was detected. To ensure that the aldehyde functionality was not interfering with the transformation, a small amount of **4.14** was prepared by treating keto-aldehyde **4.12** with one equivalent of a Wittig reagent. The volatile product, however, also failed to give any of the deconjugated compound.

Scheme 4.2 – Attempted deconjugation reaction for introducing the isopropenyl moiety



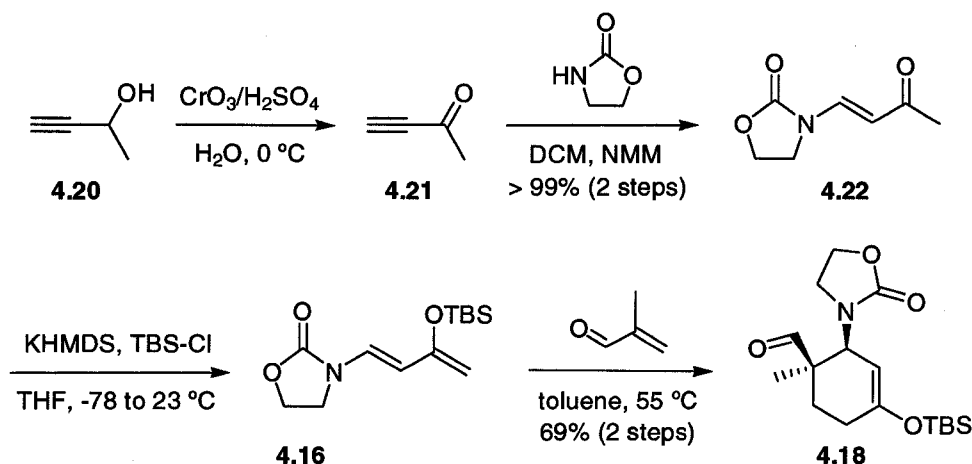
In light of the poor yields associated with the above reactions, no further attempts to prepare **4.7** by this route were made. Instead, an alternative Diels-Alder strategy was investigated. Rawal and coworkers have reported the use of an oxazolidinone auxiliary to generate adducts **4.18** and **4.19** in their respective racemic and chiral forms (Scheme 4.3).⁶ The benefit of using such an auxiliary in our synthesis would be two-fold: in addition to increasing the molecular weight of the intermediates (thus removing any issues of product volatility), its use would open the door to a future chiral synthesis of the LL-S491 β .

Scheme 4.3 – Rawal's Diels-Alder using an oxazolidinone auxiliary

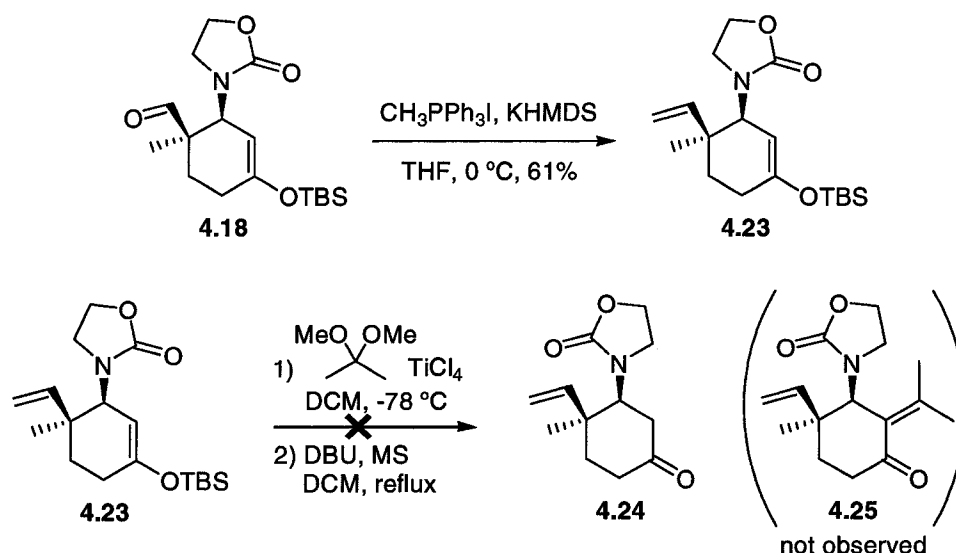


* yield was for the Diels-Alder reaction and subsequent removal of the auxiliary (not shown)

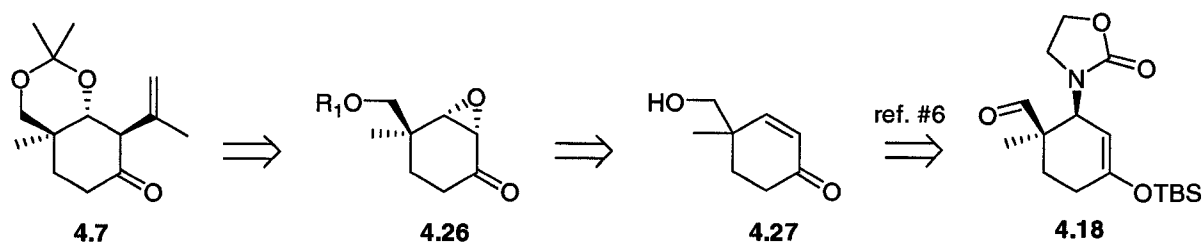
Following Rawal's procedure,⁶ racemic adduct **4.18** was prepared as shown in Scheme 4.4 below. A Jones' oxidation of **4.20** followed by a Michael addition of 2-oxazolidinone yielded a quantitative amount of **4.22**. Conversion to the silyl enol ether followed by a Diels-Alder with methacrolein gave adduct **4.18** in 69% yield for the two steps.

Scheme 4.4 – Preparation of Rawal's racemic Diels-Alder adduct, **4.18**

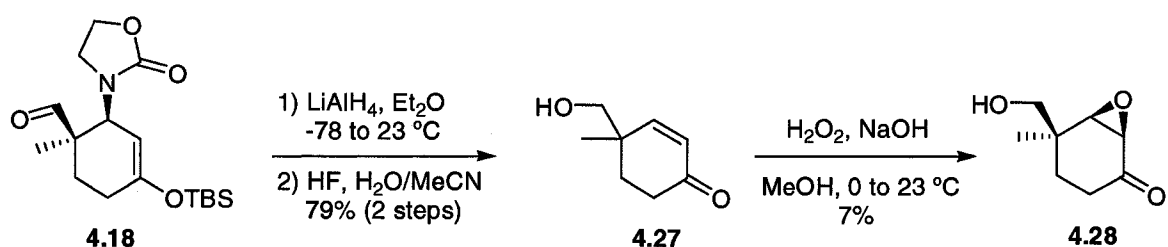
To avoid interference of the free aldehyde in subsequent transformations, **4.18** was converted to alkene **4.23** via a Wittig reaction in 61% yield (Scheme 4.5). Next, the previously attempted aldol reaction with 2,2-dimethoxypropane was repeated. Rather than the desired enone, ketone **4.24** was isolated as the product of silyl enol ether hydrolysis.

Scheme 4.5 – Attempted aldol condensation on modified Diels-Alder adduct **4.23**

At this point, it was decided that a new approach for introducing the isopropenyl group was needed. A retrosynthetic analysis of ketone **4.7** revealed that an epoxide opening of **4.26** with isopropenylmagnesium bromide could introduce the required functional groups with the desired stereochemistry (Figure 4.3). The epoxide could be prepared from **4.27**, which is itself readily available from Diels-Alder adduct **4.18**.

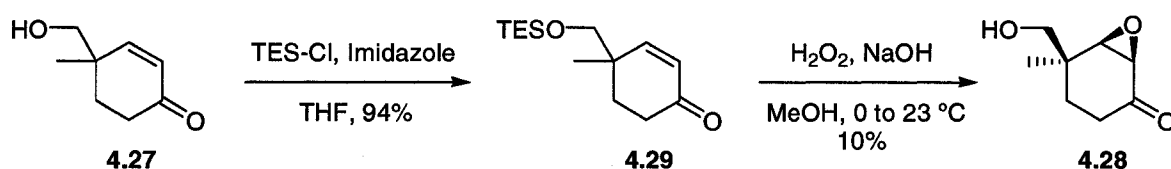
Figure 4.3 – New retrosynthesis for ketone **4.7**: an epoxide opening strategy

Following Rawal's literature procedure for the removal of the oxazolidinone auxiliary and simultaneous hydrolysis of the silyl enol ether, **4.18** was treated first with LiAlH_4 , and then with a 10% aqueous solution of hydrofluoric acid to give **4.27** in 79% yield (Scheme 4.6). Epoxidation of the resulting enone using H_2O_2 ,⁷ however, proceeded in low yield and gave exclusively the undesired isomer, **4.28**, with the epoxide *anti* to the methyl group.

Scheme 4.6 – Preparation and epoxidation of enone **4.27**

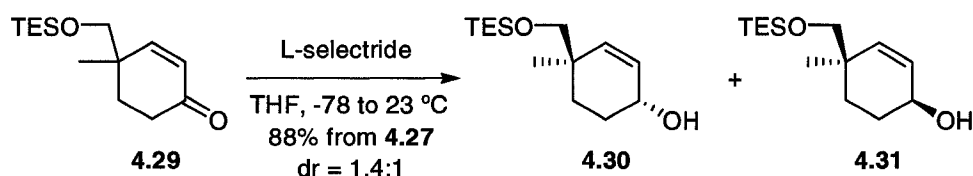
Hoping that a bulky protecting group on the alcohol might reverse the facial selectivity of the epoxidation, **4.27** was treated with TES-Cl to give **4.29** in 94% yield (Scheme 4.7). The subsequent epoxidation reaction once again proceeded *anti* to the methyl group, this time with concomitant removal of the silyl protecting group leaving **4.28** in 10% yield.

Scheme 4.7 – Attempt to reverse the epoxidation selectivity with a bulky protecting group



In order to direct the epoxidation *syn* to the methyl group, a selective reduction of the enone to allylic alcohol **4.30** was attempted (Scheme 4.8). Several reducing agents were investigated, however, the best ratio achieved was 1.4:1 using L-selectride. Although the selectivity was poor, the two products were readily separable making recycling of the minor isomer possible via its re-oxidation to **4.29**.

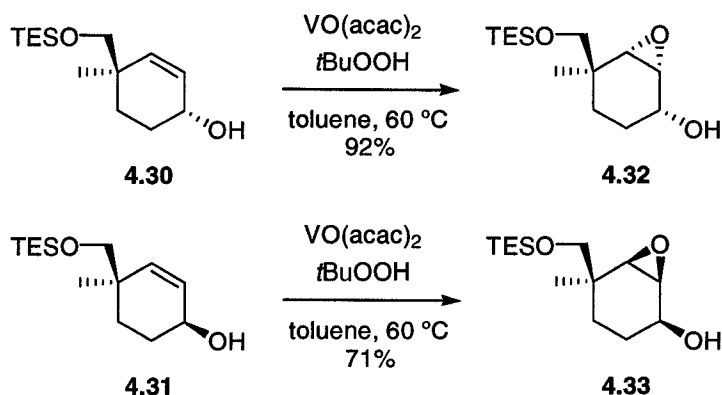
Scheme 4.8 – Enone reduction to give an allylic alcohol directing group



Assigning the relative stereochemistry of the two allylic alcohols proved to be difficult and it was not until after subsequent transformations that we were able to confirm the identity of **4.30** and **4.31** with absolute certainty (*vide infra*). Consequently, both isomers

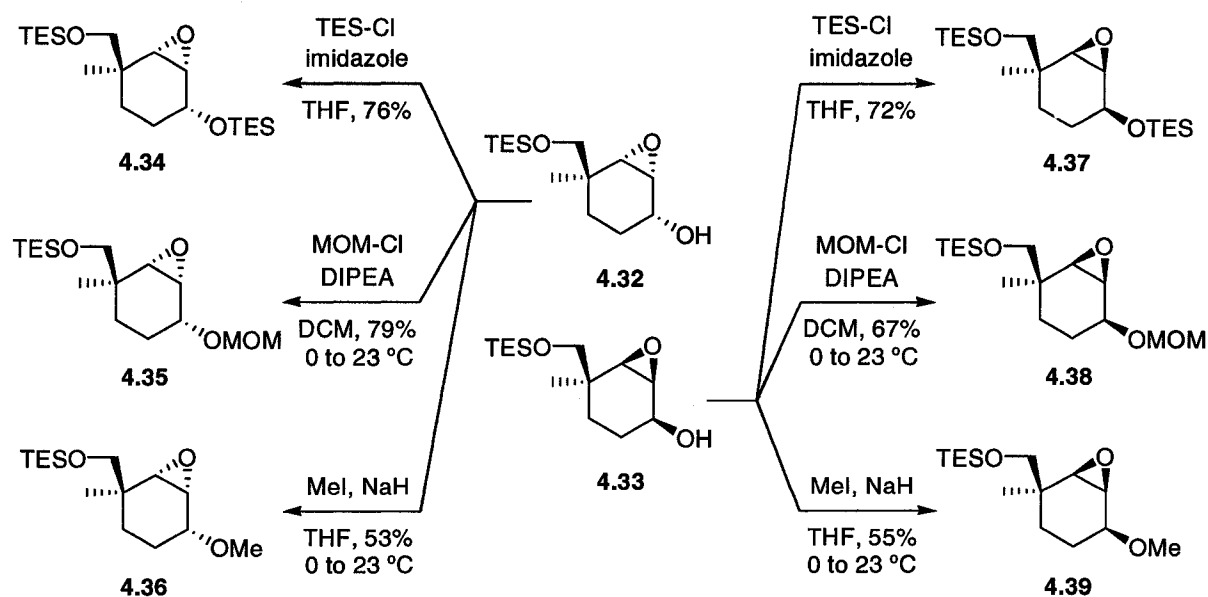
were carried forward. The allylic epoxidation of **4.30** and **4.31** with VO(acac)₂ and *t*BuOOH proceeded well giving **4.32** and **4.33** in 92% and 71% yield, respectively (Scheme 4.9).

Scheme 4.9 – Directed epoxidation of allylic alcohols 4.30 and 4.31



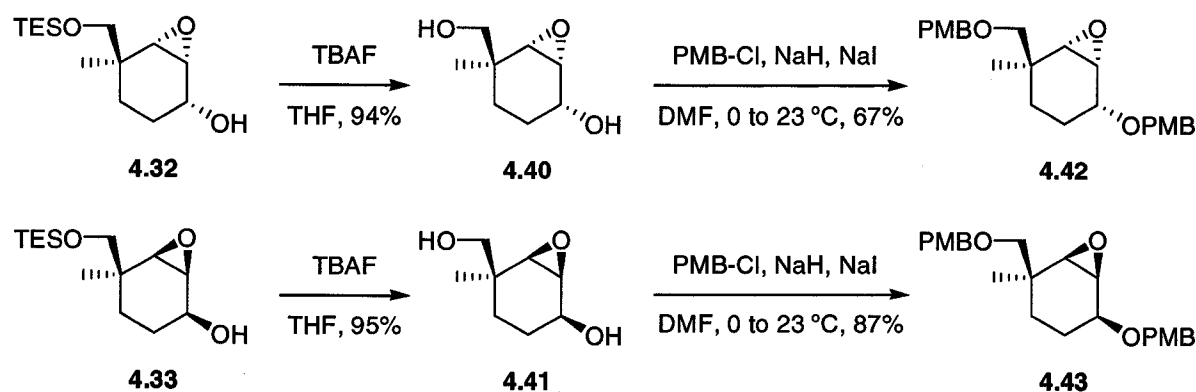
Protection of the secondary alcohol in **4.32** with a variety of protecting groups (TES, MOM, Me) also proceeded well and epoxides **4.34–4.36** were obtained in yields ranging from 53–79% (Scheme 4.10). Likewise, compound **4.33** was treated under analogous conditions to give TES, MOM and Me protected substrates **4.37–4.39** in 55–72% yield.

Scheme 4.10 – Protection of secondary alcohols 4.32 and 4.33



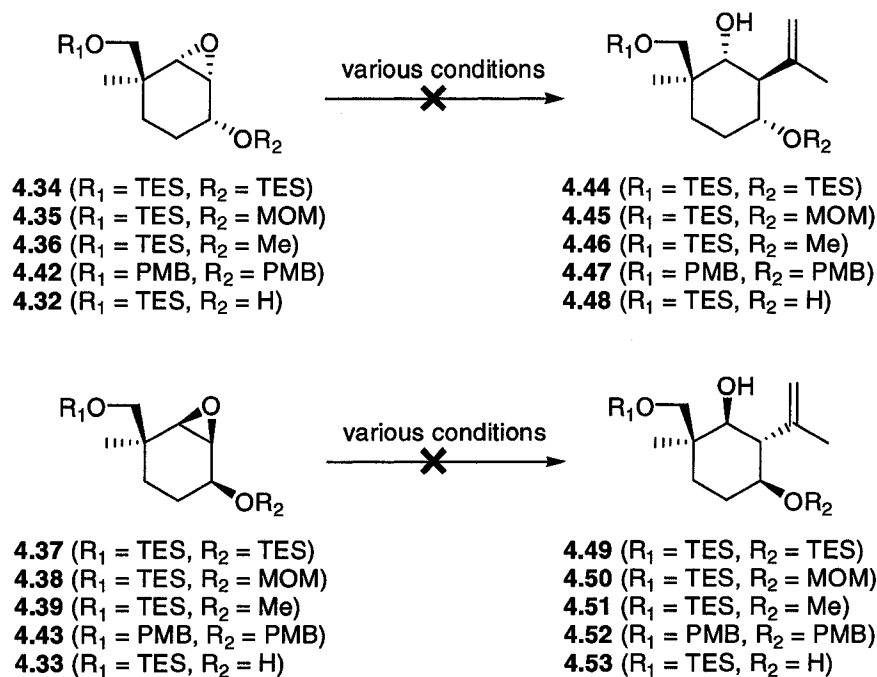
In addition to the above compounds, bis-PMB protected epoxides **4.42** and **4.43** were prepared by treating **4.32** and **4.33** first with TBAF, and then with PMB-Cl (Scheme 4.11).

Scheme 4.11 – Preparation of bis-PMB protected epoxides

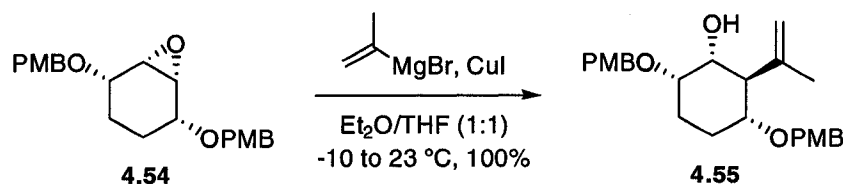


With the protected substrates in hand, our attention was turned to the epoxide opening. An extensive survey of reaction conditions was performed including the use of isopropenylmagnesium bromide and its vinyl lithium equivalent, both with and without the addition of Lewis acids such as BF_3OEt_2 .⁸ Higher and lower-order cuprates derived from various copper sources (CuI , CuBr , CuCN) were also tried, both with and without the addition of TMS-Cl .⁹ Mixed cuprates such as $(\text{R})\text{CuCH}_2\text{TMSLi}\cdot\text{LiI}$ ¹⁰ and $(\text{R})\text{Cu}(2\text{-thienyl})\text{Li}\cdot\text{LiCN}$ ¹¹ were also attempted. Finally, a variety of solvents and solvent mixtures were investigated (THF , Et_2O , HMPA) with temperatures ranging from -78 to 23 $^\circ\text{C}$. Almost without exception, no detectable reaction was observed for the epoxides. In those few cases where starting material was consumed, complex mixtures of products were obtained from which no discernable products were isolated.

Scheme 4.12 – Failed epoxide opening of compounds 4.32-4.39, 4.42-4.43



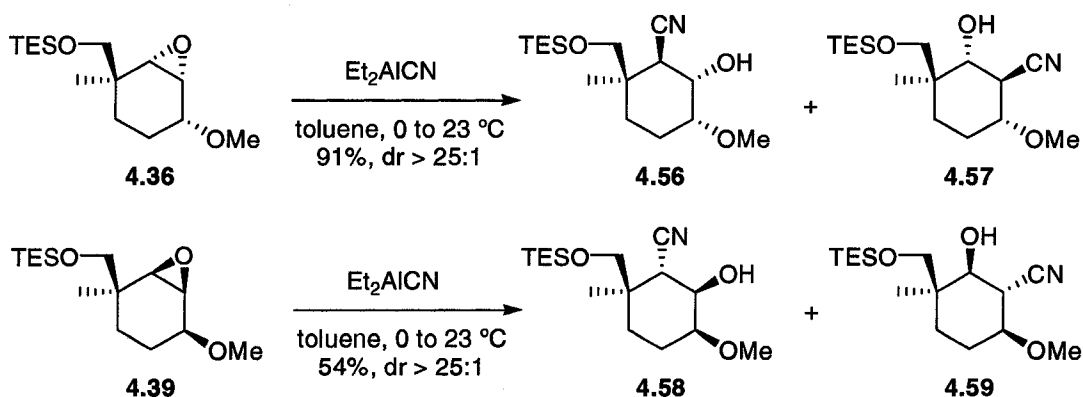
The remarkable stability of these epoxides was surprising given that the opening of bis-PMB protected **4.54** with isopropenylmagnesium bromide is known to proceed quantitatively in the presence of CuI (Scheme 4.13).¹² The similarity between **4.54** and the above epoxides suggests that the steric hindrance of the quaternary carbon centre is likely responsible for the low reactivity of our substrates. To combat this problem, cyanide, a much smaller nucleophile, was selected to replace the bulky Grignard reagent. Still a carbon based nucleophile, a cyano moiety could later be transformed into the requisite isopropenyl group.

Scheme 4.13 – Comparison to the known epoxide opening of analogous substrate **4.54**

Treatment of **4.36** and **4.39** with excess KCN in toluene gave no reaction at ambient temperature, while heating the mixture to reflux led to a complex mixture of products (results not shown). In contrast, their reactions with Et_2AlCN ¹³ proceeded cleanly to give **4.56** and

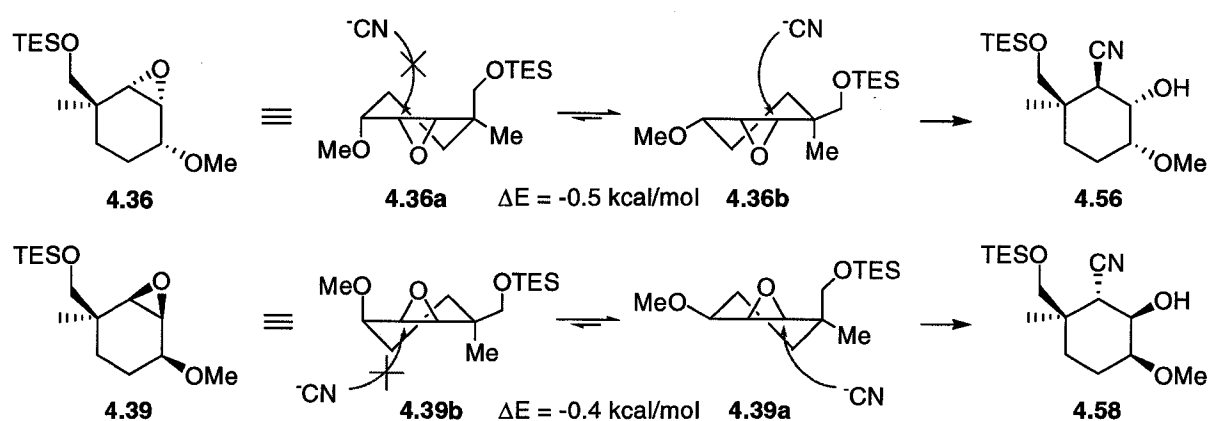
4.58 in 54% and 91% yield respectively (Scheme 4.14). Spectral data from these compounds, however, revealed that the cyanide had attacked on the more hindered side of the epoxide. While these products were not synthetically useful, the fact that the epoxide had successfully opened left room for optimism. (It is to be noted that the stereochemical assignment of these products provided confirmation that the stereochemistry of allylic alcohols **4.30** and **4.31** had been correctly assigned. Consequently, substrates derived from **4.31** were no longer carried forward).

Scheme 4.14 – Successful epoxide opening with Et₂AlCN



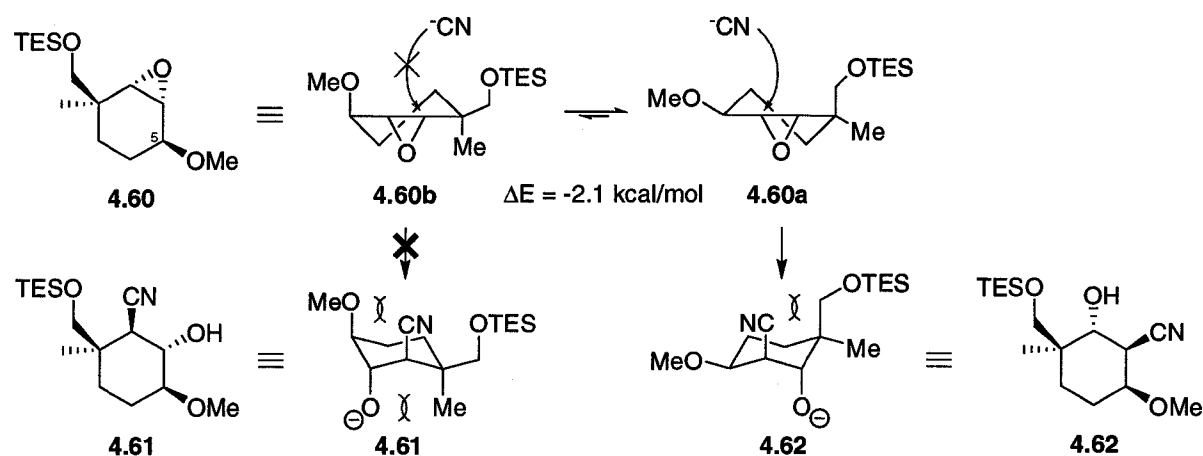
Looking at epoxides **4.36** and **4.39** in 3D (Figure 4.4), it becomes clear that the steric hindrance caused by axial attack adjacent to the quaternary centre is overridden by a conformational preference for structures **4.36b** and **4.39a** at the transition state. Calculations at the semi-empirical PM3 level of theory indicate an energy difference of 0.5 kcal/mol favouring **4.36b** over **4.36a**, and 0.4 kcal/mol favouring **4.39a** over **4.39b**. These minimal values, however, do not reflect the developing 1,3-diaxial interactions between the incoming nucleophile and the axial CH₂OTES (**4.36a**) and Me (**4.39b**) groups. It is likely for this reason that the transition states resulting from conformers **4.36b** and **4.39a** are so highly favoured.

Figure 4.4 – Epoxide opening in 3D



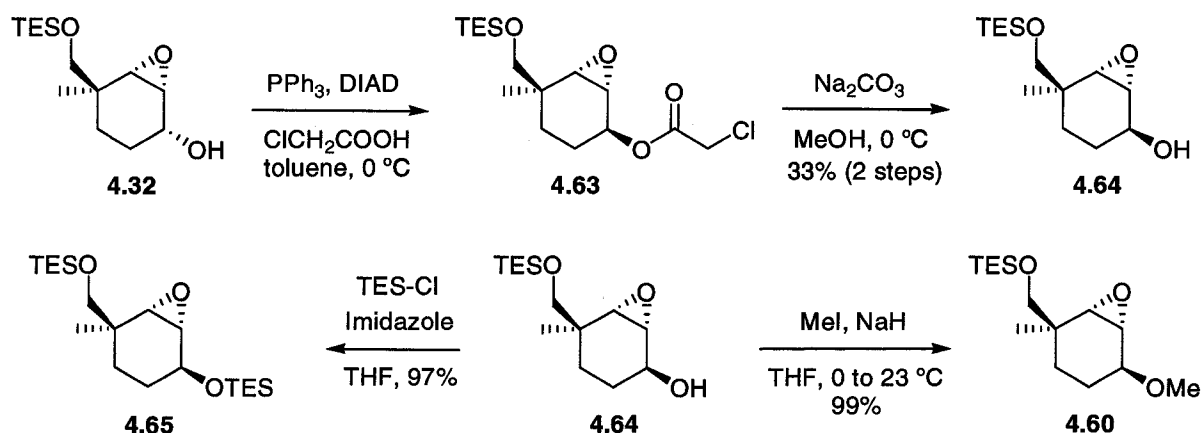
The above analysis suggests that a C5 epimer of **4.36** should open on the opposite side of the epoxide to give the desired stereochemistry. Examining the two conformers of epimeric substrate **4.60** reveals that conformer **4.60a** is now favoured over **4.60b** by 2.1 kcal/mol. Moreover, the developing 1,3-diaxial interactions are expected to be more severe for the formation of **4.61** further suggesting that **4.60a** should be the reactive conformer.

Figure 4.5 – Proposed epoxide opening of C5 epimer 4.60

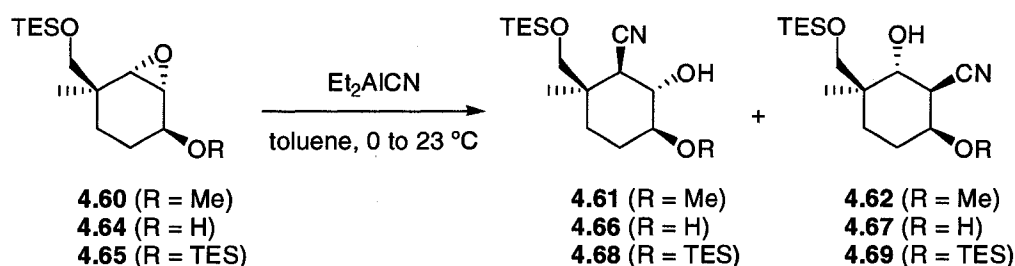


To test this theory, epimeric substrates **4.60** and **4.65** were prepared. A Mitsunobu inversion¹⁴ of intermediate **4.32** using chloroacetic acid as the nucleophile gave **4.64** in 33% yield after basic hydrolysis of the intermediary ester. Capping the secondary alcohol with a methyl group gave **4.60** in 99% yield while protection with TES-Cl gave **4.65** in 97% yield.

Scheme 4.15 – Preparation of epimeric substrates for epoxide opening

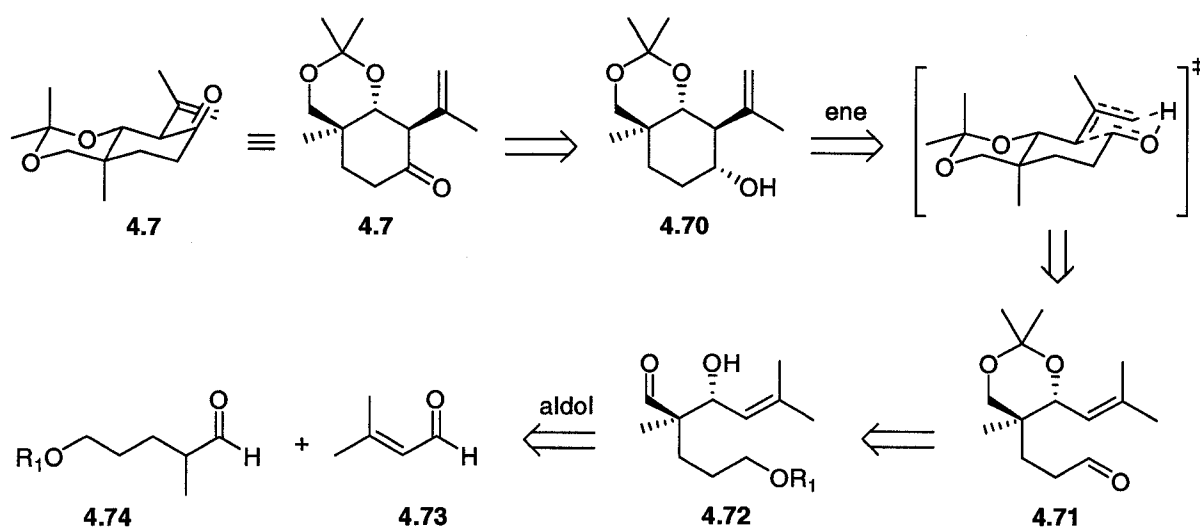


Epimeric epoxides **4.60**, **4.65**, as well as the unprotected **4.64** were each treated with Et_2AlCN in toluene (Table 4.1). With either **4.65** as the substrate ($\text{R} = \text{TES}$), or **4.64** ($\text{R} = \text{H}$) no reaction was detected (entries 1 and 2). In contrast, a 79% yield was obtained when **4.60** ($\text{R} = \text{Me}$) was subjected to the reaction conditions confirming the sensitivity of this reaction to steric hindrance (entry 3). To our surprise, the product of this reaction turned out to be isomer **4.61** rather than the predicted **4.62**, indicating that the epoxide had once again opened on the more hindered side. To account for this result, we speculated that the aluminum might be coordinating to the oxygen of the $-\text{OTES}$ group and directing the nucleophilic attack. To combat this problem, the reaction was repeated with the addition of $\text{BF}_3 \cdot \text{OEt}_2$. It was hoped that the presence of this second Lewis-acid would break apart any aluminum-oxygen interactions and prevent a directed attack of the cyanide. Under these conditions, however, little change to the reaction outcome was observed and **4.61** was again isolated, this time in 57% yield (entry 4).

Table 4.1 – Epoxide openings of epimeric substrates with Et₂AlCN

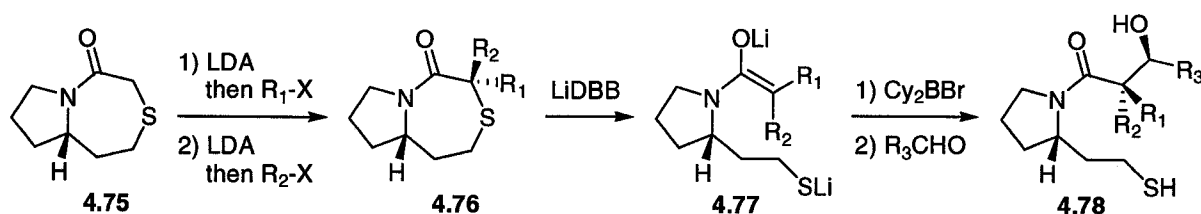
Entry	Substrate	Additive	Result
1	4.65	---	no reaction
2	4.64	---	no reaction
3	4.60	---	79% of 4.61
4	4.60	BF ₃ ·OEt ₂	57% of 4.61

Having spent considerable effort on this epoxide opening route while achieving limited progress, we decided to forego this approach. Based on the earlier successes of Lewis-acid catalyzed carbonyl ene reactions for the preparation of substrates **2.33** and **2.80**, we decided to investigate a similar method for the preparation of **4.7** (Figure 4.6). An ene reaction of **4.71** could be expected to give **4.70**, which, following an oxidation, could provide the desired ketone. The synthesis of **4.71** was envisioned to proceed via an aldol reaction between an enolate equivalent of **4.74** and aldehyde **4.73**.

Figure 4.6 – Retrosynthesis of ketone **4.7**: a carbonyl ene approach

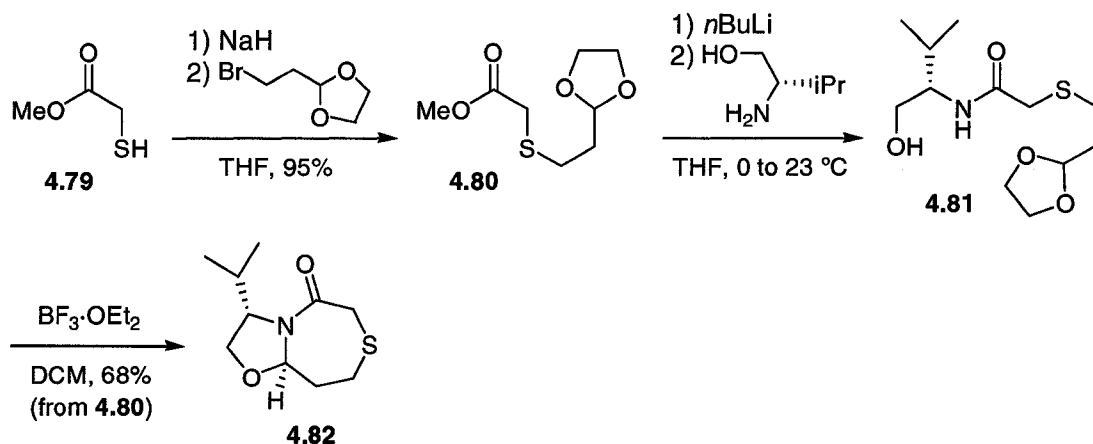
Assuming a closed Zimmerman-Traxler transition state for the aldol reaction, the *E* enolate of **4.74** would be required to ensure the proper stereochemistry of aldol **4.72**. The selective formation of acyclic α,α -disubstituted enolates, however, is a non-trivial problem. An elegant solution by Gleason et al. was reported in 2001 wherein the reduction of a bicyclic thioglycolate lactam (**4.75**) was found to generate either the *E* or *Z* enolate (**4.77**), depending on the relative stereochemistry of R_1 and R_2 (Scheme 4.16).¹⁵ Moreover, subsequent conversion to the boron enolate and treatment with an aldehyde led to aldol adducts of type **4.78** with high selectivity.¹⁶ The approach, however, suffered from a lengthy synthesis for the auxiliary. A second generation thioglycolate lactam, **4.82**, was consequently developed (Scheme 4.17).¹⁷ Its use in the aldol reaction, however, has yet to be reported. Nonetheless, we decided to try and extend the use of **4.82** to an aldol reaction equivalent to that between **4.74** and **4.73**. If successful, this reaction could provide the basis for an enantioselective synthesis of LL-S491 β .

Scheme 4.16 – Gleason's reported aldol reactions using a thioglycolate lactam auxiliary



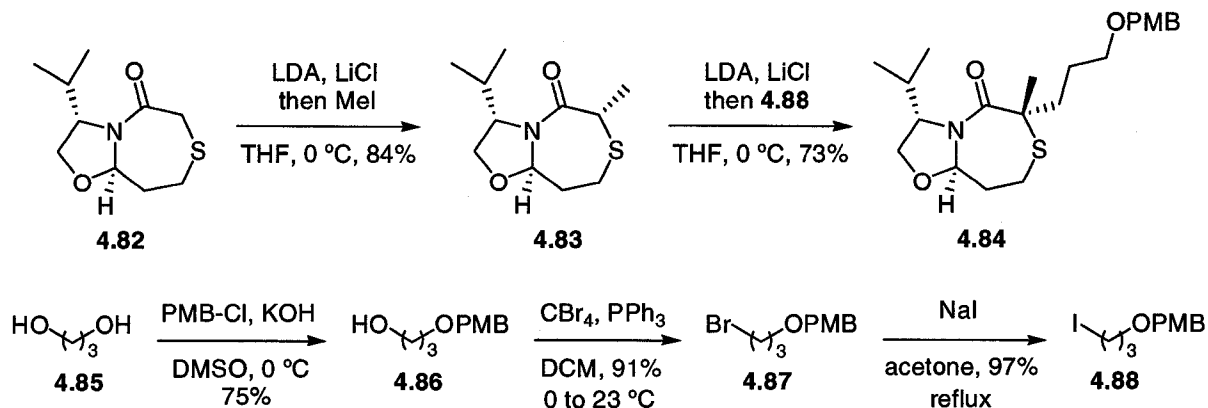
The preparation of the second generation auxiliary began with the S-alkylation of methyl thioglycolate (**4.79**) with commercially available 2-(2-bromo-ethyl)-[1,3]dioxolane to give **4.80** in 95% yield. Subsequent transesterification with valinol followed by an *in situ* O to N acyl transfer afforded **4.81**. Finally, transacetalization with $\text{BF}_3 \cdot \text{OEt}_2$ provided the desired thioglycolate lactam, **4.82**, in 68% yield (65% overall, compared to the reported overall yield of 71%).

Scheme 4.17 – Preparation of Gleason's second generation thioglycolate lactam auxiliary



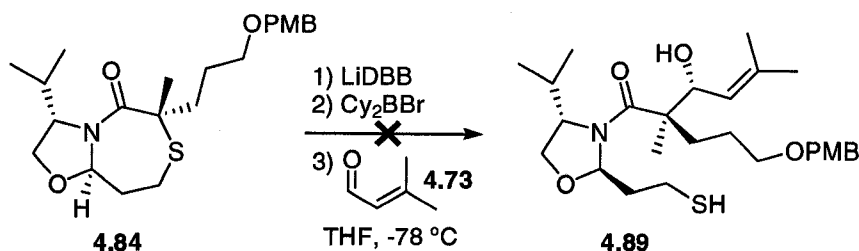
As with Gleason's first auxiliary, the order of alkylation dictates the relative stereochemistry of the alkyl groups and, ultimately, the geometry of the enolate. To ensure formation of the *E* enolate, we would have to alkylate sequentially with iodomethane, followed by the longer chain alkyl halide. The first step proceeded well and **4.83** was isolated in 84% yield (Scheme 4.18). The second alkylation required the preparation of PMB protected alkyl iodide **4.88** (alkylation with alkyl bromide **4.87** was not successful. Results not shown). Beginning with the mono-protection of 1,3-propanediol (**4.85**) using PMB-Cl (0.5 equiv) and KOH in DMSO, the remaining primary alcohol was converted to a bromide by treatment with CBr₄ and PPh₃. Conversion of **4.87** to the alkyl iodide was accomplished by an S_N2 displacement with NaI in acetone to give **4.88** in 97% yield. Subsequent alkylation of **4.83** thus gave our enolate precursor, **4.84**, in 73% yield.

Scheme 4.18 – Step-wise alkylation of Gleason's second generation chiral auxiliary



With **4.84** in hand, we were ready to try the aldol reaction. Following the procedures developed by Gleason et al. for the first generation auxiliary,¹⁶ we treated **4.84** with LiDBB followed by Cy₂BBr and aldehyde **4.73** (Scheme 4.19). While the starting material was consumed, none of the desired product was isolated. Rather, a complex mixture was obtained, the constituents of which were unidentifiable.

Scheme 4.19 – Attempted aldol reaction with Gleason's second generation auxiliary

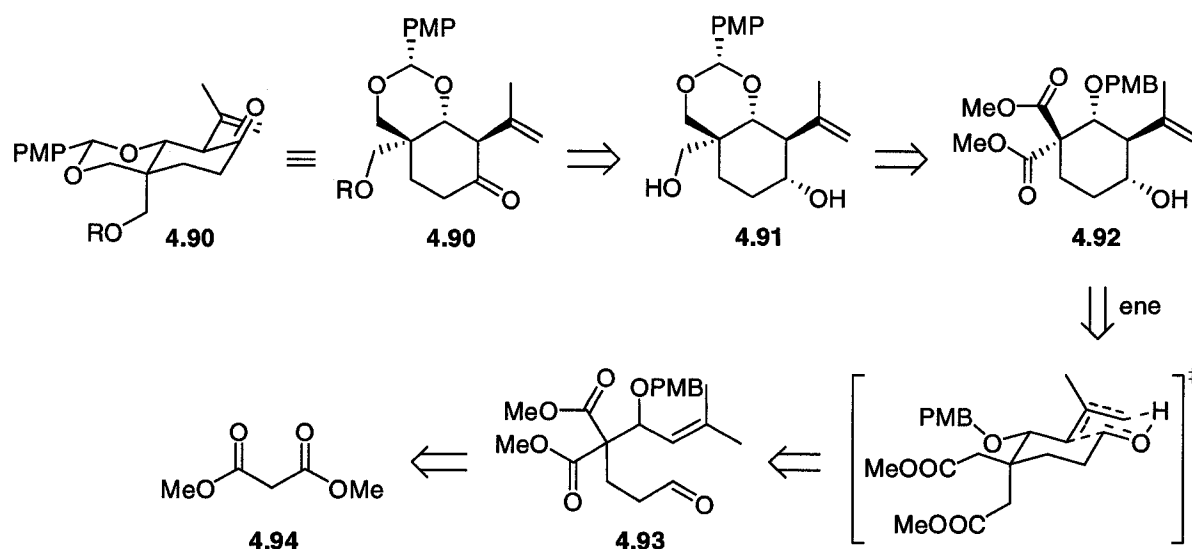


Although benzyl groups were known to be compatible with the LiDBB reducing conditions, we considered that reduction of the OPMB group might be interfering with the above protocol. To be sure, we began to prepare the analogous TBS protected substrate in order to re-test the aldol reaction (results not shown). While embarking on this path, however, we began to consider the scalability of this route. From our initial attempts on substrate **4.84**, concerns about generating sufficient quantities of material had been raised: Because of the high dilution resulting from the need for excess LiDBB solution,¹⁸ as well as the strict requirement for a -78 °C reaction temperature,¹⁹ this method seemed limited to a ~ 1 g scale. Accounting for the mass of the auxiliary and protecting group, such a reaction would correspond to no more than 0.5 g of ene precursor **4.71** assuming a 100% yield for the aldol reaction and all subsequent steps. For this reason, together with emerging reports suggesting that the second generation auxiliary might not be compatible with the aldol reaction conditions,¹⁹ we chose not to pursue this route any further.

In keeping with the idea of a carbonyl ene reaction for the preparation of ketone **4.7**, a simplified version of the above chemistry was proposed (Figure 4.7). An ene reaction of **4.93** could be expected to give **4.92** with the desired stereochemistry resulting from the favoured chair-chair ene transition state. Reduction of the ester groups would give a triol which could be expected to selectively give **4.91** upon treatment with DDQ. From here, manipulation of the protecting groups and oxidation states could yield ketone **4.90** as a slightly modified

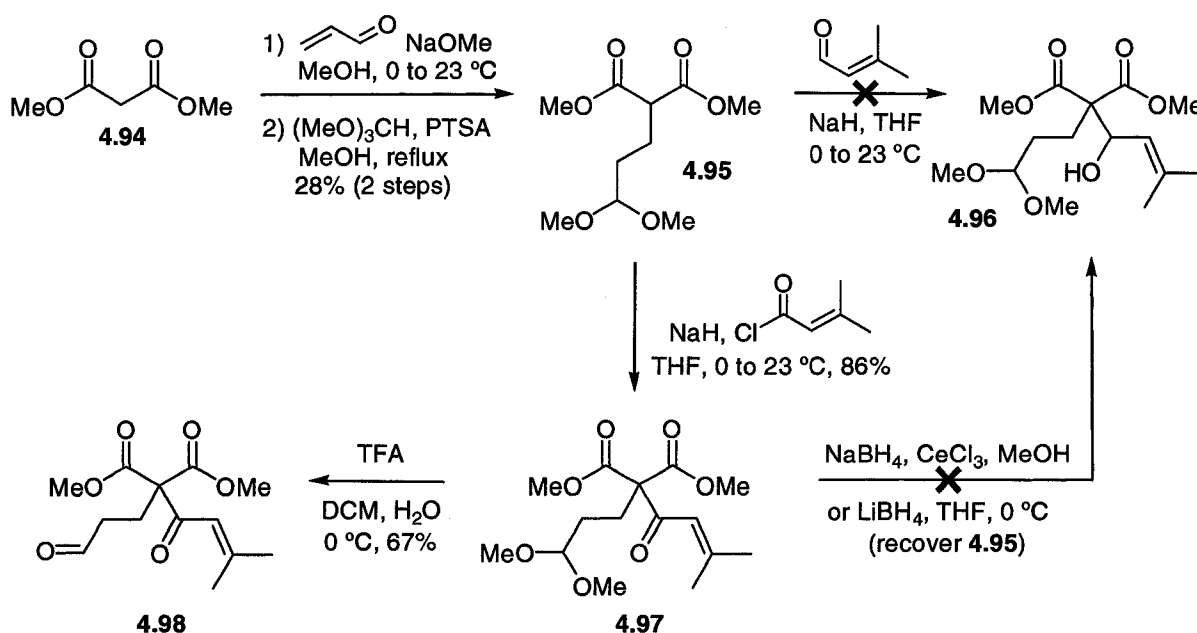
version of the originally targeted **4.7**. Alternatively, differentiation of the ester moieties in **4.92** could be left until later in the synthesis when their reactivity could be distinguished by their axial/equatorial placement.²⁰

Figure 4.7 – Retrosynthesis for a simplified carbonyl ene approach

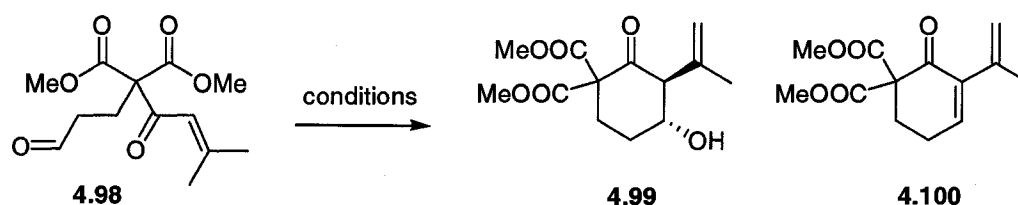


Preparation of **4.93** began by treating dimethylmalonate (**4.94**) with NaOMe and acrolein²¹ followed by protection of the aldehyde as the dimethyl acetal (Scheme 4.20). Although the yield for these two steps was only 28%, the starting materials were inexpensive and the reaction was easily scalable. From **4.95**, an aldol reaction with 3-methylbut-2-enal (**4.73**) was envisioned to give **4.96**. Unfortunately, no reaction was observed and unreacted starting material was recovered. Treating **4.95** with sodium hydride and 3-methylbut-2-enoyl chloride was more successful and **4.97** was isolated in 86% yield. All attempts to reduce the ketone to **4.96**, however, either by Luche conditions or LiBH₄, gave back **4.95**. In hindsight, this same retro-aldol reaction was likely behind the failed preparation of **4.96** from **4.95**. In light of this difficulty, the ene reaction of the α,β -unsaturated system was proposed instead. To this end, the dimethyl acetal was removed using aqueous trifluoroacetic acid to give **4.98** in 67% yield.

Scheme 4.20 – Preparation of an achiral carbonyl-ene precursor



The use of an electron poor alkene as our new carbonyl ene substrate came with the undesired effect of raising the activation energy for its reaction. Treating **4.98** with SnCl_4 induced no change to the parent compound even after warming to ambient temperature for 18 hours (the analogous reactions on substrates **2.32** and **2.85** were complete at -78°C in less than one hour) (entry 1, Table 4.2). Heating **4.98** in the microwave at 200°C for 1 hour resulted in trace amounts of a new product observable by TLC and crude ^1H NMR. Increasing the temperature to 220°C and heating for an additional 4 hours led to the disappearance of the originally observed product; in its place, **4.100** (20%) was isolated along with unreacted starting material (71%) (entry 2). The isolation of **4.100** suggests that the carbonyl ene reaction did occur but that the product was unstable under the reaction conditions. Keeping the temperature at 200°C and repeating the reaction in a sealed tube gave a similar result: after 6 hours, a small amount of the presumed carbonyl ene product **4.99** was observable by TLC. Leaving the reaction longer, however, led to its gradual consumption and the formation of elimination product **4.100**. After 24 hours, only **4.100** and **4.98** were observable by crude ^1H NMR in a 1:2 ratio. In light of the apparent instability of the desired ene product, its continued pursuit seemed futile.

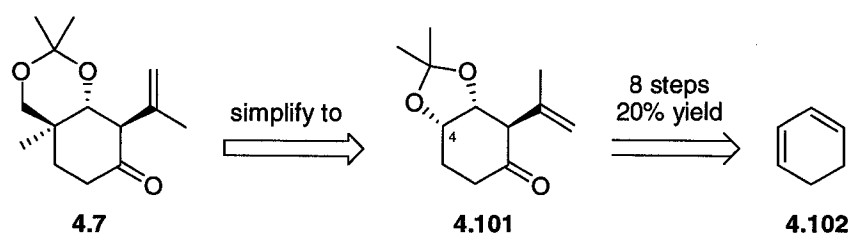
Table 4.2 – Attempted carbonyl-ene reaction of **4.98**

Entry	Conditions	Temperature	Time	Result
1	SnCl ₄ , DCM, MS	-78 to 23 °C	18 h	no reaction
3	microwaves, toluene	200 °C, then 220 °C	1 h, then 4 h	71% 4.98 ; 20% 4.100
4	sealed tube, toluene	200 °C	24 h	2:1 4.98 : 4.100

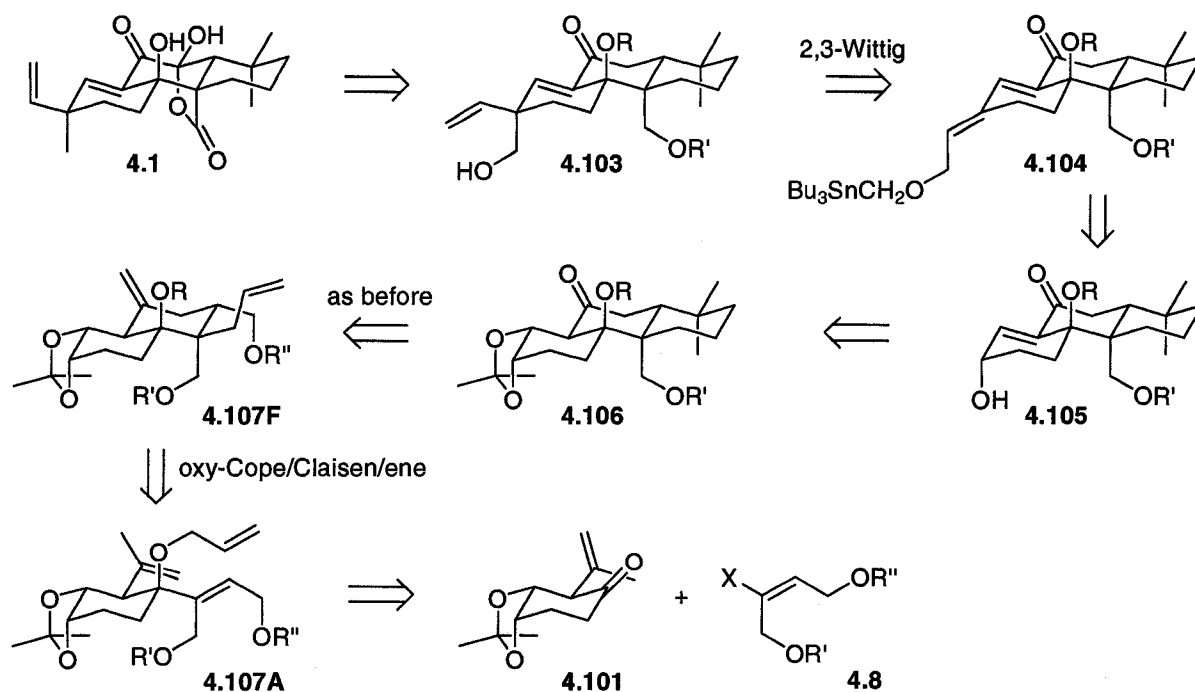
A Simplified Strategy: Delaying Formation of the Quaternary Stereocentre

Having now exhausted several approaches to prepare the precursor for the tandem oxy-Cope/Claisen/ene reaction, we felt it was necessary to re-evaluate our synthetic plan to LL-S491 β . Although it had been our hope to introduce the quaternary carbon centre at the beginning of the synthesis, the possibility of continuing to invest in this strategy only to have our key step fail prompted us to reconsider. (It should be noted that at the time of this decision, little was understood about the factors controlling the diastereoselectivity of the tandem reaction. Thus, although we were reasonably confident that the reaction of **4.6A** would work, we were less sure about the expected diastereoselectivity and, consequently, the synthetic utility of the process). Accordingly, a new synthesis was proposed beginning with ketone **4.101** (Figure 4.8). As a key intermediate in our laboratory's efforts in the total synthesis of vinigrol²² and teucrolivin A,¹² its preparation had been thoroughly optimized to a readily scalable, eight-step procedure starting from 1,3-cyclohexadiene (**4.102**). Although the quaternary carbon centre was not present, the C4 alcohol could serve as a handle for its later installation.

Figure 4.8 – Simplification of the starting ketone: removal of the quaternary carbon

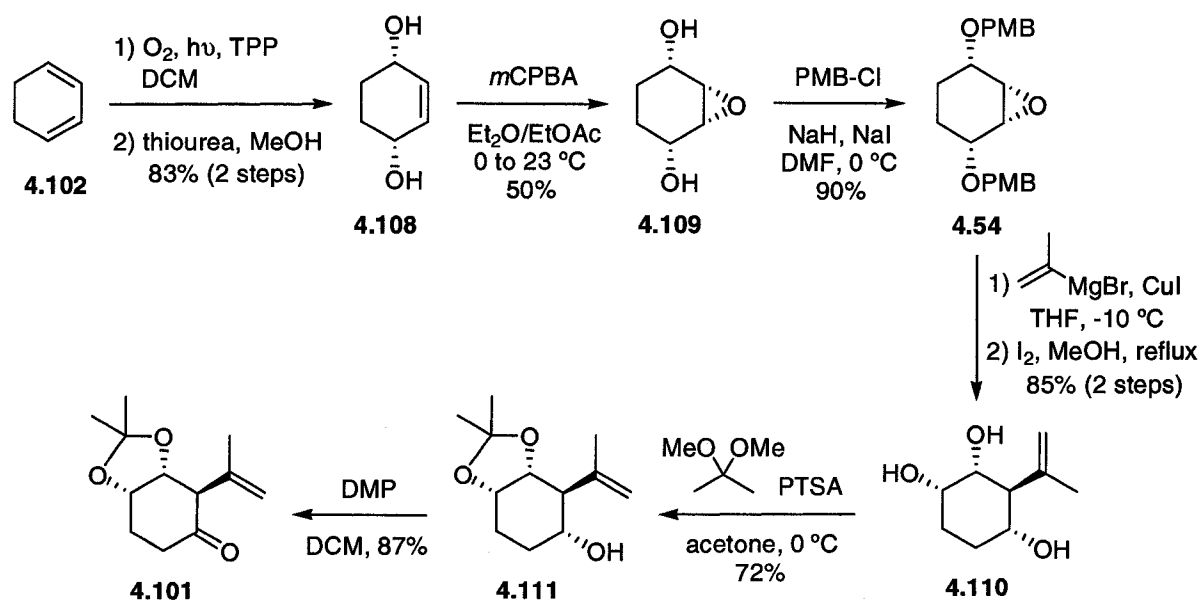


With this change in strategy came the need for a new retrosynthetic plan, particularly for the late-stage formation of the all-carbon quaternary centre (Figure 4.9). One attractive means for its introduction could be a 2,3-Wittig rearrangement²³ of **4.104** followed by deoxygenation of the resulting alcohol. Provided the protecting group, R, was sufficiently bulky, the rearrangement could be expected to take place from the bottom face of the tricyclic core as shown. From this point, the remaining transformations would be akin to those proposed above in Figure 4.2 leading to an oxy-Cope/Claisen/ene reaction of **4.107A** as our new key step.

Figure 4.9 – New retrosynthesis for LL-S491 β : delayed formation of the quaternary centre

Following the procedures optimized in our laboratory,¹² the preparation of **4.101** was initiated, beginning with a Diels-Alder reaction between 1,3-cyclohexadiene (**4.102**) and singlet oxygen (Scheme 4.21).²⁴ Reduction of the endoperoxide with thiourea²⁵ gave **4.108** in 83% for the two steps. Epoxidation with *m*CPBA (50%) was followed by protection of the two secondary alcohols with PMB-Cl giving **4.54** in 90% yield. Contrary to the epoxide openings discussed above, treatment of this epoxide with isopropenylmagnesium bromide in the presence of CuI afforded cleanly the opened product which was immediately deprotected with iodine in methanol²⁶ to give **4.110** in 85% yield for the two steps. From here, a selective protection of the 1,2-diol with 2,2-dimethoxypropene gave a 72% yield of **4.111**. Finally, oxidation with Dess-Martin periodinane gave the desired ketone, **4.101**, in 87% yield.

Scheme 4.21 – Synthesis of the simplified ketone, **4.101**

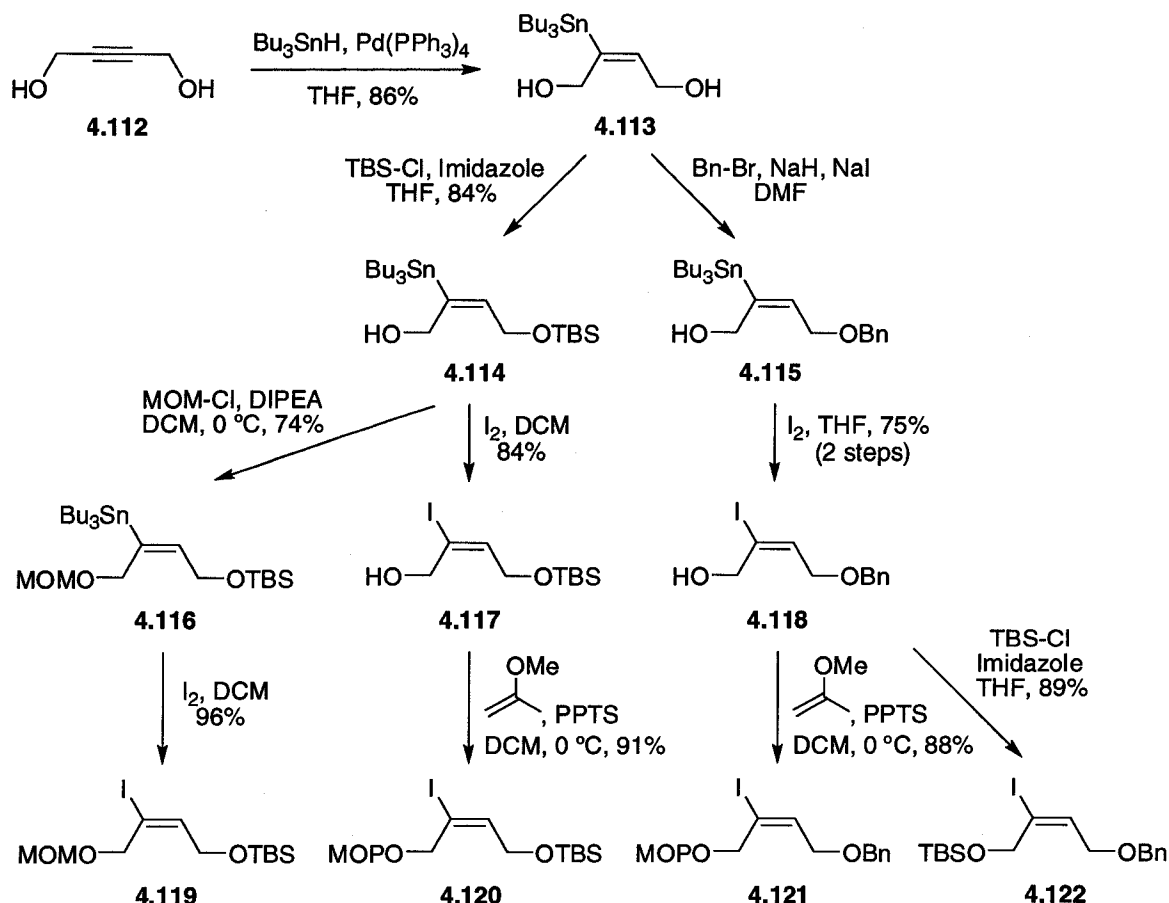


With **4.101** in hand, we were ready to move on to its alkylation. To avoid wasting any of our newly prepared substrate, however, a model study for this reaction was first undertaken using the simplified ketone **2.2**.

Model Study for the Alkylation of 4.101

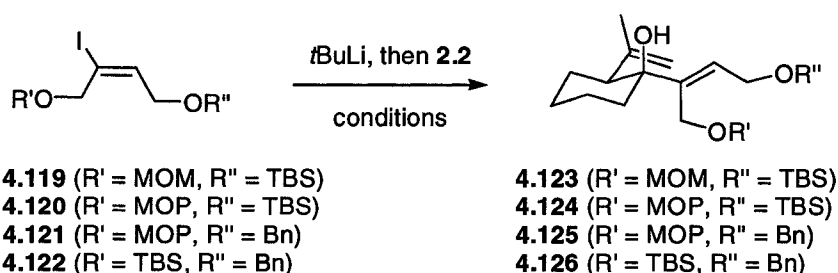
In order to facilitate their future discrimination, orthogonal protecting groups for the two primary alcohols in **4.8** were desired. To this end a series of vinyl iodides were prepared from 1,4-butyndiol (Scheme 4.22). Hydrostannylation of **4.112** yielded vinylstannane **4.113** in 86% yield. Subsequent treatment with either TBS-Cl or benzyl bromide gave the mono protected compounds **4.114** and **4.115**. Exchanging the tin for an iodide by stirring in a solution of iodine in either DCM or THF afforded **4.117** and **4.118** in 84% and 75% yield respectively. From here, the remaining alcohols were protected with either a MOM or TBS group to give vinyl iodides **4.120**, **4.121** and **4.122**. A slightly different route was used for the preparation of **4.119**: the more hindered alcohol of vinylstannane **4.114** was first protected with MOM-Cl to give **4.116** in 74% yield, followed by Sn-I exchange to give the desired compound in 96% yield.

Scheme 4.22 – Preparation of vinyl halides bearing orthogonal protecting groups



Each of these four vinyl iodides was treated sequentially with *t*-butyllithium and ketone **2.2** under various conditions in order to assess their viability as an alkylating agent (Table 4.3). Of the substrates and conditions tried, only the reaction of **4.120**, treated with *t*-butyllithium in Et₂O at -100 °C, gave any of the desired product, **4.124** (entry 6). All other reactions gave unreacted starting material along with the protonated vinyl lithium and/or other, unidentified decomposition products derived from the vinyl halide. Unfortunately, efforts to scale up the successful alkylation revealed a highly unreliable reaction which gave yields ranging from 33-67%. Without the ability to produce sufficient quantities of **4.124**, an alternative alkylation was required.

Table 4.3 – Alkylation attempts with vinyl iodides bearing orthogonal protecting groups



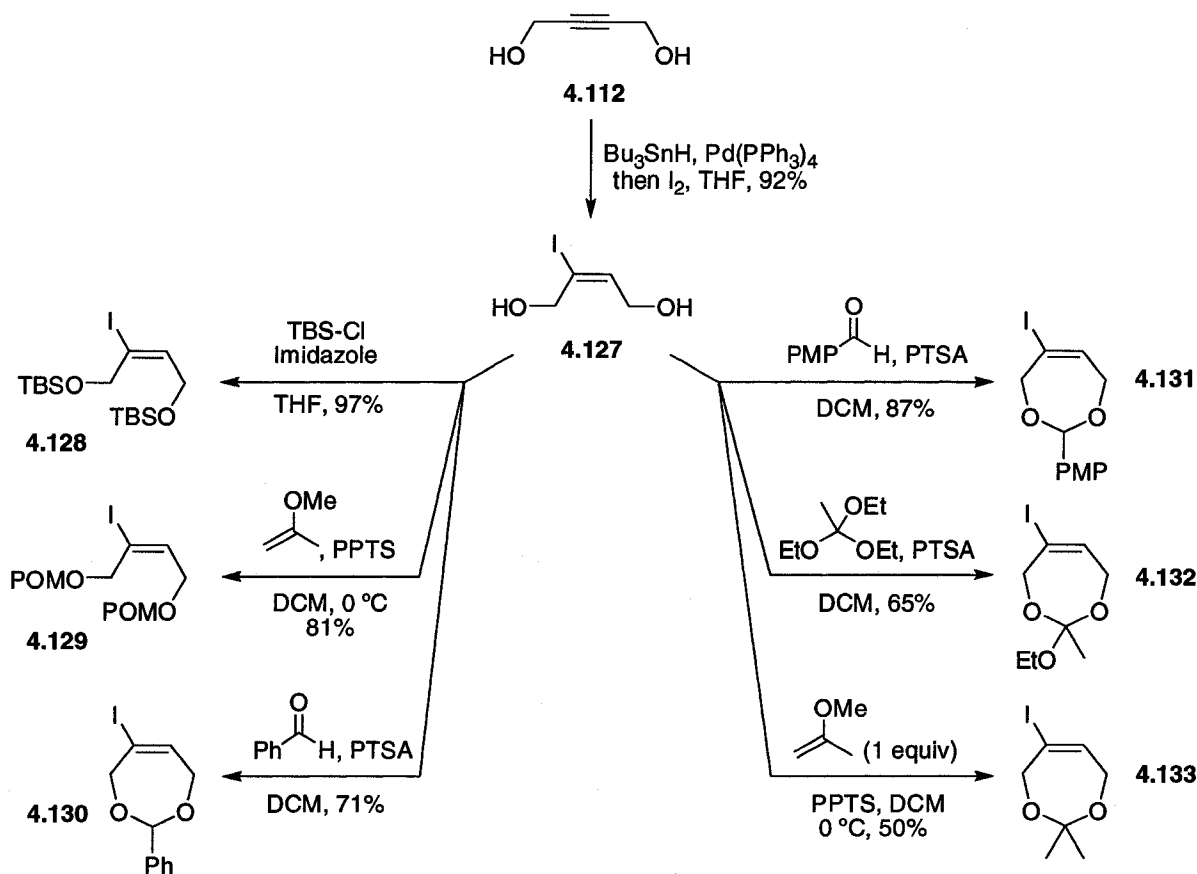
Entry	Substrate	Solvent	Temp ^a	Result
1	4.119	THF	-78 °C	recovered 2.2
2	4.119	THF, CeCl ₃	-78 °C	recovered 2.2
3	4.119	Et ₂ O	-100 °C	recovered 2.2
4	4.120	THF	-78 °C	recovered 2.2 + protonated vinyl lithium
5	4.120	THF, CeCl ₃	-78 °C	recovered 2.2 + protonated vinyl lithium
6	4.120	Et ₂ O	-100 °C	33-67% 4.124
7	4.121	Et ₂ O	-100 °C	recovered 2.2 + protonated vinyl lithium
8	4.122	Et ₂ O	-100 °C	recovered 2.2 + unidentified products

^a Temperature for Li-I exchange and initial addition of **2.2**; all reactions were allowed to warm gradually to ambient temperature before quenching (between 2-4 hours).

Noting the success of the MOP and TBS groups on substrate **4.120**, bis-TBS and bis-MOP protected substrates were targeted. Although the two alcohols would no longer be differentiated, the prospect of a high yielding alkylation seemed worth pursuing on the chance that the two alcohols could later be distinguished by their unique steric environments. Accordingly, **4.112** was treated first with tributyltin hydride and Pd(PPh₃)₄ followed by

iodine to give a 92% yield for vinyl iodide **4.127** (Scheme 4.23). Reaction with excess TBS-Cl afforded **4.128** in 97% yield while excess 2-methoxypropene gave **4.129** in 81% yield. In addition to these compounds, several acetal-protected vinyl iodides were also prepared in the hopes that the acetal could be selectively opened later in the synthesis. To this end, diol **4.127** was treated with benzaldehyde, *para*-anisaldehyde, triethylorthoester, and 2-methoxypropene to give compounds **4.130-4.133** in yields of 71%, 87%, 65% and 50% respectively.

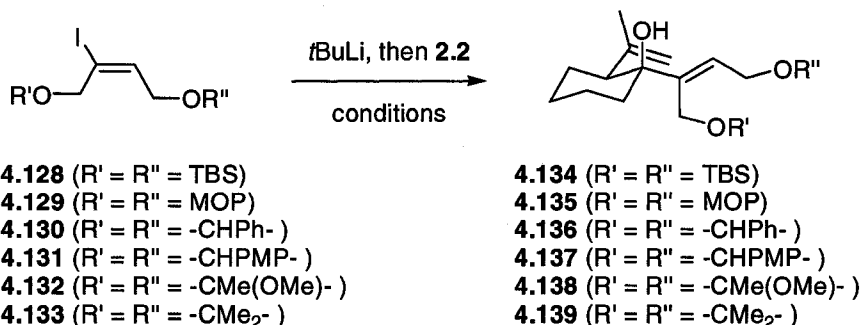
Scheme 4.23 – Preparation of vinyl iodides lacking orthogonal protecting groups



Alkylation of **2.2** with the vinyl lithium species of **4.128-4.133** suffered from similar problems as the previously tested, orthogonally protected substrates (Table 4.4). Most reactions gave unreacted ketone **2.2** along with either the protonated vinyl lithium species, or unidentifiable decomposition products resulting from the vinyl halide. The exception to this trend was the reaction of bis-MOP protected **4.129** in Et_2O at -78 °C which reliably gave

4.135 in yields of 75-77% (entry 4). Further lowering the temperature to -100 °C gave a similar result with **4.135** being obtained in 66% yield.

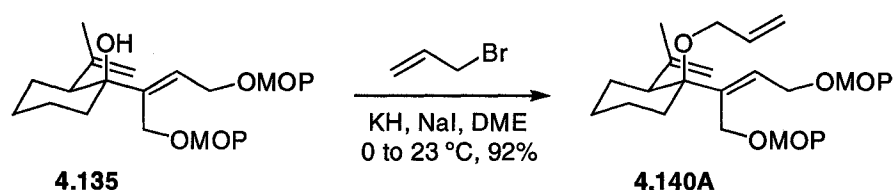
Table 4.4 – Alkylation attempts with vinyl iodides bearing identical protecting groups



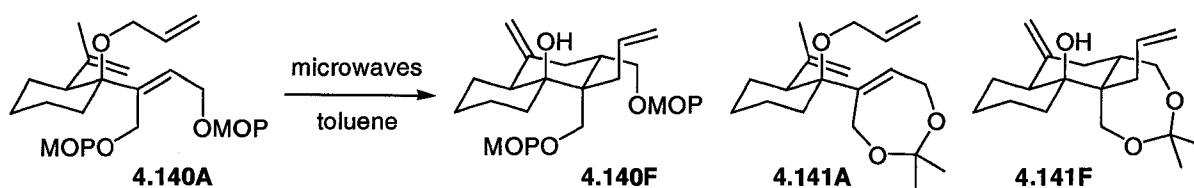
Entry	Substrate	Solvent	Temp ^a	Result
1	4.128	THF	-78 °C	recovered 2.2 + protonated vinylolithium
2	4.128	Et ₂ O	-78 °C	recovered 2.2 + protonated vinylolithium
3	4.128	Et ₂ O	-100 °C	recovered 2.2 + protonated vinylolithium
4	4.129	Et ₂ O	-78 °C	75-77% 4.135
5	4.129	Et ₂ O	-100 °C	66% 4.135
6	4.130	Et ₂ O	-100 °C	recovered 2.2 + protonated vinylolithium
7	4.131	THF	-78 °C	recovered 2.2 + decomposition of 4.131
8	4.131	Et ₂ O	-78 °C	recovered 2.2 + decomposition of 4.131
9	4.132	Et ₂ O	-100 °C	recovered 2.2
10	4.133	THF	-78 °C	recovered 2.2 + unidentified products
11	4.133	Et ₂ O	- 100 °C	recovered 2.2 + unidentified products

^a Temperature for Li-I exchange and initial addition of **2.2**; all reactions were allowed to warm gradually to ambient temperature before quenching (between 2-4 hours).

While it was encouraging to have found a set of successful alkylating conditions, we needed to establish whether the labile MOP protecting groups would be tolerated by the tandem reaction conditions, and, more importantly, whether the two MOP-protected alcohols would be distinguishable after the oxy-Cope/Claissen/ene reaction. To this end, **4.135** was treated with allyl bromide, potassium hydride and a catalytic amount of sodium iodide in DME to give allylated substrate **4.140A** in 92% yield (Scheme 4.24).

Scheme 4.24 – Allylation of bis-MOP protected **4.135**

The oxy-Cope/Claisen/ene reaction of **4.140A** proceeded well, giving a single observable diastereomer after 1.5 hours in the microwave at 200 °C. Upon closer examination of the spectral data, however, we were surprised to learn that the product was in fact acetonide **4.141F**, rather than the expected bis-MOP protected product, **4.140F** (Table 4.5, entry 1). Interestingly, when the reaction was repeated at a lower temperature (140 °C), varying amounts of **4.141A** were observed (< 10% to 87%) along with unreacted starting material (entry 2). These results suggest that trace amounts of acid may be catalyzing the transacetalization of the bis-MOP protected starting material to the more thermodynamically favoured acetonide, **4.141A**. Moreover, it appears that this process occurs prior to the tandem reaction as evidenced by the isolation of **4.141A**. In an effort to shut down this process, an excess of triethylamine was added to the reaction mixture. After 30 minutes at 140 °C with 6 equivalents of the base, no reaction was observed (entry 3). Heating to 180 °C, however, resulted in the isolation of the expected product, **4.140F** in 40% yield (entry 4). Conversely, the deliberate addition of a proton source, such as silica gel or BHT, led, once again, to the formation of cyclic acetal **4.141F** with yields of 54% and 60% respectively (entries 5 and 6). It should be noted that in the latter case, TLC analysis indicated that **4.140F** was also present in significant proportions immediately after the reaction. Purification by silica gel flash chromatography, however, led only to the isolation of **4.141F**. It thus appears that both the bis-MOP protected starting material (**4.140A**) and the product (**4.140F**) are prone to transacetalization reactions under even mildly acidic conditions. Accordingly, the 40% yield originally obtained for product **4.140F** was increased to 62% by pre-treating the silica gel with triethylamine prior to chromatography (entry 7).

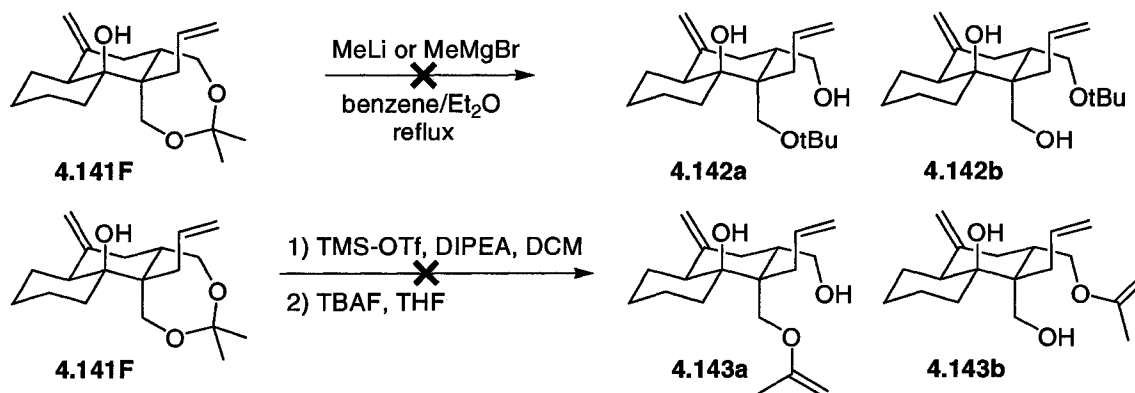
Table 4.5 – Tandem oxy-Cope/Claisen/ene reaction of bis-MOP protected **4.140A**

Entry	Additive	Temp (°C)	Time (h)	4.140F	4.141A	4.141F
1	---	200	1.5	---	---	55%
2	---	140	0.5	---	<10% to 87%	---
3	Et ₃ N	140	0.5	no reaction		
4	Et ₃ N	180	0.5	40%	---	---
5	silica	140 then 180	0.5, then 0.5	---	---	54%
6	BHT	140 then 180	0.5, then 0.5	---	---	60% ^a
7	Et ₃ N	180	0.5	62% ^b	---	---

^a **4.140F** was the major product by TLC, but only **4.141F** was isolated from the flash. ^b Silica gel was pre-treated with triethylamine prior to silica gel flash chromatography

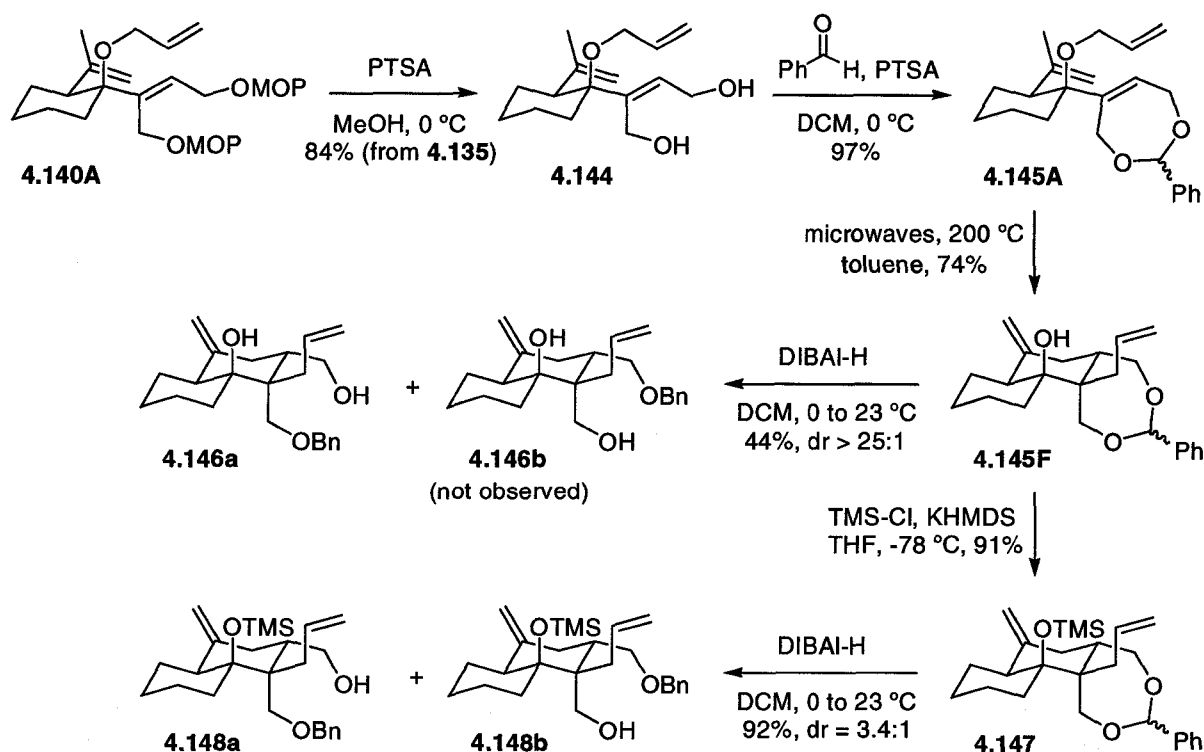
While the isolation of **4.141F** had been unexpected, we were happy for the opportunity to test the known methods for selectively opening a dimethyl acetal. Though these procedures are typically used to distinguish primary from secondary alcohols (or a secondary from a tertiary alcohol), we hoped that the steric environments of the axial and equatorial alcohols would be sufficiently different so as to afford some selectivity. Unfortunately, treating **4.141F** with either MeMgBr or MeLi²⁷ gave no detectable reaction (Scheme 4.25). Equally disappointing was the reaction with TMS-OTf²⁸ which led to a mixture of unidentifiable products rather than the expected enol ethers **4.143a** and **4.143b**.

Scheme 4.25 – Attempts to selectively open the dimethyl acetal



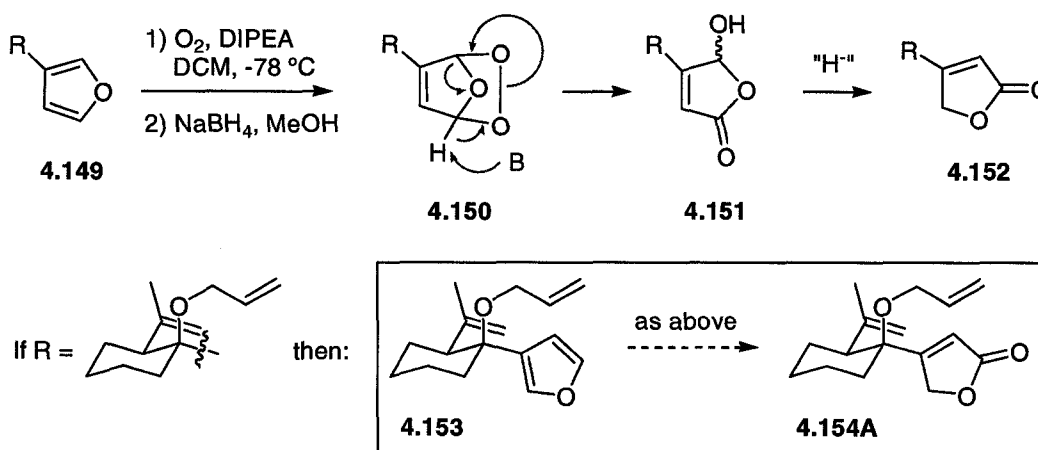
Since the attempts to open dimethyl acetal **4.141F** were unsuccessful, we turned our attention to the selective opening of a benzilidene acetal. The direct alkylation with the vinyl lithium of **4.130** had been ineffective (See Table 4.4 above), so the preparation of **4.145A** was carried by an indirect means. Removal of the two acetal protecting groups from unpurified **4.140A** using PTSA in methanol gave diol **4.144** in 84% yield for the two steps (Scheme 4.26). Subsequent treatment with benzaldehyde and PTSA gave the desired benzilidene acetal **4.145A** as a ~ 1:1 mixture of diastereomers. Heating this compound to 200 °C with microwave irradiation thus gave the oxy-Cope/Claisen/ene product **4.145F** in 74% yield. Though the product remained a mixture of epimers, no other diastereomers resulting from the tandem reaction were observed. To effect the opening of the benzilidene acetal, **4.145F** was treated with excess DIBAL-H.²⁹ Coordination to the less hindered equatorial oxygen led to the exclusive formation of **4.146a**, along with unreacted starting material. Interestingly, when the tertiary alcohol was first protected with TMS-Cl, the reaction with DIBAL-H now gave a yield of 92%, but with a diastereomeric ratio of only 3.4:1. This decrease in selectivity, however, was not considered to be problematic since the products were easily separable and both could be of synthetic utility.

Scheme 4.26 – Formation and selective opening of the benzilidene acetal



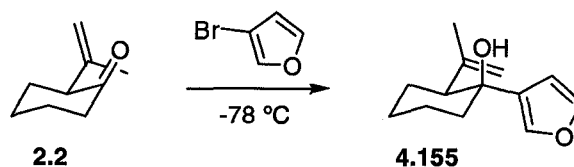
Though the formation of the above mono-benzylated products constituted a viable route towards LL-S491 β , their preparation was lengthy and involved numerous protecting group manipulations. Thus, before accepting this route and moving away from the model system, an alternative approach was considered. It is known in the literature³⁰ that a 3-alkylfuran (**4.149**) will undergo a Diels-Alder reaction with singlet oxygen to give bicyclic intermediate **4.150**. If the reaction is carried out in the presence of a base, **4.150** readily opens to give **4.151** which, upon reduction, affords the 3-alkyllactone **4.152**. This unsaturated lactone is equivalent to our targeted diol with the two alcohols differentially protected according to their oxidation state. Thus, if the R group in **4.149** were the backbone of our cyclohexane ring, as in **4.153**, the above sequence could provide us with **4.154A** without the need for any protecting groups.

Scheme 4.27 – Literature precedent for the conversion of a 3-alkylfuran into a 3-alkyllactone



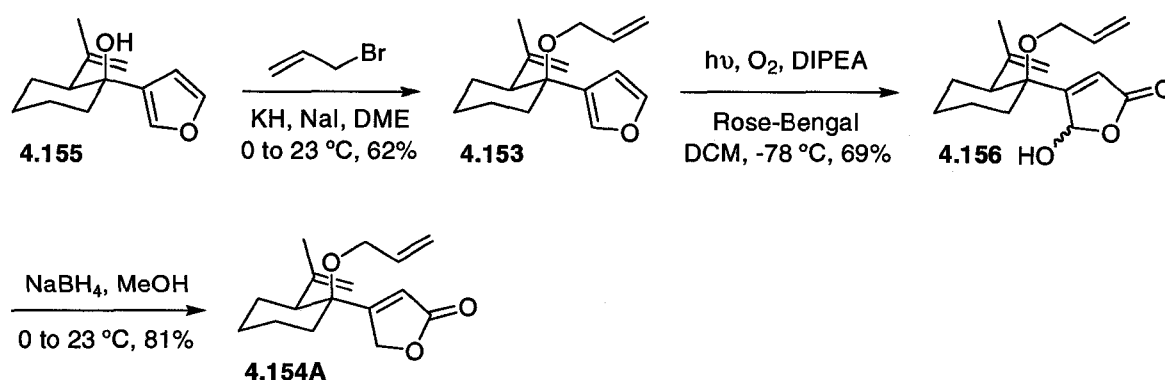
The alkylation of ketone **2.2** with the lithium species of 3-bromofuran required some initial optimization (Table 4.6). Isomerization of the 3-lithiofuran species often resulted in the isolation of complex product mixtures (entries 1-5). Changing the base to *n*-butyllithium and performing the reaction in Et₂O minimized this problem *provided ketone 2.2 was added at a sufficiently slow rate so as to ensure the internal temperature was maintained at $-78\text{ }^\circ\text{C}$* (entry 6). Increasing the length of time for Li-Br exchange from 30 minutes to an hour afforded **4.155** in a slightly better yield of 63% (entry 7).

Table 4.6 – Optimization of the 3-lithiofuran alkylation



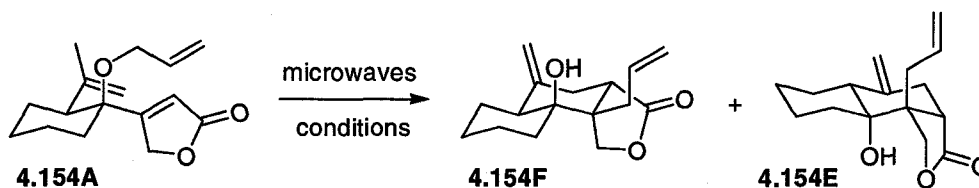
Entry	Base	Solvent	Li-Br exchange (Time)	Result
1	<i>t</i> BuLi	THF	60 min	complex mixture
2	<i>t</i> BuLi	Et ₂ O	60 min	complex mixture
3	<i>t</i> BuLi	THF	30 min	complex mixture
4	<i>t</i> BuLi	Et ₂ O	30 min	complex mixture
5	<i>n</i> BuLi	THF	30 min	complex mixture
6	<i>n</i> BuLi	Et ₂ O	30 min	58% 4.155
7	<i>n</i> BuLi	Et ₂ O	60 min	63% 4.155

From alkylated substrate **4.155**, conversion to the desired tandem reaction precursor was accomplished according to Scheme 4.28 below. Allylation of the tertiary alcohol gave **4.153** in 62% yield which was then reacted with singlet oxygen (generated by shining light on the oxygenated solution in the presence of a sensitizer, Rose-Bengal) and Hünig's base to give a mixture of hemi-acetals, **4.156** (69%). Reduction with NaBH₄ afforded **4.154A** in 81% yield. With **4.154A** in hand, we were ready to test the oxy-Cope/Claisen/ene reaction.

Scheme 4.28 – Conversion of 3-alkylfuran **4.155** to tandem reaction precursor **4.154A**

To our surprise, reacting **4.154A** under our previously optimized conditions (microwaves, 200 °C, 1 hour) gave only a trace amount of the desired product, **4.154F** (Table 4.7, entry 1). Raising the temperature to 220 °C and heating for 5 hours showed negligible improvement (entry 2). Changing the solvent from toluene to chlorobenzene, however, greatly increased the reactivity of the substrate.³¹ Thus, microwave irradiation for 1 hour at 200 °C followed by an additional 1.5 hours at 220 °C now afforded an 80% yield of the oxy-Cope/Claisen/ene products, along with 15% of unreacted starting material (entry 3). [For 100% conversion, a reaction time of 15 hours was required, leading to a combined yield of 91% (entry 4)]. Unfortunately, the diastereoselectivity for this reaction was poor and although the desired isomer was favoured, the ratio of **4.154F** to **4.154E** was a meager 1.4:1. Despite this poor selectivity, we remained optimistic that the product ratio might be improved upon with the additional substituents present on the backbone of the substrate derived from ketone **4.101**.

Table 4.7 – Oxy-Cope/Claisen/ene reaction of lactone **4.154A**



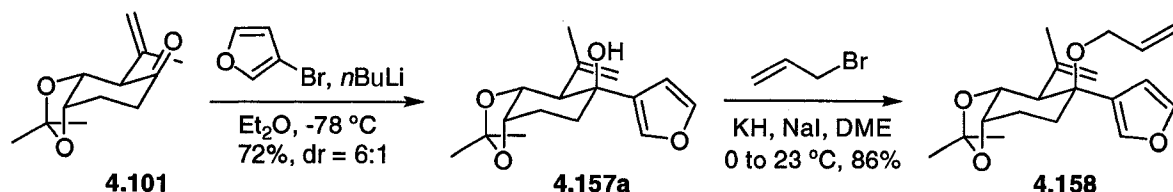
Entry	Solvent	Temp (°C)	Time (h)	Result
1	toluene	200	1	< 5% conversion
2	toluene	220	5	< 5% conversion
3	chlorobenzene	200, then 220	1.0, then 1.5	15% 4.154A + 47% 4.154F + 33% 4.154E
4	chlorobenzene	220	15	54% 4.154F + 37% 4.154E

Application of the Optimized Strategy to the Real System

Taking advantage of the newly optimized procedures for the preparation of oxy-Cope/Claisen/ene precursor **4.154A**, ketone **4.101** was treated with the lithio species of 3-bromofuran (Scheme 4.29). Unlike the model system, however, the alkylation now gave some of the undesired isomer, **4.157b**, resulting from axial attack (not shown). This is likely

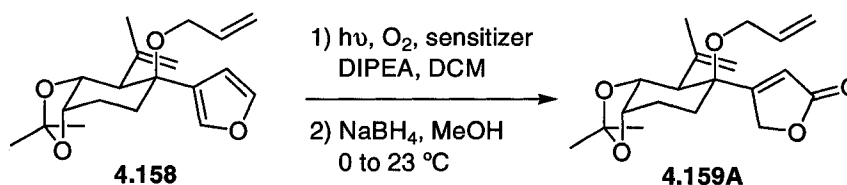
the result of added steric hindrance to the bottom face of the ketone owing to the presence of the dimethyl acetal. Nonetheless, a 72% combined yield with a selectivity of 6:1 could be obtained by carefully controlling the addition rate of *n*-butyllithium and ketone **4.101** so as to ensure that the temperature did not rise above -78 °C.³² Subsequent allylation of the tertiary alcohol proceeded well giving **4.158** in 86% yield.

Scheme 4.29 – Preparation of 3-alkylfuran **4.158**



The Diels-Alder reaction of **4.158** with singlet oxygen proceeded well by TLC, however, the reported work-up using oxalic acid led to the apparent hydrolysis of the acetal (Table 4.8, entry 1). Replacing the acidic work-up with water alone resulted in a 67% yield of **4.159A** (entry 2). While this yield was acceptable, concerns regarding the scalability of the process remained. The originally reported conditions required high dilution and low temperatures. The latter was especially problematic given the heat generated by the 200 W lamps shining on the reaction vessel. In addition, reaction times appeared to increase with scale making it impractical to carry out the reaction on more than 150 mg of material at a time (entry 3). Initial attempts to raise the reaction concentration led a decrease in yield from > 60% to 32% (entry 4). Raising the reaction temperature to 0 °C, on the other hand, was more successful and a 62% yield of **4.159A** was obtained (entry 5). Additional success was met by switching the sensitizer from Rose-Bengal to TPP: not only was the yield increased (69%), but a 5-fold acceleration in the reaction rate was also observed (entry 6). Furthermore, the use of TPP allowed for a concentration of 0.05 M (entry 7).³³ Finally, the removal of the aqueous work-up all together provided an 88% yield of the reduced product (entry 8).

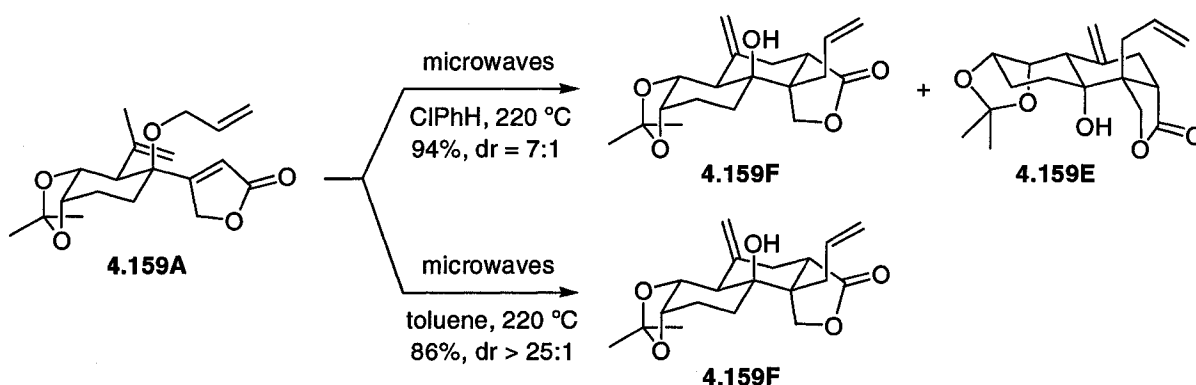
Table 4.8 – Optimizing the conversion of the 3-alkylfuran into the corresponding lactone



Entry	Sensitizer	Scale (mg)	Concentration (M)	Temp (°C)	Time (h)	Work-up	Yield ^a
1	Rose-Bengal	25	0.008	-78	5.5	oxalic acid	---
2	Rose-Bengal	25	0.008	-78	5.5	water	67%
3	Rose-Bengal	150	0.008	-78	9.0	water	61%
4	Rose-Bengal	150	0.05	-78	9.0	water	32%
5	Rose-Bengal	50	0.005	0	10.0	water	62%
6	TPP	50	0.005	0	2	water	69%
7	TPP	150	0.05	0	3	water	65%
8	TPP	150	0.05	0	3	none ^b	88%

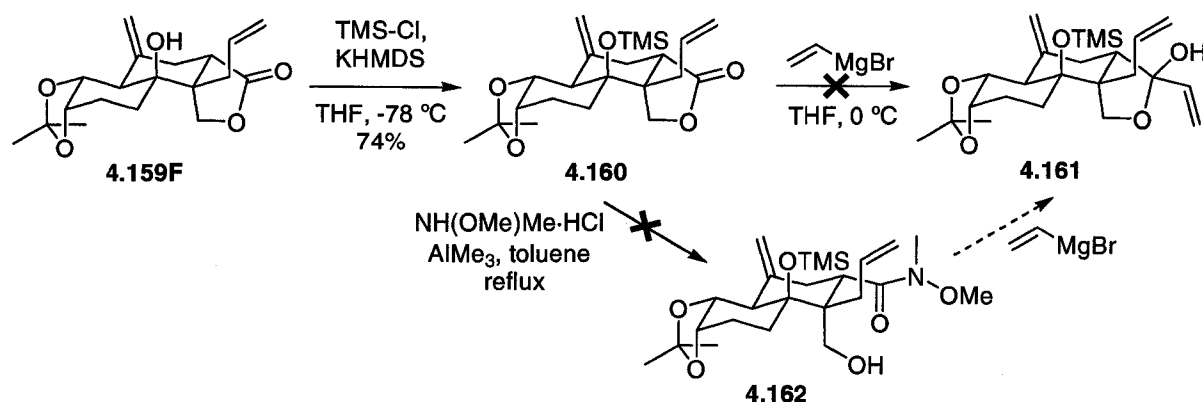
^a Yield of **4.159A** after reduction of the crude material with NaBH₄. ^b Once complete by TLC, the reaction was concentrated directly and the crude material was treated with NaBH₄ in methanol.

Having successfully adapted the 3-alkylfuran rearrangement for our new substrate, we were ready to test its oxy-Cope/Claisen/ene reaction. Trying first in chlorobenzene, **4.159A** was heated in the microwave at 220 °C (Scheme 4.30). Remarkably, the reaction was complete in just 7 hours whereas the model substrate, **4.154A**, had required 15 hours. The yield and diastereoselectivity were also improved and 94% of the product was isolated as a 7:1 mixture of inseparable isomers. Noting that this substrate was more reactive than the model, we decided to repeat the reaction in toluene. To our surprise, the reaction was not only complete in just 4.5 hours, but an 86% yield was obtained with **4.159F** as the solely observable diastereomer. Since all other factors were identical, this dramatic change in selectivity can only be attributed to a solvent effect between chlorobenzene and toluene. Though the nature of this effect remains unclear, we were nonetheless delighted to have in our hands the desired compound in both excellent yield and diastereoselectivity.

Scheme 4.30 – Solvent effect on the oxy-Cope/Claisen/ene reaction of **4.159A**

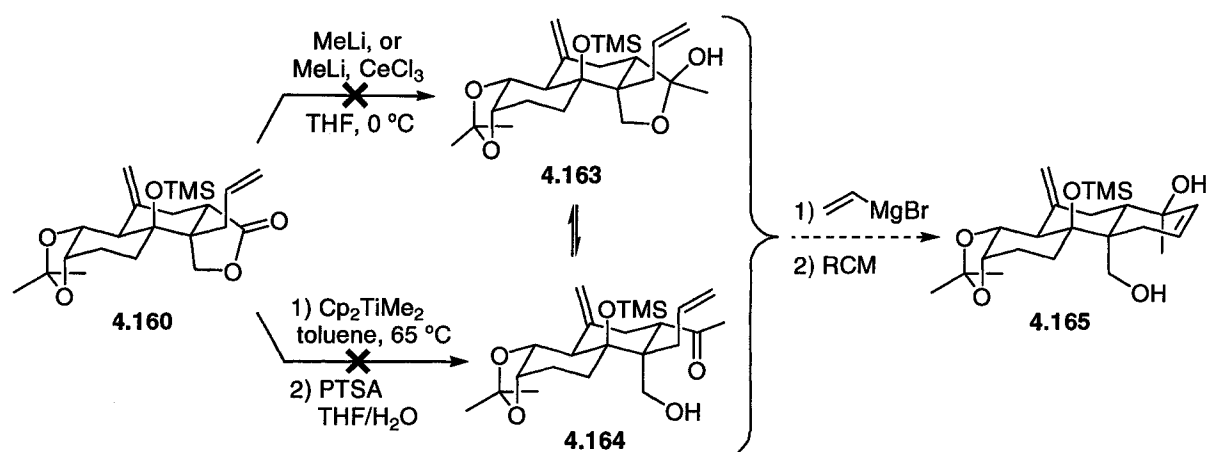
Formation of the A Ring

With a handle in place for the future introduction of the quaternary carbon centre and two differentially protected alcohols on the backbone of our decalin core, we were ready to turn our attention to forming the A ring of LL-S491 β (see Figure 4.1). Hoping to capitalize on the successful RCM approach used for closing the A ring of wiedemannic acid, we needed to introduce a second olefin by alkylating onto the lactone. Preliminary protection of the tertiary alcohol with TMS-Cl proceeded well giving **4.160** in 74% yield (Scheme 4.31). Treating this compound with excess vinylmagnesium bromide, however, gave no reaction. Alternatively, alkylation of an intermediary Weinreb amide³⁴ was envisioned. Attempts to prepare **4.162**, however, were unsuccessful and unreacted **4.160** was once again recovered.

Scheme 4.31 – Attempted alkylation of lactone **4.160** with vinylmagnesium bromide

Since a *gem*-dimethyl group would ultimately need to be introduced, it was proposed that the order of alkylation could be changed in the hopes that success would be met using methyllithium as the alkylating agent (Scheme 4.32). In practice, however, neither methyllithium nor its organocerium equivalent gave any detectable reaction. As an alternative route to **4.163**, olefination of the carbonyl followed by hydrolysis of the resulting enol ether was envisioned. While treatment with Petasis' reagent³⁵ did lead to the consumption of the starting material, a mixture of unidentified products was formed, none of which corresponded to the expected enol ether (not shown) or its hydrolyzed form, **4.164**.

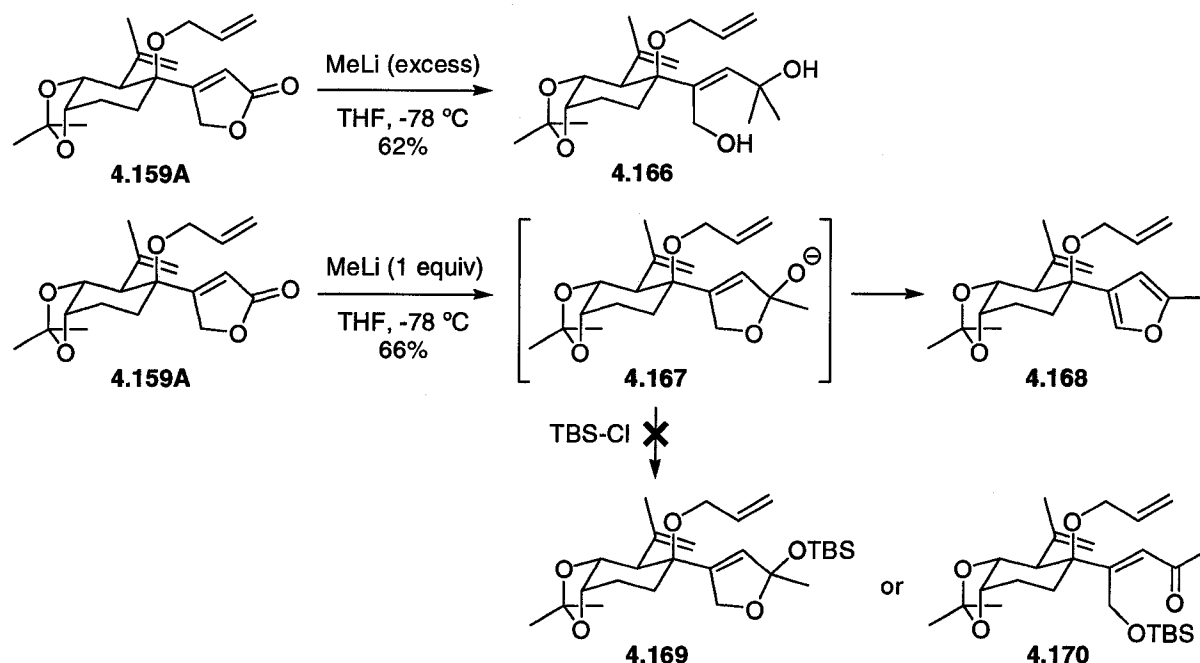
Scheme 4.32 – Attempted alkylation of lactone **4.160** with methyllithium



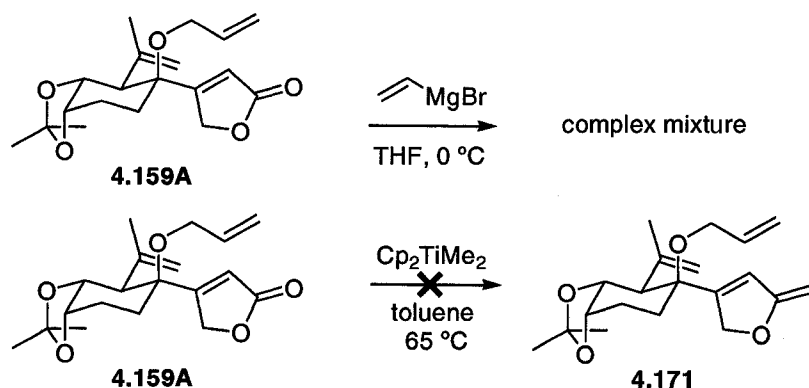
Given the observed lack of reactivity for **4.160**, we decided to investigate the manipulation of the lactone prior to the tandem reaction sequence. In the absence of an acidic proton alpha to the carbonyl, the lactone could be expected to behave as an electrophile rather than protonating the incoming nucleophiles. Indeed, **4.159A** proved to be significantly more reactive and its treatment with methyllithium led to complete consumption of the starting material (Scheme 4.33). Initially, the dialkylated product **4.166** was isolated in 62% yield. Although this substrate did bear the requisite *gem*-dimethyl group, it lacked any obvious means for introducing the vinyl group making it synthetically uninteresting. Reducing the amount of methyllithium to just 1 equivalent gave the monoalkylated substrate, **4.167**, however, this compound readily aromatized to give **4.168** as the solely isolable compound in 66% yield. Attempts to trap **4.167** in situ with a silyl protecting group were also unsuccessful and **4.168** continued to be isolated. While neither **4.166** nor **4.168** would

be of use for our total synthesis, we remained encouraged by the increased reactivity of lactone **4.159A** and moved on to explore other options.

Scheme 4.33 – Manipulating the lactone prior to the tandem reaction

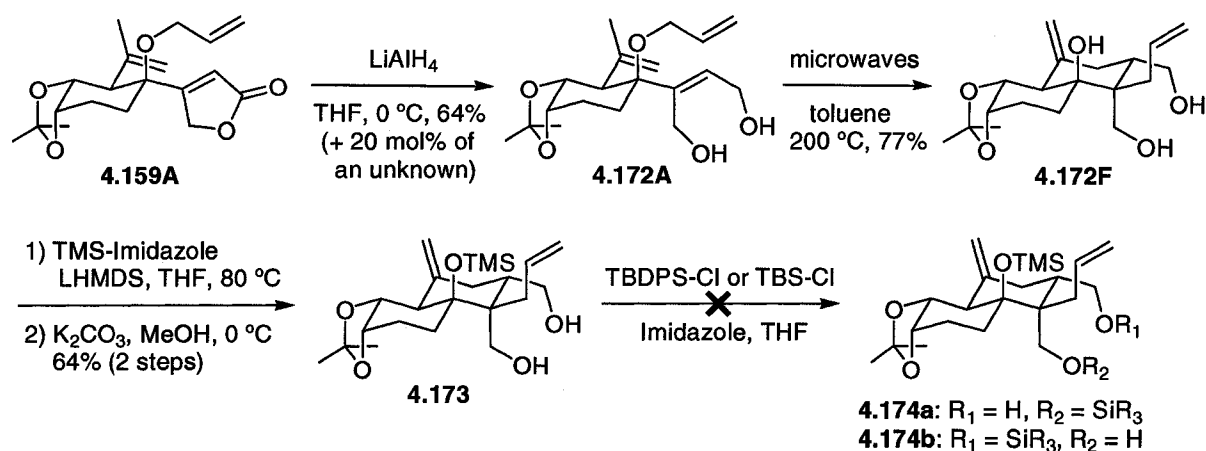


Based on the above results, we were not surprised to find that the reaction of **4.159A** with vinylmagnesium bromide led to a complex mixture of products, presumed to be composed of compounds analogous to **4.166–4.168** above (Scheme 4.34). Unlike the reaction with methyllithium, however, control of stoichiometry did not afford control over the product distribution and the complex mixtures obtained were uncharacterizable. Moving away from traditional nucleophiles, the Petasis' reagent was also re-explored. Unexpectedly, **4.159A** was found to be less reactive to this reagent than the TMS-protected oxy-Cope/Claisen/ene product, **4.160**, and no reaction was observed.

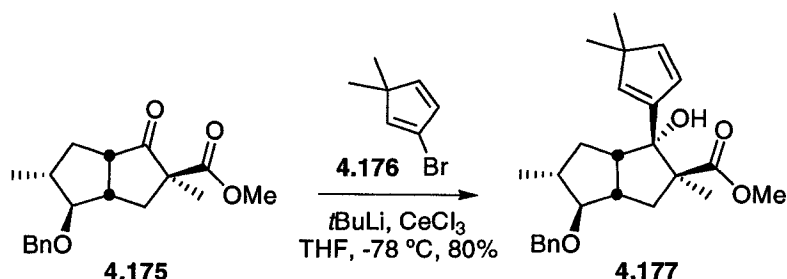
Scheme 4.34 – Reaction of vinylmagnesium bromide and Petasis' reagent with **4.159A**

While the alkylation and olefination reactions of **4.159A** had failed to provide useful intermediates, its reduction with LiAlH_4 did successfully afford diol **4.172A** in 64% yield (Scheme 4.35). The product, however, was contaminated with a second, unidentified compound constituting 20 mol% of the isolated material. Fortunately, this impurity did not interfere with the subsequent oxy-Cope/Claisen/ene reaction which proceeded well giving **4.172F** in 77% yield. Admittedly, the reduction of **4.159A** to the diol did negate any advantage we had gained by using the lactone as a “protected diol.” Moreover, the preparation of **4.172A** via the deprotection of bis-MOP protected **4.140A** would likely have been a more efficient route to this compound. However, with triol **4.172F** in hand, we decided to go ahead and investigate whether the steric environments of the three alcohols might permit their differential protection. To this end, **4.172F** was treated with excess TMS-Cl followed by deprotection of the more labile primary silyl groups to give mono-protected **4.173**. (It was, in fact, hoped that the more hindered primary alcohol would remain protected). Subjecting this diol to one equivalent of TBDPS-Cl or TBS-Cl was expected to give a mixture of **4.174a** and **4.174b** with, ideally, one being favoured over the other. In fact, no reaction was observed, even when an excess of the silyl chloride was used. Evidently the steric environment of both alcohols was significantly more hindered than expected.

Scheme 4.35 – Reduction of the lactone to a diol

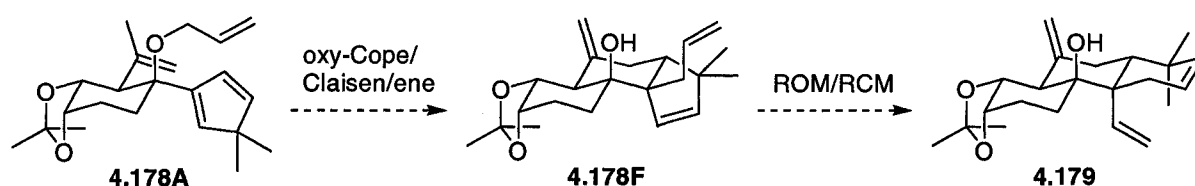


Without the ability to effectively manipulate either the lactone or the diol, we were forced to reconsider our approach for introducing the A-ring of LL-S491 β . While the selective opening of the benzilidene remained a possibility (Scheme 4.26 above), it was lengthy and lacked elegance. Looking to the literature for new ideas, we took note of a total synthesis by Paquette et al. which relied on an alkylation step using the vinyl lithium species of **4.176**.³⁶

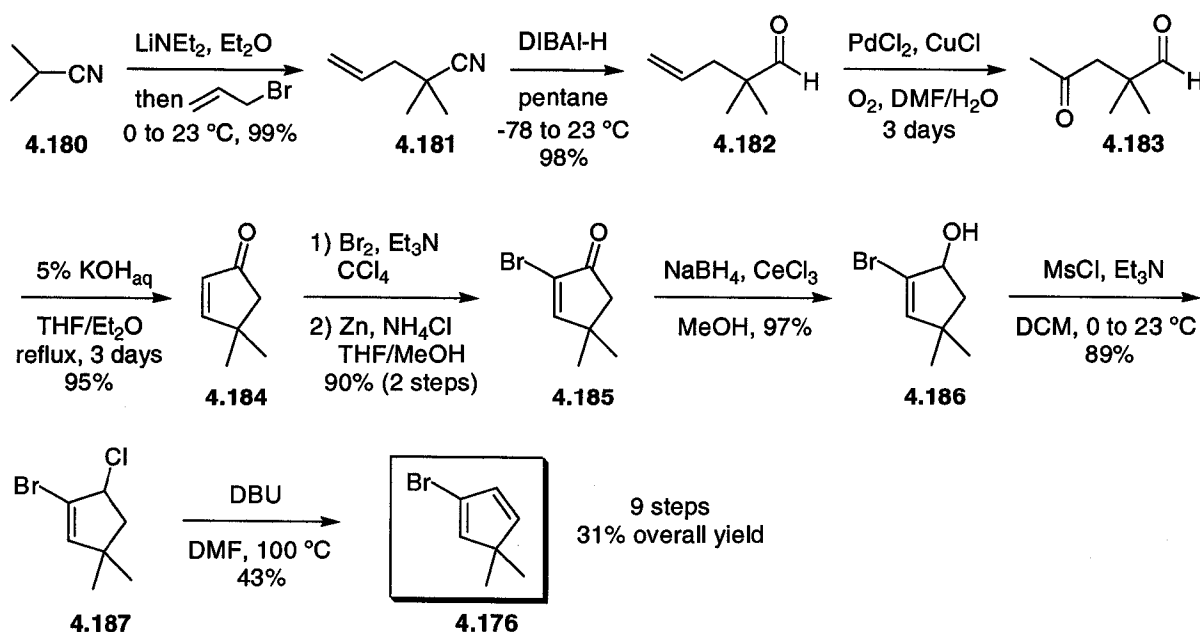
Scheme 4.36 – Paquette's reported alkylation with the vinyl lithium of **4.176**

Noting the presence of the *gem*-dimethyl group on the vinyl bromide, a new approach to the core of LL-S491 β was envisioned wherein the oxy-Cope/Claissen/ene product of **4.178F** could undergo a tandem ring-opening, ring-closing metathesis reaction to give **4.179** (Scheme 4.37). If successful, this sequence would serve to complete the A-ring and introduce the *gem*-dimethyl group *without the use of any protecting groups*. Moreover, an estimated 14 linear steps could be avoided as compared to the alternative benzilidene acetal approach.

Scheme 4.37 – A tandem ring-opening/ring-closing approach for the formation of the A-ring



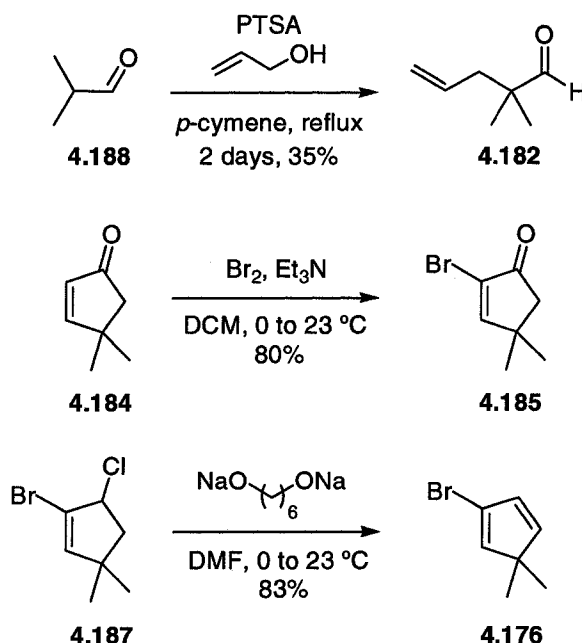
To test the proposed route, we first needed to prepare vinyl bromide **4.176**. The originally reported procedure by Paquette et al. is shown in Scheme 4.38 below.^{36,37} Several modifications, however, were found to be necessary based on our own findings as well as additional information provided by one of the co-authors, Dr. Y. O. Long. In particular, difficulties were encountered with the DIBAL-H reduction of **4.181**. Regardless of the DIBAL-H source (neat or as a solution in DCM, toluene or hexanes), in our hands, the reaction gave only trace amounts of the desired product. To circumvent this problem, an alternative procedure was used. Isobutyraldehyde was condensed with allyl alcohol in the presence of PTSA in refluxing *p*-cymene to give a 35% yield of aldehyde **4.182** (Scheme 4.39).³⁸ While the yield was substantially lower than Paquette's reported sequence, the reagents were inexpensive and only a single step was required (compared to two in the published procedure).

Scheme 4.38 – Reported procedure for the preparation of vinyl bromide **4.176**

In addition to the first step, difficulties were encountered reproducing the bromination of **4.184**. Significant quantities of recovered starting material were being isolated despite complete conversion by TLC after the initial treatment with bromine and triethylamine. Speculating that the product, **4.185**, might be converting back to starting material under the Zn/NH₄Cl conditions, we repeated the reaction, this time omitting the second step. Under this new protocol, an 80% yield of the desired product was obtainable (Scheme 4.39).

Lastly, the final elimination of HCl from **4.187** required optimization. The reported conditions using DBU in DMF gave only 12-15% yield of the desired product (compared to the reported 43% yield). An updated procedure from Dr. Long, however, indicated that the disodium alkoxide of 1,6-hexandiol led to more reliable results. Furthermore, purification by Florisil chromatography allowed the desired vinyl bromide to be isolated in 83% yield (Scheme 4.39).

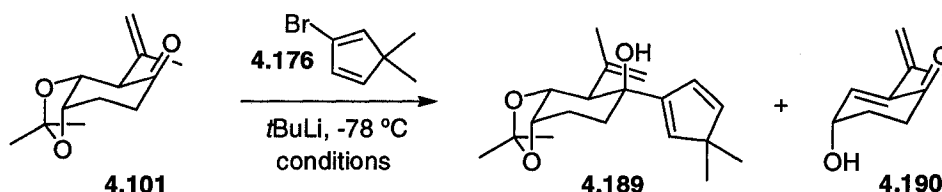
Scheme 4.39 – Modified procedures for the preparation of vinyl bromide **4.176**



With a reliable means of generating vinyl bromide **4.176**, we began investigating its alkylation onto ketone **4.101** (Table 4.9). Treating **4.176** with *t*-butyllithium in THF at -78 °C gave a 64% yield of the elimination product **4.190** (entry 1). Hoping to avoid this by-product by attenuating the basicity of our vinyl lithium species, the reaction was repeated in the presence of cerium (III) chloride. Pre-complexing the ketone with the cerium led to a 20%

yield of the desired product (**4.189**) along with unreacted **4.101** (entry 2). Unfortunately, these two compounds were inseparable making subsequent transformations difficult. Following the procedure reported by Paquette et al. for the alkylation of **4.175** (see Scheme 4.36 above), we tried titrating the cerium/THF mixture with *t*-butyllithium prior to adding the vinyl lithium species. This protocol again led to a 20% yield of the product as an inseparable mixture with the starting ketone (entry 3). Omitting the titration step and simply complexing the vinyl lithium species with the cerium (III) chloride gave no detectable reaction (entry 4). Finally, success came by changing the solvent to diethyl ether. Under these conditions, a 68% yield of the alkylated substrate was obtained with no contamination by either **4.101** or **4.190**.

Table 4.9 – Optimization of the alkylation with Paquette's vinyl bromide, **4.176**

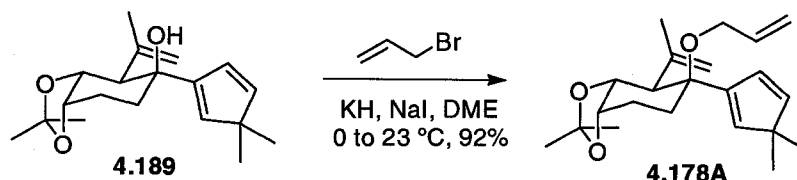


Entry	Solvent	Additive	Procedure ^a	Result
1	THF	---	---	63% 4.190
2	THF	CeCl ₃	A	20% 4.189
3	THF	CeCl ₃	B	20% 4.189
4	THF	CeCl ₃	C	no reaction
5	Et ₂ O	---	---	68% 4.189

^a A: Pre-complex CeCl₃ with **4.101**; B: Pre-complex CeCl₃ with the vinyl lithium of **4.176**; C: Titrate the CeCl₃/THF suspension with *t*BuLi (until an orange colour persists) before complexing with the vinyl lithium of **4.176** (ref. 36)

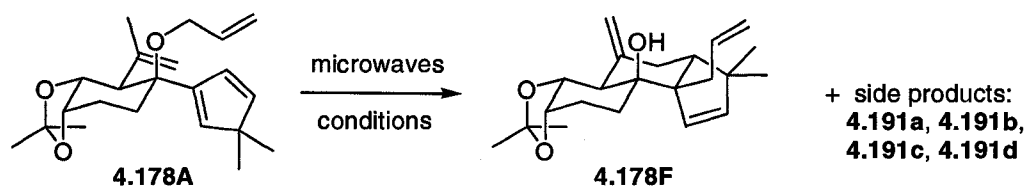
From **4.189**, we next needed to install the allyl group onto the tertiary alcohol. This reaction proceeded cleanly giving **4.178A** in 92% yield (Scheme 4.40). With this substrate in hand, we were ready to try the oxy-Cope/Claisen/ene reaction.

Scheme 4.40 – Allylation of alkylation product **4.189**



Our initial attempt at inducing the tandem reaction cascade on **4.178A** gave a disappointing 20% yield of the expected product **4.178F** (Table 4.10, entry 1). The remainder of the material isolated was a mixture of four side products, **4.191a-4.191d**. Though their structures were not identified, it was clear from their spectral data that they did not correspond to diastereomers of **4.178F**. Lowering the reaction time from 2 hours to 20 minutes led to a similar mix of products, along with unreacted starting material (entry 2). By gradually lowering the temperature and increasing the reaction time, we were able to reduce the number of side products to just one, **4.191a**, however, the yield of the desired product remained low at just 29% (entry 4). Adding BHT as a radical trap improved the yield of **4.178F** to 45% (entry 5). Similarly, the use of triethylamine as a proton sponge offered a 39% yield of **4.178F** (entry 6). Noting the success of acetonitrile for controlling side product formation in some microwave reactions,³⁹ we changed solvents and repeated our reaction at 200 °C (entry 7). While the yield of the desired compound was still only 39%, the nature of the side products had changed such that **4.191a** was no longer being formed. Encouraged by this result, we hoped to combine the benefits of acetonitrile with those obtained with BHT (entry 8) and triethylamine (entry 9). In both cases, however, **4.191a** remained a prominent impurity and yields for **4.178F** remained at 45% and 41% respectively.

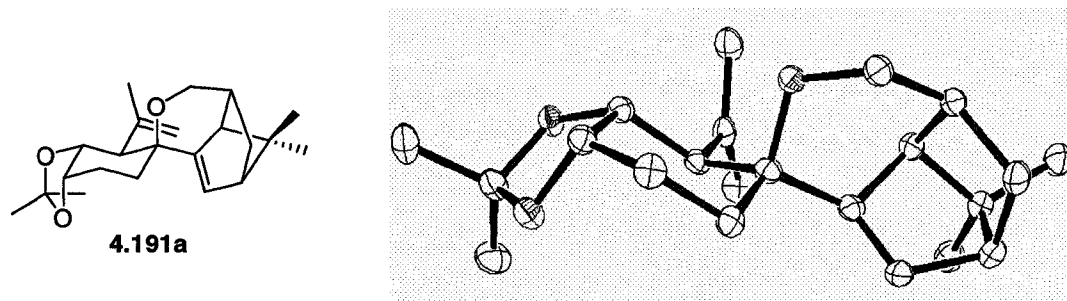
Table 4.10 – Optimization of the oxy-Cope/Claisen/ene reaction of **4.178A**



Entry	Solvent	Additive	Temp (°C)	Time	Result
1	toluene	---	200	2 hours	20% 4.178F + 4.191a-4.191d
2	toluene	---	200	20 minutes	4.178A + 4.178F + 4.191a-4.191d
3	toluene	---	180	30 minutes	4.178A + 4.178F + 4.191a-4.191c
4	toluene	---	160	14 hours	29% 4.178F + 50% 4.191a
5	toluene	BHT	200	1 hour	45% 4.178F + 33% 4.191a
6	toluene	Et ₃ N	200	1 hour	39% 4.178F + 35% 4.191a
7	MeCN	---	200	1 hour	39% 4.178F + 4.191b-d
8	MeCN	BHT	200	1 hour	45% 4.178F + 35% 4.191a
9	MeCN	Et ₃ N	200	1 hour	41% 4.178F + 35% 4.191a

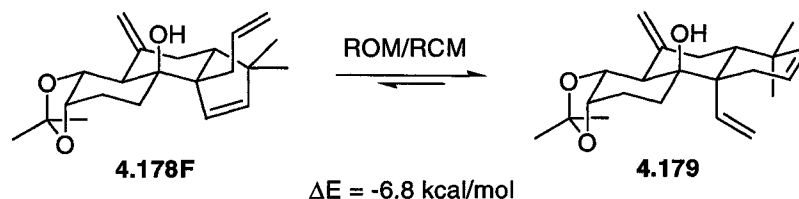
Before making any further attempts to optimize the oxy-Cope/Claisen/ene reaction of **4.178A**, we felt it would be beneficial to first identify the structure of the remaining side product, **4.191a**. Extensive 2D NMR data, and finally a single crystal X-ray analysis revealed that **4.191a** was in fact a result of a Diels-Alder reaction between the allyl ether and cyclopentadiene moieties of **4.178A** (Figure 4.10). While the electronics of the dienophile would not predict a favourable Diels-Alder reaction, the spatial arrangement of the fragments clearly supports this intramolecular reaction. Knowing that Diels-Alder reactions can be reversible, the identification of **4.191a** opened the door to a possible means of recovering our valuable substrate. Heating **4.191a** in the microwave at 200 °C for 1 hour, however, led only to the recovery of the Diels-Alder adduct.

Figure 4.10 – ORTEP plot of Diels-Alder adduct **4.191a**



While further efforts could have been made to minimize the formation of **4.191a** (including alkylating with a protected version of **4.186** and introducing the requisite olefin after the tandem sequence), we were anxious to carry forward with our synthesis and explore the proposed ring-opening/ring-closing metathesis sequence of **4.178F**. To begin, we performed some preliminary calculations to ensure that the proposed reaction was thermodynamically favoured. Indeed, a 6.8 kcal/mol difference in energy was found favouring the desired product, **4.179** (Figure 4.11).⁴⁰

Figure 4.11 – Calculated thermodynamics of the proposed metathesis sequence



Confident that the ring-opening/ring-closing metathesis sequence should be feasible, we began exploring the reaction of **4.178F** under a variety of metathesis conditions. As a first attempt, a small amount of **4.178F** was treated with 20 mol% of Grubbs' first generation catalyst⁴¹ in DCM at ambient temperature. After 1.5 hours, no reaction was detected by TLC so the reaction was opened to air, concentrated, and a crude NMR taken. The ¹H NMR revealed a 4.4:1 molar ratio of the starting material and a new product. Re-subjecting the crude material to the same reaction conditions led to a further increase in the percentage of new product. Ultimately, four cycles of the above process were completed before full consumption of the starting material was achieved. The result was a 60% isolated yield of a new compound (Scheme 4.41). From the number of vinylic protons in the ¹H NMR, however, it was clear that the isolated material was not the desired product, **4.179**. A single crystal X-ray analysis confirmed our suspicions and revealed that oxidation of the allyl group followed by cyclization with the tertiary alcohol had afforded lactone **4.192** (Figure 4.12).

Scheme 4.41 – Initial attempt at the ROM/RCM sequence

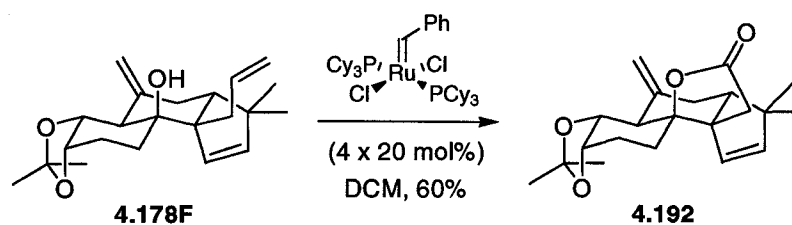
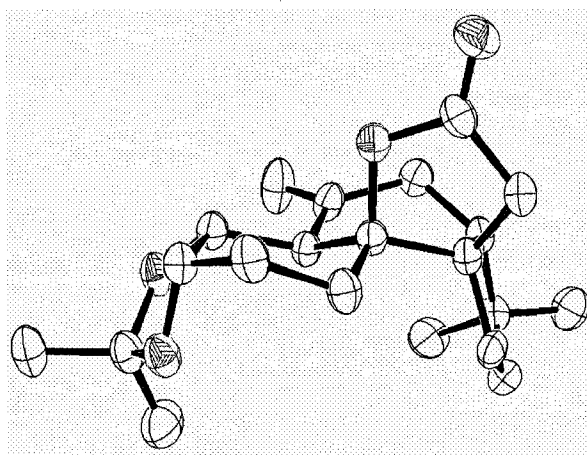
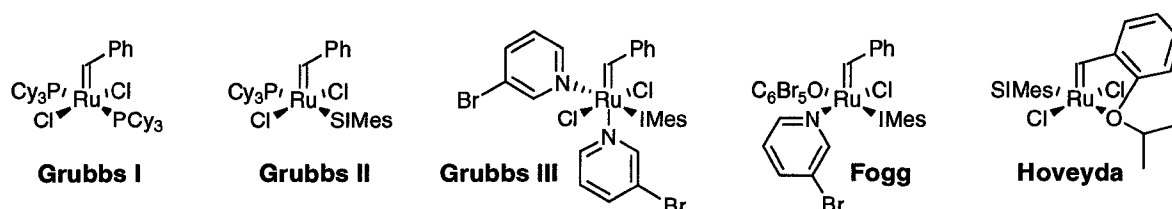


Figure 4.12 – ORTEP plot of lactone 4.192

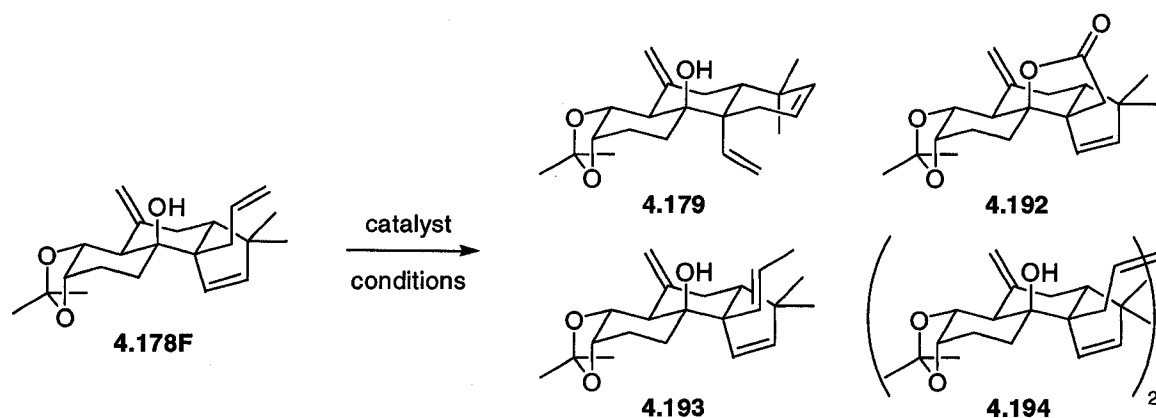


Further investigation into this curious result was carried out, the details of which can be found in Chapter 5. With respect to our synthesis, however, this product lactone was of little synthetic value and our attention was returned to exploring various reaction conditions and catalysts to affect the desired transformation. Moving away from the less reactive Grubbs I, we began screening new conditions using the Grubbs II,⁴² Grubbs III,⁴³ Fogg⁴⁴ and Hoveyda⁴⁵ catalysts (Figure 4.13).

Figure 4.13 – Metathesis catalysts used for the attempted ROM/RCM sequence



Typical metathesis conditions⁴⁶ using DCM as the solvent at ambient, or slightly higher reaction temperatures, under an argon or ethylene atmosphere, gave primarily unreacted **4.178F** with trace amounts of lactone **4.192** being observed in some cases (Table 4.11, entries 1-6).⁴⁷ To avoid possible catalyst deactivation by the coordinating hydroxyl group, the reactions were repeated in the presence of Ti(OiPr)₄.⁴⁸ Again, unreacted starting material was recovered (entries 7-9). Changing the solvent to toluene and heating the reactions to reflux for 20 hours led to a significant amount of isomerization product **4.193** being isolated (entries 10-12). Such side products are known to be a problem in aromatic solvents where ruthenium hydride species are readily generated.⁴⁹ Repeating the reaction with Grubbs II in dichloroethane at 80 °C, however, continued to give substantial quantities of the isomerization product, along with a second, unidentified product (entry 13).⁵⁰ The addition of benzoquinone has also been reported as an effective means of shutting down ruthenium hydride formation,⁵¹ however, its addition to our reaction mixture failed to eliminate the formation of **4.193** (entry 14). The addition of phenol to Grubbs I has been reported to greatly enhance the lifetime of the active catalyst.⁵² In our hands, these conditions did lead to a previously unobserved product, dimer **4.194**, though none of the desired compound was formed. Similarly, the slower initiating Hoveyda-Grubbs II catalyst gave a mixture of products, including dimer **4.194**, but still none of the desired ROM/RCM product was isolated.

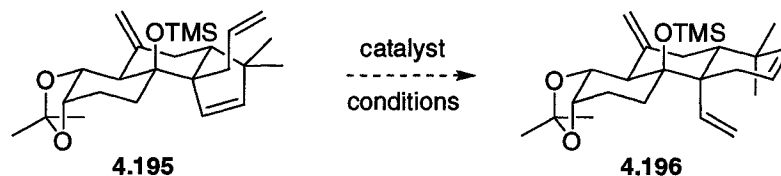
Table 4.11 – Subsequent attempts at the ring-opening/ring-closing metathesis of **4.178F**

Entry	Catalyst	Additive	Solvent	Temp (°C)	Time (h)	Result
1	Grubbs II	---	DCM	40	30	recovered 4.178F + 4.192 (< 5%)
2	Grubbs III	---	DCM	40	30	recovered 4.178F + 4.192 (< 5%)
3	Fogg	---	DCM	40	30	recovered 4.178F
4	Grubbs II	ethylene	DCM	23	24	recovered 4.178F
5	Grubbs III	ethylene	DCM	23	24	recovered 4.178F
6	Fogg	ethylene	DCM	23	24	recovered 4.178F
7	Grubbs II	Ti(OiPr) ₄	DCM	23	18	recovered 4.178F
8	Grubbs III	Ti(OiPr) ₄	DCM	23	18	recovered 4.178F
9	Fogg	Ti(OiPr) ₄	DCM	23	18	recovered 4.178F
10	Grubbs II	---	toluene	85	20	recovered 4.178F + 47% 4.193
11	Grubbs III	---	toluene	85	20	recovered 4.178F + 29% 4.193
12	Fogg	---	toluene	85	20	recovered 4.178F + 25% 4.193
13	Grubbs II	---	DCE	80	18	68% 4.193 + unidentified product
14	Grubbs II	benzoquinone	DCM	60	18	recovered 4.178F + 30% 4.193 + 12% 4.192
15	Grubbs I	phenol	DCM	60	18	recovered 4.178F + 7% 4.192 + 29% 4.194
16	Hoveyda	---	DCM	23	48	recovered 4.178F + 10% 4.192 + 12% 4.193 + 32% 4.194
17	Hoveyda	---	DCM	50	48	as above

In addition to the reaction of **4.178F**, TMS protected **4.195** was prepared (TMS-Imidazole, KHMDS, THF, 92%) and its ROM/RCM sequence attempted (Table 4.12). Similarly disappointing results were obtained and the reaction in DCM under either an argon

or ethylene atmosphere failed to give anything other than recovered starting material (entries 1-6). Changing the solvent to DCE and raising the temperature to 80 °C gave multiple new products, but by ^1H NMR, it was clear that they did not correspond to the desired compound, **4.196** (entry 7). No further efforts were made to assign their structures.

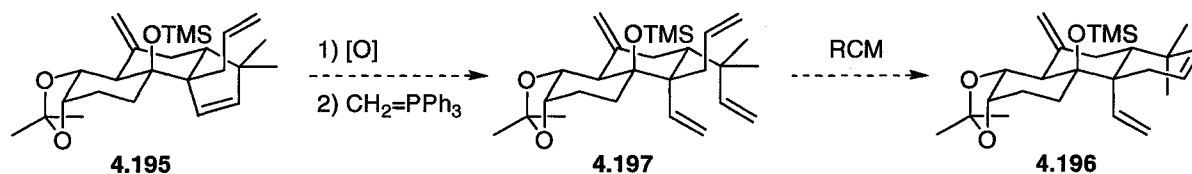
Table 4.12 – Attempted ROM/RCM sequence on TMS-protected **4.195**



Entry	Catalyst	Additive	Solvent	Temp (°C)	Time (h)	Result
1	Grubbs II	---	DCM	23	18	recovered 4.195
2	Grubbs III	---	DCM	23	18	recovered 4.195
3	Fogg	---	DCM	23	18	recovered 4.195
4	Grubbs II	ethylene	DCM	23	18	recovered 4.195
5	Grubbs III	ethylene	DCM	23	18	recovered 4.195
6	Fogg	ethylene	DCM	23	18	recovered 4.195
7	Grubbs II	---	DCE	80	18	recovered 4.195 + unidentified products

While this reaction may be theoretically achievable, the kinetic barrier to the ring-opening of the cyclopentene moiety in **4.178F** and **4.195** is perhaps just too high to be overcome by traditional metathesis catalysts and conditions. An indirect route to **4.196** could be taken whereby oxidative cleavage of the three olefins followed by a Wittig reaction could yield RCM precursor **4.197** (Scheme 4.42).⁵³ With the cyclopentene ring now open, the more facile ring-closing metathesis should yield the thermodynamic product, **4.196**. At this point in the project, however, insufficient material remained for the exploration of this route.

Scheme 4.42 – An alternative route to **4.196**



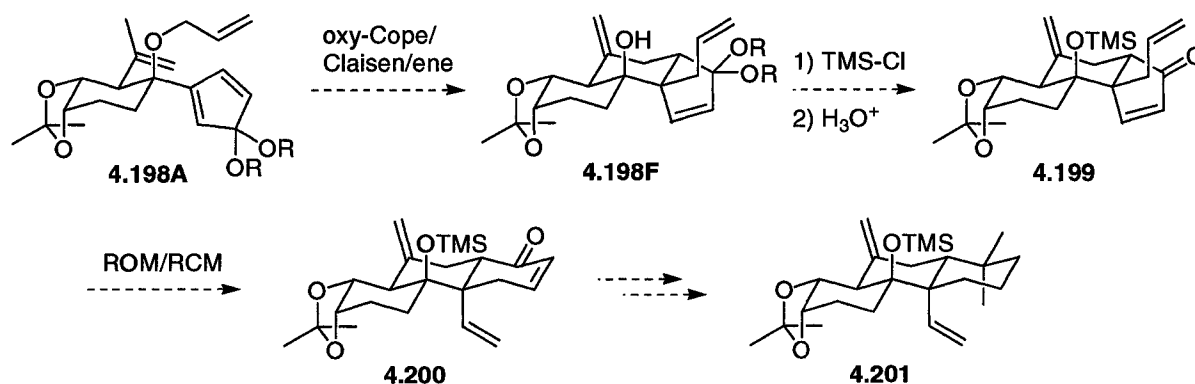
Conclusions and Future Directions

In the absence of sufficiently advanced intermediates and with little time available for their preparation, no further efforts were made towards the total synthesis of LL-S491 β . While its synthesis was not achieved, several innovative routes were thoroughly explored and some interesting chemistry was uncovered along the way. Most importantly, the rigor of the oxy-Cope/Claisen/ene reaction was put to the test and six new examples of highly functionalized substrates were found to successfully undergo this tandem reaction.

With additional time and resources, the synthesis of LL-S491 β should be an achievable goal. In addition to revisiting the selective opening of the benzilidene acetal (Scheme 4.26) or the proposed alternative to the ring-opening/ring-closing metathesis sequence (Scheme 4.42), there remain numerous routes to this natural product which have yet to be investigated. Two of these possibilities are detailed below.

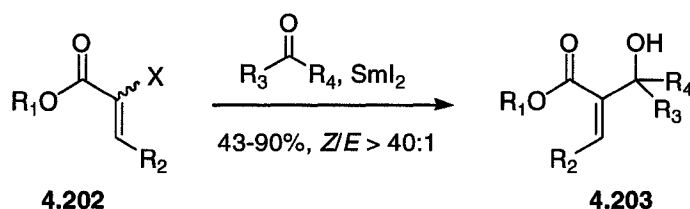
On the assumption that the ring-opening/ring-closing metathesis sequence failed, at least in part, because of the steric hindrance associated with the *gem*-dimethyl group, an alternative approach worth considering would be to replace the *gem*-dimethyl group with a less hindered ketone (Scheme 4.43). While such a change would mean additional steps later on to introduce the two methyl groups, we could rely on the chemistry which was established during the synthesis of wiedemannic acid analogue **3.16**. Moreover, such a route would avoid the potential difficulty in differentiating the olefin of the A-ring from the other two double bonds.

Scheme 4.43 – An alternative ROM/RCM substrate



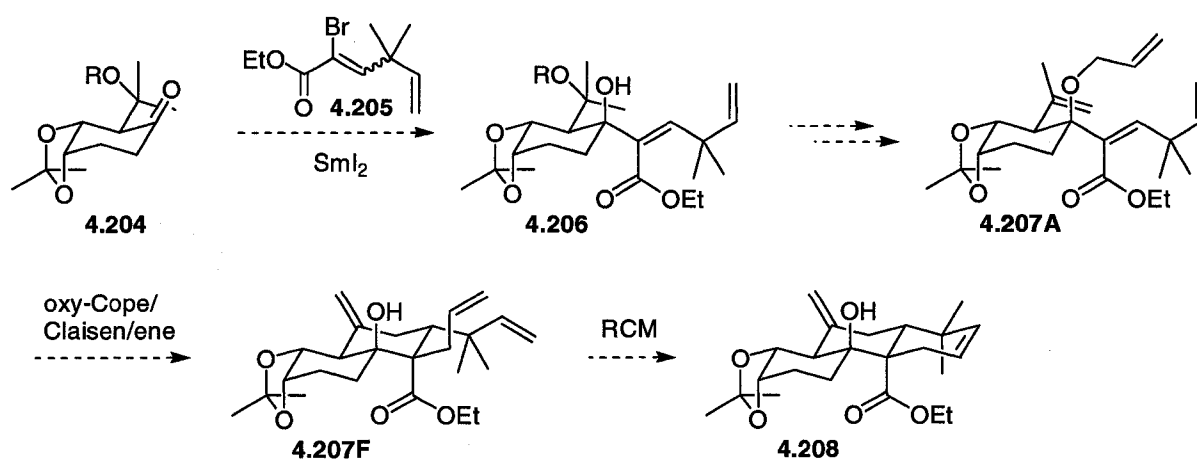
Moving away from the metathesis strategy all together, one final approach to LL-S491 β might take advantage of a recently reported SmI_2 promoted coupling reaction.⁵⁴ Concellón and Huerta found that α -halo- α,β -unsaturated esters of type **4.202** could be coupled with ketones and aldehydes to give Baylis-Hillman type adducts such as **4.203** (Scheme 4.44). Notably, the *Z* isomer of the final product was heavily favoured regardless of the starting geometry of the vinyl halide.

Scheme 4.44 – Concellón and Huerta's recently reported SmI_2 coupling



Applying this reaction to our natural product synthesis might allow us to take advantage of a more convergent approach by using a more functionalized coupling partner than would be tolerated by the traditional alkylation step. For instance, coupling ketone **4.204**⁵⁵ with vinyl bromide **4.205** should give **4.206** which could be rapidly transformed into the oxy-Cope/Claisen/ene precursor **4.207A** (Scheme 4.45). The product of our tandem reaction sequence could then immediately undergo a ring-closing metathesis reaction to give **4.208** as an advanced synthetic intermediate.

Scheme 4.45 – A SmI_2 coupling for a more convergent approach to LL-S491 β



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⁵⁵ Some preliminary studies into this reaction have indicated that the isopropenyl group in **4.101** readily isomerizes to give the unsaturated system. Use of **4.204** should effectively avoid this problem.

5

Ongoing and Future Work

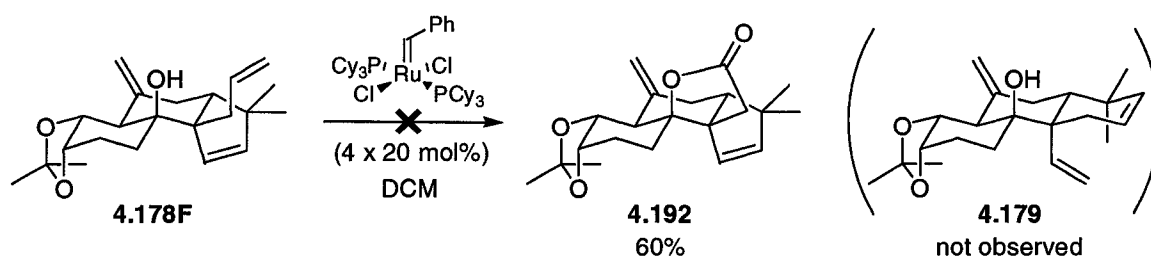
Introduction

A significant part of the value associated with pursuing new methods and synthesizing new molecules, comes, not always from the attainment of the originally proposed goal, but from the unexpected discoveries that can be made along the way. During the investigation of the oxy-Cope/Claisen/ene reaction and its application to total synthesis, several new findings were uncovered which we felt warranted further exploration. Two of these will be discussed in greater detail in the pages that follow.

Ruthenium-Induced Lactonization

As part of our efforts to synthesize LL-S491 β (Chapter 4), we had proposed a ring-opening/ring-closing metathesis sequence of **4.178F** which we had hoped would afford us the isomeric compound, **4.179** (Scheme 5.1). Our first attempt at executing this reaction, however, led instead to the unexpected lactonized product, **4.192**.

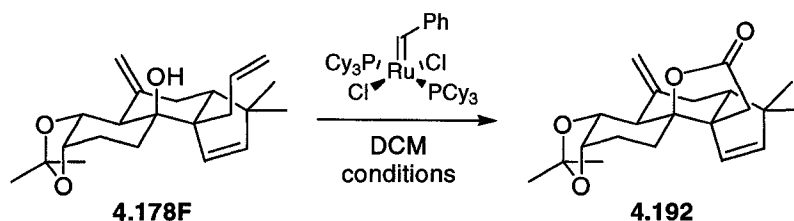
Scheme 5.1 – Revisiting the unexpected product of the ROM/RCM sequence



While the product of this reaction was of little synthetic interest, its formation did represent a highly unusual outcome for an otherwise standard reaction with Grubbs' first generation catalyst. Of three possible olefins, only one was oxidized leaving the other two intact. Moreover, no cross-metathesis was observed, neither with itself nor with the catalyst's benzilidene moiety. Given the amount of attention that has been devoted in the recent literature to the various side products of metathesis reactions,¹ we decided to further investigate this curious observation.

As already described, the original conditions under which **4.192** was first obtained involved the repeated exposure of the reaction mixture to air, prompting us to suggest that either adventitious water and/or oxygen was leading to an oxidative environment. In an effort to intentionally recreate these conditions in a more controlled manner, we repeated the reaction with 20 mol% of the catalyst under an atmosphere of oxygen (Table 5.1, entry 1). Lactone **4.192** was isolated in 19% yield along with unreacted **4.178F** (no other products were observable by crude NMR). Maintaining an anaerobic environment and instead introducing a small amount of water led to only trace amounts of the lactone being formed (entry 2). Noting that the amount of lactone isolated in the first case closely correlated with the amount of catalyst used, we repeated the above two experiments with a catalyst loading of 100 mol%. Under the aerobic-anhydrous conditions, a 78% yield of **4.192** was isolated (entry 3) while the anaerobic-aqueous conditions gave only a 27% yield (Entry 4). Notably, in the latter case, no starting material was recovered. Rather, a significant number of other, unidentified products were formed. Thus, while both the introduction of water and oxygen appear capable of generating the required oxidative conditions for the formation of **4.192**, an oxygen atmosphere appears to be more effective. Moreover, these experiments confirm that the active "catalyst" is, in fact, non-catalytic and is required in stoichiometric amounts.

Table 5.1 – Determining the reaction conditions responsible for the lactonization of 4.178F

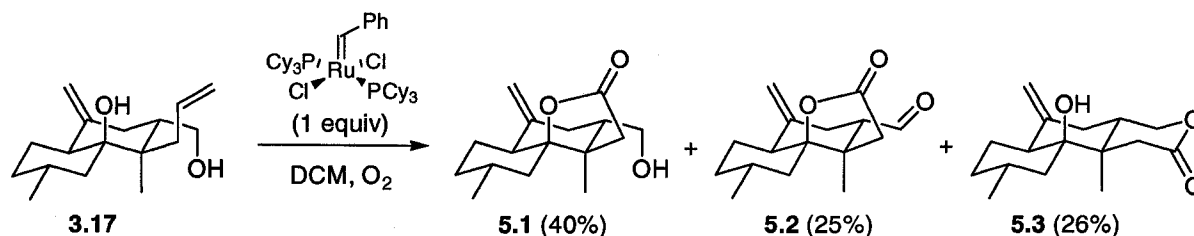


Entry	Catalyst (mol %)	Oxygen ^a	Water ^b	Result
1	20	Yes	No	4.178F + 19% 4.192
2	20	No	Yes	4.178F + < 5% 4.192
3	100	Yes	No	4.178F + 78% 4.192
4	100	No	Yes	27% 4.192 + unidentified products

^a Reactions were sparged with oxygen prior to being sealed. ^b 0.01 mL was added (20 equiv with respect to **4.178F**).

To further probe this lactonization, we moved away from our synthetically valuable substrate (**4.178F**) and began investigating the reaction of some previously prepared oxy-Cope/Claisen/ene products. To begin, diol **3.17** was subjected to the reaction conditions (1 equivalent of Grubbs' I, DCM, O₂). A mixture of products was obtained and compounds **5.1**, **5.2** and **5.3** were isolated with yields of 40%, 25% and 26% respectively (Scheme 5.2). The formation of **5.2** was particularly interesting as it suggested that a ruthenium catalyzed transfer dehydrogenation may be occurring.²

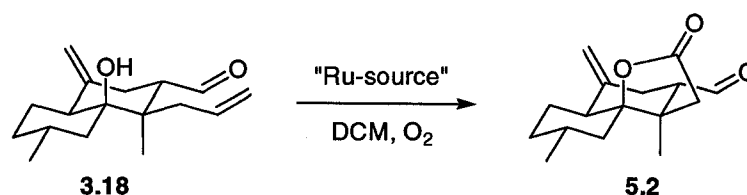
Scheme 5.2 – Mixture of lactones obtained from the reaction of diol 3.17



Though the reaction of **3.17** had been successful, we opted to carry out subsequent transformations on substrate **3.18** in order to minimize the number of possible products formed. As expected, lactone **5.2** was obtained in good yield when **3.18** was treated with Grubbs' first generation catalyst under an atmosphere of oxygen (Table 5.2). This was true

regardless of whether the solution was first sparged with oxygen for 15 minutes (entry 1) or if the oxygen was simply blown into the space above the flask prior to sealing (entry 2). Lactone **5.2** was also obtained when Grubbs' second generation catalyst was used, although the yield was slightly diminished (entry 3). Moving away from an alkylidene as the ruthenium source led to the recovery of unreacted starting material when either $\text{Cl}_2\text{Ru}(\text{PPh}_3)_4$ (entry 4) or RuCl_3 (entry 5) was used.

Table 5.2 – Investigating alternative ruthenium sources for the lactonization reaction

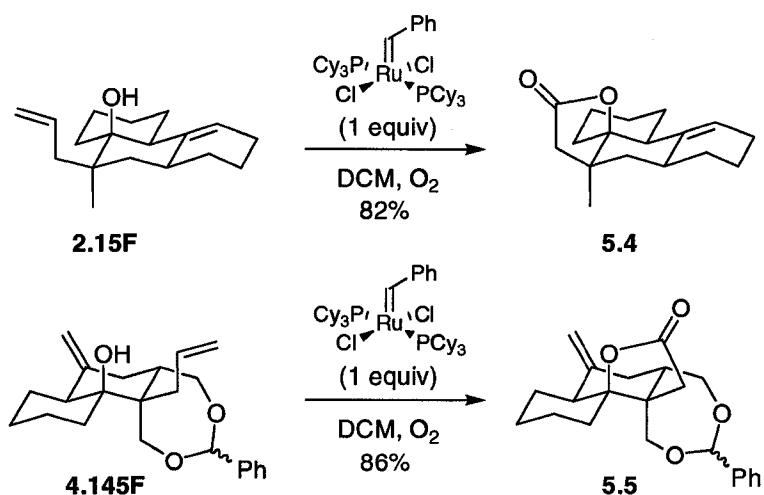


Entry	Ru-Source (1 equiv.)	Method ^a	Result
1	Grubbs' I	A	80% 5.2
2	Grubbs' I	B	78% 5.2
3	Grubbs' II	A	68% 5.2
4	$\text{Cl}_2\text{Ru}(\text{PPh}_3)_3$	A	No reaction
5	RuCl_3	A	No reaction

^a A: Reaction was sparged with oxygen for 15 minutes prior to sealing. B: Reaction space above the flask was filled with oxygen prior to sealing.

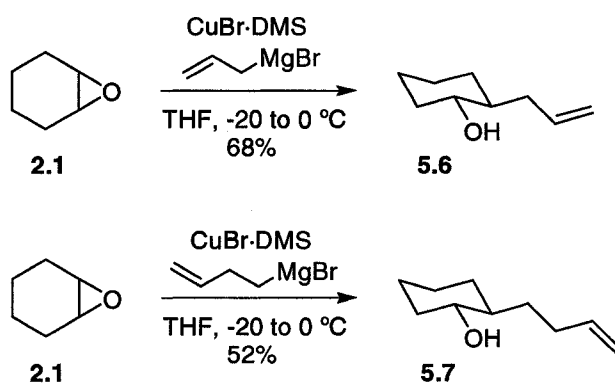
In addition to the above oxy-Cope/Claisen/ene substrates, substrates **2.15F** and **4.145F** were also tested. In both cases, the reaction proceeded well giving lactones **5.4** and **5.5** in yields of 82% and 86% respectively (Scheme 5.3). Beyond this class of substrates, however, we were interested in knowing whether or not the reaction would proceed with simple alkenols such as those derived from cyclohexene oxide (**2.1**) or cyclohexanone (**5.8**).

Scheme 5.3 – Extending the lactonization to other oxy-Cope/Claisen/ene products



To this end, cyclohexene oxide was treated with allylmagnesium bromide in the presence of copper (I) bromide to give **5.6** in 68% yield (Scheme 5.4). Similarly, the reaction between cyclohexene oxide and 3-butenylmagnesium bromide gave **5.7** in 52% yield.

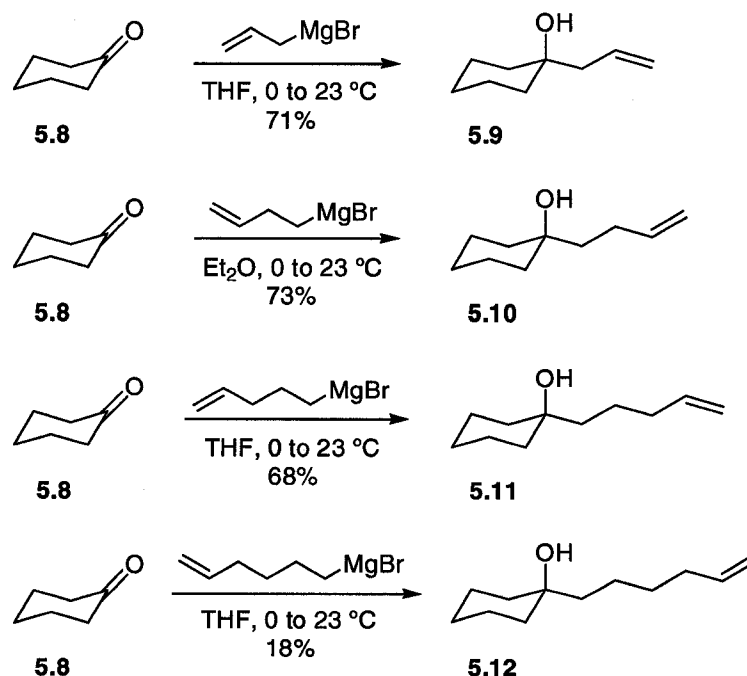
Scheme 5.4 – Preparation of alkenols derived from cyclohexene oxide



Substrates derived from cyclohexanone were prepared by reacting the ketone with the corresponding Grignard reagent (Scheme 5.5). The use of commercially available allylmagnesium bromide and 3-butenylmagnesium bromide afforded alkenols **5.9** and **5.10** in yields of 71% and 73% respectively. For the preparation of compounds **5.11** and **5.12**, the Grignard reagents were prepared from the corresponding alkyl bromides and treated directly with cyclohexanone to give the desired compounds in 68% and 18% yield. In the latter case,

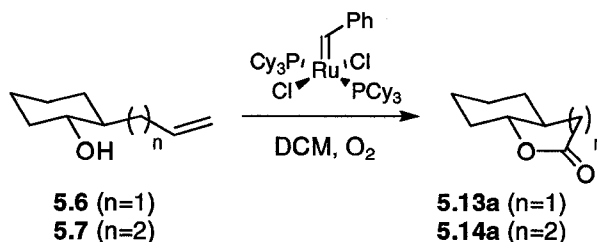
difficulties in the preparation of the Grignard led to a low quality reagent which in turn gave a low yield of **5.12**.

Scheme 5.5 – Preparation of alkenols derived from cyclohexanone



With a variety of simple alkenols in hand, we began subjecting the new compounds to stoichiometric amounts of Grubbs' first generation catalyst in the presence of molecular oxygen. The reaction of **5.6** led to a 60% yield of **5.13a** (Table 5.3, entry 1). Formation of the six-membered lactone was less successful and **5.14a** was isolated in only 24% yield along with a number of unidentified products (entry 2).

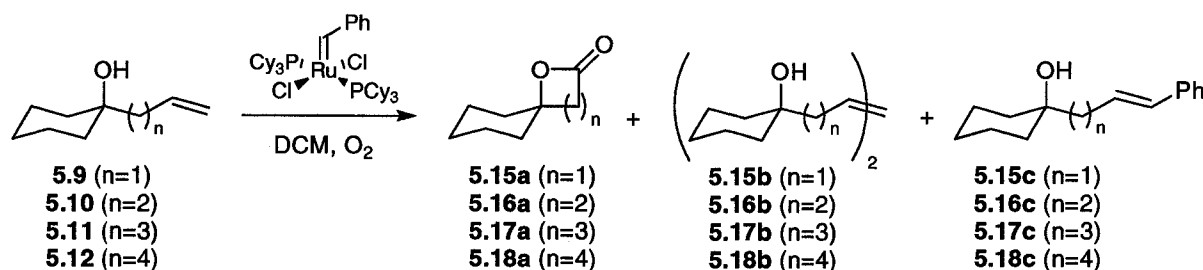
Table 5.3 – Lactonization attempts on alkenols derived from cyclohexene oxide



Entry	Substrate	n	Result
1	5.6	1	60% 5.13a
2	5.7	2	24% 5.14a + unknown compounds

The substrates derived from cyclohexanone showed a similar pattern of reactivity. Compound **5.10** reacted cleanly to give a 70% yield of the 5-membered lactone (Table 5.4, entry 2). Increasingly the ring size, however, led to a decrease in the amount of lactone formed: Substrate **5.11** gave a mixture of lactone **5.17a**, dimer **5.17b**, and the product of cross metathesis between **5.11** and the catalyst's benzilidene moiety, **5.17c** (entry 3). Further increasing the ring size of the targeted product lactone to a 7-membered ring led to the exclusive formation of the dimerized substrate, **5.18b** (entry 4). Likewise, formation of a more strained four-membered lactone was also unsuccessful and a complex mixture of products was obtained. (Though no structures were absolutely identified, several of the compounds had peaks in ~ 9.5-10 ppm region of the ^1H NMR suggesting that at least some of the olefin had been oxidized to the aldehyde).

Table 5.4 – Lactonization attempts on alkenols derived from cyclohexanone



Entry	Substrate	n	Result
1	5.9	1	Unidentified products
2	5.10	2	70% 5.16a
3	5.11	3	<5% 5.17a ^a + 25% 5.17b + 46% 5.17c
4	5.12	4	99% 5.18b

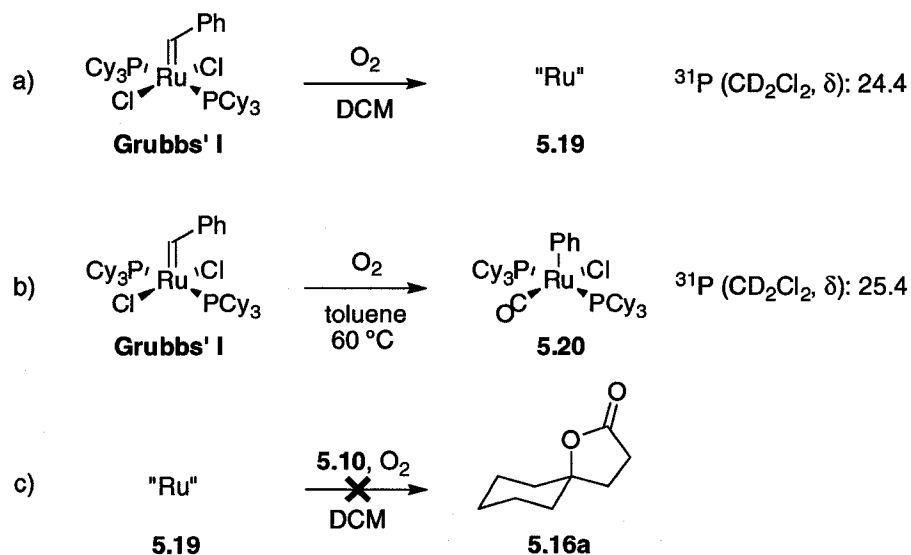
^a obtained as an inseparable mixture with a second, unidentified compound.

From the above results, it seems clear that this reaction is best suited for the formation of five-membered lactones. This limitation in scope, combined with the requirement for a stoichiometric amount of Grubbs' "catalyst," leaves this reaction unable to compete against the existing means of affecting such transformations. That said, a catalytic version of this method could be more interesting, particularly when one considers the selectivity observed in the reaction of tri-olefinic **4.178F** and di-olefinic substrates **2.15F**, **3.17**, **3.18** and **4.145F**. Whether a result of steric differentiation or proximity to the tertiary alcohol, the exclusive

oxidation of the allyl group on these compounds seems to be quite general. More importantly, such selectivity would likely prove difficult under standard ozonolysis or osmylation conditions.

In order to facilitate our efforts in achieving catalytic turnover, we hoped to first gain some insight into the reaction mechanism and/or the active species' involved. As an initial step in this direction, Grubbs' first generation catalyst was subjected to the reaction conditions in the absence of substrate (Scheme 5.6a). An aliquot of the resulting dark brown solution was taken and a ^{31}P NMR of the concentrated material (**5.19**) revealed a single peak at 24.4 ppm. A search of the literature for known decomposition products of Grubbs' I revealed that ruthenium complex **5.20** could be prepared by heating a solution of Grubbs' I in toluene in the presence of oxygen (Scheme 5.6b).³ Based on their similar spectral properties and modes of preparation, it seems reasonable to assume that **5.19** is composed primarily of **5.20**. Unfortunately, the addition of alkenol **5.10** to a solution of **5.19** failed to give spiro lactone **5.16a** indicating that **5.19** is neither the active species nor a precatalyst for our reaction (Scheme 5.6c).

Scheme 5.6 – Attempt at elucidating the structure of the active species



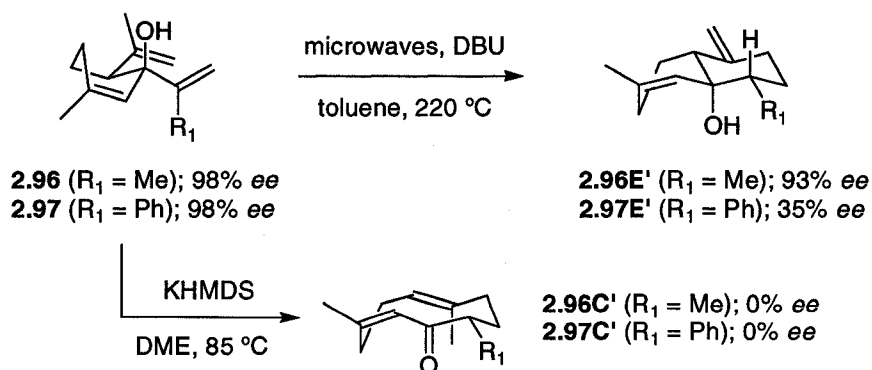
Since the above decomposition product of Grubbs' catalyst appears to be inactive for this reaction,⁴ it is reasonable to suggest that the formation of the active species involves the substrate itself. Efforts to monitor the reaction by ^{31}P and ^1H NMR, as well as by MALDI-

MS are underway and will hopefully prove insightful. In the absence of such data, however, it remains premature at this time to speculate as to the reaction mechanism for this transformation.

Revisiting the Oxy-Cope/Ene Reaction

In addition to the discoveries made while attempting to apply the oxy-Cope/Claisen/ene reaction to natural product synthesis, some new ideas were borne while elucidating the reaction mechanism of this tandem process. In particular, questions were raised about the mechanism of racemization observed for the previously reported oxy-Cope/ene reaction.⁵ When enantioenriched substrates **2.96** and **2.97** (98% *ee*) were heated in the microwave to 220 °C in the presence of DBU, their products, **2.96E'** and **2.97E'** were isolated with *ee*'s measuring 93% and 35% respectively (Scheme 5.7). Even more dramatic was the anionic oxy-Cope of these substrates which yielded macrocyclic enones **2.96C'** and **2.97C'** in their racemic form. (For ease of comparison, the notation of intermediates and products mimics that used previously for the oxy-Cope/Claisen/ene reaction – a “'” has been added to distinguish the oxy-Cope/ene intermediates from those of the oxy-Cope/Claisen/ene).

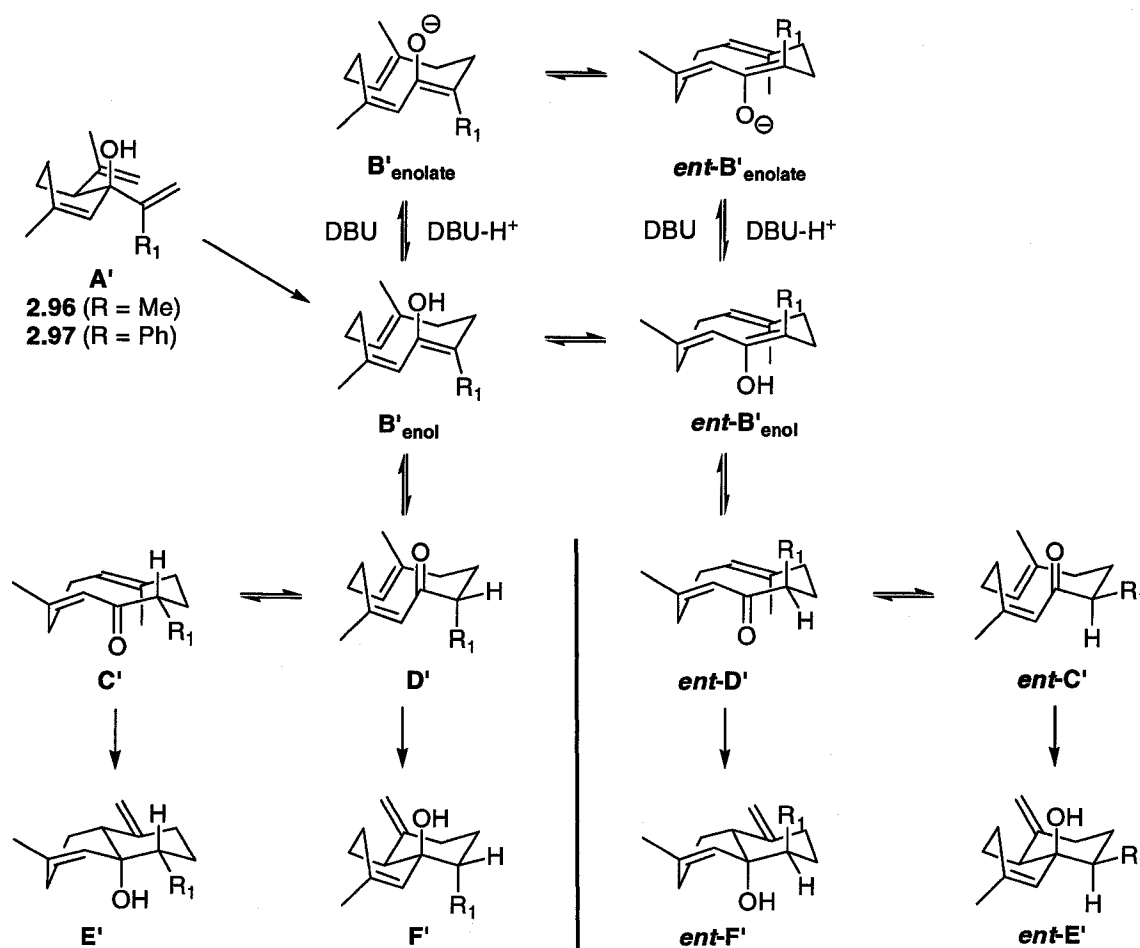
Scheme 5.7 – Loss of *ee* during the oxy-Cope/ene reaction (results of Danny Gauvreau)



At the time, these results were interpreted using the mechanism depicted below in Figure 5.1 Following the oxy-Cope rearrangement of **A'**, intermediate **B'**_{enol} was assumed to undergo a rapid tautomerization to **D'**, relative to a slow inversion of **B'**_{enol} to *ent*-**B'**_{enol}. In

the presence of a strong base, however, deprotonation would lead to the formation of **B'**_{enolate}, thus increasing the opportunity for racemization to occur (now via the inversion of **B'**_{enolate} to *ent*-**B'**_{enolate}). This explanation fit well with the observation that increased amounts of DBU led to further losses in *ee*. Likewise, the total racemization during the anionic oxy-Cope could be seen as resulting from the absence of **B'**_{enol} and its competing tautomerization process.

Figure 5.1 – Original explanation for racemization in the oxy-Cope/ene reaction



Based on studies carried out on the oxy-Cope/Claisen/ene reaction (see Chapter 2), the inversion of both **B'**_{enol} and **B'**_{enolate}, which require a tetrasubstituted olefin to pass through a ten-membered ring, should be a high energy process. The above explanation, however, requires that such a process is relatively facile. In light of this apparent contradiction, we began to explore alternative theories.

One of the first considerations was that the inversion of $\mathbf{B'}_{enolate}$ was somehow lower in energy than that of $\mathbf{B'}_{enol}$. To quantify the corresponding transition states, gas-phase, relative free energies at 473 K were calculated for the relevant intermediates and transition states for substrate **2.96** ($R_1 = \text{Me}$) according to the procedures detailed in Chapter 2. For the anionic species, the molecules were given a molecular charge of -1; the counterion was not included. The results of these calculations are summarized in Table 5.5 and Figures 5.2 and 5.3 below.

For both the enol and enolate intermediates, the first step of the ring inversion ($\mathbf{B-L'}$) was calculated to be relatively low in energy (< 20 kcal/mol) suggesting it occurs quite readily under the reaction conditions. The second step, as expected, was found to be much higher in energy: In the case of the enol ether intermediate, the activation energy for putting the hydroxyl group through the 10-membered ring ($\mathbf{L-ent-B'}_{enol}$) was calculated to be 89 kcal/mol, while the corresponding transition state for the enolate intermediate ($\mathbf{L-ent-B'}_{enolate}$) came in at a slightly lower energy of 80 kcal/mol. Though these numbers do suggest that the inversion of the anionic intermediate is more facile than that of the neutral enol ether, the difference is not substantial and the activation barrier of both remains quite high. Moreover, the inclusion of the enolate counterion could reasonably be assumed to increase the ring inversion's energy barrier by either requiring the ion pair to pass through the ring together (thus increasing its steric bulk) or requiring the ion pair to first separate (at a cost in energy). Consequently, a new hypothesis was pursued.

Table 5.5 – Relative free energies for the neutral and anionic ring inversion of **2.96**

Species (enol)	ΔG^a (kcal/mol)	Species (enolate)	ΔG^b (kcal/mol)
$\mathbf{B'}_{enol}$	0.0	$\mathbf{B'}_{enolate}$	0.0
$\mathbf{B-L'}_{enol}^\ddagger$	18.9	$\mathbf{B-L'}_{enolate}^\ddagger$	17.5
$\mathbf{L'}_{enol}$	4.8	$\mathbf{L'}_{enolate}$	5.3
$\mathbf{L'-ent-B'}_{enol}^\ddagger$	88.8	$\mathbf{L-ent-B'}_{enolate}^\ddagger$	80.0
$\mathbf{ent-B'}_{enol}$	0.0	$\mathbf{ent-B'}_{enolate}$	0.0

^a Gas-phase relative free energies at 473 K calculated at the B3LYP/6-311G** level using DFT, zeroed to $\mathbf{B'}_{enol}$. ^b Gas-phase relative free energies at 473 K calculated at the B3LYP/6-311G*** level using DFT, zeroed to $\mathbf{B'}_{enolate}$.

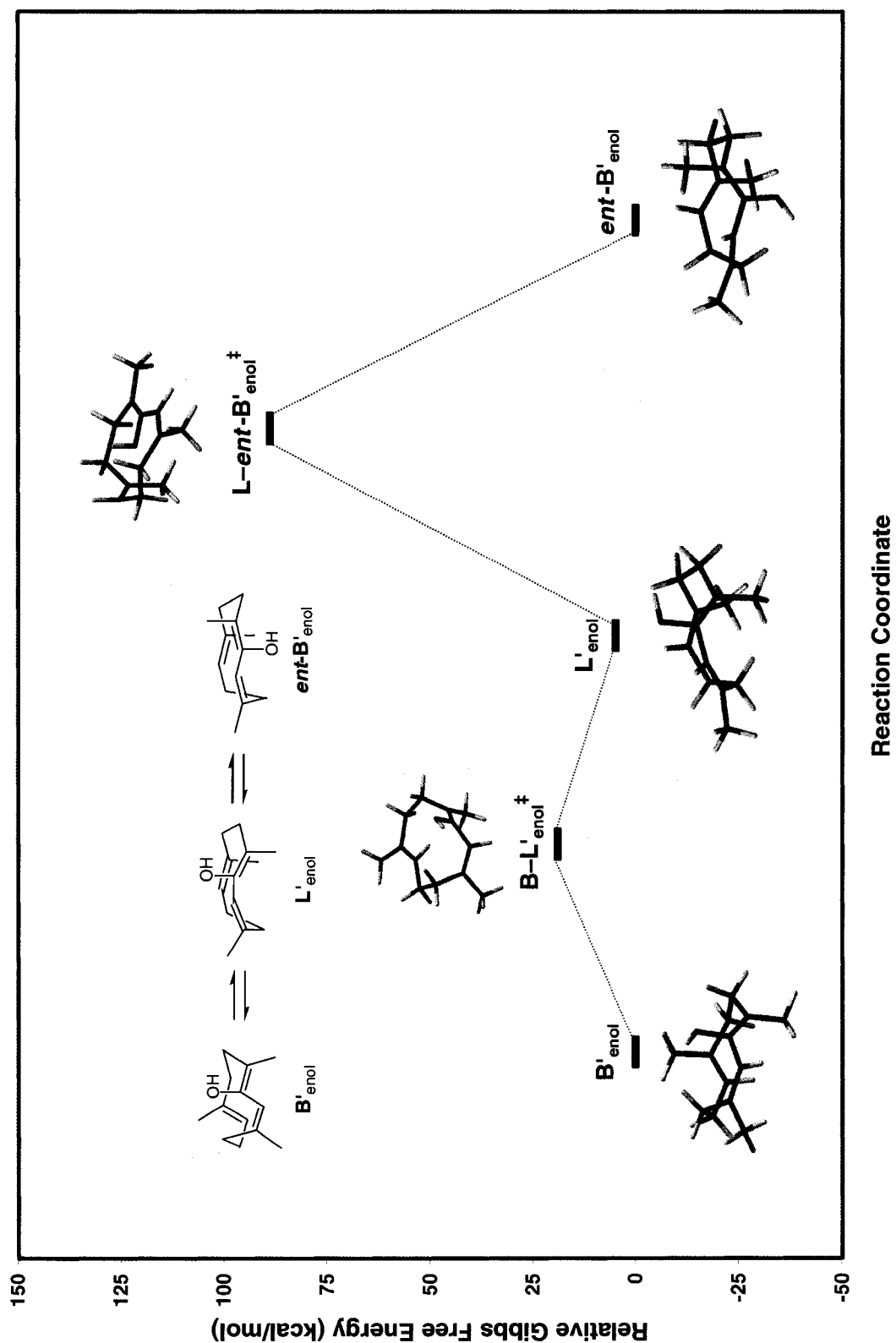
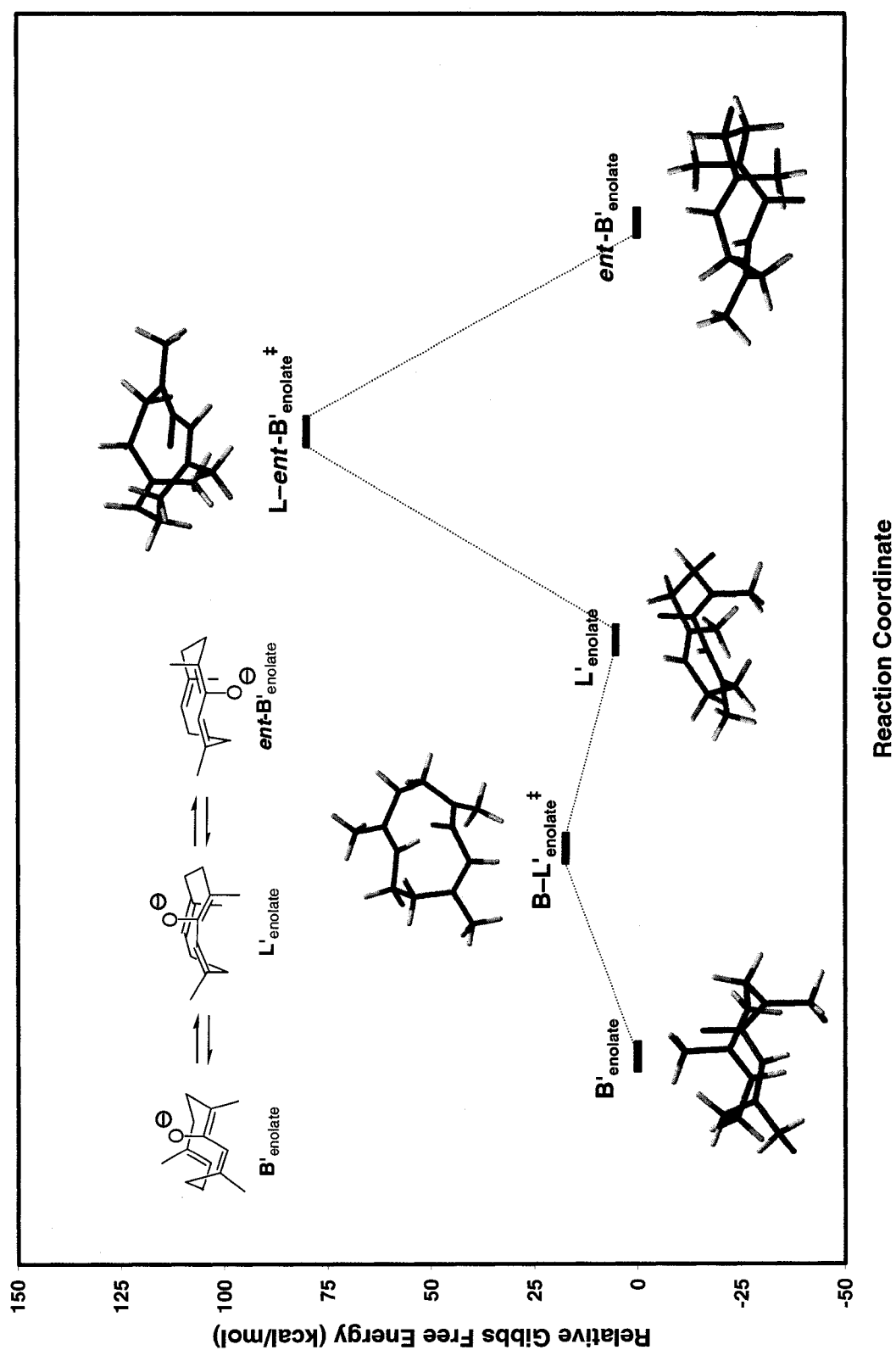
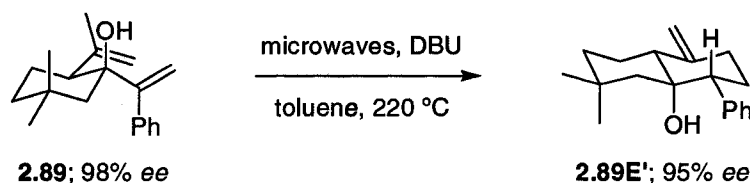
Figure 5.2 – Free energy profile for the neutral ring inversion of **2.96**, zeroed to B'_{enol} 

Figure 5.3 – Free energy profile for the anionic ring inversion of **2.96**, zeroed to B'_{enolate} 

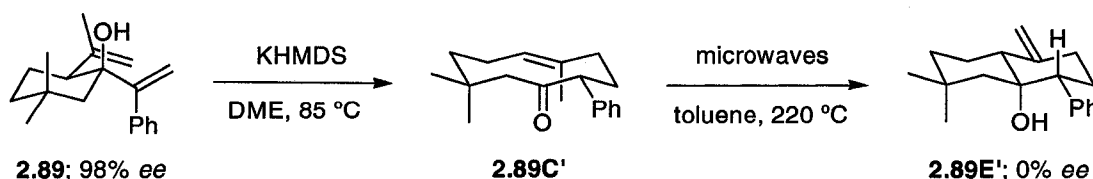
While searching for an alternative explanation for the apparently facile ring inversion of **B'**_{enolate}, a second result of Danny Gauvreau's caught our attention. The thermal oxy-Cope/ene reaction of **2.89** (220 °C in the microwave, 10 equivalents of DBU) was found to give **2.89E'** with near retention of chirality (Scheme 5.8).⁵ In contrast, the analogous substrate, **2.97**, had afforded **2.97E'** in only 35% *ee* (see Scheme 5.7 above). This discrepancy had been interpreted as evidence of a lower ground state energy for **2.89** relative to that of **2.97** (a result of removing the *Z* olefin and liberating ring strain) resulting in a higher activation energy for its ring inversion process. By this argument, the anionic oxy-Cope of this substrate should also proceed with retention of configuration. This experiment, however, was never performed.

Scheme 5.8 – The oxy-Cope/ene reaction of **2.89** (result by Danny Gauvreau)



To evaluate the above argument, **2.89** was treated with KHMDS in refluxing DME for 1 hour (Scheme 5.9). The resulting macrocyclic product exhibited no optical rotation suggesting that racemization may have occurred. Difficulties separating the enantiomers, however, prevented its *ee* from being accurately determined. To circumvent this problem, **2.89C'** was heated in the microwave at 220 °C to afford the ene product, **2.89E'**. Injection into a chiral GC confirmed an *ee* of 0% indicating that, contrary to the originally reported hypothesis, the anionic oxy-Cope rearrangement of **2.89** had proceeded with racemization.⁶

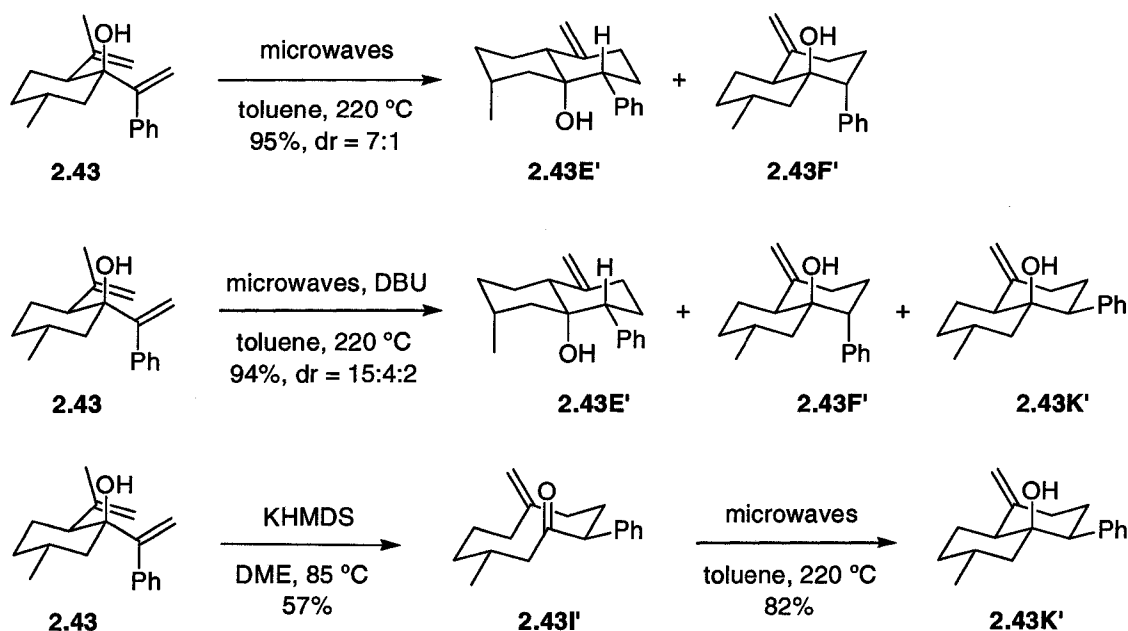
Scheme 5.9 – Investigating the racemization of **2.89** under anionic oxy-Cope conditions



A similar pattern was observed when **2.43** was subjected to three sets of oxy-Cope/ene conditions (Scheme 5.10). Under neutral conditions and in the absence of base, a 7:1 ratio of

diastereomers **2.43E'** and **2.43F'** was obtained. When the reaction was repeated in the presence of DBU (10 equivalents), isomers **2.43E'** and **2.43F'** were isolated, along with a third product, **2.43K'**, in a 15:4:2 ratio. Finally, when the oxy-Cope rearrangement was carried out under anionic conditions, followed by a thermal ene reaction, **2.43K'** became the solely observable product.

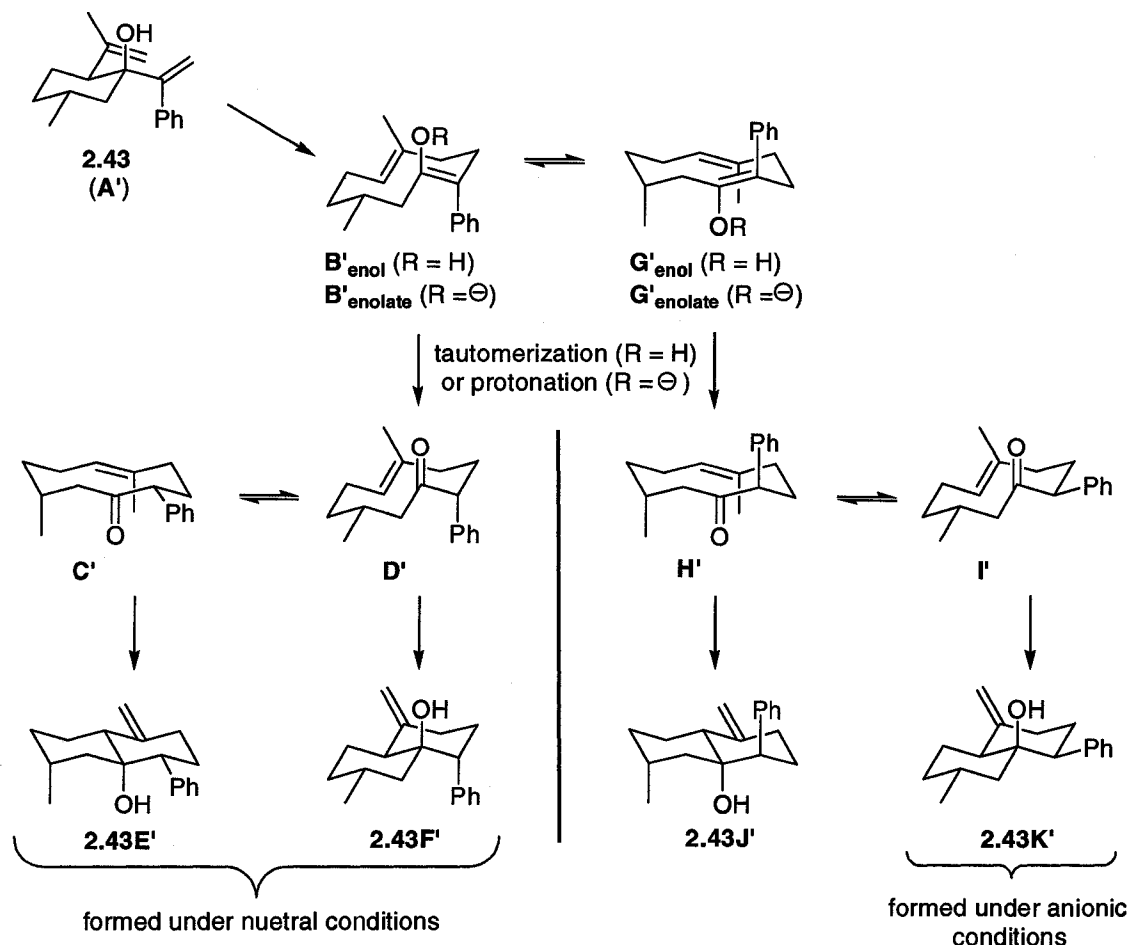
Scheme 5.10 – Anionic versus neutral reaction conditions: altered diastereomeric ratios



While attempting to make sense of these variable product distributions, it became clear that the current mechanistic picture for the reaction of these substrates was problematic, particularly for substrate **2.43**: An analysis of the results using the mechanism depicted in Figure 5.5 requires not only that the ring inversion of **B'**_{enolate} is fast under anionic conditions (against what the above calculations predict), but also that the protonation of **G'**_{enolate} occurs exclusively over that of **B'**_{enolate}. It is this latter condition that is especially difficult to reconcile. Since acid-base reactions are typically fast, low-energy processes, the ratio of protonated intermediates **D'** and **H'** (and thus of products **F'/E'** and **J'/K'**) should reflect the ground-state population distribution of the two enolate intermediates, **B'**_{enolate} and **G'**_{enolate}. Both intuition and molecular mechanics calculations, however, predict that **B'**_{enolate}, with its equatorial methyl group, is more stable than **G'**_{enolate} for this substrate (an energy difference

of 2.3 kcal/mol was found to favour **B'**_{enolate}). Consequently, **D'** should be the major protonated species, not **H'**.

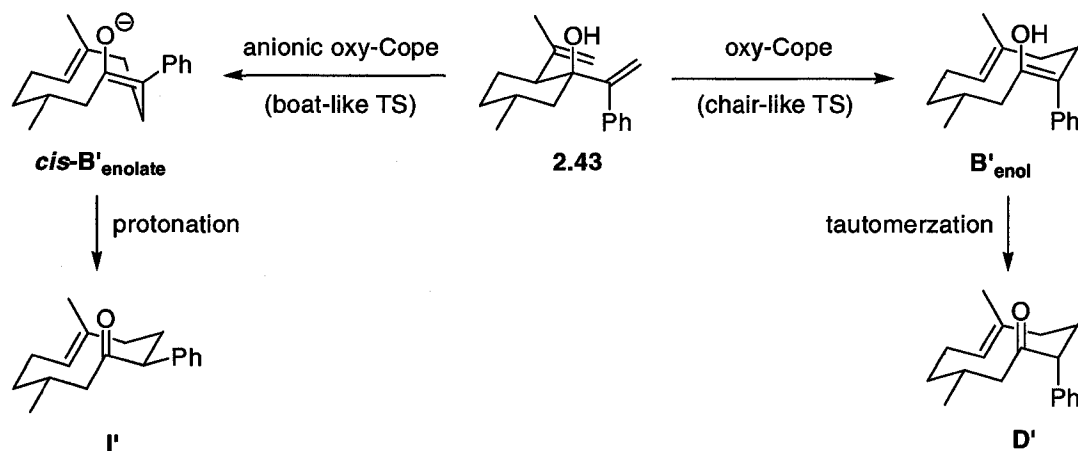
Figure 5.4 – Proposed mechanism of the oxy-Cope/ene reaction of **2.43**



In light of these difficulties, we began to consider alternative means by which **2.43** could be accessing the right-hand side of the reaction mechanism. One possibility which we briefly examined was a preference of the anionic oxy-Cope rearrangement for a boat-like transition state (Figure 5.5). Although the chair-like transition state is typically lower in energy for these reactions, we postulated that a through-space stabilization of the anion by the aromatic ring might be able to invert this preference.⁷ The resulting product of such a transition state would be the intermediate *cis*-**B'**_{enolate}, which, following protonation, would give intermediate **I'** without ever undergoing an inversion of the ring system. While such a scenario could easily explain the exclusive formation of **2.43K'** from **2.43** under anionic

conditions, the same argument would falsely predict that substrates **2.89**, **2.96** and **2.97** should yield optically pure *ent*-**F'** rather the observed equal mixture of **F'** and *ent*-**F'**.⁸

Figure 5.5 – Comparison of chair- and boat-like transition states



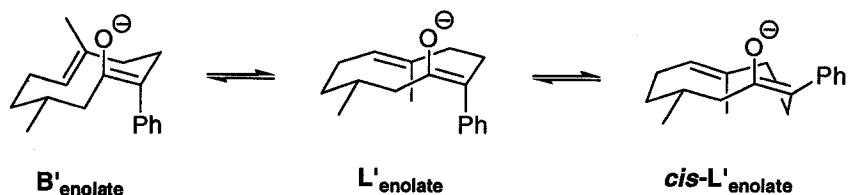
Due to its inability to predict key experimental results, the above theory was necessarily abandoned. Nonetheless, the possibility of a structure such as *cis*-**B'** enolate giving rise to intermediate **I** prompted us to investigate alternative means of generating *cis*-**B'** enolate. To aid in this endeavor, a series of ab initio molecular dynamics simulations was performed on intermediates **B'** enol, **B'** enolate, **G'** enol and **G'** enolate in order to theoretically model and visualize the evolution of our chemical system over time (simulations performed by James Hooper).

The Car-Parrinello molecular dynamics method⁹ was used, as programmed into the publicly available CPMD¹⁰ software package. The structures were first optimized using the default optimizers and the resulting structures were used as the starting geometries of a 30 picosecond molecular dynamics simulation. For both the optimizations and the molecular dynamics simulations, Kohn-Sham DFT¹¹ was used with the gradient-corrected PBE functional,¹² and the norm-conserving Martins-Troullier pseudopotentials¹³ with the Kleinman-Bylander transformation to the fully non-local form¹⁴ to describe the core electronic states. The Kohn-Sham orbitals were expanded in plane waves with an energy cutoff of 60 Ry. A fictitious electronic mass of 400 a.u. was chosen (required by the CPMD program in order to provide a quantum mechanical description of the electronic component of the system) based on a series of initial tests to ensure that the electronic kinetic energy

remained negligible and constant throughout the simulation. In an effort to increase the chances of observing energetically demanding transformations, the system was simulated at a higher temperature than those used in the laboratory. The integration time step was 0.12 femtoseconds and the temperature was kept close to 1100 K by intermittently rescaling the velocities throughout the simulation.

The simulations of species $\mathbf{B'}_{enol}$, $\mathbf{G'}_{enol}$ and $\mathbf{G'}_{enolate}$ revealed nothing out of the ordinary, but a transformation was seen during the simulation of $\mathbf{B'}_{enolate}$ after only 12 picoseconds: through a series of conformational changes, $\mathbf{B'}_{enolate}$ was ultimately converted into $\mathbf{cis-L'}_{enolate}$ (Figure 5.6). Notably, this transformation did not occur with the protonated species, $\mathbf{B'}_{enol}$.

Figure 5.6 – Isomerization of $\mathbf{B'}_{enolate}$ during a Molecular Dynamics calculation

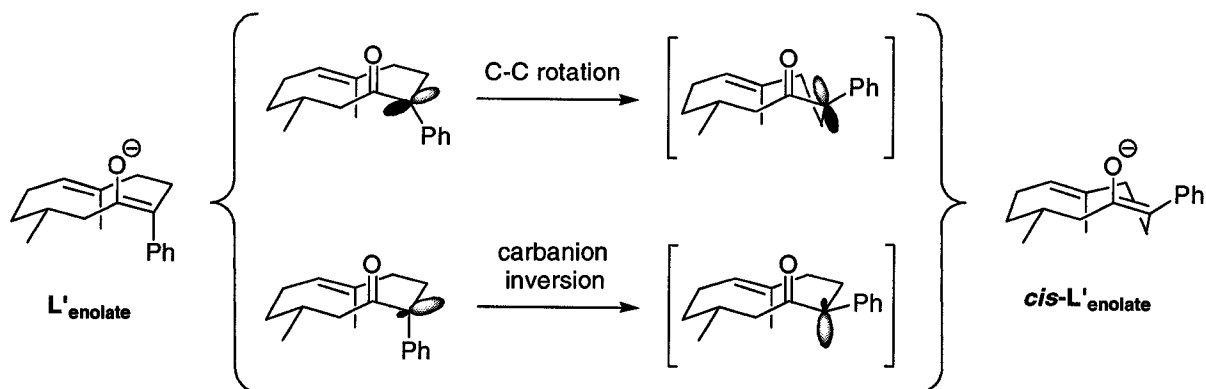


The widely accepted configurational stability of enolate geometries required us to view the above result with a degree of skepticism, particularly in light of the high temperatures used for the molecular dynamics simulations. Nonetheless, we were sufficiently intrigued by this new mode of isomerization that we decided to investigate further.

It was not clear from the molecular dynamics simulations whether the interconversion of $\mathbf{L'}_{enolate}$ to $\mathbf{cis-L'}_{enolate}$ was the result of a simple rotation about the C-C enolate bond, or whether a pyramidal inversion of the carbanion¹⁵ was also involved (Figure 5.7). For either mode of isomerization, however, the negative charge would need to be centred primarily on the alpha carbon of the enolate rather than delocalized into the carbonyl's π system (a scenario which seems increasingly likely given the presence of the alpha phenyl group). In the first case, the corresponding transition state would be expected to have a trigonal planar carbon atom alpha to the carbonyl (owing to conjugation of the anion with the aromatic ring) and a 90° angle between the two π systems. Likewise, a transition state involving a carbanion inversion would also require a trigonal planar alpha carbon, making the two transition states potentially difficult to distinguish in their static form. We thus hoped that by modeling the

transition state through computational means, we could examine the vibrational mode of the imaginary frequency and discern by which mechanism the isomerization was occurring.

Figure 5.7 – Possible modes of enolate isomerization: rotation versus inversion

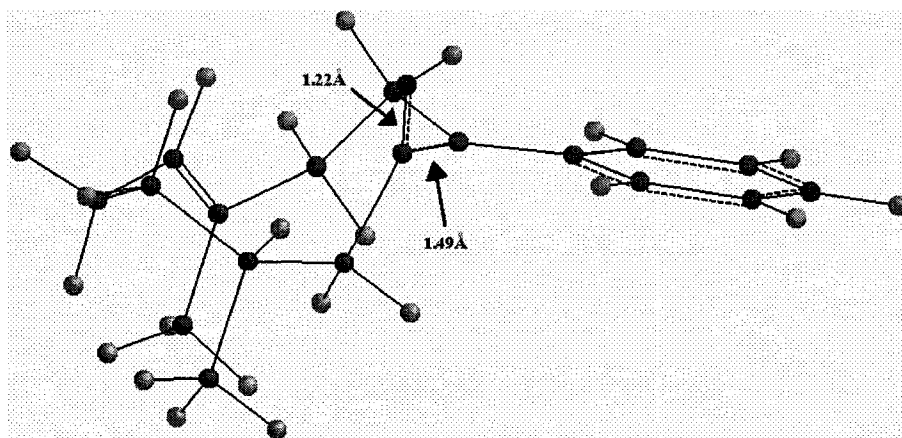


As an initial attempt to locate the transition state, structures taken from the molecular dynamics simulation were optimized (B3LYP/6-31G**⁺⁺) and a frequency calculation performed to determine whether the species were in fact saddle points with one imaginary frequency. By this method, no transition states were found which corresponded to either the C-C rotation or a carbanion inversion.¹⁶ Incrementally changing the dihedral angle between the enolate oxygen and the phenyl group proved more successful and a viable transition state was located (initial result by James Hooper). Using this structure as a template, a Monte-Carlo based conformational search (semi-empirical/PM3 level of theory) was carried out on the backbone of the ring with the coordinates of the enolate atoms frozen, as well as the three atoms bound to the trigonal planar alpha carbon. The three lowest energy structures thus found were then re-optimized at the B3LYP/6-311G**⁺⁺ level of theory, followed by the B3LYP/6-311G**⁺⁺ level of theory.

The newly optimized transition state, **L-cis-L'**_{enolate}, was found to have an activation barrier of 19.7 kcal/mol relative to its starting material, **L'**_{enolate}. An examination of its structure revealed a nearly trigonal planar alpha carbon (puckered slightly by 4.4°) with the carbonyl moiety bisecting the plane at an 80° angle (Figure 5.8). The bond length of the enolate atoms showed a shortening of the C-O bond and a lengthening of the C-C bond (C-O: 1.22 Å versus 1.26 Å; C-C: 1.49 Å versus 1.41 Å)¹⁷ relative to **L'**_{enolate} suggesting a change in bond order. In addition to these static parameters, the eigenvector of the imaginary

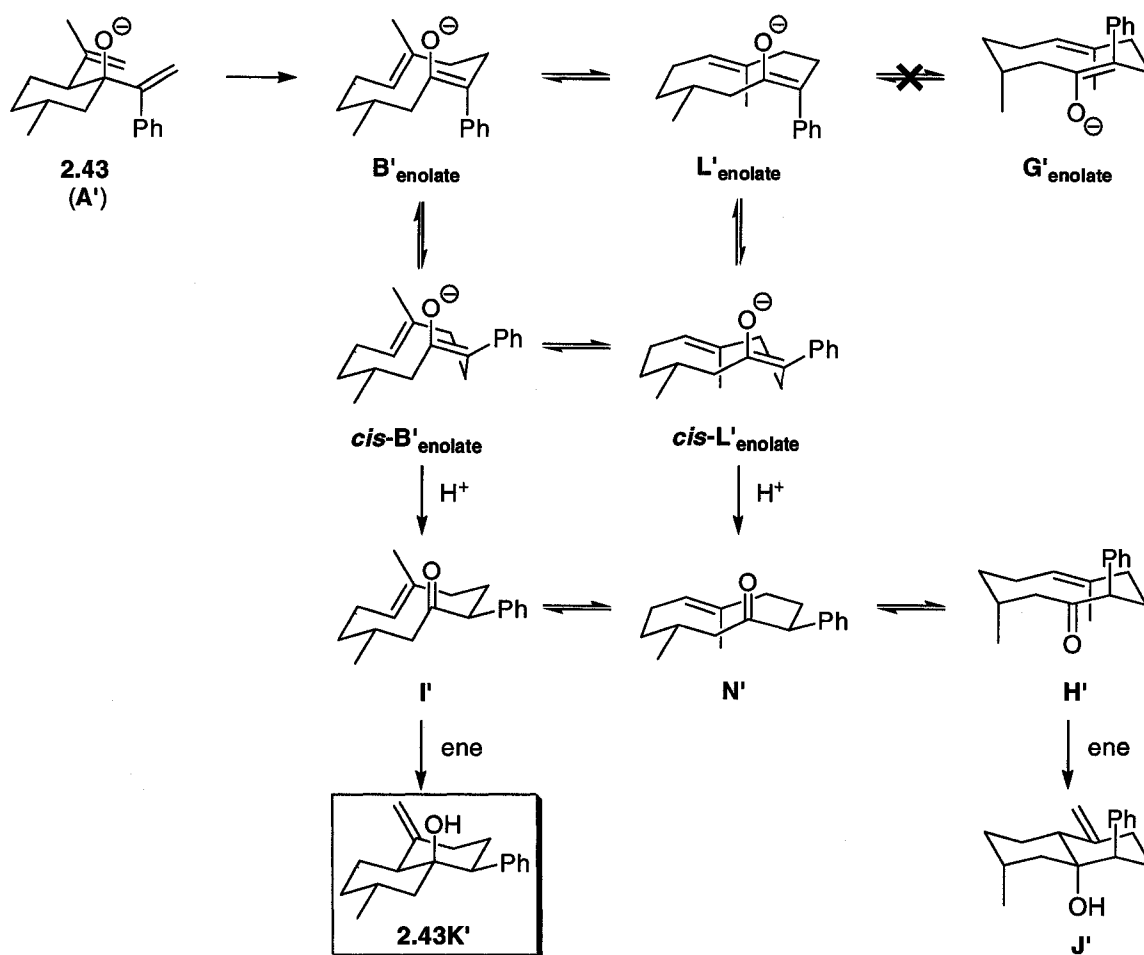
frequency was examined. If a carbanion inversion were taking place, one would expect to see a change in the degree and orientation of the “puckering” of the near-trigonal planar alpha carbon. Unfortunately, when the frequency was analyzed, no discernable movement could be elucidated. An IRC of the transition state, however, suggested that the alpha carbon remains nearly planar throughout the isomerization process. From this result, it seems that the olefin isomerization is likely a result of C-C rotation alone.

Figure 5.8 – Calculated transition state for enolate isomerization, L -*cis*- L' _{enolate}



With a viable transition state in hand, we set out to evaluate the relative energetics of the remaining processes in order to assess the feasibility of this pathway (Figure 5.9). In particular, we needed to evaluate the relative energies of the intermediates: in order for the exclusive formation of K' to be predicted, equilibrating conditions between the anionic species would need to favour either *cis*- B' _{enolate} or *cis*- L' _{enolate} so as to ensure their preferential protonation upon acidic quench.

Figure 5.9 – New hypothesis for the anionic oxy-Cope/ene reaction mechanism



Following the procedures detailed in Chapter 2, gas-phase, relative free energies were calculated at 358 K (85 °C) for the anionic intermediates and transition states depicted in Figure 5.9 above. For the isomerization of **L' enolate** to **cis-L' enolate**, an analogous procedure to that described above was used to locate the transition state. The results of these calculations are summarized in Table 5.6 and Figures 5.10 and 5.11 below.

Table 5.6 – Relative free energies for the proposed isomerization mechanism of **2.43**

Species	ΔG^a (kcal/mol)
B' _{enolate}	0.0
B-L' _{enolate} [‡]	15.3
L' _{enolate}	4.5
L-G' _{enolate} [‡]	74.3
G' _{enolate}	2.3
B-cis-B' _{enolate} [‡]	19.0
cis-B' _{enolate}	0.4
cis-B-cis-L' _{enolate} [‡]	12.9
cis-L' _{enolate}	-0.4
L-cis-L' _{enolate} [‡]	24.2

^a Gas-phase relative free energies at 358 K calculated at the B3LYP/6-311G*** level of theory using DFT, zeroed to **B'**_{enolate}

Comparing the transition state energy for the second step of the ring inversion, **L-G'**_{enolate} (74.3 kcal/mol, Figure 5.10) with that of the olefin isomerization transition states (19.0 and 24.2 kcal/mol, Figure 5.11), it becomes clear that the isomerization of **B'**_{enolate} and **L'**_{enolate} should be the favoured pathway. In addition to being lower in energy, this mechanism predicts the establishment of an equilibrium between the four enolates with **cis-L'**_{enolate} as the major species. Protonation of **cis-L'**_{enolate} would give **N'**, which in turn would afford the observed product, **2.43K'**. While this overall thermodynamic picture fits with the experimental results, the 0.43 kcal/mol energy difference favouring **cis-L'**_{enolate} is insufficient to explain the exclusive formation of **K'**. Rather, the ground state energies obtained predict a population distribution of 29.2%, 0.1%, 17.3% and 53.4% for intermediates **B'**_{enolate}, **L'**_{enolate}, **cis-B'**_{enolate}, and **cis-L'**_{enolate}, respectively. While experimental error inherent to the method could account for this discrepancy, more definitive proof to support this pathway was desired.

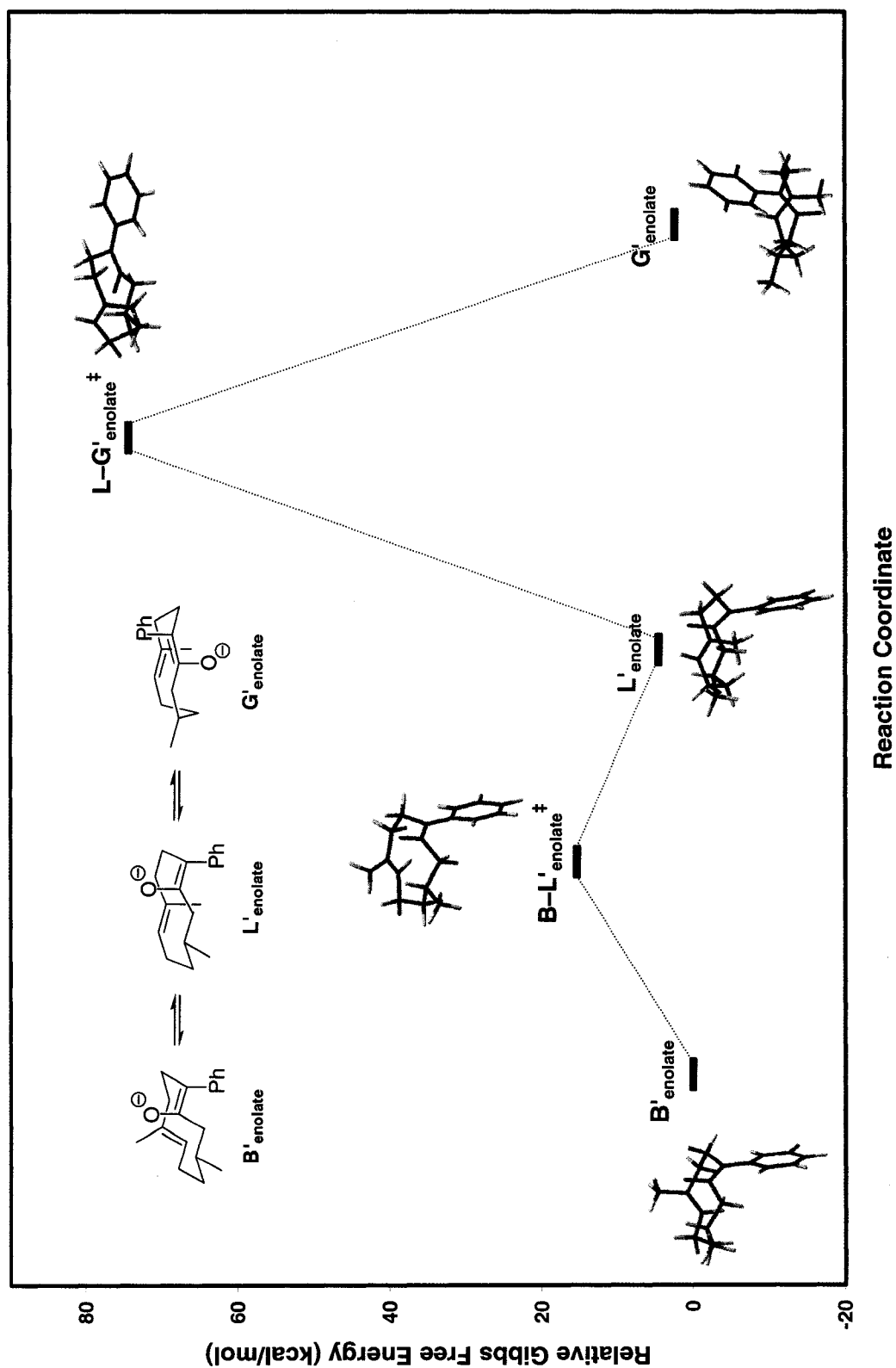
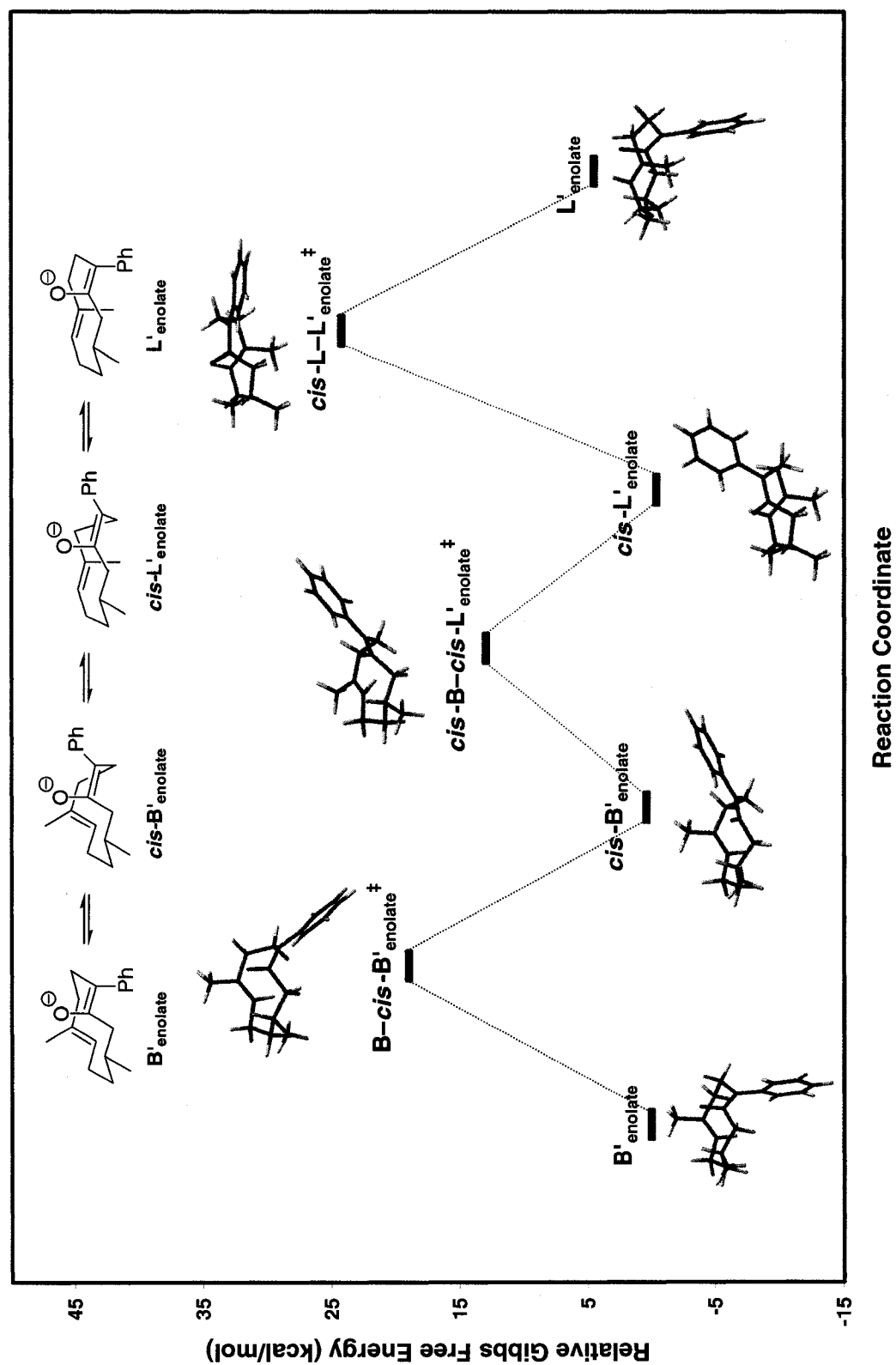
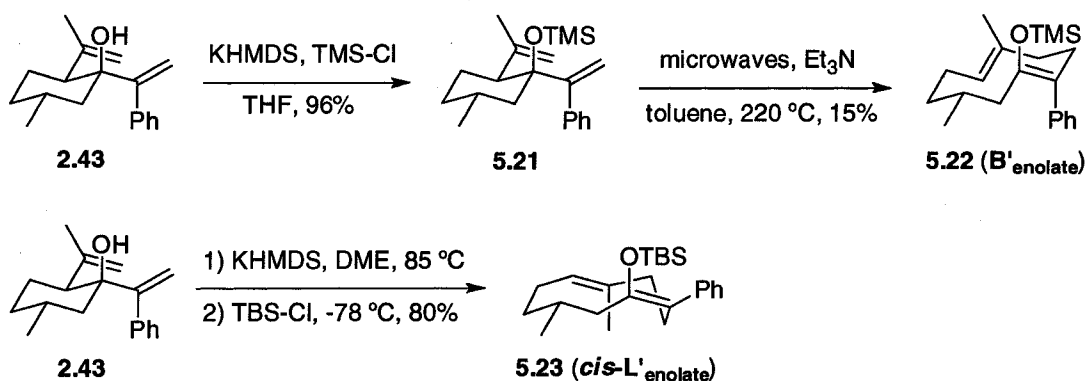
Figure 5.10 – Free energy profile for the anionic oxy-Cope of **2.43**: ring inversion

Figure 5.11 – Free energy profile for the anionic oxy-Cope of 2.43: enolate isomerization



To this end, a series of experiments was carried out on substrate **2.43** by fellow graduate student Steve Arns (Scheme 5.11). In the first case, the tertiary alcohol of **2.43** was protected with a TMS group prior to being subjected to a thermal oxy-Cope rearrangement. Silyl enol ether **5.22** (corresponding to **B'**_{enolate}) was isolated in 15% yield along with 75% of the unreacted starting material, **5.21**.¹⁸ A series of NOE's established a *trans* relationship between the -OTMS and phenyl groups as shown, as well as the orientation of the second double bond. In contrast, when the anionic oxy-Cope of **2.43** was quenched with TBS-Cl, the product was found to have a *cis* geometry between the -OTBS and phenyl groups, suggesting that under these reaction conditions, isomerization of the enolate olefin can and does occur.¹⁹

Scheme 5.11 – Trapping the *E* and *Z* enolates (results by Steve Arns)



From the above experimental and theoretical results, it seems increasingly likely that the mechanism of the anionic oxy-Cope of **2.43** is as illustrated in Figure 5.9 above. It follows that an analogous pathway could be responsible for the racemization of substrates **2.89**, **2.96** and **2.97** under anionic conditions. Theoretical and experimental results to support this assertion are currently under investigation.

References

- ¹ For key reviews on the non-metathetic behavior of Grubbs' catalysts, see (a) Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, 9, 1258. (b) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865.

- ² Several reports of Grubbs' first and second generation catalysts acting as transfer hydrogenation catalysts in the oxidation of alcohols to ketones/aldehydes have been noted. For leading references, see: (a) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.
- ³ Dinger, M. B.; Mol, J. *Organometallics* **2003**, *22*, 1089.
- ⁴ It should be noted that complex **5.20** was found to be an effective precatalyst for the isomerization of 1-octene to 2-octene. See reference 3 above.
- ⁵ Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2004**, *70*, 1382.
- ⁶ It should be noted that the presence of the stereogenic centre in intermediate **2.89C'** ensures that ring inversion during the ene reaction could only give rise to its diastereomer, not its enantiomer. Thus, the observed racemization can be assumed to have occurred during the anionic oxy-Cope reaction.
- ⁷ Though anion- π interactions might be expected to be repulsive in nature, both theoretical and experimental studies have indicated that such interactions can be favourable. For leading references, see (a) Schottel, B.L.; Chifotides, H. T.; Shatruk, M.; Chouai, A.; Perez, L. M.; Basca, J.; Dunbar, K. R. *J. Am. Chem. Soc.* **2006**, *128*, 5895. (b) Casellas, H.; Massera, C.; Buda, F.; Gamez, P.; Reedijk, J. *New. J. Chem.* **2006**, *30*, 1561. (c) Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2289.
- ⁸ Preliminary calculations did show that the energy difference between the boat- and chair-like transition states of the anionic oxy-Cope of **2.43A'** is significantly reduced compared to that of the neutral reaction (~ 2 kcal/mol difference between the transition states of the anionic oxy-Cope reaction versus ~ 8 kcal/mol for the oxy-Cope). However, the chair-like transition state was still favoured overall in both cases.
- ⁹ Car, R.; Parinello, M. *Phys. Rev. Lett.* **1985**, *55*, 2471.
- ¹⁰ *CPMD, Version 3.9.2*, Copyright IBM Corp. 1990-2001; Copyright MPI für Festkörperforschung. Stuttgart, 1997-2005. <http://www.cpmd.org>.

- ¹¹ (a) Hohenburg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864. (b) Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133.
- ¹² (a) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865. (b) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1997**, *78*, 1396.
- ¹³ Trouillier, N.; Martins, J. L. *Phys. Rev. B* **1991**, *43*, 1993.
- ¹⁴ Kleinman, L.; Bylander, D. M. *Phys. Rev. Lett.* **1982**, *48*, 1425.
- ¹⁵ Though much less common than the pyramidal inversion of nitrogen, carbanion inversions are known. For an indepth review, see: (a) Lambert, J. B. *Top. Stereochem.* **1971**, *6*, 19. For additional references, see (b) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709. (c) Ellison, G. B.; Engelking, P. C.; Lineberger, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 2556. (d) Rauk, A.; Andose, J. D.; Frick, W. G.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1971**, *93*, 6507.
- ¹⁶ In most cases, the transition states optimized to give a conformer of **L'**_{enolate}. In some instances, saddle points were found which corresponded to a rotating methyl group.
- ¹⁷ Typical bond lengths (Å): C_{sp2}-C_{sp2}: 1.43-1.48; C_{sp2}=C_{sp2}: 1.29-1.36; C_{sp2}-O: 1.29-1.41; C_{sp2}=O: 1.19-1.26. Values taken from "Bond lengths in crystalline organic compounds", in *CRC Handbook of Chemistry and Physics, Internet Version 2007, (87th Edition)*, Lide, D. R. Ed., Taylor and Francis, Boca Ratan, FL.
- ¹⁸ Re-subjecting the product to the reaction conditions gave back a 5:1 ratio of starting material and the silyl enol ether confirming the existence of an equilibrium between these two compounds.
- ¹⁹ Note that in this case, the orientation of the second double bond was not determined. It is possible that the actual structure corresponds to **cis-B'**_{enolate} rather than **cis-L'**_{enolate} as shown.

6

Summary

Summary of Results

The body of this thesis has been divided between two pursuits: the development of a novel tandem pericyclic reaction cascade, and its application to total synthesis. Building on the oxy-Cope/ene reaction developed previously in our laboratory, we successfully expanded this reaction sequence by functionalizing the tertiary alcohol of the starting 1,2-vinylcyclohexanols. The resulting oxy-Cope/Claisen/ene reaction was found to be a rapid and efficient means of generating highly functionalized decalin cores bearing up to four contiguous stereogenic centres, including an all carbon quaternary centre. In addition to demonstrating the broad scope of this reaction (> 25 examples), we devoted a significant amount of time to understanding the origins of the observed diastereoselectivity. Through a combination of theoretical and experimental means, we were able to uncover the requirements for achieving good stereochemical control ($R_1 \neq H$) and propose a means of improving poorly selective reactions by the introduction of a remote stereocentre for conformational control over the macrocyclic intermediates.

Having successfully established the oxy-Cope/Claisen/ene as a viable pericyclic reaction cascade, we turned our attention to its application in total synthesis. Initially, wiedemannic acid was chosen as our target. After successfully completing a model study for the preparation of a closely related analogue, we were forced to conclude that the reported structure for the known compound had been mis-assigned. Consequently, a new natural product was targeted. The fungal metabolite LL-S491 β contained a similar core structure to that found in wiedemannic acid, however, additional functionality and a third all-carbon quaternary centre made it considerably more challenging. Several unique routes to this molecule were developed, leading to some advanced intermediates, however, the final product remains to be synthesized.

In addition to pursuing the two primary aims of this thesis, several unexpected findings were explored along the way. From our work towards the total synthesis of LL-S491 β , a novel lactonization was observed to be mediated by Grubbs' first generation catalyst in the presence of an aerobic environment. While the reaction remains non-catalytic, the unique reactivity observed for this system is noteworthy in itself. Efforts to elucidate the reaction mechanism and generate catalytic turnover are underway.

Finally, as a result of the mechanistic studies carried out on the oxy-Cope/Claisen/ene reaction, questions were raised about the interpretation of previously reported results from the study of the oxy-Cope/ene reaction. Additional experiments confirmed that the accepted mechanistic picture was flawed. Theoretical studies suggested a highly unusual enolate isomerization pathway which has since been confirmed by Steve Arns through experimental means. The breadth of this unique process is currently being explored.

Publicatlons Resulting from this Work

Sauer, E. L. O.; Barriault, L. **"Highly Efficient Transfer of Chirality from Macrocyclic Conformation in the Tandem Oxy-Cope/Claisen/Ene Reaction."** *J. Am. Chem. Soc.* **2004**, *126*, 8569.

Sauer, E. L. O., Barriault, L. **"Studies Toward the Total Synthesis of Wiedemannic Acid."** *Org. Lett.* **2004**, *6*, 3329.

Sauer, E. L. O.; Hooper, J.; Woo, T.; Barriault, L. **"The Origin of Diastereoselectivity in the Tandem Oxy-Cope/Claisen/Ene Reaction: Experimental and Theoretical Studies of the Ring Inversion Mechanism."** *J. Am. Chem. Soc.* **2007**, *129*, 2112.

Sauer, E. L. O.; Barriault, L. **"Unexpected Lactonization of Alkenols Using Grubbs' First Generation Catalyst Under an Aerobic Atmosphere."** *Manuscript in preparation.*

Sauer, E. L. O.; Hooper, J.; Woo, T.; Barriault, L. **"Non-Rigid Enolate Geometries: Olefin Isomerization During an Anionic Oxy-Cope Rearrangement."** *Manuscript in preparation.*

Presentations of this Work

Oral: "The Origin of Diastereoselectivity in the Oxy-Cope/Claisen/Ene Reaction: Experimental and Theoretical Results" **18th Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry**, London, Ontario, November 2006.

Poster: "New Mechanistic Insights into the Tandem Oxy-Cope/Claisen/Ene Reaction." **University of Ottawa Synthesis Day**, Ottawa, Ontario, August 2006.

Poster: "The Tandem Oxy-Cope/Claisen/Ene Reaction: New Mechanistic Insights and Applications to Total Synthesis." **Pacificchem**, Honolulu, Hawaii, December 2005.

Poster: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Application to the Total Synthesis of Wiedemannic Acid and LL-S491 β ." **University of Ottawa Synthesis Day**, Ottawa, Ontario, June 2005.

Poster: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Application to the Total Synthesis of Wiedemannic Acid and LL-S491 β ." **4th Symposium International en Synthèse Organique de L'Université de Montréal**, Montreal, Quebec, April 2005.

Poster: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Scope, Limitations, and Application to the Total Synthesis of Wiedemannic Acid and LL-S491 β ." **16th Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry**, Aylmer, Quebec, November 2004.

Poster: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Scope, Limitations and Application to the Total synthesis of Wiedemannic Acid and LL-S491B." **15th IUPAC International Conference on Organic Synthesis**, Nagoya, Japan, August 2004.

Oral: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Application to the Total Synthesis of Wiedemannic Acid." **1st Banff Symposium on Organic Chemistry**, Banff, Alberta, November 2003.

Oral: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Application to the Total Synthesis of Wiedemannic Acid." **39th IUPAC Congress and 86th Conference of the Canadian Society for Chemistry**, Ottawa, Ontario, August 2003.

Poster: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Application to the Total Synthesis of Wiedemannic Acid." **Ottawa-Carleton Chemistry Institute Day**, Ottawa, Ontario, April 2003.

Poster: "A Tandem Oxy-Cope/Claisen/Ene Reaction: Application to the Total Synthesis of Wiedemannic Acid." **University of Ottawa Synthesis Day**, Ottawa, Ontario, April 2003.

7

Experimental

General Experimental Considerations

Unless otherwise indicated, all reactions were performed under either an argon or nitrogen atmosphere in flame-dried glassware equipped with a Teflon coated magnetic stir bar and a rubber septum. Where no temperature was specified, the reactions were run at ambient temperature (23 °C). Reagent quantities (mmol) were calculated based on their reported purities.

Anhydrous solvents and some liquid reagents were freshly distilled prior to use as listed in Table 7.1 below. *n*-Butyllithium and *tert*-butyllithium were titrated using 2,6-di-*tert*-butyl-4-methylphenol and fluorene. Grignard reagents were titrated according to Love's protocol.¹ The following reagents were prepared according to literature procedures: Dess-Martin periodinane;² Diazomethane;³ Jones' reagent;⁴ tetrakis(triphenylphosphine) palladium (0);⁵ Petasis' reagent.⁶ Benzoquinone was recrystallized from chloroform. *N*-chlorosuccinimide was recrystallized from acetic acid.⁷ Cerium (III) chloride hydrate was dried according to Dimitrov's procedure to afford anhydrous cerium chloride.⁸ Copper (I) iodide was purified from a saturated solution of potassium iodide, treated with activated

charcoal and filtered over celite, washed with water, acetone and ether, and dried overnight under high vacuum in a desiccator containing phosphorus pentoxide.⁹ 18-Crown-6 was dried overnight under high vacuum in a desiccator containing phosphorus pentoxide. Methyl triphenylphosphonium iodide was prepared from triphenylphosphine and methyl iodide in benzene. *p*-Toluenesulphonic acid was recrystallized from ethyl acetate. All other commercial reagents were used as received.

Table 7.1 – Drying agent used for distilling common solvents and reagents

Solvent or reagent	Drying agent
Acetonitrile	Calcium hydride
Allyl bromide	Calcium hydride
1,2-Dibromoethane	Calcium hydride
1,8-Diazabicyclo(5.4.0)undec-7-ene	Calcium hydride
Dichloroethane	Calcium hydride
Dichloromethane	Calcium hydride
<i>N,N</i> -Diisopropylamine	Calcium hydride
Diethyl ether	LiAlH ₄ , then sodium/benzophenone
1,2-Dimethoxyethane	Sodium/benzophenone
Hexamethylphosphoramide	Calcium hydride (2x)
Methanol	refluxed over Mg turnings with a trace of I ₂
Pyridine	Calcium hydride
Tetrahydrofuran	Sodium/benzophenone
Triethylamine	Calcium hydride
Trimethylsilyl chloride	Calcium hydride
Toluene	Calcium hydride

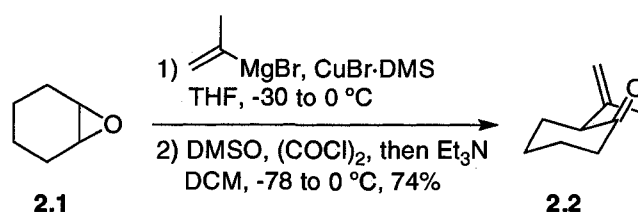
Microwave reactions were performed using a CEM Model ESP-1500 Plus microwave oven equipped with a pressure monitoring device and an EST-300 Plus fiber optic temperature probe. The reaction vessel was a quartz tube to which was added the reaction mixture as well as a carboflonTM to aid in the absorption of microwave radiation.

Reactions were monitored by TLC analysis using glass plates pre-coated (250 μ m thickness) with ultra pure silica gel (60Å, SiliCycle). TLC plates were viewed using UV light

and stained with either *p*-anisaldehyde, potassium permanganate, or phosphomolybdic acid staining solutions. Flash chromatography was carried out on 230-400 mesh silica gel (60Å, SiliCycle). When mentioned, triethylamine was added to the slurry of silica gel until a persistent odor was maintained. Once the basified slurry was loaded on the column, an equal volume of eluent (without triethylamine) was passed through prior to substrate loading.

^1H , ^{13}C NMR, ^{19}F and ^{31}P spectra were recorded on either Bruker Avance 300 MHz, Bruker Avance 500 MHz, Bruker AMX 500 or Varian INOVA 500 MHz spectrometers in the specified deuterated solvents. IR spectra were recorded on a Bomen Michaelson 100 FT-IR spectrometer. HRMS spectra were obtained using a Kratos Analytical Concept spectrometer. Melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus. Optical rotations were measured with a Perkins-Elmer model 241 polarimeter. Enantiomeric excesses were determined either by HPLC or GLC, as indicated: GLC was performed on an Agilent 6890 Series gas chromatograph equipped with a split-mode capillary injection system and a flame ionization detector using Agilent/J&W CycloSil-B column; HPLC was performed on a Waters 2690 HPLC equipped with a ChiralPak AS (4.6 x 250 mm) chiral column and a Waters 996 photodiode array detector at isocratic elution.

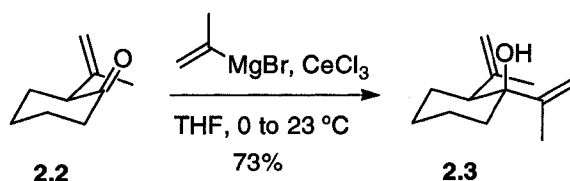
Experimental Procedures and Characterization Data



(±)-2-Isopropenyl-cyclohexanone (2.2):

A suspension of copper (I) bromide-dimethyl sulfide complex (1.05 g, 5.13 mmol) in 140 mL of tetrahydrofuran was cooled to -30 °C. Isopropenylmagnesium bromide (133 mL of a 0.5 M solution in tetrahydrofuran, 66.5 mmol) was added slowly during which time the reaction went from tan to dark orange. After 15 minutes, cyclohexene oxide (5.15 mL, 50.9 mmol) was added and the reaction was warmed gradually to 0 °C over a period of 2 hours.

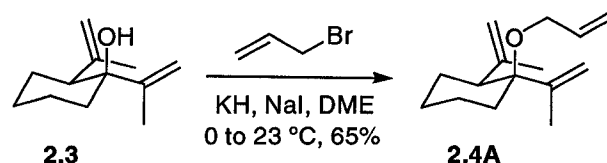
The reaction was quenched with a saturated aqueous solution of ammonium chloride and the resulting bright blue aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate, filtered and concentrated to give a yellow oil which was used directly without further purification. A solution of oxalyl chloride (5.27 mL, 60.4 mmol) in 200 mL of dichloromethane was cooled to -78 °C. Dimethylsulfoxide (8.57 mL, 121 mmol) was added slowly and the reaction was stirred for 20 minutes. (*Note: large amounts of gas are evolved during the addition of dimethylsulfoxide. Adequate venting of the reaction vessel must be ensured*). A solution of the unpurified alcohol (50.9 mmol, maximum) in 10 mL of dichloromethane was cannulated into the reaction mixture and the resulting solution stirred at -78 °C for another 1.5 hours. Triethylamine (35.9 mL, 258 mmol) was added slowly and the thick, pale-yellow mixture was warmed to 0 °C for 1 hour. The now pale orange reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes → 15% ethyl acetate/hexanes) yielded 5.21 g (74%) of ketone **2.2** as a yellow oil. Spectral data for this compound was in agreement with that reported previously: Holt, D. A. *Tetrahedron Lett.* **1981**, 22, 2243.



(±)-(1S,2S)-1,2-Diisopropenyl-cyclohexanol (2.3):

Cold tetrahydrofuran (4 mL) was added to a flask containing anhydrous cerium (III) chloride (245 mg, 0.995 mmol). After stirring for 2 hours, a solution of ketone **2.2** (94 mg, 0.68 mmol) in an additional 2 mL of tetrahydrofuran was added and the reaction was stirred for another hour before cooling to 0 °C. Isopropenylmagnesium bromide (4.0 mL of a 0.5 M solution in tetrahydrofuran, 2.0 mmol) was added and the reaction was warmed to ambient temperature. After 3 hours, an additional 4.0 mL of the Grignard was added (2.0 mmol). After another hour, the reaction was quenched with a saturated aqueous solution of

ammonium chloride and the aqueous phase extracted three times with diethyl ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes $\rightarrow$ 2.5% ethyl acetate/hexanes) yielded 89 mg (73%) of **2.3** as a light yellow oil. Spectral data for this compound was in agreement with that reported previously: Warrington, J. M. Ph.D. Thesis, University of Ottawa, Ottawa, Canada, 2005.



(±)-(1S,2S)-1-Allyloxy-1,2-diisopropenyl-cyclohexane (2.4A):

Sodium iodide (3 mg, 0.02 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (50 mg of a 30% suspension in mineral oil, 0.37 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (0.5 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated **2.3** (9 mg, 0.05 mmol) as a solution in another 0.5 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (30.0 μ L, 0.347 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 7 mg of a colourless oil (65%).

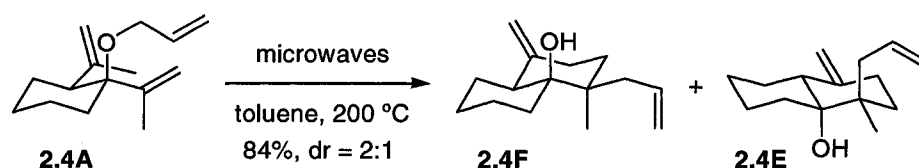
Data for 2.4A:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.96-5.84 (m, 1H), 5.33 (dddd, $J = 17.2, 2.0, 2.0, 2.0$ Hz, 1H), 5.08 (dddd, $J = 10.5, 1.8, 1.8, 1.8$ Hz, 1H), 4.85 (dq, $J = 1.6, 1.6$ Hz, 1H), 4.79 (d, $J = 2.0$ Hz, 1H), 4.63 (dq, $J = 1.4, 1.4$ Hz, 1H), 4.59 (d, $J = 2.6$ Hz, 1H), 3.86-3.72 (m, 2H), 2.11-1.96 (m, 2H), 1.89-1.84 (m, 1H), 1.79-1.74 (m, 1H), 1.74 (s, 3H), 1.65 (s, 3H), 1.60-1.21 (m, 5H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.50, 146.22, 135.74, 114.26, 111.84, 111.43, 82.04, 62.20, 54.21, 31.33, 27.45, 26.32, 21.64, 21.60, 20.45.

IR (neat, cm^{-1} , ν): 3078 (w), 2926 (s), 2855 (s), 1639 (w), 1449 (m), 1376 (w), 1260 (w), 1206 (w), 1152 (m), 1064 (s), 1025 (s).

HRMS (EI, m/z): calculated 220.1827 for $[\text{M}]^+$, found 220.1841.



(±)-(4S,4aS,8aS)-4-Allyl-4-methyl-1-methylene-octahydro-naphthalen-4a-ol (2.4F) and (±)-(4R,4aS,8aS)-4-Allyl-4-methyl-1-methylene-octahydro-naphthalen-4a-ol (2.4E):

A solution of **2.4A** (61 mg, 0.28 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour the reaction was concentrated and the crude material injected into a GC. A mixture of isomers in a 2:1 ratio was detected. Purification by silica gel flash chromatography (100% hexanes → 1% ethyl acetate/hexanes) yielded 34 mg of **2.4F** and 17 mg of **2.4E** (84% combined yield), both as clear colourless oils.

Data for **2.4F** (major isomer):

^1H NMR (CDCl_3 , 500 MHz, δ): 5.83-5.76 (m, 1H), 5.00-4.99 (m, 1H), 4.97-4.96 (m, 1H), 4.86-4.85 (m, 1H), 4.62 (s, 1H), 2.35-2.31 (m, 1H), 2.29 (dd, $J = 13.2, 7.9$ Hz, 1H), 2.19-2.15 (m, 2H), 2.08 (dd, $J = 13.4, 7.5$ Hz, 1H), 1.80-1.71 (m, 2H), 1.58-1.48 (m, 5H), 1.42-1.33 (m, 3H), 1.22-1.16 (m, 1H), 1.05 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 150.61, 136.18, 116.85, 108.60, 76.37, 44.24, 41.05, 40.82, 35.56, 32.36, 30.14, 25.62, 24.66, 21.57, 20.43.

IR (neat, cm^{-1} , ν): 3567 (w), 3075 (w), 2933 (s), 2859 (m), 1640 (w), 1448 (m), 1286 (w), 1235 (w), 1090 (w).

HRMS (EI, m/z): calculated 220.1827 for $[\text{M}]^+$, found 220.1809.

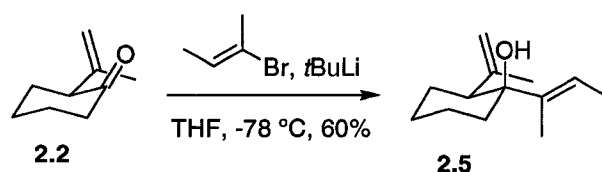
Data for **2.4E** (minor isomer):

^1H NMR (CDCl_3 , 300 MHz, δ): 5.86-5.72 (m, 1H), 5.07-5.02 (m, 2H), 4.86 (d, $J = 1.6$ Hz, 1H), 4.63 (s, 1H), 2.48 (dd, $J = 13.5, 8.1$ Hz, 1H), 2.35 (dd, $J = 10.7, 4.7$ Hz, 1H), 2.20-2.01 (m, 3H), 1.76-1.68 (m, 2H), 1.58-1.32 (m, 7H), 1.35 (d, $J = 1.7$ Hz, 1H), 1.26-1.10 (m, 1H), 0.86 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 150.32, 135.32, 117.11, 108.93, 76.37, 43.60, 40.87, 38.49, 33.46, 32.06, 30.00, 25.67, 24.70, 21.44, 20.39.

IR (neat, cm^{-1} , ν): 3572 (w), 3079 (w), 2934 (s), 2861 (m), 1640 (w), 1463 (m), 1448 (m), 1375 (m), 1335 (w), 1287 (w), 1257 (w), 1232 (w), 1147 (w), 1091 (w).

HRMS (EI, m/z): calculated 220.1827 for $[\text{M}]^+$, found 220.1826.



(±)-(1S,2S)-2-Isopropenyl-1-((E)-1-methyl-propenyl)-cyclohexanol (2.5):

To a solution of (*E*)-2-bromo-2-butene (39 μL , 0.29 mmol) in 3 mL of tetrahydrofuran, cooled to $-78\text{ }^\circ\text{C}$, was added *tert*-butyllithium (0.330 mL of a 1.74 M solution in pentane, 0.574 mmol) drop-wise. After stirring for 30 minutes the reaction was warmed to $0\text{ }^\circ\text{C}$ for 10 minutes and then re-cooled to $-78\text{ }^\circ\text{C}$. A solution of ketone **2.2** (22 mg, 0.16 mmol) in 1 mL of tetrahydrofuran (also at $-78\text{ }^\circ\text{C}$) was slowly cannulated into the reaction mixture. After 2.5 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% diethyl ether/hexanes) gave 19 mg of a colourless oil (60%).

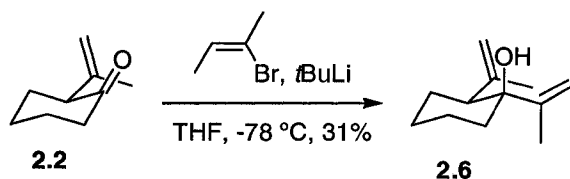
Data for **2.5**:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.52 (q, $J = 6.7\text{ Hz}$, 1H), 4.81 (s, 1H), 4.69 (s, 1H), 2.29 (dd, $J = 12.5, 3.7\text{ Hz}$, 1H), 1.78-1.72 (m, 2H), 1.72-1.67 (m, 2H), 1.67-1.63 (m, 1H), 1.63-1.58 (m, 6H), 1.55 (d, $J = 6.2\text{ Hz}$, 3H), 1.52-1.39 (m, 3H), 1.25-1.17 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.85, 141.12, 116.67, 111.62, 75.11, 49.26, 36.41, 27.80, 26.30, 24.89, 21.55, 14.03, 13.49.

IR (neat, cm^{-1} , ν): 3548 (br, m), 2934 (s), 2859 (s), 1635 (w), 1447 (m), 1386 (m), 1285 (m), 1128 (m), 1073 (m).

HRMS (EI, m/z): calculated 194.1671 for $[\text{M}]^+$, found 194.1671.



(±)-(1S,2S)-2-Isopropenyl-1-((Z)-1-methyl-propenyl)-cyclohexanol (2.6):

To a solution of (Z)-2-bromo-2-butene (42 μL , 0.41 mmol) in 1 mL of tetrahydrofuran, cooled to $-78\text{ }^\circ\text{C}$, was added *tert*-butyllithium (0.460 mL of a 1.77 M solution in pentane, 0.814 mmol) drop-wise. After stirring for 30 minutes the reaction was warmed to $0\text{ }^\circ\text{C}$ for 10 minutes and then re-cooled to $-78\text{ }^\circ\text{C}$. A solution of ketone **2.2** (28 mg, 0.20 mmol) in 1 mL of tetrahydrofuran (also at $-78\text{ }^\circ\text{C}$) was slowly cannulated into the reaction mixture. After 1 hour, little reaction had occurred so the reaction was warmed to $-10\text{ }^\circ\text{C}$ and allowed to stir for another hour. The reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% diethyl ether/hexanes) gave 12 mg of a colourless oil (31%).

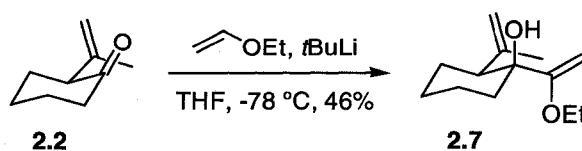
Data for 2.6:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.25 (qq, $J = 7.4, 1.3\text{ Hz}$, 1H), 4.86 (dq, $J = 1.5, 1.5\text{ Hz}$, 1H), 4.79-4.78 (m, 1H), 2.41 (dd, $J = 12.5, 3.7\text{ Hz}$, 1H), 1.97 (d, $J = 1.7\text{ Hz}$, 1H), 1.78 (s, 3H), 1.77 (dq, $J = 7.2, 1.4\text{ Hz}$, 3H), 1.74-1.54 (m, 4H), 1.67, (dd, $J = 1.4, 1.4\text{ Hz}$, 3H), 1.51-1.39 (m, 3H), 1.28-1.17 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.03, 141.47, 120.21, 111.77, 76.45, 49.84, 36.67, 27.70, 26.22, 25.07, 23.83, 21.27, 15.52.

IR (neat, cm^{-1} , ν): 3549 (br, m), 3069 (w), 2934 (s), 2859 (s), 1635 (w), 1448 (m), 1374 (m).

HRMS (EI, m/z): calculated 194.1671 for $[\text{M}]^+$, found 194.1688.



(±)-(1S,2S)-1-(1-Ethoxy-vinyl)-2-isopropenyl-cyclohexanol (2.7):

A solution of ethyl vinyl ether (0.20 mL, 2.1 mmol) in 0.1 mL of tetrahydrofuran was cooled to $-78\text{ }^\circ\text{C}$. *tert*-Butyllithium (0.400 mL of a 1.75 M solution in pentane, 0.700 mmol) was

added drop-wise and the reaction stirred for 30 minutes and then immersed in an ice bath for ten minutes during which time the reaction went from pale yellow/green to colourless. Following re-immersion into the $-78\text{ }^{\circ}\text{C}$ bath, a solution of ketone **2.2** (20 mg, 0.15 mmol) in 1 mL of tetrahydrofuran (also at $-78\text{ }^{\circ}\text{C}$) was slowly cannulated into the reaction mixture. Monitoring by TLC showed no further conversion after 45 minutes so the reaction was quenched with isopropanol, then water, and the aqueous phase extracted three times with diethyl ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% diethyl ether/hexanes, basified with triethylamine) gave 14 mg of a colourless oil (46%).

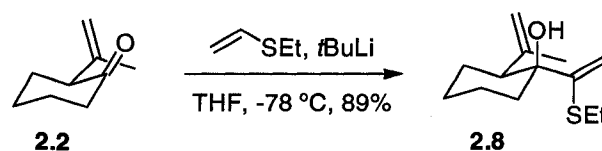
Data for 2.7:

^1H NMR (C_6D_6 , 300 MHz, δ): 4.86 (dq, $J = 1.6, 1.6\text{ Hz}$, 1H), 4.78 (s, 1H), 4.50 (d, $J = 1.9\text{ Hz}$, 1H), 3.85 (d, $J = 1.9\text{ Hz}$, 1H), 3.43-3.27 (m, 2H), 2.61 (dd, $J = 13.0, 3.5\text{ Hz}$, 1H), 2.05-1.92 (m, 1H), 1.90-1.75 (m, 4H), 1.72 (s, 3H), 1.70-1.62 (m, 1H), 1.50-1.44 (m, 2H), 1.28-1.13 (m, 1H), 1.02 (t, $J = 7.0\text{ Hz}$, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 168.19, 148.63, 111.77, 79.35, 73.61, 62.61, 49.26, 36.97, 27.61, 26.35, 24.66, 21.63, 14.52.

IR (neat, cm^{-1} , ν): 3543 (w), 3079 (w), 2983 (m), 2939 (s), 2854 (m), 1650 (w), 1635 (w), 1610 (w), 1445 (m), 1280 (m), 1252 (s), 1135 (s), 1067 (s).

HRMS (EI, m/z): calculated 210.1620 for $[\text{M}]^+$, found 210.1624.



(±)-(1S,2S)-1-(1-Ethylsulfanyl-vinyl)-2-isopropenyl-cyclohexanol (2.8):

Ethyl vinyl sulfide (370 μL , 3.65 mmol) was dissolved in 2 mL of tetrahydrofuran and cooled to $-78\text{ }^{\circ}\text{C}$. *tert*-Butyllithium (1.70 mL of a 1.60 M solution in pentane, 2.72 mmol) was added drop-wise and the reaction stirred for 30 minutes and then immersed in an ice bath for ten minutes during which time the reaction turned medium yellow in colour. Following re-immersion into a $-78\text{ }^{\circ}\text{C}$ bath, a solution of **2.2** (75 mg, 0.54 mmol) in 1 mL of tetrahydrofuran (also at $-78\text{ }^{\circ}\text{C}$) was slowly cannulated into the reaction mixture. Monitoring by TLC showed no further conversion after 50 minutes so the reaction was quenched with

isopropanol, then water, and the aqueous phase extracted three times with diethyl ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes, basified with triethylamine) gave 109 mg of a colourless oil (89%).

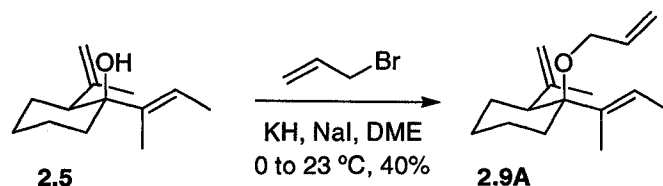
Data for 2.8:

^1H NMR (C_6D_6 , 500 MHz, δ): 5.45 (s, 1H), 4.86 (s, 1H), 4.86 (s, 1H), 4.66 (s, 1H), 2.58 (dd, $J = 12.8, 3.7$ Hz, 1H), 2.45-2.34 (m, 2H), 2.02 (ddd, $J = 14.3, 13.5, 4.2$ Hz, 1H), 1.89 (d, $J = 1.1$ Hz, 1H), 1.86 (s, 3H), 1.83 (dddd, $J = 13.0, 13.0, 13.0, 3.6$ Hz, 1H), 1.77-1.68 (m, 2H), 1.67-1.62 (m, 1H), 1.48-1.40 (m, 2H), 1.23-1.13 (m, 1H), 1.04 (dd, $J = 7.4, 7.4$ Hz, 3H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 154.08, 148.26, 112.37, 104.42, 76.33, 51.03, 39.02, 28.18, 26.48, 26.30, 24.44, 21.79, 13.11.

IR (neat, cm^{-1} , ν): 3541 (br, m), 3077 (w), 2936 (s), 2852 (m), 1712 (w), 1628 (w), 1596 (m), 1442 (m), 1371 (m), 1100 (m).

HRMS (EI, m/z): calculated 226.1391 for $[\text{M}]^+$, found 226.1389.



(±)-(1S,2S)-1-Allyloxy-2-isopropenyl-1-((E)-1-methyl-propenyl)-cyclohexane-1-Allyloxy-2-isopropenyl-1-(1-methyl-propenyl)-cyclohexane (2.9A):

Sodium iodide (3 mg, 0.02 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (50 mg of a 30% suspension in mineral oil, 0.37 mmol) was then added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (0.5 mL) was then added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated **2.5** (18 mg, 0.093 mmol) in another 0.5 mL of dimethoxyethane and the reaction stirred for 10 minutes. Allyl bromide (50 μL , 0.58 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 16 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with

magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 9 mg of a colourless oil (40%).

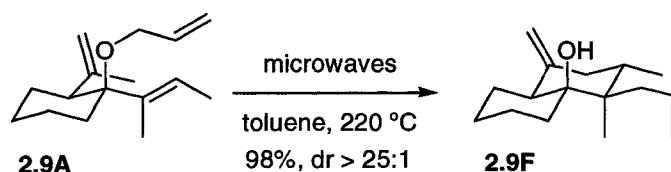
Data for 2.9A:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.96-5.84 (m, 1H), 5.39-5.29 (m, 2H), 5.07 (dddd, $J = 10.6$, 1.9, 1.9, 1.9 Hz, 1H), 4.61 (s, 1H), 4.55 (s, 1H), 3.80-3.72 (m, 1H), 3.67-3.60 (m, 1H), 2.03-1.97 (m, 2H), 1.81-1.70 (m, 2H), 1.71 (s, 3H), 1.62-1.39 (m, 4H), 1.56 (d, $J = 6.7$ Hz, 3H), 1.49 (s, 3H), 1.37-1.31 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 148.58, 137.49, 136.02, 119.18, 114.13, 111.79, 82.28, 62.17, 54.84, 31.55, 29.70, 27.76, 26.44, 21.98, 21.71, 13.62.

IR (neat, cm^{-1} , ν): 2925 (s), 2856 (m), 1638 (w), 1449 (s), 1376 (w), 1204 (w), 1151 (m), 1117 (m), 1061 (s).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.2001.



(±)-(3S,4R,4aS,8aS)-4-Allyl-3,4-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.9F):

A solution of **2.9A** (7.7 mg, 0.033 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 220 °C. After 1 hour the reaction was concentrated and the crude material injected into a GC. Only one product was detected. Purification by silica gel flash chromatography (3% diethyl ether/hexanes) yielded 7.6 mg of a colourless oil as a single isomer (98%).

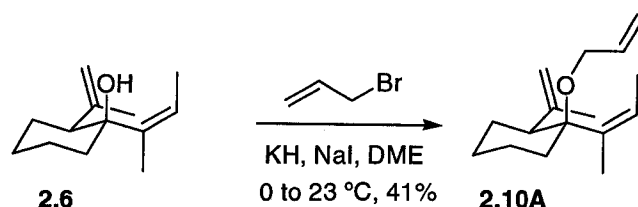
Data for 2.9F:

^1H NMR (CDCl_3 , 500 MHz, δ): 6.13-6.05 (m, 1H), 4.98 (dq, $J = 17.2$, 2.1 Hz, 1H), 4.94-4.92 (m, 1H), 4.81 (q, $J = 1.6$ Hz, 1H), 4.58 (q, $J = 1.3$ Hz, 1H), 2.32 (dd, $J = 15.3$, 8.3 Hz, 1H), 2.20-2.03 (m, 5H), 1.86-1.83 (m, 1H), 1.73-1.70 (m, 1H), 1.59-1.46 (m, 6H), 1.21-1.13 (m, 1H), 0.89 (s, 3H), 0.87 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 150.26, 138.54, 115.34, 107.87, 78.18, 44.72, 44.34, 41.00, 39.99, 34.65, 31.66, 25.51, 24.66, 21.60, 16.83, 15.95.

IR (neat, cm^{-1} , ν): 3365 (br, w), 2953 (m), 2928 (s), 2854 (m), 1642 (w), 1458 (m), 1439 (m), 1258 (w), 1236 (w), 1076 (m).

HRMS (EI, m/z): calculated 216.1878 for $[\text{M}-\text{H}_2\text{O}]^+$, found 216.1843.



(±)-(1S,2S)-1-Allyloxy-2-isopropenyl-1-((Z)-1-methyl-propenyl)-cyclohexane (2.10A):

Sodium iodide (3 mg, 0.02 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (140 mg of a 30% suspension in mineral oil, 1.05 mmol) was added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated **2.6** (37 mg, 0.19 mmol) as a solution in another 1 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (80 μL , 0.93 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 18 mg of a colourless oil (41%).

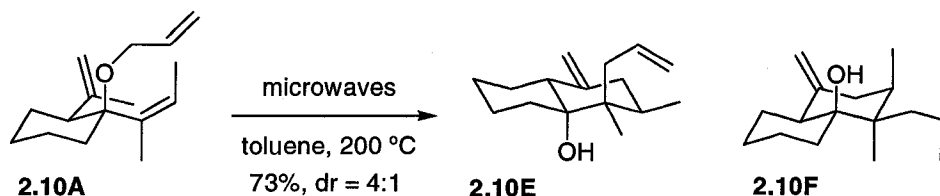
Data for 2.10A:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.99-5.87 (m, 1H), 5.40-5.28 (m, 2H), 5.06 (d, $J = 10.6$ Hz, 1H), 4.72 (s, 1H), 4.62 (s, 1H), 3.85-3.80 (m, 1H), 3.73-3.68 (m, 1H), 2.13-1.96 (m, 3H), 1.78 (s, 3H), 1.75-1.68 (m, 1H), 1.63-1.60 (m, 6H), 1.57-1.20 (m, 5H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 147.42, 136.27 (2C), 124.67, 114.29, 112.97, 83.27, 62.18, 51.64, 32.69, 27.47, 26.57, 24.43, 23.28, 21.06, 15.44.

IR (neat, cm^{-1} , ν): 3078 (w), 2929 (s), 2857 (m), 1648 (w), 1453 (m), 1127 (m), 1064 (m).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.1977.



(±)-(3S,4S,4aS,8aS)-4-Allyl-3,4-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.10E) and (±)-(3R,4R,4aS,8aS)-4-Allyl-3,4-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.10F):

A solution of **2.10A** (33.8 mg, 0.144 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1.5 hours the reaction was concentrated and the crude material injected into a GC. A 4:1 mixture of isomers was found to be present and purification by silica gel flash chromatography (7% diethyl ether/hexanes) yielded 19.5 mg of **2.10E** and 5 mg of **2.10F**, both as colourless oils (73% combined yield).

Data for **2.10E** (major isomer):

¹H NMR (CDCl₃, 500 MHz, δ): 5.95-5.87 (m, 1H), 5.00 (dddd, *J* = 16.9, 1.7, 1.7, 1.7 Hz, 1H), 4.96 (dddd, *J* = 10.0, 1.1, 1.1, 1.1 Hz, 1H), 4.85 (s, 1H), 4.63 (s, 1H), 2.33 (d, *J* = 11.7 Hz, 1H), 2.30-2.20 (m, 2H), 2.06-2.04 (m, 2H), 1.82-1.71 (m, 3H), 1.61-1.43 (m, 6H), 1.22-1.50 (m, 1H), 0.91 (s, 3H), 0.90 (d, *J* = 5.7 Hz, 3H).

¹H NMR (C₆D₆, 500 MHz, δ): 5.89-5.80 (m, 1H), 4.99-4.94 (m, 2H), 4.79 (d, *J* = 1.1 Hz, 1H), 4.58 (d, *J* = 0.7 Hz, 1H), 2.15-2.03 (m, 3H), 1.94-1.87 (m, 2H), 1.80-1.76 (m, 1H), 1.73-1.62 (m, 3H), 1.49-1.42 (m, 3H), 1.37 (ddd, *J* = 14.0, 13.2, 2.6 Hz, 1H), 1.15 (d, *J* = 1.7 Hz, 1H), 1.08-0.99 (m, 1H), 0.97 (s, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (C₆D₆, 125 MHz, δ): 150.33, 138.49, 115.63, 108.66, 77.02, 43.99, 43.93, 41.15, 39.54, 35.39, 31.38, 25.77, 24.24, 22.01, 18.13, 16.85.

IR (neat, cm⁻¹, ν): 3454 (br, m), 3076 (w), 2929 (s), 1641 (w), 1458 (m), 1094 (w).

HRMS (EI, *m/z*): calculated 234.1984 for [M]⁺, found 234.1958.

Data for **2.10F** (minor isomer):

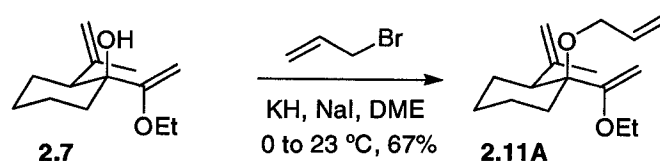
¹H NMR (CDCl₃, 300 MHz, δ): 5.90-5.76 (m, 1H), 5.08 (d, *J* = 13.0 Hz, 1H), 5.04 (d, *J* = 9.5 Hz, 1H), 4.84 (s, 1H), 4.72 (s, 1H), 2.65-2.54 (m, 2H), 2.37-2.34 (m, 1H), 2.00 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.90 (dd, *J* = 12.9, 3.0 Hz, 1H), 1.78-1.70 (m, 4H), 1.56-1.46 (m, 5H), 1.26-1.45 (m, 1H), 1.10 (s, 3H), 1.00 (d, *J* = 7.3 Hz, 3H).

^1H NMR (C_6D_6 , 500 MHz, δ): 5.86-5.78 (m, 1H), 5.13-5.09 (m, 2H), 4.80 (d, $J = 1.7$ Hz, 1H), 4.66 (s, 1H), 2.77 (dd, $J = 14.1, 6.8$ Hz, 1H), 2.41 (dd, $J = 12.7, 5.2$ Hz, 1H), 2.09-2.06 (m, 1H), 1.98 (dd, $J = 13.9, 7.8$ Hz, 1H), 1.79 (dd, $J = 13.0, 2.2$ Hz, 1H), 1.64-1.52 (m, 5H), 1.45-1.40 (m, 2H), 1.36-1.33 (m, 1H), 1.06 (d, $J = 7.3$ Hz, 3H), 1.04-1.00 (m, 1H), 0.91 (s, 3H), 0.86 (d, $J = 1.4$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.47, 135.64, 117.36, 110.14, 78.40, 44.82, 42.75, 39.51, 38.83, 37.69, 31.54, 25.64, 24.50, 23.41, 21.29, 17.08.

IR (neat, cm^{-1} , ν): 3470 (br, w), 3075 (w), 2925 (s), 2853 (s), 1739 (w), 1642 (w), 1455 (m), 1380 (m), 1079 (w).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.1958.



(±)-(1S,2S)-1-Allyloxy-1-(1-ethoxy-vinyl)-2-isopropenyl-cyclohexane (2.11A):

Sodium iodide (4 mg, 0.03 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (155 mg of a 30% suspension in mineral oil, 1.16 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated **2.7** (52 mg, 0.25 mmol) in another 1.5 mL of dimethoxyethane and the resulting solution stirred for 20 minutes. Allyl bromide (0.110 mL, 1.27 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes, basified with triethylamine) yielded 41.3 mg of a colourless oil (67%).

Data for 2.11A:

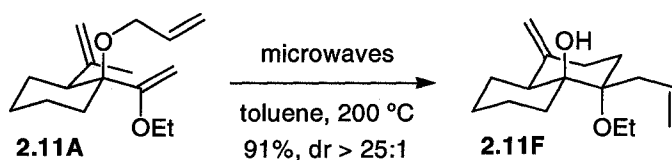
^1H NMR (C_6D_6 , 300 MHz, δ): 5.95-5.83 (m, 1H), 5.44 (dddd, $J = 17.2, 1.9, 1.9, 1.9$ Hz, 1H), 5.09 (dddd, $J = 10.6, 1.7, 1.7, 1.7$ Hz, 1H), 4.86 (dq, $J = 1.3, 1.3$ Hz, 1H), 4.83 (d, $J = 2.6$ Hz, 1H), 4.29 (d, $J = 1.9$ Hz, 1H), 4.04-3.97 (m, 1H), 3.95 (d, $J = 1.9$ Hz, 1H), 3.83-3.76 (m,

1H), 3.39 (q, $J = 7.0$ Hz, 2H), 2.43 (dd, $J = 12.8, 3.2$ Hz, 1H), 2.14 (dddd, $J = 12.8, 12.8, 12.8, 3.9$ Hz, 1H), 1.97 (s, 3H), 1.88-1.83 (m, 2H), 1.78-1.64 (m, 1H), 1.54-1.17 (m, 4H), 1.07 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 162.67, 148.30, 136.05, 114.53, 112.08, 81.30, 81.00, 63.16, 62.61, 54.03, 30.38, 27.42, 26.50, 21.99, 21.82, 14.61.

IR (neat, cm^{-1} , ν): 3070 (w), 2979 (m), 2932 (s), 2859 (m), 1619 (m), 1450 (m), 1372 (w), 1284 (m), 1255 (m), 1153 (m), 1136 (s), 1065 (s).

HRMS (EI, m/z): calculated 250.1933 for $[\text{M}]^+$, found 250.1937.



(±)-(4R,4aS,8aS)-4-Allyl-4-ethoxy-1-methylene-octahydro-naphthalen-4a-ol (2.11F):

A solution of **2.11A** (38 mg, 0.18 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour, the reaction appeared incomplete by TLC so it was resubjected to microwave irradiation for another hour. The reaction was concentrated and purified by silica gel flash chromatography (4% diethyl ether/hexanes, basified with triethylamine) to yield 35 mg of a colourless oil (91%).

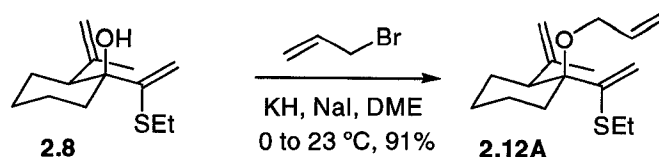
Data for 2.11F:

^1H NMR (C_6D_6 , 500 MHz, δ): 6.07-5.99 (m, 1H), 5.04 (d, $J = 18.5$ Hz, 1H), 5.00 (d, $J = 10.4$, 1H), 4.86 (s, 1H), 4.63 (s, 1H), 3.33-3.28 (m, 1H), 3.20-3.14 (m, 1H), 2.79 (br d, $J = 12.0$ Hz, 1H), 2.56-2.47 (m, 2H), 2.17 (ddd, $J = 13.4, 13.4, 4.1$ Hz, 1H), 1.99-1.92 (m, 2H), 1.87-1.84 (m, 1H), 1.76-1.66 (m, 3H), 1.57-1.41 (m, 4H), 1.32 (d, $J = 1.5$ Hz, 1H), 1.27-1.18 (m, 1H), 1.09 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 150.51, 137.10, 115.85, 108.52, 79.31, 77.01, 57.13, 43.77, 38.38, 32.11, 29.94 (2C), 25.72, 24.75, 21.86, 16.15.

IR (neat, cm^{-1} , ν): 3558 (w), 3083 (w), 2974 (m), 2932 (m), 2861 (m), 1641 (m), 1441 (m), 1178 (m), 1097 (s), 1079 (s).

HRMS (EI, m/z): calculated 250.1933 for $[\text{M}]^+$, found 250.1918.



(±)-(1S,2S)-1-Allyloxy-1-(1-ethylsulfanyl-vinyl)-2-isopropenyl-cyclohexane (2.12A):

Sodium iodide (7 mg, 0.05 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (315 mg of a 30% suspension in mineral oil, 2.36 mmol) was then added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (3 mL) was then added to the flask and the suspension cooled to 0 °C. A solution of **2.8** (107 mg, 0.473 mmol) in another 2 mL of dimethoxyethane was cannulated into the flask and stirred for 20 minutes. Allyl bromide (0.200 mL, 2.31 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes, basified with triethylamine) yielded 115 mg of a colourless oil (91%).

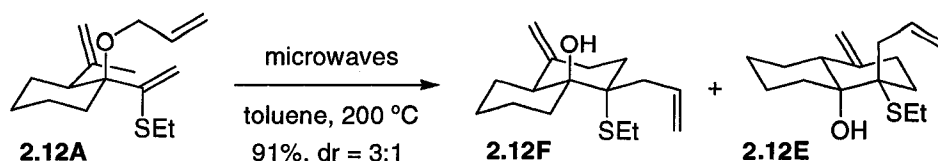
Data for 2.12A:

¹H NMR (C₆D₆, 500 MHz, δ): 6.01-5.93 (m, 1H), 5.51 (dddd, *J* = 17.2, 2.0, 2.0, 2.0 Hz, 1H), 5.43 (s, 1H), 5.19 (dddd, *J* = 10.6, 1.8, 1.8, 1.8 Hz, 1H), 5.07 (d, *J* = 2.8 Hz, 1H), 4.99 (ddd, *J* = 1.4, 1.4, 1.4 Hz, 1H), 4.82 (s, 1H), 4.04-4.00 (m, 1H), 3.84-3.80 (m, 1H), 2.62 (dd, *J* = 12.7, 3.4 Hz, 1H), 2.53 (q, *J* = 7.4 Hz, 2H), 2.21 (dddd, *J* = 13.0, 13.0, 13.0, 3.9 Hz, 1H), 2.05-2.00 (m, 1H), 2.04 (s, 3H), 1.96-1.90 (m, 1H), 1.78-1.73 (m, 1H), 1.63-1.59 (m, 1H), 1.51-1.42 (m, 2H), 1.37-1.27 (m, 1H), 1.18 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (C₆D₆, 125 MHz, δ): 147.52, 147.37, 135.71, 114.70, 112.94, 105.05, 83.23, 62.68, 54.30, 31.94, 27.77, 26.44, 26.05, 22.20, 21.93, 13.14.

IR (neat, cm⁻¹, ν): 3072 (w), 3014 (w), 2933 (s), 2858 (m), 1695 (w), 1640 (w), 1594 (m), 1447 (m), 1374 (m), 1264 (m), 1105 (m), 1059 (m).

HRMS (EI, *m/z*): calculated 266.1704 for [M]⁺, found 266.1682.



(±)-(4R,4aS,8aS)-4-Allyl-4-ethylsulfanyl-1-methylene-octahydro-naphthalen-4a-ol

(2.12F) and (±)-(4S,4aS,8aS)-4-Allyl-4-ethylsulfanyl-1-methylene-octahydro-naphthalen-4a-ol (2.12E):

A solution of **2.12A** (109 mg, 0.409 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1.5 hours the reaction was concentrated and the crude material injected into a GC. A 3:1 mixture of isomers was found to be present. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 99 mg of an inseparable mixture of products as a colourless oil (91% combined yield).

Data for **2.12F** (major isomer):

¹H NMR (C₆D₆, 300 MHz, δ): 6.13-5.95 (m, 1H), 5.12-5.01 (m, 2H), 4.78 (ddd, *J* = 1.6, 1.6, 1.6 Hz, 1H), 4.56 (d, *J* = 1.3 Hz, 1H), 3.12 (d, br, *J* = 11.5, 1H), 2.63 (dd, *J* = 7.3, 1.0 Hz, 1H), 2.51-1.30 (m, 14H), 1.35 (s, 1H), 1.26-1.11 (m, 1H), 1.05 (dd, *J* = 7.4, 7.4 Hz, 3H).

¹³C NMR (C₆D₆, 75 MHz, δ): 150.10, 136.70, 116.82, 109.01, 78.12, 56.60, 44.16, 40.43, 34.16, 32.61, 31.42, 25.64, 24.96, 23.54, 21.92, 14.00.

Data for **2.12E** (minor isomer):

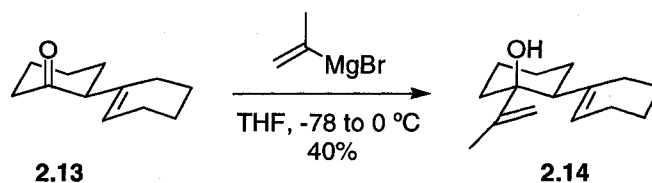
¹H NMR (C₆D₆, 300 MHz, δ): 6.13-5.95 (m, 1H), 5.12-5.01 (m, 2H), 4.85 (d, *J* = 1.2 Hz, 1H), 4.72 (d, *J* = 1.1 Hz, 1H), 2.51-1.30 (m, 16H), 1.35 (s, 1H), 1.26-1.11 (m, 1H), 0.97 (dd, *J* = 7.5, 7.5 Hz, 3H).

¹³C NMR (C₆D₆, 75 MHz, δ): 148.56, 135.37, 117.35, 107.98, 77.30, 59.68, 44.36, 37.72, 33.20, 32.51, 31.48, 26.21, 25.39, 23.99, 21.79, 14.00.

Data for **2.12F** and **2.12E** (major and minor isomer together):

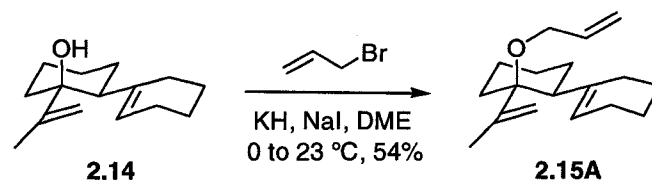
IR (neat, cm⁻¹, ν): 3554 (w), 3077 (w), 2932 (s), 2859 (m), 1641 (m), 1447 (m), 1256 (m).

HRMS (EI, *m/z*): calculated 266.1704 for [M]⁺, found 266.1676.



(±)-(1S,2S)-2-Isopropenyl-bicyclohexyl-1'-en-2-ol (2.14):

A solution of **2.13** (510 mg, 2.86 mmol) in 2 mL of tetrahydrofuran was cooled to -78 °C. Isopropenylmagnesium bromide (10 mL of a 0.5 M solution in tetrahydrofuran, 5 mmol) was added portion-wise over 5 minutes and the resulting solution was warmed gradually to 0 °C. After 4 hours stirring at 0 °C, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 252 mg of a colourless oil (40%). Spectral data for this compound was in agreement with that reported previously: Warrington, J. M. Ph.D. Thesis, University of Ottawa, Ottawa, Canada, 2005.



(±)-(1'S,2'S)-2'-Allyloxy-2'-isopropenyl-bicyclohexyl-1-ene (2.15A):

Sodium iodide (6 mg, 0.04 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (317 mg of a 30% suspension in mineral oil, 2.37 mmol) was then added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (3 mL) was then added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated a solution of **32** (90 mg, 0.41 mmol) in another 1 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (180 µL, 2.08 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 57 mg of a colourless oil (54%).

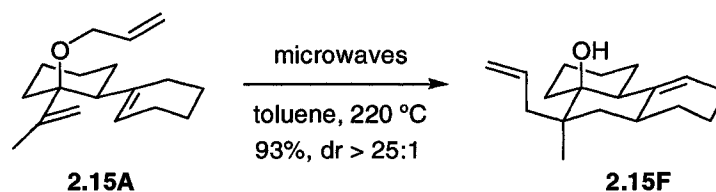
Data for 2.15A:

¹H NMR (CDCl₃, 300 MHz, δ): 5.96-5.84 (m, 1H), 5.36-5.28 (m, 2H), 5.07 (dddd, $J = 10.6$, 1.9, 1.9, 1.9 Hz, 1H), 4.84 (dq, $J = 1.5$, 1.5 Hz, 1H), 4.77 (d, $J = 2.0$ Hz, 1H), 3.83-3.67 (m, 2H), 2.27-2.18 (m, 1H), 2.08-1.82 (m, 6H), 1.76-1.68 (m, 1H), 1.63 (d, $J = 0.7$ Hz, 3H), 1.58-1.18 (m, 9H).

¹³C NMR (CDCl₃, 75 MHz, δ): 147.10, 139.97, 135.91, 122.83, 114.07, 111.52, 82.12, 62.20, 55.00, 31.56, 27.50, 27.34, 26.55, 25.57, 23.31, 22.60, 21.67, 20.51.

IR (neat, cm⁻¹, ν): 3088 (w), 2927 (s), 2856 (s), 1641 (m), 1447 (s), 1405 (m), 1373 (m), 1148 (m), 1129 (s), 1063 (s), 1025 (m).

HRMS (EI, m/z): calculated 260.2140 for [M]⁺, found 260.2143.



(±)-(4bS,8aS,9R,10aS)-9-Allyl-9-methyl-1,3,4b,5,6,7,8,9,10,10a-decahydro-2H-phenanthren-8a-ol (2.15F):

A solution of **2.15A** (16 mg, 0.062 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 220 °C. After 1 hour the reaction was concentrated and purified by silica gel flash chromatography (5% diethyl ether/hexanes) to yield 15 mg of a white solid (93%).

Data for 2.15F:

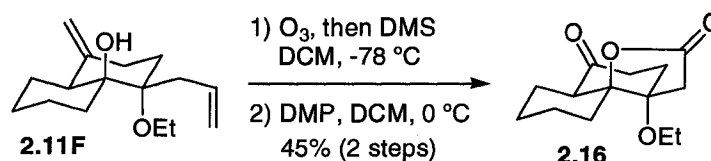
¹H NMR (C₆D₆, 300 MHz, δ): 5.93-5.79 (m, 1H), 5.29 (m, 1H), 5.12-5.09 (m, 1H), 5.06 (s, 1H), 2.56 (dd, $J_{AB} = 13.4$, $J_{AX} = 7.6$ Hz, 1H), 2.14 (dd, $J_{AB} = 13.4$, $J_{BX} = 7.5$ Hz, 1H), 2.02-2.02 (m, 1H), 1.98-1.92 (m, 1H), 1.87-1.80 (m, 2H), 1.78-1.60 (m, 3H), 1.52-1.25 (m, 8H), 1.23-1.10 (m, 4H), 0.92 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 141.13, 136.29, 121.42, 116.78, 76.24, 43.96, 42.87, 40.99, 40.88, 32.87, 30.81, 29.90, 25.87, 25.81, 24.44, 21.60, 21.10, 20.80.

IR (neat, cm⁻¹, ν): 3470 (w), 2927 (s), 2856 (m), 1635 (w), 1448 (m).

HRMS (EI, m/z): calculated 260.2140 for [M]⁺, found 260.2143.

mp = 61.9-63.4 °C.



(±)-(3aR,6aR,10aS)-3a-Ethoxy-octahydro-1-oxa-cyclopenta[d]naphthalene-2,6-dione (2.16):

A solution of **2.11F** (31 mg, 0.15 mmol) in 1 mL of wash-bottle-grade dichloromethane and one drop of methanol was cooled to -78°C . Ozone was bubbled through the reaction mixture for 30 minutes until a faint blue colour appeared. The ozone atmosphere was removed by sparging with oxygen and the reaction quenched with 100 μL of dimethyl sulfide. After warming to ambient temperature the reaction was concentrated to remove excess dimethyl sulfide and the crude material dissolved in 1 mL of dichloromethane. The mixture was cooled to 0°C and Dess-Martin periodinane (32 mg, 0.075 mmol) was added. After gradually warming to ambient temperature and stirring for an additional 2 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 17 mg of a colourless oil (45%).

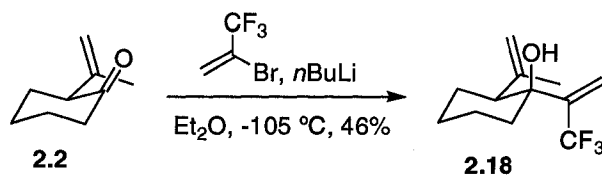
Data for 2.16:

^1H NMR (CDCl_3 , 500 MHz, δ): 3.63 (dq, $J = 14.7, 7.0$ Hz, 1H), 3.35 (dq, $J = 14.7, 7.0$ Hz, 1H), 2.98 (dd, $J = 17.4, 0.8$ Hz, 1H), 2.60 (d, $J = 17.3$ Hz, 1H), 2.56–2.50 (m, 2H), 2.24–2.01 (m, 4H), 1.92–1.86 (m, 1H), 1.83–1.77 (m, 2H), 1.67–1.64 (m, 1H), 1.58–1.50 (m, 2H), 1.27–1.17 (m, 1H), 1.22 (t, $J = 6.9$ Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 207.90, 172.60, 89.93, 78.67, 60.17, 49.63, 39.87, 34.30, 31.67, 31.14, 24.13, 22.28, 20.80, 15.70.

IR (neat, cm^{-1} , ν): 2937 (m), 2862 (w), 1779 (s), 1722 (s), 1269 (w), 1219 (w), 1194 (w), 1125 (w), 1095 (m).

HRMS (EI, m/z): calculated 252.1362 for $[\text{M}]^+$, found 252.1345.



(±)-(1S,2S)-2-Isopropenyl-1-(1-trifluoromethyl-vinyl)-cyclohexanol (2.18):

To a solution of 2-bromo-3,3,3-trifluoropropene (60 mg, 0.34 mmol) in 2 mL of diethyl ether at -105 °C was added *n*-butyllithium (0.120 mL of a 2.79 M solution in pentane, 0.34 mmol) in four equal portions, alternating with the addition of **2.2** (50 mg, 0.36 mmol) as a solution in 0.5 mL of diethyl ether. After 1 hour the reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted three times with diethyl ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% diethyl ether/pentane) yielded 37 mg of a colourless *volatile* oil (46%).

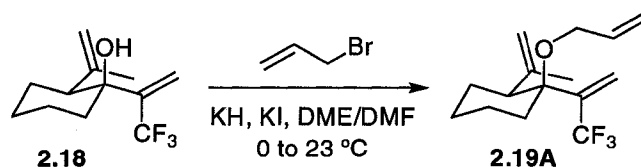
Data for 2.18:

¹H NMR (C₆D₆, 500 MHz, δ): 5.62 (q, *J* = 1.3 Hz, 1H), 5.40 (q, *J* = 1.6 Hz, 1H), 4.82 (dq, *J* = 1.6, 1.6 Hz, 1H), 4.75 (s, 1H), 2.33 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.76 (dddd, *J* = 13.0, 13.0, 13.0, 3.3 Hz, 1H), 1.69 (s, 3H), 1.64 (dd, *J* = 13.4, 4.6 Hz, 1H), 1.59-1.49 (m, 3H), 1.42-1.37 (m, 1H), 1.35-1.29 (m, 1H), 1.32 (s, 1H), 1.08 (dddd, *J* = 13.2, 13.2, 13.2, 3.9, 3.9 Hz, 1H).

¹³C NMR (C₆D₆, 125 MHz, δ): 147.12, 144.81 (q, *J*_{CF} = 26 Hz), 124.48 (q, *J*_{CF} = 274 Hz), 119.76 (q, *J*_{CF} = 6 Hz), 113.36, 74.36, 51.58, 38.17, 27.70, 25.92, 23.55, 21.19.

IR (neat, cm⁻¹, ν): 3536 (br, m), 3074 (w), 2937 (s), 2861 (m), 1638 (w), 1449 (m), 1319 (s), 1171 (s), 1156 (s), 1125 (s), 1101 (s), 1046 (m).

HRMS (EI, *m/z*): calculated 234.1231 for [M]⁺: too volatile to obtain MS.



(±)-(1S,2S)-1-Allyloxy-2-isopropenyl-1-(1-trifluoromethyl-vinyl)-cyclohexane (2.19A):

Sodium iodide (8 mg, 0.05 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (633 mg of a 30% suspension in mineral oil, 4.73 mmol) was added to the flask and the system was put under nitrogen. The potassium hydride was then washed three

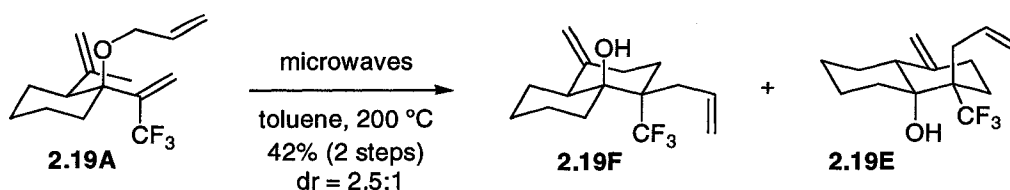
times with hexanes and dried under a flow of nitrogen. Dimethylformamide (4 mL) and tetrahydrofuran (2 mL) were added to the flask and the suspension cooled to 0 °C. A solution of **2.18** (220 mg, 0.941 mmol) in another 2 mL of dimethylformamide and 1 mL of tetrahydrofuran was cannulated into the flask and stirred for 20 minutes. Allyl bromide (0.410 mL, 4.74 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was diluted with 20 mL of water and extracted three times with diethyl ether. The combined organic layers were washed twice with brine and dried with magnesium sulfate, filtered and concentrated to a volume of 1 mL. Purification by silica gel flash chromatography (100% petroleum ether) led to **2.19A** as a solution in petroleum ether. Due to the extreme volatility of the compound, however, concentration of the combined fractions to less than 0.5 mL was not possible without significant loss of the material. In addition, the high dilution of the sample prevented ^{13}C NMR data from being obtained. Finally, the mixture of hydrocarbons present in petroleum ether prevented an accurate yield from being obtained by integration of the ^1H NMR spectra. For the purposes of subsequent reactions, a yield of 100% was assumed giving the 0.5 mL solution a concentration of 1.9 M.

Data for 2.19A:

^1H NMR (CDCl_3 , 30 MHz, δ): 5.94-5.81 (m, 1H), 5.87 (d, $J = 1.5$ Hz, 1H), 5.48 (d, $J = 1.7$ Hz, 1H), 5.33 (dddd, $J = 17.2, 1.9, 1.8, 1.8$ Hz, 1H), 5.11 (dddd, $J = 10.6, 1.7, 1.7, 1.7$ Hz, 1H), 4.74 (s, 1H), 4.61 (d, $J = 2.0$ Hz, 1H), 3.90-3.83 (m, 1H), 3.69-3.62 (m, 1H), 2.26 (dd, $J = 12.6, 3.3$ Hz, 1H), 2.11-1.97 (m, 2H), 1.79-0.66 (m, 6H), 1.68 (s, 3H).

IR (neat, cm^{-1} , ν): 3074 (w), 3017 (w), 2934 (s), 2861 (s), 1640 (m), 1452 (s), 1395 (s), 1320 (s), 1169 (s), 1123 (s), 1097 (s), 1061 (s).

HRMS (EI, m/z): calculated 274.1544 for $[\text{M}]^+$, found 274.1553.



(±)-(4R,4aS,8aS)-4-Allyl-1-methylene-4-trifluoromethyl-octahydro-naphthalen-4a-ol (2.19F) and (±)-(4R,4aR,8aR)-4-Allyl-1-methylene-4-trifluoromethyl-octahydro-naphthalen-4a-ol (2.19E):

A solution of **2.19A** (0.15 mL of a ~ 1.9 M solution in petroleum ether, 0.29 mmol maximum) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1.5 hours. Following removal of the solvent, a crude ^{19}F NMR showed a 2.5:1 mixture of products. Purification of the concentrated material by silica gel flash chromatography (10% → 30% dichloromethane/hexanes) yielded 24 mg of **2.19F** and 10 mg of **2.19E** (42% combined yield, 2 steps), both as colourless oils.

Data for 2.19F (major isomer):

^1H NMR (C_6D_6 , 300 MHz, δ): 5.92-5.78 (m, 1H), 5.06-4.99 (m, 2H), 4.73-4.71 (m, 1H), 4.50 (d, $J = 1.1$ Hz, 1H), 2.57-2.48 (m, 3H), 2.23-2.12 (m, 1H), 1.97-1.83 (m, 3H), 1.65-1.09 (m, 7H), 1.21 (d, $J = 1.8$ Hz, 1H), 1.07-0.93 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.61, 133.81, 128.58 (q, $J_{\text{CF}} = 285$ Hz), 117.93, 109.84, 74.93, 51.37 (q, $J_{\text{CF}} = 20$ Hz), 45.59, 35.91, 32.15, 29.98, 25.12, 25.06, 24.81, 21.24.

IR (neat, cm^{-1} , ν): 3083 (w), 2939 (s), 2864 (s), 1642 (w), 1451 (m), 1349 (w), 1298 (w), 1264 (w), 1236 (w), 1223 (w), 1182 (m), 1155 (s), 1112 (s).

HRMS (EI, m/z): calculated 274.1544 for $[\text{M}]^+$, found 274.1549.

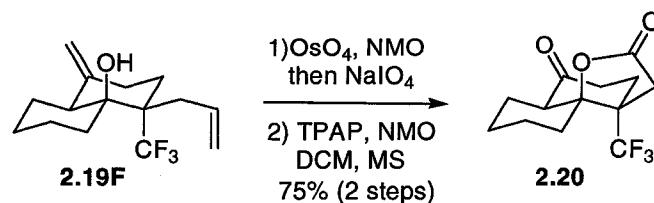
Data for 2.19E (minor isomer):

^1H NMR (C_6D_6 , 300 MHz, δ): 5.89-5.77 (m, 1H), 5.03-4.95 (m, 2H), 4.74-4.73 (m, 1H), 4.56 (s, 1H), 2.40 (ddd, $J_{\text{AB}} = 15.0$ Hz, $J_{\text{AX}} = 6.1$ Hz, $J_{\text{AY}} = 0.9$ Hz, 1H), 2.18 (ddd, $J_{\text{AB}} = 15.1$ Hz, $J_{\text{BX}} = 8.4$ Hz, 1H), 1.96-1.15 (m, 13H), 1.01-0.88 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 147.82, 133.37, 128.95 (q, $J_{\text{CF}} = 287$ Hz), 118.32, 109.84, 75.91, 51.00 (q, $J_{\text{CF}} = 19$ Hz), 44.06, 33.82, 31.52, 30.23, 25.51, 25.06, 24.36, 21.17.

IR (neat, cm^{-1} , ν): 3564 (w), 3083 (w), 2940 (s), 2863 (m), 1643 (m), 1450 (m), 1363 (w), 1339 (w), 1301 (m), 1261 (m), 1239 (m), 1197 (s), 1170 (s), 1149 (s), 1132 (s).

HRMS (EI, m/z): calculated 274.1544 for $[\text{M}]^+$, found 274.1530.



(±)-(3aR,6aR,10aS)-3a-Trifluoromethyl-octahydro-1-oxa-cyclopenta[d]naphthalene-2,6-dione (2.20):

To a solution of **2.19F** (20 mg, 0.073 mmol) in 3 mL of a 5:1 solution of tetrahydrofuran and water was added 4-methylmorpholine N-oxide (38 mg, 0.32 mmol) followed by osmium tetroxide (0.05 mL of a 4% solution in water, 0.008 mmol). After stirring for 4 hours, sodium periodate (95 mg, 0.44 mmol) was added and the reaction was stirred for an additional 15 hours before quenching with a saturated aqueous solution of sodium sulfite. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were washed twice with brine, dried with magnesium sulfate, filtered and concentrated. The crude material was dissolved in 2 mL of dichloromethane. Molecular sieves (30 mg, 4Å), tetrapropylammonium perruthenate (3 mg, 0.009 mmol), and 4-methylmorpholine N-oxide (13 mg, 0.11 mmol) were added in succession. The reaction was stirred for 30 minutes and then filtered over silica, rinsing with a 5% solution of methanol in ethyl acetate. Purification by silica gel flash chromatography (25% ethyl acetate/hexanes) yielded 15 mg (75%) of a colourless oil.

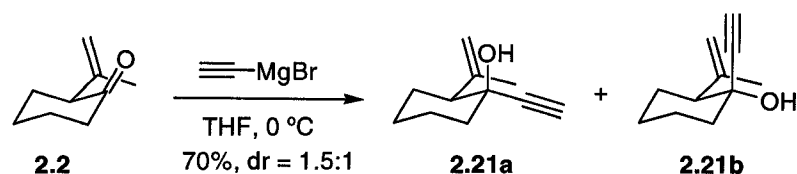
Data for 2.20:

¹H NMR (C₆D₆, 300 MHz, δ): 3.28 (d, J_{AB} = 18.0 Hz, 1H), 2.64-2.43 (m, 2H), 2.55 (d, J_{AB} = 18.1 Hz, 1H), 2.40-2.22 (m, 2H), 2.21-2.13 (m, 1H), 2.07-1.99 (m, 2H), 1.89-1.49 (m, 4H), 1.27 (dddd, J = 13.4, 13.2, 13.0, 3.5, 3.5 Hz, 1H).

¹³C NMR (CDCl₃, 75 MHz, δ): 206.28, 171.35, 126.62 (q, J_{CF} = 280 Hz), 87.24, 50.15, 36.65, 33.80, 33.64, 33.60, 27.88, 23.73, 22.99, 20.92.

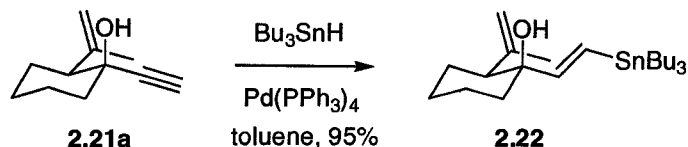
IR (neat, cm⁻¹, ν): 2946 (s), 2871 (m), 1785 (s), 1725 (s), 1450 (w), 1422 (w), 1367 (w), 1316 (m), 1280 (w), 1268 (w), 1200 (m), 1158 (s), 1140 (s).

HRMS (EI, m/z): calculated 274.1544 for [M]⁺, found 274.1560.



(±)-(1S,2S)-1-Ethynyl-2-isopropenyl-cyclohexanol (2.21a) and (±)-(1R,2S)-1-ethynyl-2-isopropenyl-cyclohexanol (2.21b):

A solution of **2.2** (206.5 mg, 1.494 mmol) in 5 mL of tetrahydrofuran was cooled to 0 °C. Ethynylmagnesium bromide (10 mL of a 0.5 M solution in tetrahydrofuran, 5 mmol) was added portion-wise and the reaction warmed to ambient temperature. After 45 minutes, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (7% diethyl ether/hexanes) yielded 103 mg of **2.21a** and 69 mg of **2.21b**, both as colourless oils (70% combined yield). Spectral data was in agreement with that reported previously for these compounds: Warrington, J. M. Ph.D. Thesis, University of Ottawa, Ottawa, Canada, 2005.



(±)-(1S,2S)-2-Isopropenyl-1-((E)-2-tributylstannanyl-vinyl)-cyclohexanol (2.22):

To a solution of **2.21a** (29 mg, 0.18 mmol) in 1.5 mL of toluene was added tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.0087 mmol). After stirring for 5 minutes, tributyltin hydride (0.060 mL, 0.22 mmol) was added and the reaction stirred for an additional 20 minutes. The crude reaction mixture was then filtered over a pad of silica, rinsing thoroughly with hexanes, concentrated and purified by silica gel flash chromatography (100% hexanes → 2% ethyl acetate/hexanes) to yield 68 mg of a colourless oil (95%).

Data for 2.22:

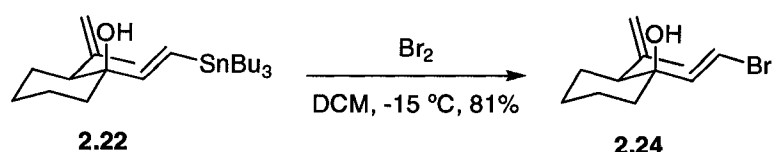
$^1\text{H NMR}$ (CDCl_3 , 500 MHz, δ): 6.03 (d, $J_{\text{AB}} = 19.2$ Hz, 1H), 5.96 (d, $J_{\text{AB}} = 19.3$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 2.04 (dd, $J = 12.9, 3.3$ Hz, 1H), 1.77 (d, $J = 1.7$ Hz, 1H), 1.74–1.70

(m, 2H), 1.70 (s, 3H), 1.64-1.55 (m, 2H), 1.52-1.40 (m, 8H), 1.31-1.21 (m, 8H), 0.95-0.78 (m, 15H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 155.68, 148.27, 121.85, 111.50, 74.18, 52.29, 38.04, 29.07 (3C), 27.44, 27.25 (3C), 26.16, 25.76, 21.36, 13.69 (3C), 9.40 (3C).

IR (neat, cm^{-1} , ν): 3357 (w), 3077 (w), 2956 (s), 2927 (s), 2871 (s), 2853 (s), 1638 (w), 1599 (w), 1461 (m), 1376 (m), 1284 (w), 1071 (m).

HRMS (EI, m/z): calculated 399.1710 for $[\text{M}-n\text{Bu}]^+$, found 399.1785.



(±)-(1S,2S)-1-((E)-2-Bromo-vinyl)-2-isopropenyl-cyclohexanol (2.24):

To a solution of **2.22** (68 mg, 0.15 mmol) in 1 mL of dichloromethane at $-15\text{ }^\circ\text{C}$ was slowly added bromine (0.16 mL of a 0.93 M solution in dichloromethane, 0.15 mmol). After ten minutes the reaction was concentrated and purified by silica gel flash chromatography (100% hexanes $\rightarrow$ 3% ethyl acetate/hexanes) to yield 29.6 mg of a pale yellow oil (81%).

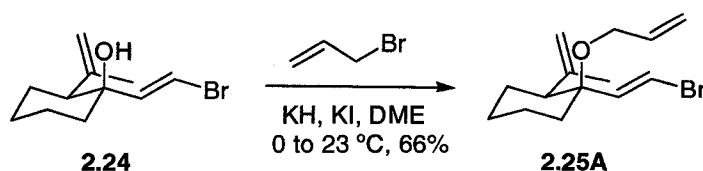
Data for 2.24:

^1H NMR (C_6D_6 , 500 MHz, δ): 6.12 (d, $J = 13.5$ Hz, 1H), 6.04 (d, $J = 13.5$ Hz, 1H), 4.79 (s, 1H), 4.64 (s, 1H), 1.71-1.61 (m, 1H), 1.64 (s, 3H), 1.59-1.54 (m, 1H), 1.49-1.45 (m, 2H), 1.32-1.30 (m, 3H), 1.10-0.98 (m, 3H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 147.55, 145.93, 112.61, 104.43, 74.14, 52.36, 37.95, 27.12, 26.00, 24.69, 21.12.

IR (neat, cm^{-1} , ν): 3536 (m), 3080 (w), 2934 (s), 2856 (m), 1695 (w), 1635 (w), 1446 (m), 1374 (m), 1289 (m), 1207 (m), 1072 (m).

HRMS (EI, m/z): calculated 165.1279 for $[\text{M}-\text{Br}]^+$, found 165.1270.



(±)-(1S,2S)-1-Allyloxy-1-((E)-2-bromo-vinyl)-2-isopropenyl-cyclohexane (2.25A):

Sodium iodide (4 mg, 0.03 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (75 mg of a 30% suspension in mineral oil, 0.56 mmol) was then added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (0.5 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated in a solution of **2.24** (25 mg, 0.10 mmol) in 1 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (50 µL, 0.58 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 19.3 mg of a colourless oil (66%).

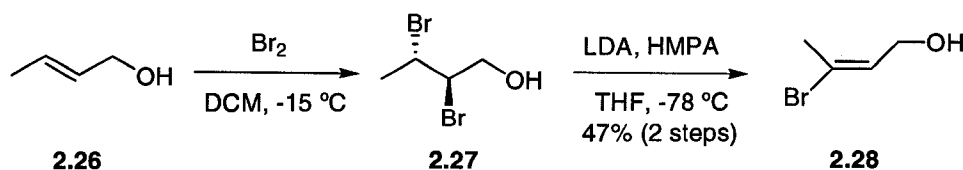
Data for **2.25A**:

¹H NMR (C₆D₆, 300 MHz, δ): 6.28 (d, *J* = 14.1 Hz, 1H), 5.84 (d, *J* = 14.0 Hz, 1H), 5.77-5.64 (m, 1H), 5.23 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.99 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.89 (s, 1H), 4.83 (s, 1H), 3.49 (d, *J* = 4.8 Hz, 2H), 2.00 (dddd, *J* = 12.8, 12.8, 12.8, 3.7 Hz, 1H), 1.82 (s, 3H), 1.77 (dd, *J* = 12.8, 3.3 Hz, 1H), 1.58-1.54 (m, 2H), 1.41-1.23 (m, 3H), 1.10-0.92 (m, 1H), 0.80 (ddd, *J* = 13.5, 13.4, 4.4 Hz, 1H).

¹³C NMR (C₆D₆, 75 MHz, δ): 146.59, 142.84, 135.73, 114.89, 114.32, 106.52, 79.12, 62.93, 55.53, 30.64, 27.45, 26.23, 22.47, 21.14.

IR (neat, cm⁻¹, ν): 3077 (w), 2933 (s), 2858 (m), 1639 (w), 1611 (w), 1449 (m), 1114 (m), 1061 (m).

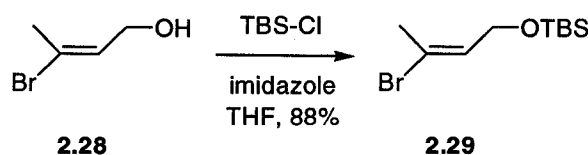
HRMS (EI, *m/z*): calculated 205.1592 for [M-Br]⁺, found 205.1586.



(*E*)-3-Bromo-but-2-en-1-ol (2.28**):**

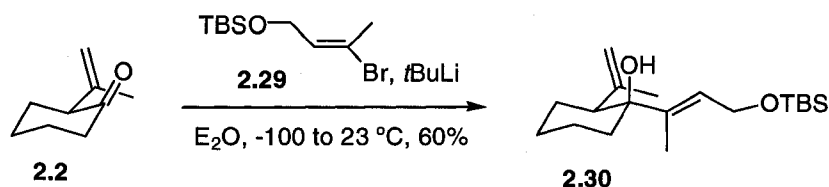
(Procedure adapted from: Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, *19*, 1051). A solution of **2.26** (1.00 mL, 11.7 mmol) in 60 mL of dichloromethane was cooled to -15 °C. Bromine (0.600 mL, 11.7 mmol)

was added drop-wise. After 1.5 hours, during which time the reaction was warmed to ambient temperature, the reaction was quenched with a saturated aqueous solution of sodium sulphite. The aqueous phase was extracted three times with dichloromethane and the combined organic layers dried with magnesium sulfate, filtered and concentrated. In a separate flask, a solution of diisopropylamine (4.20 mL, 30.0 mmol) in 40 mL of tetrahydrofuran and HMPA (0.99 mL, 5.7 mmol) was prepared and cooled to -78 °C. *n*-Butyllithium was added drop-wise and after 5 minutes, a solution of unpurified **2.27** (11.7 mmol, maximum) in 20 mL of tetrahydrofuran was added over a period of 80 minutes via a syringe pump. Once the addition was complete, the reaction was stirred for 1 hour and then quenched with water. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification of the dark brown oil by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 0.83 g (47%) of **2.28** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2268.



((E)-3-Bromo-but-2-enyloxy)-tert-butyl-dimethyl-silane (2.29):

To a stirring solution of **2.28** (0.76 g, 5.0 mmol) in 50 mL of tetrahydrofuran was added imidazole (1.03 g, 15.1 mmol) followed by *tert*-butyl(chloro)dimethylsilane (915 mg, 6.07 mmol). The resulting cloudy mixture was stirred for 40 minutes and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) gave 1.17 g of **2.29** as a colourless oil (88%). Spectral data for this compound was in agreement with that reported previously: Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5058.



(±)-(1S,2S)-1-[(E)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-propenyl]-2-isopropenyl-cyclohexanol (2.30):

A solution of **2.29** (46 mg, 0.15 mmol) in 1.5 mL of diethyl ether was cooled to -100 °C. *tert*-Butyllithium (0.160 mL of a 1.79 M solution in pentane, 0.286 mmol) was then added drop-wise and stirred for 30 minutes. To this solution was slowly cannulated a cooled solution of **2.2** (13 mg, 0.092 mmol) in 0.5 mL of diethyl ether. After 25 minutes the reaction was quenched with a saturated aqueous solution of ammonium chloride and warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) gave 18 mg of a colourless oil (60%).

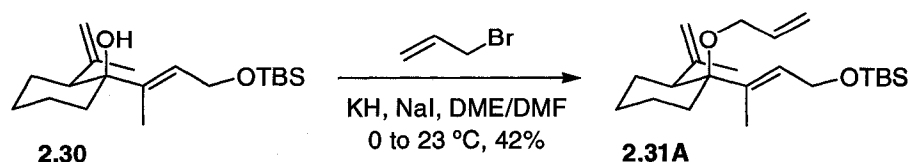
Data for 2.30:

¹H NMR (CDCl₃, 300 MHz, δ): 5.60 (ddq, *J* = 5.9, 5.9, 1.2 Hz, 1H), 4.80 (dq, *J* = 1.6, 1.6 Hz, 1H), 4.70 (s, 1H), 4.19 (dd, *J* = 5.8, 0.8 Hz, 2H), 2.29 (dd, *J* = 12.3, 3.4 Hz, 1H), 1.82-1.68 (m, 5H), 1.64 (s, 3H), 1.61 (d, *J* = 1.0 Hz, 3H), 1.51-1.43 (m, 3H), 1.30-1.14 (m, 1H), 0.87 (s, 9H), 0.03 (s, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 148.42, 141.43, 123.40, 112.01, 75.01, 60.85, 49.37, 36.32, 27.74, 26.25, 26.11 (3C), 24.73, 21.47, 18.50, 14.26, -4.96 (2C).

IR (neat, cm⁻¹, ν): 3554 (w), 3471 (w), 3065 (w), 2923 (s), 2846 (s), 1629 (m), 1461 (s), 1378 (m), 1242 (s), 1069 (s).

HRMS (EI, *m/z*): calculated 324.2485 for [M]⁺, found 324.2499.



(±)-[(E)-3-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-but-2-enyloxy]-*tert*-butyl-dimethyl-silane (2.31A):

Sodium iodide (1 mg, 0.007 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (60 mg of a 30% suspension in mineral oil, 0.45 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (0.4 mL) and dimethylformamide (0.1 mL) were added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated a solution of **2.30** (17 mg, 0.052 mmol) in another 0.4 mL of dimethoxyethane and 0.1 mL of dimethylformamide. After stirring for 20 minutes, allyl bromide (30 μ L, 0.35 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (3% diethyl ether/hexanes) yielded 8 mg of a colourless oil (42%).

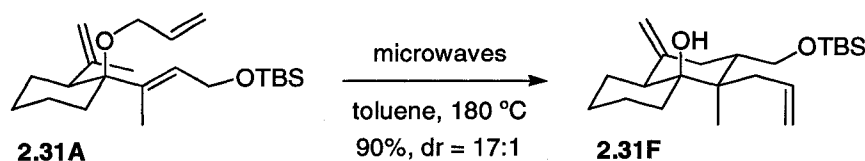
Data for 2.31A:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.95-5.83 (m, 1H), 5.41 (ddq, $J = 5.6, 5.6, 1.2$ Hz, 1H), 5.32 (dddd, $J = 17.2, 2.0, 2.0, 2.0$ Hz, 1H), 5.07 (dddd, $J = 10.6, 1.9, 1.9, 1.9$ Hz, 1H), 4.60 (dq, $J = 1.4, 1.4$ Hz, 1H), 4.56 (d, $J = 2.3$ Hz, 1H), 4.20 (d, $J = 5.1$ Hz, 2H), 3.82-3.62 (m, 2H), 2.08-1.93 (m, 2H), 1.85-1.68 (m, 2H), 1.73 (s, 3H), 1.63-1.18 (m, 5H), 1.48 (d, $J = 1.0$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.46, 137.55, 135.84, 126.38, 114.54, 112.31, 82.14, 62.49, 61.12, 55.14, 31.43, 27.79, 26.46, 26.10 (3C), 21.98, 21.79, 18.49, 14.12, -4.95 (2C).

IR (neat, cm^{-1} , ν): 3078 (w), 2929 (s), 2852 (s), 1635 (w), 1461 (m), 1365 (m), 1249 (m), 1094 (s), 1062 (s).

HRMS (EI, m/z): calculated 364.2798 for $[\text{M}]^+$, found 364.2782.



($\pm$)-(3S,4R,4aS,8aS)-4-Allyl-3-(*tert*-butyl-dimethyl-silanyloxymethyl)-4-methyl-1-methylene-octahydro-naphthalen-4a-ol (2.31F**):**

A solution of **2.31A** (6.7 mg, 0.018 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 180 °C. After 1 hour the reaction was concentrated and the crude material injected into a GC. A 17:1 ratio of isomers was found to be present. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 99 mg of an inseparable mixture of **2.31F** and an unidentified minor isomer as a colourless oil (90% combined yield).

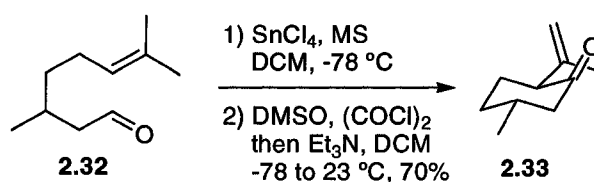
Data for 2.31F:

¹H NMR (CDCl₃, 500 MHz, δ): 6.16-6.09 (m, 1H), 4.99 (dddd, *J* = 17.2, 1.4, 1.4, 1.4 Hz, 1H), 4.95 (dddd, *J* = 10.1, 1.3, 1.0, 1.0 Hz, 1H), 4.86 (ddd, 1.7, 1.7, 1.6 Hz, 1H), 4.62 (s, 1H), 3.78 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.43 (dd, *J* = 9.9, 7.0 Hz, 1H), 2.43 (dd, *J* = 12.2, 2.7 Hz, 1H), 2.37 (dd, *J*_{AB} = 15.4, *J*_{AX} = 8.3 Hz, 1H), 2.25 (ddq, *J*_{AB} = 15.4, *J*_{BX} = 6.4, *J*_{BY} = 1.6 Hz, 1H), 2.20-2.18 (m, 1H), 2.09-2.04 (m, 2H), 1.82-1.80 (m, 1H), 1.73-1.71 (m, 1H), 1.58-1.46 (m, 5H), 1.25-1.24 (m, 1H), 1.17-1.14 (m, 1H), 0.95 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

¹³C NMR (C₆D₆, 75 MHz, δ): 149.87, 139.04, 115.59, 108.93, 78.05, 64.41, 44.82, 44.05, 43.54, 40.82, 36.35, 30.96, 26.22 (3C), 25.89, 25.01, 21.99, 18.54, 18.47, -5.13 (2C).

IR (neat, cm⁻¹, ν): 3381 (br, m), 2932 (s), 2357 (w), 1644 (w), 1458 (m), 1446 (m), 1254 (m), 1080 (s).

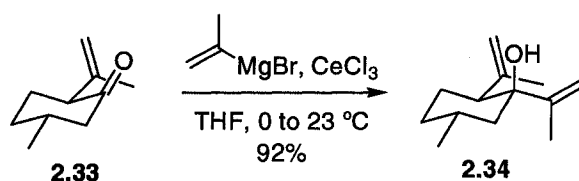
HRMS (EI, *m/z*): calculated 364.2798 for [M]⁺, found 364.2784.



(±)-(2S,5R)-2-Isopropenyl-5-methyl-cyclohexanone (2.33):

Citronellal (10.0 mL, 55.2 mmol) was added to a suspension of 4Å molecular sieves (5.5 g) in 100 mL of dichloromethane. After cooling to -78 °C, tin tetrachloride (5.52 mL of a 1.0 M solution in dichloromethane, 5.52 mmol) was added slowly. The reaction was stirred for 45 minutes before quenching with a saturated aqueous solution of ammonium chloride. The aqueous phase was thawed and then extracted three times with ethyl acetate. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. In a separate flask, a solution of oxalyl chloride (2.95 mL, 33.8 mmol) in 100 mL of dichloromethane was

prepared and cooled to $-78\text{ }^{\circ}\text{C}$. Dimethylsulfoxide (4.80 mL, 67.6 mmol) was added slowly and the reaction was stirred for 20 minutes. (*Note: large amounts of gas are evolved during the addition of dimethylsulfoxide. Adequate venting of the reaction vessel must be ensured*). A solution of the crude alcohol (55.2 mmol, maximum) in 10 mL of dichloromethane was cannulated into the reaction mixture and the resulting solution stirred at $-78\text{ }^{\circ}\text{C}$ for another 1.5 hours. Triethylamine (20.1 mL, 144 mmol) was added slowly and the thick, pale-yellow mixture warmed to $0\text{ }^{\circ}\text{C}$ for 1 hour. The now pale orange reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 5.88 g (70% over 2 steps) of ketone **2.33** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Moreira, J. A.; Correa, A. G. *Tetrahedron: Asymmetry* **2003**, *14*, 3787.



(±)-(1S,2S,5R)-1,2-Diisopropenyl-5-methyl-cyclohexanol (2.34):

Anhydrous Cerium (III) chloride (210 mg, 0.852 mmol) was suspended in 4 mL of cold tetrahydrofuran and stirred for 1 hour. A solution of **2.33** (65 mg, 0.43 mmol) in 1 mL of tetrahydrofuran was cannulated into the suspension and cooled to $0\text{ }^{\circ}\text{C}$. Isopropenylmagnesium bromide (4.0 mL of a 0.5 M solution in tetrahydrofuran, 2.0 mmol) was added slowly and the reaction was warmed to ambient temperature. After 3 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) gave 76 mg of a colourless oil (92%).

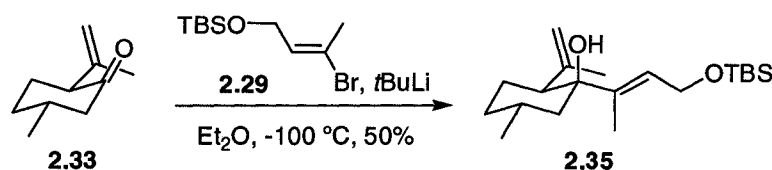
Data for 2.34:

^1H NMR (CDCl_3 , 300 MHz, δ): 4.96 (s, 1H), 4.82 (s, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 2.23 (dd, $J = 12.6, 3.5$ Hz, 1H), 1.87-1.81 (m, 2H), 1.80-1.72 (m, 2H), 1.77 (s, 3H), 1.69 (s, 3H), 1.54-1.22 (m, 3H), 0.98-0.88 (m, 1H), 0.85 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 150.86, 148.21, 111.67, 109.41, 75.58, 49.16, 45.18, 34.79, 27.66, 27.28, 24.56, 22.22, 20.01.

IR (neat, cm^{-1} , ν): 3551 (w), 3486 (w), 3080 (w), 2949 (s), 2926 (s), 2866 (m), 2842 (m), 1636 (m), 1453 (m), 1376 (m), 1139 (w), 1079 (w).

HRMS (EI, m/z): calculated 194.1671 for $[\text{M}]^+$, found 194.1675.



(±)-(1S,2S,5R)-1-[(E)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-propenyl]-2-isopropenyl-5-methyl-cyclohexanol (2.35):

A solution of **2.29** (94 mg, 0.30 mmol) in 3 mL of diethyl ether was cooled to $-100\text{ }^{\circ}\text{C}$. *tert*-Butyllithium (0.330 mL of a 1.79 M solution in pentane, 0.591 mmol) was added drop-wise and stirred for 30 minutes. To this solution was slowly cannulated a cooled solution of **2.33** (33 mg, 0.22 mmol) in 1 mL of diethyl ether. After 30 minutes the reaction was quenched with a saturated aqueous solution of ammonium chloride and warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) gave 36 mg of a colourless oil (50%).

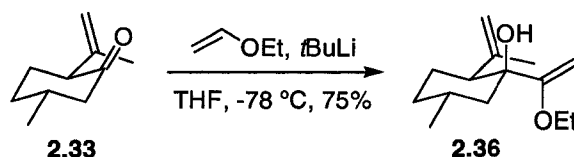
Data for 2.35:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.59 (ddq $J = 5.6, 5.6, 1.1$ Hz, 1H), 4.81 (dq, $J = 1.5, 1.5$ Hz, 1H), 4.70 (s, 1H), 4.18 (dd, $J = 5.8, 0.7$ Hz, 2H), 2.24 (dd, $J = 12.5, 3.5$ Hz, 1H), 1.85-1.67 (m, 4H), 1.64 (s, 3H), 1.61 (d, $J = 0.8$ Hz, 3H), 1.49-1.43 (m, 2H), 1.34-1.29 (m, 1H), 0.92-0.86 (m, 1H), 0.87 (s, 9H), 0.85 (d, $J = 6.5$ Hz, 3H), 0.03 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.21, 141.26, 123.44, 112.06, 75.46, 60.86, 48.93, 44.92, 34.95, 27.78, 27.48, 26.11 (3C), 24.88, 22.39, 18.50, 14.27, -4.96 (2C).

IR (neat, cm^{-1} , ν): 3548 (w), 3471 (w), 2955 (s), 2852 (s), 1629 (w), 1468 (m), 1384 (m), 1249 (m), 1094 (s), 1056 (s).

HRMS (EI, m/z): calculated 338.2641 for $[\text{M}]^+$, found 338.2654.



(±)-(1S,2S,5R)-1-(1-Ethoxy-vinyl)-2-isopropenyl-5-methyl-cyclohexanol (2.36):

Ethyl vinyl ether (1.00 mL, 10.5 mmol) was dissolved in 0.5 mL of tetrahydrofuran and cooled to $-78\text{ }^\circ\text{C}$. *tert*-Butyllithium (2.40 mL of a 1.75 M solution in pentane, 4.20 mmol) was added drop-wise and the reaction stirred for 30 minutes, then immersed in an ice bath for ten minutes during which time the reaction went from pale yellow/green to colourless. Following re-immersion into the $-78\text{ }^\circ\text{C}$ bath, a solution of **2.33** (90 mg, 0.59 mmol) in 5 mL of tetrahydrofuran (also at $-78\text{ }^\circ\text{C}$) was slowly cannulated into the reaction mixture. Monitoring by TLC showed no further conversion after 45 minutes so the reaction was quenched with isopropanol, then water, diluted with diethyl ether and the aqueous phase extracted three times with diethyl ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% diethyl ether/hexanes, basified with triethylamine) gave 100 mg of a colourless oil (75%).

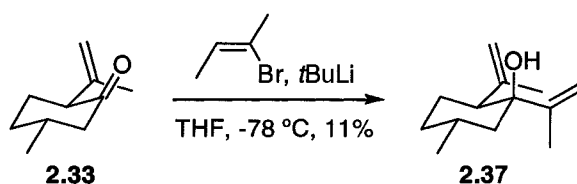
Data for 2.36:

^1H NMR (C_6D_6 , 300 MHz, δ): 4.86 (dq, $J = 1.6, 1.6\text{ Hz}$, 1H), 4.78 (s, 1H), 4.48 (d, $J = 1.9\text{ Hz}$, 1H), 3.85 (d, $J = 1.9\text{ Hz}$, 1H), 3.45-3.28 (m, 2H), 2.56 (dd, $J = 13.1, 3.6\text{ Hz}$, 1H), 2.02-1.85 (m, 3H), 1.82-1.76 (m, 1H), 1.72 (s, 3H), 1.69-1.60 (m, 2H), 1.52-1.44 (m, 1H), 1.03 (t, $J = 7.8\text{ Hz}$, 3H), 0.96-0.83 (m, 1H), 0.84 (d, $J = 6.6\text{ Hz}$, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 168.13, 148.43, 111.81, 79.36, 74.13, 62.66, 48.92, 45.56, 35.01, 27.66, 27.55, 24.68, 22.46, 14.54.

IR (neat, cm^{-1} , ν): 3544 (m), 3078 (w), 2978 (m), 2948 (s), 2868 (m), 2846 (m), 1656 (m), 1635 (m), 1612 (m), 1455 (m), 1445 (m), 1374 (m), 1276 (s), 1222 (s), 1145 (s), 1079 (s), 1066 (s).

HRMS (EI, m/z): calculated 224.1776 for $[\text{M}]^+$, found 224.1776.



(±)-(1S,2S,5R)-2-Isopropenyl-5-methyl-1-((Z)-1-methyl-propenyl)-cyclohexanol (2.37):

To a solution of 2-bromo-*trans*-2-butene (0.060 mL, 0.59 mmol) in 2.0 mL of tetrahydrofuran at -78 °C was added *tert*-butyllithium (0.730 mL of a 1.60 M solution in pentane, 1.17 mmol). After stirring for 30 minutes, ketone **2.33** (45 mg, 0.30 mmol) was cannulated into the reaction mixture with 1 mL of tetrahydrofuran. The reaction was allowed to stir for 45 minutes and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (1.5% ethyl acetate/hexanes) yielded 7 mg of **2.37** as a colourless oil (11%).

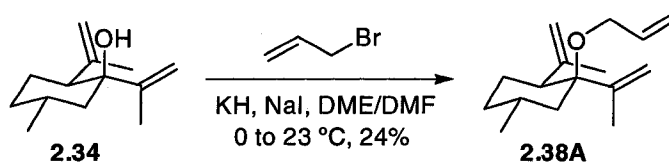
Data for 2.37:

¹H NMR (C₆D₆, 500 MHz, δ): 5.28 (dddd, *J* = 7.5, 7.4, 7.4, 1.4 Hz, 1H), 4.89 (s, 1H), 4.88 (s, 1H), 2.28 (dd, *J* = 12.8, 3.5 Hz, 1H), 1.95-1.80 (m, 2H), 1.83 (s, 6H), 1.73-1.70 (m, 1H), 1.71 (s, 3H), 1.67-1.64 (m, 2H), 1.47 (dddd, *J* = 13.1, 3.6, 3.5, 3.5 Hz, 1H), 1.38 (dd, *J* = 12.8, 12.7 Hz, 1H), 0.89-0.81 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H).

¹³C NMR (C₆D₆, 125 MHz, δ): 148.47, 141.28, 120.55, 111.98, 77.46, 49.92, 46.11, 35.15, 27.88, 27.25, 24.41, 23.73, 22.41, 15.49.

IR (neat, cm⁻¹, ν): 3535 (br, w), 3069 (w), 2934 (s), 2861 (s), 1634 (w), 1449 (m), 1375 (m).

HRMS (EI, *m/z*): calculated 208.1827 for [M]⁺, found 208.1835.



(±)-(1S,2S,5R)-1-Allyloxy-1,2-diisopropenyl-5-methyl-cyclohexane (2.38A):

Sodium iodide (4 mg, 0.03 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (195 mg of a 30% suspension in mineral oil, 1.46 mmol) was then added

to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1.2 mL) and dimethylformamide (0.3 mL) were added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated a solution of **2.34** (59 mg, 0.30 mmol) in another 1.1 mL of dimethoxyethane and 0.4 mL of dimethylformamide. After stirring for 20 minutes, allyl bromide (130 μ L, 1.50 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 17.2 mg of a colourless oil (24%).

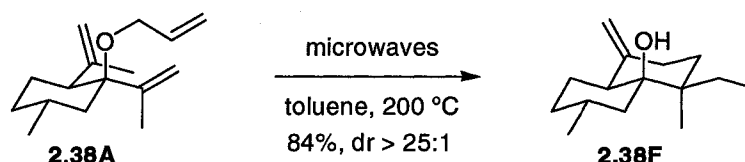
Data for 2.38A:

^1H NMR (C_6D_6 , 500 MHz, δ): 5.92-5.88 (m, 1H), 5.43 (dddd, $J = 17.4, 1.6, 1.6, 1.6$ Hz, 1H), 5.11 (dd, $J = 10.8, 1.6$ Hz, 1H), 4.98 (s, 1H), 4.97 (s, 1H), 4.89 (s, 1H), 4.86 (s, 1H), 3.77-3.69 (m, 2H), 2.22 (dddd, $J = 12.6, 12.6, 12.6, 4.0$ Hz, 1H), 2.04 (dd, $J = 12.4, 3.8$ Hz, 1H), 1.97 (s, 3H), 1.75-1.57 (m, 3H), 1.66 (s, 3H), 1.52-1.47 (m, 1H), 1.12 (dd, $J = 14.1, 12.3$ Hz, 1H), 0.92-0.83 (m, 1H), 0.86 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 148.04, 146.39, 135.93, 114.46, 112.75, 112.04, 82.75, 62.68, 54.39, 40.42, 35.32, 27.87, 27.81, 22.51, 22.02, 20.06.

IR (neat, cm^{-1} , ν): 3071 (w), 2949 (s), 2926 (s), 2866 (m), 1646 (w), 1455 (m), 1375 (m), 1192 (m), 1137 (m), 1114 (m), 1064 (m).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.1968.



(±)-(4S,4aS,6R,8aS)-4-Allyl-4,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.38F):

A solution **2.38A** (15 mg, 0.064 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1.5 hours the reaction was

concentrated and purified by silica gel flash chromatography (4% ethyl acetate/hexanes) to yield 12.5 mg of a colourless oil (84%).

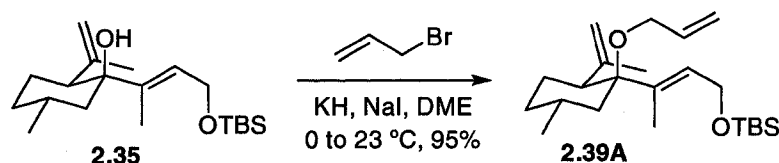
Data for 2.38F:

^1H NMR (C_6D_6 , 300 MHz, δ): 5.87-5.73 (m, 1H), 5.07 (s, 1H), 5.03 (d, $J = 6.7$ Hz, 1H), 4.79 (s, 1H), 4.58 (s, 1H), 2.50 (dd, $J = 13.3, 7.8$ Hz, 1H), 2.14-1.96 (m, 4H), 1.83-1.76 (m, 2H), 1.63-1.24 (m, 6H), 1.13 (s, 1H), 0.92-0.68 (m, 1H), 0.85 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 150.49, 136.49, 117.02, 108.64, 76.86, 44.01, 41.28, 40.82, 39.24, 35.62, 34.47, 32.61, 27.69, 24.90, 22.74, 20.20.

IR (neat, cm^{-1} , ν): 3563 (w), 3075 (w), 2927 (s), 2865 (m), 1640 (m), 1451 (w), 1376 (m), 1088 (w).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.1980.



(±)-[(E)-3-((1S,2S,5R)-1-Allyloxy-2-isopropenyl-5-methyl-cyclohexyl)-but-2-enyloxy]-*tert*-butyl-dimethyl-silane (2.39A):

Sodium iodide (2 mg, 0.01 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (75 mg of a 30% suspension in mineral oil, 0.56 mmol) was added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (0.5 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated in a solution of **2.35** (35 mg, 0.10 mmol) in another 0.5 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (50 μL , 0.578 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% diethyl ether/hexanes) yielded 38 mg of a colourless oil (95%).

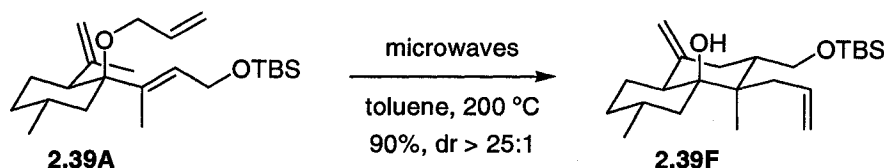
Data for 2.39A:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.94-5.82 (m, 1H), 5.41 (ddq, $J = 5.6, 5.6, 1.2$ Hz, 1H), 5.31 (dddd, $J = 17.2, 2.0, 2.0, 2.0$ Hz, 1H), 5.07 (dddd, $J = 10.6, 2.0, 2.0, 2.0$ Hz, 1H), 4.61 (dq, $J = 1.4, 1.4$ Hz, 1H), 4.56 (d, $J = 2.5$ Hz, 1H), 4.26-4.14 (m, 2H), 3.78-3.63 (m, 2H), 2.12-1.93 (m, 2H), 1.80-1.68 (m, 2H), 1.72 (s, 3H), 1.67-1.56 (m, 1H), 1.48 (d, $J = 1.1$ Hz, 3H), 1.38-1.20 (m, 2H), 0.89-0.87 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.11, 137.19, 135.64, 126.15, 114.37, 112.27, 82.35, 62.38, 60.95, 54.57, 40.03, 35.07, 27.59, 27.58, 25.94 (3C), 22.45, 21.83, 18.34, 13.90, -5.13 (2C).

IR (neat, cm^{-1} , ν): 2923 (s), 2852 (s), 1642 (w), 1448 (m), 1365 (m), 1249 (m), 1056 (m).

HRMS (EI, m/z): calculated 378.2954 for $[\text{M}]^+$, found 378.2964.



(±)-(3S,4R,4aS,6R,8aS)-4-Allyl-3-(*tert*-butyl-dimethyl-silanyloxymethyl)-4,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.39F):

A solution of 2.39A (62 mg, 0.16 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour the reaction was concentrated and purified by silica gel flash chromatography (4% diethyl ether/hexanes) to yield 59 mg of a colourless oil (90%).

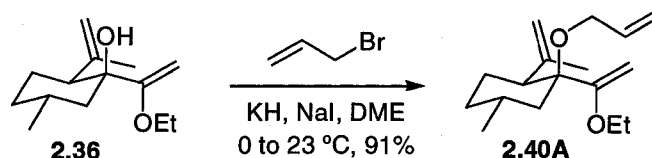
Data for 2.39F:

^1H NMR (CDCl_3 , 300 MHz, δ): 6.19-6.05 (m, 1H), 5.00 (d, $J = 16.3$ Hz, 1H), 4.95 (dd, $J = 9.0, 1.0$ Hz, 1H), 4.87 (d, $J = 1.6$ Hz, 1H), 4.62 (s, 1H), 3.78 (dd, $J = 9.9, 3.7$ Hz, 1H), 3.42 (dd, $J = 9.9, 7.1$ Hz, 1H), 2.44 (d, $J = 9.7$ Hz, 1H), 2.39 (dd, $J_{\text{AB}} = 15.4, J_{\text{AX}} = 8.1$ Hz, 1H), 2.24 (dd, $J_{\text{AB}} = 15.4, J_{\text{BX}} = 6.5$ Hz, 1H), 2.15-1.98 (m, 3H), 1.80-1.67 (m, 3H), 1.59-1.54 (m, 4H), 1.10 (dd, $J = 12.6, 12.0$ Hz, 1H), 0.93 (s, 3H), 0.88 (d, $J = 8.2$ Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.64, 138.49, 115.59, 108.38, 78.76, 64.03, 43.96 (2C), 42.52, 40.14, 39.77, 35.74, 34.07, 27.50, 25.92 (3C), 24.63, 22.60, 18.41, 18.25, -5.38 (2C).

IR (neat, cm^{-1} , ν): 3381 (br, m), 2944 (s), 2926 (s), 2854 (m), 1638 (w), 1458 (m), 1254 (m), 1110 (s), 1080 (s).

HRMS (EI, m/z): calculated 378.2954 for $[M]^+$, found 378.2897.



(±)-(1S,2S,5R)-1-Allyloxy-1-(1-ethoxy-vinyl)-2-isopropenyl-5-methyl-cyclohexane (2.40A):

Sodium iodide (7 mg, 0.05 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (285 mg of a 30% suspension in mineral oil, 2.13 mmol) was then added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (2 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated **2.36** (97 mg, 0.43 mmol) in another 2.3 mL of dimethoxyethane and the reaction was stirred for 20 minutes. Allyl bromide (0.190 mL, 2.196 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes, basified with triethylamine) yielded 104 mg of a colourless oil (91%).

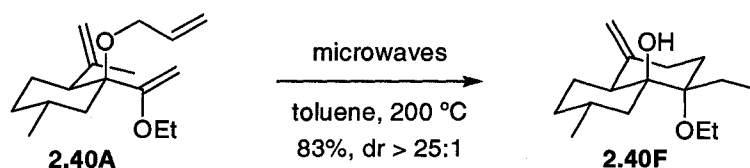
Data for 2.40A:

^1H NMR (C_6D_6 , 300 MHz, δ): 5.94-5.82 (m, 1H), 5.43 (dddd, $J = 17.2, 2.0, 1.9, 1.9$ Hz, 1H), 5.09 (dddd, $J = 10.6, 1.9, 1.8, 1.8$ Hz, 1H), 4.87 (dq, $J = 1.3, 1.4$ Hz, 1H), 4.83 (d, $J = 2.7$ Hz, 1H), 4.28 (d, $J = 1.9$ Hz, 1H), 4.05-3.98 (m, 1H), 3.96 (d, $J = 1.9$ Hz, 1H), 3.83-3.76 (m, 1H), 3.41 (q, $J = 7.0$ Hz, 2H), 2.39 (dd, $J = 12.9, 3.2$ Hz, 1H), 2.16 (dddd, $J = 12.9, 12.9, 12.9, 3.3$ Hz, 1H), 1.96 (s, 3H), 1.91-1.80 (m, 1H), 1.67-1.47 (m, 4H), 1.07 (t, $J = 7.0$ Hz, 3H), 0.98-0.87 (m, 1H), 0.83 (d, $J = 5.8$ Hz, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 162.56, 148.10, 136.02, 114.52, 112.23, 81.69, 80.98, 63.24, 62.66, 53.62, 39.02, 35.20, 27.80, 27.40, 22.58, 22.03, 14.63.

IR (neat, cm^{-1} , ν): 3069 (w), 2979 (s), 2950 (s), 2868 (s), 1645 (m), 1619 (m), 1456 (m), 1374 (m), 1290 (m), 1270 (s), 1228 (s), 1143 (s), 1113 (m), 1066 (s).

HRMS (EI, m/z): calculated 264.2089 for $[M]^+$, found 264.2091.



(±)-(4R,4aS,6R,8aS)-4-Allyl-4-ethoxy-6-methyl-1-methylene-octahydro-naphthalen-4a-ol (2.40F):

A solution of **2.40A** (36 mg, 0.14 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour the reaction was concentrated and purified by silica gel flash chromatography (4% diethyl ether/hexanes, basified with triethylamine) to yield 30 mg of a colourless oil (83%).

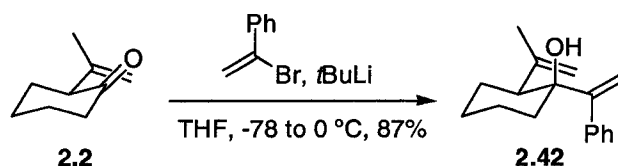
Data for 2.40F:

¹H NMR (C₆D₆, 300 MHz, δ): 6.09-5.95 (m, 1H), 5.02 (d, *J* = 15.2 Hz, 1H), 4.98 (d, *J* = 8.1, 1H), 4.83 (s, 1H), 4.62 (s, 1H), 3.28 (dq, *J* = 8.5, 7.0 Hz, 1H), 3.12 (dq, *J* = 8.5, 7.0 Hz, 1H), 2.76-2.70 (m, 1H), 2.59-2.43 (m, 2H), 2.17-2.09 (m, 1H), 1.96-1.81 (m, 3H), 1.68-1.39 (m, 6H), 1.29 (s, 1H), 1.04 (t, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.96-0.83 (m, 1H).

¹³C NMR (C₆D₆, 75 MHz, δ): 150.32, 137.12, 115.97, 108.63, 79.27, 77.41, 57.21, 43.40, 38.70, 38.47, 34.25, 32.08, 29.94, 27.83, 24.74, 22.83, 16.17.

IR (neat, cm⁻¹, ν): 3559 (w), 3077 (w), 2974 (s), 2927 (s), 2868 (m), 1641 (m), 1454 (m), 1351 (w), 1281 (w), 1175 (w), 1103 (s), 1083 (s).

HRMS (EI, *m/z*): calculated 264.2089 for [M]⁺, found 264.2080.



(±)-(1S,2S)-2-Isopropenyl-1-(1-phenyl-vinyl)-cyclohexanol (2.42):

A solution of α-bromostyrene (0.160 mL, 1.11 mmol) in 5 mL of tetrahydrofuran was cooled to -78 °C. *tert*-Butyllithium (1.3 mL of a 1.7 M solution in pentane, 2.2 mmol) was added drop-wise and the resulting blood-red solution was stirred for 10 minutes. A solution of ketone **2.2** (75 mg, 0.54 mmol) in 0.5 mL of tetrahydrofuran was added slowly and the reaction was warmed gradually to 0 °C. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl

acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 114 mg of a colourless oil (87%).

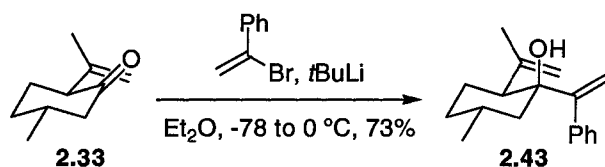
Data for 2.42:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.32 (s, 5H), 5.43 (d, $J = 1.4$ Hz, 1H), 5.09 (d, $J = 1.4$ Hz, 1H), 4.95-4.93 (m, 1H), 4.90-4.89 (m, 1H), 2.44 (dd, $J = 12.6, 3.6$ Hz, 1H), 1.93-1.68 (m, 6H), 1.86 (s, 3H), 1.63-1.54 (m, 2H), 1.33-1.26 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 157.33, 148.79, 142.16, 129.17 (2C), 128.11 (2C), 127.33, 114.59, 113.38, 76.26, 51.77, 40.64, 28.89, 26.47, 24.86, 21.92.

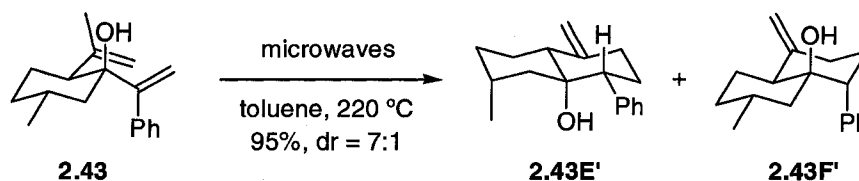
IR (neat, cm^{-1} , ν): 3563 (br, w), 3079 (m), 3025 (w), 2934 (s), 2855 (s), 1636 (m), 1596 (w), 1574 (w), 1492 (m), 1443 (m), 1373 (m), 1285 (w), 1188 (w), 1144 (m), 1073 (m), 1029 (m).

HRMS (EI, m/z): calculated 242.1671 for $[\text{M}]^+$, found 242.1671.



(±)-(1S,2S,5R)-2-Isopropenyl-5-methyl-1-(1-phenyl-vinyl)-cyclohexanol (2.43):

A solution of α -bromostyrene (0.34 mL, 2.64 mmol) in 10 mL of diethyl ether was cooled to -78 °C. *tert*-Butyllithium (2.5 mL of a 1.7 M solution in pentane, 4.2 mmol) was added dropwise and the reaction was stirred for 1.5 hours. A solution of ketone **2.33** (99 mg, 0.66 mmol) in 1 mL of diethyl ether was added by cannula and the resulting mixture was warmed gradually to 0 °C. The reaction was then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 122.5 mg of a pale yellow oil (73%). Spectral data for this compound was in agreement with that reported previously: Denissova, I. Ph.D Thesis, University of Ottawa, Ottawa, Canada, 2004.



(±)-(4R,4aR,6R,8aR)-6-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.43E') and (±)-(4R,4aS,6R,8aS)-6-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.43F'):

A solution of **2.43** (18.5 mg, 0.0722 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 220 °C. After 1 hour the reaction was concentrated. Purification by silica gel flash chromatography (2% → 5% ethyl acetate/hexanes) yielded 15.4 mg of **2.43E'** (83%) as a white solid, and 2.2 mg of **2.43F'** (12%) as a colourless oil.

Data for 2.43E':

¹H NMR (CDCl₃, 500 MHz, δ): 7.28-7.21 (m, 5H), 4.97 (d, *J* = 1.5 Hz, 1H), 4.78 (s, 1H), 2.55 (dd, *J* = 12.9, 3.9 Hz, 1H), 2.43 (ddd, *J* = 12.9, 4.2, 2.4 Hz, 1H), 2.20 (ddd, *J* = 13.2, 13.2, 4.9 Hz, 1H), 2.10 (d, *J* = 12.0 Hz, 1H), 1.98 (dddd, *J* = 13.2, 13.2, 13.2, 4.4 Hz, 1H), 1.92-1.87 (m, 1H), 1.80 (dddd, *J* = 12.7, 12.7, 12.0, 5.1 Hz, 1H), 1.76-1.71 (m, 1H), 1.60-1.56 (m, 2H), 1.47-1.41 (m, 2H), 1.34 (d, *J* = 1.2 Hz, 1H), 1.11 (d, *J* = 14.4 Hz, 1H), 1.00 (d, *J* = 7.3 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.73, 142.32, 129.13, 127.88, 126.25 (2C), 108.68 (2C), 74.17, 55.26, 50.59, 41.64, 36.33, 31.21, 30.74, 26.99, 20.16, 18.74.

IR (neat, cm⁻¹, ν): 3553 (w, br), 3084 (w), 3061 (w), 3026 (w), 2988 (w), 2934 (s), 2907 (s), 2872 (s), 2849 (m), 1645 (m), 1491 (m), 1453 (m), 1376 (m), 1361 (w), 1326 (w), 1211 (w), 1157 (w), 1138 (w), 1091 (w).

HRMS (EI, *m/z*): calculated 256.1827 for [M]⁺, found 256.1839.

mp = 82.1-84.3 °C.

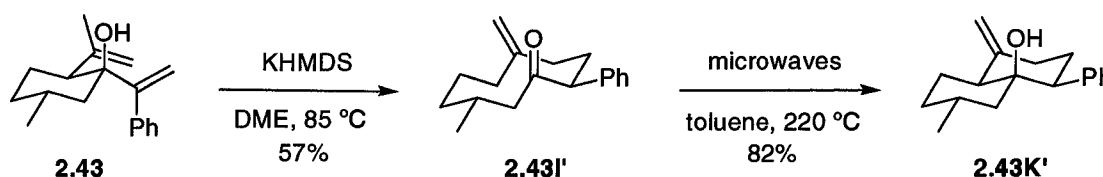
Data for 2.43F':

¹H NMR (CDCl₃, 500 MHz, δ): 7.39 (d, *J* = 7.3 Hz, 2H), 7.30-7.27 (m, 2H), 7.25-7.22 (m, 1H), 5.01 (d, *J* = 1.5 Hz, 1H), 4.77 (d, *J* = 1.5 Hz, 1H), 2.84 (dd, *J* = 5.9, 0.8 Hz, 1H), 2.63 (ddd, *J* = 13.7, 13.7, 4.6 Hz, 1H), 2.53 (dd, *J* = 10.0, 6.6 Hz, 1H), 2.32-2.19 (m, 2H), 1.91 (d, *J* = 1.7 Hz, 1H), 1.80-1.57 (m, 5H), 1.46 (ddd, *J* = 13.9, 3.2, 2.3 Hz, 1H), 0.83-0.75 (m, 1H), 0.72-0.67 (m, 1H), 0.71 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.62, 144.22, 129.21 (2C), 128.34 (2C), 126.31, 109.68, 75.25, 53.12, 44.96, 44.26, 34.13, 32.62, 29.64, 27.39, 24.35, 22.08.

IR (neat, cm^{-1} , ν): 3476 (w, br), 3085 (w), 3060 (w), 3023 (w), 2928 (s), 2866 (m), 1642 (w), 1488 (w), 1448 (m), 1368 (w), 1346 (w), 1269 (w), 1214 (w), 1090 (m);

HRMS (EI, m/z): calculated 256.1827 for $[\text{M}]^+$, found 256.1819;



(±)-(4S,4aS,6R,8aS)-6-Methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.43K'):

Potassium bis(trimethylsilyl)amide (168 mg, 0.842 mmol) was added to a solution of **2.43** (15.7 mg, 0.0612 mmol) in 1.5 mL of dimethoxyethane and 0.5 mL of toluene. The reaction was heated to 85 °C for 1.5 hours, cooled to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 9 mg of **2.43I'** (57%) which was then re-dissolved in 15 mL of toluene. After sparging with argon for 15 minutes, the solution was heated to 220 °C in a microwave for 30 minutes, cooled and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 7.4 mg of **2.43K'** (82%) as a white solid.

Data for 2.43K':

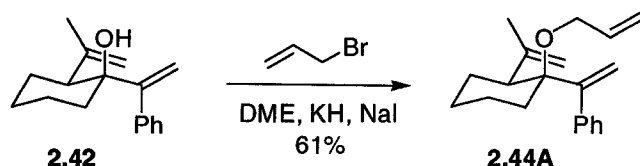
^1H NMR (CDCl_3 , 500 MHz, δ): 7.27-7.18 (m, 5H), 4.95 (d, $J = 1.5$ Hz, 1H), 4.74 (d, $J = 1.0$ Hz, 1H), 2.58 (dd, $J = 12.9, 3.7$ Hz, 1H), 2.44 (ddd, $J = 12.9, 4.2, 2.4$ Hz, 1H), 2.19 (ddd, $J = 13.2, 13.2, 4.5$ Hz, 1H), 2.07-2.03 (m, 1H), 2.00 (dddd, $J = 13.2, 13.2, 13.2, 4.4$ Hz, 1H), 1.80-1.69 (m, 2H), 1.62-1.54 (m, 3H), 1.40 (d, $J = 1.2$ Hz, 1H), 1.25 (ddd, $J = 13.7, 3.7, 2.0$ Hz, 1H), 0.97-0.89 (m, 1H), 0.86 (dd, $J = 13.1, 12.5$ Hz, 1H), 0.74 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.47, 142.22, 127.89, 127.88 (2C), 126.26 (2C), 108.83, 73.64, 54.60, 49.58, 45.26, 36.44, 34.29, 31.03, 27.29, 24.11, 22.11.

IR (neat, cm^{-1} , ν): 3557 (w), 3084 (w), 3061 (w), 3026 (w), 2926 (s), 2866 (m), 2837 (m), 1644 (m), 1603 (w), 1493 (m), 1453 (s), 1378 (w), 1223 (w), 1130 (w), 1095 (w)

HRMS (EI, m/z): calculated 256.1827 for $[\text{M}]^+$, found 256.1804.

mp = 75.9-78.6 °C.



(±)-[1-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-vinyl]-benzene (2.44A):

Sodium iodide (2 mg, 0.01 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (87 mg, 2.2 mmol) was then added to the flask and 2 mL of dimethoxyethane was added. The suspension was cooled to 0 °C and a solution of **2.42** (78 mg, 0.32 mmol) in another 1 mL of dimethoxyethane was added via cannula and the reaction stirred for 10 minutes. Allyl bromide (0.11 mL, 1.3 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 56 mg of a colourless oil (61%).

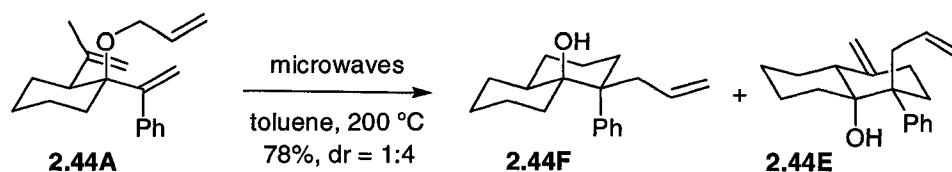
Data for 2.44A:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.35-7.20 (m, 5H), 6.04-5.92 (m, 1H), 5.41 (dddd, $J = 17.2$, 1.9, 1.9, 1.9 Hz, 1H), 5.31 (d, $J = 2.2$ Hz, 1H), 5.16 (dddd, $J = 10.6$, 1.9, 1.7, 1.7 Hz, 1H), 5.09 (d, $J = 2.2$ Hz, 1H), 4.87-4.86 (m, 2H), 4.03-3.86 (m, 2H), 2.36 (dd, $J = 12.4$, 3.3 Hz, 1H), 2.15 (dddd, $J = 12.8$, 12.7, 12.6, 3.7 Hz, 1H), 1.92-1.88 (m, 1H), 1.91 (s, 3H), 1.78-1.71 (m, 1H), 1.54-1.37 (m, 3H), 1.31-1.16 (m, 2H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.45, 148.29, 142.74, 135.66, 128.55 (2C), 127.58 (2C), 126.56, 116.05, 114.52, 113.33, 82.15, 61.97, 53.69, 32.39, 27.87, 25.99, 22.26, 21.32.

IR (neat, cm^{-1} , ν): 3077 (s), 3015 (m), 2932 (s), 2857 (s), 1638 (m), 1491 (m), 1448 (m), 1384 (w), 1152 (m), 1114 (m), 1087 (w), 1061 (s), 1028 (s).

HRMS (EI, m/z): calculated 282.1984 for $[\text{M}]^+$, found 282.1961.



(±)-(4S,4aS,8aS)-4-Allyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.44F) and (±)-(4S,4aR,8aR)-4-Allyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.44E):

A solution of **2.44A** (41.6 mg, 0.147 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour the reaction was concentrated and a crude NMR taken to reveal a 1:4 ratio of isomers. Purification by silica gel flash chromatography (100% hexanes → 2% ethyl acetate/hexanes) yielded 6.9 mg of **2.44F** and 25.6 mg of **2.44E**, both as colourless oils (78%, combined yield).

Data for 4.44F (minor isomer):

¹H NMR (CDCl₃, 500 MHz, δ): 7.60-7.58 (m, 2H), 7.30-7.18 (m, 3H), 5.31-5.23 (m, 1H), 5.02 (d, *J* = 1.6 Hz, 1H), 4.98-4.93 (m, 1H), 4.83-4.80 (m, 1H), 4.77 (d, *J* = 1.7 Hz, 1H), 2.99 (dd, *J* = 14.4, 5.3 Hz, 1H), 2.82 (ddd, *J* = 14.1, 14.1, 5.8 Hz, 1H), 2.50 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.46 (ddd, *J* = 14.4, 6.1, 2.1 Hz, 1H), 2.20-2.15 (m, 2H), 2.04-2.01 (m, 1H), 1.80 (ddd, *J* = 14.4, 14.2, 6.2 Hz, 1H), 1.68 (d, *J* = 1.7 Hz, 1H), 1.67-1.59 (m, 1H), 1.53-1.41 (m, 5H), 0.98-0.90 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.72, 144.18, 135.88, 130.26 (2C), 127.38 (2C), 125.95, 116.91, 110.19, 76.67, 49.29, 43.93, 41.71, 34.66 (2C), 32.36, 25.14, 25.05, 21.65.

IR (neat, cm⁻¹, ν): 3551 (w), 3069 (w), 3058 (w), 2931 (s), 2860 (m), 1638 (w), 1497 (w), 1452 (m), 1348 (w), 1289 (w), 1259 (w), 1229 (w).

HRMS (EI, *m/z*): calculated 282.1984 for [M]⁺, found 282.1957.

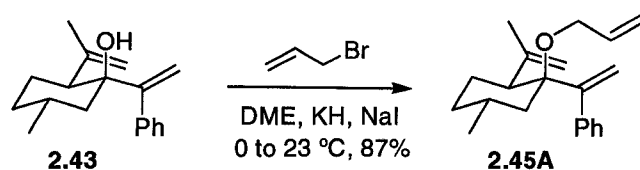
Data for 4.44E (major isomer):

¹H NMR (CDCl₃, 500 MHz, δ): 7.45-7.43 (m, 2H), 7.33-7.29 (m, 2H), 7.24-7.19 (m, 1H), 5.51-5.43 (m, 1H), 5.12 (d, *J* = 17.1 Hz, 1H), 4.96-4.94 (m, 1H), 4.92 (d, *J* = 1.7 Hz, 1H), 4.69 (d, *J* = 1.4 Hz, 1H), 3.11-3.07 (m, 1H), 2.87 (dd, *J* = 14.9, 9.2 Hz, 1H), 2.55-2.38 (m, 3H), 2.27 (ddd, *J* = 13.3, 3.8, 3.1 Hz, 1H), 1.74-1.53 (m, 5H), 1.40-1.32 (m, 2H), 1.25-1.12 (m, 2H), 1.02 (s, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.67, 140.90, 135.13, 129.33 (2C), 127.43 (2C), 126.13, 116.85, 108.12, 75.71, 49.24, 43.94, 34.41, 32.06, 31.46, 29.81, 25.57, 24.94, 21.25.

IR (neat, cm^{-1} , ν): 3571 (w), 3078 (w), 2933 (s), 2858 (m), 1640 (m), 1499 (w), 1465 (w), 1444 (m), 1362 (w), 1342 (w), 1134 (w), 1122 (w), 1068 (w).

HRMS (EI, m/z): calculated 282.1984 for $[\text{M}]^+$, found 282.1973.



(±)-[1-((1S,2S,5R)-1-Allyloxy-2-isopropenyl-5-methyl-cyclohexyl)-vinyl]-benzene (2.45A):

Sodium iodide (2 mg, 0.01 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (77 mg, 1.9 mmol) was then added to the flask and 2 mL of dimethoxyethane was added. The suspension was cooled to 0 °C and a solution of **2.43** (50.1 mg, 0.195 mmol) in another 1 mL of dimethoxyethane was added via cannula and the reaction stirred for 10 minutes. Allyl bromide (0.090 mL, 1.0 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 50.4 mg of a colourless oil (87%).

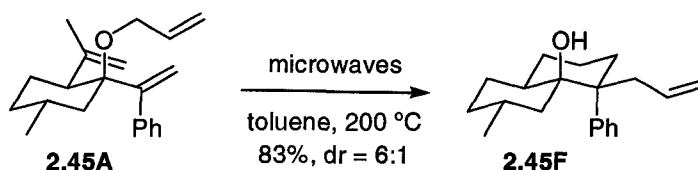
Data for 2.45A:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.36-7.25 (m, 5H), 6.03-5.91 (m, 1H), 5.40 (dddd, $J = 17.3$, 2.0, 1.9, 1.9 Hz, 1H), 5.31 (d, $J = 2.2$ Hz, 1H), 5.15 (dddd, $J = 10.6$, 1.9, 1.7, 1.7 Hz, 1H), 5.09 (d, $J = 2.2$ Hz, 1H), 4.88-4.86 (m, 2H), 3.99 (dddd, $J_{\text{AB}} = 12.9$ Hz, $J_{\text{AX}} = 4.5$ Hz, $J_{\text{AY}} = 1.9$ Hz, $J_{\text{AZ}} = 1.8$ Hz, 1H), 3.87 (dddd, $J_{\text{AB}} = 12.9$ Hz, $J_{\text{BX}} = 4.7$ Hz, $J_{\text{AY}} = 1.8$ Hz, $J_{\text{AZ}} = 1.7$ Hz, 1H), 2.31 (dd, $J = 12.5$, 2.9 Hz, 1H), 2.19 (dddd, $J = 12.6$, 12.6, 12.2, 3.7 Hz, 1H), 1.92 (s, 3H), 1.87 (ddd, $J = 14.5$, 2.6, 2.6 Hz, 1H), 1.78-1.59 (m, 2H), 1.52 (dddd, $J = 12.0$, 2.8, 3.3, 3.1 Hz, 1H), 1.02-0.86 (m, 2H), 0.83 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.89, 148.59, 143.09, 136.06, 129.01 (2C), 128.03 (2C), 127.01, 116.53, 114.95, 113.91, 83.04, 62.49, 53.88, 41.36, 35.23, 28.31, 27.83, 22.72, 22.69.

IR (neat, cm^{-1} , ν): 3081 (w), 3019 (w), 2948 (s), 2925 (s), 2865 (m), 1641(w), 1489 (m), 1452 (m), 1374 (w), 1196 (w), 1143 (w), 1119 (w), 1061 (m), 1028 (w).

HRMS (EI, m/z): calculated 296.2140 for $[\text{M}]^+$, found 296.2128.



(±)-(4S,4aS,6R,8aS)-4-Allyl-6-methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (4.45F):

A solution of **2.44A** (19.8 mg, 0.0668 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour the reaction was concentrated and a crude NMR taken to reveal a 6:1 ratio of isomers. Purification by silica gel flash chromatography (100% hexanes $\rightarrow$ 2% ethyl acetate/hexanes) yielded 16.4 mg of **2.45F** as an inseparable mixture with a second isomer (83% combined yield).

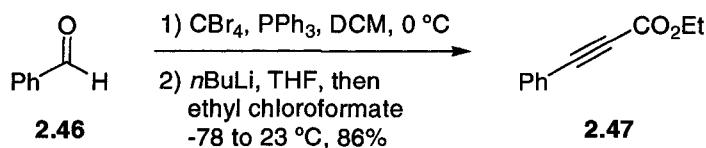
Data for **4.45F** (major isomer):

^1H NMR (CDCl_3 , 300 MHz, δ): 7.65-7.61 (m, 2H), 7.37-7.21 (m, 3H), 5.38-5.24 (m, 1H), 5.07 (d, $J = 1.6$ Hz, 1H), 5.03-4.94 (m, 1H), 4.88-4.83 (m, 1H), 4.82 (d, $J = 1.6$ Hz, 1H), 3.05 (dd, $J = 14.4, 5.2$ Hz, 1H), 2.87 (ddd, $J = 14.5, 14.3, 6.0$ Hz, 1H), 2.58-2.43 (m, 2H), 2.26-2.02 (m, 3H), 1.83 (ddd, $J = 14.4, 14.3, 6.2$ Hz, 1H), 1.74 (d, $J = 2.1$ Hz, 1H), 1.72-1.50 (m, 4H), 1.17 (ddd, $J = 12.0, 12.0, 2.0$ Hz, 1H), 0.86 (d, $J = 6.5$ Hz, 3H), 0.75-0.61 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.51, 144.04, 135.82, 130.26 (2C), 127.36 (2C), 125.95, 116.93, 110.28, 77.18, 49.24, 43.45, 41.76, 41.00, 34.69, 34.56, 33.52, 27.64, 25.10, 22.43.

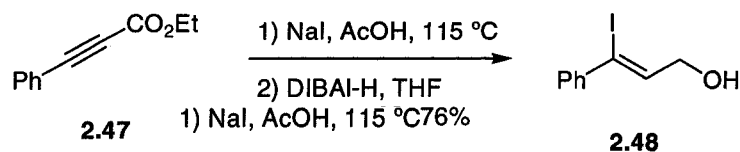
IR (neat, cm^{-1} , ν): 3553 (w), 3071 (w), 2948 (s), 2926 (s), 2866 (m), 1639 (m), 1495 (w), 1454 (m), 1372 (w), 1351 (w), 1224 (w), 1088 (w).

HRMS (EI, m/z): calculated 296.2140 for $[\text{M}]^+$, found 296.2142.



Phenyl-propynoic acid ethyl ester (2.47):

Triphenylphosphine (11.6 g, 44.2 mmol) was dissolved in 35 mL of dichloromethane and cooled to 0 °C. Carbontetrabromide (7.80 g, 23.5 mmol) was added portion-wise over 10 minutes and the resulting dark orange suspension was stirred for 30 minutes. Benzaldehyde (1.00 mL, 9.84 mmol) was added drop-wise and after 1 hour the reaction was complete by TLC. An equal volume of petroleum ether was added to the reaction and the precipitate filtered off over a pad of celite. The filtrate was concentrated and passed through a short pad of silica with hexanes. Following concentration, this crude material was dissolved in tetrahydrofuran and cooled to -78 °C. *n*-Butyllithium (8.80 mL of a 2.15 M solution in pentane, 18.9 mmol) was added drop-wise and the reaction was stirred for 45 minutes during which time its colour changed from light to dark red. Ethyl chloroformate (1.20 mL, 12.6 mmol) was added and the reaction was stirred for 20 minutes at -78 °C, and then 40 minutes at ambient temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with diethyl ether. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% diethyl ether/hexanes) yielded 1.43 g (86% over 2 steps) of **2.47** as a medium yellow oil. Spectral data was in agreement with that of the commercially available compound.



(Z)-3-Iodo-3-phenyl-prop-2-en-1-ol (2.48):

(Procedure adapted from Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, 72, 1816). A suspension of sodium iodide (156 mg, 1.04 mmol), acetic acid (0.27 mL, 4.7 mmol), and **2.47** (60.4 mg, 0.347 mmol) was heated in a sealed tube to 115 °C for four hours. During the course of the reaction, the mixture became a brown homogeneous solution. The reaction was cooled to ambient temperature, diluted with diethyl ether and quenched with water. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. The crude vinyl iodide was then dissolved in 5 mL of tetrahydrofuran and cooled to -78 °C. Diisobutylaluminum hydride (0.69 mL of a 1.5 M solution in toluene, 1.0 mmol) was added

drop-wise and the reaction warmed to 0 °C. After 1 hour, the reaction was quenched with a 0.5 M aqueous solution of sodium tartrate and the reaction stirred vigorously for 3 hours at which point two distinct phases were present. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% diethyl ether/hexanes) gave 69 mg of **2.48** (76% over 2 steps).

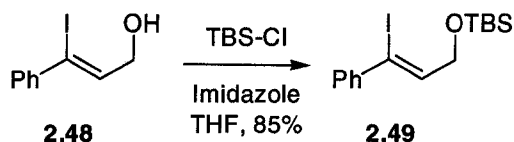
Data for 2.48:

¹H NMR (C₆D₆, 300 MHz, δ): 7.35-7.32 (m, 2H), 7.00-6.90 (m, 3H), 6.02 (t, J = 5.4 Hz, 1H), 4.12 (d, J = 5.2 Hz, 2H), 1.74 (s, br, 1H).

¹³C NMR (C₆D₆, 75 MHz, δ): 142.55, 138.28, 128.70 (2C), 128.65, 128.46 (2C), 104.05, 68.47.

IR (neat, cm⁻¹, ν): 3320 (br, s), 3079 (m), 3060 (m), 3031 (m), 2919 (m), 2875 (m), 1619 (m), 1487 (s), 1442 (s), 1217 (s), 1070 (m), 1034 (s).

HRMS (EI, m/z): calculated 259.9698 for [M]⁺, found 259.9686.



***tert*-Butyl-((*Z*)-3-iodo-3-phenyl-allyloxy)-dimethyl-silane (2.49):**

To a solution of **2.48** (90 mg, 0.35 mmol) in 3 mL of tetrahydrofuran was added imidazole (72 mg, 1.06 mmol) followed by *tert*-butyl(chloro)dimethylsilane (64 mg, 0.42 mmol). After stirring for 1.5 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) gave 110 mg (85%) of **2.49** as a colourless oil.

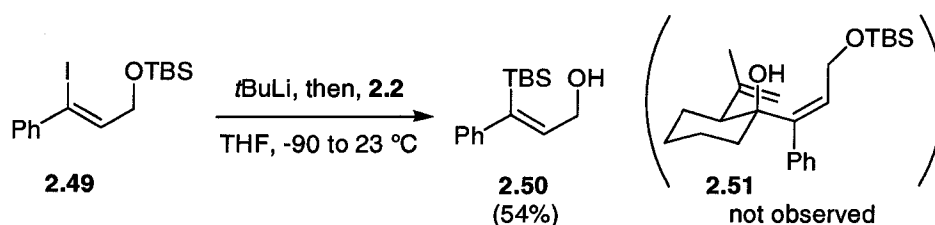
Data for 2.49:

¹H NMR (C₆D₆, 300 MHz, δ): 7.37-7.34 (m, 2H), 6.97-6.91 (m, 3H), 6.20 (t, J = 5.1, Hz, 1H), 4.43 (d, J = 5.1 Hz, 2H), 0.97 (s, 9H), 0.07 (s, 6H).

¹³C NMR (C₆D₆, 75 MHz, δ): 142.65, 138.90, 128.67 (2C), 128.60, 128.47 (2C), 102.75, 69.73, 26.05 (3C), 18.39, -5.08 (2C).

IR (neat, cm^{-1} , ν): 2954 (s), 2928 (s), 2887 (m), 2856 (s), 1489 (w), 1475 (w), 1442 (w), 1364 (w), 1252 (s), 1211 (w), 1106 (s), 1064 (s).

HRMS (EI, m/z): calculated 316.9859 for $[\text{M}-t\text{Bu}]^+$, found 316.9836.



(Z)-3-Phenyl-3-trimethylsilylanyl-prop-2-en-1-ol (2.50):

A solution of **2.49** (28.0 mg, 0.161 mmol) in 1 mL of tetrahydrofuran was cooled to $-90\text{ }^\circ\text{C}$. *tert*-Butyllithium (0.18 mL of a 1.73 M solution in pentane, 0.31 mmol) was added and the reaction stirred for 30 minutes. A solution of ketone **2.2** (18.1 mg, 0.131 mmol) in 1 mL of tetrahydrofuran was transferred to the reaction via a cold cannula. After 45 minutes at $-90\text{ }^\circ\text{C}$, the reaction was warmed gradually to ambient temperature over a period of 3 hours. The reaction was then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% diethyl ether/hexanes) gave 21.6 mg of **2.50** along with 12 mg of unreacted **2.2**. None of the desired compound, **2.51**, was observed.

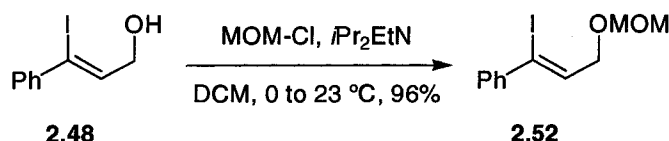
Data for **2.50**:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.31-7.20 (m, 3H), 7.09-7.06 (m, 2H), 6.32 (t, $J = 7.0$ Hz, 1H), 4.36 (d, $J = 7.0$ Hz, 2H), 0.94 (s, 9H), 0.12 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 147.37, 146.18, 145.20, 128.24 (2C), 128.11 (2C), 126.06, 63.27, 27.76 (3C), 18.60, -2.33 (2C).

IR (neat, cm^{-1} , ν): 3313 (s, br), 2956 (s), 2931 (s), 2882 (m), 2856 (s), 1594 (w), 1487 (m), 1471 (m), 1462 (m), 1439 (m), 1406 (w), 1387 (w), 1361 (w), 1251 (s), 1030 (s), 1021 (s).

HRMS (EI, m/z): calculated 191.0892 for $[\text{M}-t\text{Bu}]^+$, found 191.0869.



(±)-((Z)-1-Iodo-3-methoxymethoxy-propenyl)-benzene (2.52):

A solution of **2.48** (20 mg, 0.077 mmol) in 0.7 mL of dichloromethane was cooled to 0 °C. N,N,N-Diisopropylethyl amine (0.060 mL, 0.34 mmol) was added, followed by chloromethyl methyl ether (0.020 mL, 0.27 mmol). The solution was warmed to ambient temperature and stirred for three hours. A saturated aqueous solution of ammonium chloride was added and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% diethyl ether/hexanes) gave 22.6 mg of a colourless oil (96%).

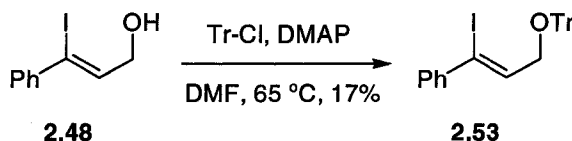
Data for 2.52:

¹H NMR (C₆D₆, 500 MHz, δ): 7.38-7.36 (m, 2H), 7.01-6.96 (m, 3H), 6.20 (t, *J* = 5.3 Hz, 1H), 4.50 (s, 2H), 4.30 (d, *J* = 5.4 Hz, 2H), 3.18 (s, 3H).

¹³C NMR (C₆D₆, 125 MHz, δ): 142.77, 135.96, 128.67 (2C), 128.64, 128.43 (2C), 104.98, 96.34, 73.10, 55.03.

IR (neat, cm⁻¹, ν): 2925 (s), 2853 (m), 1488 (w), 1463 (w), 1443 (m), 1212 (m), 1151 (m), 1107 (m), 1041 (s).

HRMS (EI, *m/z*): calculated 303.9960 for [M]⁺, found 303.9889.

**(Z)-2-iodo-2-phenylvinyl trityl ether (2.53):**

To a solution of **2.48** (40 mg, 0.15 mmol) in 1.5 mL of dimethylformamide was added 4-di(methylamino)pyridine (60 mg, 0.49 mmol), followed by triphenylmethyl chloride (110 mg, 0.395 mmol). The solution was heated to 65 °C for 5 hours, cooled to ambient temperature, and a saturated aqueous solution of ammonium chloride added. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% diethyl ether/hexanes) gave 13.3 mg of a white solid (17%).

Data for 2.53:

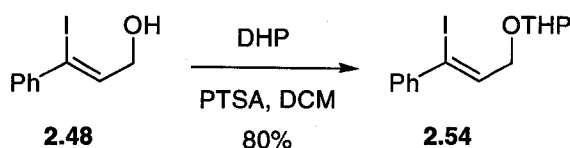
^1H NMR (CDCl_3 , 300 MHz, δ): 7.49-7.46 (m, 5H), 7.42-7.39 (m, 2H), 7.34-7.21 (m, 13H), 6.25 (t, $J = 5.1$ Hz, 1H), 3.91 (d, $J = 5.1$ Hz, 2H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 143.97 (3C), 142.35, 136.23, 128.82 (6C), 128.59, 128.52 (2C), 128.32 (2C), 128.06 (6C), 127.25 (3C), 103.46, 87.24, 70.48.

IR (neat, cm^{-1} , ν): 3057 (w), 2923 (w), 2852 (w), 2360 (w), 1489 (s), 1059 (s), 1031 (m).

HRMS (EI, m/z): calculated 242.9671 for $[\text{M}-\text{OTr}]^+$, found 243.0790.

mp: product decomposed upon heating.



2-((Z)-3-Iodo-3-phenyl-allyloxy)-tetrahydro-pyran (2.54):

To a solution of **2.48** (38 mg, 0.15 mmol) in 1.5 mL of dichloromethane was added a small crystal of *p*-toluenesulfonic acid, followed by dihydropyran (0.040 mL, 0.44 mmol). After stirring for five minutes, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with dichloromethane and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% diethyl ether/hexanes) gave 40 mg of a colourless oil (80%).

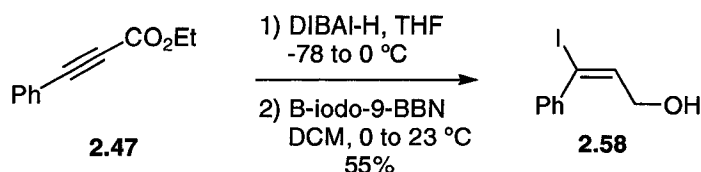
Data for 2.54:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.48-7.44 (m, 2H), 7.35-7.20 (m, 3H), 6.24 (dd, $J_{\text{AX}} = 5.4$, $J_{\text{BX}} = 5.4$ Hz, 1H), 4.70 (t, $J = 3.3$ Hz, 1H), 4.45 (dd, $J_{\text{AB}} = 14.0$ Hz, $J_{\text{AX}} = 5.1$ Hz, 1H), 4.23 (dd, $J_{\text{AB}} = 14.0$ Hz, $J_{\text{BX}} = 5.7$ Hz, 1H), 3.94-3.87 (m, 1H), 3.58-3.51 (m, 1H), 1.88-1.68 (m, 2H), 1.63-1.51 (m, 4H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 142.42, 135.64, 128.68, 128.55 (2C), 128.38 (2C), 104.75, 98.71, 72.89, 62.49, 30.70, 25.52, 19.54.

IR (neat, cm^{-1} , ν): 2943 (s), 2865 (m), 1488 (m), 1442 (m), 1344 (m), 1201 (m), 1121 (m), 1033 (s).

HRMS (EI, m/z): calculated 344.0273 for $[\text{M}]^+$, found 344.0297.



(E)-3-Iodo-3-phenyl-prop-2-en-1-ol (2.58):

A solution of **2.47** (0.390 g, 2.24 mmol) in 15 mL of tetrahydrofuran was cooled to -78 °C. Diisobutylaluminum hydride (4.5 mL of a 1.5 M solution in toluene, 6.75 mmol) was added slowly and the reaction was warmed gradually to 0 °C over 1 hour. Several drops of acetone were added to quench the excess diisobutylaluminum hydride, followed by 10 mL of a 1 M aqueous solution of sodium tartrate and 10 mL of a 1 M aqueous solution of sodium hydroxide. The cloudy mixture was stirred vigorously for 2 hours (or until two distinct phases were present). The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. The crude material was filtered through a short pad of silica with 50% ethyl acetate/hexanes and the concentrated material was dissolved in 16 mL of dichloromethane. After cooling to 0 °C, B-iodo-9-BBN (2.18 mL of a 1.0 M solution in hexanes, 2.18 mmol) was added slowly and the resulting cherry red solution was warmed to ambient temperature and stirred for 30 minutes. Acetic acid (2.5 mL) was then added and the reaction stirred for 1 hour. The reaction was slowly quenched with a premixed aqueous solution containing 25 mL of a 3 M aqueous sodium hydroxide solution and 4.5 mL of a 30% hydrogen peroxide solution in water. The biphasic mixture was stirred vigorously for 2 hours before extracting the aqueous phase three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 318 mg (55% over 2 steps) of **2.58** as a colourless oil.

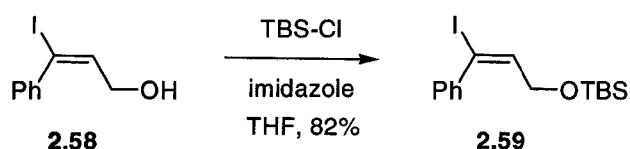
Data for **2.58**:

¹H NMR (acetone-d₆, 300 MHz, δ): 7.40-7.26 (m, 5H), 6.70 (t, *J* = 6.8 Hz, 1H), 4.13 (t, *J* = 6.0 Hz, 1H), 3.95 (dd, *J* = 6.8, 5.9 Hz, 2H).

¹³C NMR (acetone-d₆, 75 MHz, δ): 144.08, 141.84, 129.31 (2C), 129.20, 128.89 (2C), 97.87, 61.06.

IR (neat, cm⁻¹, ν): 3324 (s, br), 2959 (s), 2922 (s), 2869 (s), 1620 (w), 1488 (s), 1441 (s), 1222 (w), 1171 (w), 1073 (s), 1019 (s).

HRMS (EI, *m/z*): calculated 259.9698 for [M]⁺, found 259.9611.



***tert*-Butyl-((E)-3-iodo-3-phenyl-allyloxy)-dimethyl-silane (2.59):**

To a stirring solution of **2.58** (318 mg, 1.22 mmol) in 10 mL of tetrahydrofuran was added imidazole (250 mg, 3.67 mmol) followed by *tert*-butyl(chloro)dimethylsilane (220 mg, 1.46 mmol). The now cloudy mixture was stirred for 40 minutes and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% diethyl ether/hexanes) gave 374 mg of a colourless oil (82%).

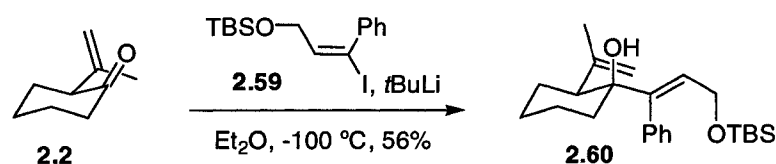
Data for 2.59:

¹H NMR (CDCl₃, 300 MHz, δ): 7.21-7.17 (m, 2H), 7.15-6.90 (m, 3H), 6.72 (t, *J* = 6.9 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 2H), 0.87 (s, 9H), -0.11 (s, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 142.69, 141.54, 131.84, 128.88 (2C), 128.67, 128.57 (2C), 61.87, 25.94 (3C), 18.32, -5.24 (2C).

IR (neat, cm^{-1} , v): 2954 (m), 2929 (m), 2857 (m), 1488 (w), 1470 (w), 1462 (w), 1442 (w), 1255 (m), 1095 (s), 1005 (w).

HRMS (EI, m/z): calculated 316.9859 for $[M-tBu]^+$, found 316.9848.



(±)-(1S,2S)-1-[(E)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-propenyl]-2-isopropenyl-cyclohexanol (2.60):

A solution of **2.59** (166 mg, 0.444 mmol) was dissolved in 4 mL of diethyl ether and cooled to -100 °C. *tert*-Butyllithium (0.510 mL of a 1.74 M solution in pentane, 0.887 mmol) was then added drop-wise and the reaction was stirred for 30 minutes. To this solution was then slowly cannulated in a cooled solution of ketone **2.2** (54 mg, 0.39 mmol) in another 1 mL of diethyl ether. After 30 minutes the reaction was quenched with a saturated aqueous solution

of ammonium chloride and warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% ethyl acetate/hexanes) gave 83 mg of a colourless oil (56%).

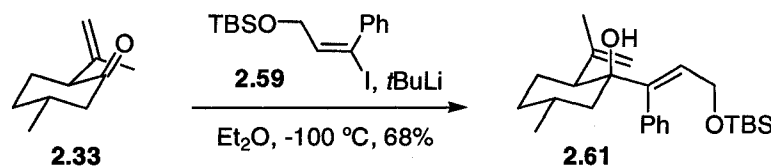
Data for 2.60:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.31-7.24 (m, 3H), 7.09-7.06 (m, 2H), 5.87 (t, $J = 6.2$ Hz, 1H), 4.87 (s, 1H), 4.85 (s, 1H), 3.82 (d, $J = 6.2$ Hz, 2H), 2.27 (dd, $J = 12.5, 3.4$ Hz, 1H), 1.83 (s, 3H), 1.79-1.46 (m, 8H), 1.25-1.15 (m, 1H), 0.81 (s, 9H), -0.09 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.43, 147.93, 138.34, 129.17 (2C), 127.82 (2C), 126.99, 126.92, 113.10, 75.49, 61.30, 51.17, 40.08, 28.56, 25.96, 25.87 (3C), 24.27, 21.42, 18.23, -5.22 (2C).

IR (neat, cm^{-1} , ν): 3559 (w), 3478 (w), 3078 (w), 2929 (s), 2856 (s), 1638 (w), 1492 (w), 1472 (m), 1442 (m), 1375 (m), 1255 (s), 1191 (m), 1147 (m), 1060 (s).

HRMS (EI, m/z): calculated 386.2641 for $[\text{M}]^+$, found 386.2645.



(±)-(1S,2S,5R)-1-[(E)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-propenyl]-2-isopropenyl-5-methyl-cyclohexanol (2.61):

A solution of **2.59** (124 mg, 0.331 mmol) was dissolved in 3 mL of diethyl ether and cooled to $-100\text{ }^{\circ}\text{C}$. *tert*-Butyllithium (0.380 mL of a 1.74 M solution in pentane, 0.661 mmol) was then added drop-wise and the reaction was stirred for 30 minutes. To this solution was then slowly cannulated in a cooled solution of ketone **2.2** (45 mg, 0.30 mmol) in 1 mL of diethyl ether. After 30 minutes the reaction was quenched with a saturated aqueous solution of ammonium chloride and warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% ethyl acetate/hexanes) gave 81 mg of a colourless oil (68%).

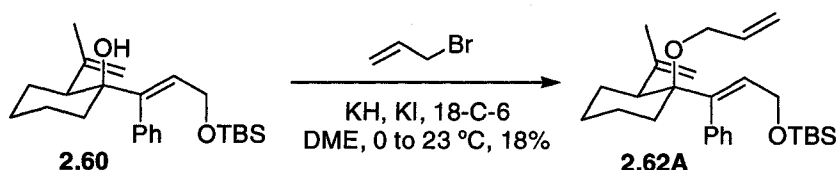
Data for 2.61:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.31-7.24 (m, 3H), 7.10-7.07 (m, 2H), 5.86 (t, $J = 6.2$ Hz, 1H), 4.88 (s, 1H), 4.85 (s, 1H), 3.82 (d, $J = 6.2$ Hz, 2H), 2.22 (dd, $J = 12.6, 3.6$ Hz, 1H), 1.83 (s, 3H), 1.81-1.65 (m, 4H), 1.58 (s, 1H), 1.53-1.48 (m, 1H), 1.24-1.15 (m, 1H), 0.88-0.81 (m, 1H), 0.82 (d, $J = 6.2$ Hz, 3H), 0.81 (s, 9H), -0.08 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.22, 147.85, 138.24, 129.16 (2C), 127.83 (2C), 127.00, 126.92, 113.15, 75.93, 61.29, 50.86, 48.75, 34.69, 28.55, 27.51, 25.87 (3C), 24.42, 22.16, 18.22, -5.23 (2C).

IR (neat, cm^{-1} , ν): 3555 (w), 3478 (w), 3078 (w), 2951 (s), 2928 (s), 2857 (s), 1639 (w), 1471 (m), 1442 (m), 1376 (m), 1255 (m), 1070 (s), 1006 (m).

HRMS (EI, m/z): calculated 400.2798 for $[\text{M}]^+$, found 400.2809.



(±)-[(E)-3-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-3-phenyl-allyloxy]-tert-butyl-dimethyl-silane (2.62A):

Potassium iodide (2 mg, 0.01 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (75 mg of a 30% suspension in mineral oil, 0.56 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1.5 mL) followed by 18-crown-6 (160 mg, 0.605 mmol) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated a solution of **2.60** (46 mg, 0.12 mmol) in another 1 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (50 μL , 0.58 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 9 mg of a colourless oil (18%).

Data for 2.62A:

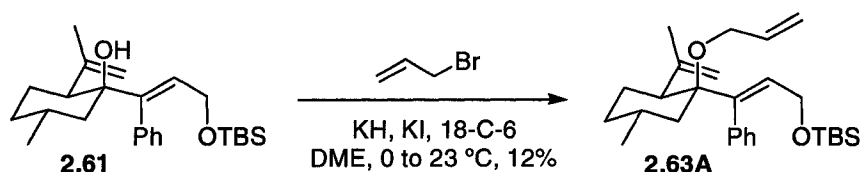
^1H NMR (CDCl_3 , 300 MHz, δ): 7.30-7.24 (m, 3H), 7.07-7.05 (m, 2H), 5.99-5.89 (m, 1H), 5.77 (dd, $J = 6.4, 6.4$ Hz, 1H), 5.37 (d, $J = 17.0$ Hz, 1H), 5.11 (d, $J = 10.8$ Hz, 1H), 4.80 (s,

2H), 4.00 (dd, $J = 12.7, 4.6$ Hz, 1H), 3.89-3.73 (m, 3H), 2.34-2.03 (m, 3H), 1.87 (s, 3H), 1.82 (d, $J = 14.6$ Hz, 1H), 1.66-1.62 (m, 1H), 1.42-1.35 (m, 2H), 1.13-1.06 (m, 1H), 0.92-0.84 (m, 1H), 0.81 (s, 9H), -0.09 (s, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.40, 139.94, 139.47, 135.66, 129.39 (2C), 127.85 (3C), 126.59, 114.72, 113.57, 81.49, 61.95, 61.26, 53.25, 32.36, 28.06, 25.92, 25.84 (3C), 22.32, 21.18, 18.17, -5.21 (2C).

IR (neat, cm^{-1} , ν): 3077 (w), 2929 (s), 2856 (s), 1639 (w), 1446 (m), 1254 (m), 1096 (s), 1063 (s).

HRMS (EI, m/z): calculated 426.2954 for $[\text{M}]^+$, found 426.2947.



(±)-[(E)-3-((1S,2S,5R)-1-Allyloxy-2-isopropenyl-5-methyl-cyclohexyl)-3-phenyl-allyloxy]-*tert*-butyl-dimethyl-silane (**2.63A**):

Potassium iodide (2 mg, 0.01 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (105 mg of a 30% suspension in mineral oil, 0.785 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1.5 mL), followed by 18-crown-6 (210 mg, 0.794 mmol), was added to the flask and the suspension was cooled to 0 °C. To this suspension was cannulated in a solution of **2.61** (66 mg, 0.17 mmol) in another 2 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (70 μL , 0.81 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% diethyl ether/hexanes) yielded 9 mg of a colourless oil (12%).

Data for **2.63A**:

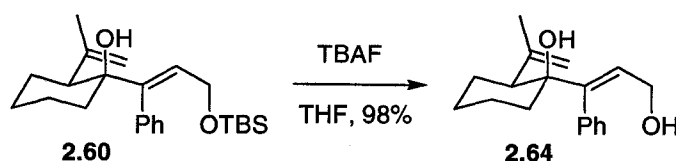
^1H NMR (CDCl_3 , 300 MHz, δ): 7.30-7.23 (m, 3H), 7.07-7.05 (m, 2H), 6.00-5.87 (m, 1H), 5.76 (dd, $J = 6.9, 5.3$ Hz, 1H), 5.36 (dddd, $J = 17.2, 1.9, 1.9, 1.9$ Hz, 1H), 5.10 (dddd, $J =$

10.6, 1.7, 1.7, 1.7 Hz, 1H), 4.80 (s, 2H), 4.03-3.98 (m, 1H), 3.88-3.72 (m, 3H), 2.34-2.31 (m, 1H), 2.18-2.06 (m, 2H), 1.87 (s, 3H), 1.80-1.74 (m, 1H), 1.65-1.60 (m, 2H), 1.43-1.39 (m, 1H), 0.80 (s, 9H), 0.73 (d, $J = 6.5$ Hz, 3H), 0.58 (dd, $J = 14.4, 12.2$ Hz, 1H), -0.09 (s, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 148.29, 139.88, 139.34, 135.62, 129.36, 127.84 (3C), 126.60 (2C), 114.70, 113.69, 81.92, 62.01, 61.27, 52.89, 40.84, 34.68, 28.05, 27.21, 25.84 (3C), 22.30, 22.27, 18.17, -5.21 (2C).

IR (neat, cm^{-1} , v): 3077 (m), 2950 (s), 2927 (s), 2857 (m), 1699 (m), 1640 (m), 1441 (m), 1255 (w), 1067 (m).

HRMS (EI, m/z): calculated 440.3111 for $[M]^+$, found 440.3107.



(±)-(1*S*,2*S*)-1-((*E*)-3-Hydroxy-1-phenyl-propenyl)-2-isopropenyl-cyclohexanol (2.64):

To a solution of **2.60** (34 mg, 0.088 mmol) in 1 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.17 mL of a 1.0 M solution in tetrahydrofuran, 0.17 mmol). The reaction was stirred at ambient temperature for 1 hour and then concentrated. Purification by silica gel flash chromatography (40% ethyl acetate/hexanes) yielded 23.5 mg of a clear colourless oil (98%).

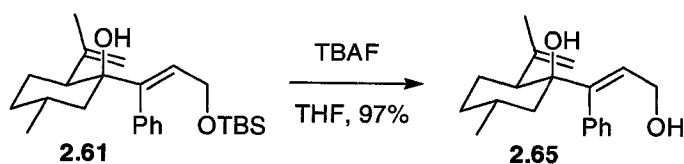
Data for 2.64:

¹H NMR (CDCl₃, 300 MHz, δ): 7.33-7.24 (m, 3H), 7.11-7.07 (m, 2H), 5.99 (t, *J* = 6.7 Hz, 1H), 4.88 (s, 1H), 4.86 (s, 1H), 3.81 (d, *J* = 6.8 Hz, 2H), 2.25 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.82 (s, 3H), 1.79-1.46 (m, 8H), 1.26-1.13 (m, 2H).

¹³C NMR (CDCl₃, 75 MHz, δ): 150.29, 148.28, 138.06, 129.12 (2C), 127.95 (2C), 127.09, 125.79, 113.24, 75.66, 60.60, 51.00, 39.90, 28.90, 28.43, 25.89, 23.98, 21.36.

IR (neat, cm^{-1} , ν): 3387 (br, m), 3062 (w), 2931 (s), 2856 (m), 1637 (w), 1492 (w), 1441 (m), 1374 (w), 1147 (w), 1074 (w).

HRMS (EI, m/z): calculated 272.1776 for $[M]^+$, found 272.1741.



(±)-(1S,2S,5R)-1-((E)-3-Hydroxy-1-phenyl-propenyl)-2-isopropenyl-5-methyl-cyclohexanol (2.65):

To a solution of **2.61** (46 mg, 0.12 mmol) in 1 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.30 mL of a 1.0 M solution in tetrahydrofuran, 0.30 mmol). The reaction was stirred at ambient temperature for 1 hour and then concentrated. Purification by silica gel flash chromatography (40% ethyl acetate/hexanes) yielded 32 mg of a clear colourless oil (97%).

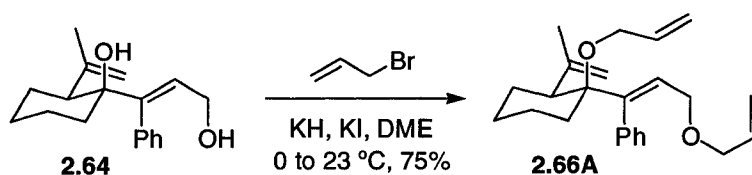
Data for 2.65:

¹H NMR (CDCl₃, 300 MHz, δ): 7.33-7.22 (m, 3H), 7.10-7.07 (m, 2H), 5.97 (t, *J* = 6.7 Hz, 1H), 4.89-4.88 (m, 1H), 4.86 (s, 1H), 3.80 (d, *J* = 6.7 Hz, 2H), 2.20 (dd, *J* = 12.5, 3.6 Hz, 1H), 2.15 (s, 1H), 1.87-1.77 (m, 1H), 1.81 (s, 3H), 1.76-1.65 (m, 2H), 1.63 (s, 1H), 1.55-1.48 (m, 1H), 1.30-1.15 (m, 2H), 0.92-0.78 (m, 1H), 0.82 (d, *J* = 6.5 Hz, 3H);

¹³C NMR (CDCl₃, 75 MHz, δ): 150.20, 148.08, 137.96, 129.11 (2C), 127.95 (2C), 127.09, 125.82, 113.29, 76.12, 60.58, 50.75, 48.62, 34.62, 28.43, 27.51, 24.13, 22.14;

IR (neat, cm⁻¹, ν): 3384 (br, m), 3074 (w), 2947 (s), 2935 (s), 2866 (m), 1638 (w), 1492 (w), 1454 (m), 1441 (m), 1234 (w), 1177 (w), 1050 (m), 1007 (m);

HRMS (EI, *m/z*): calculated 286.1933 for [M]⁺, found 286.1929.



(±)-[(E)-3-Allyloxy-1-((1S,2S)-1-allyloxy-2-isopropenyl-cyclohexyl)-propenyl]-benzene (2.66A):

Sodium iodide (1.5 mg, 0.010 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (150 mg of a 30% suspension in mineral oil, 1.12 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1 mL) was added

to the flask and the suspension cooled to 0 °C. To this suspension was cannulated in a solution of **2.64** (23.5 mg, 0.086 mmol) in another 1 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (90 μ L, 1.04 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 23 mg of a colourless oil (75%).

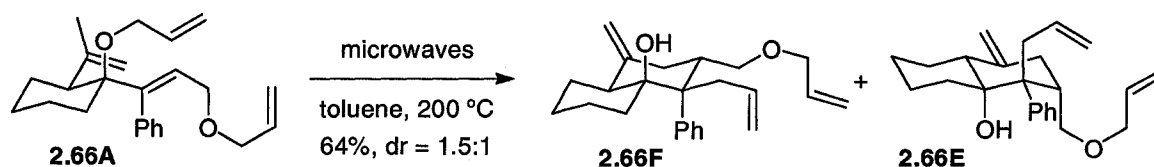
Data for 2.66A:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.32-7.22 (m, 3H), 7.09-7.07 (m, 2H), 6.02-5.90 (m, 1H), 5.86-5.73 (m, 1H), 5.81 (t, J = 6.5 Hz, 1H), 5.37 (dddd, J = 17.2, 1.8, 1.8, 1.8 Hz, 1H), 5.19-5.05 (m, 3H), 4.82 (s, 1H), 4.81 (s, 1H), 4.02-3.95 (m, 1H), 3.88-3.71 (m, 3H), 3.67 (d, J = 6.5 Hz, 2H), 2.25 (dd, J = 12.4, 3.2 Hz, 1H), 2.08 (dddd, J = 12.7, 12.7, 12.7, 3.8 Hz, 1H), 1.88 (s, 3H), 1.85-1.80 (m, 1H), 1.67-1.63 (m, 1H), 1.58-1.35 (m, 3H), 1.19-1.03 (m, 1H), 0.97-0.82 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.65, 143.02, 139.31, 135.54, 135.01, 127.89 (3C), 126.68 (2C), 126.11, 116.56, 114.81, 113.58, 81.92, 70.40, 67.64, 62.02, 53.21, 32.42, 28.00, 25.89, 22.12, 21.15.

IR (neat, cm^{-1} , ν): 3079 (w), 2935 (s), 2859 (m), 1641 (m), 1370 (m), 1117 (m), 1092 (m), 1059 (s), 1027 (m).

HRMS (EI, m/z): calculated 311.2011 for $[\text{M}]^+$, found 311.2041.



($\pm$)-((3S,4R,4aS,8aS)-4-Allyl-3-allyloxymethyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.66F) and ($\pm$)-((3S,4R,4aR,8aR)-4-Allyl-3-allyloxymethyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.66E):

A solution of **2.66A** (21 mg, 0.060 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1.5 hours the reaction was concentrated and the crude material injected into a GC. Two isomers were found to be

present in a 1.5:1 ratio. Purification by silica gel flash chromatography (4% ethyl acetate/hexanes) yielded 9.5 mg of **2.66F**, as well as 4.0 mg of **2.66E** (64% combined yield).

Data for **2.66F** (major isomer):

¹H NMR (C₆D₆, 500 MHz, δ): 7.59 (d, J = 8.0 Hz, 2H), 7.23-7.15 (m, 3H), 6.55-6.47 (m, 1H), 5.95-5.87 (m, 1H), 5.28 (d, J = 19.8 Hz, 1H), 5.24 (d, J = 18.5 Hz, 1H), 5.16 (d, J = 9.1 Hz, 1H), 5.11-5.10 (m, 2H), 4.81 (s, 1H), 3.78 (d, J = 4.9 Hz, 2H), 3.53 (dd, J = 9.3, 2.6 Hz, 1H), 3.35-3.28 (m, 2H), 3.18 (dd, J = 13.4, 4.9 Hz, 1H), 2.89 (dd, J = 14.9, 7.9 Hz, 1H), 2.87-2.75 (m, 2H), 2.62-2.60 (m, 1H), 1.97 (d, J = 13.5 Hz, 1H), 1.74-1.66 (m, 1H), 1.67 (s, 1H), 1.57-1.50 (m, 3H), 1.35-1.33 (m, 1H), 0.82-0.75 (m, 2H).

¹³C NMR (C₆D₆, 125 MHz, δ): 148.91, 144.65, 139.11, 135.85, 130.29 (2C), 127.66 (2C), 126.29, 116.55, 115.61, 110.79, 77.83, 72.81, 71.84, 51.84, 44.02, 42.69, 41.91, 39.45, 32.54, 25.31, 25.29, 21.74.

IR (neat, cm⁻¹, ν): 3381 (br, w), 3082 (w), 2922 (s), 2851 (m), 1636 (w), 1448 (s), 1359 (m).

HRMS (EI, m/z): calculated 352.2402 for [M]⁺, found 352.2369.

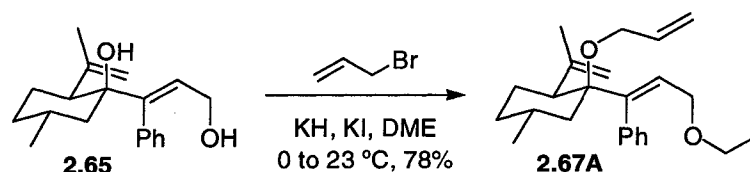
Data for **2.66E** (minor isomer):

¹H NMR (C₆D₆, 500 MHz, δ): 7.98 (d, J = 8.0 Hz, 2H), 7.32 (dd, J = 7.6, 7.6 Hz, 2H), 7.18 (dd, J = 7.2, 7.2 Hz, 1H), 5.82-5.75 (m, 2H), 5.20 (dd, J = 17.2, 1.5 Hz, 1H), 5.09 (s, 1H), 5.06-5.04 (m, 2H), 4.96 (d, J = 10.2 Hz, 1H), 4.85 (s, 1H), 3.66-3.64 (m, 2H), 3.45 (dd, J = 9.5, 7.2 Hz, 1H), 3.15 (dd, J = 9.6, 2.4 Hz, 1H), 3.03 (dd, J = 16.3, 6.8 Hz, 1H), 2.71-2.66 (m, 4H), 2.42 (dd, J = 7.8, 7.4 Hz, 1H), 2.34 (d, J = 13.5 Hz, 1H), 2.22-2.21 (m, 1H), 1.95-1.91 (m, 1H), 1.76 (d, J = 12.0 Hz, 1H), 1.67-1.50 (m, 5H).

¹³C NMR (C₆D₆, 125 MHz, δ): 147.50, 144.13, 138.47, 135.28, 130.57 (2C), 127.81 (2C), 125.62, 115.81, 115.44, 110.60, 78.03, 71.90, 71.67, 52.67, 50.30, 45.93, 43.29, 35.52, 33.74, 26.03, 25.00, 21.38.

IR (neat, cm⁻¹, ν): 3364 (br, m), 3079 (w), 2926 (s), 2857 (m), 1642 (w), 1495 (m), 1443 (m), 1090 (s).

HRMS (EI, m/z): calculated 352.2402 for [M]⁺, found 352.2361.



(±)-[(E)-3-Allyloxy-1-((1S,2S,5R)-1-allyloxy-2-isopropenyl-5-methyl-cyclohexyl)-propenyl]-benzene (2.67A):

Sodium iodide (1.5 mg, 0.010 mmol) was flame dried under vacuum and allowed to cool. Potassium hydride (165 mg of a 30% suspension in mineral oil, 1.23 mmol) was then added to the flask and the system put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (1 mL) was added to the flask and the suspension cooled to 0 °C. To this suspension was cannulated in a solution of **2.65** (30 mg, 0.11 mmol) in another 1 mL of dimethoxyethane. After stirring for 20 minutes, allyl bromide (90 µL, 1.04 mmol) was added drop-wise and the reaction warmed gradually to ambient temperature. After stirring for 16 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 30 mg of a colourless oil (78%).

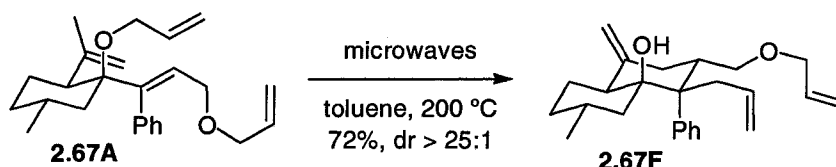
Data for 2.67A:

¹H NMR (C₆D₆, 300 MHz, δ): 7.10-7.07 (m, 5H), 6.14 (t, *J* = 6.6 Hz, 1H), 5.98-5.72 (m, 2H), 5.47 (dddd, *J* = 17.2, 1.9, 1.9, 1.9 Hz, 1H), 5.18 (dddd, *J* = 17.2, 1.8, 1.8, 1.8 Hz, 1H), 5.11 (dddd, *J* = 10.5, 1.8, 1.8, 1.8 Hz, 1H), 5.02 (s, 1H), 5.01 (s, 1H), 4.96 (dddd, *J* = 10.5, 1.8, 1.8, 1.8 Hz, 1H), 4.05-3.99 (m, 1H), 3.80 (d, *J* = 6.7 Hz, 2H), 3.84-3.71 (m, 3H), 2.32-2.15 (m, 2H), 2.07 (s, 3H), 1.81-1.76 (m, 1H), 1.54-1.48 (m, 2H), 1.27-1.22 (m, 1H), 0.96-0.86 (m, 1H), 0.74-0.62 (m, 1H), 0.63 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 148.52, 142.97, 139.17, 135.50, 135.01, 127.88 (3C), 126.68 (2C), 126.08, 116.55, 114.79, 113.70, 82.34, 70.38, 67.63, 62.07, 52.86, 40.90, 34.64, 27.98, 27.18, 22.24, 22.11.

IR (neat, cm⁻¹, ν): 3077 (m), 3016, (w), 2948 (s), 2925 (s), 2859 (m), 1698 (w), 1640, (m), 1455 (m), 1374 (w), 1192 (w), 1147 (m), 1092 (m), 1061 (s).

HRMS (EI, *m/z*): calculated 366.2559 for [M]⁺, found 366.2581.



(±)-(3S,4R,4aS,6R,8aS)-4-Allyl-3-allyloxymethyl-6-methyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.67F):

A solution of **2.67A** (20 mg, 0.055 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1.5 hours the reaction was concentrated and the crude material injected into a GC. Only one isomer was detected. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 14.5 mg of a colourless oil (72%).

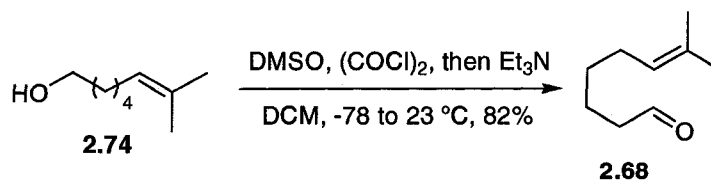
Data for 2.67F:

¹H NMR (C₆D₆, 500 MHz, δ): 7.60 (d, *J* = 8.0 Hz, 2H), 7.22-7.19 (m, 2H), 7.15-7.13 (m, 1H), 6.55-6.47 (m, 1H), 5.95-5.87 (m, 1H), 5.28 (d, *J* = 17.5 Hz, 1H), 5.24 (d, *J* = 17.5 Hz, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 5.12 (s, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.84 (s, 1H), 3.79 (d, *J* = 5.1 Hz, 2H), 3.54 (dd, *J* = 9.3, 2.6 Hz, 1H), 3.37 (dd, *J* = 14.7, 6.3 Hz, 1H), 3.31 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.19 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.92 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.84 (dd, *J* = 14.0, 13.8 Hz, 1H), 2.81-2.75 (m, 1H), 2.60 (d, *J* = 10.3 Hz, 1H), 2.02 (d, *J* = 13.2 Hz, 1H), 1.87-1.85 (m, 1H), 1.69 (s, 1H), 1.62-1.50 (m, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.58-0.51 (m, 2H).

¹³C NMR (C₆D₆, 125 MHz, δ): 148.78, 144.52, 139.10, 135.86, 130.33 (2C), 127.64 (2C), 126.37, 116.55, 115.63, 110.83, 78.34, 72.85, 71.87, 51.88, 43.63, 42.67, 41.92, 41.32, 39.52, 33.90, 27.64, 25.32, 22.39.

IR (neat, cm⁻¹, ν): 3542 (w), 3075 (w), 2948 (s), 2926 (s), 2867 (m), 1640 (w), 1499 (w), 1454 (m), 1351 (w), 1089 (s), 1029 (w).

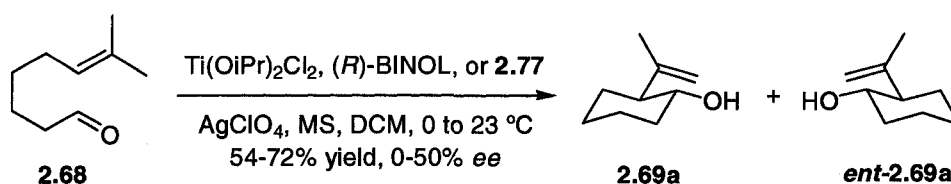
HRMS (EI, *m/z*): calculated 366.2559 for [M]⁺, found 366.2542.



7-Methyl-oct-6-enal (2.68):

A solution of oxalyl chloride (0.63 mL, 7.2 mmol) in 50 mL of dichloromethane was cooled to -78 °C. Dimethylsulfoxide (1.02 mL, 14.4 mmol) was added slowly and the reaction was stirred for 10 minutes. A solution of **2.74** (930 mg, 6.54 mmol) in 15 mL of dichloromethane

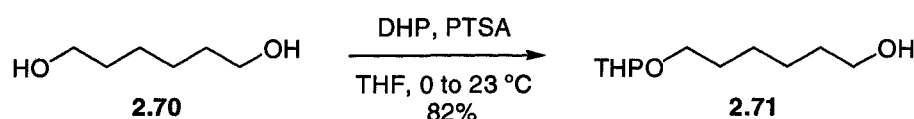
was cannulated into the reaction mixture and the resulting solution stirred at $-78\text{ }^{\circ}\text{C}$ for another 30 minutes. Triethylamine (4.56 mL, 32.7 mmol) was added slowly and the thick, pale-yellow mixture warmed to ambient temperature for 1 hour. The reaction was quenched with a 1 M aqueous solution of hydrochloric acid and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% $\rightarrow$ 20% ethyl acetate/hexanes) yielded 750 mg (82%) of **2.68** as a colourless oil. (*Note, this compound has a pungent odor which is best removed from glassware by soaking in a base bath*). Spectral data was in agreement with that reported previously: Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203.



(1R,2S)-2-Isopropenyl-cyclohexanol (2.69a) and (1S,2R)-2-Isopropenyl-cyclohexanol (ent-2.69a):

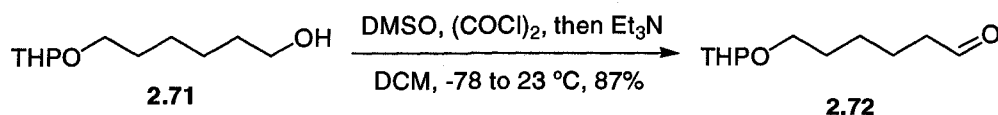
Method A: A suspension of (*R*)-(1,1')-binaphthalenyl-2,2'-diol (152 mg, 0.534 mmol) and 5.5 g of activated 4Å molecular sieves in 10 mL of dichloromethane was cooled to $0\text{ }^{\circ}\text{C}$. Silver perchlorate (252 mg, 1.12 mmol) followed by, after stirring for 10 minutes, diisopropoxy titanium dichloride (126 mg, 0.532 mmol). The reaction was stirred for 1 hour, a solution of aldehyde **2.68** (300 mg, 2.62 mmol) in 5 mL of dichloromethane was added, and the reaction was warmed to ambient temperature and stirred for another 48 hours. The solution was then poured into a saturated aqueous solution of sodium bicarbonate (5 mL) and the molecular sieves filtered off through a pad of celite. The filtrate was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash column chromatography (100 hexanes $\rightarrow$ 30% ethyl acetate/hexanes) yielded 206 mg (54%) of racemic **2.69a** as a colourless oil (*ee* determined by conversion to the MTPA esters, **2.75a** and **2.75b**).

Method B: To a suspension of activated 4Å molecular sieves (240 mg) and silver perchlorate (35 mg, 0.17 mmol) in 4 mL of dichloromethane was added **2.77** (34 mg, 0.084 mmol). The mixture was cooled to 0 °C and a solution of aldehyde **2.68** (59 mg, 0.42 mmol) in 1 mL of dichloromethane was added via cannula addition. After stirring for 1 hour, the reaction was warmed to ambient temperature and stirring was continued for 17 hours. Work-up of the reaction proceeded as in Method A above, and following purification by silica gel flash chromatography (10% → 30% diethyl ether/petroleum ether), 42.5 mg (72%) of the desired alcohol was isolated with *ee*'s ranging from 6% to 50% depending on the batch of catalyst **2.77** used. Spectral data for alcohol **2.69a** was in agreement with that reported previously for this compound: Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, 2, 1403.



6-(Tetrahydro-pyran-2-yloxy)-hexan-1-ol (2.71):

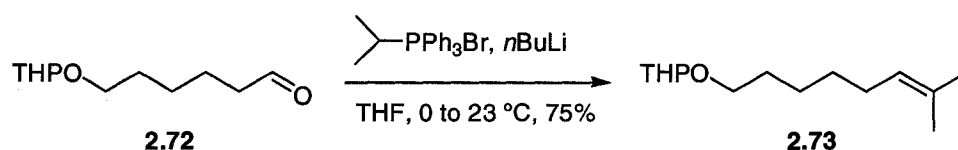
A solution of **2.70** (20.0 g, 169 mmol) in 400 mL of dichloromethane was cooled to 0 °C. Dihydropyran (7.70 mL, 84.4 mmol) was added followed by *para*-toluenesulfonic acid (1.60 g, 8.41 mmol). The reaction was warmed to ambient temperature and stirred for 18 hours before quenching with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with diethyl ether and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% → 40% ethyl acetate/hexanes) gave 13.96 g (82%) of **2.71** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203.



6-(Tetrahydro-pyran-2-yloxy)-hexanal (2.72):

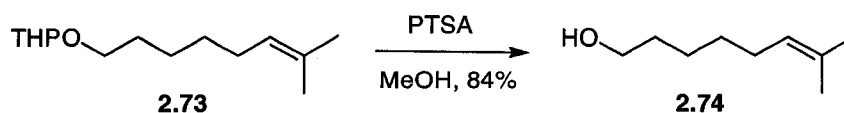
A solution of oxalyl chloride (6.5 mL, 74.5 mmol) in 350 mL of dichloromethane was cooled to -78 °C. Dimethylsulfoxide (11.5 mL, 148 mmol) was added slowly and the reaction was stirred for 10 minutes. A solution of **2.71** (13.96 g, 69.01 mmol) in 50 mL of

dichloromethane was cannulated into the reaction mixture and the resulting solution stirred at $-78\text{ }^{\circ}\text{C}$ for another 30 minutes. Triethylamine (48.0 mL, 446 mmol) was added slowly and the thick, pale-yellow mixture warmed to ambient temperature for 1 hour. The reaction was quenched with a 1 M aqueous solution of hydrochloric acid and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 12.08 g (87%) of aldehyde **2.72** as a colourless oil. Spectral data was in agreement with that reported previously: Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203.



2-(7-Methyl-oct-6-enyloxy)-tetrahydro-pyran (**2.73**):

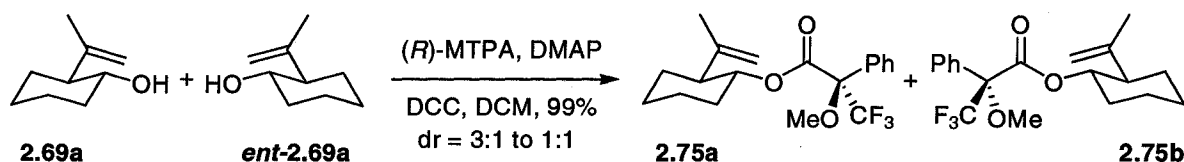
A suspension of isopropyltriphenylphosphonium bromide (7.09 g, 18.5 mmol) in 100 mL of tetrahydrofuran was cooled to $0\text{ }^{\circ}\text{C}$. *n*-Butyllithium (7.41 mL of a 2.49 M solution in pentane, 18.5 mmol) was added and the reaction was stirred for 1 hour. A solution of **2.72** (2.46 g, 12.3 mmol) in 20 mL of tetrahydrofuran was slowly added via cannula and the resulting blood red mixture was warmed to ambient temperature and stirred for 16 hours. An equal volume of petroleum ether was added to the reaction and the resulting precipitate was filtered off over celite. The filtrate was concentrated and purified by silica gel flash chromatography (100% hexanes $\rightarrow$ 10% ethyl acetate/hexanes) yielding 2.09 g of **2.73** (75%) as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203.



7-Methyl-oct-6-en-1-ol (**2.74**):

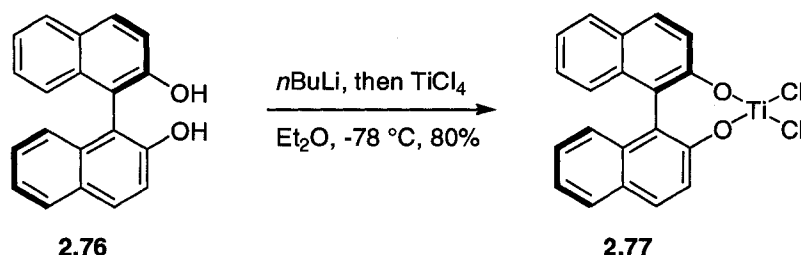
para-Toluenesulfonic acid (150 mg, 0.789 mmol) was added to a solution of **2.73** (1.77 g, 7.82 mmol) in 40 mL of methanol and the reaction was stirred for 18 hours. After quenching with a saturated aqueous solution of sodium bicarbonate, the aqueous phase was extracted

three times with ethyl acetate. The combined organic layers were washed once with brine and dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 84 mg (84%) of **2.74** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203.



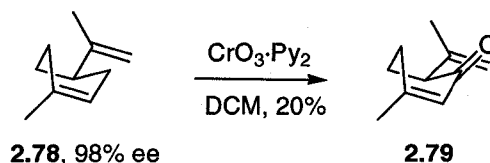
(R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (1R,2S)-2-isopropenyl-cyclohexyl ester (2.75a) and (R)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid (1S,2R)-2-isopropenyl-cyclohexyl ester (2.75b):

To a solution of **2.69a** and *ent*-**2.69a** (12.0 mg, 0.086 mmol) in 1 mL of dichloromethane was added (R)-(-)-alpha-methoxyphenylacetic acid (41.0 mg, 0.175 mmol), followed by N,N-dicyclohexylcarbodiimide (0.51 mL of a 1.0 M solution in dichloromethane, 0.51 mmol) and 4-di(methylamino)pyridine (11 mg, 0.090 mmol). The reaction was stirred for 18 hours to ensure complete consumption of the starting material and then quenched with 2 mL of distilled water. The aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 30 mg (99%) of **2.75a** and **2.75b** as an inseparable mixture of isomers. Depending on the sample of starting alcohol (**2.69a**) the diastereomeric ratio for these compounds varied from 3:1 to 1:1 (determined by integration of the methoxy signals in the ^1H NMR spectrum) indicating a range of *ee* from 50% to 0%. Spectral data for these MTPS esters was in agreement with that reported previously: Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, 2, 1403.



Dichloro[(R)-(+)-binaphtholate] titanium (2.77):

(Procedure adapted from: Reetz, M.; Kyung, S.; Bolm, C.; Zierke, T. *Chem. Ind.* **1986**, 23, 824). A solution of (*R*)-(1,1')-binaphthalenyl-2,2'-diol (583 mg, 2.04 mmol) in 20 mL of diethyl ether was sparged with argon for 20 minutes and cooled to $-78\text{ }^\circ\text{C}$. *n*-Butyllithium (1.80 mL of a 2.26 M solution in hexane) was added drop-wise and the resulting white slurry was warmed to room temperature and stirred for 30 minutes. After re-cooling to $-78\text{ }^\circ\text{C}$, titanium tetrachloride (0.22 mL, 2.01 mmol) was added. After 20 minutes, the now rust-brown reaction was warmed to ambient temperature and the diethyl ether was removed under a flow of argon. The red-brown solid was then further dried under vacuum and the reaction flask was refilled with argon. Freshly distilled benzene (30 mL) was added and the suspension stirred vigorously for 10 minutes. The fine slurry was then filtered over a sintered glass frit *while under an atmosphere of argon* and the filtrate collected. The solvent was removed by rotovap (the static vacuum of the rotovap was filled with argon at the end of the evaporation) and the resulting solid dried under vacuum. Air- and moisture-sensitive **2.77** was obtained with a mass of 663 mg (80%) as a bright orange solid. This compound was used directly without any further purification.

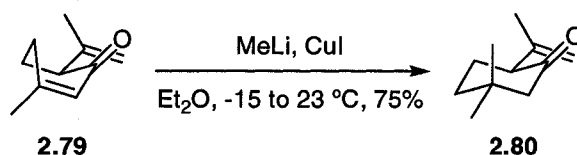


(S)-6-Isopropenyl-3-methyl-cyclohex-2-enone (2.79):

Method A: (Procedure taken from: Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, 34, 1369). A suspension of $\text{CrO}_3\cdot\text{Py}_2$ (38.0 g, 147 mmol) in 225 mL of dichloromethane was stirred vigorously for 10 minutes (or until the $\text{CrO}_3\cdot\text{Py}_2$ is nearly dissolved). (*S*)-(–)-Limonene (3.00 mL, 18.5 mmol) was added slowly over 10 minutes and the reaction was stirred for 24 hours. (A dark purple precipitate crashes out during this time

which makes stirring difficult; for larger reactions, use of a mechanical stirrer is recommended). The reaction was transferred to a separatory funnel, diluted with 600 mL of diethyl ether, and washed six times with 50 mL portions of a saturated aqueous solution of sodium bicarbonate. The combined aqueous washes were extracted once with 100 mL of diethyl ether and the organic layers combined. The organic phases were then washed three times with a 5% aqueous solution of hydrochloric acid, once with a saturated aqueous solution of sodium bicarbonate, and finally with brine before drying over magnesium sulfate, filtering and concentrating. Purification by silica gel flash chromatography (10% → 20% diethyl ether/petroleum ether) yielded 0.56 g (20%) of **2.79** as a colourless oil.

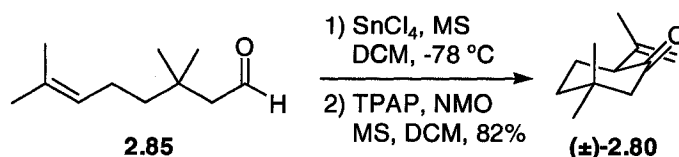
Method B: (Procedure adapted from: Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.) To a solution of freshly distilled pyridine (9.70 mL, 120 mmol) in 150 mL of dichloromethane was added anhydrous chromium (vi) oxide (dried under vacuum for 3 hours in a desiccator containing P₂O₅). The burgundy solution was stirred vigorously for 15 minutes before (S)-(-)-limonene (1.20 mL, 7.40 mmol) was added. The reaction was equipped with a drying tube (filled with drierite and potassium hydroxide) and left to stir for 24 hours. Work-up and purification, as described above, yielded 160 mg (14%) of ketone **2.79**. Spectral data for **2.79** was in agreement with that reported previously for this compound: Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 1369.



(S)-2-Isopropenyl-5,5-dimethyl-cyclohexanone (2.80):

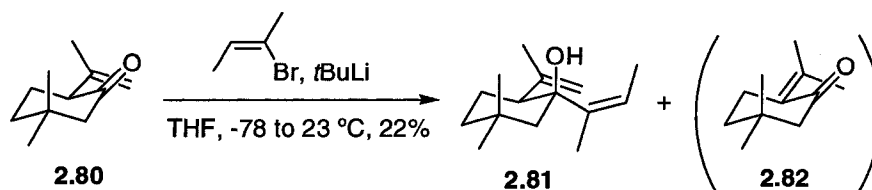
A suspension of copper (I) iodide (865 mg, 4.54 mmol) in 20 mL of diethyl ether was cooled to -15 °C. Methyllithium (5.68 mL of a 1.6 M solution in diethyl ether, 9.1 mmol) was added and the reaction was stirred for 20 minutes. A solution of **2.79** (327 mg, 2.18 mmol) in 4 mL of diethyl ether was added by cannula and the reaction was warmed to ambient temperature. After another 20 minutes, the reaction was quenched with a saturated aqueous solution of ammonium chloride titrated to pH 8 with ammonium hydroxide. The biphasic mixture was stirred vigorously for 1 hour and the aqueous phase extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate,

filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 272 mg (75%) of **2.80** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Gauvreau, D. M.Sc. Thesis, University of Ottawa, Ottawa, Canada, 2003.



(±)-2-Isopropenyl-5,5-dimethyl-cyclohexanone (2.80):

Activated 4Å molecular sieves (5.5 g) were added to a solution of **2.84** (2.07 g, 12.3 mmol) in 100 mL of dichloromethane. After cooling to -78 °C, tin tetrachloride (0.62 mL of a 1.0 M solution in dichloromethane, 0.62 mmol) was added slowly. The reaction was stirred for 45 minutes before quenching with a saturated aqueous solution of ammonium chloride. The aqueous phase was thawed and then extracted three times with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated. The crude material was next dissolved in 120 mL of dichloromethane. Activated 4Å molecular sieves (6.0 g) were added followed by 4-methylmorpholine N-oxide (2.20 g, 18.8 mmol) and tetrapropylammonium perruthenate (110 mg, 0.313 mmol). After 20 minutes the reaction mixture was filtered over a pad of silica, rinsing first with dichloromethane, followed by a 5% solution of methanol in ethyl acetate. The filtrate was concentrated and purified by silica gel flash chromatography (5% ethyl acetate/hexanes) to yield 1.67 g (82% over 2 steps) of ketone **2.80** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Gauvreau, D. M.Sc. Thesis, University of Ottawa, Ottawa, Canada, 2003.



(±)-(1S,2S)-2-Isopropenyl-5,5-dimethyl-1-((Z)-1-methyl-propenyl)-cyclohexanol (2.81) and 2-Isopropylidene-5,5-dimethyl-cyclohexanone (2.82):

A solution of (Z)-2-bromo-2-butene (180 μ L, 1.78 mmol) in 3 mL of tetrahydrofuran was cooled to -78 $^{\circ}$ C. *tert*-Butyllithium (2.22 mL of a 1.60 M solution in pentane, 3.55 mmol) was added slowly. After stirring for 30 minutes the reaction was warmed to 0 $^{\circ}$ C for 10 minutes and then re-cooled to -78 $^{\circ}$ C. A solution of ketone **2.80** (93 mg, 0.56 mmol) in 1 mL of tetrahydrofuran was added slowly via syringe. After gradually warming to ambient temperature over 5 hours, the reaction was stirred for an additional 18 hours before quenching with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% $\rightarrow$ 10% ethyl acetate/hexanes) gave 27 mg of the desired product, **2.81** (22%), as well as 39 mg of the isomerized ketone, **2.82** (42%), both as colourless oils.

Data for **2.81**:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.24 (qq, $J = 7.4, 1.3$ Hz, 1H), 4.91 (dd, $J = 1.6, 1.6$ Hz, 1H), 4.82 (s, 1H), 2.38 (dd, $J = 12.7, 3.5$ Hz, 1H), 1.96 (d, $J = 2.0$ Hz, 1H), 1.90 (dddd, $J = 13.4, 13.4, 12.9, 3.2$ Hz, 1H), 1.79 (s, 3H), 1.76 (dd, $J = 7.4, 1.4$ Hz, 3H), 1.65 (dd, $J = 1.4, 1.4$, 3H), 1.59 (dd, $J_{\text{AB}} = 14.5$ Hz, $J_{\text{AX}} = 1.8$ Hz, 1H), 1.53 (dd, $J_{\text{AB}} = 14.5$ Hz, $J_{\text{BX}} = 2.3$ Hz, 1H), 1.45 (dddd, $J = 13.1, 3.1, 3.1, 2.6$ Hz, 1H), 1.33 (dddd, $J = 13.4, 3.5, 3.5, 3.4$, 1H), 1.24, (ddd, $J = 13.4, 13.3, 3.4$ Hz, 1H), 1.11 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 148.81, 142.55, 120.74, 112.41, 77.88, 50.38, 48.40, 40.12, 34.90, 30.72, 27.49, 25.16, 25.02, 24.32, 15.76.

IR (neat, cm^{-1} , ν): 3545 (w), 3068 (w), 2947 (s), 2848 (s), 1644 (w), 1455 (m), 1364 (m), 1030 (m), 1015 (m), 955 (m), 894 (m).

HRMS (EI, m/z): calculated 222.1984 for $[\text{M}]^+$, found 222.1989.

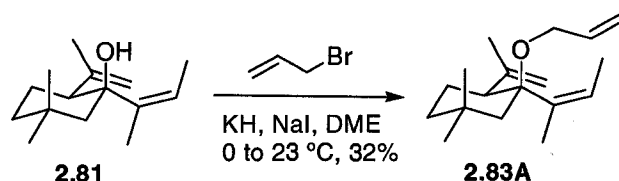
Data for **2.82**:

^1H NMR (CDCl_3 , 500 MHz, δ): 2.46 (dd, $J = 6.6, 6.6$ Hz, 2H), 2.17 (s, 2H), 1.94 (s, 3H), 1.74 (s, 3H), 1.55 (dd, $J = 6.7, 6.7$ Hz, 2H), 0.94 (s, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 204.07, 141.99, 131.07, 56.03, 37.33, 33.45, 28.22 (2C), 25.91, 22.89, 22.08.

IR (neat, cm^{-1} , ν): 2955 (s), 2925 (s), 2868 (s), 1715 (m), 1682 (s), 1614 (m), 1454 (m), 1387 (m), 1368 (s), 1287 (s), 1262 (m), 1202 (m), 1169 (m), 1107 (w), 1059 (w).

HRMS (EI, m/z): calculated 166.1358 for $[\text{M}]^+$, found 166.1376.



(±)-(1S,2S)-1-Allyloxy-2-isopropenyl-5,5-dimethyl-1-((Z)-1-methyl-propenyl)-cyclohexane (2.83A):

Sodium iodide (2 mg, 0.01 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (120 mg of a 30% suspension in mineral oil, 0.898 mmol) was added to the flask and the system was put under argon. The potassium hydride was then washed three times with dry hexanes and dried under a flow of argon. Dimethoxyethane (1.0 mL) was added to the flask and the suspension cooled to 0 °C. A solution of **2.81** (25 mg, 0.11 mmol) in another 1.0 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.100 mL, 1.16 mmol) was added and the reaction warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 9.5 mg of a colourless oil (32%) along with 13 mg (52%) of recovered **2.81**.

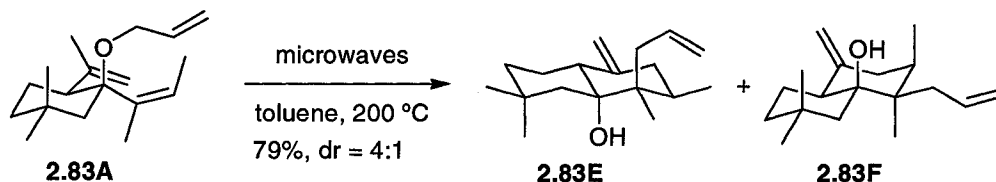
Data for 2.83A:

¹H NMR (CDCl₃, 500 MHz, δ): 5.92-5.85 (m, 1H), 5.41 (qq, *J* = 7.4, 1.3 Hz, 1H), 5.27 (dddd, *J* = 17.3, 2.0, 2.0, 2.0 Hz, 1H), 5.04 (dddd, *J* = 10.6, 2.0, 2.0, 1.8 Hz, 1H), 4.74-4.73 (m, 1H), 4.60 (d, *J* = 1.7 Hz, 1H), 3.91-3.86 (m, 1H), 3.75-3.70 (m, 1H), 2.17 (dddd, *J* = 13.3, 13.2, 13.1, 3.3 Hz, 1H), 1.97 (dd, *J* = 12.7, 3.2 Hz, 1H), 1.88 (dd, *J*_{AB} = 14.9, *J*_{AX} = 2.4 Hz, 1H), 1.81 (s, 3H), 1.60 (dd, *J* = 1.4, 1.4 Hz, 3H), 1.56 (dd, *J* = 7.4, 1.5 Hz, 3H), 1.44 (dddd, *J* = 13.0, 3.2, 3.1, 2.7 Hz, 1H), 1.35 (dddd, *J* = 13.2, 3.4, 3.4, 3.4 Hz, 1H), 1.32 (d, *J*_{AB} = 14.9 Hz, 1H), 1.20 (ddd, *J* = 13.4, 13.4, 3.5 Hz, 1H), 1.09 (s, 3H), 0.88 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 146.85, 135.78, 133.22, 125.56, 113.99, 113.45, 84.66, 62.61, 51.79, 41.34, 40.40, 34.71, 30.62, 24.98, 24.89, 24.21, 22.85, 15.49.

IR (neat, cm⁻¹, ν): 3069 (w), 2951 (s), 2921 (s), 2868 (m), 1646 (w), 1456 (s), 1382 (m), 1329 (w), 1204 (m), 1111 (m), 1062 (s), 1044 (m).

HRMS (EI, m/z): calculated 262.2297 for $[M]^+$, found 262.2291.



(±)-(3*S*,4*S*,4*aS*,8*aS*)-4-Allyl-3,4,6,6-tetramethyl-1-methylene-octahydro-naphthalen-4a-ol (**2.83E**) and (±)-(3*R*,4*R*,4*aS*,8*aS*)-4-Allyl-3,4,6,6-tetramethyl-1-methylene-octahydro-naphthalen-4a-ol (**2.83F**):

A solution of **2.83A** (9.5 mg, 0.036 mmol) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1.5 hours. Following removal of the solvent, a crude NMR was taken to reveal a 4:1 ratio of diastereomers. Purification by silica gel flash chromatography (100% hexanes) yielded 7.5 mg of an inseparable mixture of **2.83E** and **2.83F** as a colourless oil (79%).

Data for **2.83E** (major isomer):

¹H NMR (CDCl₃, 300 MHz, δ): 5.95-5.81 (m, 1H), 5.03-4.93 (m, 2H), 4.87 (s, 1H), 4.69 (s, 1H), 2.29-2.02 (m, 5H), 1.81-1.60 (m, 2H), 1.51-1.42 (m, 4H), 1.30 (d, $J = 1.5$ Hz, 1H), 1.27-0.98 (m, 1H), 1.04 (s, 3H), 0.89-0.86 (m, 9H).

¹³C NMR (CDCl₃, 75 MHz, δ): 150.06, 138.14, 115.72, 108.77, 78.36, 44.06, 43.97, 42.34, 40.75, 39.02, 38.53, 35.25, 34.70, 30.63, 26.89, 21.34, 17.82, 16.62.

Data for **2.83F** (minor isomer):

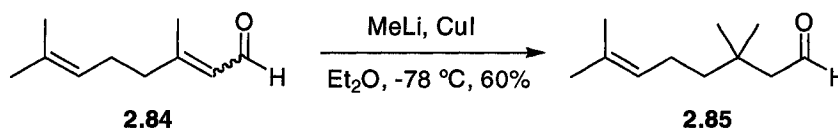
¹H NMR (CDCl₃, 300 MHz, δ): 5.95-5.74 (m, 1H), 5.12-4.93 (m, 2H), 4.87 (s, 1H), 4.79 (s, 1H), 2.68-2.53 (m, 2H), 2.29-2.02 (m, 4H), 1.91-1.60 (m, 4H), 1.51-1.42 (m, 1H), 1.27-0.98 (m, 2H), 1.08 (s, 3H), 0.89-0.86 (m, 9H).

¹³C NMR (CDCl₃, 75 MHz, δ): 147.47, 135.57, 117.42, 110.43, 79.92, 45.16, 43.21, 42.91, 39.34, 38.85, 38.82, 37.84, 34.84, 30.74, 27.16, 23.91, 21.15, 17.24.

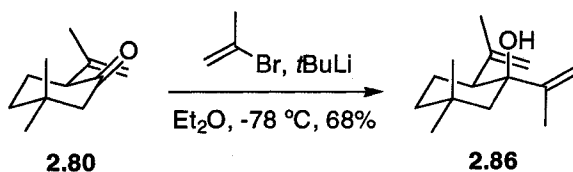
Data for **2.83E** and **2.83F** (major and minor isomers together):

IR (neat, cm⁻¹, ν): 3562 (w), 3076 (w), 2948 (s), 1642 (m), 1455 (m), 1382 (m), 1363 (m), 1277 (w), 1244 (w), 1873 (w), 1173 (m), 1106 (m).

HRMS (EI, m/z): calculated 262.2297 for $[M]^+$, found 262.2322.

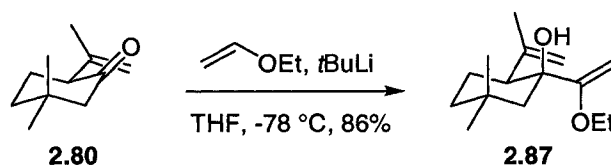
**3,3,7-Trimethyl-oct-6-enal (2.85):**

(Procedure adapted from: Clive, D. J.; Farina, V.; Beaulieu, P. *J. Chem. Soc., Chem. Commun.* **1981**, 13, 643.) A suspension of copper (I) iodide (3.34 g, 17.5 mmol) in 55 mL of diethyl ether was cooled to 0 °C. Methyllithium (18.5 mL of a 1.6 M solution in diethyl ether, 29 mmol) was added slowly and the resulting yellow-orange slurry was cooled further to -78 °C. A solution of **2.84** (1.07 mL, 5.93 mmol) in 5 mL of diethyl ether was added dropwise over 10 minutes and the reaction was stirred at -78 °C for 2 hours, warmed to 0 °C for 30 minutes, and then re-cooled to -78 °C before quenching with 10 mL of acetic acid. After warming to ambient temperature, water was added and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed, first with a saturated aqueous solution of sodium bicarbonate, and then with brine, before being dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 601 mg of **2.85** as a colourless oil (60%). Spectral data for this compound was in agreement with that reported previously: Demailly, G.; Solladie, G. *J. Org. Chem.* **1981**, 46, 3102.

**(1S,2S)-1,2-Diisopropenyl-5,5-dimethyl-cyclohexanol (2.86):**

A solution of 2-bromopropene (40 μL , 0.45 mmol) in 3 mL of diethyl ether was cooled to -78 °C. *tert*-Butyllithium (0.42 mL of a 2.1 M solution in pentane, 0.88 mmol) was added and the mixture was stirred for 15 min. In a separate flask, ketone **2.80** (50 mg, 0.23 mmol) was dissolved in 1 mL of diethyl ether and cooled to -78 °C. This solution was then added via a cold cannula to the solution of alkylolithium. After stirring for 60 minutes, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography

(5% ethyl acetate/hexanes) gave 32 mg (68%) of **2.86** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Gauvreau, D. M.Sc. Thesis, University of Ottawa, Ottawa, Canada, 2003.



(1S,2S)-1-(1-Ethoxy-vinyl)-2-isopropenyl-5,5-dimethyl-cyclohexanol (2.87):

To a solution of ethyl vinyl ether (0.800 mL, 8.35 mmol) in 8 mL of tetrahydrofuran and cooled to $-78\text{ }^\circ\text{C}$ was slowly added *tert*-butyllithium (1.17 mL of a 2.05 M solution in pentane, 2.40 mmol). After stirring for 20 minutes, the reaction was immersed in an ice bath for ten minutes and then re-cooled to $-78\text{ }^\circ\text{C}$. A solution of ketone **2.80** (100 mg, 0.602 mmol) in 1 mL of tetrahydrofuran was added drop-wise by syringe and the reaction was warmed gradually to ambient temperature over 1.5 hours. After quenching with water and extracting three times with diethyl ether, the combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes, basified with triethylamine) gave 124 mg of a colourless oil (86%).

Data for 2.87:

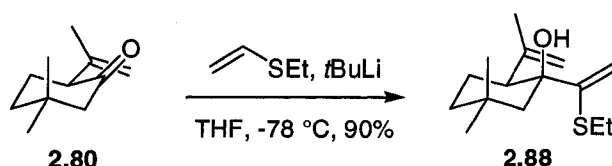
^1H NMR (C_6D_6 , 300 MHz, δ): 4.88-4.86 (m, 1H), 4.78 (d, $J = 0.8\text{ Hz}$, 1H), 4.52 (d, $J = 2.0\text{ Hz}$, 1H), 3.85 (d, $J = 1.9\text{ Hz}$, 1H), 3.42-3.25 (m, 2H), 2.61 (dd, $J = 13.3, 3.1\text{ Hz}$, 1H), 2.02 (dddd, $J = 13.2, 13.2, 13.2, 3.3\text{ Hz}$, 1H), 1.93-1.88 (m, 2H), 1.72-1.66 (m, 1H), 1.70 (dd, $J = 1.3, 0.8\text{ Hz}$, 3H), 1.47-1.34 (m, 2H), 1.32 (s, 3H), 1.31-1.18 (m, 1H), 1.01 (dd, $J = 7.0, 7.0\text{ Hz}$, 3H), 0.91 (s, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 168.48, 148.41, 112.08, 79.93, 74.71, 62.70, 48.99, 48.02, 39.74, 34.47, 30.63, 27.23, 25.06, 24.53, 14.51.

IR (neat, cm^{-1} , ν): 3538 (w), 3079 (w), 2978 (m), 2949 (s), 2907 (s), 2878 (m), 2845 (m), 1656 (w), 1636 (m), 1615 (m), 1453 (m), 1372 (m), 1364 (m), 1278 (s), 1267 (s), 1217 (m), 1175 (m), 1155 (m), 1090 (m), 1067 (m).

HRMS (EI, m/z): calculated 238.1933 for $[\text{M}]^+$, found 238.1938.

$[\alpha]_D^{23}$ = $+4.1^\circ$ ($c = 8.7\text{ mg/ml}$, dichloromethane).



(1S,2S)-1-(1-Ethylsulfanyl-vinyl)-2-isopropenyl-5,5-dimethyl-cyclohexanol (2.88):

To a solution of ethyl vinyl sulfide (0.670 mL, 6.60 mmol) in 8 mL of tetrahydrofuran and cooled to $-78\text{ }^\circ\text{C}$ was slowly added *tert*-butyllithium (1.17 mL of a 2.05 M solution in pentane, 2.40 mmol). After stirring for 20 minutes, the reaction was immersed in an ice bath for ten minutes and then re-cooled to $-78\text{ }^\circ\text{C}$. A solution of ketone **2.80** (100 mg, 0.602 mmol) in 1 mL of tetrahydrofuran was added drop-wise by syringe and the reaction was warmed gradually to ambient temperature over 1.5 hours. After quenching with water and extracting three times with diethyl ether, the combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (3% ethyl acetate/hexanes, basified with triethylamine) gave 138 mg of a colourless oil (90%).

Data for 2.88:

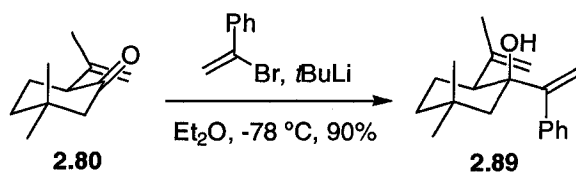
$^1\text{H NMR}$ (C_6D_6 , 500 MHz, δ): 5.44 (s, 1H), 4.87-4.86 (m, 1H), 4.83 (d, $J = 0.8\text{ Hz}$, 1H), 4.64 (s, 1H), 2.56 (dd, $J = 12.9, 3.2\text{ Hz}$, 1H), 2.43-2.30 (m, 2H), 2.06-1.97 (m, 2H), 1.94 (d, $J = 1.9\text{ Hz}$, 1H), 1.76 (dd, $J = 1.4, 0.8\text{ Hz}$, 3H), 1.62 (dd, $J = 14.3, 2.5\text{ Hz}$, 1H), 1.43-1.35 (m, 2H), 1.24 (s, 3H), 1.24-1.18 (m, 1H), 1.02 (dd, $J = 7.4, 7.4\text{ Hz}$, 3H), 0.88 (s, 3H).

$^{13}\text{C NMR}$ (C_6D_6 , 125 MHz, δ): 154.41, 147.91, 112.26, 104.52, 76.96, 50.48, 49.66, 39.35, 34.14, 30.45, 26.62, 26.38, 24.82, 24.81, 12.73.

IR (neat, cm^{-1} , ν): 3528 (w), 3078 (w), 2949 (s), 2928 (s), 2903 (s), 2869 (m), 2845 (w), 1634 (w), 1596 (m), 1450 (s), 1373 (m), 1364 (m), 1343 (m), 1126 (m), 1083 (m), 1057 (m), 1028 (m), 1016 (m).

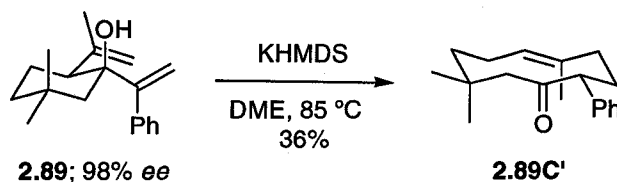
HRMS (EI, m/z): calculated 254.1704 for $[\text{M}]^+$, found 254.1700.

$[\alpha]_{\text{D}}^{23} = +54.4^\circ$ ($c = 3.1\text{ mg/ml}$, dichloromethane).



(1S,2S)-2-Isopropenyl-5,5-dimethyl-1-(1-phenyl-vinyl)-cyclohexanol (2.89):

A solution of α -bromostyrene (47 μL , 0.36 mmol) in 2 mL of diethyl ether was cooled to $-78\text{ }^\circ\text{C}$. *tert*-Butyllithium (0.34 mL of a 2.14 M solution in hexane, 0.728 mmol) was added and the mixture was stirred at $-78\text{ }^\circ\text{C}$ for 10 minutes. In a separate flask, ketone **2.80** (30 mg, 0.18 mmol) was dissolved in 1 mL of diethyl ether and cooled to $-78\text{ }^\circ\text{C}$. This solution was then added via a cold cannula to the solution of alkyllithium. After stirring for 60 minutes, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) gave 43.9 mg (90%) of **2.89** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Gauvreau, D. M.Sc. Thesis, University of Ottawa, Ottawa, Canada, 2003.



($\pm$)-(E)-(R)-5,9,9-Trimethyl-2-phenyl-cyclodec-5-enone (2.89C'):

Potassium bis(trimethylsilyl)amide (168 mg, 0.842 mmol) was added to a solution of **2.89** (45.7 mg, 0.169 mmol) in 3 mL of dimethoxyethane and 1.5 mL of toluene. The reaction was heated to $85\text{ }^\circ\text{C}$ for 1.5 hours, cooled to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) gave 36 mg (78%) of a white solid.

Data for 2.89C':

$^1\text{H NMR}$ (acetone- d_6 , 500 MHz, δ): 7.30-7.18 (m, 5H), 5.63 (s, br, 1H), 3.72 (d, $J = 11.6\text{ Hz}$, 1H), 2.96 (d, br, $J = 17.4\text{ Hz}$, 1H), 2.75 (dddd, $J = 13.0, 13.0, 13.0, 3.5\text{ Hz}$, 1H), 2.23-2.20

(m, 1H), 2.16-1.96 (m, 5H), 1.62 (d, $J = 13.4$ Hz, 1H), 1.55 (s, 3H), 1.16-1.09 (m, 1H), 1.06 (s, 3H), 0.90 (s, 3H).

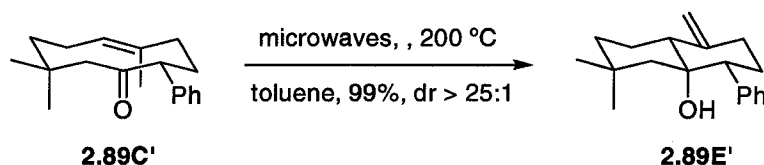
^{13}C NMR (CDCl_3 , 75 MHz, δ): broad signals due to interchanging conformers prevented all peaks from being detected. High temperature NMR to resolve the conformers was impossible due to the resulting carbonyl ene reaction.

IR (neat, cm^{-1} , ν): 2952 (s), 2926 (s), 2855 (m), 1698 (s), 1495 (w), 1450 (m), 1409 (w), 1357 (m), 1338 (w), 1104 (w), 1055 (w).

HRMS (EI, m/z): calculated 270.1984 for $[\text{M}]^+$, found 270.2042.

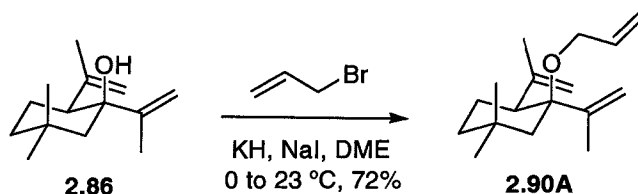
mp = 99.4-101.2 °C.

$[\alpha]_{\text{D}}^{23} = +1.4^\circ$ ($c = 8.2$ mg/ml, dichloromethane).



(4R,4aR,8aR)-6,6-Dimethyl-1-methylene-4-phenyl-octahydro-naphthalen-4a-ol (2.89E'):

A solution of **2.89C'** (11.0 mg, 0.0407 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 220 °C. After 1 hour the reaction was concentrated. A ^1H NMR of the crude material confirmed the presence of a single isomer. Purification by silica gel flash chromatography (8% ethyl acetate/hexanes) yielded 10.9 mg of **2.89E'** (99%) as a white solid. Spectral data for this compound was in agreement with reported previously: Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2004**, *70*, 1382.



(1S,2S)-1-Allyloxy-1,2-diisopropenyl-5,5-dimethyl-cyclohexane (2.90A):

Sodium iodide (3 mg, 0.02 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (100 mg of a 30% suspension in mineral oil, 0.748 mmol) was added to the flask and the system was put under argon. The potassium hydride was then washed three times with

dry hexanes and dried under a flow of argon. Dimethoxyethane (2.0 mL) was added and the suspension was cooled to 0 °C. A solution of **2.86** (29 mg, 0.14 mmol) in another 1.0 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.070 mL, 0.81 mmol) was added and the reaction was warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 25 mg of a colourless oil (72%).

Data for 2.90A:

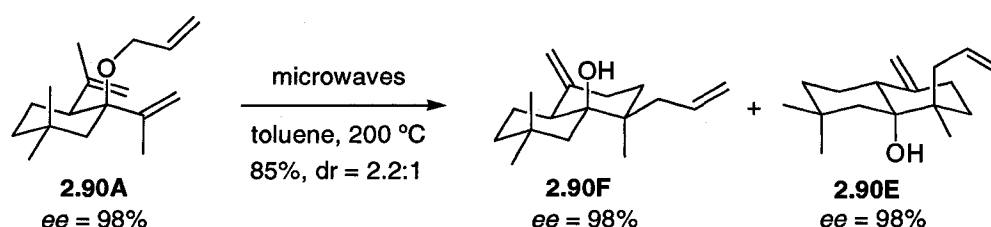
¹H NMR (CDCl₃, 300 MHz, δ): 5.92-5.80 (m, 1H), 5.28 (dddd, *J* = 17.3, 2.0, 2.0, 2.0 Hz, 1H), 5.05 (dddd, *J* = 10.6, 2.0, 1.8, 1.7 Hz, 1H), 4.92-4.90 (m, 1H), 4.77 (d, *J* = 1.2 Hz, 1H), 4.66 (dd, *J* = 2.7, 1.3 Hz, 1H), 4.60 (d, *J* = 2.7 Hz, 1H), 3.89-3.82 (m, 1H), 3.76-3.69 (m, 1H), 2.17 (dddd, *J* = 13.1, 12.5, 12.4, 3.2 Hz, 1H), 1.92 (dd, *J* = 12.4, 3.0 Hz, 1H), 1.78 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.74 (dd, *J* = 14.9, 2.3 Hz, 1H), 1.65 (dd, *J* = 1.3, 0.5 Hz, 3H), 1.49-1.43 (m, 1H), 1.40 (d, *J* = 14.9 Hz, 1H), 1.34-1.17 (m, 2H), 1.11 (s, 3H), 0.91 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 148.46, 146.81, 135.60, 144.35, 112.64, 112.38, 83.17, 63.17, 55.04, 40.77, 40.46, 34.61, 30.97, 25.70, 24.77, 21.99, 20.84.

IR (neat, cm⁻¹, ν): 3073 (w), 2950 (s), 2924 (s), 2865 (m), 1636 (m), 1460 (m), 1453 (m), 1432 (m), 1375 (m), 1327 (w), 1216 (w), 1204 (w), 1152 (m), 1111 (m), 1075 (s), 1060 (s), 1040 (s), 1021 (m).

HRMS (EI, *m/z*): calculated 233.1905 for [M-Me]⁺, found 233.1896.

[α]_D²³ = +35.6° (c = 5.2 mg/ml, dichloromethane).



(4S,4aS,8aS)-4-Allyl-4,6,6-trimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.90F)
and (4R,4aS,8aS)-4-Allyl-4,6,6-trimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.90E):

A solution of **2.90A** (16.5 mg, 0.0664 mmol) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1.5 hours. Following removal of the solvent, a crude NMR was taken to reveal a 2.2:1 ratio of diastereomers. Purification by silica gel flash chromatography (1% ethyl acetate/hexanes) yielded 7.8 mg of **2.90F**, 2.0 mg of **2.90E**, and 4.3 mg of a mixture of the two isomers, all as colourless oils (85% combined yield).

Data for **2.90F** (major isomer):

¹H NMR (CDCl₃, 500 MHz, δ): 5.84-5.75 (m, 1H), 5.01-4.99 (m, 1H), 4.97 (s, 1H), 4.88 (s, 1H), 4.68 (s, 1H), 2.30 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.28-2.25 (m, 1H), 2.18-2.13 (m, 2H), 2.08 (dd, *J* = 13.4, 7.3 Hz, 1H), 1.75-1.66 (m, 1H), 1.55-1.42 (m, 4H), 1.36 (ddd, *J* = 12.7, 3.7, 3.9 Hz, 1H), 1.29-1.25 (m, 2H), 1.16 (ddd, *J* = 13.5, 13.5, 3.7 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 0.88 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 150.48, 136.16, 116.89, 108.70, 77.83, 44.50, 41.55, 41.27, 41.05, 38.72, 35.11, 34.69, 32.18, 30.57, 26.86, 21.18, 20.78.

IR (neat, cm⁻¹, ν): 3563 (w), 3076 (w), 2938 (s), 2865 (m), 1640 (m), 1454 (m), 1364 (m), 1330 (w), 1277 (w), 1173 (w), 1162 (w), 1092 (w).

HRMS (EI, *m/z*): calculated 248.2140 for [M]⁺, found 248.2134.

[α]_D²³ = +27.8° (c = 2.0 mg/ml, dichloromethane).

ee = 98%; determined to be 98% using GLC, method: 100 °C for 3 min, 100 – 170 °C at 0.5 °C/min, T_{r(major)}: 99.8 min, T_{r(minor)}: 98.0 min.

Data for **2.90E** (minor isomer):

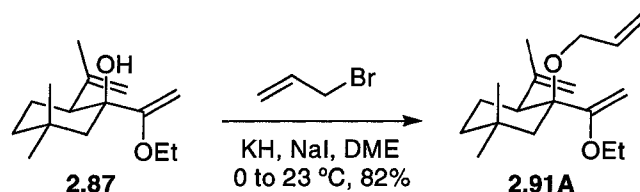
¹H NMR (CDCl₃, 500 MHz, δ): 5.82-5.74 (m, 1H), 5.06-5.02 (m, 2H), 4.88 (d, *J* = 1.6 Hz, 1H), 4.69 (d, *J* = 0.9 Hz, 1H), 2.46 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.28 (d, *J* = 11.6 Hz, 1H), 2.14-2.01 (m, 3H), 1.74-1.67 (m, 1H), 1.51-1.41 (m, 4H), 1.36 (ddd, *J* = 13.5, 13.5, 4.4 Hz, 1H), 1.29-1.04 (m, 3H), 1.06 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 150.22, 135.47, 117.05, 108.97, 77.20, 43.96, 41.37, 41.27, 38.86, 38.85, 34.73, 33.08, 31.95, 30.57, 26.86, 21.30, 20.42.

IR (neat, cm⁻¹, ν): 3561 (w), 3076 (w), 2939 (s), 2865 (m), 1640 (m), 1454 (m), 1363 (m), 1330 (w), 1279 (w), 1173 (w), 1162 (w), 1092 (w).

HRMS (EI, *m/z*): calculated 248.2140 for [M]⁺, found 248.2134.

[α]_D²³ = -22.4° (c = 2.0 mg/ml, dichloromethane).



(1S,2S)-1-Allyloxy-1-(1-ethoxy-vinyl)-2-isopropenyl-5,5-dimethyl-cyclohexane (2.91A):

Sodium iodide (10 mg, 0.067 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (321 mg of a 30% suspension in mineral oil, 2.40 mmol) was added to the flask and the system was put under argon. The potassium hydride was then washed three times with dry hexanes and dried under a flow of argon. Dimethoxyethane (5 mL) was added to the flask and the suspension cooled to 0 °C. A solution of **2.87** (124 mg, 0.520 mmol) in another 2 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.230 mL, 2.66 mmol) was added and the reaction was warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 119 mg of a colourless oil (82%).

Data for 2.91A:

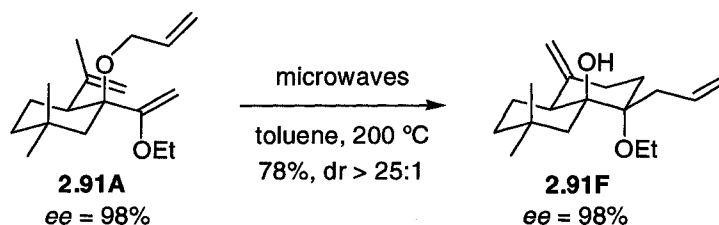
¹H NMR (C₆D₆, 500 MHz, δ): 5.94-5.87 (m, 1H), 5.41 (dddd, *J* = 17.3, 2.0, 2.0, 2.0 Hz, 1H), 5.08 (dddd, *J* = 10.5, 2.0, 1.7, 1.7 Hz, 1H), 4.87-4.86 (m, 1H), 4.81 (d, *J* = 2.4 Hz, 1H), 4.24 (d, *J* = 2.2 Hz, 1H), 4.05-4.01 (m, 1H), 3.98 (d, *J* = 2.2 Hz, 1H), 3.90-3.85 (m, 1H), 3.37 (q, *J* = 7.1 Hz, 2H), 2.31-2.25 (m, 2H), 2.02 (d, *J* = 0.7 Hz, 3H), 1.78-1.72 (m, 2H), 1.44-1.39 (m, 2H), 1.26-1.20 (m, 1H), 1.14 (s, 3H), 1.06 (dd, *J* = 7.1, 7.1 Hz, 3H), 0.90 (s, 3H).

¹³C NMR (C₆D₆, 125 MHz, δ): 162.43, 148.28, 135.70, 114.30, 111.64, 82.17, 81.79, 63.83, 62.27, 54.88, 40.17, 39.49, 34.41, 30.53, 25.90, 24.39, 21.82, 14.17.

IR (neat, cm⁻¹, ν): 3069 (w), 2979 (s), 2951 (s), 2866 (s), 1647 (m), 1637 (m), 1619 (m), 1457 (m), 1384 (w), 1371 (w), 1363 (w), 1274 (s), 1218 (w), 1171 (w), 1154 (s), 1111(m), 1066 (s), 1016 (w).

HRMS (EI, *m/z*): calculated 278.2246 for [M]⁺, found 278.2212.

[α]_D²³ = +47.9° (c = 5.8 mg/ml, dichloromethane).



(4R,4aS,8aS)-4-Allyl-4-ethoxy-6,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.91F):

A solution of **2.91A** (10.6 mg, 0.0381 mmol) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1.5 hours. Following removal of the solvent, a crude NMR was taken to reveal a single detectable diastereomer. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 8.3 mg of a colourless oil (78%).

Data for 2.91F:

^1H NMR (C_6D_6 , 300 MHz, δ): 6.08-5.94 (m, 1H), 5.05-4.95 (m, 2H), 4.83 (ddd, $J = 1.7, 1.6, 1.6$ Hz, 1H), 4.67 (d, $J = 1.3$ Hz, 1H), 3.26 (dq, $J = 8.5, 7.0$ Hz, 1H), 3.10 (dq, $J = 8.5, 7.0$ Hz, 1H), 2.75 (d, br, $J = 12.0$ Hz, 1H), 2.55 (dddd, $J_{\text{AB}} = 14.9, J_{\text{AX}} = 7.1, J_{\text{AY}} = 1.5, J_{\text{AZ}} = 1.5$ Hz, 1H), 2.45 (dd, $J_{\text{AB}} = 15.0, J_{\text{BX}} = 7.6$ Hz, 1H), 2.11 (ddd, $J = 13.1, 13.1, 3.4$ Hz, 1H), 1.95-1.87 (m, 2H), 1.76-1.54 (m, 3H), 1.46-1.33 (m, 3H), 1.29-1.18 (m, 2H), 1.26 (s, 3H), 1.03 (dd, $J = 6.9, 6.9$ Hz, 3H), 0.97 (s, 3H).

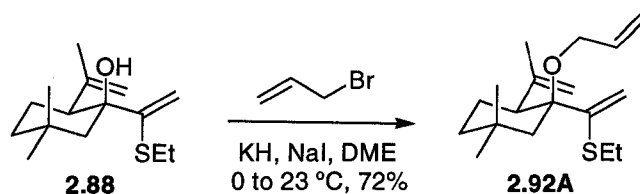
^{13}C NMR (C_6D_6 , 75 MHz, δ): 150.25, 137.15, 116.01, 108.80, 79.37, 78.13, 57.36, 44.07, 41.19, 38.86, 38.51, 34.87, 31.95, 30.74, 29.21, 27.58, 21.32, 16.19.

IR (neat, cm^{-1} , ν): 3554 (w), 3078 (w), 2974 (m), 2946 (s), 2930 (s), 2901 (s), 2871 (m), 2847 (m), 1642 (m), 1455 (m), 1441 (m), 1387 (w), 1362 (m), 1315 (w), 1275 (m), 1181 (m), 1107 (s), 1071 (s), 1030 (w).

HRMS (EI, m/z): calculated 278.2246 for $[\text{M}]^+$, found 278.2263.

$[\alpha]_{\text{D}}^{23} = +105.3^\circ$ ($c = 0.5$ mg/mL, dichloromethane).

$ee = 98\%$; determined using GLC, method: 100 °C for 3 min, 100 – 150 °C at 5.0 °C/min, 150 – 200 °C at 5.0 °C/min, $T_{\text{r(major)}}$: 47.1 min, $T_{\text{r(minor)}}$: 45.5 min.



(1S,2S)-1-Allyloxy-1-(1-ethylsulfanyl-vinyl)-2-isopropenyl-5,5-dimethyl-cyclohexane (2.92A):

Sodium iodide (10 mg, 0.067 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (342 mg of a 30% suspension in mineral oil, 2.56 mmol) was added to the flask and the system was put under argon. The potassium hydride was then washed three times with dry hexanes and dried under a flow of argon. Dimethoxyethane (6 mL) was added to the flask and the suspension cooled to 0 °C. A solution of **2.88** (153 mg, 0.602 mmol) in another 2 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.260 mL, 3.00 mmol) was added and the reaction was warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 127 mg of a colourless oil (72%).

Data for 2.92A:

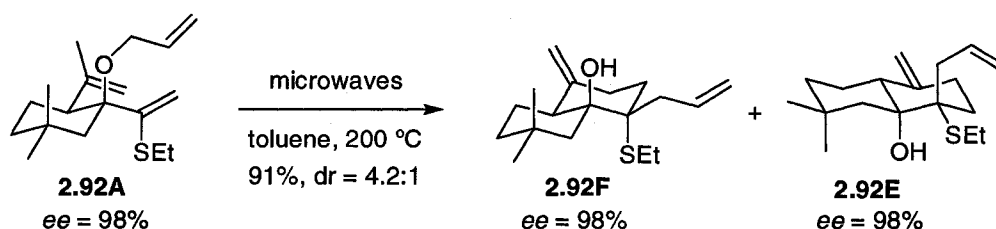
¹H NMR (C₆D₆, 300 MHz, δ): 5.91-5.79 (m, 1H), 5.40 (dddd, *J* = 17.2, 2.0, 2.0, 2.0 Hz, 1H), 5.32 (s, 1H), 5.07 (dddd, *J* = 10.6, 2.0, 1.8, 1.8 Hz, 1H), 4.95-4.93 (m, 2H), 4.77 (s, 1H), 4.04-3.97 (m, 1H), 3.83-3.76 (m, 1H), 2.47-2.34 (m, 3H), 2.25 (dddd, *J* = 13.1, 13.1, 12.8, 3.3 Hz, 1H), 1.97 (dd, *J* = 1.3, 0.9 Hz, 3H), 1.89-1.77 (m, 2H), 1.48-1.34 (m, 2H), 1.21 (ddd, *J* = 13.3, 12.9, 3.5 Hz, 1H), 1.09 (s, 3H), 1.06 (dd, *J* = 7.4, 7.3 Hz, 3H), 0.88 (s, 3H).

¹³C NMR (C₆D₆, 75 MHz, δ): 147.26, 146.92, 135.56, 114.76, 113.38, 106.18, 84.57, 63.44, 54.48, 40.98, 40.49, 34.57, 31.10, 26.39, 25.93, 24.71, 22.56, 13.02.

IR (neat, cm⁻¹, ν): 3070(w), 2950 (s), 2926 (s), 2872 (s), 1646 (m), 1638 (m), 1594 (m), 1452 (s), 1373 (m), 1363 (m), 1330 (w), 1263 (m), 1216 (m), 1205 (w), 1130 (m), 1107 (s), 1075 (m), 1057 (s), 1038 (m), 1011 (m).

HRMS (EI, *m/z*): calculated 294.2017 for [M]⁺, found 294.2024.

[α]_D²³ = -2.6° (c = 6.3 mg/ml, dichloromethane).



(4R,4aS,8aS)-4-Allyl-4-ethylsulfanyl-6,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.92F) and (4S,4aS,8aS)-4-Allyl-4-ethylsulfanyl-6,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.92E):

A solution of **2.92A** (23 mg, 0.078 mmol) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1.5 hours. Following removal of the solvent, a crude NMR was taken to reveal a 4:1 ratio of diastereomers. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 17 mg of **2.92F** and 4 mg of the **2.92E**, both as colourless oils (91%).

Data for **2.92F** (major isomer):

¹H NMR (C_6D_6 , 500 MHz, δ): 6.09–6.01 (m, 1H), 5.09 (dddd, $J = 17.0, 2.3, 1.5, 1.5$ Hz, 1H), 5.03 (dddd, $J = 10.1, 2.2, 1.1, 1.1$ Hz, 1H), 4.79 (dd, $J = 1.6, 1.6$ Hz, 1H), 4.63 (d, $J = 1.3$ Hz, 1H), 3.11 (dd, $J = 12.1, 1.5$ Hz, 1H), 2.70–2.61 (m, 2H), 2.45 (ddd, $J = 13.1, 13.1, 2.1$ Hz, 1H), 2.39–2.32 (m, 1H), 2.27–2.21 (m, 1H), 1.94 (ddd, $J = 13.1, 4.1, 4.1$ Hz, 1H), 1.75 (d, $J_{AB} = 15.1$ Hz, 1H), 1.72 (d, $J_{AB} = 15.0$ Hz, 1H), 1.68–1.58 (m, 2H), 1.51 (ddd, $J = 13.8, 13.8, 4.2$ Hz, 1H), 1.41–1.35 (m, 2H), 1.32 (d, $J = 0.8$ Hz, 1H), 1.23–1.17 (m, 1H), 1.20 (s, 3H), 1.05 (dd, $J = 7.5, 7.5$ Hz, 3H), 0.92 (s, 3H).

¹³C NMR (C_6D_6 , 125 MHz): 149.89, 136.74, 116.84, 109.23, 79.16, 57.02, 44.60, 42.76, 41.04, 38.77, 34.78, 33.48, 32.49, 30.88, 27.22, 23.74, 21.54, 14.03.

IR (neat, cm^{-1} , ν): 3549 (w), 3077 (w), 2932 (s), 2866 (s), 1642 (m), 1454 (m), 1363 (m), 1274 (m), 1174 (m), 1104 (m), 1075 (w), 1021 (m), 1000 (m).

HRMS (EI, m/z): calculated 294.2017 for $[M]^+$, found 294.2025.

$[\alpha]_D^{23} = +68.1^\circ$ ($c = 17.2$ mg/ml, dichloromethane).

$ee = 98\%$; determined using GLC, method: 100 °C for 3 min, 100 – 140 °C at 5.0 °C/min, 140 °C for 200 min, $T_{r(\text{major})}$: 199.1 min, $T_{r(\text{minor})}$: 193.6 min.

Data for **2.92E** (minor isomer):

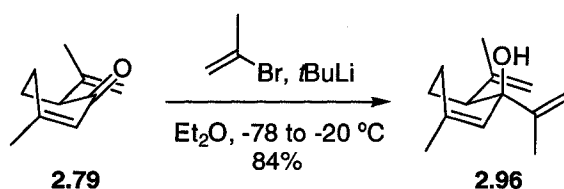
^1H NMR (C_6D_6 , 300 MHz, δ): 6.07-5.93 (m, 1H), 5.10-5.05 (m, 2H), 4.88 (s, 1H), 4.79 (s, 1H), 2.44 (dd, $J = 14.8, 8.8$ Hz, 1H), 2.38-2.25 (m, 4H), 2.10-1.88 (m, 5H), 1.71-1.62 (m, 2H), 1.59-1.44 (m, 2H), 1.28 (s, 3H), 1.19 (d, $J = 13.7$ Hz, 1H), 1.01 (ddd, $J = 13.2, 13.2, 3.7$ Hz, 1H), 0.98 (dd, $J = 7.4, 7.4$ Hz, 3H), 0.90 (s, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 148.32, 135.47, 117.34, 107.99, 78.41, 60.15, 44.66, 44.57, 39.39, 38.19, 34.94, 32.43, 31.26, 31.11, 27.14, 23.96, 22.35, 14.63.

IR (neat, cm^{-1} , ν): 3493 (w), 3082 (w), 2946 (s), 2929 (s), 2866 (s), 1642 (w), 1450 (m), 1364 (m), 1261 (m), 1185 (m), 1036 (m).

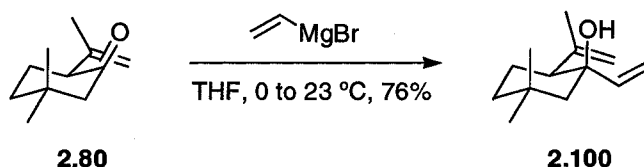
HRMS (EI, m/z): calculated 294.2017 for $[\text{M}]^+$, found 294.2028.

$[\alpha]_D^{23} = +6.0^\circ$ ($c = 4.4$ mg/ml, dichloromethane).



(1S,6S)-1,6-Diisopropenyl-3-methyl-cyclohex-2-enol (2.96):

A solution of 2-bromopropene (0.130 mL, 1.46 mmol) in 6 mL of diethyl ether was cooled to -78°C . *tert*-Butyllithium (1.95 mL of a 1.5 M solution in pentane, 2.9 mmol) was added and the mixture was stirred for 15 min. In a separate flask, ketone **2.79** (114 mg, 0.759 mmol) was dissolved in 1 mL of diethyl ether and cooled to -78°C . This solution was then added via a cold cannula to the solution of vinylolithium. After stirring for 60 minutes, the reaction was warmed to -20°C , quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) gave 122.4 mg (84%) of **2.96** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2004**, *70*, 1382.



(1R,2S)-2-Isopropenyl-5,5-dimethyl-1-vinyl-cyclohexanol (2.100):

To a solution of vinylmagnesium bromide (2.40 mL of a 1.0 M solution in tetrahydrofuran, 2.4 mmol) in 6 mL of tetrahydrofuran, cooled to 0 °C, was added a solution of ketone **2.80** in 0.5 mL of tetrahydrofuran. The reaction was warmed gradually to ambient temperature and stirred for 3 hours. After quenching with a saturated aqueous solution of ammonium chloride, the aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) gave 93 mg (76%) of a colourless oil.

Data for 2.100:

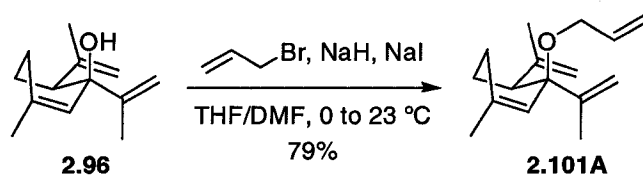
¹H NMR (CDCl₃, 300 MHz, δ): 5.81 (dd, J = 17.1, 10.6 Hz, 1H), 5.14 (dd, J = 17.1, 1.4 Hz, 1H), 4.94 (dd, J = 10.5, 1.4 Hz, 1H), 4.90 (dd, J = 1.5, 1.5 Hz, 1H), 4.75 (s, 1H), 1.99-1.84 (m, 2H), 1.74 (s, 3H), 1.58 (s, br, 1H), 1.54-1.16 (m, 5H), 1.11 (s, 3H), 0.87 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 147.21 (2C), 111.83, 110.66, 73.64, 52.47, 49.12, 39.60, 34.14, 30.30, 26.52, 26.16, 24.23.

IR (neat, cm⁻¹, ν): 3551 (w), 3081 (w), 2949 (s), 2922 (s), 2901 (s), 2870 (m), 2846 (m), 1636 (m), 1453 (m), 1363 (m), 1284 (w), 1229 (w), 1166 (w), 1090 (w), 1056 (w).

HRMS (EI, m/z): calculated 176.1565 for [M-H₂O]⁺, found 176.1576.

$[\alpha]_D^{23}$ = -23.9° (c = 9.2 mg/mL, dichloromethane).

**(3S,4S)-3-Allyloxy-3,4-diisopropenyl-1-methyl-cyclohexene (2.101A):**

Sodium iodide (3 mg, 0.02 mmol) was flame dried in a flask and allowed to cool. Sodium hydride (44 mg of a 60% suspension in mineral oil, 1.1 mmol) was added to the flask and the system was put under argon. Tetrahydrofuran (2 mL) and dimethylformamide (1 mL) were added to the flask and the suspension was cooled to 0 °C. A solution of **2.96** (60.2 mg, 0.313 mmol) in 1 mL of tetrahydrofuran was cannulated into the flask and the reaction was stirred for 5 minutes. Allyl bromide (0.080 mL, 0.95 mmol) was added and the reaction was warmed gradually to ambient temperature. After stirring for 3 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous

phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% ethyl acetate/hexanes) yielded 57.6 mg of a colourless oil (79%).

Data for 2.101A:

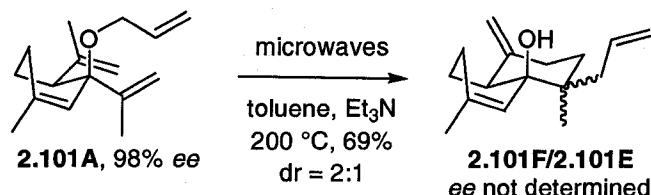
^1H NMR (CDCl_3 , 300 MHz, δ): 5.90-5.83 (m, 1H), 5.38 (dd, $J = 2.9, 1.5$ Hz, 1H), 5.25 (dddd, $J = 17.3, 2.0, 2.0, 2.0$ Hz, 1H), 5.04 (dddd, $J = 10.6, 1.7, 1.7, 1.7$ Hz, 1H), 4.91-4.89 (m, 1H), 4.88 (s, 1H), 4.73-4.72 (m, 1H), 4.62-4.61 (m, 1H), 3.93-3.89 (m, 1H), 3.83-3.79 (m, 1H), 2.20 (dd, $J = 12.3, 2.3$ Hz, 1H), 2.16-2.08 (m, 1H), 2.03-2.01 (m, 2H), 1.78 (s, 3H), 1.72 (d, $J = 0.6$ Hz, 3H), 1.64 (s, 3H), 1.53-1.47 (m, 1H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 147.46, 147.06, 139.39, 136.30, 124.86, 114.15, 112.36, 111.59, 80.34, 64.26, 50.44, 30.96, 24.14, 23.61, 21.84, 19.82.

IR (neat, cm^{-1} , ν): 3075 (m), 3011 (m), 2968 (s), 2928 (s), 2861 (s), 2830 (m), 2668 (w), 1638 (m), 1614 (w), 1448 (s), 1405 (w), 1375 (m), 1176 (w), 1118 (w), 1080 (s), 1060 (m), 1020 (w).

HRMS (EI, m/z): calculated 217.1592 for $[\text{M-Me}]^+$, found 217.1569.

$[\alpha]_{\text{D}}^{23} = -92.9^\circ$ ($c = 3.1$ mg/ml, dichloromethane).



(4S,4aS,8aS)-4-Allyl-4,6-dimethyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (2.101F) and (4R,4aS,8aS)-4-Allyl-4,6-dimethyl-1-methylene-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (2.101E):

A solution of **2.101A** (29 mg, 0.12 mmol) and triethylamine (0.200 mL, 1.44 mmol) in 15 mL of toluene was sparged with argon for 20 minutes before heating in a microwave for 1 hour at 200 °C. The crude material was concentrated and a ^1H NMR taken to reveal a product ratio of 2:1. Purification by silica gel flash chromatography (7% ethyl acetate/hexanes) yielded 20 mg (69%) of an inseparable mixture of **2.101F** and **2.101E** as a colourless oil. The products were unstable and decomposed before GC conditions for measuring their *ee* could

be developed. Likewise, 2D NMR spectra were not obtainable and the assignment of stereochemistry was not made.

Data for 2.101F and 2.101E (major and minor isomers together):

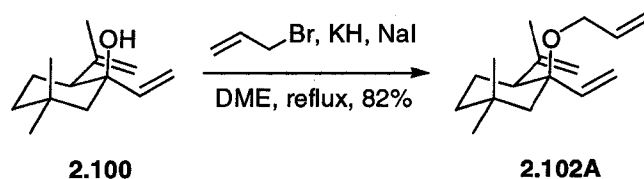
^1H NMR (C_6D_6 , 500 MHz, δ): 5.90-5.82 and 5.79-5.70 (m, 1H), 5.65 and 5.58 (s, 1H), 5.11-4.99 (m, 2H), 4.89 (s, 1H), 4.65 and 4.64 (s, 1H), 2.68 and 2.34 (dd, $J = 13.2, 7.3$ Hz and dd, $J = 13.9, 8.1$ Hz, 1H), 2.30 and 1.96 (dd, $J = 13.4, 7.3$ Hz and dd, $J = 14.2, 6.3$ Hz, 1H), 2.24-2.05 (m, 3H), 1.72-1.58 (m, 4H), 1.55-1.45 (m, 4H), 1.36-1.32 (m, 1H), 1.17 and 1.15 (s, 1H), 1.09 and 0.91 (s, 3H).

^{13}C NMR: (C_6D_6 , 125 MHz, δ): 149.66, 149.41, 137.89, 137.87, 136.05, 135.37, 124.25, 124.02, 116.79, 116.69, 107.35, 107.14, 74.37, 73.96, 42.63, 41.96, 40.64, 40.35, 40.10, 38.31, 34.09, 32.71, 32.09, 31.93, 30.32, 30.23, 23.47, 23.42, 20.80, 20.76, 20.03, 18.99.

IR (neat, cm^{-1} , ν): 3517 (w, br), 3075 (w), 2965 (s), 2932 (s), 2868 (s), 2830 (w), 1651 (m), 1445 (m), 1377 (m), 1280 (w), 1179 (w), 1065 (w), 1023 (w).

HRMS (EI, m/z): calculated 232.1827 for $[\text{M}]^+$, found 232.1828.

$[\alpha]_{\text{D}}^{23} = +92.4^\circ$ ($c = 2.7$ mg/ml, dichloromethane).



(1R,2S)-1-Allyloxy-2-isopropenyl-5,5-dimethyl-1-vinyl-cyclohexane (2.102A):

Sodium iodide (3 mg, 0.02 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (700 mg of a 30% suspension in mineral oil, 5.24 mmol) was added to the flask and the system was put under argon. The potassium hydride was then washed three times with hexanes and dried under a flow of argon. Dimethoxyethane (5 mL) was added to the flask and the suspension cooled to 0 °C. A solution of **2.100** (84 mg, 0.44 mmol) in 1 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.550 mL, 6.36 mmol) was added and the reaction was warmed first to ambient temperature, and then brought to a gentle reflux. After refluxing for 3 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were

dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 83 mg of a colourless oil (82%).

Data for 2.102A:

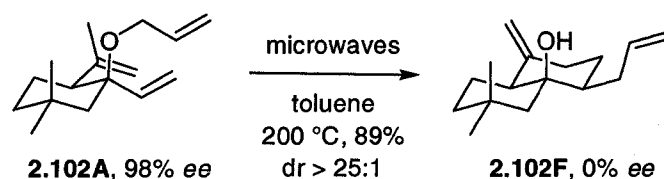
^1H NMR (CDCl_3 , 300 MHz, δ): 5.91-5.77 (m, 1H), 5.81 (dd, $J = 18.0, 11.1$ Hz, 1H), 5.23 (dd, $J = 17.3, 1.8$ Hz, 1H), 5.10 (d, $J = 11.2, 0.7$ Hz, 1H), 5.03 (dd, $J = 10.5, 1.6$ Hz, 1H), 5.00 (d, $J = 18.1$ Hz, 1H), 4.77 (d, $J = 1.0$ Hz, 1H), 4.66 (d, $J = 2.4$ Hz, 1H), 3.75-3.74 (m, 2H), 2.16 (dddd, $J = 13.0, 13.0, 13.0, 3.3$ Hz, 1H), 1.85 (dd, $J = 6.2, 2.9$ Hz, 1H), 1.82-1.79 (m, 1H), 1.80 (s, 3H), 1.50-1.43 (m, 1H), 1.33-1.16 (m, 3H), 1.08 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 147.45, 144.07, 136.04, 114.51, 113.88, 113.31, 78.39, 63.21, 56.19, 40.12, 40.00, 34.57, 30.87, 25.78, 24.53, 22.30.

IR (neat, cm^{-1} , ν): 3084 (w), 3011 (w), 2987 (w), 2949 (s), 2921 (s), 2866 (m), 1647 (w), 1637 (m), 1460 (m), 1415 (m), 1384 (w), 1370 (w), 1363 (w), 1322 (w), 1214 (w), 1166 (w), 1148 (w), 1124 (w), 1058 (s).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.1961.

$[\alpha]_D^{23} = +75.2^\circ$ ($c = 12.6$ mg/ml, dichloromethane).



(±)-(4S,4aR,8aS)-4-Allyl-6,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (2.102F):

A solution of **2.102A** (70 mg, 0.30 mmol) in 15 mL of toluene was sparged with argon for 20 minutes before heating in a microwave for 1 hour at 200 °C. The reaction was concentrated and a ^1H NMR of the unpurified material was taken to confirm the presence of a single diastereomer. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 62 mg (89%) of a colourless oil.

Data for 2.102F:

^1H NMR (C_6D_6 , 500 MHz, δ): 5.76-5.68 (m, 1H), 5.04-4.99 (m, 2H), 4.77 (d, $J = 1.4$ Hz, 1H), 4.61 (d, $J = 1.0$ Hz, 1H), 2.44-2.39 (m, 1H), 2.11 (ddd, $J = 12.8, 4.3, 2.5$ Hz, 1H), 1.94-1.87 (m, 1H), 1.84 (dd, $J = 13.8, 2.2$ Hz, 1H), 1.79 (ddd, $J = 13.0, 13.0, 4.8$ Hz, 1H), 1.70 (dddd, $J = 13.0, 12.9, 12.9, 3.2$ Hz, 1H), 1.64-1.58 (m, 2H), 1.44 (dddd, $J = 13.0, 3.1, 3.1, 2.5$

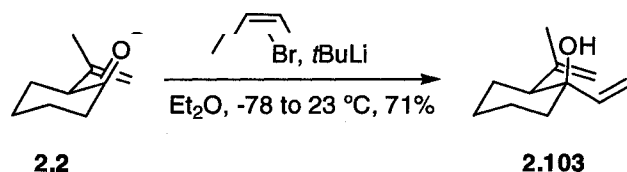
Hz, 1H), 1.31 (dddd, $J = 13.0, 3.4, 3.3, 3.3$ Hz, 1H), 1.23 (s, 3H), 1.12-1.04 (m, 2H), 0.99 (dddd, $J = 13.1, 13.1, 12.9, 4.3$ Hz, 1H), 0.96 (d, $J = 2.1$ Hz, 1H), 0.90 (s, 3H), 0.82 (dd, $J = 13.8, 1.7$ Hz, 1H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 150.10, 138.66, 115.61, 108.51, 74.29, 50.61, 47.54, 47.35, 39.34, 36.33, 34.72, 33.88, 30.84, 29.49, 27.34, 21.24.

IR (neat, cm^{-1} , ν): 3565 (m), 3081 (w), 2994 (m), 2934 (s), 2903 (s), 2865 (s), 1643 (m), 1455 (m), 1440 (m), 1386 (w), 1364 (w), 1339 (w), 1277 (m), 1219 (w), 1175 (w), 1109 (w), 1059 (w).

HRMS (EI, m/z): calculated 234.1984 for $[\text{M}]^+$, found 234.1971.

$ee = 0\%$; determined using GLC, method: 140 °C for 10 min, 140 – 180 °C at 2.0 °C/min, Tr1: 23.5 min, Tr2: 24.2 min.



(±)-(1R,2S)-2-Isopropenyl-1-((Z)-propenyl)-cyclohexanol (2.103):

A solution of (Z)-1-bromo-1-propene (0.500 mL, 5.88 mmol) in 20 mL of diethyl ether was cooled to -78 °C. To this solution was slowly added *tert*-butyllithium (8.40 mL of a 1.33 M solution in pentane, 11.2 mmol). After stirring at -78 °C for one hour, the reaction was immersed in an ice bath for ten minutes and then re-cooled to -78 °C. A solution of ketone **2.2** (300 mg, 2.17 mmol) in 2 mL of diethyl ether was cannulated into the reaction mixture and the reaction was warmed gradually to ambient temperature over 3 hours. After quenching with a saturated aqueous solution of ammonium chloride, the aqueous phase was extracted three times with ethyl acetate and the combined organic layers dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (4% ethyl acetate/hexanes) gave 276 mg (71%) of the desired product as a colourless oil.

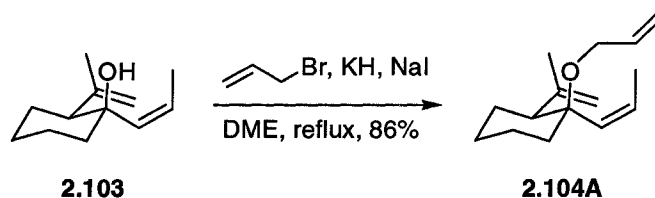
Data for 2.103:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.41-5.30 (m, 2H), 4.87-4.86 (m, 1H), 4.77 (s, 1H), 2.05 (dd, $J = 12.9, 3.4$ Hz, 1H), 1.87-1.84 (m, 2H), 1.81 (s, 3H), 1.80-1.79 (m, 3H), 1.74-1.63 (m, 2H), 1.57 (ddd, $J = 13.2, 3.7, 3.7$ Hz, 1H), 1.50-1.39 (m, 3H), 1.21 (dddd, $J = 13.2, 13.2, 3.7, 3.7$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 148.86, 137.65, 124.24, 111.86, 74.29, 52.90, 38.12, 27.36, 26.01, 25.44, 21.14, 13.93.

IR (neat, cm^{-1} , ν): 3561 (br, m), 3077 (w), 3014 (m), 2933 (s), 2855 (s), 1636 (m), 1447 (s), 1407 (w), 1372 (m), 1324 (w), 1291 (m), 1226 (w), 1201 (w), 1157(w), 1069 (m), 1030 (w).

HRMS (EI, m/z): calculated 180.1514 for $[\text{M}]^+$, found 180.1517.



(±)-(1R,2S)-1-Allyloxy-2-isopropenyl-1-((Z)-propenyl)-cyclohexane (2.104A):

Sodium iodide (3 mg, 0.02 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (700 mg of a 30% suspension in mineral oil, 5.24 mmol) was added to the flask and the system was put under argon. The potassium hydride was then washed three times with dry hexanes and dried under a flow of argon. Dimethoxyethane (10 mL) was added to the flask and the suspension cooled to 0 °C. A solution of **2.103** (95 mg, 0.53 mmol) in 1 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.50 mL, 5.8 mmol) was added and the reaction was warmed first to ambient temperature, and then brought to a gentle reflux. After refluxing for 7 hours, the reaction was cooled to 0 °C and quenched with a dilute aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 100 mg of a colourless oil (86%).

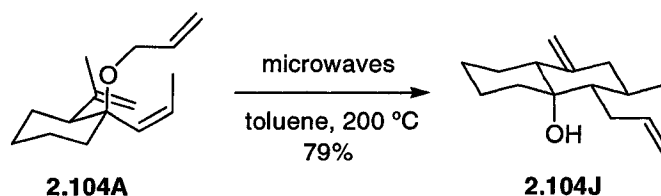
Data for 2.104A:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.96-5.89 (m, 1H), 5.52-5.45 (m, 1H), 5.29 (dd, $J = 17.3$, 2.0 Hz, 1H), 5.07-5.03 (m, 2H), 4.74-4.73 (m, 1H), 4.68-4.67 (m, 1H), 3.85-3.79 (m, 2H), 2.11 (d, $J = 13.9$ Hz, 1H), 2.07-2.03 (m, 1H), 2.00 (dddd, $J = 12.5$, 12.5, 12.5, 3.7 Hz, 1H), 1.80 (s, 3H), 1.75-1.72 (m, 1H), 1.65 (dd, $J = 7.3$, 1.7 Hz, 3H), 1.46-1.23 (m, 5H)

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.57, 136.23, 133.01, 126.26, 114.32, 113.09, 80.17, 62.27, 53.92, 34.43, 27.32, 26.20, 22.63, 21.08, 14.51.

IR (neat, cm^{-1} , ν): 3072 (w), 3015 (w), 2930 (s), 2856 (s), 1646 (m), 1449 (s), 1407 (w), 1372 (w), 1206 (w), 1157 (m), 1120 (m), 1065 (s), 1024 (m)

HRMS (EI, m/z): calculated 220.1827 for $[\text{M}]^+$, found 220.1823.



(±)-(3R,4S,4aS,8aR)-4-Allyl-3-methyl-1-methylene-octahydro-naphthalen-4a-ol

(2.104J):

A solution of **2.104A** (15.4 mg, 0.070 mmol) in 15 mL of toluene was sparged with argon for 20 minutes before heating in a microwave for 4 hours at 200 °C. The crude material was concentrated and a ^1H NMR of the crude material was taken to reveal an 8:1 mixture of products. Purification by silica gel flash chromatography (100% hexanes $\rightarrow$ 20% dichloromethane/hexanes) yielded 12.2 mg (79%) of **2.104J** as a colourless oil, along with 2 mg of a second, unidentified product (not an isomer of the oxy-Cope/Claisen/ene reaction).

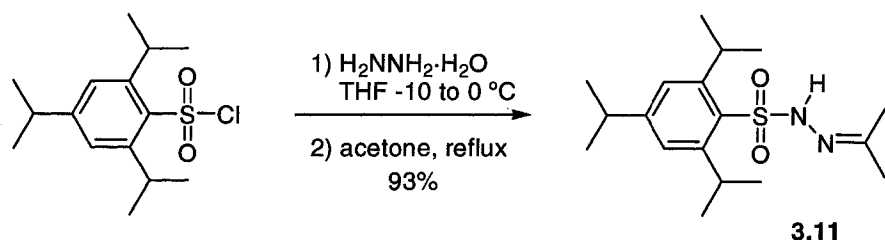
Data for **2.104J**:

^1H NMR (C_6D_6 , 500 MHz, δ): 6.07-5.95 (m, 1H), 5.02-4.95 (m, 2H), 4.77 (dd, $J = 1.5, 1.5$ Hz, 1H), 4.58 (d, $J = 1.1$ Hz, 1H), 2.46-2.40 (m, 1H), 2.12-2.06 (m, 3H), 1.76-1.64 (m, 3H), 1.58 (dd, $J = 12.4, 12.4$ Hz, 1H), 1.53-1.34 (m, 4H), 1.09 (dddd, $J = 13.2, 13.0, 12.8, 3.6$, 3.6 Hz, 1H), 1.02 (d, $J = 1.94$ Hz, 1H), 0.90 (dddd, $J = 13.3, 13.3, 4.1, 1.9$ Hz, 1H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.78 (ddd, $J = 11.3, 4.5, 3.4$ Hz, 1H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 149.75, 140.06, 114.33, 108.13, 74.24, 53.39, 50.04, 45.60, 36.23, 35.65, 32.27, 25.92, 24.40, 21.83, 20.40.

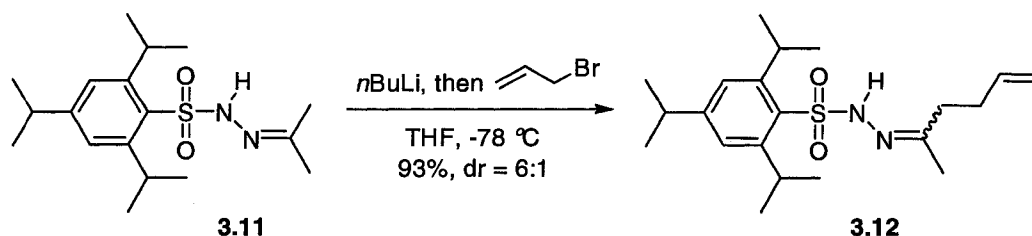
IR (neat, cm^{-1} , ν): 3565 (w), 3081 (w), 2931 (s), 2861 (m), 1644 (w), 1448 (w), 1372 (w), 1294 (w), 1231 (w), 1156 (w), 1097 (w).

HRMS (EI, m/z): calculated 220.1827 for $[\text{M}]^+$, found 220.1823.



Acetone 2,4,6-triisopropylbenzenesulfonylhydrazone (3.11):

A solution of 2,4,6-triisopropylbenzenesulfonyl chloride (1.008 g, 3.328 mmol) in 2.5 mL of tetrahydrofuran was cooled to -10 °C. Hydrazine hydrate (0.355 mL, 7.32 mmol) was added drop-wise over a period of 10 minutes. The reaction temperature was raised to 0 °C and stirring was continued for 3 hours before a small amount of water was added (~ 0.1 mL) in order to dissolve the resulting white precipitate. The material was transferred to a separatory funnel, the aqueous phase removed, and the remaining organic layer washed three times with an ice-cold brine solution. The organic phase was then dried over magnesium sulfate, filtered and concentrated at *ambient temperature* to give a white solid. Purification was accomplished by trituration, first with petroleum ether, then with cold water. Finally, the white solid was dried under vacuum in the presence of phosphorus pentoxide for 24 hours to give 919 mg (93%) of a fluffy white solid. A solution of the 2,4,6-triisopropylbenzenesulfonyl hydrazide (730 mg, 2.45 mmol) in 20 mL of acetone was heated to reflux for a period of 3 hours. The reaction was cooled to ambient temperature and crude material dried over magnesium sulfate, filtered and concentrated to give 817 mg (99%) of **3.11** as a white solid. No further purification was typically required, although recrystallization from aqueous methanol could be performed if needed. Spectral data for this compound was in agreement with that reported previously: Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, 32, 2157.



Hex-5-en-2-one 2,4,6-triisopropylbenzenesulfonylhydrazone (3.12):

A solution of **3.11** (214.5 mg, 0.6337 mmol) in 6 mL of tetrahydrofuran was cooled to -78 °C. *n*-Butyllithium (0.53 mL of a 2.61 M solution in pentane, 1.38 mmol) was added drop-wise followed by allyl bromide (67 μ L, 0.77 mmol). The reaction was stirred for 1.5 hours and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% diethyl ether/hexanes) gave 223 mg of a white solid (93%) as a 6:1 inseparable mixture of regioisomers (ratio determined by proton NMR).

Data for **3.12** (major and minor isomers together):

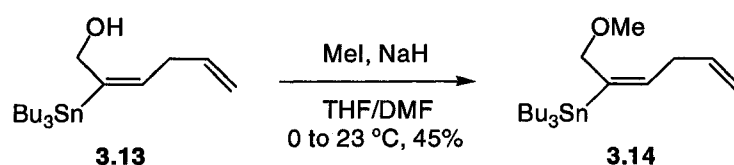
¹H NMR (CDCl₃, 300 MHz, δ): 7.83 (s, 1H), 7.15 (s, 2H), 5.58-5.56 and 5.56-5.54 (m and m, 1H), 5.00 and 4.79 (d, J = 17.1 Hz and d, J = 17.2 Hz, 1H), 4.94 and 4.72 (d, J = 10.2 Hz and d, J = 10.0 Hz, 1H), 4.26 (sept, J = 6.6 Hz, 2H), 2.88 (sept, J = 6.8 Hz, 1H), 2.26-2.21 (m, 2H), 2.16-2.12 (m, 2H), 1.87 and 1.76 (s and s, 3H), 1.26-1.22 (m, 18H).

¹³C NMR (CDCl₃, 75 MHz, δ): major isomer only: 155.23, 153.09, 151.31 (2C), 137.20, 131.52, 123.79 (2C), 115.04, 37.395, 34.22, 29.98, 29.90 (2C), 24.89 (4C), 23.65 (2C), 15.79.

IR (neat, cm⁻¹, ν): 3260 (s), 2960 (s), 2867 (m), 1643 (w), 1601 (m), 1565 (w), 1461 (m), 1428 (m), 1382 (m), 1361 (m), 1325 (s), 1259 (m), 1168 (s).

HRMS (EI, m/z): calculated 378.2341 for [M]⁺, found 378.2310.

mp = 107.5-107.9 °C.



Tributyl-((E)-1-methoxymethyl-penta-1,4-dienyl)-stannane (3.14**):**

To a suspension of sodium hydride (52 mg of a 60% suspension in mineral oil, 1.3 mmol) in 0.75 mL of dimethylformamide and 0.75 mL of tetrahydrofuran was cannulated **3.13** (140.2 mg, 0.3621 mmol, provided by P. R. MacLean) as a solution in 0.75 mL of dimethylformamide and 0.75 mL of tetrahydrofuran. The suspension was cooled to 0 °C and iodomethane (0.040 mL, 0.64 mmol) was added. The mixture was warmed to ambient temperature, stirred for four hours and then quenched with a saturated aqueous solution of

ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were washed three times with water, dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) gave 64 mg of a colourless oil (45%).

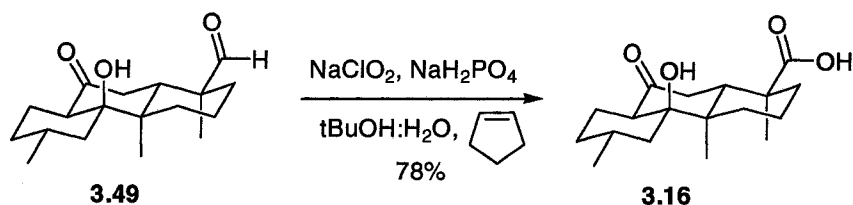
Data for 3.14:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.84-5.73 (m, 1H), 5.56-5.54 (m, 1H), 5.01 (d, $J = 16.9$ Hz, 1H), 4.97 (d, $J = 9.8$ Hz, 1H), 4.07 (s, 2H), 3.29 (s, 3H), 2.81 (dd, $J = 6.5, 6.5$ Hz, 2H), 1.56-1.35 (m, 6H), 1.32-1.22 (m, 6H), 0.96-0.73 (m, 15H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 145.64, 136.69, 135.91, 114.92, 73.79, 58.11, 34.21, 29.29 (3C), 27.54 (3C), 13.91 (3C), 10.18 (3C).

IR (neat, cm^{-1} , ν): 2956 (s), 2923 (s), 2871 (m), 2853 (m), 2815 (m), 1464 (w), 1376 (w), 1195 (w), 1116 (m).

HRMS (EI, m/z): calculated 345.1240 for $[\text{M}-n\text{Bu}]^+$, found 345.1325.



(±)-(1S,4aR,4bS,6R,8aR)-4b-Hydroxy-1,4a,6-trimethyl-9-oxo-tetradecahydro-phenanthrene-1-carboxylic acid (3.16):

To a solution of **3.49** (12.5 mg, 0.0427 mmol) in 1 mL of a 3:1 *tert*-butanol/water solution was added sodium phosphate monobasic (49 mg, 0.41 mmol) followed by cyclopentene (0.36 mL, 4.1 mmol). The reaction was cooled to 0 °C and a solution of sodium chlorite (22 mg, 0.24 mmol) in 0.5 mL of a 3:1 *tert*-butanol:water solution was added. After 15 minutes the reaction was quenched with a saturated aqueous solution of sodium sulfite and brine. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (1:29:70 AcOH/ethyl acetate/hexanes) yielded 9.2 mg (78%) of **3.16** as a white solid.

Data for 3.16:

^1H NMR (CDCl_3 , 300 MHz, δ): 2.92 (dd, $J = 13.8$, 3.0 Hz, 1H), 2.34 (dd, $J = 11.9$, 3.8 Hz, 1H), 2.33 (dd, $J = 14.4$, 13.4 Hz, 1H), 2.09 (dd, $J = 14.4$, 3.2 Hz, 1H), 1.82-1.75 (m, 2H), 1.68-1.47 (m, 9H), 1.25-1.17 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 0.88 (d, $J = 6.1$ Hz, 3H), 0.82-0.69 (m, 1H), 2 exchangeable protons do not appear.

^1H NMR (CD_3OD , 500 MHz, δ): 3.01 (dd, $J = 14.0$, 3.4 Hz, 1H), 2.48 (dd, $J = 13.9$, 14.0 Hz, 1H), 2.47 (dd, $J = 10.9$, 4.6 Hz, 1H), 1.97 (dd, $J = 14.5$, 3.3 Hz, 1H), 1.84-1.75 (m, 1H), 1.74-1.58 (m, 9H), 1.52-1.49 (m, 1H), 1.31-1.26 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.89-0.79 (m, 1H), 2 exchangeable protons do not appear.

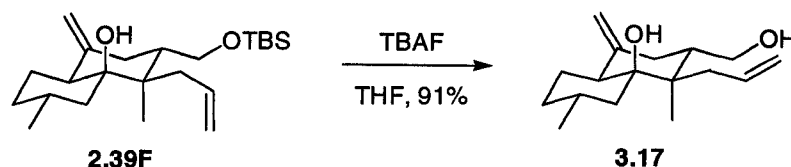
^{13}C NMR (CDCl_3 , 75 MHz, δ): 211.86, 182.69, 80.58, 52.09, 47.10, 41.54, 41.14, 40.80, 38.98, 36.55, 33.35, 30.72, 27.98, 22.78, 21.47, 18.18, 16.88, 16.44.

^{13}C NMR (CD_3OD , 125 MHz, δ): 212.72, 180.28, 79.71, 51.43, 46.48, 41.19, 40.41, 40.31, 37.95, 36.22, 32.91, 30.15, 27.02, 21.35, 20.81, 17.49, 15.51, 15.26.

IR (neat, cm^{-1} , ν): 3526 (m, br), 2952 (s), 2873 (m), 1698 (s), 1454 (m), 1390 (m), 1367 (m), 1268 (m), 1242 (s), 1151 (s), 1128 (m).

HRMS (EI, m/z): calculated 308.1988 for $[\text{M}]^+$, found 308.1974.

mp = 178.6-180.9 °C.



(±)-(3S,4R,4aS,6R,8aS)-4-Allyl-3-hydroxymethyl-4,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (3.17):

To a solution of **2.39F** (20 mg, 0.053 mmol) in 0.4 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.10 mL of a 1.0 M solution in tetrahydrofuran, 1.0 mmol). After stirring for 2 hours the reaction was concentrated and purified by silica gel flash chromatography (40% ethyl acetate/hexanes) to give 13 mg of a white solid (91%).

Data for 3.17:

^1H NMR (CDCl_3 , 500 MHz, δ): 6.19-6.10 (m, 1H), 5.01 (dddd, $J = 17.2$, 0.7, 0.7, 0.7 Hz, 1H), 4.97 (dddd, $J = 10.2$, 1.1, 1.1, 1.1 Hz, 1H), 4.91 (d, $J = 1.5$ Hz, 1H), 4.65 (s, 1H), 3.92-3.89 (m, 1H), 3.39-3.35 (m, 1H), 2.57-2.50 (m, 1H), 2.45 (dd, $J_{\text{AB}} = 15.6$ Hz, $J_{\text{AX}} = 7.6$ Hz, 1H), 2.20 (dd, $J_{\text{AB}} = 15.6$ Hz, $J_{\text{AX}} = 7.3$ Hz, 1H), 2.18-2.15 (m, 1H), 2.07-2.01 (m, 2H), 1.81

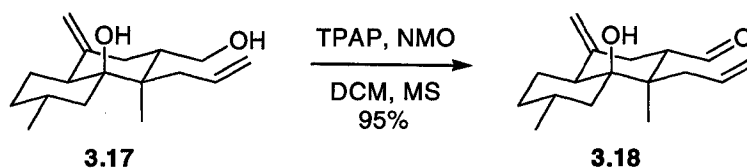
(ddd, $J = 13.2, 3.3, 2.3$ Hz, 1H), 1.77-1.69 (m, 2H), 1.60-1.52 (m, 2H), 1.50 (d, $J = 1.1$ Hz, 1H), 1.15 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.09 (dd, $J = 13.0, 13.0$ Hz, 1H), 0.91 (s, 3H), 0.88 (d, $J = 6.5$ Hz, 3H), 0.86-0.83 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 148.97, 138.34, 115.77, 108.85, 78.57, 64.21, 44.12, 43.72, 43.52, 40.06, 39.66, 35.87, 34.03, 27.53, 24.61, 22.52, 18.33.

IR (neat, cm^{-1} , v): 3363 (br, m), 3076 (w), 2950 (m), 2357 (m), 2339 (m), 1632 (w), 1356 (s), 1050 (w), 1002 (w).

HRMS (EI, m/z): calculated 264.2089 for $[M]^+$, found 264.2099.

mp = 75.8-77.6 °C.



(±)-(1R,2S,4aS,7R,8aS)-1-Allyl-8a-hydroxy-1,7-dimethyl-4-methylene-decahydro-naphthalene-2-carbaldehyde (3.18):

To a stirring solution of **3.17** (130 mg, 0.4927 mmol) in 5 mL of dichloromethane was added 4Å molecular sieves (250 mg), 4-methylmorpholine N-oxide (86 mg, 0.734 mmol) and tetrapropylammonium perruthenate (9 mg, 0.026 mmol). The mixture was stirred for 45 minutes and then filtered through a pad of silica washing first with dichloromethane, then with a 5% solution of methanol in ethyl acetate. The filtrate was concentrated and purified by silica gel flash chromatography (5% → 10% ethyl acetate/hexanes) to give 122 mg of a white solid (95%).

Data for 3.18:

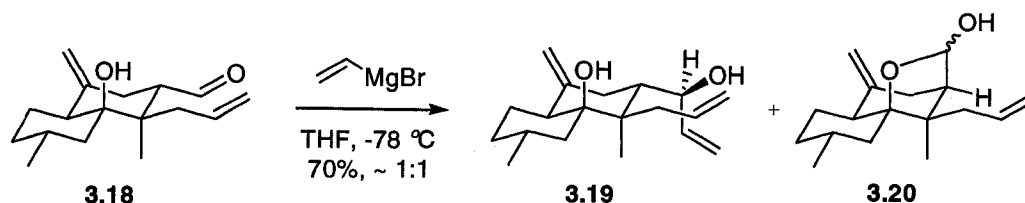
¹H NMR (CDCl₃, 300 MHz, δ): 9.85 (d, *J* = 2.1 Hz, 1H), 6.16-6.02 (m, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 4.89 (d, *J* = 1.5 Hz, 1H), 4.67 (d, *J* = 1.4 Hz, 1H), 2.93 (ddd, *J* = 12.9, 4.1, 2.1 Hz, 1H), 2.56 (dd, *J* = 15.2, 7.9 Hz, 1H), 2.42-2.14 (m, 4H), 1.82-1.42 (m, 6H), 1.10-1.02 (m, 1H), 1.06 (s, 3H), 0.92-0.77 (m, 1H), 0.87 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 205.15, 147.13, 136.99, 117.55, 110.09, 78.27, 53.32, 44.84, 43.41, 40.46, 38.99, 33.73, 32.19, 27.47, 24.42, 22.40, 18.41.

IR (neat, cm^{-1} , ν): 3556 (m), 3075 (w), 2948 (m), 2926 (s), 2867 (m), 2846 (m), 2739 (w), 1715 (s), 1644 (m), 1445 (m), 1347 (m).

HRMS (EI, m/z): calculated 262.1933 for $[\text{M}]^+$, found 262.1937.

mp = 52.8-54.3 °C.



(±)-(4R,4aS,6R,8aS)-4-Allyl-3-((S)-1-hydroxy-allyl)-4,6-dimethyl-1-methylene-octahydro-naphthalen-4a-ol (**3.19**) and (±)-(1S,3R,6S,10R,12R)-12-Allyl-3,12-dimethyl-7-methylene-11-oxa-tricyclo[7.2.1.0*1,6*]dodecan-10-ol (**3.20**):

A solution of **3.18** (122 mg, 0.465 mmol) in 4 mL of tetrahydrofuran was cooled to -78 °C. Vinylmagnesium bromide (1.2 mL of a 0.9 M solution in tetrahydrofuran, 1.1 mmol) was added drop-wise and the reaction was stirred for 45 minutes. A saturated aqueous solution of ammonium chloride was added and the reaction was warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% → 4% ethyl acetate/hexanes) yielded 90 mg of a colourless oil as a ~1:1 inseparable mixture of **3.19** and acetal **3.20** (70% combined yield). For the purpose of characterization, **3.19** was also prepared according to the following procedure: To a solution of **3.28** (7.0 mg, 0.019 mmol) in 1 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.04 mL of a 1.0 M solution in tetrahydrofuran, 0.04 mmol). After stirring for 24 hours the reaction was concentrated. Purification of the crude material by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 5 mg of **3.19** as a colourless oil (89%).

Data for 3.19:

¹H NMR (CDCl_3 , 500 MHz, δ): 6.14-6.05 (m, 1H), 5.90 (ddd, $J = 17.2, 10.6, 4.5$ Hz, 1H), 5.20 (ddd, $J = 17.1, 1.6, 1.4$ Hz, 1H), 5.12 (ddd, $J = 10.5, 1.6, 1.3$ Hz, 1H), 5.00 (dddd, $J = 17.2, 1.6, 1.5, 1.5$ Hz, 1H), 4.98-4.94 (m, 1H), 4.84 (d, $J = 1.6$ Hz, 1H), 4.62 (d, $J = 1.4$ Hz, 1H), 4.55 (s, br, 1H), 2.52 (dd, $J = 15.7, 7.6$ Hz, 1H), 2.33 (dd, $J = 15.7, 7.2$ Hz, 1H), 2.27 (dd, $J = 14.0, 13.2$ Hz, 1H), 2.20-2.17 (m, 1H), 2.12 (dd, $J = 13.3, 3.6$ Hz, 1H), 2.04 (dd, $J =$

14.0, 2.8 Hz, 1H), 1.82-1.78 (m, 1H), 1.73-1.68 (m, 2H), 1.59-1.48 (m, 4H), 1.17-1.14 (m, 1H), 1.15 (s, 3H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.88-0.81 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.67, 141.62, 138.13, 115.88, 113.22, 108.29, 78.93, 70.47, 44.98, 43.95, 43.90, 40.23, 39.75, 33.85, 30.03, 27.45, 24.51, 22.42, 19.49.

IR (neat, cm^{-1} , ν): 3427 (m, br), 3075 (w), 2948 (s), 2925 (s), 2867 (m), 1727 (w), 1637 (w), 1455 (m), 1380 (w), 1204 (w), 1111 (m), 1087 (m).

HRMS (EI, m/z): calculated 272.2140 for $[\text{M}-\text{H}_2\text{O}]^+$, found 272.2134.

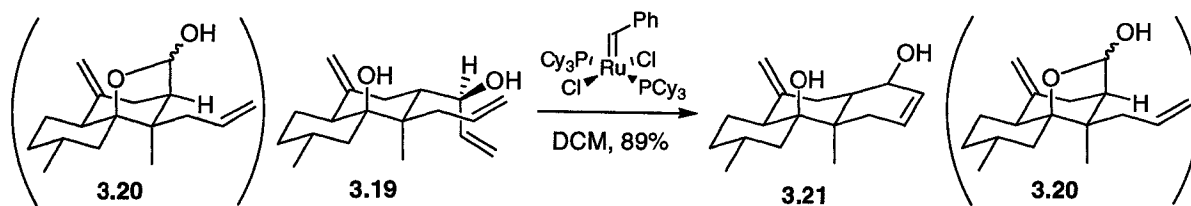
Data for **3.20** (a ~ 2:1 mixture of isomers, recovered from the reaction of **3.19** to **3.21**):

^1H NMR (CDCl_3 , 300 MHz, δ): 5.94-5.69 (m, 1H), 5.37 and 5.11-5.05 (s, br, and m, 1H), 5.11-5.05 (m, 2H), 4.93 (s, 1H), 4.82 (s, 1H), 2.87-2.78 (m, 1H), 2.58-2.45 (m, 2H), 2.34-1.52 (m, 9H), 1.49-1.32 (m, 1H), 1.07 and 1.01 (s and s, 3H), 0.94-0.77 (m, 1H), 0.88 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.37, 147.01, 136.46, 134.75, 118.74, 118.37, 112.57, 112.06, 101.19, 100.04, 89.71, 86.17, 47.94, 45.98, 45.54, 43.42, 43.01, 42.62, 39.90, 39.54, 38.28, 37.84, 35.32, 34.23, 34.21, 31.57, 28.95, 28.81, 26.90 (2C), 23.10, 23.04, 17.64, 17.09.

IR (neat, cm^{-1} , ν): 3400 (s, br), 3075 (w), 2993 (w), 2948 (s), 2925 (s), 2867 (s), 2843 (m), 1636 (m), 1447 (m), 1381 (m), 1204 (w), 1157 (w), 1139 (w), 1112 (m), 1088 (m).

HRMS (EI, m/z): calculated 262.1933 for $[\text{M}]^+$, found 262.1954.



(±)-(1S,4aR,4bS,6R,8aS)-4a,6-Dimethyl-9-methylene-4,4a,5,6,7,8,8a,9,10,10a-decahydro-1H-phenanthrene-1,4b-diol (3.21**):**

A solution of **3.19** (17 mg of a 50 mol% mixture with acetal **3.20**, 0.03 mmol) in 7 mL of dichloromethane was sparged with argon for 20 minutes. Grubbs' first generation catalyst (2 mg, 0.002 mmol) was added and the solution went from pink to dark brown over time. After 45 minutes, no further reaction was observed and the solution was concentrated and purified

by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) to give 7 mg (89%) of a **3.21** as a white solid, as well as 8 mg of unreacted acetal **3.20**.

Data for 3.21:

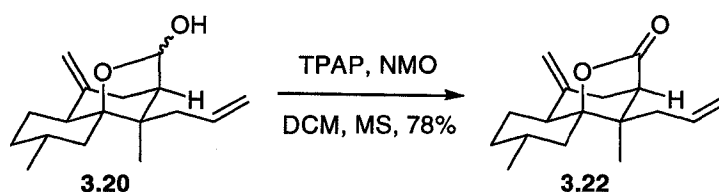
¹H NMR (CDCl₃, 300 MHz, δ): 5.74-5.70 (m, 1H), 5.59 (d, *J* = 10.1 Hz, 1H), 4.97 (d, *J* = 1.3 Hz, 1H), 4.70 (s, 1H), 3.82 (d, *J* = 7.7 Hz, 1H), 2.66 (dd, *J* = 13.3, 4.1 Hz, 1H), 2.48 (d, *J* = 18.9 Hz, 1H), 2.28 (d, *J* = 10.0 Hz, 1H), 1.99 (dd, *J* = 14.8, 13.1 Hz, 1H), 1.73-1.68 (m, 3H), 1.65-1.59 (m, 3H), 1.56-1.49 (m, 3H), 1.39 (s, 1H), 1.08 (dd, *J* = 12.9, 12.5 Hz, 1H), 0.99 (s, 3H), 0.87 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 148.69, 128.69, 128.17, 110.06, 76.43, 71.47, 45.75, 43.15, 41.91, 38.15, 35.00, 34.01, 32.46, 27.39, 24.71, 22.42, 15.06.

IR (neat, cm⁻¹, ν): 3349 (s), 2944 (s), 2921 (s), 2867 (m), 1646 (w), 1536 (w), 1518 (m), 1443 (m), 1393 (m), 1143 (w), 1097 (w), 1041 (s).

HRMS (EI, *m/z*): calculated 244.1827 for [M-H₂O]⁺, found 244.1834.

mp = 138.2-140.1 °C.



(±)-(1S,3R,6S,10R,12R)-12-Allyl-3,12-dimethyl-7-methylene-11-oxa-tricyclo

[7.2.1.0*1,6*]dodecan-10-one (3.22):

To a stirring solution of **3.20** (10.3 mg, 0.0393 mmol) in 0.5 mL of dichloromethane was added 4Å molecular sieves (18 mg), 4-methylmorpholine N-oxide (10 mg, 0.085 mmol) and tetrapropylammonium perruthenate (0.5 mg, 0.001 mmol). The mixture was stirred for 45 minutes and then filtered through a pad of silica washing first with dichloromethane and then with a 5% solution of methanol in ethyl acetate. The filtrate was concentrated and purified by silica gel flash chromatography (10% ethyl acetate/hexanes) to give 8 mg of a colourless oil (78%).

Data for 3.22:

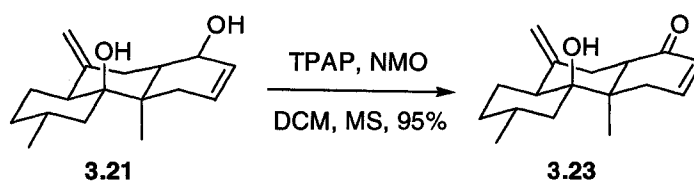
¹H NMR (CDCl₃, 300 MHz, δ): 5.78-5.64 (m, 1H), 5.14 (ddd, *J* = 10.2, 1.9, 0.9 Hz, 1H), 5.08 (dd, *J* = 16.8, 1.8 Hz, 1H), 4.98 (dd, *J* = 2.4, 2.4 Hz, 1H), 4.95 (s, 1H), 2.68-2.61 (m,

¹H), 2.56-2.49 (m, 2H), 2.35-2.31 (m, 1H), 2.23-2.09 (m, 2H), 2.03-1.94 (m, 1H), 1.92-1.86 (m, 1H), 1.79-1.64 (m, 2H), 1.52-1.39 (m, 1H), 1.09 (s, 3H), 1.02 (dd, *J* = 12.2, 12.1 Hz, 1H), 0.94-0.81 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 178.29, 142.56, 132.99, 119.89, 114.40, 89.64, 46.60, 46.05, 40.90, 39.36, 36.28, 33.35, 32.44, 28.17, 26.64, 22.39, 15.00.

IR (neat, cm⁻¹, ν): 2949 (s), 2927 (s), 2869 (m), 1775 (s), 1638 (w), 1448 (m), 1317 (w), 1279 (w), 1236 (w), 1212 (m), 1161 (m), 1104 (m).

HRMS (EI, *m/z*): calculated 260.1776 for [M]⁺, found 260.1768.



(±)-(4aR,4bS,6R,8aS,10aS)-4b-Hydroxy-4a,6-dimethyl-9-methylene-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-4H-phenanthren-1-one (3.23):

To a stirring solution of **3.21** (19 mg, 0.072 mmol) in 2 mL of dichloromethane was added 4Å molecular sieves (20 mg), 4-methylmorpholine N-oxide (25 mg, 0.213 mmol) and tetrapropylammonium perruthenate (2 mg, 0.006 mmol). The mixture was stirred for 45 minutes and then filtered through a pad of silica washing first with dichloromethane and then with a 5% solution of methanol in ethyl acetate. The filtrate was concentrated and purified by silica gel flash chromatography (30% ethyl acetate/hexanes) to give 18 mg of a white solid (95%).

Data for 3.23:

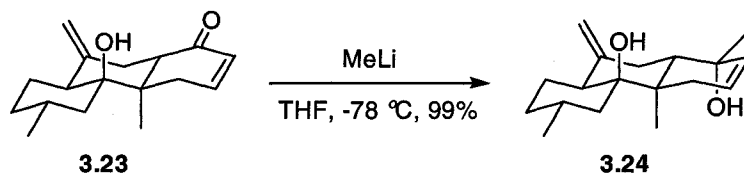
¹H NMR (CDCl₃, 500 MHz, δ): 6.84-6.80 (m, 1H), 5.95 (dd, *J* = 9.7, 2.7 Hz, 1H), 5.00 (d, *J* = 1.5 Hz, 1H), 4.73 (s, 1H), 2.94 (d, *J* = 19.0 Hz, 1H), 2.74 (dd, *J* = 12.6, 4.0 Hz, 1H), 2.61 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.27 (d, *J* = 12.6 Hz, 1H), 2.17-2.10 (m, 2H), 2.02-1.62 (m, 4H), 1.54-1.47 (m, 3H), 1.08 (dd, *J* = 13.2, 13.2 Hz, 1H), 1.05 (s, 3H), 0.89 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 201.16, 147.81, 147.70, 127.77, 110.82, 76.46, 51.05, 45.90, 42.89, 38.07, 34.09, 33.87, 31.14, 27.48, 24.60, 22.34, 15.59.

IR (neat, cm⁻¹, ν): 3450 (br, w), 2948 (s), 2923 (s), 2865 (m), 2854 (m), 1677 (s), 1644 (w), 1457 (w), 1387 (w), 1277 (w), 1121 (w), 1065 (w).

HRMS (EI, *m/z*): calculated 242.1671 for [M-H₂O]⁺, found 242.1628.

mp = 135.9-137.2 °C.



(±)-(1R,4aR,4bS,6R,8aS,10aS)-1,4a,6-Trimethyl-9-methylene-4,4a,5,6,7,8,8a,9,10,10a-decahydro-1H-phenanthrene-1,4b-diol (3.24):

A solution of **3.23** (21 mg, 0.081 mmol) in 1 mL of tetrahydrofuran was cooled to -78 °C and methyllithium (0.2 mL of a 1.3 M solution in diethyl ether, 0.26 mmol) was added dropwise. After 1.5 hours the reaction was quenched with water and warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) gave 22 mg of a white solid (99%).

Data for 3.24:

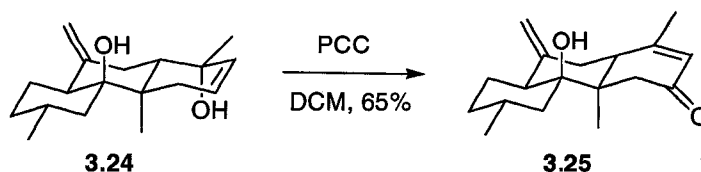
¹H NMR (C₆D₆, 500 MHz, δ): 5.58 (ddd, *J* = 9.9, 6.1, 2.0 Hz, 1H), 5.47 (ddd, *J* = 10.0, 2.7, 1.0 Hz, 1H), 4.88 (s, 1H), 4.61 (s, 1H), 2.53 (d, *J* = 17.2 Hz, 1H), 2.43 (dd, *J* = 13.1, 13.1 Hz, 1H), 2.30 (dd, *J* = 13.5, 3.7 Hz, 1H), 2.13-2.10 (m, 1H), 1.81-1.73 (m, 1H), 1.80 (dd, *J* = 13.3, 13.3 Hz, 1H), 1.66-1.53 (m, 3H), 1.50-1.39 (m, 2H), 1.18 (d, *J* = 1.9 Hz, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 1.00-0.95 (m, 1H), 0.89-0.85 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.77-0.69 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.93, 132.25, 126.97, 109.45, 76.82, 69.65, 46.29, 43.18, 40.26, 38.19, 33.96, 32.37, 32.09, 29.68, 27.53, 24.81, 22.43, 16.03.

IR (neat, cm⁻¹, ν): 3478 (m, br), 3017 (w), 2948 (s), 2925 (s), 2870 (m), 2846 (m), 1641 (w), 1454 (m), 1369 (m), 1202 (w), 1127 (m), 1042 (m).

HRMS (EI, *m/z*): calculated 258.1984 for [M-H₂O]⁺, found 258.1954.

mp = 101.8-103.5 °C.



(±)-(4aR,4bS,6R,8aS,10aR)-4b-Hydroxy-1,4a,6-trimethyl-9-methylene-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-4H-phenanthren-3-one (3.25):

To a solution of **3.24** (20 mg, 0.072 mmol) in 2 mL of dichloromethane was added pyridinium chlorochromate (47 mg, 0.218 mmol) in one portion. The reaction changed colour from a light to a very dark orange and was complete by TLC after 2 hours. An equal volume of diethyl ether was then added and the resulting precipitate filtered off over celite, rinsing thoroughly with additional diethyl ether. The filtrate was concentrated and purified by silica gel flash chromatography (40% ethyl acetate/hexanes) to give 13 mg of a white solid (65%).

Data for 3.25:

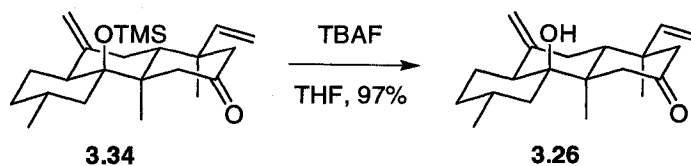
¹H NMR (CDCl₃, 500 MHz, δ): 5.85 (s, 1H), 5.00 (d, *J* = 1.3 Hz, 1H), 4.74 (s, 1H), 2.90 (d, *J* = 13.6 Hz, 1H), 2.67 (d, *J* = 16.2 Hz, 1H), 2.45 (dd, *J* = 13.1, 3.7 Hz, 1H), 2.34-2.31 (m, 2H), 2.13 (dd, *J* = 13.3, 13.3 Hz, 1H), 1.91 (s, 3H), 1.76-1.70 (m, 1H), 1.70-1.65 (m, 3H), 1.50 (dddd, *J* = 13.1, 13.1, 13.1, 3.5 Hz, 1H), 1.44 (s, 1H), 1.05 (s, 3H), 1.03 (dd, *J* = 13.2, 13.2 Hz, 1H), 0.93-0.85 (m, 1H), 0.88 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 199.67, 162.52, 148.08, 126.16, 110.69, 76.20, 46.29, 45.82, 44.27, 42.68, 38.51, 34.11, 33.88, 27.50, 24.58, 22.30, 22.20, 15.35.

IR (neat, cm⁻¹, v): 3476 (m, br), 2949 (s), 2923 (s), 1655 (s), 1451 (m), 1377 (s), 1285 (m), 1237 (w), 1131 (w), 1068 (w), 1025 (w).

HRMS (EI, m/z): calculated 274.1933 for $[M]^+$, found 274.1929.

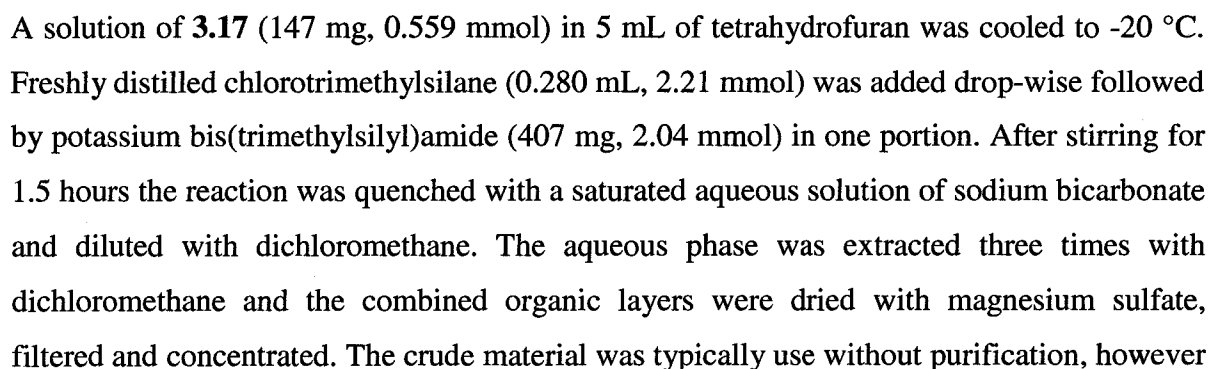
mp = 148.8-150.1 °C.



(±)-(1R,4aR,4bS,6R,8aS)-4b-Hydroxy-1,4a,6-trimethyl-9-methylene-1-vinyl-dodecahydro-phenanthren-3-one (3.26):

Data for 3.26:

mp = 127.9-129.2 °C.



a small amount was isolated by silica gel flash chromatography (5% ethyl acetate/hexanes) to give **3.27** as a clear oil.

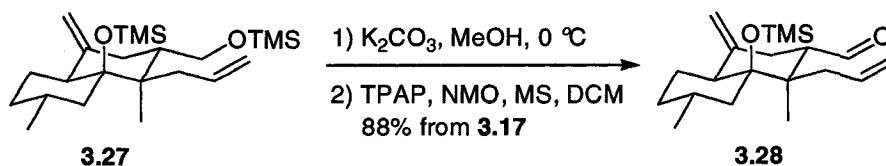
Data for 3.27:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.94-5.85 (m, 1H), 5.01 (dddd, $J = 17.0, 1.9, 1.9, 1.9$ Hz, 1H), 4.97-4.95 (m, 1H), 4.71 (d, $J = 1.7$ Hz, 1H), 4.45 (d, $J = 1.6$ Hz, 1H), 3.84 (dd, $J = 10.3, 3.4$ Hz, 1H), 3.30 (dd, $J = 10.3, 8.5$ Hz, 1H), 2.45-2.39 (m, 2H), 2.10 (dd, $J = 15.4, 7.8$ Hz, 1H), 2.06-2.04 (m, 1H), 1.96-1.85 (m, 2H), 1.76-1.68 (m, 2H), 1.64-1.46 (m, 3H), 1.04 (dd, $J = 13.5, 12.3$ Hz, 1H), 0.92-0.80 (m, 1H), 0.88 (s, 3H), 0.86 (d, $J = 6.5$ Hz, 3H), 0.10 (s, 9H), 0.08 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.62, 138.39, 115.45, 106.02, 84.93, 64.62, 46.23, 44.41, 43.86, 39.66, 35.98, 34.08, 28.15, 24.82, 22.39, 15.86, 3.00 (3C), -0.30 (3C).

IR (neat, cm^{-1} , ν): 3081 (w), 2952 (s), 2926 (s), 2869 (m), 1648 (w), 1454 (w), 1249 (s), 1131 (m), 1079 (s).

HRMS (EI, m/z): calculated 408.2880 for $[\text{M}]^+$, found 408.598.



(±)-(1R,2S,4aS,7R,8aS)-1-Allyl-1,7-dimethyl-4-methylene-8a-trimethylsilanyloxy-decahydro-naphthalene-2-carbaldehyde (3.28):

A solution of unpurified **3.27** (224 mg, 0.549 mmol maximum) in 5 mL of methanol was cooled to 0 °C. Anhydrous potassium carbonate was added (75 mg, 0.54 mmol) and the reaction was stirred for 30 minutes. The reaction was then diluted with water, extracted three times with dichloromethane and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. The crude oil was then dissolved in 5 mL of dichloromethane and put under an atmosphere of nitrogen. Activated 4 Å molecular sieves (250 mg) were added, followed by 4-methylmorpholine N-oxide (87 mg, 0.747 mmol) and tetrapropylammonium perruthenate (5 mg, 0.014 mmol). After stirring for 20 minutes, the reaction was filtered over a pad of silica and washed with a 5% solution of methanol in ethyl acetate followed by dichloromethane. The filtrate was concentrated and purified by silica gel

flash chromatography (5% ethyl acetate/hexanes) to give 162 mg of **3.28** as a white solid (88% over three steps from **3.17**).

Data for 3.28:

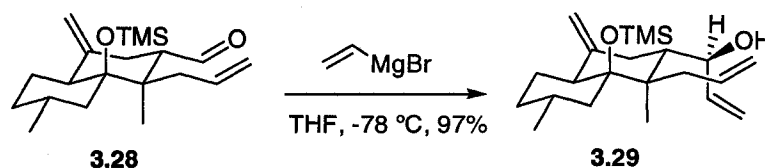
¹H NMR (CDCl₃, 500 MHz, δ): 9.83 (d, J = 3.4 Hz, 1H), 5.82-5.74 (m, 1H), 5.08 (d, J = 1.0 Hz, 1H), 5.06-5.05 (m, 1H), 4.74 (d, J = 1.6 Hz, 1H), 4.53 (d, J = 1.6 Hz, 1H), 2.77 (ddd, J = 13.1, 3.7, 3.7 Hz, 1H), 2.43 (dd, J_{AB} = 14.4, J_{AX} = 6.7 Hz, 1H), 2.34 (dd, J = 13.8, 13.8 Hz, 1H), 2.28 (dd, J_{AB} = 14.4, J_{BX} = 8.3 Hz, 1H), 2.11-2.06 (m, 2H), 1.77-1.71 (m, 2H), 1.67-1.58 (m, 2H), 1.54-1.46 (m, 1H), 1.15 (s, 3H), 1.07 (dd, J = 13.4, 12.4 Hz, 1H), 0.92-0.83 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.13 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz, δ): 205.68, 147.13, 136.18, 118.74, 107.89, 84.26, 56.21, 45.43, 43.96, 40.33, 38.90, 33.88, 33.01, 28.21, 24.69, 22.33, 16.48, 2.90 (3C).

IR (neat, cm⁻¹, ν): 2950 (s), 2925 (s), 1715 (s), 1443 (m), 1249 (s), 1176 (w), 1127 (m), 1090 (m).

HRMS (EI, m/z): calculated 334.2328 for [M]⁺, found 334.2327.

mp = 59.1-60.6 °C.



(±)-1-((1R,4aS,7R,8aS)-1-Allyl-1-(S)-methyl-7-methyl-4-methylene-8a-trimethylsilanyloxy-decahydro-naphthalen-2-yl)-prop-2-en-1-ol (3.29):

A solution of **3.28** (127 mg, 0.380 mmol) in 3 mL of tetrahydrofuran was cooled to -78 °C. Vinylmagnesium bromide (0.87 mL of a 0.87 M solution in tetrahydrofuran, 0.76 mmol) was added drop-wise and the reaction was stirred for 45 minutes. A saturated aqueous solution of ammonium chloride was added and the reaction was warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. No further purification was required and 133 mg of a white solid (97%) was obtained.

Data for 3.29:

¹H NMR (CDCl₃, 500 MHz, δ): 6.04-5.99 (m, 1H), 5.88-5.83 (m, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.10 (d, J = 10.6 Hz, 1H), 5.05-4.98 (m, 2H), 4.66 (s, 2H), 4.45 (s, 1H), 2.49 (dd, J =

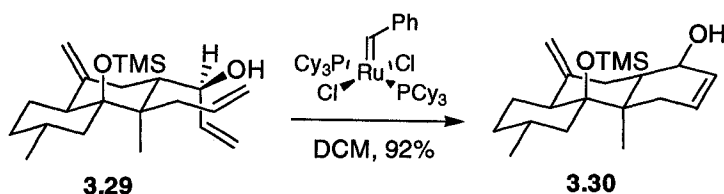
15.1, 5.5 Hz, 1H), 2.21 (dd, $J = 12.7, 12.7$ Hz, 1H), 2.11-2.02 (m, 3H), 1.91 (d, $J = 13.4$ Hz, 1H), 1.75-1.69 (m, 2H), 1.59-1.48 (m, 3H), 1.24-1.06 (m, 2H), 1.14 (s, 3H), 0.87-0.85 (m, 1H), 0.87 (d, $J = 3.5$ Hz, 3H), 0.08 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.85, 142.38, 138.27, 115.70, 112.91, 106.11, 85.33, 71.42, 47.75, 46.17, 45.03, 39.99, 39.66, 34.08, 30.40, 28.21, 24.84, 22.41, 17.33, 2.96 (3C).

IR (neat, cm^{-1} , ν): 3435 (br, w), 3081 (w), 2950 (s), 2926 (s), 2868 (m), 1646 (w), 1455 (w), 1248 (s), 1119 (s), 1092 (m), 1063 (m).

HRMS (EI, m/z): calculated 362.2641 for $[\text{M}]^+$, found 362.2643.

mp = 61.4-63.8 °C.



(±)-(4aR,4bS,6R,8aS)-4a,6-Dimethyl-9-(S)-methylene-4b-trimethylsilanyloxy-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthren-1-ol (3.30):

A solution of **3.29** (133 mg, 0.398 mmol) in 40 mL of dichloromethane was sparged with argon for 20 minutes. Grubbs' first generation catalyst was added (16 mg, 0.019 mmol) and the resulting pink solution was stirred for 10 minutes. The solution was concentrated and purified *twice* by silica gel flash chromatography (5% → 15% ethyl acetate/hexanes) to yield 122 mg of the allylic alcohol (92%) as a colourless oil.

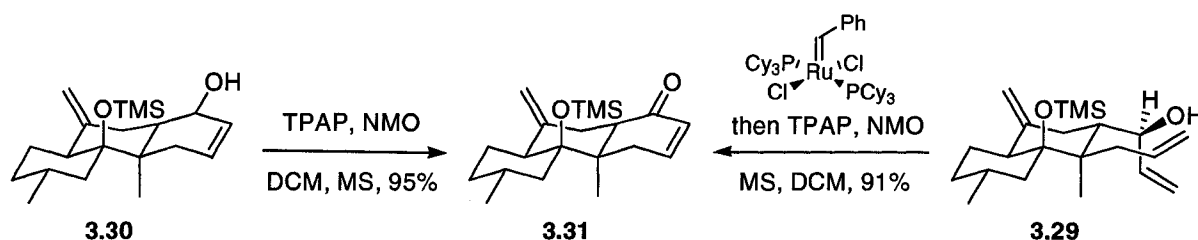
Data for 3.30:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.72-5.69 (m, 1H), 5.63-5.61 (m, 1H), 4.74 (s, 1H), 4.49 (s, 1H), 3.77-3.76 (m, 1H), 2.61 (dd, $J = 13.4, 4.1$ Hz, 1H), 2.21 (d, $J = 17.7$ Hz, 1H), 2.08 (d, $J = 9.3$ Hz, 1H), 1.98 (dd, $J = 13.6, 13.1$ Hz, 1H), 1.75-1.70 (m, 3H), 1.62-1.45 (m, 4H), 1.13-1.08 (m, 2H), 0.98 (s, 3H), 0.91-0.83 (m, 1H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.08 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 148.91, 128.99, 127.74, 106.80, 83.28, 71.79, 44.67, 43.62, 42.59, 38.54, 35.14, 34.11, 32.97, 27.96, 24.80, 22.28, 15.90, 2.85 (3C).

IR (neat, cm^{-1} , ν): 3332 (br, w), 3085 (w), 3025 (w), 2949 (s), 2926 (s), 2869 (m), 2846 (m), 1645 (w), 1454 (m), 1249 (s), 1149 (m), 1118 (m), 1087 (s), 1056 (m), 1017 (m).

HRMS (EI, m/z): calculated 334.2328 for $[\text{M}]^+$, found 334.2331.



(±)-(4aR,4bS,6R,8aS,10aS)-4a,6-Dimethyl-9-methylene-4b-trimethylsilanyloxy-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-4H-phenanthren-1-one (3.31):

Method A: A solution of **3.30** (127 mg, 0.380 mmol) in 4 mL of dichloromethane was put under an atmosphere of nitrogen. Activated 4 Å molecular sieves were added (190 mg) followed by 4-methylmorpholine N-oxide (66.0 mg, 0.563 mmol) and tetrapropylammonium perruthenate (5.0 mg, 0.014 mmol). After stirring for 25 minutes, the reaction was filtered over a pad of silica and washed several times with a 5% solution of methanol in ethyl acetate followed by dichloromethane. The filtrate was concentrated and purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 114 mg of **3.31** as a clear oil (95%).

Method B: A solution of **3.29** (611.7 mg, 1.687 mmol) in 150 mL of dichloromethane was sparged with argon for 20 minutes. Grubbs' first generation catalyst was added (52 mg, 0.063 mmol) and the resulting pink solution was stirred for 30 minutes. Activated 4 Å molecular sieves (840 mg), 4-methylmorpholine N-oxide (401 mg, 3.41 mmol) and tetrapropylammonium perruthenate (15 mg, 0.043 mmol) were added in succession and the mixture was stirred for 45 minutes. The resulting dark brown solution was then filtered over a pad of silica, washing twice with a 5% solution of methanol in ethyl acetate followed by several washes with dichloromethane. The filtrate was concentrated and purified *twice* by silica gel flash chromatography (100% hexanes → 8% ethyl acetate/hexanes) to yield 511 mg of enone **3.31** as a colourless oil (91%).

Data for 3.31:

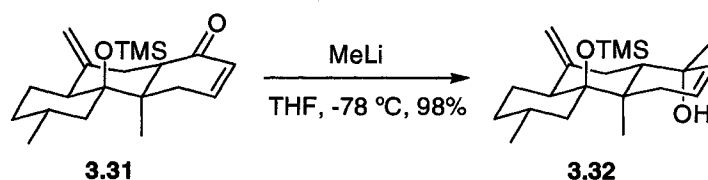
¹H NMR (CDCl₃, 500 MHz, δ): 6.82-6.76 (m, 1H), 5.93 (dd, *J* = 10.0, 2.9 Hz, 1H), 4.77 (d, *J* = 1.7 Hz, 1H), 4.50 (d, *J* = 1.7 Hz, 1H), 2.80 (dd, *J* = 12.3, 4.1 Hz, 1H), 2.64-2.60 (m, 1H), 2.57 (dd, *J* = 14.4, 4.1 Hz, 1H), 2.17-2.03 (m, 3H), 1.75-1.71 (m, 1H), 1.64-1.59 (m, 3H),

1.47 (dddd, $J = 13.2, 13.2, 11.8, 3.5$ Hz, 1H), 1.09 (dd, $J = 13.9, 13.0$ Hz, 1H), 1.03 (s, 3H), 0.93-0.80 (m, 1H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.09 (s, 9H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 202.17, 147.72, 146.65, 128.11, 107.75, 83.23, 50.26, 46.59, 43.30, 38.20, 34.30, 33.87, 30.95, 27.93, 24.51, 22.19, 16.34, 2.87 (3C).

IR (neat, cm^{-1} , ν): 2950 (s), 2931 (s), 2866 (m), 1729 (w), 1681 (s), 1647 (w), 1456 (w), 1387 (m), 1250 (m), 1194 (m), 1135 (m), 1058 (m).

HRMS (EI, m/z): calculated 332.2172 for $[\text{M}]^+$, found 332.2158.



(±)-(4aR,4bS,6R,8aS,10aS)-1,6-Dimethyl-4a-(R)-methyl-9-methylene-4b-trimethylsilyloxy-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-phenanthren-1-ol (3.32):

A solution of **3.31** (114 mg, 0.343 mmol) in 3 mL of tetrahydrofuran was cooled to $-78\text{ }^{\circ}\text{C}$ and methyllithium (0.69 mL of a 1.3 M solution in diethyl ether, 0.90 mmol) was added drop-wise. After 20 minutes the reaction was quenched with water and warmed to ambient temperature. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) gave 117 mg of a white solid (98%).

Data for **3.32**:

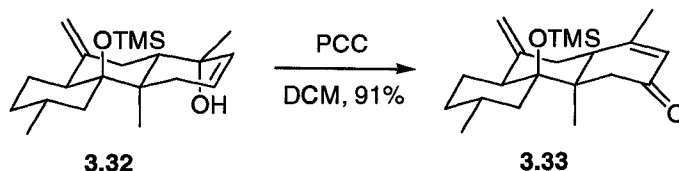
^1H NMR (CDCl_3 , 500 MHz, δ): 5.70-5.67 (m, 1H), 5.60-5.57 (m, 1H), 4.73 (s, 1H), 4.48 (s, 1H), 2.39-2.28 (m, 2H), 2.12-2.08 (m, 2H), 1.96 (dd, $J = 12.8, 4.0$ Hz, 1H), 1.80 (dd, $J = 17.3, 5.9$ Hz, 1H), 1.72-1.68 (m, 1H), 1.63-1.44 (m, 4H), 1.21 (s, 3H), 1.18 (dd, $J = 9.3, 9.3$ Hz, 1H), 1.14-1.11 (m, 1H), 1.13 (s, 3H), 0.91-0.83 (m, 1H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.05 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 150.01, 132.92, 126.03, 106.36, 83.80, 69.53, 44.72, 43.67, 40.80, 38.43, 34.07, 32.82, 31.95, 29.82, 28.07, 24.90, 22.29, 16.81, 2.77 (3C).

IR (neat, cm^{-1} , ν): 3450 (br, m), 3083 (w), 3019 (m), 2949 (s), 2871 (m), 2847 (m), 1646 (m), 1455 (m), 1368 (m), 1249 (s), 1183 (m), 1149 (m), 1061 (s), 1020 (m).

HRMS (EI, m/z): calculated 348.2485 for $[M]^+$, found 348.2465.

mp = 92.1-93.2 °C.



(±)-(4aR,4bS,6R,8aS,10aR)-1,4a,6-Trimethyl-9-methylene-4b-trimethylsilanyloxy-4a,4b,5,6,7,8,8a,9,10,10a-decahydro-4H-phenanthren-3-one (3.33):

To a solution of **3.32** (115 mg, 0.330 mmol) in 3 mL of dichloromethane was added pyridinium chlorochromate (200 mg, 0.928 mmol) in one portion. The reaction changed colour from a light to a very dark orange and was complete by TLC after 2 hours. An equal volume of diethyl ether was then added and the resulting precipitate was filtered off over celite, rinsing thoroughly with additional diethyl ether. The filtrate was concentrated and purified by silica gel flash chromatography (10% ethyl acetate/hexanes) to yield a 104 mg of **3.33** as a white solid (91%).

Data for 3.33:

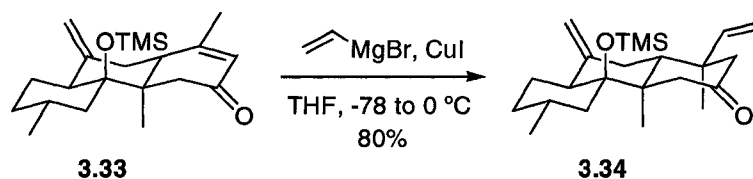
^1H NMR (CDCl_3 , 500 MHz, δ): 5.84 (s, 1H), 4.81 (s, 1H), 4.56 (s, 1H), 2.95 (d, $J = 13.3$ Hz, 1H), 2.51 (dd, $J = 13.2, 3.4$ Hz, 1H), 2.43 (d, $J_{\text{AB}} = 15.5$ Hz, 1H), 2.32 (d, $J_{\text{AB}} = 15.7$ Hz, 1H), 2.16 (d, $J = 10.9$ Hz, 1H), 2.10 (dd, $J = 13.3, 13.3$ Hz, 1H), 1.91 (s, 3H), 1.76-1.74 (m, 1H), 1.65-1.61 (m, 3H), 1.54-1.46 (m, 1H), 1.07-1.02 (m, 1H), 1.05 (s, 3H), 0.93-0.85 (m, 1H), 0.88 (d, $J = 6.3$ Hz, 3H), 0.10 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 199.64, 163.84, 148.17, 125.76, 108.19, 82.86, 47.19, 46.46, 43.78, 43.54, 38.44, 34.12, 34.02, 27.94, 24.52, 22.39, 22.18, 15.99, 2.89 (3C).

IR (neat, cm^{-1} , ν): 2952 (m), 2925 (m), 2865 (w), 1673 (w), 1454 (m), 1473 (m), 1251 (m), 1146 (m), 1105 (m), 1056 (m).

HRMS (EI, m/z): calculated 346.2328 for $[M]^+$, found 346.2332.

mp = 132.2-134.8 °C.



(±)-(1R,4aR,4bS,6R,8aS,10aR)-1,4a,6-Trimethyl-9-methylene-4b-trimethylsilanyloxy-1-vinyl-dodecahydro-phenanthren-3-one (3.34):

A suspension of copper (I) iodide (104 mg, 0.546 mmol) in 2 mL of tetrahydrofuran was cooled to -78 °C. Vinylmagnesium bromide (1.25 mL of a 0.87 M solution in tetrahydrofuran, 1.1 mmol) was added drop-wise and the resulting pale yellow mixture was immersed in a -10 °C bath (acetone/ice) for ten minutes. The resulting olive green suspension was then re-cooled to -78 °C and enone **3.33** (60 mg, 0.17 mmol) was cannulated into the reaction mixture using 1 mL of tetrahydrofuran. After 1 hour at -78 °C, the reaction, now rust brown in colour, was warmed to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 52.2 mg of a white solid (80%).

Data for 3.34:

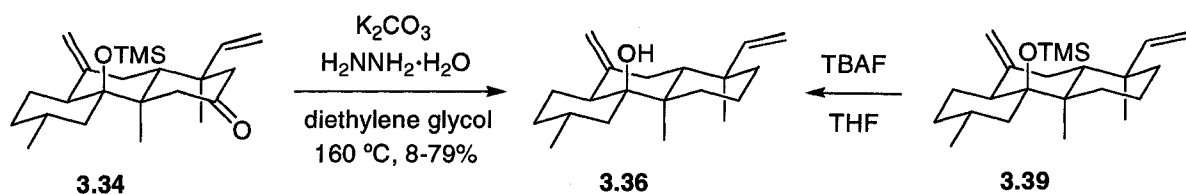
¹H NMR (C₆D₆, 500 MHz, δ): 5.68 (dd, *J* = 17.3, 10.7 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.87 (d, *J* = 17.5 Hz, 1H), 4.85-4.84 (m, 1H), 4.64-4.63 (m, 1H), 2.43-2.37 (m, 2H), 2.31-2.25 (m, 3H), 2.17 (dd, *J* = 12.7, 2.2 Hz, 1H), 1.94 (dd, *J* = 13.9, 12.9 Hz, 1H), 1.83 (d, *J* = 10.7 Hz, 1H), 1.65-1.50 (m, 4H), 1.34-1.32 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H), 0.92-0.87 (m, 1H), 0.81 (d, *J* = 6.5 Hz, 1H), 0.75-0.67 (m, 1H), 0.14 (s, 9H).

¹³C NMR (C₆D₆, 125 MHz, δ): 209.01, 149.29, 149.23, 111.69, 107.22, 84.55, 54.46, 48.56, 48.44, 44.78, 44.46, 43.87, 38.10, 34.13, 33.43, 28.48, 25.25, 22.24, 18.50, 18.05, 2.97 (3C).

IR (neat, cm⁻¹, ν): 3081 (w), 2947 (m), 2928 (m), 2871 (w), 2851 (w), 1709 (s), 1642 (w), 1448 (w), 1279 (m), 1261 (m), 1247 (s), 1123 (m), 1059 (m).

HRMS (EI, m/z): calculated 374.2641 for $[M]^+$, found 374.263.

mp = 112.2-113.0 °C.



(±)-(3R,4aS,4bR,8R,8aR,10aS)-3,4b,8-Trimethyl-10-methylene-8-vinyl-dodecahydro-phenanthren-4a-ol (3.36):

Method A: A suspension of **3.34** (19 mg, 0.063 mmol), hydrazine hydrate (0.020 mL, 0.41 mmol) and potassium carbonate (130 mg, 0.941 mmol) in 2 mL of diethylene glycol was gradually heated in a sealed tube to 160 °C and stirred for 18 hours. The reaction was diluted with 10 mL of water and extracted three times with diethyl ether. The combined organic layers were washed once with brine, dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded a white solid of mass 14.3 mg (79%). *Note, this yield was highly variable despite precautions to keep the reaction conditions the same.*

Method B: To a solution of **3.39** (34 mg, 0.094 mmol) in 2 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.28 mL of a 1.0 M solution in tetrahydrofuran, 0.28 mmol). After stirring for 5 hours at ambient temperature, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Further purification was not required and the crude material was carried on to subsequent reactions.

Data for 3.36:

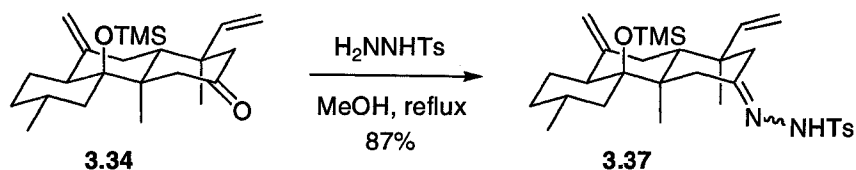
¹H NMR (C₆D₆, 300 MHz, δ): 5.59 (dd, *J* = 17.4, 10.8 Hz, 1H), 4.97 (dd, *J* = 10.6, 1.3 Hz, 1H), 4.93 (dd, *J* = 17.4, 1.2 Hz, 1H), 4.84 (d, *J* = 1.7 Hz, 1H), 4.58 (d, *J* = 1.2 Hz, 1H), 2.19 (dd, *J* = 13.0, 2.9 Hz, 1H), 2.06-2.01 (m, 1H), 1.91 (dd, *J* = 13.3, 13.3 Hz, 1H), 1.82-1.73 (m, 1H), 1.70-1.57 (m, 4H), 1.53-1.39 (m, 3H), 1.37-1.22 (m, 4H), 1.19 (d, *J* = 1.7 Hz, 1H), 0.98 (s, 3H), 0.94-0.90 (m, 1H), 0.92 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.80-0.66 (m, 1H).

¹³C NMR (C₆D₆, 125 MHz, δ): 151.83, 150.74, 110.93, 108.60, 77.41, 46.01, 43.75, 41.87, 40.28, 40.02, 38.27, 34.42, 33.81, 31.48, 27.90, 25.16, 22.76, 18.65, 17.33, 16.92.

IR (neat, cm⁻¹, ν): 3486 (br, m), 3081 (w), 2924 (s), 2866 (s), 1638 (m), 1455 (m), 1369 (w), 1343 (w).

HRMS (EI, m/z): calculated 288.2453 for $[M]^+$, found 288.2431.

mp = 72.4-74.9 °C.



(±)-(1R,4aR,4bS,6R,8aS,10aR)-1,4a,6-Trimethyl-9-methylene-4b-trimethylsilyloxy-1-vinyl-dodecahydro-phenanthren-3-one 4-toluenesulfonylhydrazone (3.37):

para-Toluenesulfonylhydrazide (6.7 mg, 0.036 mmol) was added to a solution of **3.34** (13.5 mg, 0.0360 mmol) in 2 mL of methanol. After stirring for 30 minutes at ambient temperature the reaction was brought to reflux for 5 hours, cooled and then concentrated. Purification by silica gel flash chromatography (25% ethyl acetate/hexanes) yielded 17 mg of **3.37** as a white solid (87%).

Data for **3.37** (~ 1:1 mixture of regioisomers):

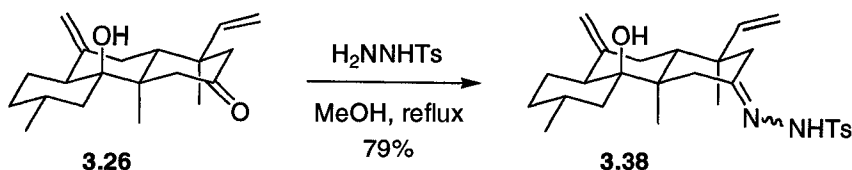
¹H NMR (C_6D_6 , 500 MHz, δ): Isomer A: 8.98 (s, 1H), 8.21 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 5.64 (dd, J = 17.3, 10.7 Hz, 1H), 4.95-4.85 (m, 2H), 4.79 (s, 1H), 4.60 (s, 1H), 2.95 (d, J = 12.9 Hz, 1H), 2.28-2.06 (m, 3H), 1.88 (s, 3H), 1.86-1.18 (m, 10H), 0.99-0.63 (m, 10H), 0.13 (s, 9H). Isomer B: 8.16 (d, J = 8.2 Hz, 2H), 7.86 (s, 1H), 6.83 (d, J = 8.0 Hz, 2H), 5.54 (dd, J = 17.3, 10.7 Hz, 1H), 4.95-4.85 (m, 2H), 4.79 (s, 1H), 4.59 (s, 1H), 2.28-2.06 (m, 4H), 1.89 (s, 3H), 1.86-1.18 (m, 10H), 0.99-0.63 (m, 10H), 0.09 (s, 9H).

¹³C NMR (C_6D_6 , 125 MHz, δ): 159.19, 158.13, 149.67, 149.45, 149.37, 148.61, 143.60, 143.42, 137.03, 136.75, 129.61 (2C), 129.58 (2C), 128.70 (2C), 128.66 (2C), 112.45, 111.87, 107.10, 107.02, 84.66, 84.47, 48.69, 47.53, 46.89, 44.84, 44.78, 44.15, 44.11, 43.71, 43.55, 42.10, 39.50, 38.27, 38.11, 34.27, 34.13, 33.99, 33.22, 33.19, 28.69, 28.45, 25.31, 25.17, 22.30, 22.29, 21.08, 17.80, 17.71, 17.47, 17.19, 14.28, 3.04 (3C), 2.97 (3C).

IR (neat, cm^{-1} , ν): 3436 (br, w), 3228 (m), 2950 (s), 1644 (m), 1454 (m), 1390 (w), 1345 (m), 1249 (m), 1168 (s), 1126 (w), 1090 (m), 1061 (w).

HRMS (EI, m/z): calculated 542.2998 for $[M]^+$, found 542.2988.

mp = 177.6-179.9 °C.



(±)-(1R,4aR,4bS,6R,8aS)-4b-Hydroxy-1,4a,6-trimethyl-9-methylene-1-vinyl-dodecahydro-phenanthren-3-one 4-toluenesulfonylhydrazone (3.38):

para-Toluenesulfonylhydrazide (26 mg, 0.14 mmol) was added to a solution of **3.26** (46.4 mg, 0.153 mmol) in 3 mL of methanol. After stirring for 30 minutes at ambient temperature, the reaction was brought to reflux for 5 hours, cooled and then concentrated. Purification by silica gel flash chromatography (20% → 40% ethyl acetate/hexanes) yielded 52 mg of **3.38** as a white solid (79%).

Data for **3.38** (~ 1:1 mixture of regioisomers):

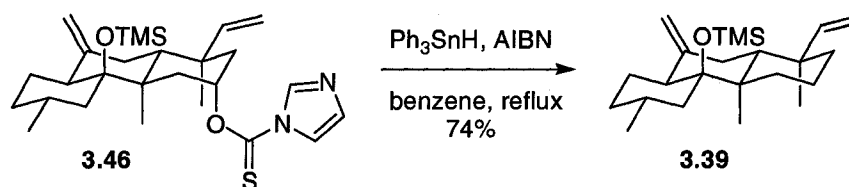
¹H NMR (CDCl₃, 500 MHz, δ): Isomer A: 7.84-7.81 (m, 3H), 7.29-7.26 (m, 2H), 5.66-5.58 (m, 1H), 4.97 (d, *J* = 10.7 Hz, 1H), 4.90 (d, *J* = 17.3 Hz, 1H), 4.81 (s, 1H), 4.61 (s, 1H), 2.46-2.27 (m, 2H), 2.40 (s, 3H), 2.14-1.99 (m, 3H), 1.90-1.50 (m, 4H), 1.43-1.38 (m, 2H), 1.28-1.23 (m, 2H), 1.10-1.05 (m, 1H), 0.87-0.70 (m, 11H). Isomer B: 7.84-7.81 (m, 2H), 7.52 (s, 1H), 7.29-7.26 (m, 2H), 5.66-5.58 (m, 1H), 5.02 (d, *J* = 10.7 Hz, 1H), 4.92 (d, *J* = 17.3 Hz, 1H), 4.85 (s, 1H), 4.61 (s, 1H), 2.46-2.27 (m, 2H), 2.40 (s, 3H), 2.14-1.99 (m, 3H), 1.90-1.50 (m, 4H), 1.43-1.38 (m, 2H), 1.28-1.23 (m, 2H), 1.10-1.05 (m, 1H), 0.87-0.70 (m, 11H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.05, 148.78, 148.03, 143.90, 135.37, 135.32, 129.49 (2C), 129.45 (2C), 128.08 (2C), 128.06 (2C), 112.83, 112.20, 109.78, 109.74, 77.21, 47.96, 46.20, 46.12, 46.06, 45.81, 43.56, 43.16, 43.14, 43.10, 41.51, 39.63, 38.05, 37.94, 34.66, 33.82, 33.76, 32.97, 32.81, 32.74, 31.57, 27.78, 27.72, 24.78, 22.63, 22.35, 22.24, 21.58, 17.75, 17.34, 16.97, 16.42, 14.09.

IR (neat, cm⁻¹, ν): 3537 (br, s), 3227 (m), 2949 (s), 2867 (m), 1699 (m), 1640 (m), 1599 (m), 1455 (m), 1376 (m), 1342 (s), 1167 (s), 1094 (m), 1071 (w), 1019 (m).

HRMS (EI, *m/z*): calculated 284.2140 for [M-H₂NNHTs]⁺, found 284.2138.

mp = 192.9-194.1 °C.



(±)-Trimethyl-((3R,4aS,4bR,8R,10aS)-3,4b,8-trimethyl-10-methylene-8-vinyl-dodecahydro-phenanthren-4a-yloxy)-silane (3.39):

A solution of triphenyltin hydride (29 mg, 0.083 mmol) in 1 mL of degassed benzene was added to a solution of **3.46** (20 mg, 0.041 mmol) in 2 mL of degassed benzene, followed by the addition of 2,2'-azobis(2-methylpropionitrile) (1.5 mg, 0.0091 mmol). The reaction mixture was brought to reflux and allowed to react for 75 minutes. After cooling to ambient temperature, the reaction was concentrated and purified by silica gel flash chromatography (100% hexanes) to give 11 mg of a clear colourless oil (74%).

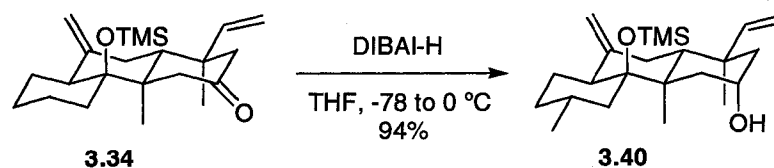
Data for 3.39:

¹H NMR (CDCl₃, 500 MHz, δ): 5.58 (dd, *J* = 17.5, 10.8 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 17.8 Hz, 1H), 4.59 (s, 1H), 4.39 (s, 1H), 2.06-1.92 (m, 3H), 1.79 (dd, *J* = 12.8, 3.4 Hz, 1H), 1.70-1.67 (m, 1H), 1.63-1.50 (m, 5H), 1.48-1.41 (m, 2H), 1.35 (dd, *J* = 13.0, 3.8 Hz, 1H), 1.31-1.20 (m, 2H), 1.10-1.05 (m, 1H), 1.08 (s, 3H), 0.98 (s, 3H), 0.88-0.80 (m, 1H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.12 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz, δ): 151.95, 150.80, 110.36, 105.73, 84.62, 44.23, 43.66, 42.43, 39.87, 39.68, 37.90, 34.24, 33.38, 31.90, 28.22, 24.93, 22.36, 18.50, 17.61, 17.22, 2.99 (3C).

IR (neat, cm⁻¹, ν): 3085 (w), 2949 (s), 2869 (m), 1645 (m), 1455 (m), 1246 (s), 1181 (m), 1124 (s), 1090 (s), 1059 (s).

HRMS (EI, *m/z*): calculated 360.2848 for [M]⁺, found 360.2825.



(±)-(1R,3S,4aR,4bS,6R,8aS)-1,4a,6-Trimethyl-9-methylene-4b-trimethylsilanyloxy-1-vinyl-tetradecahydro-phenanthren-3-ol (3.40):

A solution of **3.34** (52 mg, 0.14 mmol) in 1 mL of tetrahydrofuran was cooled to -78 °C. Diisobutylaluminum hydride (0.26 mL of a 1.0 M solution in toluene, 0.39 mmol) was added

drop-wise and the reaction was warmed to 0 °C. After stirring for 30 minutes, the reaction was quenched with equal volumes of a 1 M aqueous sodium hydroxide solution and a 1 M aqueous sodium tartrate solution. The mixture was stirred vigorously for 1 hour (or until two distinct phases appeared) and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were then dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 49 mg of a **3.40** as a white solid (94%).

Data for **3.40**:

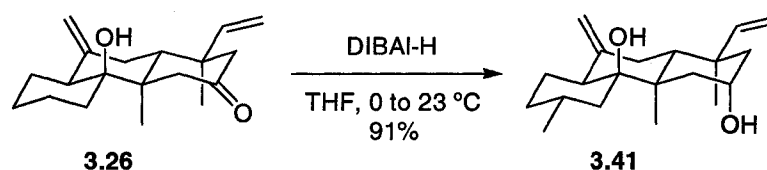
¹H NMR (CDCl₃, 500 MHz, δ): 5.60 (dd, J = 17.4, 10.8 Hz, 1H), 4.93 (dd, J = 10.8, 1.0 Hz, 1H), 4.91 (dd, J = 17.4, 1.0 Hz, 1H), 4.61 (d, J = 1.5 Hz, 1H), 4.41 (d, J = 1.5 Hz, 1H), 4.21 (dddd, J = 4.4, 4.4, 4.4, 4.4 Hz, 1H), 2.11-2.01 (m, 3H), 1.84 (dd, J = 12.4, 4.0 Hz, 1H), 1.78 (dd, J = 13.9, 4.9 Hz, 1H), 1.71-1.67 (m, 1H), 1.60-1.45 (m, 6H), 1.48-1.39 (m, 1H), 1.35 (s, 3H), 1.22-1.24 (m, 1H), 1.19 (s, 3H), 1.14 (dd, J = 14.0, 12.7 Hz, 1H), 0.90-0.81 (m, 1H), 0.86 (d, J = 6.4 Hz, 3H), 0.09 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz, δ): 151.08, 150.47, 110.46, 105.94, 84.98, 67.79, 44.79, 43.33, 42.71, 42.40, 38.90, 38.54, 38.24, 34.14, 33.20, 28.17, 24.89, 22.32, 20.22, 19.99, 3.00 (3C).

IR (neat, cm⁻¹, ν): 3381 (br, m), 3082 (w), 2950 (s), 2927 (s), 2869 (m), 1645 (m), 1456 (m), 1249 (s), 1132 (s), 1111 (m), 1003 (m).

HRMS (EI, m/z): calculated 376.2798 for [M]⁺, found 376.2785.

mp = 96.9-98.5 °C.

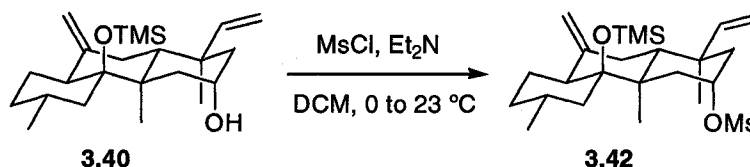


(±)-(1R,3S,4aR,4bS,6R,8aS)-1,4a,6-Trimethyl-9-methylene-1-vinyl-dodecahydro-phenanthrene-3,4b-diol (3.41**):**

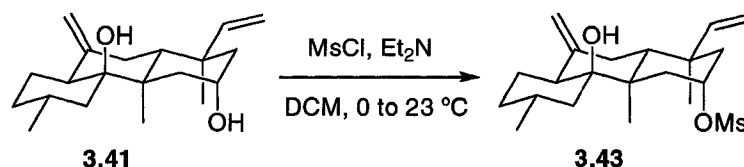
A solution of **3.26** (38 mg, 0.13 mmol) in 2.5 mL of tetrahydrofuran was cooled to 0 °C. Diisobutylaluminum hydride (0.25 mL of a 1.0 M solution in toluene, 0.38 mmol) was added drop-wise and the reaction was warmed to ambient temperature. After stirring for 2 hours, the reaction was quenched with a few drops of acetone, followed by equal volumes of a 1 M aqueous sodium hydroxide solution and a 1 M aqueous sodium tartrate solution. The mixture

Data for 3.41:

mp = 113.1-116.6 °C.

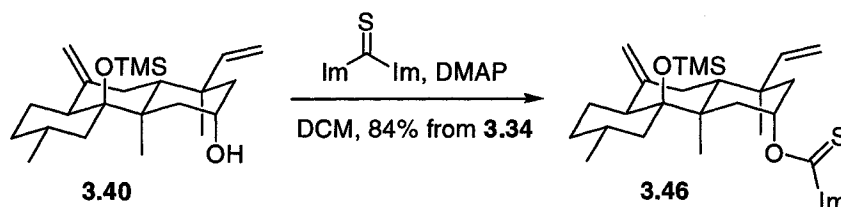


A solution of **3.40** (10 mg, 0.027 mmol) in 0.5 mL of dichloromethane was cooled to 0 °C. Triethylamine (0.12 mL, 0.86 mmol) was added, followed by methanesulfonyl chloride (0.050 mL, 0.65 mmol). The reaction was warmed to ambient temperature and stirred for 48 hours. Following dilution with additional dichloromethane, the reaction was washed twice with a saturated aqueous solution of sodium bicarbonate and the organic phase dried with magnesium sulfate, filtered and concentrated. Due to its instability, the crude product was used immediately without further purification.



(±)-Methanesulfonic acid (1R,3S,4aR,4bS,6R,8aS)-4b-hydroxy-1,4a,6-trimethyl-9-methylene-1-vinyl-tetradecahydro-phenanthren-3-yl ester (3.43):

A solution of **3.41** (38 mg, 0.13 mmol) in 3 mL of dichloromethane was cooled to 0 °C. Triethylamine (0.12 mL, 0.86 mmol) was added, followed by methanesulfonyl chloride (0.050 mL, 0.65 mmol). The reaction was warmed to ambient temperature and stirred for an addition 2 hours. Following dilution with dichloromethane, the reaction was washed twice with a saturated aqueous solution of sodium bicarbonate and the organic phase was dried with magnesium sulfate, filtered and concentrated. Due to its instability the crude product was used immediately without further purification.



(±)-3H-Imidazole-1-carbothioic acid O-((1R,3S,4aR,4bS,6R,8aS)-1,4a,6-trimethyl-9-methylene-4b-trimethylsilanyloxy-1-vinyl-tetradecahydro-phenanthren-3-yl) ester (3.46):

To a solution of unpurified **3.40** (21 mg, 0.056 mmol maximum) in 3 mL of dichloromethane was added thiocarbonyldiimidazole (34 mg of 90% purity, 0.17 mmol) followed by 4-di(methylamino)pyridine (7 mg, 0.06 mmol). The reaction was stirred at ambient temperature for 36 hours and then concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 23 mg of a clear, colourless oil (84% for two steps from **3.34**).

Data for 3.46:

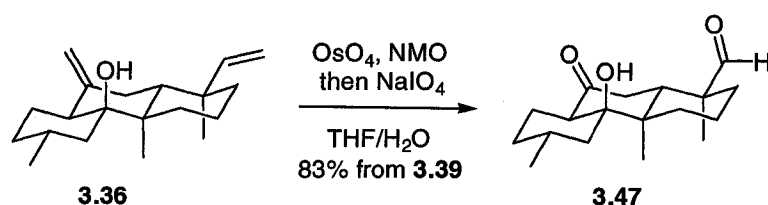
¹H NMR (CDCl₃, 500 MHz, δ): 8.35 (s, 1H), 7.64 (s, 1H), 7.03 (s, 1H), 5.96-5.93 (m, 1H), 5.59 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.96 (d, *J* = 17.4 Hz, 1H), 4.65 (s, 1H), 4.45 (s, 1H), 2.15-2.02 (m, 3H), 1.99-1.94 (m, 2H), 1.89 (dd, *J* = 14.7, 14.5 Hz, 1H), 1.73-1.70 (m, 1H), 1.65 (dd, *J* = 15.6, 3.5 Hz, 1H), 1.62-1.54 (m, 3H), 1.49-1.41 (m, 1H),

1.32 (s, 3H), 1.26-1.24 (m, 1H), 1.19 (s, 3H), 1.11 (dd, $J = 13.1, 12.6$ Hz, 1H), 0.90-0.83 (m, 1H), 0.85 (d, $J = 6.4$ Hz, 3H), 0.13 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 183.48, 150.16, 149.57, 136.91, 130.88, 118.02, 111.83, 106.61, 84.73, 81.34, 43.36, 43.07, 41.86, 40.96, 38.51, 38.09, 34.70, 34.02, 32.93, 28.16, 24.79, 22.25, 19.58, 19.30, 3.05 (3C).

IR (neat, cm^{-1} , ν): 3085 (w), 2952 (s), 2926 (s), 2869 (m), 1728 (w), 1645 (m), 1573 (w), 1531 (w), 1458 (m), 1386 (s), 1327 (s), 1281 (s), 1247 (s), 1232 (s), 1188 (s), 1113 (s), 1092 (s), 1061 (m).

HRMS (EI, m/z): calculated 330.2378 for $[\text{M-OTMS-Im}]^+$, found 330.2017.



(±)-(1S,4aR,4bS,6R,8aR)-4b-Hydroxy-1,4a,6-trimethyl-9-oxo-tetradecahydro-phenanthrene-1-carbaldehyde (3.47):

To a solution of unpurified **3.36** (27 mg, 0.094 mmol maximum) in 4 mL of a 5:1 tetrahydrofuran/water solution was added osmium tetroxide (0.06 mL of a 4% aqueous solution, 0.009 mmol) followed by 4-methylmorpholine N-oxide (44 mg, 0.38 mmol). After 4 hours of stirring at ambient temperature, sodium periodate (121 mg, 0.566 mmol) was added and the reaction was stirred for another 10 hours. A saturated aqueous solution of sodium sulfite was added and the biphasic mixture was stirred vigorously for 30 minutes. The aqueous phase was extracted three times with diethyl ether and the combined organic phases were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 23 mg of **3.47** as a white solid (83% for two steps).

Data for 3.47:

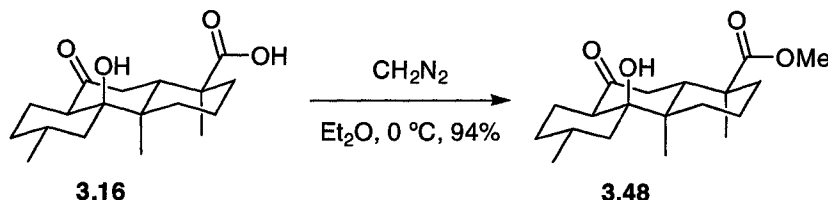
^1H NMR (CDCl_3 , 500 MHz, δ): 9.19 (s, 1H), 2.72 (dd, $J = 14.1, 3.4$ Hz, 1H), 2.39 (dd, $J = 12.0, 4.1$ Hz, 1H), 2.31 (dd, $J = 14.2, 14.2$ Hz, 1H), 1.85-1.79 (m, 2H), 1.76-1.64 (m, 3H), 1.62-1.54 (m, 6H), 1.50-1.42 (m, 1H), 1.30-1.21 (m, 2H), 1.23 (s, 3H), 1.11 (s, 3H), 0.91 (d, $J = 6.4$ Hz, 3H), 0.79 (dddd, $J = 12.8, 12.8, 12.8, 3.6$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 209.56, 205.02, 80.17, 51.77, 49.43, 40.86, 40.62, 38.73, 38.48, 32.91, 31.93, 30.37, 27.74, 22.36, 21.13, 17.03, 16.49, 13.64.

IR (neat, cm^{-1} , ν): 3514 (br, w), 2946 (s), 2868 (w), 1712 (s), 1456 (m), 1374 (m), 1315 (w), 1247 (w), 1156 (w), 1066 (w), 1023 (w).

HRMS (EI, m/z): calculated 292.2038 for $[\text{M}]^+$, found 292.2054.

mp = 117.3-119.6 °C.



(±)-(1S,4aR,4bS,6R,8aR)-4b-Hydroxy-1,4a,6-trimethyl-9-oxo-tetradecahydro-phenanthrene-1-carboxylic acid methyl ester (3.48):

A solution of **3.16** (4.5 mg, 0.015 mmol) in 0.5 mL of diethyl ether was cooled to 0 °C. A solution of diazomethane in diethyl ether was added drop-wise until a faint yellow colour persisted. A small amount of silica gel (0.2 mL) was added and the reaction mixture was concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 4.4 mg of **3.48** as a white solid (94%).

Data for **3.48**:

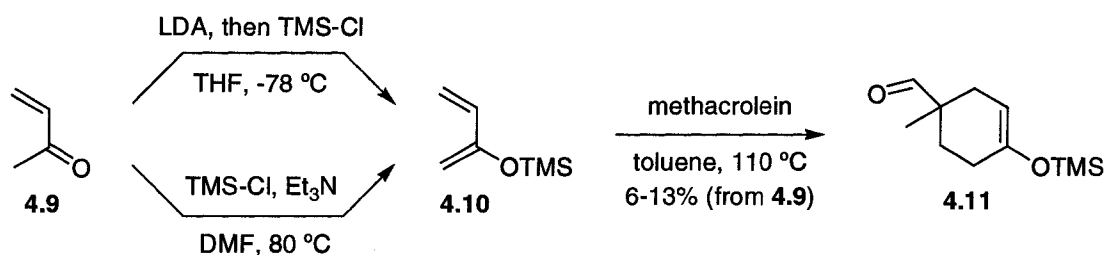
^1H NMR (CDCl_3 , 300 MHz, δ): 3.63 (s, 3H), 2.93 (dd, $J = 14.0, 3.5$ Hz, 1H), 2.37-2.28 (m, 2H), 1.93 (dd, $J = 14.3, 3.5$ Hz, 1H), 1.85-1.69 (m, 3H), 1.67-1.40 (m, 9H), 1.27-1.19 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H), 0.90 (d, $J = 6.2$ Hz, 3H), 0.86-0.70 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 210.20, 178.07, 80.02, 52.19, 51.65, 47.17, 41.27, 40.98, 40.60, 38.73, 36.25, 33.01, 30.45, 27.75, 22.39, 21.20, 17.88, 16.53, 16.38.

IR (neat, cm^{-1} , ν): 3522 (m, br), 2948 (s), 2867 (m), 1710 (s), 1456 (m), 1391 (w), 1372 (w), 1255 (m), 1241 (m), 1197 (w), 1152 (m), 1092 (w).

HRMS (EI, m/z): calculated 322.2144 for $[\text{M}]^+$, found 322.2135.

mp = 186.3-191.6 °C.



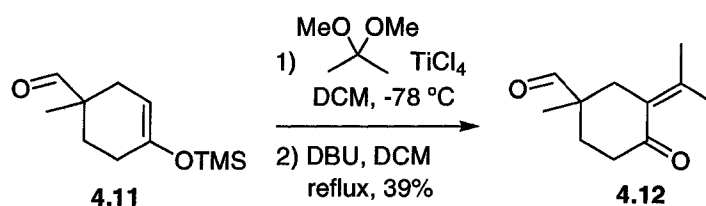
1-Methyl-4-trimethylsilanyloxy-cyclohex-3-enecarbaldehyde (4.11):

Step1, Method A: (Procedure adapted from Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6677.) To a solution of diisopropylamine (10.0 mL, 71.4 mmol) in 100 mL of tetrahydrofuran, cooled to -78 °C, was added *n*-butyllithium (29.0 mL of a 2.43 M solution in pentane, 70.8 mmol). After five minutes, methyl vinyl ketone (5.00 mL, 60.1 mmol) was added drop-wise during which time the reaction went from yellow to pale green in colour. After another ten minutes, chlorotrimethylsilane (9.0 mL, 71 mmol) was added and the resulting yellow solution was warmed to ambient temperature and stirred for 1.5 hours. The reaction was poured into a separatory funnel containing 100 mL of diethyl ether. A saturated aqueous solution of ammonium chloride was added and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate and filtered. The volatiles were distilled off and the remaining liquid was used directly for the subsequent step. (A ¹H NMR confirmed the presence of the desired diene, 4.10, along with traces of tetrahydrofuran, diethyl ether and diisopropylamine).

Step1, Method B: (Procedure adapted from Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6677.) A three-neck round-bottom flask equipped with two addition funnels and a reflux condenser was charged with triethylamine (9.30 mL, 66.7 mmol) and 30 mL of dimethylformamide. After immersing the flask in an 80 °C oil bath, solutions of methyl vinyl ketone (5.00 mL, 60.1 mmol) and chlorotrimethylsilane (8.50 mL, 67.0 mmol), each in 4 mL of dimethylformamide, were added simultaneously to the flask over 15 minutes via the addition funnels. Once the reagents were added, the reaction was stirred for 14 hours. The resulting dark red mixture was then cooled, filtered and poured into a separatory funnel containing 200 mL of a 5% aqueous sodium bicarbonate solution. The aqueous phase was extracted three times with petroleum ether and the combined organic layers were washed with water and dried over magnesium sulfate. The volatiles were

removed by fractional distillation leaving diene **4.10** along with trace amounts of dimethylformamide and triethylamine.

Step 2: (Procedure adapted from Rigby, J. H.; Kotnis, A.; Kramer, J. *J. Org. Chem.* **1990**, *55*, 5078.) Unpurified **4.10** (8.55 g, 60.1 mmol maximum) was dissolved in 75 mL of toluene along with methacrolein (17.1 mL, 288 mmol) and a few crystals of hydroquinone. The reaction was heated to reflux for 48 hours, cooled to ambient temperature and concentrated. The crude material was purified by silica gel flash chromatography (4% ethyl acetate/hexanes, basified with triethylamine) to yield 1.65 g of **4.11** (13%) as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Rigby, J. H.; Kotnis, A.; Kramer, J. *J. Org. Chem.* **1990**, *55*, 5078.



3-Isopropylidene-1-methyl-4-oxo-cyclohexanecarbaldehyde (**4.12**):

A stirring solution of 2,2-dimethoxypropane (0.030 mL, 0.24 mmol) and titanium tetrachloride (0.21 mL of a 1.0 M solution in dichloromethane, 0.21 mmol) in 2 mL of dichloromethane was cooled to -78°C . A solution of **4.11** (45 mg, 0.21 mmol) in 0.5 mL of dichloromethane was added by cannula and the reaction was warmed to ambient temperature gradually over 4.5 hours before slowly quenching with water. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude material was then dissolved in 1 mL of dichloromethane. Activated 4 Å molecular sieves (50 mg) were added followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.060 mL, 0.40 mmol) and the resulting suspension was brought to reflux for 8 hours. After cooling to ambient temperature, the reaction was quenched with a 1:1 mixture of a saturated aqueous solution of ammonium chloride and a 10% aqueous hydrochloric acid solution. The aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 15 mg of **4.12** as a colourless oil (39%).

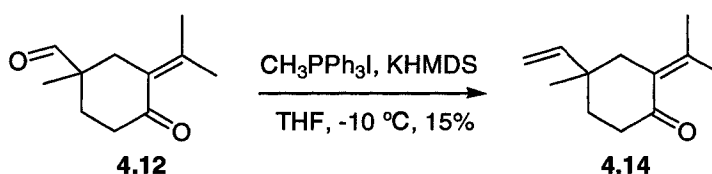
Data for 4.12:

^1H NMR (CDCl_3 , 300 MHz, δ): 9.52 (s, 1H), 2.82 (d, $J_{\text{AB}} = 15.1$ Hz, 1H), 2.42-2.37 (m, 2H), 2.29 (d, $J_{\text{AB}} = 15.2$ Hz, 1H), 2.19-2.10 (m, 1H), 1.97 (s, 3H), 1.81 (s, 3H), 1.74-1.64 (m, 1H), 1.14 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 204.70, 203.11, 145.19, 128.84, 46.98, 38.52, 35.73, 30.01, 23.43, 22.58, 21.49.

IR (neat, cm^{-1} , ν): 2958 (s), 2929 (s), 2871 (m), 2704 (w), 1729 (s), 1687 (s), 1619 (w), 1455 (m), 1372 (m), 1324 (w), 1282 (m), 1148 (m), 1106 (m), 1071 (m).

HRMS (EI, m/z): calculated 180.1150 for $[\text{M}]^+$, found 180.1150.

**2-Isopropylidene-4-methyl-4-vinylcyclohexanone (4.14):**

A suspension of methyltriphenylphosphonium iodide (50 mg, 0.12 mmol) in 1 mL of tetrahydrofuran was cooled to $-10\text{ }^\circ\text{C}$. Potassium bis(trimethylsilyl)amide (25 mg, 0.12 mmol) was added in one portion and the resulting yellow suspension was stirred for 30 minutes before cannulating in 4.12 (23 mg, 0.13 mmol) as a solution in 1 mL of tetrahydrofuran. After 5 minutes the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 3.5 mg of a colourless *volatile* oil (15%).

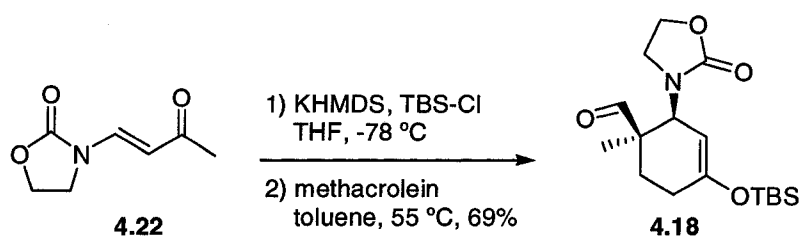
Data for 4.14:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.83 (dd, $J = 17.5, 10.9$ Hz, 1H), 5.01 (dd, $J = 4.4, 0.9$ Hz, 1H), 4.98 (dd, $J = 11.0, 1.0$ Hz, 1H), 2.52 (d, $J = 15.0$ Hz, 1H), 2.44-2.33 (m, 2H), 2.29 (d, $J = 14.8$ Hz, 1H), 1.97 (s, 3H), 1.85-1.79 (m, 1H), 1.77 (s, 3H), 1.74-1.68 (m, 1H), 1.09 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 203.72, 145.98, 142.73, 130.31, 111.89, 40.60, 38.53, 37.01, 35.20, 26.35, 22.85, 21.91.

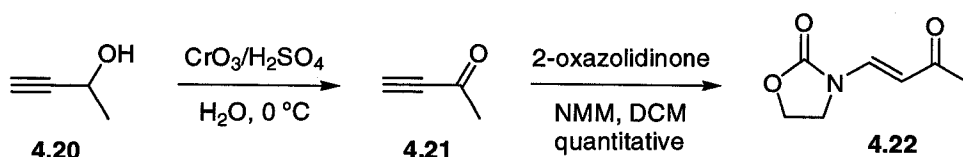
IR (neat, cm^{-1} , ν): 3084 (w), 2956 (s), 2925 (s), 2857 (m), 1686 (s), 1638 (m), 1619 (m), 1452 (m), 1417 (m), 1372 (m), 1280 (m), 1142 (m), 1000 (w).

HRMS (EI, m/z): calculated 178.1358 for $[\text{M}]^+$, found 178.1349.



(±)-(1R,2S)-4-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-2-(2-oxo-oxazolidin-3-yl)-cyclohex-3-enecarbaldehyde (4.18):

A solution of potassium bis(trimethylsilyl)amide (8.10 g, 38.6 mmol) in 90 mL of tetrahydrofuran was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of **4.22** (5.70 g, 36.7 mmol) in another 90 mL of tetrahydrofuran was added drop-wise. Following the addition, the reaction was warmed to $-45\text{ }^{\circ}\text{C}$ over a period of 2.5 hours and then re-cooled to $-78\text{ }^{\circ}\text{C}$ before a solution of *tert*-butyl(chloro)dimethylsilane (6.12 g, 40.6 mmol) in 30 mL of tetrahydrofuran was added. The reaction was then warmed to ambient temperature and the blood-red mixture was diluted with diethyl ether and filtered over celite. The filtrate was concentrated and the crude material was dissolved in 35 mL of toluene. Methacrolein (10.0 mL, 120 mmol) was added and the reaction was heated to $55\text{ }^{\circ}\text{C}$ for 20 hours. After cooling to ambient temperature the reaction was concentrated to a medium orange solid. Purification by trituration in hexanes provided 8.59 g of **4.18** as a pale yellow solid (69%, 2 steps). Spectral data for this compound was in agreement with that reported previously: Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, 65, 9059.

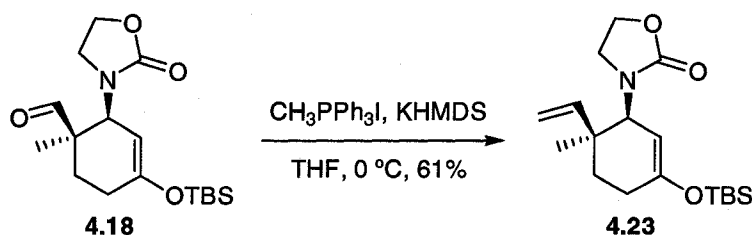


3-((E)-3-Oxo-but-1-enyl)-oxazolidin-2-one (4.22):

Step 1: A solution of **4.20** (1.25 mL, 15.9 mmol) in 10.8 mL of concentrated sulfuric acid and 36 mL of water was cooled to $0\text{ }^{\circ}\text{C}$. Over a period of 30 minutes, a solution of chromium

(vi) oxide (2.00 g, 20.0 mmol) in 7.2 mL of concentrated sulfuric acid and 36 mL of water was added portion-wise. The reaction was stirred for 4 hours, keeping the temperature between 2-10 °C. After diluting with dichloromethane, the aqueous phase was extracted three times and the combined organic layers were washed twice with a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate and filtered *but not concentrated*.

Step 2: To a solution of 2-oxazolidinone (520 mg, 6.00 mmol) in 40 mL of dichloromethane was added 4-methylmorpholine (1.32 mL, 12.0 mmol) followed by the solution of unpurified, unconcentrated **4.21** (1.08 g, 15.9 mmol maximum). The reaction was stirred for 14 hours. The resulting deep red mixture was concentrated and purified by silica gel flash chromatography (5% methanol/ethyl acetate) to give 950 mg of **4.22** as a pale yellow solid (100% with respect to the oxazolidinone). Spectral data for this compound was in agreement with that reported previously: Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059.



(±)-3-[(1S,6S)-3-(*tert*-Butyl-dimethyl-silyloxy)-6-methyl-6-vinyl-cyclohex-2-enyl]-oxazolidin-2-one (4.23**):**

A suspension of methyltriphenylphosphonium iodide (360 mg, 0.891 mmol) in 5 mL of tetrahydrofuran was cooled to 0 °C. Potassium bis(trimethylsilyl)amide (177 mg, 0.887 mmol) was added in one portion and the resulting yellow suspension was stirred for 30 minutes before adding, by cannula, **4.18** (200 mg, 0.589 mmol) as a solution in 3 mL of tetrahydrofuran. After 15 minutes, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% → 30% ethyl acetate/hexanes) yielded 121 mg of a colourless oil (61%).

Data for **4.23**:

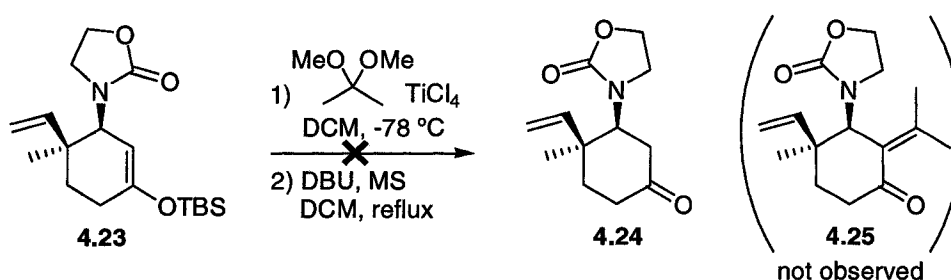
^1H NMR (acetone- d_6 , 300 MHz, δ): 6.05 (dd, $J = 17.6$ 10.9 Hz, 1H), 5.06 (dd, $J = 17.6$, 1.4 Hz, 1H), 5.00 (dd, $J = 10.9$, 1.4 Hz, 1H), 4.71 (dddd, $J = 4.6$, 1.3, 1.3, 1.3 Hz, 1H), 4.20–4.13 (m, 3H), 3.56–3.48 (m, 2H), 2.16–2.11 (m, 2H), 1.78–1.62 (m, 2H), 1.06 (s, 3H), 0.94 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (acetone- d_6 , 75 MHz, δ): 158.46, 154.61, 144.64, 111.87, 101.33, 62.06, 56.83, 42.51, 39.60, 30.16, 26.99, 25.52 (3C), 24.15, 18.06, -4.74 (2C).

IR (neat, cm^{-1} , ν): 2953 (s), 2855 (s), 1735 (s), 1664 (m), 1474 (w), 1418 (m), 1369 (w), 1248 (m), 1226 (m), 1185 (w), 1071 (w), 1033 (w).

HRMS (EI, m/z): calculated 337.2073 for $[\text{M}]^+$, found 337.2076.

mp = 116.3–118.9 °C.



(±)-3-((1S,2S)-2-Methyl-5-oxo-2-vinyl-cyclohexyl)-oxazolidin-2-one (4.24**):**

(Procedure adapted from: Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770.) A solution of 2,2-dimethoxypropane (0.010 mL, 0.081 mmol) and titanium tetrachloride (0.080 mL of a 1.0 M solution in dichloromethane, 0.080 mmol) in 1 mL of dichloromethane was cooled to $-78\text{ }^\circ\text{C}$. Silyl enol ether **4.23** (26.5 mg, 0.0785 mmol) was added by cannula as a solution in 1 mL of dichloromethane. The reaction was warmed to ambient temperature over a period of 4.5 hours before slowly quenching with water. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude material was dissolved in 6 mL of dichloromethane. Activated $4\text{ \AA}$ molecular sieves (20 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.030 mL, 0.20 mmol) were added in succession and the resulting suspension was heated to reflux for 14 hours. After cooling to ambient temperature, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate,

filtered and concentrated. A ^1H NMR of the crude material revealed that ketone **4.24** was the sole product rather than the desired enone, **4.25**.

Data for 4.24:

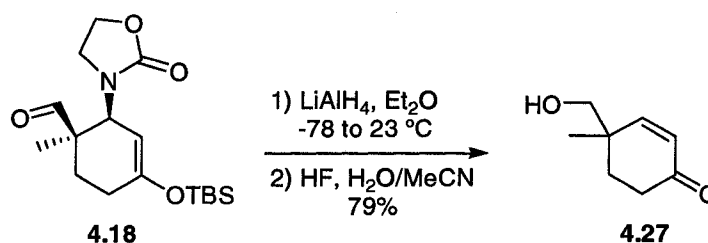
^1H NMR (CDCl_3 , 300 MHz, δ): 6.32 (dd, $J = 17.6, 10.8$ Hz, 1H), 5.26 (dd, $J = 17.4, 0.9$ Hz, 1H), 5.25 (d, $J = 12.4$ Hz, 1H), 4.28-4.19 (m, 2H), 4.03 (dd, $J = 12.1, 4.9$ Hz, 1H), 3.73-3.62 (m, 1H), 3.42 (dd, $J = 8.8, 8.5$ Hz, 1H), 2.71 (dd, $J = 14.1, 12.6$ Hz, 1H), 2.55-2.32 (m, 3H), 1.89-1.68 (m, 2H), 1.23 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 207.75, 158.32, 139.38, 116.09, 61.91, 58.68, 41.97, 41.55, 40.73, 37.47, 35.57, 24.18.

IR (neat, cm^{-1} , ν): 2960 (m), 2916 (s), 2852 (m), 1737 (s), 1719 (s), 1644 (w), 1480 (m), 1427 (m), 1274 (m), 1212 (m), 1112 (w), 1054 (m).

HRMS (EI, m/z): calculated 223.1208 for $[\text{M}]^+$, found 223.1207.

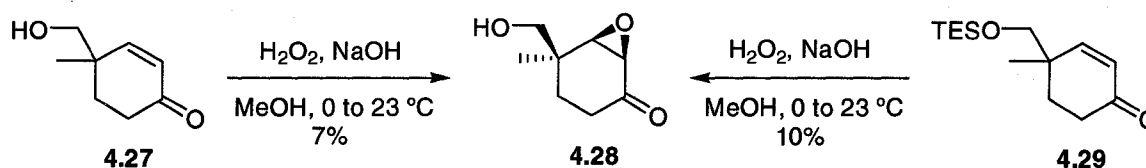
mp = 136.0-137.4 $^\circ\text{C}$.



4-Hydroxymethyl-4-methyl-cyclohex-2-enone (4.27):

(Procedure adapted from Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059.) A suspension of lithium aluminum hydride (331 mg, 8.72 mmol) in 25 mL of diethyl ether was cooled to -78°C . Silyl enol ether **4.18** (298 mg, 0.878 mmol) in 5 mL of diethyl ether was added drop-wise over a period of 30 minutes. The cold bath was removed and the reaction was warmed to ambient temperature. After stirring for 4 days, the reaction was re-cooled to 0°C , diluted with 30 mL of diethyl ether and quenched slowly with several drops of water (until the evolution of H_2 ceased). Solid sodium sulfate (~ 15 g) was added and the diethyl ether layer was decanted from the remaining solid, rinsing several times with additional diethyl ether. The combined organic layers were then dried over magnesium sulfate, filtered and concentrated. The crude material was dissolved in 1.5 mL of acetonitrile and transferred to a small plastic beaker equipped with a stir-bar. Using a

calibrated plastic pipette, an 8.3% solution of HF in acetonitrile (prepared from 49% aqueous HF) was added (0.77 mL, 2.5 mmol). After stirring for 2.5 hours, the reaction mixture was purified directly by silica gel flash chromatography (70% ethyl acetate/hexanes) to give 96 mg (79%) of **4.27** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165.



(±)-(1R,5S,6R)-5-Hydroxymethyl-5-methyl-7-oxa-bicyclo[4.1.0]heptan-2-one (4.28):

Method A: A stirring solution of **4.27** (15 mg, 0.11 mmol) in 1 mL of methanol was cooled to 0 °C. Sodium hydroxide (0.02 mL of a 3 M solution in water, 0.06 mmol) was added followed by hydrogen peroxide (0.04 mL of a 30% wt. solution in water). After warming to ambient temperature and stirring for 18 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (60% ethyl acetate/hexanes) yielded 1.2 mg of a colourless oil (7%).

Method B: A stirring solution of **4.29** (15 mg, 0.059 mmol) in 0.5 mL of methanol was cooled to 0 °C. Sodium hydroxide (0.02 mL of a 3 M solution in water, 0.06 mmol) was added followed by hydrogen peroxide (0.04 mL of a 30% wt. solution in water). After warming to ambient temperature and stirring for 18 hours the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (60% ethyl acetate/hexanes) yielded 0.9 mg of a colourless oil (10%).

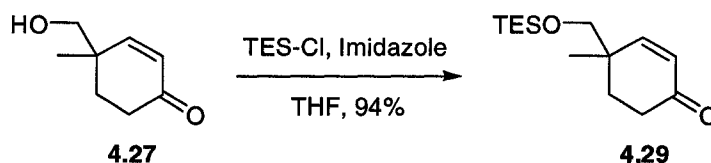
Data for 4.28:

¹H NMR (CDCl₃, 500 MHz, δ): 3.68 (d, *J* = 10.6 Hz, 1H), 3.59 (d, *J* = 10.6 Hz, 1H), 3.39 (dd, *J* = 4.0, 1.0 Hz, 1H), 3.25 (d, *J* = 4.0 Hz, 1H), 2.47 (ddd, *J* = 18.8, 6.4, 3.6 Hz, 1H), 2.22 (ddd, *J* = 18.8, 11.3, 7.1 Hz, 1H), 1.94 (ddd, *J* = 13.4, 11.4, 6.7 Hz, 1H), 1.35-1.30 (m, 1H), 1.19 (s, 1H), 1.07 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 205.62, 69.65, 60.93, 54.62, 35.62, 32.42, 25.24, 18.05.

IR (neat, cm^{-1} , ν): 3409 (s, br), 2933 (s), 2877 (s), 1711 (s), 1467 (w), 1413 (w), 1334 (w), 1251 (w), 1057 (m), 1017 (w).

HRMS (EI, m/z): calculated 156.0786 for $[\text{M}]^+$, found 156.0797.



4-Methyl-4-triethylsilyloxymethyl-cyclohex-2-enone (4.29):

To a stirring solution of **4.27** (27 mg, 0.19 mmol) in 2 mL of tetrahydrofuran was added 27 mg of imidazole (0.40 mmol) followed by chlorotriethylsilane (0.040 mL, 0.24 mmol). The resulting milky white reaction was stirred for 5 minutes and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 46 mg (94%) of a colourless oil.

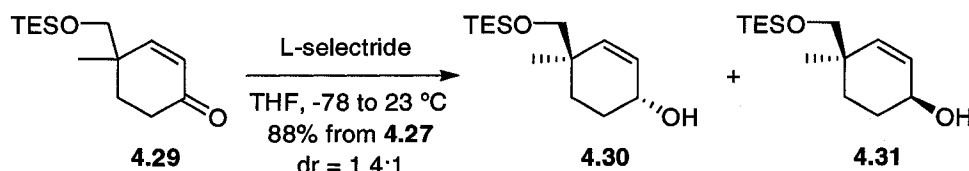
Data for **4.29**:

^1H NMR (CDCl_3 , 500 MHz, δ): 6.70 (d, $J = 10.2$ Hz, 1H), 5.91 (d, $J = 10.2$ Hz, 1H), 3.46 (d, $J_{\text{AB}} = 9.6$ Hz, 1H), 3.42 (d, $J_{\text{AB}} = 9.6$ Hz, 1H), 2.50-2.39 (m, 2H), 2.01 (ddd, $J = 13.6, 8.8, 6.5$ Hz, 1H), 1.71-1.66 (m, 1H), 1.09 (s, 3H), 0.92 (t, $J = 8.0$ Hz, 9H), 0.56 (q, $J = 7.9$ Hz, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 199.83, 156.55, 128.53, 69.78, 38.30, 34.03, 31.05, 22.10, 6.72 (3C), 4.28 (3C).

IR (neat, cm^{-1} , ν): 2956 (s), 2908 (m), 2877 (s), 1686 (s), 1459 (w), 1417 (w), 1238 (m), 1095 (s), 1009 (m).

HRMS (EI, m/z): calculated 225.1311 for $[\text{M-Et}]^+$, found 225.1293.



(±)-(1R,4R)-4-Methyl-4-triethylsilanyloxymethyl-cyclohex-2-enol (4.30) and (±)-(1S,4R)-4-Methyl-4-triethylsilanyloxymethyl-cyclohex-2-enol (4.31):

Unpurified **4.29** (296 mg, 1.16 mmol maximum) was dissolved in 11 mL of tetrahydrofuran and cooled to -78 °C. L-selectride (1.2 mL of a 1.0 M solution in tetrahydrofuran, 1.2 mmol) was slowly added and the reaction was warmed gradually to ambient temperature over 1.5 hours. The reaction was quenched with the addition of 0.5 mL of acetone followed by equal portions of a 1 M aqueous sodium hydroxide solution and a 1 M aqueous sodium tartrate solution. Ethyl acetate was added and the reaction was stirred vigorously until two distinct phases were present (approximately one hour). Extraction of the aqueous phase three times with ethyl acetate was followed by drying of the combined organic phases over magnesium sulfate, filtering and concentrating. Injection of the crude material into a GC showed a 1.4:1 mixture of isomers. Purification by silica gel flash chromatography (5% → 10% ethyl acetate/hexanes) yielded 164 mg (55%) of **4.30** and 101 mg (33%) of **4.31**, both as clear, colourless oils.

Data for **4.30** (major isomer):

¹H NMR (CDCl₃, 300 MHz, δ): 5.64 (dd, *J* = 10.1, 2.6 Hz, 1H), 5.48 (d, *J* = 10.1 Hz, 1H), 4.10 (s, br, 1H), 3.27 (d, *J*_{AB} = 9.4 Hz, 1H), 3.22 (d, *J*_{AB} = 9.4 Hz, 1H), 2.05 (s, 1H), 1.92-1.77 (m, 1H), 1.60-1.48 (m, 2H), 1.43-1.34 (m, 1H), 0.95 (s, 3H), 0.90 (t, *J* = 7.9 Hz, 9H), 0.52 (q, *J* = 7.9 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 136.40, 129.92, 70.52, 66.35, 37.31, 28.76, 28.60, 23.68, 6.72 (3C), 4.31 (3C).

IR (neat, cm⁻¹, ν): 3333 (s, br), 3017 (w), 2954 (s), 2877 (s), 2732 (w), 1651 (w), 1459 (s), 1414 (s), 1395 (m), 1239 (s), 1146 (m), 1095 (s), 1005 (s).

HRMS (EI, *m/z*): calculated 227.1467 for [M-Et]⁺, found 227.1415.

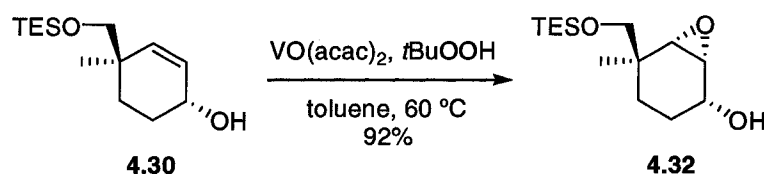
Data for **4.31** (minor isomer):

¹H NMR (CDCl₃, 300 MHz, δ): 5.71 (dd, *J* = 10.1, 3.5 Hz, 1H), 5.50 (d, *J* = 10.1 Hz, 1H), 4.09-4.07 (m, 1H), 3.35 (d, *J*_{AB} = 9.4 Hz, 1H), 3.25 (d, *J*_{AB} = 9.4 Hz, 1H), 1.85-1.71 (m, 3H), 1.64-1.56 (m, 1H), 1.25-1.18 (m, 1H), 0.91 (t, *J* = 8.1 Hz, 9H), 0.90 (s, 3H), 0.54 (q, *J* = 8.0 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 136.88, 129.48, 69.98, 65.50, 37.14, 28.52, 27.63, 23.66, 6.75 (3C), 4.31 (3C).

IR (neat, cm^{-1} , ν): 3340 (s, br), 3022 (w), 2954 (s), 2877 (s), 1458 (m), 1417 (w), 1239 (m), 1093 (s), 1017 (m).

HRMS (EI, m/z): calculated 238.1753 for $[\text{M}-\text{H}_2\text{O}]^+$, found 238.1756.



(±)-(1R,2R,5S,6S)-5-Methyl-5-triethylsilanyloxymethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (4.32):

To a stirring solution of **4.30** (177 mg, 0.690 mmol) in 7 mL of toluene was added vanadyl acetylacetonate (9.0 mg, 0.035 mmol) followed by *tert*-butylhydroperoxide (0.17 mL of a 6.0 M solution in pentane, 1.0 mmol). The reaction rapidly changed colour from pale green to dark red. After heating to 60 °C in an oil bath for 1 hour, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) yielded 173 mg (92%) of a colourless oil.

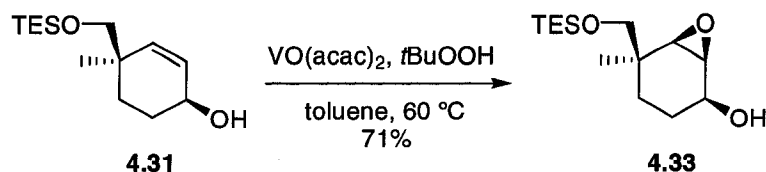
Data for 4.32:

^1H NMR (CDCl_3 , 500 MHz, δ): 3.91 (dd, $J = 6.5, 5.7$ Hz, 1H), 3.39 (d, $J = 9.7$ Hz, 1H), 3.33 (d, $J = 9.6$ Hz, 1H), 3.29 (d, $J = 1.0$ Hz, 1H), 3.10 (d, $J = 2.8$ Hz, 1H), 1.97 (s, br, 1H), 1.62–1.58 (m, 1H), 1.43 (dddd, $J = 12.6, 2.7, 2.7, 2.7$ Hz, 1H), 1.34 (ddd, $J = 13.2, 2.4, 2.4$ Hz, 1H), 1.11–1.08 (m, 1H), 0.98 (s, 3H), 0.92 (t, $J = 8.0$ Hz, 1H), 0.55 (q, $J = 8.0$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 69.87, 68.54, 61.59, 56.87, 34.25, 29.57, 25.25, 19.83, 6.73 (3C), 4.31 (3C).

IR (neat, cm^{-1} , ν): 3397 (m, br), 2955 (s), 1459 (m), 1415 (w), 1364 (w), 1239 (m), 1099 (s), 1062 (s), 1004 (m).

HRMS (EI, m/z): calculated 272.1808 for $[\text{M}]^+$, found 272.1832.



(±)-(1S,2S,5S,6R)-5-Methyl-5-triethylsilanyloxymethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (4.33):

To a stirring solution of **4.31** (524 mg, 2.04 mmol) in 20 mL of toluene was added vanadyl acetylacetonate (26 mg, 0.10 mmol) followed by *tert*-butylhydroperoxide (0.51 mL of a 6.0 M solution in pentane, 3.1 mmol). The reaction rapidly changed colour from pale green to dark red. After heating to 60 °C in an oil bath for 1 hour, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 30% ethyl acetate/hexanes) yielded 397 mg (71%) of a colourless oil.

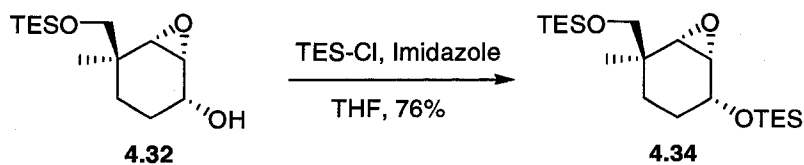
Data for 4.33:

¹H NMR (CDCl₃, 300 MHz, δ): 4.02-3.98 (m, 1H), 3.57 (d, *J* = 9.4 Hz, 1H), 3.33 (d, *J* = 9.3 Hz, 1H), 3.32 (d, *J* = 4.2 Hz, 1H), 3.04 (d, *J* = 4.0 Hz, 1H), 2.04 (d, *J* = 9.7 Hz, 1H), 1.70 (s, 1H), 1.58-1.23 (m, 3H), 1.01 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.58 (d, *J* = 7.8 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 67.93, 66.53, 60.75, 55.45, 34.39, 26.73, 25.87, 21.38, 6.76 (3C), 4.30 (3C).

IR (neat, cm^{-1} , v): 3382 (b, m), 2954 (s), 2916 (s), 2876 (s), 1457 (m), 1416 (w), 1240 (m), 1105 (s), 1089 (s), 1015 (m).

HRMS (EI, m/z): calculated 243.1416 for $[M-Et]^+$, found 243.1400.



(±)-(1S,2S,5R,6S)-2-Methyl-5-triethylsilanyloxy-2-triethylsilanyloxymethyl-7-oxabicyclo[4.1.0]heptane (4.34):

To a solution of **4.32** (188 mg, 0.690 mmol) in 7 mL of tetrahydrofuran was added imidazole (70 mg, 1.0 mmol) followed by chlorotriethylsilane (0.120 mL, 0.715 mmol). After stirring

for 10 minutes, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% → 10% ethyl acetate/hexanes) yielded 202 mg (76%) of **4.34** as a colourless oil.

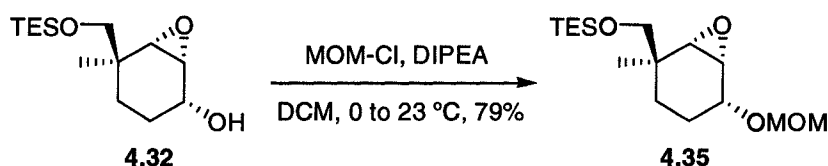
Data for 4.34:

¹H NMR (CDCl₃, 300 MHz, δ): 3.93 (ddd, *J* = 10.2, 5.1, 1.4 Hz, 1H), 3.38 (d, *J*_{AB} = 9.6 Hz, 1H), 3.29 (d, *J*_{AB} = 9.6 Hz, 1H), 3.14 (d, *J* = 3.8 Hz, 1H), 3.02 (dd, *J* = 4.0, 1.5 Hz, 1H), 1.59-1.30 (m, 3H), 1.09-1.02 (m, 1H), 0.98 (s, 3H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.93 (t, *J* = 7.7 Hz, 9H), 0.61 (q, *J* = 7.9 Hz, 6H), 0.56 (q, *J* = 7.9 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 70.37, 70.20, 60.78, 57.34, 34.18, 30.61, 24.94, 19.58, 6.81 (3C), 6.77 (3C), 4.85 (3C), 4.34 (3C).

IR (neat, cm^{-1} , ν): 2961 (s), 2919 (m), 2877 (s), 1458 (s), 1412 (m), 1233 (s), 1099 (s), 1007 (s).

HRMS (EI, m/z): calculated 357.2281 for $[M-Et]^+$, found 357.2291.



(±)-Triethyl-((1S,2S,5R,6R)-5-methoxymethoxy-2-methyl-7-oxa-bicyclo[4.1.0]hept-2-ylmethoxy)-silane (4.35):

A solution of **4.32** (50 mg, 0.18 mmol) in 2 mL of dichloromethane was cooled to 0 °C. N,N,N-Diisopropylethyl amine (0.080 mL, 0.46 mmol) was added, followed by chloromethyl methyl ether (0.030 mL, 0.40 mmol). The reaction was warmed gradually to ambient temperature, stirred for 20 hours and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with dichloromethane and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (10% ethyl acetate/hexanes) to yield 46 mg of a colourless oil (79%).

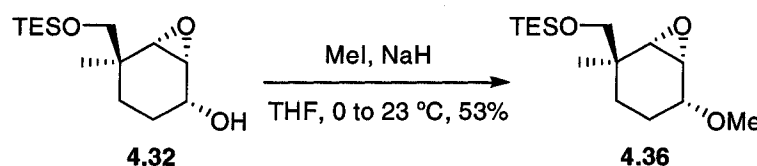
Data for 4.35:

¹H NMR (acetone-d₆, 300 MHz, δ): 4.69 (s, 2H), 3.88-3.83 (m, 1H), 3.48 (d, J_{AB} = 9.6 Hz, 1H), 3.41 (d, J_{AB} = 9.9 Hz, 1H), 3.32 (s, 3H), 3.24 (d, J = 4.2 Hz, 1H), 2.98 (dd, J = 3.9, 1.2 Hz, 1H), 1.57-1.34 (m, 3H), 1.15-1.10 (m, 1H), 0.98 (s, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.5 Hz, 6H).

¹³C NMR (acetone-d₆, 75 MHz, δ): 95.43, 75.13, 70.38, 59.76, 55.25, 54.66, 34.46, 30.59, 22.26, 19.52, 6.61 (3C), 4.40 (3C).

IR (neat, cm^{-1} , v): 2954 (s), 2916 (m), 2878 (s), 1459 (m), 1232 (m) 1148 (m), 1104 (s), 1051 (s).

HRMS (EI, m/z): calculated 255.1780 for $[M-OCH_2OCH_3]^+$, found 255.1742.



(±)-Triethyl-((1S,2S,5R,6R)-5-methoxy-2-methyl-7-oxa-bicyclo[4.1.0]hept-2-ylmethoxy)-silane (4.36):

A solution of **4.32** (50 mg, 0.18 mmol) in 3 mL of tetrahydrofuran was cooled to 0 °C. Sodium hydride (15 mg of a 60% dispersion in mineral oil, 0.38 mmol) was added, followed by iodomethane (0.050 mL, 0.80 mmol). After warming to ambient temperature and stirring for 5 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 28 mg of a colourless oil (53%).

Data for 4.36:

¹H NMR (CDCl₃, 300 MHz, δ): 3.58-3.51 (m, 1H), 3.42 (s, 3H), 3.39 (d, *J*_{AB} = 9.6 Hz, 1H), 3.32-3.30 (m, 1H), 3.31 (d, *J*_{AB} = 9.6 Hz, 1H), 3.05 (dd, *J* = 4.1, 1.6 Hz, 1H), 1.66-1.42 (m, 2H), 1.34 (ddd, *J* = 13.3, 12.8, 2.7 Hz, 1H), 1.15-1.08 (m, 1H), 0.98 (s, 3H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.56 (q, *J* = 8.1 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 77.85, 70.19, 60.22, 56.14, 54.20, 34.46, 29.96, 20.95, 19.68, 6.78 (3C), 4.33 (3C).

HRMS (EI, m/z): calculated 257.1573 for $[M-Et]^+$, found 257.1578.



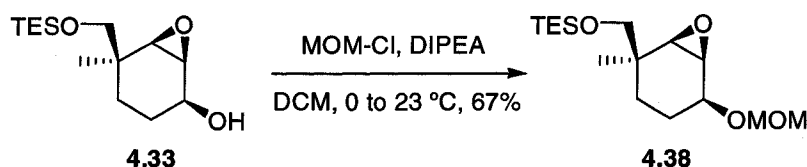
To a stirring solution of **4.33** (137 mg, 0.503 mmol) in 5 mL of tetrahydrofuran was added imidazole (51 mg, 0.75 mmol) followed by chlorotriethylsilane (0.090 mL, 0.54 mmol). After 10 minutes, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (2% → 10% ethyl acetate/hexanes) yielded 140 mg (72%) of **4.37** as a colourless oil.

¹H NMR (CDCl₃, 300 MHz, δ): 3.96 (ddd, *J* = 9.3, 5.4, 1.7 Hz, 1H), 3.58 (d, *J*_{AB} = 9.4 Hz, 1H), 3.37 (*J*_{AB} = 9.4 Hz, 1H), 3.13 (dd, *J* = 3.9, 0.8 Hz, 1H), 2.87 (dd, *J* = 4.0, 1.4 Hz, 1H), 1.53-1.31 (m, 3H), 0.99 (s, 3H), 0.94 (t, *J* = 7.7 Hz, 9H), 0.92-0.85 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 9H), 0.60 (q, *J* = 7.7 Hz, 6H), 0.55 (q, *J* = 7.8 Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 69.82, 66.44, 60.14, 56.20, 33.62, 29.74, 25.44, 23.65, 6.75 (3C), 6.72 (3C), 4.77 (3C), 4.28 (3C).

IR (neat, cm⁻¹, v): 2955 (s), 2910 (s), 2877 (s), 1458 (s), 1415 (m), 1364 (w), 1239 (s), 1095 (s), 1005 (s).

HRMS (EI, m/z): calculated 357.2281 for $[M-Et]^+$, found 357.2274.



gel flash chromatography (10% ethyl acetate/hexanes) yielded 23 mg of a colourless oil (55%).

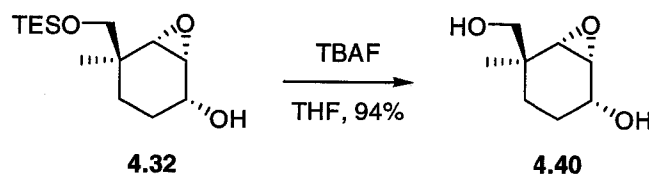
Data for 4.39:

^1H NMR (CDCl_3 , 300 MHz, δ): 3.63-3.59 (m, 1H), 3.60 (d, $J = 9.6$ Hz, 1H), 3.42 (s, 3H), 3.35 (d, $J = 9.3$ Hz, 1H), 3.32 (dd, $J = 4.2, 2.4$ Hz, 1H), 2.94 (d, $J = 3.9$ Hz, 1H), 1.54-1.42 (m, 3H), 1.01 (s, 3H), 0.98-0.83 (m, 1H), 0.93 (t, $J = 7.8$ Hz, 9H), 0.57 (q, $J = 8.1$ Hz, 6H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 76.90, 67.61, 59.76, 56.62, 53.35, 34.69, 28.73, 22.94, 22.16, 7.18 (3C), 4.73 (3C).

IR (neat, cm^{-1} , ν): 2954 (s), 2197 (s), 2876 (s), 2813 (m), 1461 (s), 1416 (m), 1239 (m), 1196 (w), 1169 (w), 1090 (s), 1004 (s).

HRMS (EI, m/z): calculated 257.1573 for $[\text{M-Et}]^+$, found 257.1591.



(±)-(1R,2R,5S,6S)-5-Hydroxymethyl-5-methyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (4.40):

To a solution of **4.32** (73 mg, 0.19 mmol) in 3 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.57 mL of a 1.0 M solution in tetrahydrofuran, 0.57 mmol). After 1 hour at ambient temperature, silica gel was added and the reaction was concentrated. Direct purification by silica gel flash chromatography (80% ethyl acetate/hexanes $\rightarrow$ 10% methanol/ethyl acetate) yielded 28 mg of a colourless oil (94%).

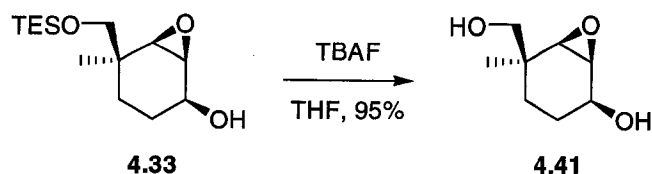
Data for 4.40:

^1H NMR (CDCl_3 , 300 MHz, δ): 3.98-3.93 (m, 1H), 3.48 (d, $J = 10.7$ Hz, 1H), 3.40 (d, $J = 10.7$ Hz, 1H), 3.33-3.32 (m, 1H), 3.14-3.12 (m, 1H), 2.01 (s, 1H), 1.99 (s, 1H), 1.67-1.58 (m, 1H), 1.51-1.39 (m, 1H), 1.31 (ddd, $J = 13.2, 13.2, 2.7$ Hz, 1H), 1.25-1.12 (m, 1H), 1.02 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 70.33, 68.76, 61.51, 57.24, 34.43, 29.90, 25.50, 20.03.

IR (neat, cm^{-1} , ν): 3320 (s, br), 3022 (w), 2933 (s), 2867 (s), 1650 (w), 1454 (m), 1371 (w), 1281 (w), 1042 (s).

HRMS (EI, m/z): calculated 140.0837 for $[\text{M-H}_2\text{O}]^+$, found 140.0826.



(±)-(1S,2S,5S,6R)-5-Hydroxymethyl-5-methyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (4.41):

To a solution of **4.33** (93 mg, 0.24 mmol) in 4 mL of tetrahydrofuran was added tetrabutylammonium fluoride (0.72 mL of a 1.0 M solution in tetrahydrofuran, 0.72 mmol). After 1 hour at ambient temperature, silica gel was added and the reaction was concentrated. Direct purification by silica gel flash chromatography (80% → 90% ethyl acetate/hexanes) yielded 36 mg of a colourless oil (95%).

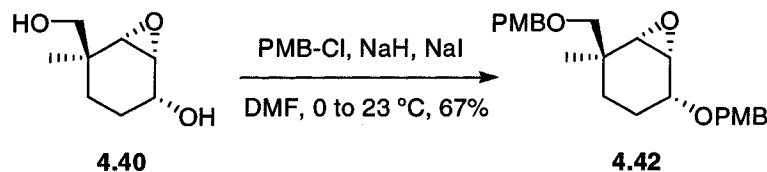
Data for 4.41:

¹H NMR (CDCl₃, 300 MHz, δ): 4.00-3.96 (m, 1H), 3.62 (d, *J* = 10.7 Hz, 1H), 3.39 (d, *J* = 10.8 Hz, 1H), 3.37-3.35 (m, 1H), 3.05 (d, *J* = 3.7 Hz, 1H), 2.59 (s, br, 2H), 1.57-1.39 (m, 3H), 1.04-0.96 (m, 1H), 1.00 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 69.53, 67.47, 61.56, 56.27, 34.09, 28.91, 26.17, 22.53;

IR (neat, cm⁻¹, ν): 3367 (s, br), 3018 (w), 2976 (s), 2935 (s), 2868 (s), 1692 (m), 1464 (m), 1380 (s), 1365 (m), 1154 (w), 1041 (s).

HRMS (EI, *m/z*): calculated 140.0837 for [M-H₂O]⁺, found 140.0830.



(±)-(1S,2S,5R,6R)-5-(4-Methoxy-benzyloxy)-2-(4-methoxy-benzyloxymethyl)-2-methyl-7-oxa-bicyclo[4.1.0]heptane (4.42):

Sodium iodide (2 mg, 0.01 mmol) was flame-dried in a flask allowed to cool. Sodium hydride was added (20 mg of a 60% suspension in mineral oil, 0.50 mmol) followed by 0.75 mL of dimethylformamide, and the suspension was cooled to 0 °C. Diol **4.40** (13 mg, 0.082 mmol) was cannulated into the flask with another 0.75 mL of dimethylformamide. After stirring for 10 minutes, 4-methoxybenzyl chloride (0.070 mL, 0.47 mmol) was added and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was then quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase

was diluted with another 10 mL of water before extracting three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) yielded 22 mg (67%) of the **4.42** as a colourless oil.

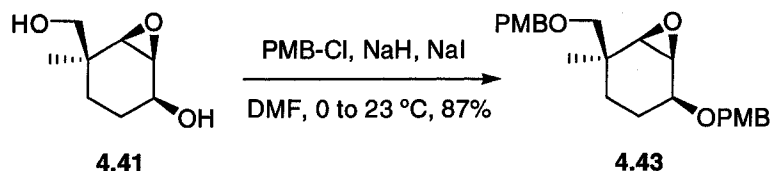
Data for 4.42:

¹H NMR (CDCl₃, 500 MHz, δ): 7.28 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.87-6.84 (m, 4H), 4.60 (d, *J*_{AB} = 11.8 Hz, 1H), 4.56 (d, *J*_{AB} = 11.7 Hz, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76-3.72 (m, 1H), 3.31-3.30 (m, 1H), 3.20 (d, *J*_{AB} = 8.9 Hz, 1H), 3.14 (d, *J*_{AB} = 8.9 Hz, 1H), 3.04 (dd, *J* = 4.1, 1.5 Hz, 1H), 1.61-1.52 (m, 2H), 1.38 (ddd, *J* = 12.8, 12.8, 4.4 Hz, 1H), 1.17-1.14 (m, 1H), 1.02 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 158.98 (2C), 130.59, 130.27, 129.10 (2C), 128.85 (2C), 113.63 (2C), 113.59 (2C), 77.30, 74.90, 72.81, 69.80, 60.16, 55.13, 55.12, 54.57, 33.43, 30.43, 21.33, 19.90.

IR (neat, cm⁻¹, ν): 2945 (s), 2872 (s), 1613 (w), 1516 (m), 1460 (w), 1253 (s), 1173 (m), 1068 (s), 1028 (s).

HRMS (EI, *m/z*): calculated 398.2093 for [M]⁺, found 398.2102.



(±)-(1R,2S,5S,6S)-5-(4-Methoxy-benzyloxy)-2-(4-methoxy-benzyloxymethyl)-2-methyl-7-oxa-bicyclo[4.1.0]heptane (4.43):

Sodium iodide (2 mg, 0.01 mmol) was flame-dried in a flask and allowed to cool. Sodium hydride was added (20 mg of a 60% suspension in mineral oil, 0.50 mmol), followed by 0.75 mL of dimethylformamide, and the suspension was cooled to 0 °C. Diol **4.41** (15 mg, 0.095 mmol) was cannulated into the flask as a solution in 0.75 mL of dimethylformamide. After stirring for 10 minutes, 4-methoxybenzyl chloride (0.070 mL, 0.47 mmol) was added and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was then quenched with a saturated aqueous solution of ammonium chloride, and the aqueous phase was diluted with another 10 mL of water before being extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and

concentrated. Purification by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) yielded 33 mg (87%) of **4.43** as a colourless oil.

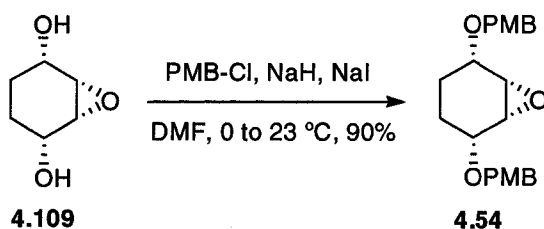
Data for 4.43:

^1H NMR (CDCl_3 , 500 MHz, δ): 7.29-7.23 (m, 4H), 6.87-6.84 (m, 4H), 4.59 (d, $J_{\text{AB}} = 11.8$ Hz, 1H), 4.57 (d, $J_{\text{AB}} = 11.7$ Hz, 1H), 4.51 (d, $J_{\text{AB}} = 11.8$ Hz, 1H), 4.43 (d, $J_{\text{AB}} = 11.8$ Hz, 1H), 3.78 (s, 6H), 3.77-3.73 (m, 1H), 3.46 (d, $J = 8.8$ Hz, 1H), 3.31 (dd, $J = 4.0, 2.1$ Hz, 1H), 3.22 (d, $J = 8.8$ Hz, 1H), 2.98 (d, $J = 3.9$ Hz, 1H), 1.53-1.48 (m, 3H), 1.05 (s, 3H), 0.94-0.89 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 159.02, 158.85, 130.75 (2C), 130.47 (2C), 129.14 (2C), 128.88 (2C), 113.64 (2C), 113.53 (2C), 74.67, 74.02, 72.91, 69.78, 59.52, 55.13, 55.11, 53.65, 33.30, 29.47, 23.22, 21.95.

IR (neat, cm^{-1} , ν): 2938 (s), 2861 (s), 1611 (w), 1512 (s), 1463 (w), 1299 (w), 1250 (s), 1170 (m), 1076 (s), 1028 (s).

HRMS (EI, m/z): calculated 398.2093 for $[\text{M}]^+$, found 398.2098.



(±)-(1R,2R,5S,6S)-2,5-Bis-(4-methoxy-benzyloxy)-7-oxa-bicyclo[4.1.0]heptane (4.54):

Sodium iodide (220 mg, 1.47 mmol) was flame-dried in a flask and allowed to cool. Sodium hydride was added (5.84 g of a 60% suspension in mineral oil, 146 mmol), followed by 250 mL of dimethylformamide, and the suspension was cooled to 0 °C. Diol **4.109** (3.33 g, 29.2 mmol) was cannulated into the flask as a solution in 50 mL of dimethylformamide. After stirring for 5 minutes, 4-methoxybenzyl chloride (16.0 mL, 118 mmol) was added and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was then quenched with a saturated aqueous solution of ammonium chloride, and the aqueous phase was diluted with 1.5 L of water before being extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 9.73 g (90%) of **4.54** as a white solid.

Data for 4.54:

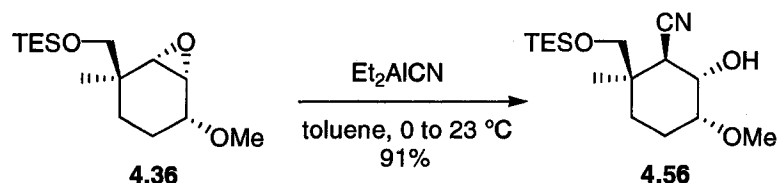
^1H NMR (CDCl_3 , 500 MHz, δ): 7.29 (d, $J = 8.5$ Hz, 4H), 6.86 (d, $J = 8.5$ Hz, 4H), 4.62 (d, $J_{\text{AB}} = 11.7$ Hz, 2H), 4.57 (d, $J_{\text{AB}} = 11.7$ Hz, 2H), 3.78 (s, 6H), 3.74 (dd, $J = 4.9, 4.6$ Hz, 2H), 3.36 (s, 2H), 1.83-1.74 (m, 2H), 1.46-1.41 (m, 2H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 159.09 (2C), 130.45 (2C), 129.25 (4C), 113.70 (4C), 71.72 (2C), 69.80 (2C), 55.19 (2C), 53.68 (2C), 24.23 (2C).

IR (neat, cm^{-1} , ν): 2999 (m), 2940 (m), 2910 (m), 2862 (m), 2839 (m), 1612 (s), 1586 (m), 1513 (s), 1459 (m), 1441 (m), 1378 (w), 1326 (w), 1299 (s), 1247 (s), 1173 (s), 1085 (s), 1034 (s).

HRMS (EI, m/z): calculated 249.1127 for $[\text{M}-\text{CH}_2(\text{PMP})]^+$, found 249.1145.

mp = 72-73 °C.



(±)-(1S,2R,5R,6S)-6-Hydroxy-5-methoxy-2-methyl-2-triethylsilyloxymethyl-cyclohexanecarbonitrile (4.56):

A solution of **4.36** (15 mg, 0.052 mmol) in 0.7 mL of toluene was cooled to 0 °C. Diethylaluminum cyanide (0.050 mL of a 1.0 M solution of in toluene, 0.050 mmol) was added and the reaction was warmed to ambient temperature. After 1 hour, no reaction was observable by TLC so another 0.15 mL of diethylaluminum cyanide (0.15 mmol) was added. After another two hours the reaction was quenched with a saturated aqueous solution of sodium carbonate and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (30% ethyl acetate/hexanes) to yield 15 mg of **4.56** as a colourless oil (91%).

Data for 4.56:

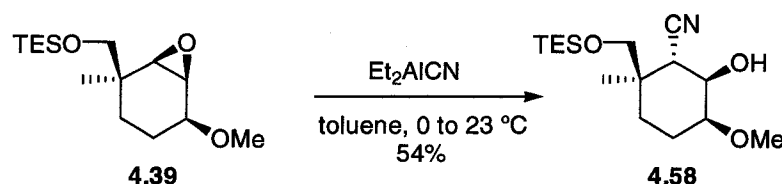
^1H NMR (CDCl_3 , 500 MHz, δ): 4.01 (ddd, $J = 10.2, 10.2, 3.3$ Hz, 1H), 3.70 (d, $J = 10.0$ Hz, 1H), 3.54 (ddd, $J = 3.5, 3.3, 2.5$ Hz, 1H), 3.50 (d, $J = 10.0$ Hz, 1H), 3.34 (s, 3H), 2.69 (d, $J = 10.4$ Hz, 1H), 2.58 (d, $J = 10.1$ Hz, 1H), 1.90 (dddd, $J = 14.7, 3.8, 3.8, 3.8$ Hz, 1H), 1.67-

1.62 (m, 1H), 1.58 (ddd, $J = 13.8, 3.8, 3.8$ Hz, 1H), 1.29 (ddd, $J = 13.7, 13.7, 4.1$ Hz, 1H), 1.04 (s, 3H), 0.93 (t, $J = 7.9$ Hz, 9H), 0.58 (q, $J = 7.9$ Hz, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 119.54, 76.68, 68.62, 66.87, 56.23, 42.54, 38.49, 27.48, 25.41, 22.12, 6.62 (3C), 4.04 (3C).

IR (neat, cm^{-1} , ν): 3448 (s, br), 2956 (s), 2877 (s), 2832 (w), 2241 (w), 1461 (m), 1414 (w), 1363 (w), 1234 (w), 1090 (s), 1016 (m).

HRMS (EI, m/z): calculated 284.1682 for $[\text{M-Et}]^+$, found 284.1692.



(±)-(1R,2R,5S,6R)-6-Hydroxy-5-methoxy-2-methyl-2-triethylsilanyloxymethyl-cyclohexanecarbonitrile (4.58):

A solution of **4.39** (14 mg, 0.049 mmol) in 0.7 mL of toluene was cooled to 0 °C. Diethylaluminum cyanide (0.050 mL of a 1.0 M solution of in toluene, 0.050 mmol) was added and the reaction was warmed to ambient temperature. After 1 hour, no reaction was observable by TLC so another 0.15 mL of diethylaluminum cyanide (0.15 mmol) was added. After another two hours the reaction was quenched with a saturated aqueous solution of sodium carbonate and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (30% ethyl acetate/hexanes) to yield 8.3 mg of **4.58** as a colourless oil (54%).

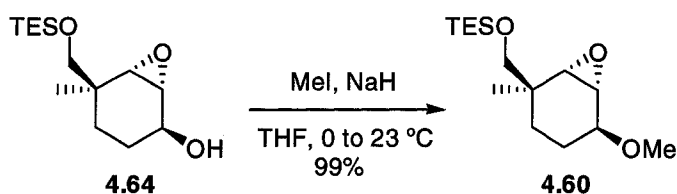
Data for 4.58:

^1H NMR (CDCl_3 , 500 MHz, δ): 3.75 (ddd, $J = 10.9, 10.9, 3.1$ Hz, 1H), 3.53 (ddd, $J = 2.9, 2.9, 2.9$ Hz, 1H), 3.51 (d, $J = 9.9$ Hz, 1H), 3.33 (s, 3H), 3.25 (d, $J = 9.9$ Hz, 1H), 3.02 (d, $J = 11.1$ Hz, 1H), 2.60 (d, $J = 10.6$ Hz, 1H), 2.00 (dddd, $J = 15.0, 3.5, 3.5, 3.5$ Hz, 1H), 1.80 (ddd, $J = 14.1, 14.1, 4.0$ Hz, 1H), 1.44 (dddd, $J = 14.7, 14.7, 4.2, 2.1$ Hz, 1H), 1.00 (ddd, $J = 13.7, 3.7, 3.1$ Hz, 1H), 0.96 (s, 3H), 0.94 (t, $J = 8.0$ Hz, 9H), 0.58 (q, $J = 7.8$ Hz, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 120.43, 76.92, 70.08, 69.55, 56.61, 39.73, 38.78, 25.94, 21.98, 17.33, 7.10 (3C), 4.68 (3C).

IR (neat, cm^{-1} , ν): 3456 (m, br), 2954 (s), 2923 (s), 2877 (s), 2832 (m), 2239 (w), 1459 (m), 1367 (w), 1225 (m), 1191 (w), 1137 (s), 1098 (s), 1016 (m).

HRMS (EI, m/z): calculated 284.1682 for $[\text{M-Et}]^+$, found 284.1695.



(±)-Triethyl-((1S,2S,5S,6R)-5-methoxy-2-methyl-7-oxa-bicyclo[4.1.0]hept-2-ylmethoxy)-silane (4.60):

A solution of **4.64** (21 mg, 0.077 mmol) in 1 mL of tetrahydrofuran was cooled to 0 °C. Sodium hydride (6 mg of a 60% dispersion in mineral oil, 0.2 mmol) was added, followed by iodomethane (0.02 mL, 0.3 mmol). After warming to ambient temperature and stirring for 2.5 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 22 mg of **4.60** as a colourless oil (99%).

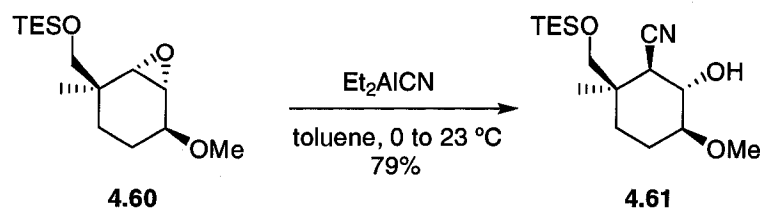
Data for 4.60:

^1H NMR (CDCl_3 , 500 MHz, δ): 3.52-3.50 (m, 1H), 3.47 (d, $J_{\text{AB}} = 9.7$ Hz, 1H), 3.42 (d, $J_{\text{AB}} = 9.7$ Hz, 1H), 3.40 (s, 3H), 3.13 (d, $J = 3.6$ Hz, 1H), 2.98 (d, $J = 3.6$ Hz, 1H), 1.66-1.60 (m, 1H), 1.41-1.30 (m, 2H), 1.02 (s, 3H), 0.94-0.88 (m, 1H), 0.93 (t, $J = 8.0$ Hz, 9H), 0.56 (q, $J = 7.8$ Hz, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 74.69, 68.12, 58.43, 56.85, 54.88, 34.81, 24.75, 22.19, 21.12, 6.62 (3C), 4.18 (3C).

IR (neat, cm^{-1} , ν): 2955 (s), 2926 (s), 2877 (s), 1459 (m), 1414 (w), 1240 (w), 1098 (s), 1010 (m).

HRMS (EI, m/z): calculated 257.1573 for $[\text{M-Et}]^+$, found 257.1516.



(±)-(1S,2R,5S,6S)-6-Hydroxy-5-methoxy-2-methyl-2-triethylsilanyloxymethyl-cyclohexanecarbonitrile (4.61):

A solution of **4.60** (22 mg, 0.077 mmol) in 1 mL of toluene was cooled to 0 °C. Diethylaluminum cyanide was added (0.39 mL of a 1.0 M solution of in toluene, 0.39 mmol). After stirring for two hours, the reaction was quenched with a saturated aqueous solution of sodium carbonate and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (20% → 30% ethyl acetate/hexanes) to yield 19 mg of **4.61** as a white solid (79%).

Data for 4.61:

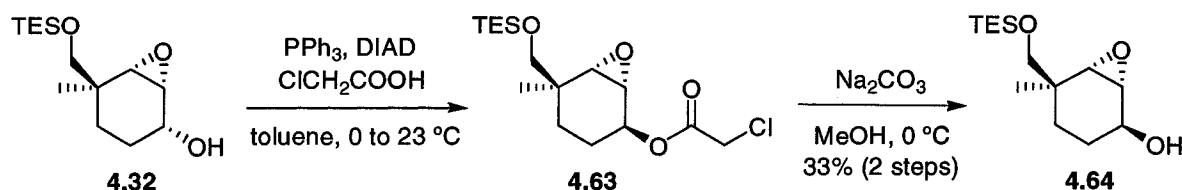
¹H NMR (CDCl₃, 500 MHz, δ): 3.81 (ddd, *J* = 10.9, 8.8, 1.9 Hz, 1H), 3.70 (d, *J* = 9.9 Hz, 1H), 3.54 (d, *J* = 9.9 Hz, 1H), 3.39 (s, 3H), 2.91 (ddd, *J* = 11.5, 8.8, 4.6 Hz, 1H), 2.86 (d, *J* = 2.1 Hz, 1H), 2.42 (d, *J* = 11.2 Hz, 1H), 2.00 (ddd, *J* = 14.1, 3.5, 3.5 Hz, 1H), 1.94 (dddd, *J* = 13.2, 4.2, 3.7, 3.7 Hz, 1H), 1.44-1.36 (m, 1H), 1.11-1.04 (m, 1H), 1.09 (s, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 7.8 Hz, 6H).

¹³C NMR (CDCl₃, 125 MHz, δ): 118.44, 83.77, 70.58, 65.23, 56.76, 44.56, 38.87, 31.67, 25.44, 23.85, 6.69 (3C), 4.14 (3C).

IR (neat, cm⁻¹, ν): 3422 (m, br), 2958 (s), 2813 (s), 2877 (s), 2238 (w), 1459 (m), 1415 (w), 1376 (w), 1241 (w), 1098 (s), 1067 (m), 1008 (m).

HRMS (EI, *m/z*): calculated 284.1682 for [M-Et]⁺, found 284.1692.

mp = 65.4-66.8 °C.



To a solution of **4.64** (27 mg, 0.099 mmol) in 1 mL of tetrahydrofuran was added imidazole (10 mg, 0.15 mmol) followed by chlorotriethylsilane (0.020 mL, 0.12 mmol). After stirring for 1 hour at ambient temperature, the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 37 mg of **4.65** as a colourless oil (97%).

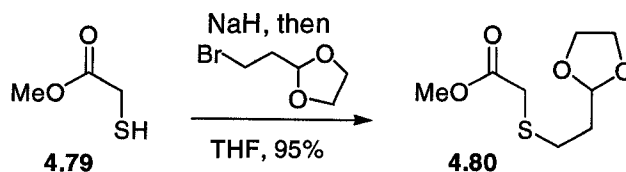
Data for 4.65:

¹H NMR (CDCl₃, 300 MHz, δ): 3.98 (dd, $J = 5.6, 5.5$ Hz, 1H), 3.47 (d, $J_{AB} = 9.7$ Hz, 1H), 3.43 (d, $J_{AB} = 9.7$ Hz, 1H), 3.03 (dd, $J = 3.7, 1.0$ Hz, 1H), 2.98 (d, $J = 3.7$ Hz, 1H), 1.65-1.56 (m, 1H), 1.47-1.39 (m, 1H), 1.36-1.25 (m, 1H), 1.00 (s, 3H), 0.94 (t, $J = 8.1$ Hz, 9H), 0.93 (t, $J = 8.1$ Hz, 9H), 0.92-0.82 (m, 1H), 0.59 (q, $J = 7.9$ Hz, 6H), 0.57 (q, $J = 8.1$ Hz, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 68.98, 66.53, 59.21, 57.88, 35.20, 26.69, 25.20, 21.50, 7.17 (6C), 5.12 (3C), 4.72 (3C).

IR (neat, cm⁻¹, ν): 2956 (s), 2910 (s), 2877 (s), 1458 (m), 1415 (w), 1239 (m), 1094 (s), 1059 (m), 1016 (s).

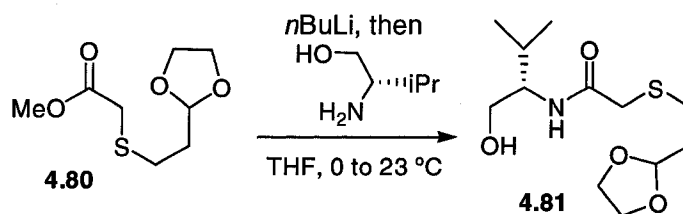
HRMS (EI, m/z): calculated 357.2281 for [M-Et]⁺, found 357.2264.



(2-[1,3]Dioxolan-2-yl-ethylsulfanyl)-acetic acid methyl ester (4.80):

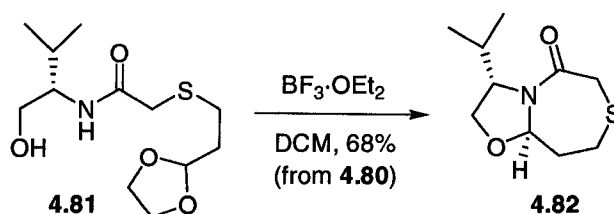
To a solution of sodium hydride (1.30 g, 32.8 mmol) in 150 mL of tetrahydrofuran was slowly added **4.79** (3.10 mL, 32.7 mmol) (*Note: vigorous evolution of gas occurs. Ensure adequate venting of the flask*). Once the addition was complete and no further gas was being evolved, 2-(2-bromo-ethyl)-[1,3]dioxolane (2.00 mL, 16.4 mmol) was slowly added and the reaction was stirred for 16 hours before quenching with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 3.20 g

(95%) of **4.80** as a yellow oil. Spectral data for this compound was in agreement with that reported previously: Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, 8, 1359.



2-(2-[1,3]Dioxolan-2-yl-ethylsulfanyl)-N-((S)-1-hydroxymethyl-2-methyl-propyl)-acetamide (4.81**):**

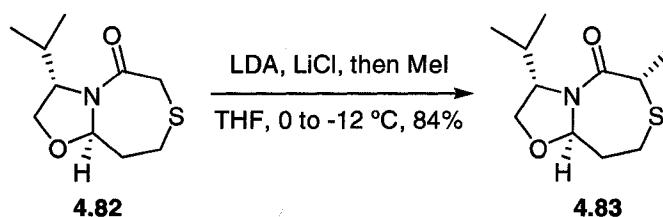
A solution of (S)-valinol (1.80 g, 17.5 mmol) in 100 mL of tetrahydrofuran was cooled to 0 °C and *n*-butyllithium was added (1.34 mL of a 2.45 M solution in pentane, 3.28 mmol). After 5 minutes, **4.80** (3.20 g, 15.5 mmol) was added by cannula as a solution in 50 mL of tetrahydrofuran. The mixture was warmed to ambient temperature and stirred for 18 hours before being quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. No further purification was necessary and the spectral data for this compound was in agreement with that reported previously: Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, 8, 1359.



(3S,8aR)-3-Isopropyl-tetrahydro-1-oxa-6-thia-3a-aza-azulen-4-one (4.82**):**

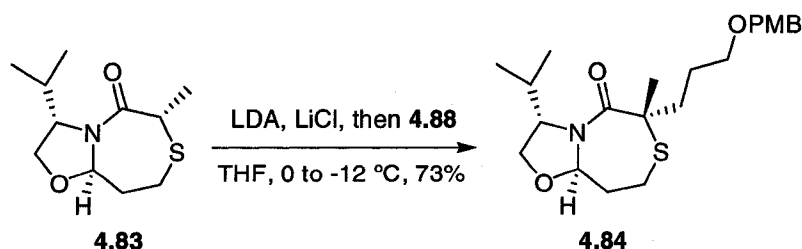
Freshly distilled $\text{BF}_3 \cdot \text{OEt}_2$ (1.64 mL, 12.9 mmol) was added drop-wise to a solution of unpurified **4.81** (3.00 g, 10.8 mmol maximum) in 100 mL of dichloromethane. After stirring for 18 hours, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (35% ethyl acetate/hexanes) gave 1.58 g of **4.82** as a pale yellow solid (68% from **4.80**). Spectral data for this compound was in

agreement with that reported previously: Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, 8, 1359.



(3S,5S,8aR)-3-Isopropyl-5-methyl-tetrahydro-1-oxa-6-thia-3a-aza-azulen-4-one (4.83):

To a suspension of flame-dried lithium chloride (294 mg, 6.94 mmol) in 5 mL of tetrahydrofuran, cooled to 0 °C, was added freshly distilled diisopropylamine (0.580 mL, 4.14 mmol) followed by *n*-butyllithium (1.61 mL of a 2.50 M solution in pentane, 4.03 mmol). After stirring for 5 minutes, **4.82** (512 mg, 2.38 mmol), previously dried by azeotropic removal of water with toluene, was cannulated into the reaction mixture with 10 mL of tetrahydrofuran. Following 10 minutes of stirring, iodomethane (0.30 mL, 4.8 mmol), previously filtered over a pad of basic alumina, was added drop-wise to the reaction. After stirring at 0 °C for two hours, the reaction was transferred to a -12 °C fridge for an additional 15 hours and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (40% ethyl acetate/hexanes) yielded 458 mg of a white solid (84%). Spectral data for this compound was in agreement with that reported previously: Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, 8, 1359.



(3S,5R,8aR)-3-Isopropyl-5-[3-(4-methoxy-benzyloxy)-propyl]-5-methyl-tetrahydro-1-oxa-6-thia-3a-aza-azulen-4-one (4.84):

To a suspension of flame-dried lithium chloride (294 mg, 6.94 mmol) in 5 mL of tetrahydrofuran, cooled to 0 °C, was added freshly distilled diisopropylamine (0.580 mL, 4.14 mmol) followed by *n*-butyllithium (1.61 mL of a 2.50 M solution in pentane, 4.03 mmol). After stirring for 5 minutes, **4.83** (458 mg, 2.00 mmol), previously dried by azeotropic removal of water with toluene, was cannulated into the flask using an addition 10 mL of tetrahydrofuran. Following 10 minutes of stirring, a solution of **4.88** (1.46 g, 4.77 mmol) in 2 mL of tetrahydrofuran, previously filtered over a pad of basic alumina, was added to the reaction. After stirring at 0 °C for two hours, the reaction was transferred to a -12 °C fridge for an additional 15 hours and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% → 30% ethyl acetate/hexanes) yielded 595 mg of a colourless oil (73%).

Data for 4.84:

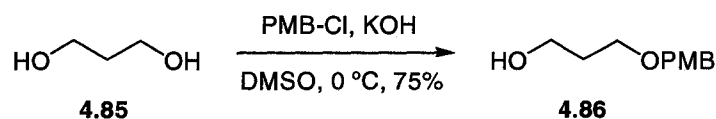
¹H NMR (CDCl₃, 500 MHz, δ): 7.24-7.22 (m, 2H), 6.86-6.83 (m, 2H), 5.61 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.41 (s, 2H), 4.24 (ddd, *J* = 6.8, 4.0, 4.0 Hz, 1H), 3.88 (dd, *J* = 9.0, 6.8 Hz, 1H), 3.81 (dd, *J* = 9.1, 3.8 Hz, 1H), 3.78 (s, 3H), 3.48-3.44 (m, 2H), 2.78 (ddd, *J* = 14.8, 8.8, 5.9 Hz, 1H), 2.68 (ddd, *J* = 14.8, 5.8, 5.8 Hz, 1H), 2.38-2.34 (m, 1H), 2.23 (dddd, *J* = 13.9, 6.2, 6.2, 6.2 Hz, 1H), 1.96-1.75 (m, 5H), 1.49 (s, 3H), 0.84 (d, *J* = 7.0, 3H), 0.80 (d, *J* = 7.0 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 172.01, 158.91, 130.56, 129.07 (2C), 113.57 (2C), 88.48, 72.34, 70.08, 63.90, 62.48, 55.12, 51.56, 36.73, 34.07, 27.21, 24.86, 24.74, 24.17, 18.96, 15.74.

IR (neat, cm⁻¹, ν): 2958 (s), 2928 (s), 2868 (m), 1633 (s), 1509 (s), 1457 (m), 1419 (m), 1393 (m), 1359 (m), 1299 (m), 1250 (s), 1175 (m), 1093 (s), 1033 (m).

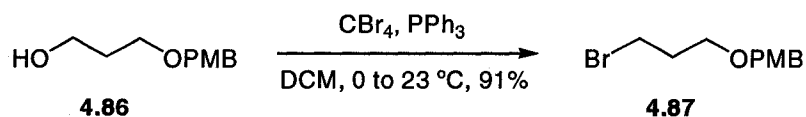
HRMS (EI, *m/z*): calculated 407.2130 for [M]⁺, found 407.2109.

[α]_D²³ = -14.8° (c = 10.7 mg/mL, dichloromethane).



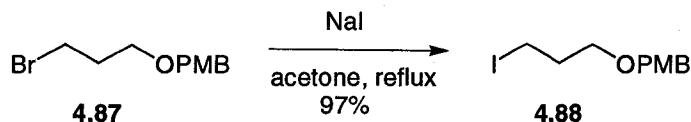
3-(4-Methoxy-benzyloxy)-propan-1-ol (4.86):

(Procedure adapted from Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, 5, 857.) A solution of 1,3-propanediol (7.50 g, 98.6 mmol) in 40 mL of dimethylsulfoxide was cooled to 0 °C. Potassium hydroxide (5.80 g, 103 mmol) was added, followed by 4-methoxybenzyl chloride (7.3 mL, 49.4 mmol). The reaction was stirred for 1.5 hours before quenching with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were washed with brine and dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (50% ethyl acetate/hexanes) yielded 7.27 g of **4.86** as a colourless oil (75%). Spectral data for this compound was in agreement with that published previously: Cordero, F. M.; Gensini, M.; Goti, A.; Brandi, A. *Org. Lett.* **2000**, 2, 2475.



1-(3-Bromo-propoxymethyl)-4-methoxy-benzene (4.87):

A solution of **4.86** (7.27 g, 37.1 mmol) in 150 mL of dichloromethane was cooled to 0 °C. Carbontetrabromide (12.90 g, 38.90 mmol) was added, followed by a portion-wise addition of triphenylphosphine (120.20 g, 38.89 mmol). The reaction was warmed to ambient temperature and stirred for 3.5 hours before being poured into an Erlenmeyer flask containing 300 mL of hexanes. The resulting white precipitate was filtered off over celite and the filtrate was concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 8.70 g (91%) of **4.87** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Dahan, A; Portnoy, M. *J. Org. Chem.* **2001**, 66, 6480.



1-(3-iodo-propoxymethyl)-4-methoxy-benzene (4.88):

Flame-dried sodium iodide (578 mg, 3.86 mmol) was dissolved in 5 mL of acetone. A solution of **4.87** (500 mg, 1.93 mmol) in 2 mL of acetone was added by cannula and the

resulting cloudy yellow solution was heated to reflux. After 15 hours, the reaction was cooled, diluted with water, and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 571 mg of **4.88** as a colourless oil (97%).

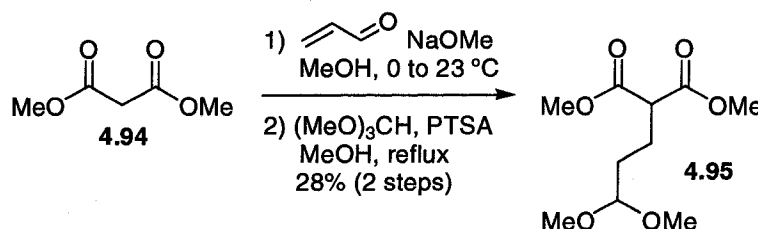
Data for 4.88:

¹H NMR (CDCl₃, 300 MHz, δ): 7.25 (d, J = 8.5 Hz, 2H), 6.90-6.85 (m, 2H), 4.43 (s, 2H), 3.77 (s, 3H), 3.49 (t, J = 5.8 Hz, 2H), 3.27 (t, J = 6.8 Hz, 2H), 2.05 (tt, J = 6.3, 6.3 Hz, 2H).

¹³C NMR (CDCl₃, 75 MHz, δ): 159.59, 130.72, 129.73 (2C), 114.21 (2C), 73.16, 69.72, 55.71, 33.94, 4.29.

IR (neat, cm⁻¹, ν): 2999 (w), 2952 (m), 2934 (m), 2902 (m), 2857 (s), 2835 (m), 2792 (w), 1613 (s), 1586 (w), 1513 (s), 1463 (m), 1361 (m), 1302 (m), 1247 (s), 1179 (s), 1099 (s), 1035 (s).

HRMS (EI, m/z): calculated 306.0117 for [M]⁺, found 306.0038.



2-(3,3-dimethoxy-propyl)-malonic acid dimethyl ester (4.95):

Sodium metal (175 mg, 7.61 mmol) was rinsed in hexanes and placed in 65 mL of methanol, cooled to 0 °C. Once the sodium had dissolved, **4.94** (17.5 g, 153 mmol) was added and the reaction was stirred for 10 minutes. A solution of acrolein (10.0 mL, 150 mmol) in 35 mL of methanol was added by syringe pump over 3 hours and the reaction was stirred for an additional hour at 0 °C before warming to ambient temperature and leaving for 24 hours. *para*-Toluenesulfonic acid (2.9 g, 15 mmol) was added portion-wise, followed by trimethyl orthoformate (33.5 mL, 306 mmol). The reaction was heated to reflux for one hour, cooled, diluted with ethyl acetate, and quenched with a saturated aqueous solution of sodium carbonate. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by

silica gel flash chromatography (25% ethyl acetate/hexanes) yielded 9.8 g of a colourless oil (28% over 2 steps).

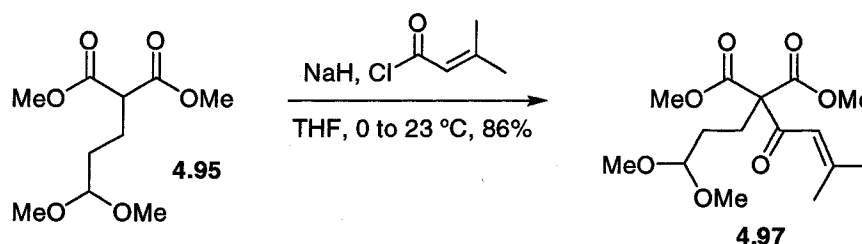
Data for 4.95:

^1H NMR (C_6C_6 , 300 MHz, δ): 4.20 (t, $J = 5.6$ Hz, 1H), 3.36 (t, $J = 7.5$ Hz, 1H), 3.27 (s, 6H), 3.07 (s, 6H), 2.13-2.05 (m, 2H), 1.70-1.62 (m, 2H).

^{13}C NMR (C_6C_6 , 75 MHz, δ): 169.67 (2C), 104.11, 52.40 (2C), 51.96 (2C), 51.59, 30.47, 24.55.

IR (neat, cm^{-1} , ν): 2955 (m), 2834 (w), 1737 (s), 1437 (m), 1345 (w), 1261 (m), 1235 (m), 1197 (m), 1157 (m), 1129 (s), 1069 (m), 1051 (m).

HRMS (EI, m/z): calculated 203.0920 for $[\text{M-OMe}]^+$, found 203.0933.



2-(3,3-dimethoxy-propyl)-2-(3-methyl-but-2-enoyl)-malonic acid dimethyl ester (4.97):

A solution of **4.95** (1.00 g, 4.27 mmol) in 40 mL of tetrahydrofuran was cooled to 0 °C. Sodium hydride (180 mg of a 60% suspension in mineral oil, 4.50 mmol) was added, followed by, after 5 minutes of stirring, 3,3-dimethylacryloyl chloride (0.710 mL, 6.38 mmol). The reaction was warmed to ambient temperature and stirred for an additional 2 hours before being quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 1.16 g of **4.97** as a colourless oil (86%).

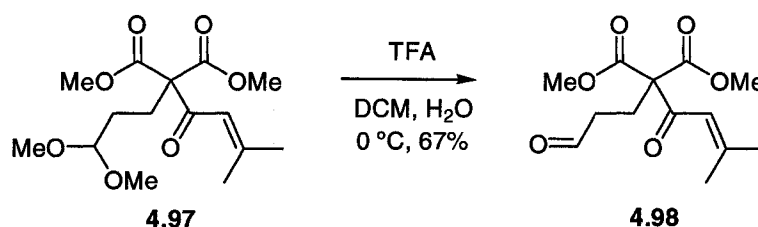
Data for 4.97:

^1H NMR (C_6C_6 , 300 MHz, δ): 6.43-6.41 (m, 1H), 4.37 (t, $J = 5.6$ Hz, 1H), 3.31 (s, 6H), 3.14 (s, 6H), 2.61-2.56 (m, 2H), 2.15-2.07 (m, 2H), 2.02 (d, $J = 1.1$ Hz, 3H), 1.39 (d, $J = 1.1$ Hz, 3H).

^{13}C NMR (C_6D_6 , 75 MHz, δ): 190.57, 168.99 (2C), 158.42, 121.94, 104.58, 70.97, 52.42 (2C), 52.40 (2C), 28.69, 28.42, 27.65, 21.26.

IR (neat, cm^{-1} , ν): 2958 (m), 2918 (m), 2851 (w), 2831 (w), 1737 (s), 1692 (m), 1619 (m), 1441 (m), 1387 (w), 1256 (m), 1129 (m), 1070 (m).

HRMS (EI, m/z): calculated 285.1338 for $[\text{M}-\text{OMe}]^+$, found 285.1315.



2-(3-methyl-but-2-enyl)-2-(3-oxo-propyl)-malonic acid dimethyl ester (4.98**):**

A solution of **4.97** (28 mg, 0.089 mmol) in 1 mL of dichloromethane was cooled to 0 °C. Trifluoroacetic acid (0.5 mL of a 50% aqueous solution) was added and after stirring for 1 hour, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 16 mg of **4.98** as a colourless oil (67%).

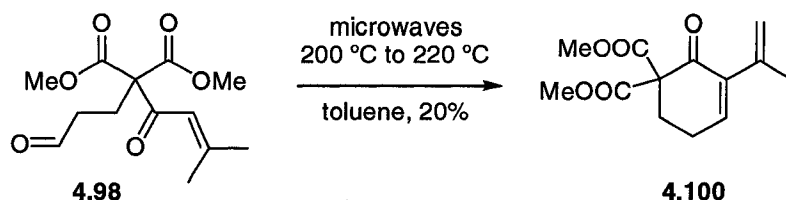
Data for **4.98:**

^1H NMR (CDCl_3 , 300 MHz, δ): 9.72 (s, 1H), 6.13 (dd, $J = 1.2, 1.2$ Hz, 1H), 3.76 (s, 6H), 2.61 (t, $J = 7.2$ Hz, 2H), 2.41 (t, $J = 7.6$ Hz, 2H), 2.14 (d, $J = 0.9$ Hz, 3H), 1.92 (d, $J = 0.9$ Hz, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 201.05, 190.38, 168.71 (2C), 160.83, 121.12, 70.04, 53.46 (2C), 40.13, 28.65, 24.86, 21.88.

IR (neat, cm^{-1} , ν): 2956 (m), 2729 (w), 1732 (s), 1693 (s), 1616 (s), 1437 (s), 1388 (w), 1258 (s), 1212 (s), 1144 (m), 1102 (m), 1042 (w).

HRMS (EI, m/z): calculated 270.1103 for $[\text{M}]^+$, found 270.1086.



3-Isopropenyl-2-oxo-cyclohex-3-ene-1,1-dicarboxylic acid dimethyl ester (**4.100**):

A solution of **4.98** (28 mg, 0.10 mmol) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1 hour, followed by another 4 hours at 220 °C. Purification of the concentrated material by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 20 mg of recovered starting material (71%) and 6 mg of **4.100** (20%) as a colourless oil:

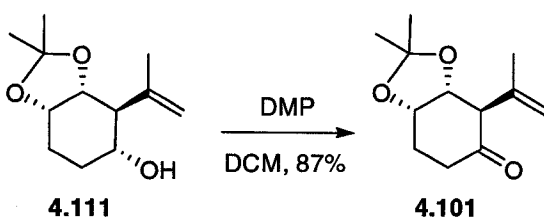
Data for **4.100**:

¹H NMR (CDCl₃, 300 MHz, δ): 6.70 (dd, *J* = 4.2, 4.2 Hz, 1H), 5.09 (s, 1H), 5.02 (dd, *J* = 1.5, 1.5 Hz, 1H), 3.79 (s, 6H), 2.64-2.60 (m, 2H), 2.46-2.40 (m, 2H), 1.87 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 190.56, 168.38 (2C), 143.94, 141.44, 141.05, 116.64, 66.92, 53.55 (2C), 29.51, 23.72, 21.92.

IR (neat, cm⁻¹, ν): 2955 (m), 2923 (m), 2852 (w), 1750 (s), 1736 (s), 1626 (w), 1434 (m), 1375 (w), 1339 (w), 1254 (s), 1198 (w), 1176 (w), 1152 (w), 1079 (m).

HRMS (EI, *m/z*): calculated 224.0682 for [M-CH₂=CH₂]⁺, found 224.0685.



(±)-(3aR,4R,7aS)-4-Isopropenyl-2,2-dimethyl-tetrahydro-benzo[1,3]dioxol-5-one (**4.101**):

To a solution of **4.111** (1.95 g, 9.19 mmol) in 90 mL of dichloromethane was added Dess-Martin periodinane (7.79 g, 18.2 mmol). After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 1.68 g of **4.101** as a colourless oil (87%).

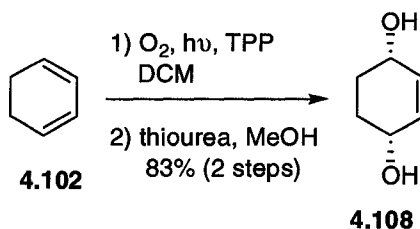
Data for 4.101:

¹H NMR (CDCl₃, 300 MHz, δ): 5.03 (d, J = 1.0 Hz, 1H), 4.71 (d, J = 0.7 Hz, 1H), 4.63 (dd, J = 7.1, 4.5 Hz, 1H), 4.55-4.08 (m, 1H), 3.22 (d, J = 4.3 Hz, 1H), 2.55-2.43 (m, 1H), 2.26-2.08 (m, 2H), 2.02-1.92 (m, 1H), 1.78 (dd, J = 0.6, 0.6 Hz, 3H), 1.45 (s, 3H), 1.35 (s, 3H).

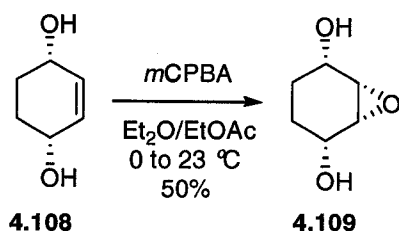
¹³C NMR (CDCl₃, 125 MHz, δ): 208.50, 139.23, 114.48, 107.92, 75.21, 71.59, 59.24, 33.80, 26.41, 24.63, 23.95, 21.92.

IR (neat, cm⁻¹, ν): 2986 (s), 2938 (s), 2911 (m), 1715 (s), 1642 (w), 1444 (w), 1403 (s), 1381 (s), 1331 (w), 1265 (s), 1210 (s), 1156 (s), 1110 (w), 1043 (s).

HRMS (EI, m/z): calculated 210.1256 for [M]⁺, found 210.1242

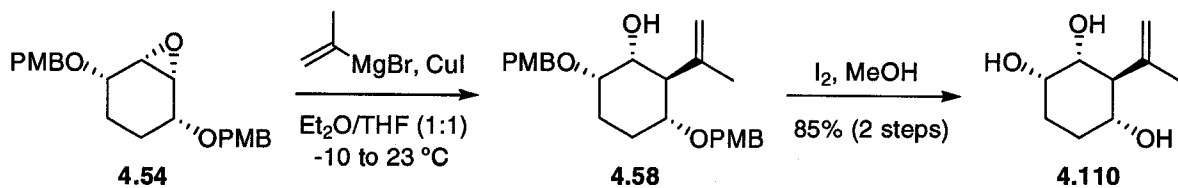
**(±)-(1S,4R)-Cyclohex-2-ene-1,4-diol (4.108):**

To a solution of **4.102** (11.9 mL, 125 mmol) in 500 mL of dichloromethane was added TPP (275 mg, 0.448 mmol). The solution was then sparged continuously with oxygen while being irradiated by a 200 W tungsten lamp for a period of 7 hours. During this time, additional dichloromethane was added as required so as to maintain the original reaction volume. The reaction was then concentrated under reduced pressure to a volume of 50 mL and then diluted with 500 mL of methanol. Thiourea (11.4 g, 150 mmol) was added and the resulting mixture was stirred for 18 hours. The mixture was then filtered through a short pad of celite and the filtrate was adsorbed onto silica for purification. Silica gel flash chromatography (100% ethyl acetate $\rightarrow$ 5% methanol/ethyl acetate) yielded 103.8 g (83%) of **4.108** as a white solid. Spectral data for this compound was in agreement with that reported previously: Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658.



(±)-(1S,2S,5R,6R)-7-Oxa-bicyclo[4.1.0]heptane-2,5-diol (4.109):

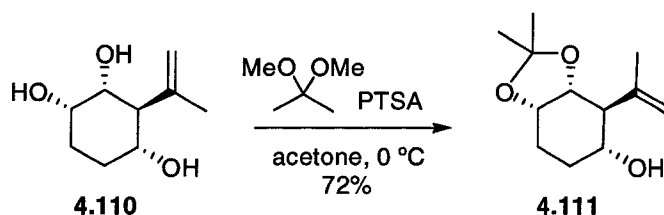
3-Chloroperbenzoic acid (33.0 g at 77% by weight purity, 147 mmol) was dissolved in 100 mL of diethyl ether and the bottom aqueous phase of the resulting biphasic mixture was removed by Pasteur pipette. The solution was then cooled to 0 °C and **4.108** (5.57 g, 48.8 mmol) was added as a solution in 150 mL of ethyl acetate. The reaction was warmed to ambient temperature and stirred for 18 hours before adsorbing the product onto silica for purification. Silica gel flash chromatography (100% ethyl acetate → 5% methanol/ethyl acetate) yielded 3.18 g (50%) of **4.109** as a white solid. Spectral data for this compound was in agreement with that reported previously: Akbulut, N.; Balci, M. *J. Org. Chem.* **1988**, 53, 3338.



(±)-(1R,2R,3R,6S)-2-Isopropenyl-3,6-bis-(4-methoxy-benzyloxy)-cyclohexanol (4.110):

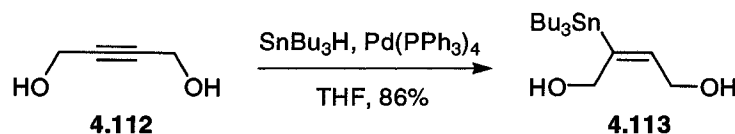
A suspension of copper (I) iodide (7.15 g, 37.5 mmol) in 300 mL of diethyl ether was cooled to -10 °C. Isopropenylmagnesium bromide (150 mL of a 0.5 M solution in tetrahydrofuran, 75 mmol) was added and the mixture was stirred for 30 minutes. Epoxide **4.57** (6.90 g, 18.6 mmol) was cannulated into the flask as a solution in 90 mL of tetrahydrofuran and the reaction was warmed to ambient temperature. After stirring for 1.5 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride, titrated to pH 8 with ammonium hydroxide and stirred for 30 minutes. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude material was used directly for the next step. In a separate flask, iodine (1.90 g, 7.49 mmol) was dissolved in 190 mL of methanol and the unpurified **4.58** (7.68 g, 18.6 mmol maximum) added. The resulting solution was brought to

reflux for 2 hours, cooled to ambient temperature, and quenched with ~ 10 g of solid sodium sulfite. The reaction was stirred until it became pale yellow in colour and then adsorbed onto silica for purification. Silica gel flash chromatography (100% ethyl acetate → 5% methanol/ethyl acetate) afforded 2.72 g (85%) of **4.110** as a pale yellow oil. Spectra data was in agreement with that reported previously for this compound: Morency, L. Ph.D.Thesis, University of Ottawa, Canada, 2006.



(±)-(3aR,4S,7aS)-4-Isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-ol (4.111):

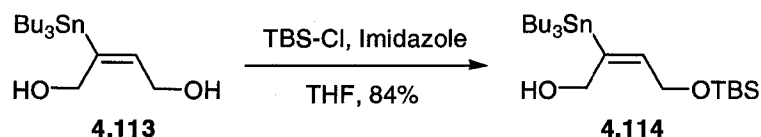
A solution of **4.110** (3.19 g, 18.5 mmol) in 180 mL of acetone was cooled to 0 °C. 2,2-Dimethoxypropane (22.0 mL, 179 mmol) was added, followed by *para*-toluenesulfonic acid (350 mg, 1.84 mmol). After stirring for 5 minutes, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% → 30% ethyl acetate/hexanes) yielded 2.83 g (72%) of **4.111** as a colourless oil. Spectra data was in agreement with that reported previously for this compound: Morency, L. Ph.D.Thesis, University of Ottawa, Canada, 2006.



(E)-2-Tributylstannanyl-but-2-ene-1,4-diol (4.113):

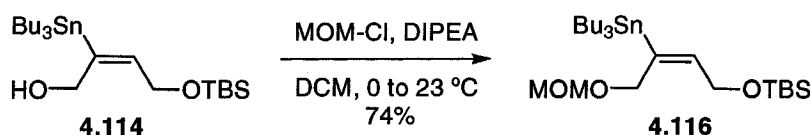
To a solution of **4.112** (366 mg, 4.25 mmol) in 20 mL of tetrahydrofuran was added tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol) followed by tributyltin hydride (1.18 mL, 4.26 mmol). After stirring for 15 minutes, the reaction was adsorbed onto silica for purification. Silica gel flash chromatography (20% → 40% ethyl acetate/hexanes) yielded 1.38 g (86%) of **4.113** as a colourless oil. Spectral data for this compound was in

agreement with that reported previously: Commieras, L.; Santelli, M.; Parrain, J. -L. *Org. Lett.* **2001**, 3, 1713.



(E)-4-(tert-Butyl-dimethyl-silanyloxy)-2-tributylstannanyl-but-2-en-1-ol (4.114):

To a solution of **4.113** (1.99 g, 5.29 mmol) in 30 mL of tetrahydrofuran was added imidazole (540 mg, 7.94 mmol) followed by *tert*-butyl(chloro)dimethylsilane (955 mg, 6.34 mmol). After 1 hour, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (1% → 5% ethyl acetate/hexanes) yielded 2.19 g (84%) of **4.114** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Commieras, L.; Santelli, M.; Parrain, J. -L. *Org. Lett.* **2001**, 3, 1713.



***tert*-Butyl-((E)-4-methoxymethoxy-3-tributylstannanyl-but-2-en-1-yl)-dimethyl-silane (4.116):**

A solution of **4.114** (463 mg, 0.942 mmol) in 10 mL of dichloromethane was cooled to 0 °C. N,N,N-Diisopropylethyl amine (0.250 mL, 1.44 mmol) was added, followed by chloromethyl methyl ether (0.09 mL, 1.185 mmol). The reaction quickly turned milky white and then eventually returned to clear and colourless as it was gradually warmed to ambient temperature. After stirring for 20 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (5% ethyl acetate/hexanes) to yield 373 mg of **4.116** as a colourless oil (74%).

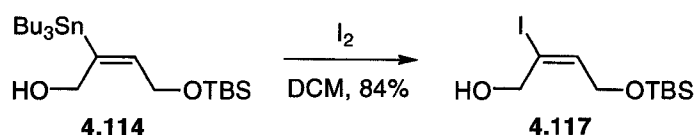
Data for **4.116**:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.68-5.66 (m, 1H), 4.59 (s, 2H), 4.19-4.18 (m, 4H), 3.33 (s, 3H), 1.49-1.43 (m, 6H), 1.28 (tq, $J = 7.4$, 7.4 Hz, 6H), 0.89-0.85 (m, 15H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 143.51, 139.32, 96.00, 69.04, 61.08, 55.22, 29.13 (3C), 27.36 (3C), 25.92 (3C), 18.33 (3C), 13.70, 10.13 (3C), -5.12 (2C).

IR (neat, cm^{-1} , ν): 2956 (s), 2929 (s), 2857 (s), 1463 (m), 1362 (w), 1255 (m), 1153 (m), 1097 (s), 1051 (s), 1006 (w).

HRMS (EI, m/z): calculated 479.2003 for $[\text{M}-n\text{Bu}]^+$, found 479.1827.



(E)-4-(tert-Butyl-dimethyl-silanyloxy)-2-iodo-but-2-en-1-ol (4.117):

Iodine (364 mg, 1.43 mmol) was added in one portion to a stirring solution of **4.114** (713 mg, 1.45 mmol) in 15 mL of dichloromethane. As the iodine dissolved, the reaction turned pink. After stirring for 30 minutes, the reaction was quenched with a saturated aqueous solution of sodium sulfite and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (100% hexanes $\rightarrow$ 30% ethyl acetate/hexanes) to yield 400 mg of **4.117** as a colourless oil (84%).

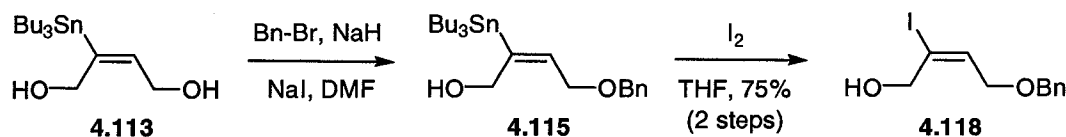
Data for 4.117:

^1H NMR (CDCl_3 , 500 MHz, δ): 6.43 (t, $J = 6.3$ Hz, 1H), 4.26 (s, 2H), 4.19 (d, $J = 6.6$ Hz, 2H), 2.49 (s, br, 1H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 141.56, 104.70, 66.73, 61.22, 25.80 (3C), 18.25, -5.33 (2C).

IR (neat, cm^{-1} , ν): 3389 (m, br), 2955 (s), 2929 (s), 2857 (s), 1631 (w), 1471 (m), 1256 (s), 1087 (s), 1040 (s), 1004 (m).

HRMS (EI, m/z): calculated 270.9651 for $[\text{M}-t\text{Bu}]^+$, found 270.9447.



(E)-4-Benzyloxy-2-iodo-but-2-en-1-ol (4.118):

Sodium iodide (5 mg, 0.03 mmol) was flame-dried under vacuum and allowed to cool. Dimethylformamide (10 mL) was added followed by sodium hydride (68.4 mg, 2.85 mmol) and a solution of **4.113** (430 mg, 1.14 mmol) in 5 mL of dimethylformamide. Benzyl bromide (0.15 mL, 1.26 mmol) was added drop-wise and the reaction was stirred for 24 hours before quenching with a saturated aqueous solution of ammonium chloride. The aqueous phase was diluted with another 100 mL of water and then extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated and then dissolved in 10 mL of tetrahydrofuran. Iodine (295 mg, 1.16 mmol) was added in a single portion and the reaction was stirred for 10 minutes before being quenched with a saturated aqueous solution of sodium sulfite. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% → 75% ethyl acetate/hexanes) yielded 260 mg of a colourless oil (75% over 2 steps).

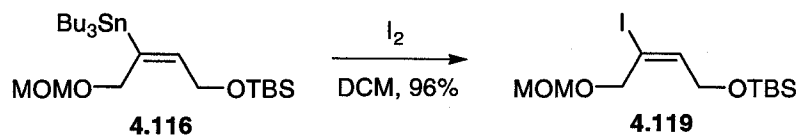
Data for 4.118:

¹H NMR (acetone-d₆, 300 MHz, δ): 7.35-7.26 (m, 5H), 6.45 (t, *J* = 6.5 Hz, 1H), 4.50 (s, 2H), 4.41 (t, *J* = 6.3 Hz, 1H), 4.20 (d, *J* = 6.1 Hz, 2H), 4.12 (d, *J* = 6.6 Hz, 2H).

¹³C NMR (acetone-d₆, 75 MHz, δ): 139.39, 138.87, 128.60 (2C), 127.97 (2C), 127.82, 107.99, 72.07, 67.36, 65.36.

IR (neat, cm⁻¹, ν): 3403 (s, br), 3029 (m), 2921 (s), 2858 (s), 1629 (m), 1495 (w), 1453 (s), 1358 (s), 1233 (w), 1204 (w), 1070 (s), 1028 (s).

(EI, *m/z*): calculated 303.9960 for [M]⁺, found 303.9947.

***tert*-Butyl-((E)-3-iodo-4-methoxymethoxy-but-2-enyloxy)-dimethyl-silane (4.119):**

Iodine (160 mg, 0.630 mmol) was added in one portion to a stirring solution of **4.116** (338 mg, 0.631 mmol) in 10 mL of dichloromethane. As the iodine dissolved, the reaction turned pink. After warming to ambient temperature and then stirring for 30 minutes, the reaction was quenched with a saturated aqueous solution of sodium sulfite and the aqueous phase was

extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography (100% hexanes $\rightarrow$ 8% ethyl acetate/hexanes) to yield 226 mg of a colourless oil (96%).

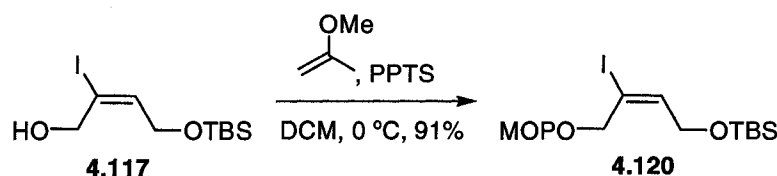
Data for 4.119:

^1H NMR (acetone- d_6 , 500 MHz, δ): 6.51 (t, $J = 6.2$ Hz, 1H), 4.59 (s, 2H), 4.29 (d, $J = 6.3$ Hz, 2H), 4.22 (s, 2H), 3.34 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (acetone- d_6 , 125 MHz, δ): 145.58, 99.82, 95.55, 69.44, 61.75, 55.80, 26.28 (3C), 18.80, -5.04 (2C).

IR (neat, cm^{-1} , ν): 2954 (s), 2930 (s), 2886 (s), 2824 (w), 1632 (w), 1472 (m), 1463 (m), 1374 (m), 1362 (m), 1256 (s), 1213 (w), 1152 (s), 1100 (s), 1048 (s), 1008 (s).

HRMS (EI, m/z): calculated 314.9913 for $[\text{M}-t\text{Bu}]^+$, found 314.9837.



***tert*-Butyl-[(E)-3-iodo-4-(1-methoxy-1-methylethoxy)-but-2-enyloxy]-dimethylsilane (4.120):**

A stirring solution of **4.117** (400 mg, 1.22 mmol) in 12 mL of dichloromethane was cooled to 0 °C. 2-Methoxypropene (0.140 mL, 1.46 mmol) was added followed by a small crystal of pyridinium *para*-toluenesulfonate. After 30 minutes, the reaction was quenched with equal portions of water and a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with dichloromethane and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 442 mg of **4.120** as a colourless oil (91%).

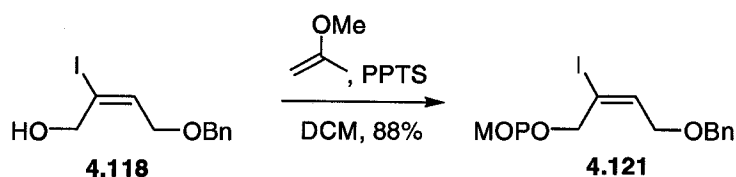
Data for 4.120:

^1H NMR (acetone- d_6 , 300 MHz, δ): 6.42 (t, $J = 6.3$ Hz, 1H), 4.30 (d, $J = 6.3$ Hz, 2H), 4.09 (s, 2H), 3.20 (s, 3H), 1.31 (s, 6H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (acetone- d_6 , 75 MHz, δ): 143.54, 100.61, 100.56, 64.05, 61.34, 48.65, 25.75 (3C), 24.41 (2C), 18.30, -5.56 (2C).

IR (neat, cm^{-1} , ν): 2991 (s), 2954 (s), 2930 (s), 2886 (m), 2857 (s), 2830 (m), 1635 (m), 1471 (s), 1463 (s), 1379 (s), 1363 (m), 1257 (s), 1212 (s), 1185 (m), 1150 (m), 1079 (s), 1046 (s).

HRMS (EI, m/z): calculated 343.0226 for $[\text{M}-t\text{Bu}]^+$, found 343.0231.



[(E)-3-Iodo-4-(1-methoxy-1-methyl-ethoxy)-but-2-enyloxymethyl]-benzene (4.121):

To a solution of **4.118** (103 mg, 0.339 mmol) in 4 mL of dichloromethane was added 2-methoxypropene (0.100 mL, 1.04 mmol) followed by a single crystal of pyridinium *para*-toluenesulfonate. After 1 hour the reaction was quenched with equal portions of water and a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 112 mg of a colourless oil (88%).

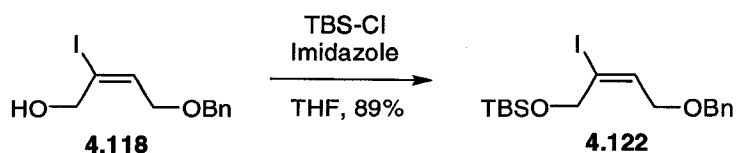
Data for 4.121:

^1H NMR (acetone- d_6 , 300 MHz, δ): 7.35–7.25 (m, 5H), 6.51 (t, $J = 6.5$ Hz, 1H), 4.51 (s, 2H), 4.11 (d, $J = 6.5$ Hz, 2H), 4.08 (s, 2H), 3.17 (s, 3H), 1.29 (s, 6H).

^{13}C NMR (acetone- d_6 , 75 MHz, δ): 140.88, 138.81, 128.64 (2C), 128.00 (2C), 127.87, 102.65, 100.64, 72.14, 67.46, 64.14, 48.63, 24.38 (2C).

IR (neat, cm^{-1} , ν): 3029 (w), 2990 (s), 2940 (s), 2859 (m), 2830 (m), 1633 (w), 1496 (w), 1454 (m), 1379 (s), 1363 (s), 1259 (m), 1211 (s), 1184 (s), 1149 (s), 1075 (s), 1047 (s).

HRMS (EI, m/z): calculated 234.1256 for $[\text{M}-\text{I}]^+$, found 234.1295.



((E)-4-Benzyloxy-2-iodo-but-2-enyloxy)-tert-butyl-dimethyl-silane (4.122):

Imidazole (116 mg, 1.71 mmol) was added to a solution of **4.118** (130 mg, 0.428 mmol) in 5 mL of tetrahydrofuran, followed by *tert*-butyl(chloro)dimethylsilane (140 mg, 0.929 mmol). After 2 hours, the reaction was quenched with a saturated aqueous solution of ammonium

chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% → 10% ethyl acetate/hexanes) yielded 159 mg of a colourless oil (89%).

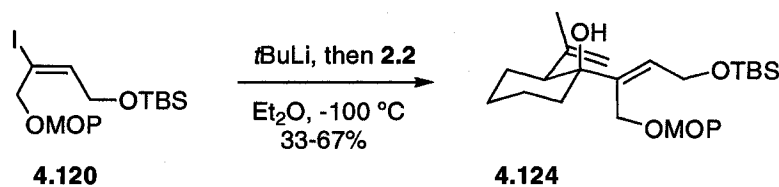
Data for 4.122:

¹H NMR (acetone-d₆, 300 MHz, δ): 7.35-7.26 (m, 5H), 6.46 (t, *J* = 6.5 Hz, 1H), 4.50 (s, 2H), 4.29 (s, 2H), 4.11 (d, *J* = 6.5 Hz, 2H), 0.91 (s, 9H), 0.10 (s, 6H).

¹³C NMR (acetone-d₆, 75 MHz, δ): 139.24, 138.78, 128.64 (2C), 128.01 (2C), 127.88, 106.96, 72.14, 67.44, 65.80, 25.78 (3C), 18.36, -5.41 (2C).

IR (neat, cm⁻¹, ν): 3065 (w), 3031 (w), 2954 (s), 2929 (s), 2884 (s), 2856 (s), 1632 (w), 1496 (w), 1471 (m), 1361 (m), 1253 (s), 1096 (s), 1027 (m), 1006 (m).

HRMS (EI, *m/z*): calculated 291.1780 for [M-I]⁺, found 291.1738.



(±)-(1*S*,2*S*)-1-[(*E*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(1-methoxy-1-methyl-ethoxymethyl)-propenyl]-2-isopropenyl-cyclohexanol (4.124):

A stirring solution of **4.120** (199 mg, 0.497 mmol) in 2.0 mL of diethyl ether was cooled to -100 °C. *tert*-Butyllithium (0.580 mL of a 1.70 M solution in pentane, 0.986 mmol) was added, and after stirring for 60 minutes, a solution of **2.2** (41 mg, 0.30 mmol) in 2.0 mL of diethyl ether was added by cannula. The reaction mixture was gradually warmed to ambient temperature over 2.5 hours. Showing no further consumption of the starting material, the reaction was quenched with water and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 41 mg of a colourless oil (33%).

Data for 4.124:

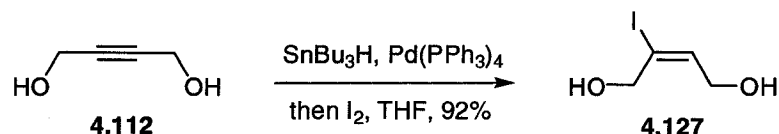
¹H NMR (acetone-d₆, 500 MHz, δ): 5.84 (dd, *J*_{AX} = 6.0 Hz, *J*_{BX} = 5.7 Hz, 1H), 4.69 (s, 1H), 4.67 (s, 1H), 4.39 (dd, *J*_{AB} = 13.7 Hz, *J*_{AX} = 6.1 Hz, 1H), 4.35 (dd, *J*_{AB} = 13.7 Hz, *J*_{BX} = 5.7

Hz, 1H), 3.99 (d, $J_{AB} = 10.9$ Hz, 1H), 3.95 (d, $J_{AB} = 10.9$ Hz, 1H), 3.21 (s, 3H), 2.82 (s, 1H), 2.30 (dd, $J = 12.5, 3.2$ Hz, 1H), 1.94 (dddd, $J = 12.9, 12.9, 12.9, 3.6$ Hz, 1H), 1.79-1.74 (m, 3H), 1.72 (s, 3H), 1.58-1.56 (m, 1H), 1.50-1.48 (m, 1H), 1.43-1.39 (m, 1H), 1.35-1.33 (m, 1H), 1.33 (s, 6H), 0.91 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (acetone- d_6 , 125 MHz, δ): 148.62, 142.38, 129.07, 112.11, 100.31, 76.08, 60.69, 57.25, 52.38, 48.49, 39.05, 28.07, 26.43, 25.79 (3C), 24.17 (2C), 22.61, 21.67, 18.31, -5.44 (2C).

IR (neat, cm^{-1} , ν): 3525 (br, w), 2990 (m), 2931 (s), 2857 (m), 1638 (w), 1472 (m), 1463 (m), 1447 (w), 1378 (m), 1256 (s), 1211 (m), 1183 (m), 1149 (m), 1094 (m), 1073 (s), 1032 (s).

HRMS (EI, m/z): calculated 322.2328 for $[\text{M}-(\text{HO})(\text{CH}_3)_2(\text{CH}_3\text{O})\text{C}]^+$, found 322.2340.



(E)-2-Iodo-but-2-ene-1,4-diol (4.127):

Into a flask containing tetrakis(triphenylphosphine)palladium (0) (50 mg, 0.043 mmol) was added a solution of **4.112** (207 mg, 2.40 mmol) in 15 mL of tetrahydrofuran by cannula. To this suspension was slowly added tributyltin hydride (0.700 mL, 2.60 mmol). After stirring for ten minutes, iodine (610 mg, 2.40 mmol) was added in a single portion and the resulting solution was stirred for another ten minutes before being quenched with a saturated aqueous solution of sodium sulfite. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (80% ethyl acetate/hexanes) yielded 472 mg of **4.127** as a colourless oil (90%).

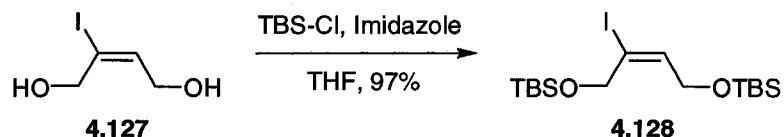
Data for 4.127:

^1H NMR (acetone- d_6 , 500 MHz, δ): 6.42 (t, $J = 6.6$ Hz, 1H), 4.56 (t, $J = 6.1$ Hz, 1H), 4.29 (t, $J = 5.7$ Hz, 1H), 4.19 (d, $J = 6.0$ Hz, 2H), 4.13 (dd, $J = 6.1, 6.1$ Hz, 2H).

^{13}C NMR (acetone- d_6 , 125 MHz, δ): 143.00, 106.32, 65.69, 60.15.

IR (neat, cm^{-1} , ν): 3312 (s, br), 2922 (s), 2971 (s), 1629 (m), 1438 (m), 1362 (m), 1226 (m), 1148 (w), 1120 (w), 1095 (s), 1029 (s).

HRMS (EI, m/z): calculated 213.9491 for $[M]^+$, found 213.9504.



(E)-1,4-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-iodo-but-2-ene (4.128):

To a stirring solution of **4.127** (156 mg, 0.729 mmol) in 8 mL of tetrahydrofuran was added imidazole (150 mg, 2.20 mmol) followed by *tert*-butyl(chloro)dimethylsilane (275 mg, 1.82 mmol). The resulting milky white reaction was stirred for 1 hour and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% hexanes) yielded 313 mg (97%) of **4.128** as a colourless oil.

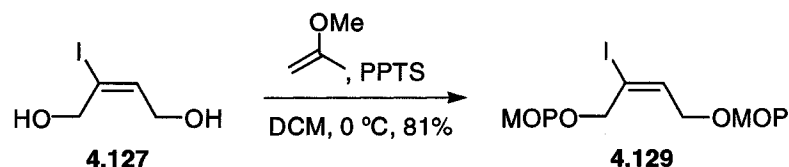
Data for 4.128:

^1H NMR (C_6D_6 , 500 MHz, δ): 6.46 (tt, $J = 6.2, 1.0$ Hz, 1H), 4.17 (d, $J = 0.9$ Hz, 2H), 4.09 (d, $J = 6.1$ Hz, 2H), 0.98 (s, 9H), 0.93 (s, 9H), 0.08 (s, 6H), 0.02 (s, 6H).

^{13}C NMR (C_6D_6 , 125 MHz, δ): 141.95, 104.18, 66.53, 61.48, 26.06 (3C), 26.00 (3C), 18.47, 18.36, -5.03 (2C), -5.18 (2C).

IR (neat, cm^{-1} , ν): 2955 (s), 2929 (s), 2887 (s), 2857 (s), 2711 (w), 1633 (w), 1472 (m), 1463 (m), 1389 (m), 1362 (m), 1275 (s), 1095 (s), 1005 (m).

(EI, m/z): calculated 385.0516 for $[M-t\text{Bu}]^+$, found 385.0539.



(E)-3-Iodo-1,5-bis-(1-methoxy-1-methyl-ethoxy)-pent-2-ene (4.129):

A solution of **4.127** (0.978 g, 4.57 mmol) in 25 mL of dichloromethane was cooled to 0 °C. 2-Methoxypropene was added (1.75 mL, 18.3 mmol) followed by a small crystal of pyridinium *para*-toluenesulfonate. After 30 minutes, the reaction was quenched with a dilute aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate,

filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 1.33 g of **4.129** as a colourless oil (81%).

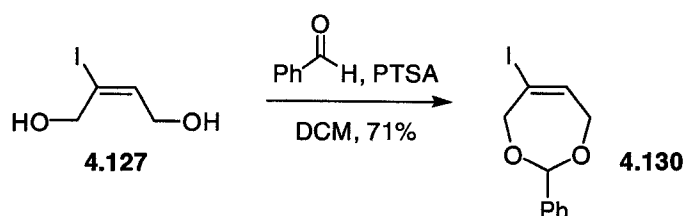
Data for **4.129**:

¹H NMR (C₆D₆, 500 MHz, δ): 6.61 (t, J = 6.5 Hz, 1H), 4.12 (s, 2H), 3.97 (d, J = 6.5 Hz, 2H), 3.14 (s, 3H), 3.01 (s, 3H), 1.27 (s, 6H), 1.22 (s, 6H).

¹³C NMR (C₆D₆, 125 MHz, δ): 141.32, 101.32, 100.62, 100.30, 64.38, 58.94, 48.78, 48.28, 24.60 (2C), 24.47 (2C).

IR (neat, cm⁻¹, ν): 2991 (s), 2941 (m), 2829 (w), 1636 (w), 1461 (w), 1379 (s), 1259 (m), 1212 (s), 1185 (s), 1151 (s), 1075 (s), 1043 (s).

HRMS (EI, m/z): calculated 199.1334 for [M-MeOH]⁺, found 199.1370.



5-Iodo-2-phenyl-4,7-dihydro-[1,3]dioxepine (4.130**):**

Benzaldehyde (0.360 mL, 3.54 mmol) was added to a solution of **4.127** (152 mg, 0.710 mmol) in 8 mL of dichloromethane, followed by a small crystal of *para*-toluenesulfonic acid. After 7 hours the reaction was quenched with a dilute aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 150 mg of **4.130** as a colourless oil (71%).

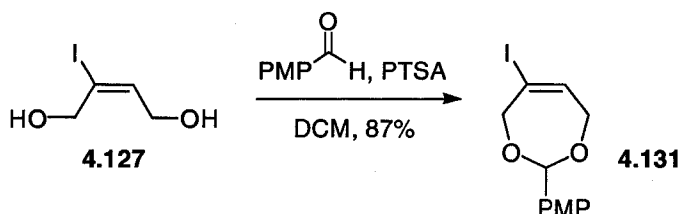
Data for **4.130**:

¹H NMR (acetone-d₆, 500 MHz, δ): 7.48 (d, J = 7.0 Hz, 2H), 7.40-7.33 (m, 3H), 6.41 (dddd, J = 2.4, 2.4, 1.6, 1.6 Hz, 1H), 5.89 (s, 1H), 4.45 (dd, J_{AB} = 16.2, J_{AX} = 1.7 Hz, 1H), 4.38 (dd, J_{AB} = 16.2, J_{BX} = 1.9 Hz, 1H), 4.24 (dddd, J_{AB} = 16.0, J_{AX} = 4.0, J_{AY} = 1.9, J_{AZ} = 1.9 Hz, 1H), 4.17 (dddd, J_{AB} = 16.0, J_{BX} = 4.1, J_{BY} = 2.1, J_{BZ} = 2.1 Hz, 1H).

¹³C NMR (acetone-d₆, 125 MHz, δ): 140.92, 139.19, 129.38, 129.00 (2C), 127.24 (2C), 102.54, 97.68, 74.44, 66.02.

IR (neat, cm^{-1} , ν): 3066 (w), 3033 (w), 2946 (m), 2891 (m), 2852 (m), 1636 (m), 1494 (w), 1451 (m), 1371 (m), 1345 (s), 1258 (s), 1208 (s), 1119 (s), 1037 (s), 1004 (s).

(EI, m/z): calculated 301.9804 for $[\text{M}]^+$, found 301.9821.



5-Iodo-2-(4-methoxy-phenyl)-4,7-dihydro-[1,3]dioxepine (4.131):

para-Anisaldehyde (0.400 mL, 3.30 mmol) was added to a solution of **4.127** (144 mg, 0.673 mmol) in 5 mL of dichloromethane, followed by a small crystal of *para*-toluenesulfonic acid. After stirring at ambient temperature for 18 hours, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 195 mg of a colourless oil (87%).

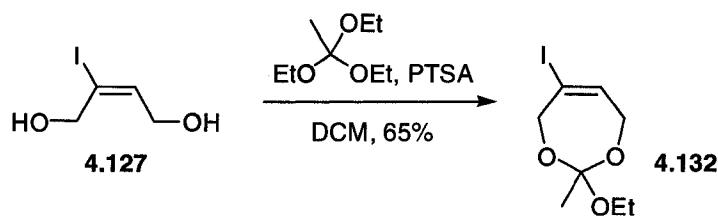
Data for 4.131:

^1H NMR (acetone- d_6 , 300 MHz, δ): 7.42-7.38 (m, 2H), 6.96-6.91 (m, 2H), 6.43-6.39 (m, 1H), 5.85 (s, 1H), 4.44 (dddd, $J_{AB} = 16.2$, $J_{AX} = 1.9$, $J_{AY} = 1.9$, $J_{AZ} = 1.9$ Hz, 1H), 4.34 (dddd, $J_{AB} = 16.2$, $J_{BX} = 2.0$, $J_{BY} = 2.0$, $J_{BZ} = 2.0$ Hz, 1H), 4.24 (dddd, $J_{AB} = 15.9$, $J_{AX} = 4.1$, $J_{AY} = 2.0$, $J_{AZ} = 2.0$ Hz, 1H), 4.14 (dddd, $J_{AB} = 15.9$, $J_{BX} = 4.1$, $J_{BY} = 1.9$, $J_{BZ} = 1.9$ Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (acetone- d_6 , 75 MHz, δ): 160.36, 140.51, 130.78, 128.12 (2C), 113.84 (2C), 101.99, 97.42, 73.73, 65.37, 55.15.

IR (neat, cm^{-1} , ν): 3065 (w), 3040 (w), 3000 (w), 2951 (s), 2897 (s), 2836 (s), 1635 (m), 1612 (s), 1586 (m), 1513 (s), 1462 (m), 1441 (m), 1370 (m), 1344 (s), 1303 (s), 1249 (s), 1210 (m), 1171 (s), 1107 (s), 1076 (s), 1036 (s), 1001 (s).

HRMS (EI, m/z): calculated 331.9909 for $[\text{M}]^+$, found 331.9900.



2-Ethoxy-5-iodo-2-methyl-4,7-dihydro-[1,3]dioxepine (4.132):

Triethyl orthoacetate (0.090 mL, 0.89 mmol) was added to a solution of **4.127** (40 mg, 0.19 mmol) in 2 mL of dichloromethane, followed by a small crystal of pyridinium *para*-toluenesulfonate. After 2 hours the reaction was quenched with a dilute aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 34 mg of **4.132** as a colourless oil (65%).

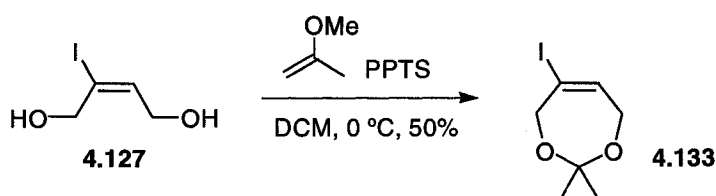
Data for **4.132**:

$^1\text{H NMR}$ (C_6D_6 , 500 MHz, δ): 5.94-5.92 (m, 1H), 4.66 (dddd, $J_{\text{AB}} = 16.4$, $J_{\text{AX}} = 1.9$, $J_{\text{AY}} = 1.9$, $J_{\text{AZ}} = 1.9$ Hz, 1H), 4.23 (dddd, $J_{\text{AB}} = 16.4$, $J_{\text{BX}} = 2.0$, $J_{\text{BY}} = 2.0$, $J_{\text{BZ}} = 2.0$ Hz, 1H), 4.14 (dddd, $J_{\text{AB}} = 16.0$, $J_{\text{AX}} = 4.2$, $J_{\text{AY}} = 2.2$, $J_{\text{AZ}} = 2.2$ Hz, 1H), 3.69 (dddd, $J_{\text{AB}} = 16.0$, $J_{\text{BX}} = 4.2$, $J_{\text{BY}} = 2.1$, $J_{\text{BZ}} = 2.1$ Hz, 1H), 3.45 (q, $J = 7.1$ Hz, 2H), 1.40 (s, 3H), 1.14 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C NMR}$ (C_6D_6 , 125 MHz, δ): 139.83, 116.77, 97.50, 71.51, 62.76, 59.48, 19.06, 15.59.

IR (neat, cm^{-1} , ν): 2977 (m), 1642 (w), 1442 (w), 1381 (m), 1219 (s), 1169 (s), 1049 (s).

HRMS (EI, m/z): none found – molecule too unstable.



5-Iodo-2,2-dimethyl-4,7-dihydro-[1,3]dioxepine (4.133):

A solution of **4.127** (66 mg, 0.31 mmol) in 3 mL of dichloromethane was cooled to 0 °C. 2-Methoxypropene was added (0.030 mL, 0.31 mmol), followed by a small crystal of pyridinium *para*-toluenesulfonate. After 3 hours and 30 minutes, the reaction was quenched with a dilute aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium

sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% ethyl acetate/hexanes) yielded 39 mg of **4.133** as a colourless oil (50%).

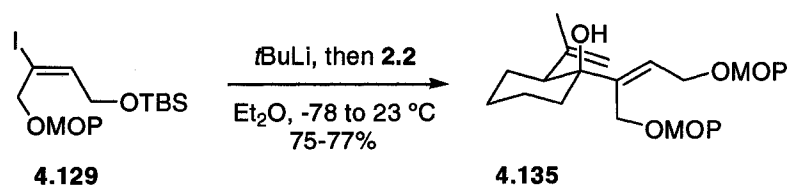
Data for 4.133:

^1H NMR (acetone- d_6 , 500 MHz, δ): 6.29-6.28 (m, 1H), 4.33-4.32 (m, 2H), 4.12-4.10 (m, 2H), 1.35 (s, 6H).

^{13}C NMR (acetone- d_6 , 125 MHz, δ): 140.60, 103.00, 97.96, 71.77, 63.01, 24.07 (2C).

IR (neat, cm^{-1} , ν): 2990 (s), 2941 (s), 2906 (s), 2855 (m), 1642 (m), 1465 (w), 1446 (m), 1374 (s), 1361 (m), 1278 (m), 1217 (s), 1158 (s), 1092 (s), 1075 (s), 1009 (s).

HRMS (EI, m/z): calculated 253.9804 for $[\text{M}]^+$, found 253.9804.



(±)-(1S,2S)-2-Isopropenyl-1-[(E)-3-(1-methoxy-1-methyl-ethoxy)-1-(1-methoxy-1-methyl-ethoxymethyl)-propenyl]-cyclohexanol (4.135):

A solution of **4.129** (129 mg, 0.360 mmol) in 2.5 mL of diethyl ether was cooled to $-78\text{ }^\circ\text{C}$. *tert*-Butyllithium (0.470 mL of a 1.53 M solution in pentane, 0.719 mmol) was added and the reaction was stirred for 90 minutes. Ketone **2.2** (16 mg, 0.12 mmol) was cannulated into the mixture with 1 mL of tetrahydrofuran and the reaction was gradually warmed to ambient temperature over 1 hour before being quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% $\rightarrow$ 20% ethyl acetate/hexanes) yielded 33 mg of **4.135** as a colourless oil (77%).

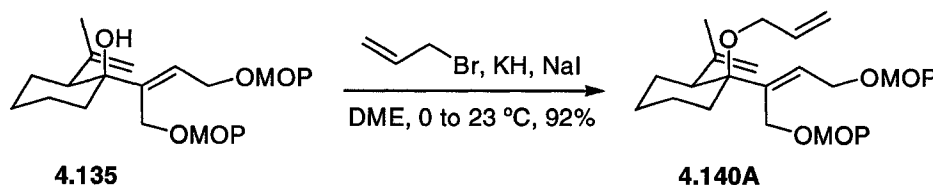
Data for 4.135:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.68 (dd, $J = 6.0, 6.0$ Hz, 1H), 4.75 (s, 1H), 4.69 (s, 1H), 4.08 (dd, $J = 6.2, 1.6$ Hz, 2H), 3.97 (s, 2H), 3.21 (s, 3H), 3.16 (s, 3H), 2.67 (s, 1H), 2.20 (dd, $J = 12.4, 3.6$ Hz, 1H), 1.85-1.72 (m, 2H), 1.70 (s, 3H), 1.67-1.61 (m, 3H), 1.51-1.43 (m, 2H), 1.34 (s, 6H), 1.32 (s, 6H), 1.28-1.22 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.99, 143.31, 126.43, 112.51, 100.45, 100.10, 76.04, 57.87, 57.38, 52.62, 48.88, 48.43, 39.63, 27.99, 26.24, 24.55, 24.50, 24.39, 24.36, 24.01, 21.58.

IR (neat, cm^{-1} , ν): 3511 (w, br), 3070 (w), 2990 (m), 2940 (s), 2859 (m), 2828 (w), 1638 (w), 1459 (w), 1378 (s), 1258 (m), 1211 (s), 1183 (s), 1151 (s), 1073 (s), 1029 (s).

HRMS (EI, m/z): calculated 280.2038 for $[\text{M}-\text{C}(\text{Me})_2(\text{OMe})\text{OH}]^+$, found 280.2057.



(±)-(1S,2S)-1-Allyloxy-2-isopropenyl-1-[(E)-3-(1-methoxy-1-methyl-ethoxy)-1-(1-methoxy-1-methyl-ethoxymethyl)-propenyl]-cyclohexane (4.140A):

Sodium iodide (2 mg, 0.01 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (180 mg of a 30% suspension in mineral oil, 1.35 mmol) was added to the flask and the system was put under nitrogen. The potassium hydride was then washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (2.0 mL) was added and the resulting suspension was cooled to 0 °C. A solution of **4.135** (99.9 mg, 0.270 mmol) in another 2.0 mL of dimethoxyethane was cannulated into the flask and the mixture was stirred for 20 minutes. Allyl bromide (0.120 mL, 1.39 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature over 1 hour. After stirring for 18 hours the reaction was quenched first with isopropanol, then with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 102 mg of **4.140** as a colourless oil (92%).

Data for 4.140A:

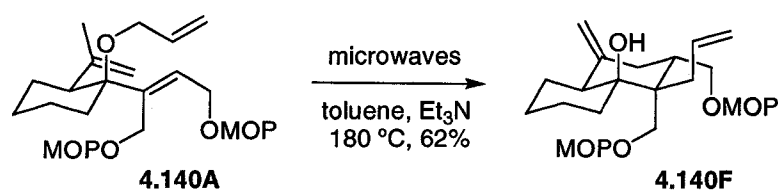
^1H NMR (CDCl_3 , 300 MHz, δ): 5.91–5.85 (m, 1H), 5.42–5.40 (m, 1H), 5.31 (dddd, $J = 17.2$, 2.0, 2.0, 2.0 Hz, 1H), 5.07 (dddd, $J = 10.6$, 1.8, 1.8, 1.8 Hz, 1H), 4.76 (s, 1H), 4.74 (s, 1H), 4.38–4.29 (m, 2H), 4.13 (dd, $J = 16.3$, 4.5 Hz, 1H), 4.00 (d, $J = 16.0$ Hz, 1H), 3.83–3.79 (m,

1H), 3.74-3.70 (m, 1H), 3.17 (s, 6H), 2.00-1.93 (m, 2H), 1.88-1.86 (m, 1H), 1.77 (s, 3H), 1.74-1.72 (m, 1H), 1.51-1.20 (m, 5H), 1.37 (s, 6H), 1.31 (s, 6H).

¹³C NMR (CDCl₃, 75 MHz, δ): 147.61, 143.51, 135.41, 124.84, 114.42, 113.16, 101.73, 80.83, 77.20, 62.24, 61.27, 61.18, 55.20, 50.89, 48.34, 31.73, 30.94, 27.81, 26.23, 24.05, 23.90, 23.78, 22.68, 21.37.

IR (neat, cm⁻¹, ν): 3076 (w), 2989 (m), 2939 (s), 2857 (m), 1644 (w), 1448 (m), 1371 (m), 1219 (s), 1177 (m), 1115 (m), 1091 (s), 1070 (s), 1027 (m).

HRMS (EI, *m/z*): calculated 320.2351 for [M-C(Me)₂(OH)(OMe)]⁺, found 320.2328.



(±)-(3S,4R,4aS,8aS)-4-Allyl-3,4-bis-(1-methoxy-1-methyl-ethoxymethyl)-1-methylene-octahydro-naphthalen-4a-ol (**4.140F**):

A solution of **4.140A** (10.0 mg, 0.0244 mmol) and triethylamine (0.020 mL, 0.14 mmol) in 10 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 180 °C. After 30 minutes the reaction was concentrated and the crude material was purified by silica gel flash chromatography (10% ethyl acetate/hexanes, basified with triethylamine) to give 6.2 mg of **4.140F** as a colourless oil (62%).

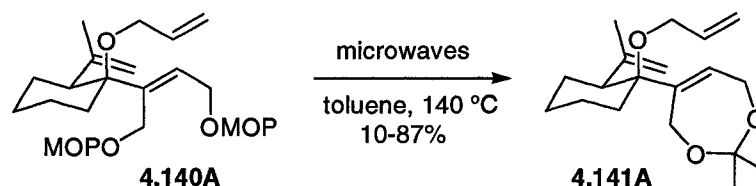
Data for 4.140F:

¹H NMR (CDCl₃, 500 MHz, δ): 6.18-6.09 (m, 1H), 5.03 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dd, *J* = 10.1, 1.1 Hz, 1H), 4.92 (s, 1H), 4.67 (s, 1H), 3.99 (d, *J* = 12.2 Hz, 1H), 3.99 (d, *J* = 12.2 Hz, 1H), 3.44 (dd, *J* = 12.2, 1.7 Hz, 1H), 3.25-3.22 (m, 1H), 3.17 (s, 6H), 2.79-2.72 (m, 2H), 2.37 (dd, *J* = 15.3, 6.8 Hz, 1H), 2.12 (dd, *J* = 14.1, 4.5 Hz, 1H), 2.03-2.00 (m, 2H), 1.85-1.82 (m, 1H), 1.73-1.68 (m, 1H), 1.60 (s, 1H), 1.56-1.47 (m, 3H), 1.38-1.36 (m, 1H), 1.33-1.28 (m, 1H), 1.32 (s, 6H), 1.31 (s, 6H), 1.17-1.10 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.61, 138.73, 115.71, 108.90, 101.58, 99.89, 76.67, 62.62, 62.28, 48.96, 48.33 (2C), 44.97, 40.90, 35.78, 35.07, 32.24, 25.24, 25.12, 24.82, 24.71, 23.90 (2C), 21.42.

IR (neat, cm^{-1} , ν): 3554 (w), 3071 (w), 2985 (m), 2935 (s), 2860 (m), 1644 (w), 1444 (w), 1372 (m), 1218 (s), 1161 (m), 1064 (s).

HRMS (EI, m/z): calculated 320.2351 for $[\text{M}-\text{C}(\text{Me})_2(\text{OH})(\text{OMe})]^+$, found 320.2328.



(±)-5-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-2,2-dimethyl-4,7-dihydro-[1,3]dioxepine (4.141A):

A solution of **4.140A** (10.0 mg, 0.0244 mmol) in 10 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 140 °C. After 30 minutes the reaction was concentrated and the crude material was purified by silica gel flash chromatography (5% ethyl acetate/hexanes) to yield 6.5 mg of a colourless oil (87%).

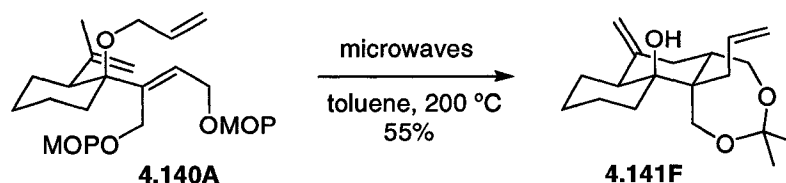
Data for 4.141A:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.92-5.84 (m, 1H), 5.42 (s, br, 1H), 5.32 (dddd, $J = 17.2$, 2.0, 2.0, 2.0 Hz, 1H), 5.07 (dddd, $J = 10.6$, 1.9, 1.9, 1.9 Hz, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 4.38-4.30 (m, 2H), 4.16-4.11 (m, 1H), 4.00 (d, $J = 16.1$ Hz, 1H), 3.83-3.79 (m, 1H), 3.74-3.70 (m, 1H), 2.00-1.93 (m, 2H), 1.88-1.87 (m, 1H), 1.77 (s, 3H), 1.74-1.72 (m, 1H), 1.57-1.32 (m, 3H), 1.37 (s, 6H), 1.24-1.21 (m, 2H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.61, 143.56, 135.45, 124.90, 114.46, 113.17, 101.74, 80.88, 62.28, 61.29, 61.20, 55.27, 31.76, 27.86, 26.26, 24.08, 23.80, 22.67, 21.40.

IR (neat, cm^{-1} , ν): 2989 (m), 2939 (s), 2856 (m), 1646 (w), 1448 (w), 1371 (s), 1220 (s), 1176 (m), 1162 (m), 1092 (m), 1069 (m).

HRMS (EI, m/z): calculated 306.2195 for $[\text{M}]^+$, found 306.2182.



(±)-(4aS,6aS,11aR,11bS)-11a-Allyl-9,9-dimethyl-5-methylene-decahydro-8,10-dioxacyclohepta[a]naphthalen-11b-ol (4.141F):

A solution of **4.140A** (14.5 mg, 0.0353 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C. After 1 hour the reaction was concentrated and the crude material was purified by silica gel flash chromatography (5% ethyl acetate/hexanes) to yield 6 mg of **4.141F** as a colourless oil (55%).

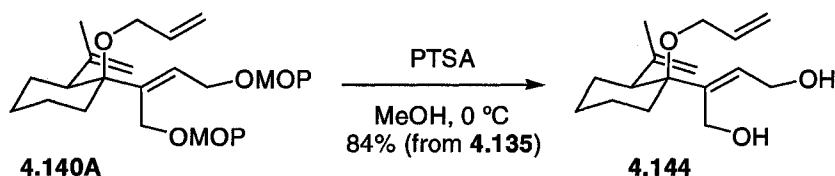
Data for 4.141F:

¹H NMR (CDCl₃, 500 MHz, δ): 6.18-6.09 (m, 1H), 5.03 (dd, J = 15.6, 2.2 Hz, 1H), 4.96 (dd, J = 10.1, 2.2 Hz, 1H), 4.92 (d, J = 1.6 Hz, 1H), 4.67 (d, J = 1.5 Hz, 1H), 3.99 (d, J = 12.2 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.44 (dd, J = 12.1, 1.8 Hz, 1H), 3.24 (dd, J = 12.8, 3.1 Hz, 1H), 2.77 (dd, J = 15.4, 7.6 Hz, 1H), 2.75 (dd, J = 14.7, 12.4 Hz, 1H), 2.37 (dd, J = 15.3, 6.9 Hz, 1H), 2.12 (dd, J = 14.1, 4.4 Hz, 1H), 2.03-2.00 (m, 2H), 1.85-1.83 (m, 1H), 1.72-1.69 (m, 1H), 1.60 (d, J = 1.1 Hz, 1H), 1.56-1.48 (m, 3H), 1.34-1.27 (m, 2H), 1.32 (s, 3H), 1.31 (s, 3H), 1.15-1.11 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 149.63, 138.74, 115.71, 108.90, 101.60, 76.68, 62.64, 62.29, 48.99, 45.00, 40.94, 35.81, 35.09, 32.25, 25.25, 25.13, 24.83, 24.73, 21.44.

IR (neat, cm⁻¹, ν): 3555 (w), 3077 (w), 2985 (m), 2935 (s), 2861 (m), 1639 (w), 1443 (w), 1372 (m), 1218 (s), 1161 (m), 1087 (m), 1064 (s), 993 (m).

HRMS (EI, m/z): calculated 306.2195 for [M]⁺, found 306.2176.



(±)-(E)-2-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-but-2-ene-1,4-diol (4.144**):**

A solution of unpurified **4.140A** (677 mg, 1.65 mmol maximum) in 15 mL of methanol was cooled to 0 °C. A small crystal of *para*-toluenesulfonic acid was added and the reaction was stirred for 1 hour before quenching with a saturated aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (40% ethyl acetate/hexanes) yielded 370 mg of a colourless oil (84% for 2 steps)

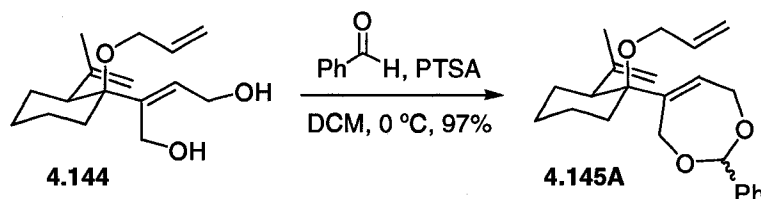
Data for 4.144:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.94-5.82 (m, 2H), 5.30 (dd, $J = 17.3, 1.8$ Hz, 1H), 5.10 (dd, $J = 10.6, 1.6$ Hz, 1H), 4.72 (ddd, $J = 1.4, 1.4, 1.4$ Hz, 1H), 4.62 (d, $J = 2.7$ Hz, 1H), 4.27 (dd, $J_{\text{AB}} = 12.7$ Hz, $J_{\text{AX}} = 6.6$ Hz, 1H), 4.20 (dd, $J_{\text{AB}} = 12.8$ Hz, $J_{\text{BX}} = 6.8$ Hz, 1H), 4.09 (d, $J_{\text{AB}} = 12.8$ Hz, 1H), 4.03 (d, $J_{\text{AB}} = 12.7$ Hz, 1H), 3.85-3.79 (m, 1H), 3.55-3.49 (m, 1H), 2.40 (s, br, 2H), 2.06-1.98 (m, 2H), 1.96-1.88 (m, 1H), 1.84 (s, 3H), 1.80-1.71 (m, 1H), 1.68-1.23 (m, 5H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 150.70, 148.33, 135.28, 130.99, 114.89, 112.78, 82.40, 62.76, 59.22, 57.61, 57.04, 31.73, 27.55, 26.09, 21.39, 21.34.

IR (neat, cm^{-1} , ν): 3344 (s, br), 2941 (s), 2857 (m), 1641 (w), 1448 (m), 1373 (m), 1151 (m), 1118 (m), 1058 (s), 1012 (s).

HRMS (EI, m/z): calculated 248.1776 for $[\text{M}-\text{H}_2\text{O}]^+$, found 248.1774.



(±)-5-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-2-phenyl-4,7-dihydro-[1,3]dioxepine (4.145A):

A solution of **4.144** (370 mg, 1.39 mmol) in 15 mL of dichloromethane was cooled to 0 °C. Benzaldehyde (0.430 mL, 4.23 mmol) was added, followed by a single crystal of *para*-toluenesulfonic acid, and the reaction stirred for 2.5 hours. A saturated aqueous solution of sodium bicarbonate was then added and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 478 mg of a colourless oil (97%).

Data for 4.145A (mixture of acetal epimers):

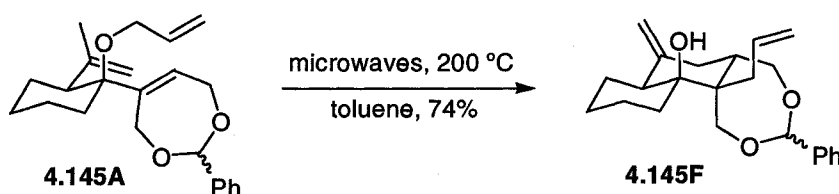
^1H NMR (CDCl_3 , 500 MHz, δ): 7.51-7.48 (m, 2H), 7.38-7.29 (m, 3H), 5.94-5.86 (m, 1H), 5.83 and 5.81 (s and s, 1H), 5.59 and 5.56 (s, br and s, br, 1H), 5.36-5.30 (m, 1H), 5.11-5.08 (m, 1H), 4.80-4.77 (m, 2H), 4.42-4.30 and 4.16 and 4.02 (m and dd and d, $J = 15.9, 4.1$ Hz and $J = 15.8$ Hz, 4H), 3.86-3.83 (m, 1H), 3.78-3.73 (m, 1H), 2.06-1.99 (m, 2H), 1.92 and

1.88 (d, br, $J = 9.8$ Hz and d, br, $J = 11.6$ Hz, 1H), 1.81 and 1.79 (s and s, 3H), 1.78-1.74 (m, 1H), 1.54-1.42 (m, 4H), 1.25-1.20 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.59, 147.24, 145.45, 144.58, 138.89, 138.82, 135.33, 135.28, 128.26 (2C), 128.04 (2C), 128.03 (2C), 126.44 (2C), 126.43 (2C), 125.96, 125.18, 114.66, 114.51, 113.40, 113.29, 102.56, 101.69, 81.23, 80.92, 65.56, 64.70, 62.86, 62.82, 62.42, 62.33, 55.53, 55.12, 31.79 (2C), 27.74, 27.72, 26.18 (2C), 22.59, 22.43, 21.34, 21.31.

IR (neat, cm^{-1} , ν): 3070 (w), 3032 (w), 2938 (s), 2856 (s), 1736 (w), 1646 (w), 1450 (s), 1374 (m), 1355 (m), 1263 (m), 1207 (m), 1177 (m), 1129 (s), 1072 (m), 1027 (s).

HRMS (EI, m/z): calculated 313.1804 for $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]^+$, found 313.1797.



(±)-(4a*S*,6a*S*,11a*R*,11b*S*)-11a-Allyl-5-methylene-9-phenyl-decahydro-8,10-dioxacyclohepta[*a*]naphthalen-11b-ol (**4.145F**):

A solution of **4.145A** (137 mg, 0.387 mmol) in 15 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1.5 hours. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 101 mg of a **4.145F** as a colourless oil (74%).

Data for **4.145F** (mixture of acetal epimers):

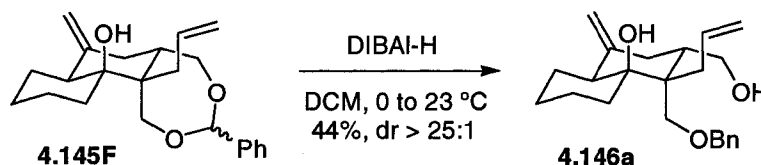
^1H NMR (CDCl_3 , 500 MHz, δ): 7.50-7.45 (m, 2H), 7.37-7.26 (m, 3H), 6.24-6.13 (m, 1H), 5.78 and 5.74 (s and s, 1H), 5.09-4.94 (m, 3H), 4.70 and 4.66 (s and s, 1H), 4.14 and 3.95 (d, $J = 12.9$ Hz and d, $J = 12.6$ Hz, 1H), 4.12 and 3.83 (d, $J = 12.0$ Hz and d, $J = 12.1$ Hz, 1H), 3.98 and 3.44 (dd, $J = 11.8$, 1.4 Hz and dd, $J = 12.2$, 1.7 Hz, 1H), 3.67 and 3.27 (dd, $J = 12.3$, 3.0 Hz and dd, $J = 12.6$, 3.1 Hz, 1H), 2.89-2.77 (m, 2H), 2.49-2.41 (m, 1H), 2.21 and 2.20 (dd, $J = 14.2$, 14.1 Hz and dd, $J = 14.3$, 14.2 Hz, 1H), 2.10-2.08 (m, 1H), 2.02-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.74-1.41 (m, 5H), 1.35-0.99 (m, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 149.43 (2C), 139.85, 139.61, 138.60, 138.50, 128.29, 128.26, 128.21 (2C), 128.19 (2C), 126.32 (2C), 126.13 (2C), 116.08, 115.86, 109.08, 109.04,

100.51, 99.86, 77.20 (2C), 68.14, 67.14, 62.47, 62.34, 49.47, 49.18, 45.19, 44.83, 41.44, 41.41, 36.15, 35.91, 35.61, 35.29, 32.40, 32.19, 25.23, 25.06, 24.71, 24.63, 21.38, 21.35.

IR (neat, cm^{-1} , ν): 3551 (w), 3069 (w), 2935 (s), 2861 (s), 1644 (m), 1494 (w), 1450 (m), 1359 (m), 1280 (w), 1206 (s), 1120 (s), 1101 (s).

HRMS (EI, m/z): calculated 354.2195 for $[\text{M}]^+$, found 354.2192.



(±)-(3S,4R,4aS,8aS)-4-Allyl-4-benzoyloxymethyl-3-hydroxymethyl-1-methylene-octahydro-naphthalen-4a-ol (4.146a):

A stirring solution of **4.145F** (17 mg, 0.048 mmol) in 0.5 mL of dichloromethane was cooled to 0 °C. Diisobutylaluminum hydride was added (0.30 mL of a 1.5 M solution in toluene, 0.45 mmol) and the reaction was warmed to ambient temperature and stirred for 18 hours. Following no further consumption of starting material, the excess diisobutylaluminum hydride was quenched with several drops of acetone, followed by equal volumes of a 1 M aqueous sodium hydroxide solution and a 1 M aqueous sodium tartrate solution. Ethyl acetate was added and the reaction was stirred vigorously until two distinct phases appeared (approximately one hour). The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 30% ethyl acetate/hexanes) yielded 3.2 mg of recovered starting material as well as 7.5 mg of the desired product as a colourless oil (44%).

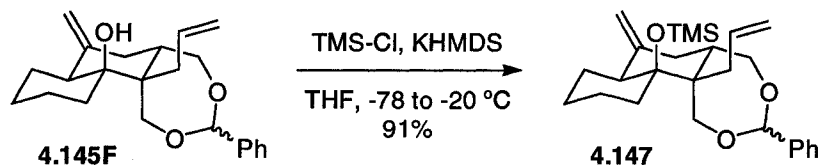
Data for 4.146a:

^1H NMR (CDCl_3 , 500 MHz, δ): 7.36-7.33 (m, 2H), 7.31-7.28 (m, 3H), 6.11-6.03 (m, 1H), 5.04 (dd, $J = 17.1, 1.6$ Hz, 1H), 4.98 (d, $J = 10.0$ Hz, 1H), 4.89 (d, $J = 1.6$ Hz, 1H), 4.63 (d, $J = 1.4$ Hz, 1H), 4.50 (s, 2H), 3.83 (d, $J = 9.7$ Hz, 1H), 3.79-3.76 (m, 1H), 3.63-3.58 (m, 1H), 3.36 (d, $J = 9.7$ Hz, 1H), 2.89 (dd, $J = 8.6, 3.7$ Hz, 1H), 2.60 (dd, $J = 15.5, 6.9$ Hz, 1H), 2.49 (dd, $J = 13.5, 13.3$ Hz, 1H), 2.38-2.31 (m, 2H), 2.20 (d, $J = 11.0$ Hz, 1H), 2.18-2.13 (m, 1H), 1.89 (d, $J = 13.5$ Hz, 1H), 1.71 (d, $J = 12.9$ Hz, 1H), 1.61-1.46 (m, 5H), 1.38 (ddd, $J = 13.5, 13.0, 4.3$ Hz, 1H), 1.15 (dddd, $J = 12.9, 12.9, 12.9, 4.0, 4.0$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.57, 137.75, 136.94, 128.45 (2C), 127.90, 127.66 (2C), 116.22, 108.58, 77.41, 73.88, 71.67, 63.09, 48.39, 44.74, 41.85, 35.64, 35.20, 32.19, 25.19, 24.60, 21.41.

IR (neat, cm^{-1} , ν): 3426 (s, br), 3071 (w), 2931 (s), 2858 (m), 1642 (w), 1447 (m), 1366 (w), 1098 (m), 1060 (m), 1029 (m).

HRMS (EI, m/z): calculated 356.2351 for $[\text{M}]^+$, found 356.2308.



(±)-((4a*S*,11a*R*,11b*S*)-11a-Allyl-5-methylene-9-phenyl-decahydro-8,10-dioxacyclohepta[*a*]naphthalen-11b-yloxy)-trimethyl-silane (**4.147**):

A solution of **4.145F** (104 mg, 0.293 mmol) in 5.0 mL of tetrahydrofuran was cooled to -78 $^\circ\text{C}$. Potassium bis(trimethylsilyl)amide (117 mg, 0.586 mmol) was added in one portion followed by freshly distilled chlorotrimethylsilane (0.110 mL, 0.867 mmol). The reaction was stirred at for one hour, warmed to -20 $^\circ\text{C}$, and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (3% ethyl acetate/hexanes) yielded 114 mg (91%) of **4.147** as a colourless oil.

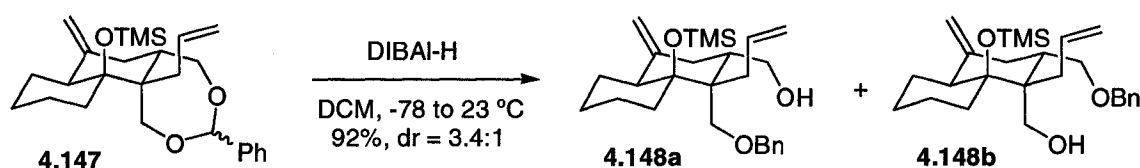
Data for **4.147** (mixture of acetal epimers):

^1H NMR (CDCl_3 , 500 MHz, δ): 7.52 (dd, $J = 8.3, 1.3$ Hz, 2H), 7.47 (dd, $J = 8.6, 1.7$ Hz, 2H), 7.38-7.30 (m, 6H), 6.36-6.23 (m, 2H), 5.78 (s, 1H), 5.75 (s, 1H), 5.14 (d, $J = 17.3$ Hz, 2H), 5.03 (ddd, $J = 10.3, 10.3, 1.9$ Hz, 2H), 4.76-4.75 (m, 2H), 4.51 (d, $J = 1.7$ Hz, 1H), 4.48 (d, $J = 1.8$ Hz, 1H), 4.20 (d, $J = 12.6$ Hz, 1H), 4.16-4.15 (m, 2H), 3.97 (d, $J = 12.8$ Hz, 1H), 3.86 (d, $J = 12.2$ Hz, 1H), 3.67-3.62 (m, 2H), 3.21 (dd, $J = 12.8, 3.1$ Hz, 1H), 2.89 (dd, $J = 14.2, 14.2$ Hz, 1H), 2.83 (dd, $J = 15.2, 15.2$ Hz, 1H), 2.56-2.52 (m, 1H), 2.43-2.38 (m, 3H), 2.20 (dd, $J = 14.5, 4.8$ Hz, 1H), 2.16 (dd, $J = 14.5, 4.7$ Hz, 1H), 2.11 (dd, $J = 13.6, 1.5$ Hz, 1H), 2.05 (dd, $J = 13.8, 1.4$ Hz, 1H), 1.91 (dd, $J = 11.1, 3.3$ Hz, 1H), 1.75-1.17 (m, 17H), 0.15 (s, 9H), 0.15 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.58, 149.50, 139.84, 139.72, 138.72, 138.54, 128.08 (2C), 128.03 (2C), 127.99 (2C), 126.28 (2C), 126.14 (2C), 115.39, 114.94, 106.11, 106.03, 100.12, 99.76, 82.81, 82.79, 67.83, 66.65, 62.87, 61.20, 49.85, 49.49, 45.38, 45.06, 42.91, 42.79, 36.28, 36.02, 35.84, 35.56, 32.84, 32.58, 25.00, 24.83, 24.81, 24.73, 21.91, 21.86, 2.92 (6C).

IR (neat, cm^{-1} , ν): 3072 (w), 3032 (w), 2940 (s), 2861 (s), 1648 (m), 1634 (w), 1450 (m), 1357 (w), 1332 (w), 1249 (s), 1206 (m), 1108 (s), 1071 (s), 1027 (s).

HRMS (EI, m/z): calculated 426.2590 for $[\text{M}]^+$, found 426.2609.



($\pm$)-((1R,4aS,8aS)-1-Allyl-1-benzyloxymethyl-4-methylene-8a-trimethylsilanyloxy-decahydro-naphthalen-2-yl)-methanol (**4.148a**) and ($\pm$)-((1R,4aS,8aS)-1-Allyl-2-benzyloxymethyl-4-methylene-8a-trimethylsilanyloxy-decahydro-naphthalen-1-yl)-methanol (**4.148b**):

A stirring solution of **4.147** (48 mg, 0.11 mmol) in 2.0 mL of dichloromethane was cooled to $-78\text{ }^{\circ}\text{C}$. Diisobutylaluminum hydride (1.0 mL of a 1.0 M solution in toluene, 1.0 mmol) was added and the reaction was warmed to ambient temperature and stirred for an additional 18 hours. The excess diisobutylaluminum hydride was quenched with several drops of acetone, followed by equal volumes of a 1 M aqueous sodium hydroxide solution and a 1 M aqueous sodium tartrate solution. Ethyl acetate was added and the reaction was stirred vigorously until two distinct phases were present (approximately one hour). The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% $\rightarrow$ 30% ethyl acetate/hexanes) yielded 34.3 mg (71%) of **4.148a**, along with 10.2 mg (21%) of **4.148b**, both as colourless oils.

Data for **4.148a** (major isomer):

^1H NMR (CDCl_3 , 300 MHz, δ): 7.40-7.33 (m, 5H), 6.08-5.99 (m, 1H), 5.08 (d, $J = 16.8$ Hz, 1H), 5.00 (d, $J = 10.0$ Hz, 1H), 4.76 (s, 1H), 4.57-4.46 (m, 3H), 3.90 (d, $J_{\text{AB}} = 9.6$ Hz, 1H), 3.92-3.86 (m, 1H), 3.59 (dd, $J = 12.2, 3.8$ Hz, 1H), 3.54 (d, $J_{\text{AB}} = 9.8$ Hz, 1H), 3.02 (s, br,

1H), 2.49 (dd, $J = 13.6, 13.4$ Hz, 1H), 2.41-2.39 (m, 2H), 2.26 (dd, $J = 14.1, 3.4$ Hz, 1H), 2.11-1.98 (m, 3H), 1.78-1.16 (m, 7H), 0.16 (s, 9H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 150.25, 138.32, 137.36, 129.01 (2C), 128.47, 128.34 (2C), 115.96, 106.90, 84.23, 74.37, 70.94, 64.28, 49.59, 46.12, 45.10, 36.62, 36.52, 32.99, 25.66, 25.26, 22.63, 3.47 (3C).

IR (neat, cm^{-1} , ν): 3401 (s, br), 3074 (m), 3032 (w), 2940 (s), 2865 (m), 1645 (m), 1496 (w), 1451 (m), 1366 (m), 1249 (s), 1131 (s), 1073 (s).

HRMS (EI, m/z): calculated 428.2747 for $[\text{M}]^+$, found 428.2755.

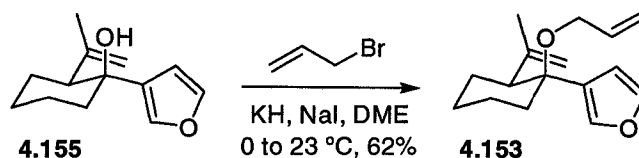
Data for **4.148b** (minor isomer):

^1H NMR (CDCl_3 , 500 MHz, δ): 7.36-7.27 (m, 5H), 6.16-6.08 (m, 1H), 5.03 (dd, $J = 17.1, 1.5$ Hz, 1H), 4.94 (dd, $J = 10.3, 1.0$ Hz, 1H), 4.70 (d, $J = 1.7$ Hz, 1H), 4.56 (d, $J_{\text{AB}} = 12.0$ Hz, 1H), 4.48-4.45 (m, 2H), 4.03 (d, $J = 12.2$ Hz, 1H), 3.87 (dd, $J = 10.3, 2.0$ Hz, 1H), 3.66 (d, $J = 12.2$ Hz, 1H), 3.40 (dd, $J = 10.3, 3.9$ Hz, 1H), 2.65 (dd, $J = 13.7, 13.7$ Hz, 1H), 2.38 (dd, $J_{\text{AB}} = 15.6, J_{\text{AX}} = 5.9$ Hz, 1H), 2.31 (dd, $J_{\text{AB}} = 15.6, J_{\text{BX}} = 8.1$ Hz, 1H), 2.12-1.97 (m, 4H), 1.70 (d, $J = 13.2$ Hz, 1H), 1.57-1.40 (m, 5H), 1.20-1.12 (m, 1H), 0.11 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 149.75, 138.32, 137.17, 128.41 (2C), 127.84, 127.75 (2C), 115.00, 106.43, 83.72, 73.40, 71.53, 61.64, 49.84, 45.11, 41.69, 36.24, 35.19, 32.25, 25.04, 24.75, 22.11, 2.99 (3C).

IR (neat, cm^{-1} , ν): 3426 (s, br), 3070 (m), 2946 (s), 2865 (s), 1777 (w), 1645 (m), 1496 (w), 1453 (s), 1409 (m), 1363 (m), 1249 (s), 1128 (s), 1059 (s).

HRMS (EI, m/z): calculated 428.2747 for $[\text{M}]^+$, found 428.2740.



(±)-3-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-furan (**4.153**):

Sodium iodide (8 mg, 0.05 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (175 mg of a 30% suspension in mineral oil, 2.62 mmol) was added to the flask and the system was put under nitrogen. The potassium hydride was washed three times with hexanes and dried under a flow of nitrogen. Dimethoxyethane (3.0 mL) was added and the resulting suspension was cooled to 0 °C. A solution of **4.155** (108 mg, 0.524 mmol) in

another 2.0 mL of dimethoxyethane was cannulated into the flask and stirred for 20 minutes. Allyl bromide (0.230 mL, 2.66 mmol) was added drop-wise and the reaction was warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (1% ethyl acetate/hexanes) yielded 80 mg of **4.153** as a colourless oil (62%).

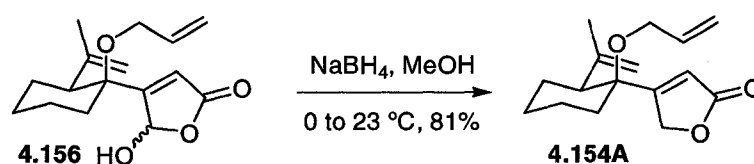
Data for 4.153:

¹H NMR (CDCl₃, 500 MHz, δ): 7.27 (s, 1H), 7.17 (s, 1H), 6.24 (s, 1H), 5.92-5.85 (m, 1H), 5.31 (dddd, J = 17.2, 1.9, 1.9, 1.9 Hz, 1H), 5.08 (dddd, J = 10.6, 1.7, 1.7, 1.7 Hz, 1H), 4.65 (s, 1H), 4.51 (s, 1H), 3.82-3.77 (m, 1H), 3.70-3.65 (m, 1H), 2.17-2.14 (m, 1H), 2.06 (dddd, J = 12.8, 12.8, 12.8, 3.6 Hz, 1H), 1.98 (dd, J = 12.7, 2.9 Hz, 1H), 1.82-1.77 (m, 1H), 1.67 (s, 3H), 1.63-1.50 (m, 3H), 1.46-1.42 (m, 1H), 1.37-1.27 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz, δ): 147.30, 141.91, 139.21, 135.82, 129.90, 114.46, 113.24, 110.49, 76.49, 62.60, 57.21, 33.26, 27.70, 26.29, 22.78, 21.21.

IR (neat, cm⁻¹, ν): 3072 (w), 2934 (m), 2857 (m), 1645 (w), 1501 (w), 1448 (m), 1372 (w), 1164 (m), 1124 (w), 1062 (m), 1023 (m).

HRMS (EI, m/z): calculated 246.1620 for [M]⁺, found 246.1606.



(±)-4-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-5H-furan-2-one:

A solution of **4.156** (50 mg, 0.18 mmol) in anhydrous methanol was cooled to 0 °C. Sodium borohydride (34 mg, 0.90 mmol) was added in one portion and the reaction was warmed to ambient temperature and stirred for 18 hours. An additional 34 mg of sodium borohydride (0.90 mmol) was then added and the reaction was stirred for an additional 2 hours. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash

chromatography (20% ethyl acetate/hexanes) yielded 38 mg of **4.154A** as a colourless oil (81%).

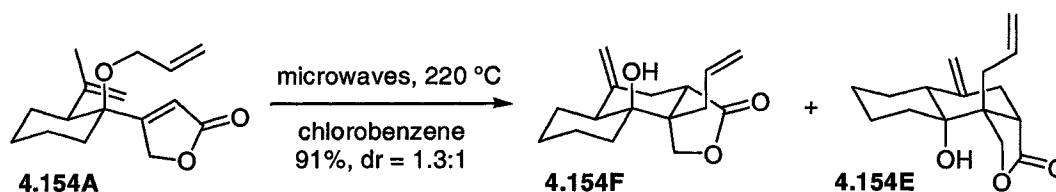
Data for 4.154A:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.90-5.84 (m, 1H), 5.83 (s, 1H), 5.31 (dd, $J = 17.3, 1.7$ Hz, 1H), 5.15 (dd, $J = 10.7, 1.6$ Hz, 1H), 4.81 (dd, $J = 17.8, 1.9$ Hz, 1H), 4.71 (s, 1H), 4.64 (dd, $J = 17.8, 1.7$ Hz, 1H), 4.60 (s, 1H), 4.02-3.99 (m, 1H), 3.68-3.64 (m, 1H), 2.19-2.13 (m, 1H), 2.07-1.99 (m, 2H), 1.83-1.81 (m, 1H), 1.73 (s, 3H), 1.65-1.63 (m, 1H), 1.51-1.44 (m, 3H), 1.38-1.30 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 173.96, 173.66, 146.27, 134.00, 116.57, 115.79, 114.31, 79.41, 72.15, 63.90, 56.35, 32.33, 26.87, 25.67, 21.43, 20.81.

IR (neat, cm^{-1} , ν): 3078 (w), 2936 (s), 2859 (m), 1783 (m), 1754 (s), 1630 (w), 1448 (m), 1192 (w), 1151 (m), 1117 (w), 1042 (m), 1023 (m).

HRMS (EI, m/z): calculated 262.1569 for $[\text{M}]^+$, found 262.1560.



(±)-(3a*S*,5a*S*,9a*S*,9b*R*)-9b-Allyl-9a-hydroxy-5-methylene-decahydro-naphtho[1,2-*c*]furan-3-one (**4.154F**) and (±)-(3a*S*,5a*R*,9a*R*,9b*R*)-9b-Allyl-9a-hydroxy-5-methylene-decahydro-naphtho[1,2-*c*]furan-3-one (**4.154E**):

A solution of **4.154A** (137 mg, 0.522 mmol) in 13 mL of chlorobenzene was sparged with argon for 15 minutes and then heated in a microwave to 220 °C for 15 hours. Following removal of the solvent, a crude NMR showed a 5:4 mixture of isomers. Purification of the concentrated material by silica gel flash chromatography (15% → 30% ethyl acetate/hexanes) yielded 74 mg (54%) of **4.154F** and 50.7 mg of **4.154E** (37%) both as white solids.

Data for 4.154F (major isomer):

^1H NMR (CDCl_3 , 500 MHz, δ): 5.86-5.78 (m, 1H), 5.14-5.08 (m, 3H), 4.81 (s, 1H), 4.38 (d, $J = 9.3$ Hz, 1H), 4.09 (d, $J = 9.3$ Hz, 1H), 2.71 (dd, $J = 13.7, 7.6$ Hz, 1H), 2.51 (dd, $J = 12.1, 7.7$ Hz, 1H), 2.46 (dd, $J = 13.6, 8.4$ Hz, 1H), 2.38 (dd, $J = 14.0, 7.3$ Hz, 1H), 2.28 (dd, $J =$

7.9, 7.5 Hz, 1H), 2.14 (dd, $J = 13.2, 12.3$ Hz, 1H), 1.99-1.96 (m, 1H), 1.80-1.76 (m, 1H), 1.60-1.54 (m, 4H), 1.43 (s, 1H), 1.28-1.17 (m, 1H), 0.95 (ddd, $J = 12.3, 12.3, 5.4$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 178.17, 144.54, 133.27, 119.70, 111.42, 74.11, 72.11, 49.78, 46.24, 45.38, 39.23, 35.06, 31.07, 24.93, 23.77, 20.56.

IR (neat, cm^{-1} , ν): 3521 (m, br), 3082 (w), 2935 (s), 2859 (m), 1773 (s), 1652 (w), 1638 (w), 1444 (m), 1370 (w), 1227 (w), 1179 (m), 1149 (m), 1006 (m).

HRMS (EI, m/z): calculated 262.1569 for $[\text{M}]^+$, found 262.1562.

mp = 123.7-125.3 °C.

Data for **4.154E** (minor isomer):

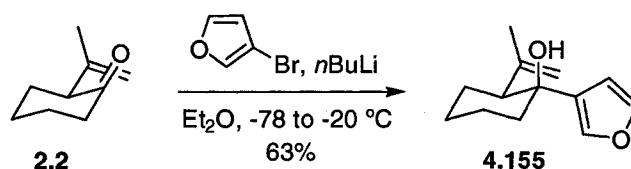
^1H NMR (CDCl_3 , 500 MHz, δ): 5.83-5.75 (m, 1H), 5.24 (d, $J = 10.1$ Hz, 1H), 5.17 (dddd, $J = 18.6, 1.4, 1.4, 1.4$ Hz, 1H), 5.15 (s, 1H), 4.82 (d, $J = 1.4$ Hz, 1H), 4.36 (d, $J = 9.2$ Hz, 1H), 3.88 (d, $J = 9.2$ Hz, 1H), 2.76 (dd, $J = 14.5, 1.5$ Hz, 1H), 2.68 (dd, $J = 7.5, 1.6$ Hz, 1H), 2.37 (dd, $J = 14.3, 8.4$ Hz, 1H), 2.31-2.27 (m, 2H), 2.24 (dd, $J = 14.4, 6.4$ Hz, 1H), 1.78-1.74 (m, 1H), 1.69 (dddd, $J = 12.9, 2.6, 2.6, 2.6$ Hz, 1H), 1.62 (dddd, $J = 13.2, 3.4, 3.4, 3.4$ Hz, 1H), 1.56-1.50 (m, 3H), 1.47 (dddd, $J = 12.2, 12.2, 12.2, 3.8$ Hz, 1H), 1.38 (ddd, $J = 13.0, 10.2, 7.3$ Hz, 1H), 1.27-1.15 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 177.49, 143.56, 133.06, 120.16, 113.07, 75.50, 68.91, 48.68, 42.87, 41.24, 35.79, 30.89, 29.88, 24.98, 24.08, 20.60.

IR (neat, cm^{-1} , ν): 3529 (m, br), 3088 (w), 2934 (s), 2869 (m), 1771 (s), 1643 (w), 1452 (w), 1383 (s), 1316 (w), 1201 (w), 1174 (w), 1147 (m), 1130 (w), 1023 (m).

HRMS (EI, m/z): calculated 221.1178 for $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]^+$, found 221.1178.

mp = 64.1-67.0 °C.



(±)-(1S,2S)-1-Furan-3-yl-2-isopropenyl-cyclohexanol (4.155):

A solution of 3-bromofuran (0.150 mL, 1.67 mmol) in 8 mL of diethyl ether was cooled to -78 °C. *n*-Butyllithium (0.690 mL of a 2.43 M solution in pentane, 1.68 mmol) was added and the reaction was stirred for 1 hour. Ketone **2.2** (115 mg, 0.832 mmol) was then added by cannula as a solution in 2 mL of diethyl ether (*Note: the addition must be done slowly in*

order to ensure the reaction temperature stays at $-78\text{ }^{\circ}\text{C}$. Otherwise, the lithium species begins to isomerize and a mixture of products is obtained). After stirring at $-78\text{ }^{\circ}\text{C}$ for 1 hour, the reaction was gradually warmed to $-20\text{ }^{\circ}\text{C}$ before quenching with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 108 mg of a colourless oil (63%).

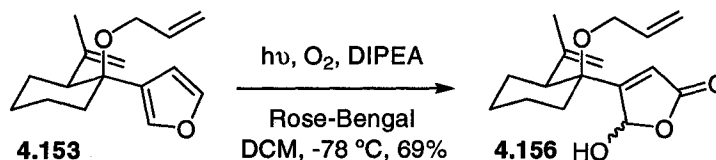
Data for 4.155:

^1H NMR (CDCl_3 , 500 MHz, δ): 7.30 (s, 1H), 7.24 (s, 1H), 6.25 (s, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 2.22 (dd, $J = 12.9, 3.4\text{ Hz}$, 1H), 2.12 (s, br, 1H), 1.88-1.84 (m, 1H), 1.82-1.62 (m, 4H), 1.58-1.49 (m, 2H), 1.43 (s, 3H), 1.36-1.26 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 148.44, 142.50, 138.03, 134.29, 111.79, 108.79, 70.51, 53.07, 39.88, 27.47, 25.92, 25.14, 21.13.

IR (neat, cm^{-1} , ν): 3542 (w, br), 2935 (s), 2856 (m), 1637 (w), 1500 (w), 1447 (w), 1373 (w), 1290 (w), 1164 (m), 1126 (w), 1071 (w), 1044 (w), 1022 (w).

HRMS (EI, m/z): calculated 206.1299 for $[\text{M}]^+$, found 206.1307.



(±)-4-((1S,2S)-1-Allyloxy-2-isopropenyl-cyclohexyl)-5-hydroxy-5H-furan-2-one (4.156):

N,N,N-Diisopropylethyl amine (0.180 mL, 1.03 mmol) was added to a stirring solution of **4.153** (64 mg, 0.26 mmol) in 50 mL of dichloromethane, followed by Rose-Bengal (5 mg, 0.005 mmol). The pale pink solution was then cooled to $-78\text{ }^{\circ}\text{C}$ and oxygen was bubbled through the solution while a 320 W tungsten lamp was shone on the flask for 4.5 hours. During this time, additional dichloromethane was added as needed in order to maintain the reaction volume. After removing the light source, the now deep fuchsia reaction was warmed to ambient temperature and quenched with a saturated aqueous solution of oxalic acid. Vigorous stirring for 30 minutes resulted in the return of the initial pale pink colour. The aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica

gel flash chromatography (30% ethyl acetate/hexanes) yielded 50 mg of **4.156** as a colourless oil (69%).

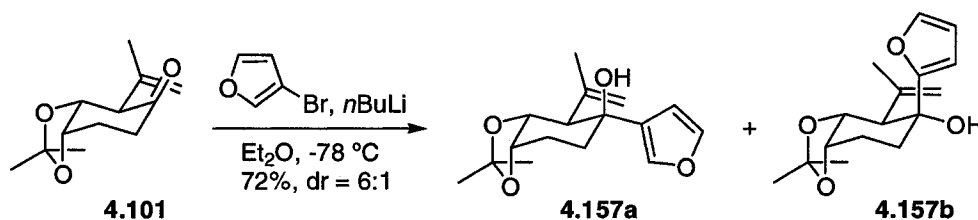
Data for 4.156 (mixture of hemi-acetal epimers):

^1H NMR (CDCl_3 , 500 MHz, δ): major epimer: 6.04 (s, 1H), 5.93-5.83 (m, 2H), 5.31 (dd, $J = 17.3, 1.8$ Hz, 1H), 5.13 (dd, $J = 10.5, 1.6$ Hz, 1H), 4.74 (s, 1H), 4.66 (s, 1H), 3.93-3.90 (m, 1H), 3.71-3.67 (m, 1H), 2.47 (dd, $J = 12.7, 3.3$ Hz, 1H), 2.19-2.01 (m, 2H), 1.85-1.73 (m, 2H), 1.73 (s, 3H), 1.68-1.59 (m, 2H), 1.52-1.42 (m, 2H), 1.41-1.32 (m, 1H). minor epimer: 6.02 (s, 1H), 5.93-5.83 (m, 2H), 5.34 (dd, $J = 17.2, 1.8$ Hz, 1H), 5.15 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 4.05-4.01 (m, 1H), 3.83-3.71 (m, 1H), 2.19-2.01 (m, 3H), 1.85-1.73 (m, 2H), 1.72 (s, 3H), 1.68-1.59 (m, 2H), 1.52-1.42 (m, 2H), 1.41-1.32 (m, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): major and minor: 170.53, 170.03, 169.90, 168.75, 147.45, 146.68, 134.24, 134.10, 119.94, 119.45, 115.56, 115.43, 114.47, 113.95, 97.78, 97.73, 80.57, 79.64, 63.47, 62.88, 55.66, 52.86, 31.17, 30.49, 26.53, 26.46, 25.48 (2C), 21.59, 20.98, 20.55, 20.37.

IR (neat, cm^{-1} , ν): 3350 (s, br), 2936 (s), 2859 (s), 1738 (s), 1637 (w), 1451 (m), 1262 (m), 1172 (m), 1113 (s), 1057 (m).

HRMS (EI, m/z): calculated 237.1127 for $[\text{M}]^+$, found 237.1220.



(±)-(3aR,4R,5S,7aS)-5-Furan-3-yl-4-isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-ol (4.157a) and (±)-(3aR,4R,5R,7aS)-5-Furan-3-yl-4-isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-ol (4.157b):

A solution of 3-bromofuran (0.340 mL, 3.78 mmol) in 15.0 mL of diethyl ether was cooled to $-78\text{ }^{\circ}\text{C}$. *n*-Butyllithium (1.58 mL of a 2.40 M solution in pentane, 3.79 mmol) was added and the reaction was stirred for 1 hour. Ketone **4.101** (400 mg, 1.90 mmol) was added by cannula as a solution in 5 mL of diethyl ether (*Note: the addition must be done slowly in order to ensure the reaction temperature stays at $-78\text{ }^{\circ}\text{C}$. Otherwise, the lithium species begins to isomerize and a mixture of products is obtained*). The reaction was kept and $-78\text{ }^{\circ}\text{C}$

for 2 hours before gradually warming to ambient temperature and quenching with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% → 30% ethyl acetate/hexanes) yielded 329 mg of **4.157a** (62%) and 52 mg of **4.157b** (10%) both as colourless oils.

Data for **4.157a** (major isomer):

¹H NMR (CDCl₃, 500 MHz, δ): 7.31 (dd, *J* = 1.7, 1.7 Hz, 1H), 7.23 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.25 (dd, *J* = 1.8, 0.9 Hz, 1H), 4.99 (s, 1H), 4.85 (s, 1H), 4.33–4.30 (m, 2H), 2.38–2.35 (m, 1H), 2.25–2.17 (m, 1H), 2.11–2.05 (m, 2H), 1.95–1.78 (m, 1H), 1.70–1.67 (m, 1H), 1.57 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 144.83, 142.78, 137.97, 132.71, 113.48, 108.55, 107.85, 77.22, 72.74, 72.18, 54.90, 33.60, 28.59, 26.22, 25.32, 21.72.

IR (neat, cm⁻¹, ν): 3462 (m, br), 2985 (s), 2933 (s), 1687 (w), 1643 (w), 1501 (m), 1447 (m), 1381 (s), 1243 (s), 1218 (s), 1159 (s), 1059 (s), 1023 (s).

HRMS (EI, *m/z*): calculated 278.1518 for [M]⁺, found 278.1525.

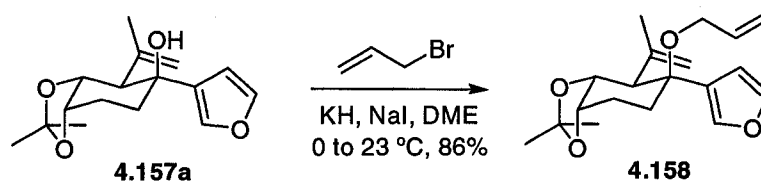
Data for **4.157b** (minor isomer):

¹H NMR (CDCl₃, 300 MHz, δ): 7.35–7.34 (m, 1H), 7.32–7.31 (m, 1H), 6.28 (dd, *J* = 1.8, 0.9 Hz, 1H), 5.02 (dd, *J* = 1.5, 1.5 Hz, 1H), 4.82 (d, *J* = 0.8 Hz, 1H), 4.41–4.33 (m, 2H), 3.14 (s, br, 1H), 2.69 (d, *J* = 7.2 Hz, 1H), 2.16–2.10 (m, 1H), 2.03–1.93 (m, 1H), 1.91–1.85 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 143.10 (2C), 139.77, 130.34, 117.35, 109.93, 108.45, 76.31, 72.93, 71.80, 57.85, 34.02, 28.96, 26.64, 23.98, 22.97.

IR (neat, cm⁻¹, ν): 3483 (br, w), 2991 (m), 2869 (m), 1646 (m), 1499 (m), 1455 (m), 1382 (m), 1243 (s), 1218 (s), 1158 (s), 1050 (s), 1032 (s).

HRMS (EI, *m/z*): calculated 263.1283 for [M-Me]⁺, found 263.1276.



(±)-(3aR,4R,5S,7aS)-5-Allyloxy-5-furan-3-yl-4-isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxole (4.158):

Sodium iodide (10 mg, 0.067 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (790 mg of a 30% suspension in mineral oil, 5.91 mmol) was added to the flask and the system was put under argon. The potassium hydride was washed three times with dry hexanes and dried under a flow of argon. Dimethoxyethane (7.0 mL) was added to the flask and the resulting suspension was cooled to 0 °C. A solution of **4.157a** (329 mg, 1.18 mmol) in another 3 mL of dimethoxyethane was cannulated into the flask. After stirring for 15 minutes, allyl bromide (0.510 mL, 5.89 mmol) was added and the reaction was warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 325 mg of a colourless oil (86%).

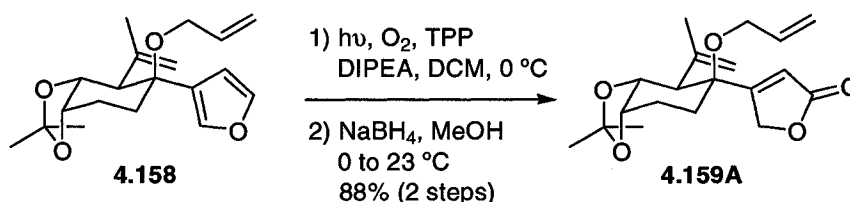
Data for 4.158:

¹H NMR (CDCl₃, 300 MHz, δ): 7.28 (dd, *J* = 1.7, 1.7 Hz, 1H), 7.20 (dd, *J* = 1.5, 0.9 Hz, 1H), 6.26 (dd, *J* = 1.8, 0.9 Hz, 1H), 5.89-5.77 (m, 1H), 5.25 (dddd, *J* = 17.2, 1.9, 1.9, 1.9 Hz, 1H), 5.07 (dddd, *J* = 10.5, 1.8, 1.7, 1.7 Hz, 1H), 4.93 (s, 1H), 4.77 (s, 1H), 4.46 (dd, *J* = 10.0, 4.8 Hz, 1H), 4.35-4.33 (m, 1H), 3.69-3.66 (m, 2H), 2.16 (d, *J* = 10.0 Hz, 1H), 2.13-1.91 (m, 4H), 1.70 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 143.62, 142.65, 139.85, 135.50, 128.49, 116.38, 115.19, 110.67, 108.29, 77.90, 77.56, 73.26, 63.24, 58.23, 29.04, 27.77, 26.84, 24.30, 22.37.

IR (neat, cm⁻¹, ν): 3075 (m), 2985 (s), 2935 (s), 2874 (s), 2739 (w), 1645 (m), 1586 (w), 1503 (m), 1454 (m), 1432 (m), 1379 (s), 1367 (s), 1283 (w), 1245 (s), 1216 (s), 1163 (s), 1060 (s), 1035 (s).

HRMS (EI, *m/z*): calculated 318.1831 for [M]⁺, found 318.1827.



(±)-4-((3aR,4R,5S,7aS)-5-Allyloxy-4-isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-yl)-5H-furan-2-one (4.159A):

N,N,N-Diisopropylethyl amine (0.110 mL, 0.632 mmol) was added to a solution of **4.158** (40 mg, 0.13 mmol) in 25 mL of dichloromethane, followed by 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (9 mg, 0.01 mmol). Oxygen was bubbled through the purple solution for five minutes before cooling to 0 °C. The bubbling of oxygen was maintained for 2 hours while a 200 W tungsten lamp was shone on the flask. After removing the light source, the reaction was warmed to ambient temperature and the solvent was evaporated. The resulting crude material was dissolved in 2 mL of methanol and cooled to 0 °C. Sodium borohydride (20 mg, 0.53 mmol) was added portion wise over two hours. At the end of the addition, the reaction was warmed to ambient temperature and stirred for 18 hours. Following a quench with a saturated brine solution, the aqueous phase was extracted three times with dichloromethane and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (30% → 50% ethyl acetate/hexanes) yielded 38 mg of a white solid (88% over 2 steps).

Data for 4.159A:

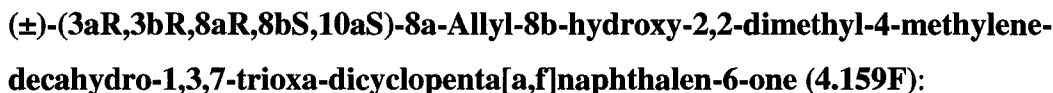
¹H NMR (CDCl₃, 300 MHz, δ): 5.89 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.87-5.76 (m, 1H), 5.28 (dddd, *J* = 17.2, 1.7, 1.7, 1.7 Hz, 1H), 5.16 (dddd, *J* = 10.6, 1.5, 1.5, 1.5 Hz, 1H), 4.98 (dd, *J* = 1.5, 1.5 Hz, 1H), 4.82 (dd, *J*_{AB} = 17.8 Hz, *J*_{AX} = 1.9 Hz, 1H), 4.78 (s, 1H), 4.63 (dd, *J*_{AB} = 17.8 Hz, *J*_{BX} = 1.7 Hz, 1H), 4.42 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.36-4.35 (m, 1H), 3.95-3.88 (m, 1H), 3.74-3.67 (m, 1H), 2.22 (d, *J* = 9.6 Hz, 1H), 2.18-2.12 (m, 1H), 2.02-1.86 (m, 3H), 1.82 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 173.50, 171.67, 142.44, 133.80, 118.06, 117.74, 116.54, 108.85, 80.75, 75.87, 72.74, 72.17, 64.55, 57.00, 29.03, 27.21, 26.72, 22.41, 22.22.

IR (neat, cm⁻¹, ν): 3079 (w), 2984 (m), 2938 (m), 2879 (m), 1783 (m), 1754 (s), 1641 (w), 1629 (w), 1453 (m), 1381 (m), 1367 (w), 1243 (m), 1217 (m), 1146 (m), 1112 (m), 1067 (s), 1042 (m).

HRMS (EI, *m/z*): calculated 334.1780 for [M]⁺, found 334.1791.

mp = 121.5-123.6 °C.



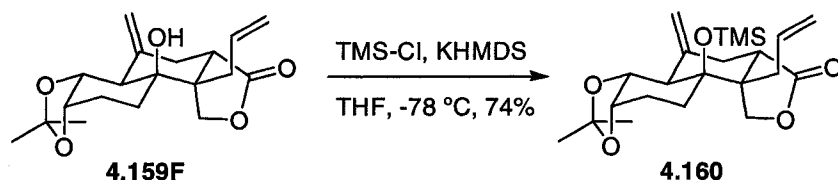
Data for 4.159F:

¹H NMR (C₆D₆, 500 MHz, δ): 5.72-5.64 (m, 1H), 4.98 (s, 1H), 4.97-4.90 (m, 2H), 4.89 (s, 1H), 4.06-4.01 (m, 2H), 3.74 (d, *J* = 9.4 Hz, 1H), 3.46 (dd, *J* = 9.5 Hz, 1H), 2.49 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.20 (d, *J* = 8.6 Hz, 1H), 2.14 (dd, *J* = 11.2, 7.5 Hz, 1H), 2.03 (dd, *J* = 14.3, 8.0 Hz, 1H), 1.94 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.86 (dd, *J* = 13.3, 12.1 Hz, 1H), 1.82-1.77 (m, 1H), 1.73-1.68 (m, 1H), 1.53 (s, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.16 (ddd, *J* = 13.6, 4.8, 3.9 Hz, 1H), 0.96-0.90 (m, 1H).

¹³C NMR (CDCl₃, 75 MHz, δ): 178.24, 140.85, 133.30, 120.68, 113.42, 108.63, 75.57, 73.65, 72.73, 72.34, 50.04, 48.27, 46.60, 39.58, 35.68, 29.07, 26.53, 25.91, 21.78.

IR (neat, cm⁻¹, v): 3483 (m), 2988 (m), 2937 (m), 1769 (s), 1638 (w), 1440 (w), 1379 (m), 1367 (m), 1244 (m), 1216 (m), 1158 (m), 1054 (m), 1017 (m).

HRMS (EI, m/z): calculated 319.1546 for $[M-Me]^+$, found 319.1525.



(±)-(3aR,3bR,8aR,8bS,10aS)-8a-Allyl-2,2-dimethyl-4-methylene-8b-trimethylsilanyloxy-decahydro-1,3,7-trioxa-dicyclopenta[a,f]naphthalen-6-one (4.160):

A solution of **4.159F** (38 mg, 0.11 mmol) in 2 mL of tetrahydrofuran was cooled to -78 °C. Potassium bis(trimethylsilyl)amide (95 mg, 0.48 mmol) was added, followed by chlorotrimethylsilane (0.150 mL, 1.18 mmol). After stirring for 2 hours, the reaction was quenched with water and the aqueous phase was extracted three times with ethyl acetate. The organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 34 mg of **4.160** as a colourless oil (74%).

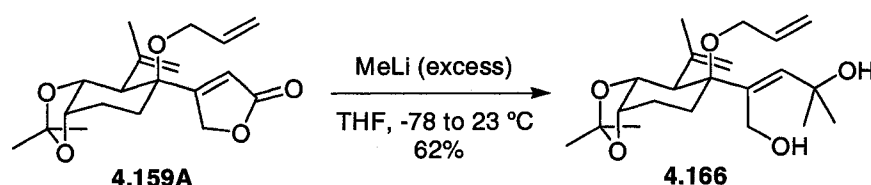
Data for 4.160:

¹H NMR (C₆D₆, 500 MHz, δ): 5.68-5.60 (m, 1H), 5.24 (s, 1H), 5.08-4.97 (m, 3H), 4.15 (dd, *J* = 9.0, 5.1 Hz, 1H), 4.11-4.09 (m, 1H), 3.78 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.54 (d, *J* = 9.6 Hz, 1H), 2.80 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.39 (dd, *J* = 7.8, 6.5 Hz, 1H), 2.32 (d, *J* = 9.0 Hz, 1H), 2.26 (dd, *J* = 7.1, 6.4 Hz, 1H), 2.03-1.94 (m, 2H), 1.82-1.77 (m, 1H), 1.67-1.59 (m, 1H), 1.41 (s, 3H), 1.30 (s, 3H), 1.16-1.11 (m, 1H), 0.93-0.88 (m, 1H), -0.09 (s, 9H).

¹³C NMR (C₆D₆, 125 MHz, δ): 177.51, 140.56, 132.20, 119.89, 113.35, 107.45, 80.50, 75.45, 72.16, 71.11, 48.97, 46.80, 45.96, 39.94, 33.73, 28.49, 26.45, 26.04, 22.75, 2.15 (3C).

IR (neat, cm⁻¹, ν): 3086 (w), 2983 (m), 2955 (s), 2940 (m), 2877 (m), 1777 (s), 1641 (w), 1440 (w), 1381 (w), 1365 (w), 1250 (s), 1215 (m), 1163 (m), 1120 (m), 1078 (m), 1038 (m).

HRMS (EI, *m/z*): calculated 406.2176 for [M]⁺, found 406.2149.



(±)-(E)-2-((3aR,4R,5S,7aS)-5-Allyloxy-4-isopropenyl-2,2-dimethyl-hexahydro-benzo [1,3]dioxol-5-yl)-4-methyl-pent-2-ene-1,4-diol (4.166):

A solution of **4.159A** (16 mg, 0.048 mmol) in 1 mL of tetrahydrofuran was cooled to -78 °C. Methyllithium (0.40 mL of a 1.6 M solution in diethyl ether, 0.64 mmol) was slowly added. After stirring for 20 minutes, the reaction was gradually warmed to ambient temperature and stirred for another two hours. The reaction was then re-cooled to 0 °C and quenched with a

saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (40% ethyl acetate/hexanes) yielded 11 mg of **4.166** as a colourless oil (62%).

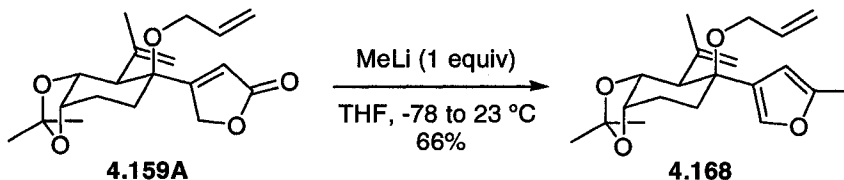
Data for 4.166:

¹H NMR (CDCl₃, 300 MHz, δ): 5.90-5.78 (m, 1H), 5.54 (s, 1H), 5.26 (dddd, $J = 17.3, 1.7, 1.7, 1.7$ Hz, 1H), 5.09 (dddd, $J = 10.6, 1.7, 1.7, 1.7$ Hz, 1H), 4.98 (s, 1H), 4.74 (s, 1H), 4.41 (dd, $J = 9.9, 4.8$ Hz, 1H), 4.34-4.32 (m, 1H), 4.28 (d, $J_{AB} = 12.9$ Hz, 1H), 4.03 (d, $J_{AB} = 12.8$ Hz, 1H), 3.72-3.70 (m, 2H), 2.65 (s, br, 2H), 2.17 (d, $J = 9.9$ Hz, 1H), 2.15-1.72 (m, 4H), 1.88 (s, 3H), 1.46 (s, 3H), 1.34 (s, 6H), 1.33 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 145.75, 137.95, 135.16, 116.57, 115.42, 115.41, 108.43, 84.28, 76.66, 73.25, 72.53, 63.22, 57.80, 57.79, 32.40, 31.26, 29.07 (2C), 26.81, 26.16, 22.66.

IR (neat, cm⁻¹, ν): 3397 (s, br), 2983 (s), 2972 (s), 2930 (s), 2874 (s), 1736 (w), 1644 (w), 1454 (m), 1379 (m), 1244 (s), 1216 (s), 1161 (m), 1115 (w), 1059 (s), 1023 (s).

HRMS (EI, m/z): calculated 348.2301 for [M-H₂O]⁺, found 348.2298.



(±)-(3aR,4R,5S,7aS)-5-Allyloxy-4-isopropenyl-2,2-dimethyl-5-(5-methyl-furan-3-yl)-hexahydro-benzo[1,3]dioxole (4.168):

A solution of **4.159A** (36.5 mg, 0.109 mmol) in 1 mL of tetrahydrofuran was cooled to -78 °C. Methylolithium (0.35 mL of a 1.6 M solution in diethyl ether, 0.56 mmol) was slowly added. After holding the temperature at -78 °C for 3 hours, the reaction was gradually warmed to ambient temperature and stirred for another two hours. The reaction was then re-cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (40% ethyl acetate/hexanes) yielded 24 mg of **4.168** as a white foam (66%).

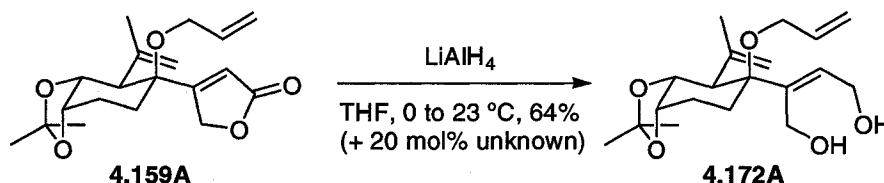
Data for 4.168:

¹H NMR (CDCl₃, 300 MHz, δ): 7.04 (d, J = 0.6 Hz, 1H), 5.89-5.77 (m, 1H), 5.84 (dd, J = 0.9, 0.9 Hz, 1H), 5.25 (dddd, J = 17.2, 1.9, 1.9, 1.9 Hz, 1H), 5.07 (dddd, J = 10.6, 1.8, 1.7, 1.7 Hz, 1H), 4.93 (s, 1H), 4.78 (s, 1H), 4.45 (dd, J = 10.0, 4.8 Hz, 1H), 4.35-4.32 (m, 1H), 3.76-3.61 (m, 2H), 2.21 (d, J = 0.7 Hz, 3H), 2.15 (d, J = 10.0 Hz, 1H), 2.11-1.90 (m, 4H), 1.71 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 152.00, 143.75, 138.02, 135.68, 129.18, 116.19, 115.02, 108.25, 106.62, 77.93, 77.62, 73.30, 63.15, 58.17, 29.04, 27.63, 26.85, 24.30, 22.37, 13.96.

IR (neat, cm⁻¹, ν): 3080 (m), 2985 (s), 2934 (s), 2876 (s), 1644 (m), 1546 (w), 1454 (m), 1380 (s), 1367 (s), 1287 (w), 1244 (s), 1217 (s), 1162 (s), 1130 (w), 1059 (s).

HRMS (EI, m/z): calculated 332.1988 for [M]⁺, found 332.2014.



(±)-(E)-2-((3aR,4R,5S,7aS)-5-Allyloxy-4-isopropenyl-2,2-dimethyl-hexahydro-benzo [1,3]dioxol-5-yl)-but-2-ene-1,4-diol (4.172A):

A solution of **4.159A** (53 mg, 0.16 mmol) in 2 mL of tetrahydrofuran was cooled to 0 °C. Lithium aluminum hydride (25 mg, 0.66 mmol) was added in one portion. After warming to ambient temperature and stirring for 18 hours, the reaction was re-cooled to 0 °C, quenched with equal portions of water and a 1 M aqueous solution of sodium tartrate and stirred vigorously for 1 hour. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (80% ethyl acetate/hexanes) yielded 35 mg of **4.172A** (64%) as an inseparable mixture with a second, unidentified compound (20 mol%).

Data for 4.172A:

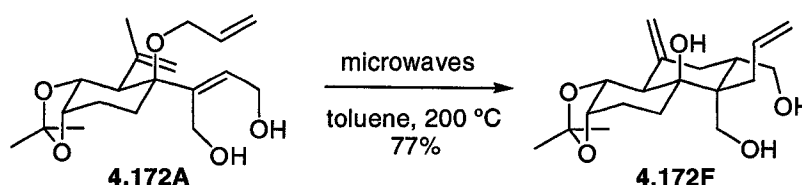
¹H NMR (CDCl₃, 500 MHz, δ): 5.94 (dd, J = 6.6 Hz, 1H), 5.88-5.80 (m, 1H), 5.26 (dddd, J = 17.1, 1.7, 1.7, 1.7 Hz, 1H), 5.10 (dddd, J = 10.7, 1.7, 1.7, 1.7 Hz, 1H), 4.99 (s, 1H), 4.77 (s, 1H), 4.41 (dd, J = 9.8, 4.9 Hz, 1H), 4.33 (dd, J = 4.4, 2.9 Hz, 1H), 4.31-4.21 (m, 2H), 4.11 (d, J_{AB} = 12.5, Hz, 1H), 4.05 (d, J_{AB} = 12.7 Hz, 1H), 3.75-3.71 (m, 1H), 3.63-3.59 (m, 1H),

2.19 (d, $J = 9.8$ Hz, 1H), 2.12-2.03 (m, 2H), 1.99-1.82 (m, 3H), 1.92 (s, 3H), 1.80-1.77 (m, 1H), 1.45 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 145.72, 134.67, 131.60, 116.56, 115.16, 114.98, 108.16, 83.73, 76.62, 72.81, 63.11, 59.12, 57.83, 57.59, 28.61 (2C), 26.43, 26.04, 22.19.

IR (neat, cm^{-1} , ν): 3401 (s, br), 3072 (w), 2983 (s), 2930 (s), 2874 (s), 1738 (w), 1643 (w), 1454 (m), 1380 (m), 1368 (m), 1244 (s), 1217 (s), 1161 (m), 1115 (w), 1059 (s), 1023 (s).

HRMS (EI, m/z): calculated 323.1859 for $[\text{M-Me}]^+$, found 323.1832.



(±)-(3a*S*,5a*S*,6*R*,9a*R*,9b*R*)-6-Allyl-6,7-bis-hydroxymethyl-2,2-dimethyl-9-methylene-octahydro-naphtho[1,2-*d*][1,3]dioxol-5a-ol (**4.172F**):

A solution of **4.172A** (18.2 mg of an 80% pure sample, 0.043 mmol) in 14 mL of toluene was sparged with argon for 15 minutes and then heated in a microwave to 200 °C for 1 hour. Following removal of the solvent, purification by silica gel flash chromatography (70% → 80% ethyl acetate/hexanes) yielded 11.2 mg of **4.172F** as a colourless oil (77%).

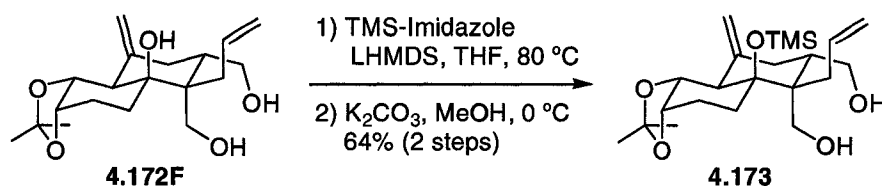
Data for 4.172F:

^1H NMR (CDCl_3 , 500 MHz, δ): 6.08-6.00 (m, 1H), 5.14 (d, $J = 17.1$ Hz, 1H), 5.09 (s, 1H), 5.04 (d, $J = 10.0$ Hz, 1H), 5.00 (s, 1H), 4.32 (dd, $J = 8.4, 5.4$ Hz, 1H), 4.26-4.24 (m, 1H), 3.98 (d, $J = 11.7$ Hz, 2H), 3.70 (dd, $J = 11.6, 4.0$ Hz, 1H), 3.50 (d, $J = 11.7$ Hz, 1H), 2.78 (dd, $J = 15.8, 5.5$ Hz, 1H), 2.66 (dd, $J = 14.8, 13.8$ Hz, 1H), 2.37 (dd, $J = 15.6, 9.3$ Hz, 1H), 2.30-2.24 (m, 3H), 2.11-2.04 (m, 1H), 1.95-1.88 (m, 2H), 1.79 (d, $J = 1.0$ Hz, 1H), 1.73-1.62 (m, 1H), 1.57 (s, br, 2H), 1.43 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 145.53, 137.61, 117.36, 110.26, 107.81, 78.41, 71.66, 72.47, 62.61, 62.39, 49.67, 47.40, 39.88, 35.31, 34.43, 28.34, 26.45, 26.09, 22.08.

IR (neat, cm^{-1} , ν): 3411 (s, br), 2924 (s), 2852 (m), 1718 (w), 1639 (w), 1455 (m), 1376 (m), 1241 (w), 1218 (m), 1162 (w), 1050 (s), 1023 (m).

HRMS (EI, m/z): calculated 320.1988 for $[\text{M-H}_2\text{O}]^+$, found 320.1992.



(±)-((3a*S*,5a*S*,6*R*,9a*R*,9b*R*)-6-Allyl-7-hydroxymethyl-2,2-dimethyl-9-methylene-5a-trimethylsilanyloxy-decahydro-naphtho[1,2-*d*][1,3]dioxol-6-yl)-methanol (4.173):

Lithium bis(trimethylsilyl)amide (38 mg, 0.23 mmol) was added to a solution of **4.172F** (4.5 mg, 0.013 mmol) in 2 mL of tetrahydrofuran, followed by 1-(trimethylsilyl)imidazole (0.200 mL, 1.36 mmol). The reaction was heated to 80 °C in a sealed tube for 70 hours, cooled to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude material was then dissolved in 2 mL of methanol and cooled to 0 °C. Potassium carbonate (20 mg, 0.14 mmol) was added and the reaction was stirred for 2 hours before being quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (60% ethyl acetate/hexanes) yielded 3.5 mg of **4.173** as a colourless oil (64% over 2 steps).

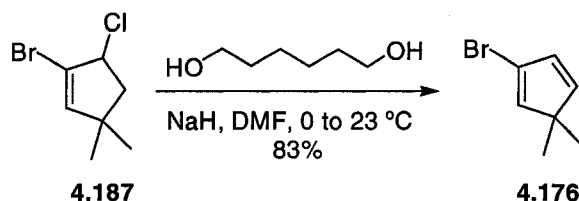
Data for 4.173:

¹H NMR (CDCl₃, 300 MHz, δ): 6.22–6.11 (m, 1H), 5.17 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.06 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.01 (s, 1H), 4.90 (s, 1H), 4.32–4.24 (m, 2H), 4.05 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.99 (d, *J*_{AB} = 11.9 Hz, 1H), 3.78 (d, *J*_{AB} = 11.8 Hz, 1H), 3.65 (dd, *J* = 11.9, 4.1 Hz, 1H), 2.65 (dd, *J* = 14.2, 12.8 Hz, 1H), 2.40 (d, *J* = 7.3 Hz, 2H), 2.29–2.23 (m, 2H), 2.06–1.89 (m, 4H), 1.82–1.74 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 0.14 (s, 9H).

¹³C NMR (CDCl₃, 75 MHz, δ): 145.93, 138.25, 117.18, 109.16, 108.29, 83.74, 74.95, 72.65, 63.85, 61.95, 50.55, 48.54, 43.70, 36.25, 36.03, 28.84, 27.19, 26.60, 23.46, 3.31 (3C).

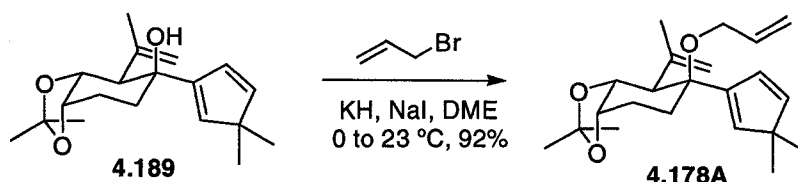
IR (neat, cm^{−1}, ν): 3386 (s, br), 2952 (s), 2924 (s), 2851 (m), 1729 (w), 1639 (w), 1458 (s), 1379 (m), 1250 (s), 1216 (w), 1163 (w), 1127 (w), 1076 (s), 1051 (s).

HRMS (EI, *m/z*): calculated 395.2254 for [M-Me]⁺, found 395.2243.



2-Bromo-5,5-dimethyl-cyclopenta-1,3-diene (4.176):

Sodium hydride (658 mg of a 60% dispersion in oil, 16.5 mmol) was washed three times with diethyl ether and dried under a flow of argon. Dimethylformamide (3.3 mL) was added and the resulting suspension was cooled to 0 °C. A solution of 1,6-hexanediol (721 mg, 6.10 mmol) in another 1.3 mL of dimethylformamide was added to the flask. A thick foam was formed, which, over a 45 minute period of stirring, gradually became less viscous. A solution of **4.187** (1.218 g, 5.183 mmol) in 0.3 mL of dimethylformamide was then added and the resulting mixture was warmed to ambient temperature, stirred for 17 hours and then quenched with 0.5 mL of water. The slurry was purified directly by Florisil chromatography (100% pentane) and the collected fractions were concentrated by *gently* distilling off the pentane leaving 1.10 g of a 75% solution of **4.176** in pentane (83%). Spectral data for this compound was in agreement with that reported previously: Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L. -Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244.



(±)-(3aR,4R,5S,7aS)-5-Allyloxy-5-(3,3-dimethyl-cyclopenta-1,4-dienyl)-4-isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxole (4.178A):

Sodium iodide (4 mg, 0.03 mmol) was flame dried in a flask and allowed to cool. Potassium hydride (160 mg of a 30% suspension in mineral oil, 1.20 mmol) was added to the flask and the system was put under argon. The potassium hydride was washed three times with dry hexanes and dried under a flow of argon. Dimethoxyethane (4 mL) was added and the resulting suspension was cooled to 0 °C. A solution of **4.189** (90 mg, 0.30 mmol) in another 2 mL of dimethoxyethane was cannulated into the flask and stirred for 5 minutes. Allyl bromide (0.10 mL, 8.7 mmol) was added and the reaction was warmed gradually to ambient temperature. After stirring for 18 hours, the reaction was cooled to 0 °C and quenched with a

saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 94 mg of **4.178A** as a colourless oil (92%).

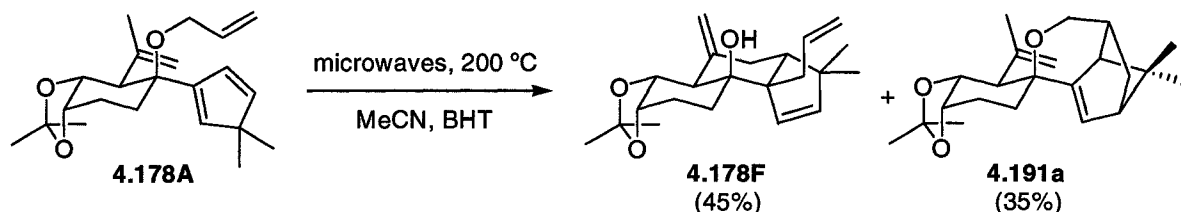
Data for 4.178A:

¹H NMR (CDCl₃, 300 MHz, δ): 6.14-6.09 (m, 2H), 5.95-5.83 (m, 2H), 5.30 (dddd, $J = 17.2$, 1.9, 1.9, 1.9 Hz, 1H), 5.11 (dddd, $J = 10.5$, 1.9, 1.7, 1.7 Hz, 1H), 4.95 (s, 1H), 4.81 (s, 1H), 4.48 (dd, $J = 10.1$, 4.8 Hz, 1H), 4.38-4.36 (m, 1H), 3.73-3.71 (m, 2H), 2.20-1.89 (m, 5H), 1.82 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 146.04, 145.54, 143.60, 142.01, 135.81, 129.13, 116.40, 115.08, 108.25, 79.49, 77.63, 73.46, 63.46, 57.71, 52.69, 29.11, 27.16, 26.90, 24.01, 22.83, 22.66, 22.55.

IR (neat, cm⁻¹, ν): 3077 (w), 2984 (m), 2960 (s), 2930 (s), 2865 (m), 1735 (w), 1700 (w), 1642 (m), 1453 (m), 1379 (m), 1366 (m), 1244 (s), 1215 (s), 1164 (m), 1105 (w), 1061 (s), 1019 (w).

HRMS (EI, m/z): calculated 286.1933 for [M-Me₂CO]⁺, found 286.1897.



(±)-(3aR,3bR,8aS,8bS,10aS)-8a-Allyl-2,2,6,6-tetramethyl-4-methylene-3a,3b,4,5,5a,6,8a,9,10,10a-decahydro-1,3-dioxo-dicyclopenta[a,f]naphthalen-8b-ol (4.178F) and Diels-Alder adduct (4.191a):

A catalytic amount of BHT was added to a solution of **4.178A** (210 mg, 0.610 mmol) in 14 mL of toluene. After sparging with argon for 15 minutes, the reaction mixture was heated in a microwave to 200 °C for 1 hour. Following removal of the solvent, purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 95 mg of **4.178F** (45%) along with 63 mg of **4.191a** (35%), both as white solids.

Data for 4.178F:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.79-5.72 (m, 1H), 5.46 (d, $J = 5.7$ Hz, 1H), 5.31 (d, $J = 5.8$ Hz, 1H), 5.24 (s, 1H), 5.06 (s, 1H), 5.04-5.02 (m, 2H), 4.25-4.22 (m, 2H), 2.79 (ddd, $J = 16.2, 6.0, 2.8$ Hz, 1H), 2.45 (d, $J = 16.3$ Hz, 1H), 2.36-2.23 (m, 3H), 2.03-1.99 (m, 1H), 1.95-1.87 (m, 3H), 1.60 (ddd, $J = 13.8, 3.9, 3.4$ Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.08, 142.06, 136.65, 131.23, 117.26, 111.54, 107.83, 78.49, 73.03, 60.38, 48.43, 47.46, 45.57, 39.01, 31.50, 31.43, 30.00, 28.33, 26.77, 26.53, 24.32, 21.60.

IR (neat, cm^{-1} , ν): 3516 (br, w), 3077 (w), 3031 (w), 2983 (s), 2929 (s), 2864 (m), 1723 (w), 1636 (m), 1461 (m), 1438 (m), 1379 (s), 1366 (s), 1241 (s), 1218 (s), 1160 (m), 1138 (w), 1046 (s), 1003 (w).

HRMS (EI, m/z): calculated 344.2351 for $[\text{M}]^+$, found 344.2355.

mp = 80.7-83.8 $^{\circ}\text{C}$.

Data for 4.191a:

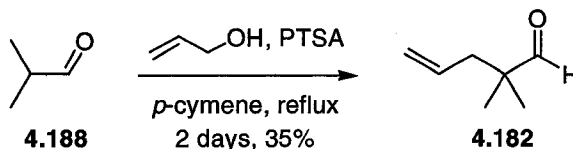
^1H NMR (CDCl_3 , 500 MHz, δ): 5.78 (d, $J = 2.4$ Hz, 1H), 5.00 (dd, $J = 1.7, 1.6$ Hz, 1H), 4.86 (s, 1H), 4.37 (dd, $J = 10.2, 4.8$ Hz, 1H), 4.24-4.22 (m, 1H), 3.66 (dd, $J = 13.2, 10.4$ Hz, 1H), 2.71-2.67 (m, 2H), 2.65-2.64 (m, 1H), 2.43 (s, 1H), 2.32 (d, $J = 10.2$ Hz, 1H), 2.17 (ddd, $J = 9.6, 6.5, 3.1$ Hz, 1H), 1.99 (s, 3H), 1.98-1.58 (m, 4H), 1.46 (s, 3H), 1.33 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H), 0.75 (d, $J = 10.9$ Hz, 1H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 148.57, 144.01, 133.68, 116.18, 107.84, 80.10, 76.29, 73.00, 66.38, 55.86, 54.89, 52.00, 48.50, 40.40, 38.86, 28.65, 26.48, 25.52, 22.81, 22.33, 20.94, 20.51.

IR (neat, cm^{-1} , ν): 3069 (w), 2986 (w), 2950 (s), 2871 (s), 1641 (w), 1465 (w), 1378 (m), 1365 (m), 1242 (s), 1215 (s), 1161 (s), 1057 (s), 1038 (s), 1000 (m).

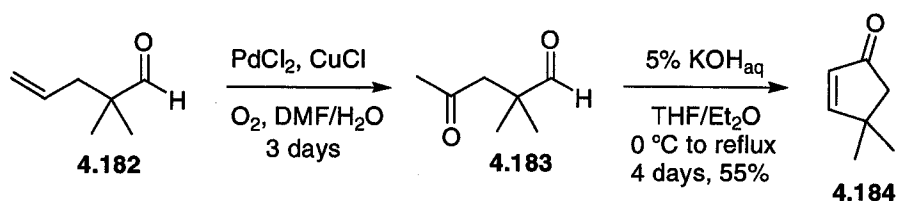
HRMS (EI, m/z): calculated 344.2351 for $[\text{M}]^+$, found 344.2322.

mp = 98.2 0-102.4 $^{\circ}\text{C}$.



2,2-Dimethyl-pent-4-enal (4.182):

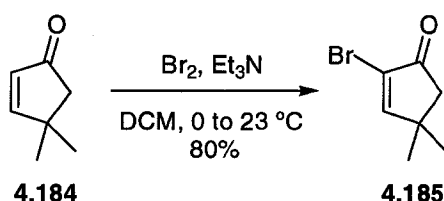
(Procedure adapted from: Magnus, P. D.; Nobbs, M. S.; *Synth. Commun.* **1980**, *10*, 273.) A round-bottomed flask equipped with a Dean-Stark apparatus and a reflux condenser was charged with 180 mL of *p*-cymene, isobutyraldehyde (90.0 mL, 986 mmol) and allyl alcohol (45.0 mL, 662 mmol). *para*-Toluenesulfonic acid (290 mg, 1.68 mmol) was added and the mixture was heated to reflux for 48 hours. Distillation of the reaction mixture gave 45.24 g of **4.182** as a 63% solution in *p*-cymene (35%). Spectral data for this compound was in agreement with that reported previously: Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 1567.



4,4-Dimethyl-cyclopent-2-enone (**4.184**):

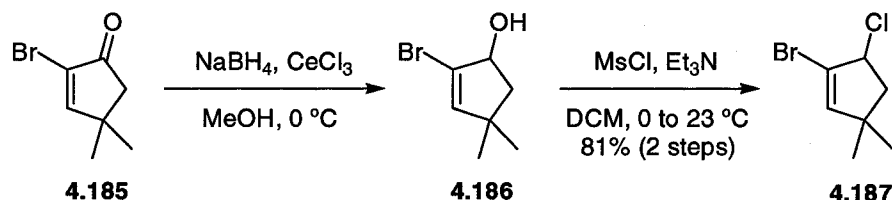
A suspension of palladium (II) chloride (1.90 g, 10.7 mmol) and copper (I) chloride (5.40 g, 5.54 mmol) in 55 mL of dimethylformamide and 6.5 mL of water was sparged with oxygen for 3 hours during which time the mixture went from black to olive green. Aldehyde **4.182** (6.0 g, 54 mmol) was then added as a solution in 2 mL of dimethylformamide and the reaction, once again black in colour, was stirred for 72 hours. The mixture was then poured into a separatory funnel containing 300 mL of water. The aqueous phase was extracted four times with petroleum ether, acidified to pH 1 with concentrated hydrochloric acid and re-extracted three times with diethyl ether. The combined organic layers were washed twice with brine, dried over magnesium sulfate, filtered and concentrated to give keto-aldehyde **4.183**. In a separate flask, 100 mL of a 5% aqueous potassium hydroxide solution, 225 mL of diethyl ether and 50 mL of tetrahydrofuran were combined and sparged with argon for 1 hour at $0\text{ }^\circ\text{C}$. This solution was then cannulated into a flask containing the unpurified keto-aldehyde and the resulting solution was warmed to reflux for 4 days. After cooling to ambient temperature, the aqueous phase was saturated with solid sodium chloride and the mixture was poured into a separatory funnel. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were washed once with brine, dried over magnesium sulfate, filtered and concentrated to give 3.26 g of **4.184** as a colourless oil. No

further purification was necessary and the spectral data was in agreement with that reported previously for this compound: Holder, R. W.; Daub, J. P.; Baker, W. E.; Gilbert, R. H.; Graf, N. A. *J. Org. Chem.* **1982**, *47*, 1445.



2-Bromo-4,4-dimethyl-cyclopent-2-enone (4.185):

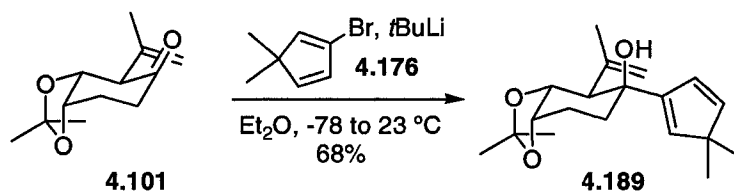
A solution of **4.184** (4.42 g, 40.1 mmol) in 50 mL of dichloromethane was cooled to 0 °C. Bromine (2.20 mL, 43.0 mmol) was added drop-wise via an additional funnel, as a solution in 10 mL of dichloromethane, over a period of 2 hours. Once the bromine addition was complete, a solution of triethylamine (8.95 mL, 64.2 mmol) in 20 mL of dichloromethane was added over 1.5 hours. The reaction was warmed to ambient temperature and was stirred for an additional 2 hours before filtering off the resulting white precipitate. The filtrate was then washed three times with a 10% aqueous solution of hydrochloric acid, three times with a saturated aqueous solution of sodium bicarbonate and once with brine. The remaining organic phase was then dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 6.05 g (80%) of **4.185** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Wakui, T.; Otsuji, Y.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2267.



1-Bromo-5-chloro-3,3-dimethyl-cyclopentene (4.187):

Enone **4.185** (8.90 g, 47.1 mmol) was dissolved in 180 mL of methanol containing cerium (III) chloride heptahydrate (26.3 g, 70.6 mmol) and the resulting suspension was cooled to 0 °C. Sodium borohydride (2.14 g, 56.6 mmol) was added portion-wise and the reaction was stirred for 15 minutes before quenching with a saturated aqueous solution of ammonium

chloride. The aqueous phase was diluted with water and extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered and concentrated. The resulting crude material was re-dissolved in 200 mL of dichloromethane and cooled to 0 °C. Triethylamine (8.00 mL, 57.4 mmol) was added, followed by methanesulfonyl chloride (4.40 mL, 56.5 mmol). After stirring for 1 hour, the reaction was warmed to ambient temperature and stirred for another 18 hours before being quenched with water. The organic phase was separated, washed with brine and dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (100% pentane) yielded 7.99 g (81%) of **4.187** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Paquette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L. -Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244.



(±)-(3aR,4R,5S,7aS)-5-(3,3-Dimethyl-cyclopenta-1,4-dienyl)-4-isopropenyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-5-ol (4.189):

A solution of vinyl bromide **4.176** (503 mg of a 75% solution in pentane, 2.19 mmol) in 20 mL of diethyl ether was cooled to -78 °C. *tert*-Butyllithium (2.50 mL of a 1.70 M solution in pentane, 4.25 mmol) was added drop-wise and the reaction was stirred for 30 minutes before a solution of **4.101** (246 mg, 1.17 mmol) in 2 mL of diethyl ether was slowly added. The reaction was kept at -78 °C for 3 hours, warmed to ambient temperature and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) yielded 242 mg (68%) of **4.189** as a colourless oil.

Data for **4.189**:

¹H NMR (CDCl₃, 300 MHz, δ): 6.22 (dd, *J* = 5.3, 2.2 Hz, 1H), 6.13 (dd, *J* = 5.3, 1.6 Hz, 1H), 5.88 (dd, *J* = 2.1, 1.8 Hz, 1H), 5.02 (s, 1H), 4.86 (s, 1H), 4.37-4.32 (m, 2H), 2.42 (ddd,

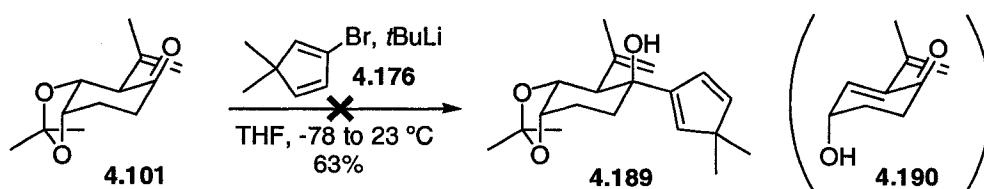
$J = 8.4, 3.5, 2.5$ Hz, 1H), 2.24-2.16 (m, 1H), 2.13-2.02 (m, 2H), 1.91 (s, 1H), 1.69 (s, 3H), 1.59-1.52 (m, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 148.48, 148.04, 145.41, 138.45, 127.50, 113.33, 108.30, 77.74, 73.79, 73.42, 53.53, 52.40, 32.02, 29.19, 26.80, 25.89, 22.66, 22.28, 22.08.

IR (neat, cm^{-1} , ν): 3469 (br, w), 3070 (w), 2964 (s), 2929 (s), 2862 (m), 1637 (m), 1462 (m), 1379 (m), 1363 (w), 1242 (m), 1217 (m), 1163 (w), 1059 (m).

HRMS (EI, m/z): calculated 304.2038 for $[\text{M}]^+$, found 304.2045.

mp = 98.7-103.4 °C.



4-Hydroxy-2-isopropenyl-cyclohex-2-enone (4.190):

A solution of vinyl bromide **4.176** (23.1 mg of a 75% solution in pentane, 0.100 mmol) in 1 mL of diethyl ether was cooled to -78 °C. *tert*-Butyllithium (0.11 mL of a 1.70 M solution in pentane, 0.19 mmol) was added drop-wise and the reaction stirred for 30 minutes before a solution of **4.101** (11 mg, 0.052 mmol) in 0.3 mL of diethyl ether was slowly added. The reaction was kept at -78 °C for 3 hours, warmed to ambient temperature and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with diethyl ether and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 20% ethyl acetate/hexanes) yielded 5 mg (63%) of **4.190** as a colourless oil.

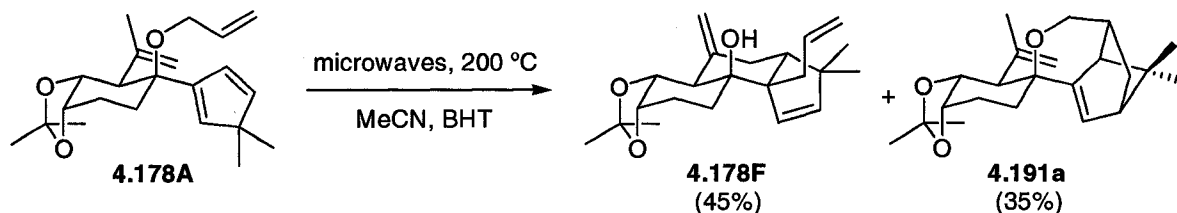
Data for 4.190:

^1H NMR (CDCl_3 , 300 MHz, δ): 6.76 (dd, $J = 2.4, 1.7$ Hz, 1H), 5.16 (d, $J = 1.0$ Hz, 1H), 5.05 (dddd, $J = 1.7, 1.6, 1.5, 1.5$ Hz, 1H), 4.61-4.55 (m, 1H), 2.65-2.56 (m, 1H), 2.43-2.24 (m, 2H), 2.01-1.89 (m, 1H), 1.88 (dd, $J = 1.2, 0.9$ Hz, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 198.13, 147.95, 141.27, 140.69, 117.37, 67.22, 36.91, 32.92, 22.69.

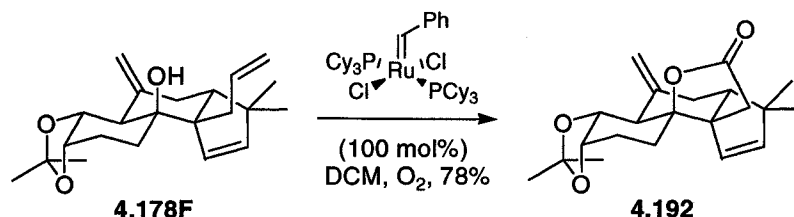
IR (neat, cm^{-1} , ν): 3404 (s, br), 2953 (m), 2929 (m), 2870 (m), 1674 (s), 1454 (m), 1426 (m), 1378 (w), 1343 (m), 1275 (w), 1152 (m), 1082 (s), 1017 (s).

HRMS (EI, m/z): calculated 152.0832 for $[M]^+$, found 152.0855.



(±)-(3aR,3bR,8aS,8bS,10aS)-8a-Allyl-2,2,6,6-tetramethyl-4-methylene-3a,3b,4,5,5a,6,8a,9,10,10a-decahydro-1,3-dioxo-dicyclopenta[a,f]naphthalen-8b-ol (**4.178F**) and Diels-Alder adduct (**4.191a**):

Refer to the preparation of compound **4.178F** above for the experimental procedure and characterization of **4.191a**.



(±)-(1S,5S,9R,12R,13R,14S)-13,14-(isopropylidenedioxy)-8,8-dimethyl-11-methylene-2-oxa-3-oxotetracyclo[10,4,0,0^{1,5},0^{5,9}]hexadeca-6-ene (**4.192**):

To a solution of **4.178F** (6 mg, 0.02 mmol) in 2 mL of dichloromethane (bulk reagent grade) was added 15 mg (0.018 mmol) of Grubbs' first generation catalyst in one portion. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (20% ethyl acetate/hexanes) to yield 4.7 mg of **4.192** as a white solid (78%).

Data for 4.192:

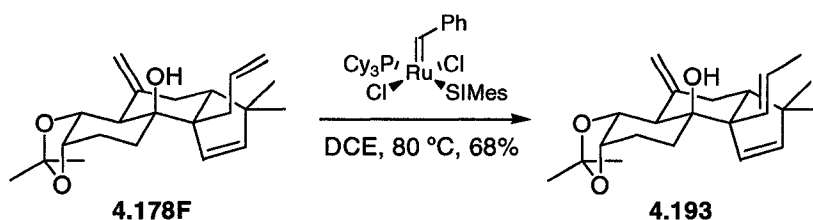
¹H NMR (CDCl₃, 500 MHz, δ): 5.66 (d, $J = 5.7$ Hz, 1H), 5.49 (d, $J = 5.7$ Hz, 1H), 5.10 (s, 1H), 5.04 (s, 1H), 4.39 (dd, $J = 9.0, 4.9$ Hz, 1H), 4.30-4.28 (m, 1H), 2.76 (d, $J_{AB} = 17.6$ Hz, 1H), 2.50 (d, $J_{AB} = 17.7$ Hz, 1H), 2.38 (dd, $J = 14.0, 6.2$ Hz, 1H), 2.21 (d, $J = 9.0$ Hz, 1H), 2.11-2.01 (m, 3H), 1.97-1.89 (m, 2H), 1.73-1.69 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.13 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 174.70, 144.25, 141.58, 126.56, 110.61, 108.04, 89.86, 75.15, 72.36, 58.43, 54.86, 48.47, 46.45, 42.97, 34.76, 31.28, 28.57, 28.11, 26.28, 23.69, 21.89.

IR (neat, cm^{-1} , ν): 3038 (w), 2984 (w), 2954 (s), 2931 (s), 1779 (s), 1659 (w), 1635 (w), 1447 (w), 1380 (m), 1366 (m), 1243 (m), 1214 (s), 1206 (s), 1163 (m), 1044 (s).

HRMS (EI, m/z): calculated 344.1988 for $[\text{M}]^+$, found 344.2012.

mp = 157.3-159.3 $^{\circ}\text{C}$.



(±)-(3aR,3bR,8aS,8bS,10aS)-2,2,6,6-Tetramethyl-4-methylene-8a-propenyl-3a,3b,4,5,5a,6,8a,9,10,10a-decahydro-1,3-dioxo-dicyclopenta[a,f]naphthalen-8b-ol (4.193):

Grubbs' second generation catalyst (1.2 mg, 0.0014 mmol) was weighed into a Schlenk tube and put under argon. A solution of **4.178F** (4.1 mg, 0.012 mmol) in 2 mL of degassed dichloroethane was added by cannula and the flask evacuated and back-filled with argon before sealing and immersing in an 80 $^{\circ}\text{C}$ oil bath. After 24 hours, the reaction was cooled, adsorbed onto silica and allowed to stand for 24 hours in the freezer before further purification. (If purification was carried out sooner, significant quantities of ruthenium were found to contaminate the product and multiple chromatographies were necessary). Silica gel flash chromatography (5% $\rightarrow$ 10% ethyl acetate/hexanes) yielded 2.9 mg of **4.193** as a colourless oil.

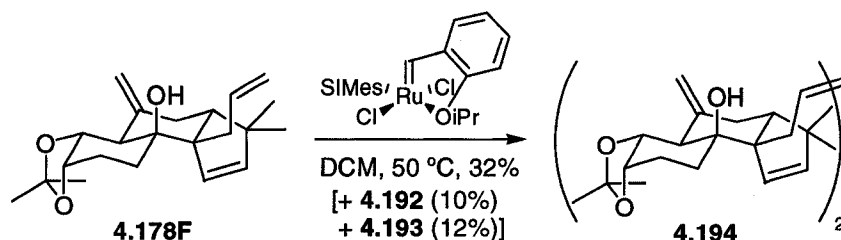
Data for **4.193**:

^1H NMR (CDCl_3 , 300 MHz, δ): 5.70 (dd, J = 15.8, 1.5 Hz, 1H), 5.51 (s, 2H), 5.50-5.38 (m, 1H), 5.16 (d, J = 1.6 Hz, 1H), 4.97 (s, 1H), 4.24-4.20 (m, 2H), 2.74 (dd, J = 14.5, 6.2 Hz, 1H), 2.29-2.22 (m, 2H), 2.07-1.82 (m, 5H), 1.69 (dd, J = 6.3, 1.5 Hz, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 146.73, 142.47, 136.68, 130.02, 125.91, 110.68, 107.75, 77.26, 75.69, 73.20, 62.20, 51.69, 48.45, 45.81, 33.50, 31.04, 28.55, 27.89, 26.52, 24.04, 21.91, 18.44.

IR (neat, cm^{-1} , ν): 3538 (w), 2985 (m), 2955 (s), 2935 (s), 2858 (s), 1459 (w), 1448 (w), 1377 (m), 1366 (m), 1243 (m), 1216 (s), 1160 (m), 1052 (s).

HRMS (EI, m/z): calculated 344.2351 for $[\text{M}]^+$, found 344.2338.



($\pm$)-dimer of 4.178 (4.194):

Hoveyda-Grubbs' second generation catalyst (13.0 mg, 0.0207 mmol) was weighed into a Schlenk tube and put under argon. A solution of **4.178F** (26.0 mg, 0.0755 mmol) in 4 mL of degassed dichloromethane was added by cannula and the flask evacuated and back-filled with argon before sealing and immersing in an 50 °C oil bath. After 24 hours, the reaction was cooled, adsorbed onto silica and allowed to stand for 24 hours in the freezer before further purification. (If purification was carried out sooner, significant quantities of ruthenium were found to contaminate the product and multiple chromatographies were necessary). Silica gel flash chromatography (5% $\rightarrow$ 70% ethyl acetate/hexanes) yielded 6.5 mg of recovered **4.178A**, 2.5 mg of **4.192** (10%), 3.0 mg of **4.193** (12%), and 8 mg of **4.194** (32%).

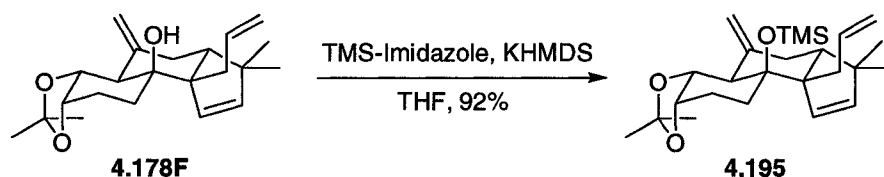
Data for 4.194:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.45 (d, $J = 5.5$ Hz, 1H), 5.41 (dd, $J = 3.9, 3.7$ Hz, 1H), 5.28 (d, $J = 5.9$ Hz, 1H), 5.23 (s, 1H), 5.02 (s, 1H), 4.23-4.22 (m, 2H), 2.74-2.69 (m, 1H), 2.42 (d, $J = 17.1$ Hz, 1H), 2.28-2.27 (m, 2H), 2.23-2.22 (m, 1H), 2.04-1.84 (m, 5H), 1.59-1.54 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 147.11, 142.00, 131.76, 130.76, 111.71, 108.02, 78.53, 76.86, 73.13, 60.56, 48.68, 47.49, 45.72, 37.47, 31.87, 29.86, 28.47, 26.74, 26.69, 24.42, 21.64.

IR (neat, cm^{-1} , ν): 3458 (w), 3033 (w), 2950 (s), 2930 (s), 2854 (m), 1718 (w), 1623 (w), 1460 (w), 1436 (w), 1377 (m), 1361 (m), 1242 (s), 1218 (s), 1042 (s).

HRMS (EI, m/z): calculated 642.4284 for $[\text{M}-\text{H}_2\text{O}]^+$, found 642.4275.



(±)-((3aR,3bR,8aS,8bS,10aS)-8a-Allyl-2,2,6,6-tetramethyl-4-methylene-3a,3b,4,5,5a,6,8a,9,10,10a-decahydro-1,3-dioxo-dicyclopenta[a,f]naphthalen-8b-yloxy)-trimethyl-silane (4.195):

Potassium bis(trimethylsilyl)amide (63 mg, 0.32 mmol) was added to a solution of **4.478F** (18 mg, 0.052 mmol) in 2 mL of tetrahydrofuran, followed by 1-(trimethylsilyl)imidazole (0.080 mL, 0.55 mmol). The reaction was stirred for 20 minutes and then quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (5% ethyl acetate/hexanes) yielded 20 mg (92%) of **4.195** as a colourless oil.

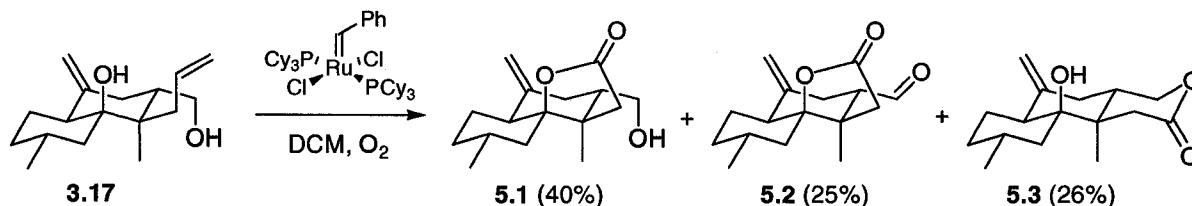
Data for 4.195:

^1H NMR (CDCl_3 , 500 MHz, δ): 5.68-5.59 (m, 1H), 5.44 (d, $J = 5.9$ Hz, 1H), 5.25 (d, $J = 5.9$ Hz, 1H), 5.11 (s, 1H), 5.03 (d, $J = 10.0$ Hz, 1H), 4.99 (d, $J = 17.1$ Hz, 1H), 4.89 (s, 1H), 4.23-4.18 (m, 2H), 2.75 (ddd, $J = 16.4, 6.1, 2.9$ Hz, 1H), 2.34 (dd, $J = 13.7, 5.6$ Hz, 1H), 2.33 (d, $J = 6.6$ Hz, 1H), 2.29-2.19 (m, 1H), 2.15 (dd, $J = 13.9, 9.0$ Hz, 1H), 1.98-1.85 (m, 3H), 1.80 (dd, $J = 6.6, 1.7$ Hz, 1H), 1.60-1.56 (m, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.09 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 148.68, 142.49, 137.17, 131.38, 117.14, 109.32, 107.78, 81.00, 78.08, 73.10, 61.88, 48.57, 47.31, 46.57, 39.00, 31.13, 29.54, 28.25, 26.59, 26.33, 24.58, 23.27, 2.53 (3C).

IR (neat, cm^{-1} , ν): 3077 (w), 3030 (w), 2986 (m), 2953 (s), 2869 (m), 1637 (w), 1458 (w), 1444 (w), 1378 (w), 1363 (w), 1250 (s), 1218 (m), 1167 (m), 1123 (s), 1105 (s), 1076 (s), 1032 (w).

HRMS (EI, m/z): calculated 416.2747 for $[M]^+$, found 416.2760.



($\pm$)-(3aR,6aS,9R,10aS)-4-Hydroxymethyl-3a,9-dimethyl-6-methylene-decahydro-1-oxa-cyclopenta[d]naphthalen-2-one (**5.1**) and ($\pm$)-(3aR,6aS,9R,10aS)-3a,9-Dimethyl-6-methylene-2-oxo-decahydro-1-oxa-cyclopenta[d]naphthalene-4-carbaldehyde (**5.2**) and ($\pm$)-(4aR,4bS,6R,8aS)-4b-Hydroxy-4a,6-dimethyl-9-methylene-dodecahydro-2-oxa-phenanthren-3-one (**5.3**):

A solution of **3.17** (15.4 mg, 0.0583 mmol) in 6 mL of dichloromethane was sparged with oxygen for 15 minutes before Grubbs' first generation catalyst (48 mg, 0.059 mmol) was added in one portion. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (30% $\rightarrow$ 40% ethyl acetate/hexanes) to yield 6.2 mg (40%) of **5.1** and 3.8 mg (25%) of **5.2**, both as white solids, as well as 4.0 mg (26%) of **5.3** as a colourless oil.

Data for 5.1:

^1H NMR (CDCl_3 , 300 MHz, δ): 4.86 (s, 1H), 4.68 (s, 1H), 3.67 (dd, $J = 10.7, 5.0$ Hz, 1H), 3.49 (dd, $J = 10.7, 7.7$ Hz, 1H), 2.63 (d, $J_{\text{AB}} = 17.2$ Hz, 1H), 2.50 (d, $J_{\text{AB}} = 17.3$ Hz, 1H), 2.40 (dd, $J = 12.7, 3.4$ Hz, 1H), 2.12-1.56 (m, 9H), 1.14 (dd, $J = 12.6, 12.5$ Hz, 1H), 1.04 (s, 3H), 1.01-0.86 (m, 1H), 0.89 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 175.61, 145.37, 108.70, 91.37, 64.34, 46.19, 43.88, 43.48, 42.18, 41.57, 34.89, 33.97, 27.80, 24.93, 22.24, 13.21.

IR (neat, cm^{-1} , ν): 3437 (s, br), 2930 (s), 2867 (m), 2848 (m), 1770 (s), 1650 (w), 1448 (m), 1316 (w), 1246 (m), 1212 (s).

HRMS (EI, m/z): calculated 264.1725 for $[M]^+$, found 264.1700.

mp = 164.5-167.2 $^{\circ}\text{C}$.

Data for 5.2:

^1H NMR (CDCl_3 , 500 MHz, δ): 9.74 (s, 1H), 4.92 (s, 1H), 4.75 (d, $J = 0.7$ Hz, 1H), 2.82 (d, $J_{\text{AB}} = 17.3$ Hz, 1H), 2.68 (d, $J_{\text{AB}} = 17.5$ Hz, 1H), 2.50 (dd, $J = 13.2, 3.4$ Hz, 1H), 2.38 (dd, $J = 13.2, 3.2$ Hz, 1H), 2.23 (dd, $J = 13.2, 12.9$ Hz, 1H), 2.03 (d, $J = 12.4$ Hz, 1H), 1.86-1.69 (m, 6H), 1.16 (s, 3H), 0.97 (dddd, $J = 12.9, 12.9, 12.7, 4.2$ Hz, 1H), 0.91 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 202.26, 174.49, 143.71, 110.13, 91.00, 55.51, 43.71, 43.08, 41.89, 40.79, 33.85, 31.52, 27.81, 24.77, 22.18, 14.48.

IR (neat, cm^{-1} , ν): 2957 (m), 2932 (s), 2876 (m), 2848 (m), 1769 (s), 1713 (s), 1651 (w), 1451 (m), 1316 (w), 1247 (w), 1208 (s), 1143 (w), 1132 (w), 1096 (w), 1085 (w).

HRMS (EI, m/z): calculated 262.1569 for $[\text{M}]^+$, found 262.1572.

mp = 138.9-141.5 $^{\circ}\text{C}$.

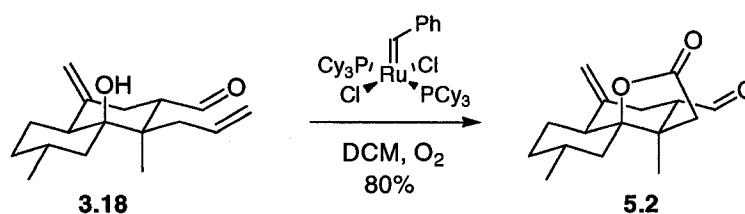
Data for 5.3:

^1H NMR (CDCl_3 , 500 MHz, δ): 4.98 (d, $J = 1.5$ Hz, 1H), 4.76 (d, $J = 1.2$ Hz, 1H), 4.26 (dd, $J = 11.2, 5.9$ Hz, 1H), 4.01 (dd, $J = 12.2, 11.5$ Hz, 1H), 2.80 (dd, $J = 17.3, 1.0$ Hz, 1H), 2.40 (d, $J = 17.3$ Hz, 1H), 2.27-2.22 (m, 2H), 2.09 (dd, $J = 13.2, 3.9$ Hz, 1H), 1.90 (dd, $J = 13.7, 12.5$ Hz, 1H), 1.76-1.45 (m, 8H), 1.11 (s, 3H), 0.89 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 171.54, 146.39, 111.31, 75.33, 69.93, 42.55, 39.42, 38.25, 38.15, 35.96, 33.70, 33.11, 27.19, 24.43, 22.16, 14.64.

IR (neat, cm^{-1} , ν): 3487 (s, br), 2925 (s), 2867 (m), 2849 (m), 1732 (s), 1713 (s), 1643 (w), 1454 (w), 1405 (w), 1283 (w), 1224 (m), 1161 (w), 1146 (w), 1075 (w), 1027 (m).

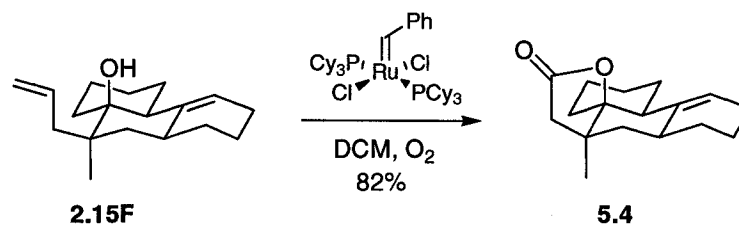
HRMS (EI, m/z): calculated 264.1725 for $[\text{M}]^+$, found 264.1734.



(±)-(3aR,6aS,9R,10aS)-3a,9-Dimethyl-6-methylene-2-oxo-decahydro-1-oxa-cyclopenta[d]naphthalene-4-carbaldehyde (5.2):

Grubbs' first generation catalyst (32 mg, 0.039 mmol) was added to a solution of **3.18** (10 mg, 0.038 mmol) in 4 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (25% ethyl

acetate/hexanes) to yield 8 mg of **5.2** as a white solid (80%). (See above for the characterization of **5.2**).



(±)-(4a*S*,7a*S*,8a*S*,12b*S*)-7a-Methyl-1,2,3,4,7,7a,8,8a,9,10,11,12b-dodecahydro-5-oxa-cyclopenta[*k*]phenanthren-6-one (5.4**):**

Grubbs' first generation catalyst (41 mg, 0.050 mmol) was added to a solution of **2.15F** (12.0 mg, 0.046 mmol) in 5 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (15% ethyl acetate/hexanes) to yield 9.8 mg (82%) of **5.4** as a colourless oil.

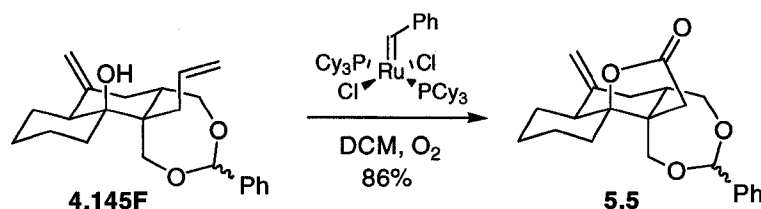
Data for **5.4:**

¹H NMR (CDCl₃, 300 MHz, δ): 5.40 (s, 1H), 2.55 (d, *J*_{AB} = 16.8 Hz, 1H), 2.08 (d, *J*_{AB} = 16.8 Hz, 1H), 2.07-1.93 (m, 4H), 1.85-1.64 (m, 4H), 1.62-1.10 (m, 13H), 1.19 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz, δ): 175.99, 137.63, 120.30, 90.43, 45.63, 44.44, 43.69, 41.25, 32.95, 32.43, 30.17, 25.62, 25.43, 24.54, 21.63, 20.17, 19.39.

IR (neat, cm⁻¹, ν): 3058 (m), 3013 (m), 2930 (s), 2855 (s), 2672 (w), 2250 (w), 1770 (s), 1447 (s), 1385 (m), 1346 (m), 1300 (m), 1266 (s), 1211 (s), 1179 (m), 1148 (m), 1111 (m), 1080 (w), 1069 (w).

HRMS (EI, *m/z*): calculated 260.1776 for [M]⁺, found 260.1793.



(±)-(1*S*,5*R*,11*S*,14*S*)-13-Methylene-2,7,9-trioxa-3-oxo-8-phenyltetracyclo[12,4,0,0^{1,5},0^{5,11}]octadecane (5.5**):**

Grubbs' first generation catalyst (27 mg, 0.033 mmol) was added to a solution of **4.145F** (11.5 mg, 0.032 mmol) in 3 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (25% ethyl acetate/hexanes) to yield 4.7 mg (41%) and 5.2 mg (45%) of the acetal epimers of **5.5**, both as white solids (the stereochemistry of the two epimers was not determined).

Data for **5.5** (epimer A):

¹H NMR (CDCl₃, 500 MHz, δ): 7.42-7.31 (m, 5H), 5.71 (s, 1H), 4.89 (d, J = 1.0 Hz, 1H), 4.71 (s, 1H), 4.12 (d, J = 12.5 Hz, 1H), 4.04 (d, J = 12.2 Hz, 1H), 3.84 (d, J = 11.7 Hz, 1H), 3.36 (d, J = 12.6 Hz, 1H), 2.88 (d, J = 17.6 Hz, 1H), 2.58 (dd, J = 13.4, 12.9 Hz, 1H), 2.41 (d, J = 17.6, 1H), 2.23 (dd, J = 13.2, 2.9 Hz, 1H), 2.06 (d, J = 9.8 Hz, 1H), 1.93 (d, J = 13.2 Hz, 1H), 1.86-1.70 (m, 5H), 1.68-1.23 (m, 3H).

¹³C NMR (DMSO-*d*₆, 90 °C, 125 MHz, δ): 173.66, 146.70, 138.81, 127.69, 127.53 (2C), 125.61 (2C), 107.07, 99.60, 87.93, 65.88, 61.82, 54.16, 48.62, 44.13, 43.51, 35.29, 32.30, 24.49, 24.08, 20.81.

IR (neat, cm⁻¹, ν): 2937 (m), 2862 (s), 1777 (s), 1653 (w), 1451 (m), 1361 (w), 1339 (w), 1262 (w), 1232 (w), 1204 (s), 1115 (s), 1101 (s).

HRMS (EI, m/z): calculated 354.1831 for [M]⁺, found 354.1802.

mp = 197.5-198.9 °C.

Data for **5.5** (epimer B):

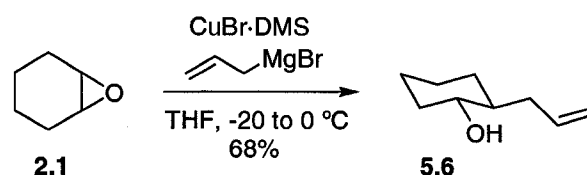
¹H NMR (CDCl₃, 500 MHz, δ): 7.46 (d, J = 7.3 Hz, 2H), 7.38-7.32 (m, 3H), 5.70 (s, 1H), 4.89 (s, 1H), 4.69 (s, 1H), 4.07 (d, J = 12.2 Hz, 1H), 3.83-3.79 (m, 2H), 3.50 (d, J = 12.2 Hz, 1H), 2.84 (d, J = 17.6 Hz, 1H), 2.54-2.49 (m, 2H), 2.27 (dd, J = 13.2, 3.4 Hz, 1H), 1.92 (dd, J = 10.7, 3.9 Hz, 1H), 1.85-1.57 (m, 6H), 1.30-1.15 (m, 3H).

¹³C NMR (CDCl₃, 125 MHz, δ): 175.03, 145.66, 138.49, 128.49, 128.20 (2C), 126.25 (2C), 108.90, 99.76, 88.82, 67.06, 60.56, 49.39, 44.88, 44.64, 40.58, 36.60, 33.68, 24.99, 24.88, 21.40.

IR (neat, cm⁻¹, ν): 2934 (m), 2865 (s), 1777 (s), 1655 (w), 1449 (m), 1361 (w), 1339 (w), 1262 (w), 1232 (w), 1206 (s), 1115 (s), 1032 (s).

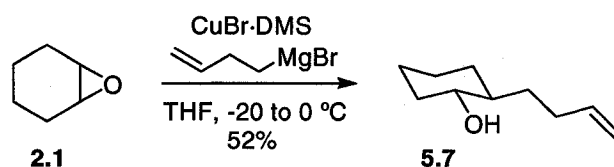
HRMS (EI, m/z): calculated 354.1831 for [M]⁺, found 354.1823.

mp = 185.4-188.9 °C.



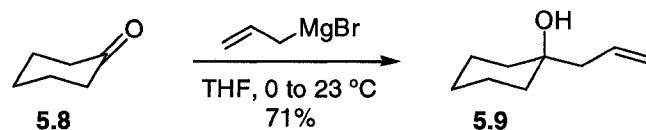
(±)-(1R,2S)-2-Allyl-cyclohexanol (5.6):

A suspension of copper (I) bromide-dimethyl sulfide complex (10 mg, 0.049 mmol) in 4 mL of tetrahydrofuran was cooled to -20 °C. Allylmagnesium bromide (0.60 mL of a 1.0 M solution in tetrahydrofuran, 0.60 mmol) was added slowly, during which time the reaction turned black. After stirring for 15 minutes, cyclohexene oxide (0.050 mL, 0.49 mmol) was added and the reaction was warmed gradually to 0 °C over a period of 2 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride and the resulting bright blue aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% → 30% ethyl acetate/hexanes) yielded 47 mg (68%) of **5.6** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Schomaker, J. M.; Travis, B. R.; Borhan, B. *Org. Lett.* **2003**, 5, 3089.



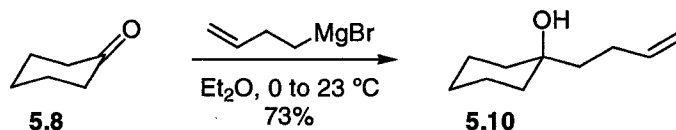
(±)-(1R,2S)-2-But-3-enyl-cyclohexanol (5.7): A suspension of copper (I) bromide-dimethyl sulfide complex (10 mg, 0.049 mmol) in 3.5 mL of tetrahydrofuran was cooled to -20 °C. 3-Butenylmagnesium bromide (1.2 mL of a 0.5 M solution in tetrahydrofuran, 0.60 mmol) was added slowly, during which time the reaction turned purple. After stirring for 15 minutes, cyclohexene oxide (0.050 mL, 0.49 mmol) was added and the reaction was warmed gradually to 0 °C over a period of 2 hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride and the resulting bright blue aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried with magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 39.6 mg (52%) of **5.7** as a colourless oil. Spectral data

for this compound was in agreement with that reported previously: Hon, Y. -S.; Liu, Y. -W.; Hsieh, C. -H. *Tetrahedron* **2004**, *60*, 4837.



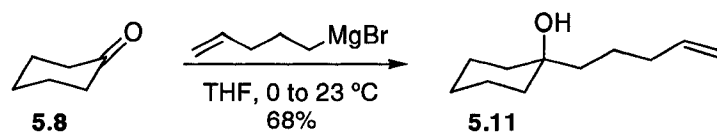
1-Allyl-cyclohexanol (5.9):

A solution of allylmagnesium bromide (0.96 mL of a 1.0 M solution in tetrahydrofuran, 0.96 mmol) in 4 mL of tetrahydrofuran was cooled to 0 °C. Cyclohexanone (0.050 mL, 0.48 mmol) was added drop-wise and the reaction was warmed to ambient temperature. After stirring for 4 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 48 mg (71%) of **5.9** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Shen, K. -H.; Yao, C. -F. *J. Org. Chem.* **2006**, *71*, 3980.

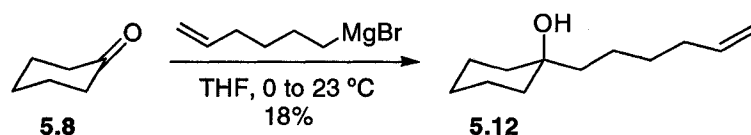


1-But-3-enyl-cyclohexanol (5.10):

A solution of 3-butenylmagnesium bromide (3.9 mL of a 0.5 M solution in diethyl ether, 2.0 mmol) in 6 mL of diethyl ether was cooled to 0 °C. cyclohexanone (0.10 mL, 0.96 mmol) was added drop-wise and the reaction was warmed to ambient temperature. After stirring for 1 hour, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (10% ethyl acetate/hexanes) yielded 108 mg (71%) of **5.10** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Org. Chem.* **1990**, *55*, 891.

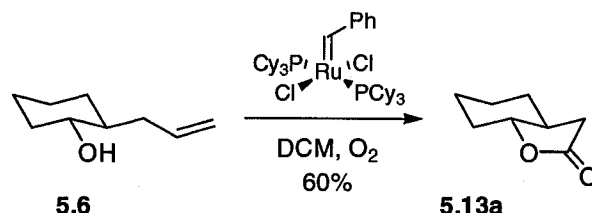
**1-Pent-4-enyl-cyclohexanol (5.11):**

Magnesium turnings (246 mg, 10.1 mmol) were added to a stirring solution of 1,2-dibromoethane (0.15 mL, 1.7 mmol) in 17 mL of tetrahydrofuran. The reaction was heated gently with a heat gun until bubbles were seen to evolve from the magnesium. The heat source was then removed and 5-bromopentene (1.0 mL, 8.5 mmol) was added drop-wise at such a rate so as to maintain a gentle reflux. Once the addition was complete, the reaction was kept at reflux for 45 minutes during which time the magnesium went into solution. The brownish liquid was cooled to ambient temperature and used directly for the subsequent step. In a separate flask, a solution of the freshly prepared Grignard (5.0 mL of a 0.5 M solution, 2.5 mmol) in 5 mL of tetrahydrofuran was cooled to 0 °C. Cyclohexanone (0.130 mL, 1.25 mmol) was added drop-wise and the reaction was warmed to ambient temperature. After stirring for 1.5 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 143 mg (68%) of **5.11** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Org. Chem.* **1990**, *55*, 891.

**1-Hex-5-enyl-cyclohexanol (5.12):**

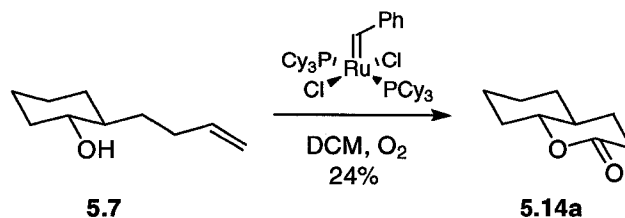
Magnesium turnings (87 mg, 3.6 mmol) were added to a stirring solution of 1,2-dibromoethane (0.050 mL, 0.58 mmol) in 6 mL of tetrahydrofuran. The reaction was heated gently with a heat gun until bubbles were seen to evolve from the magnesium. The heat source was then removed and 6-bromo-1-hexene (0.40 mL, 3.0 mmol) was added drop-wise at such a rate so as to maintain a gentle reflux. Once the addition was complete, the reaction was kept at reflux for 1.5 hours during which time the magnesium went into solution. The brownish liquid was cooled to ambient temperature and used directly for the subsequent step.

(Large amounts of precipitate formed upon cooling. Once settled, however, the clear, top phase could be removed and used alone). In a separate flask, a solution of the freshly prepared Grignard (3.0 mL of a 0.5 M solution, 1.5 mmol) in 5 mL of tetrahydrofuran was cooled to 0 °C. Cyclohexanone (0.080 mL, 0.77 mmol) was added drop-wise and the reaction was warmed to ambient temperature. After stirring for 1.5 hours, the reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (15% ethyl acetate/hexanes) yielded 26 mg (18%) of **5.12** as a colourless oil. Spectral data for this compound was in agreement with that reported previously: Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron*, **2003**, 59, 8525.



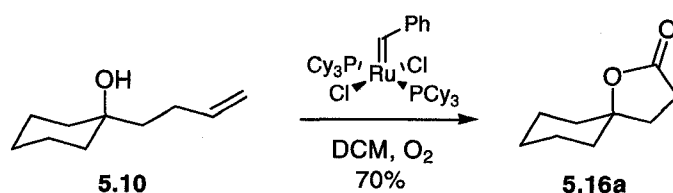
***trans*-Hexahydro-benzofuran-2-one (5.13a):**

Grubbs' first generation catalyst (70 mg, 0.085 mmol) was added to a solution of **5.6** (12.2 mg, 0.0870 mmol) in 9 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (10% → 30% ethyl acetate/hexanes) to yield 7.2 mg of **5.13a** as a colourless oil (60%). Spectral data for this compound was in agreement with that reported previously: Muller, P.; Lacrampe, F.; Bernardinelli, G. *Tetrahedron: Asymmetry* **2003**, 14, 1503.



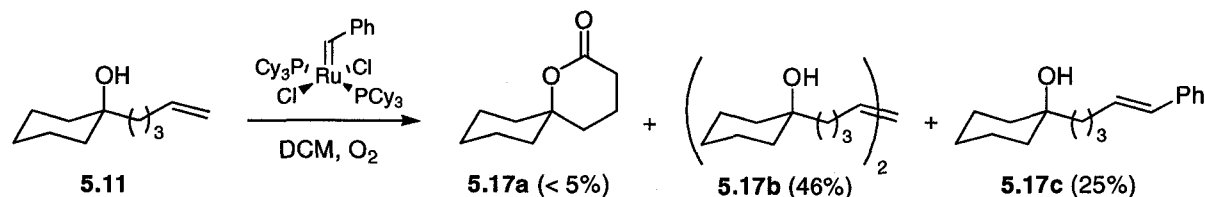
***trans*-Octahydro-chromen-2-one (5.14a):**

Grubbs' first generation catalyst (25 mg, 0.031 mmol) was added to a solution of **5.7** (4.9 mg, 0.032 mmol) in 3.5 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (15% ethyl acetate/hexanes, then 35/5/60 dichloromethane/ethyl acetate/hexanes) to yield 1.2 mg of **5.14a** (24%) as a colourless oil, along with several other unidentified compounds. Spectral data for **5.14a** was in agreement with that reported previously: Hsu, J.-L.; Fang, J.-M. *J. Org. Chem.* **2001**, 66, 8573.



1-Oxa-spiro[4.5]decan-2-one (5.16a):

Grubbs' first generation catalyst (63 mg, 0.077 mmol) was added to a solution of **5.10** (11.3 mg, 0.073 mmol) in 7 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was concentrated and purified twice by silica gel flash chromatography (20% ethyl acetate/hexanes) to yield 7.9 mg of **5.16a** as a white solid (70%). Spectral data for this compound was in agreement with that reported previously: Baskaran, S.; Islam, I.; Chandrasekaran, S. *J. Org. Chem.* **1990**, 55, 891.



1-Oxa-spiro[5.5]undecan-2-one (5.17a) and dimer of 5.11 (5.17b) and 1-((E)-5-phenylpent-4-enyl)-cyclohexanol (5.17c):

Grubbs' first generation catalyst (94.0 mg, 0.115 mmol) was added to a solution of **5.11** (19.3 mg, 0.115 mmol) in 11 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was

concentrated and purified twice by silica gel flash chromatography (5% → 30% ethyl acetate/hexanes) to yield 3.9 mg of **5.17a** (< 5%) as an inseparable mixture with a second, unidentified product, 6.9 mg of **5.17b** (25%) and 8.2 mg of **5.17c** (46%). Spectral data for **5.17a** was in agreement with that reported previously: Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, 4, 459.

Data for **5.17b**: (mixture of *cis* and *trans*)

^1H NMR (CDCl_3 , 500 MHz, δ): 5.39-5.38 and 5.36-5.34 (m and m, 2H), 2.02-1.96 (m, 4H), 1.59-1.36 (m, 26H), 1.27-1.20 (m, 4H).

^{13}C NMR (CDCl_3 , 125 MHz, δ): 130.42 and 129.94 (2C), 71.43 (2C), 41.82 (br, 2C), 37.41 (4C), 33.00 (2C), 25.83 (2C), 22.85 (2C), 22.24 (4C).

IR (neat, cm^{-1} , ν): 3381 (s, br), 2933 (s), 2859 (s), 1711 (w), 1447 (m), 1398 (w), 1351 (w), 1301 (w), 1255 (w), 1169 (w), 1146 (w).

HRMS (EI, m/z): calculated 272.2504 for $[\text{M}-2\text{H}_2\text{O}]^+$, found 272.2502.

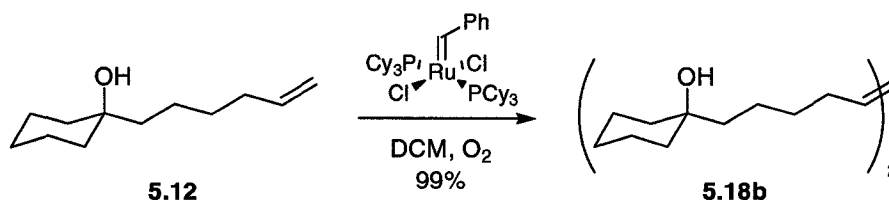
Data for **5.17c**:

^1H NMR (CDCl_3 , 300 MHz, δ): 7.38-7.31 (m, 3H), 7.23-7.19 (m, 2H), 6.41 (d, $J_{\text{AB}} = 15.8$ Hz, 1H), 6.24 (dt, $J_{\text{AB}} = 15.8$, $J_{\text{BX}} = 6.8$ Hz, 1H), 2.29-2.19 (m, 2H), 1.67-1.26 (m, 15H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 137.79, 130.81, 129.96, 128.46 (2C), 126.81, 125.90 (2C), 71.42, 41.94 (br), 37.41 (2C), 33.48, 25.82, 22.67, 22.23 (2C).

IR (neat, cm^{-1} , ν): 3411 (w, br), 3026 (w), 2932 (s), 2858 (m), 1723 (w), 1597 (w), 1495 (w), 1448 (m), 1263 (w), 1169 (w).

HRMS (EI, m/z): calculated 244.1827 for $[\text{M}]^+$, found 244.1837.



Dimer of **5.12 (**5.18b**):**

Grubbs' first generation catalyst (25 mg, 0.030 mmol) was added to a solution of **5.12** (5.6 mg, 0.030 mmol) in 3 mL of dichloromethane. A stream of oxygen was blown over the reaction space and the flask was capped. After stirring for 18 hours, the reaction was

concentrated and purified twice by silica gel flash chromatography (15% → 30% ethyl acetate/hexanes) to yield 5.1 mg of dimer **5.18c** as a colourless oil (99%).

Data for 5.18b:

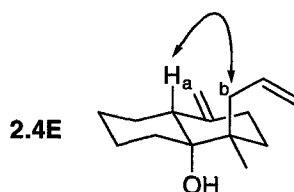
^1H NMR (CDCl_3 , 300 MHz, δ): 5.37-5.30 (m, 2H), 2.04-1.97 (m, 4H), 1.61-1.21 (m, 34H).

^{13}C NMR (CDCl_3 , 75 MHz, δ): 130.80 (2C), 71.87 (2C), 42.23 (br, 2C), 37.83 (4C), 32.95 (2C), 30.54 (2C), 26.28 (2C), 22.68 (4C), 22.65 (2C).

IR (neat, cm^{-1} , ν): 3389 (s, br), 2930 (s), 2855 (s), 2663 (w), 1955 (w), 1710 (w), 1447 (s), 1401 (m), 1350 (m), 1298 (m), 1260 (m), 1169 (m), 1144 (m), 1032 (m).

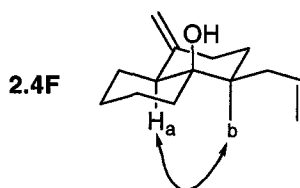
HRMS (EI, m/z): calculated 318.2923 for $[\text{M}-\text{H}_2\text{O}]^+$, found 318.2926.

Assignment of Relative Stereochemistry and/or Regioisomers



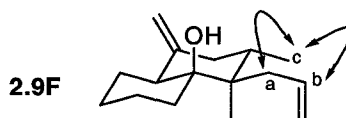
Key NOESY interactions for **2.4E**:

H_a ($\delta = 2.35$, dd, $J = 10.7, 4.7$ Hz) $\leftrightarrow$ H_b ($\delta = 2.48$, dd, $J = 13.5, 8.1$ Hz).



Key NOEs for **2.4F**:

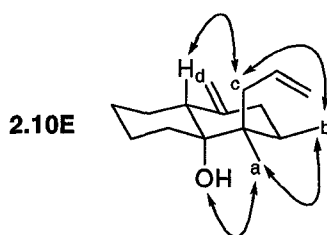
H_a ($\delta = 2.35$ -2.31, m) $\leftrightarrow$ H_b ($\delta = 1.05$, s); 1.7%



Of the four possible isomers for this substrate, two had been prepared via the reaction of **2.10A** (**2.10E** = **2.9K** and **2.10F** = **2.9J**) and could therefore be ruled out. To distinguish between the remaining two possibilities (**2.9F** and **2.9E**), the following key NOEs were used:

H_a ($\delta = 2.32$, dd, $J = 15.3, 8.3$ Hz) $\leftrightarrow$ H_c ($\delta = 0.87$, d, $J = 6.4$ Hz); 3.6%

H_b ($\delta = 6.13$ - 6.05 , m) $\leftrightarrow$ H_c ($\delta = 0.87$, d, $J = 6.4$ Hz); 1.3%



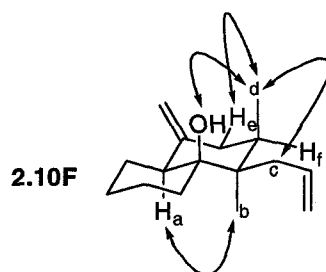
Key NOESY interactions for **2.10E** (compiled from data in $CDCl_3$ and C_6D_6):

H_a ($\delta = 0.97$, s) $\leftrightarrow$ H_b ($\delta = 0.80$, d, $J = 6.8$ Hz); C_6D_6

H_b ($\delta = 0.80$, d, $J = 6.8$ Hz) $\leftrightarrow$ H_c ($\delta = 2.15$ - 2.03 , m); C_6D_6

H_a ($\delta = 0.97$, s) $\leftrightarrow$ OH ($\delta = 1.15$, d, $J = 1.7$ Hz); C_6D_6

H_d ($\delta = 2.33$, d, br, $J = 11.7$ Hz) $\leftrightarrow$ H_c ($\delta = 2.30$ - 2.20 , m); $CDCl_3$



Key NOESY interactions for **2.10F**:

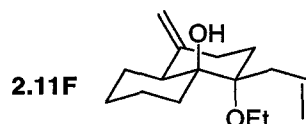
H_a ($\delta = 2.09$ - 2.06 , m) $\leftrightarrow$ H_b ($\delta = 0.91$, s)

H_c ($\delta = 2.77$, dd, $J = 14.1, 6.8$ Hz) $\leftrightarrow$ H_d ($\delta = 1.06$, d, $J = 7.3$ Hz)

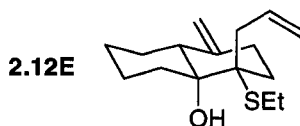
H_d ($\delta = 1.06$, d, $J = 7.3$ Hz) $\leftrightarrow$ OH ($\delta = 0.86$, d, $J = 1.4$ Hz)

H_d ($\delta = 1.06$, d, $J = 7.3$ Hz) $\leftrightarrow$ H_e ($\delta = 1.78$, dd, $J = 12.9, 3.0$ Hz)

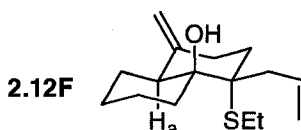
In addition, the coupling constants for H_e indicate that H_f is in an equatorial position.



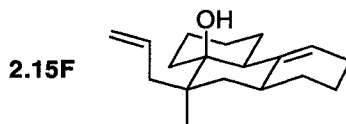
Relative stereochemistry of **2.11F** was assigned by chemical proof. See formation of **2.16**.



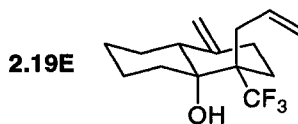
Relative stereochemistry of **2.12E** was assigned by default since the major product was assigned as the **F** isomer (no other isomers possible).



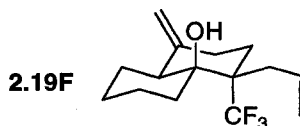
The ethyl sulfide of **2.12F** was assigned as being axial by the downfield shift of the H_a proton from its typical value of ~ 2.3 ppm to the observed value of 3.12 ppm. That this effect can be attributed to the nearby sulfur atom was further confirmed by the assignment of **2.92F** (*vide infra*).



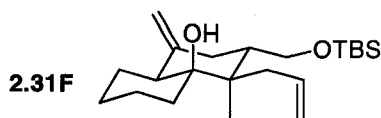
Relative stereochemistry of **2.15F** was assigned by chemical proof. See formation of **5.4**.



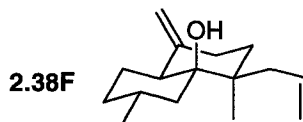
Relative stereochemistry of **2.19E** was assigned by default since the major product was assigned as the **F** isomer (no other isomers possible).



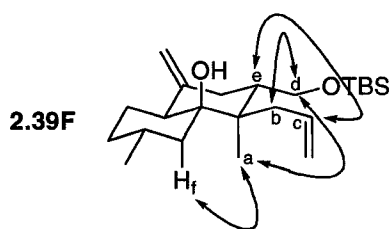
Relative stereochemistry of **2.19F** was assigned by chemical proof. See formation of **2.20**.



Relative stereochemistry of **2.31F** was assigned as being analogous to that of **2.39F** by virtue of their nearly identical ^1H NMR spectra.



Relative stereochemistry of **2.38F** was assigned as being analogous to that of **2.4F** by virtue of their nearly identical ^1H NMR spectra.



Key NOEs for **2.39F**:

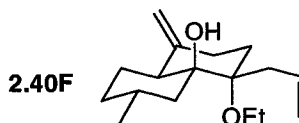
H_a ($\delta = 0.93$, s) $\leftrightarrow$ H_d (3.42, dd, $J = 9.9, 7.1$ Hz); 4.4%

H_a ($\delta = 0.93$, s) $\leftrightarrow$ H_f ($\delta = 1.1$, dd, $J = 12.6, 12.0$ Hz); 3.0%

H_b ($\delta = 2.24$, dd, $J_{AB} = 15.4, J_{BX} = 6.5$ Hz) $\leftrightarrow$ H_d (3.42, dd, $J = 9.9, 7.1$ Hz); 4.0%

H_c ($\delta = 6.19\text{--}6.05$, m) $\leftrightarrow$ H_e ($\delta = 2.15\text{--}1.98$, m); 3.0%

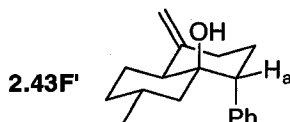
In addition, the single crystal X-ray crystallographic obtained for wiedemannic acid analogue **3.16** confirmed that the assignment of **2.39F** was correct.



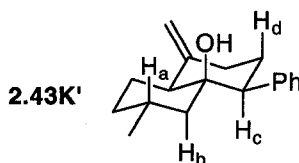
Relative stereochemistry of **2.40F** was assigned as being analogous to that of **2.11F** by virtue of their nearly identical ^1H NMR spectra.



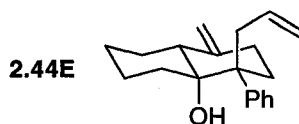
The relative stereochemistry of **2.43E'** was assigned by the coupling constants for protons H_a and H_b , as well as by the comparison of its NMR spectra to that of **2.43K'**: H_a ($\delta = 2.55$, dd, $J = 12.9, 3.9$ Hz) was assigned as being axial based on its large vicinal coupling constant with H_b ($\delta = 1.98$, dddd, $J = 13.2, 13.2, 13.2, 4.4$ Hz); The methyl group was assigned as being axial since the alternative structure with the equatorial methyl group was known (**2.43K'**) and had unique NMR spectra.



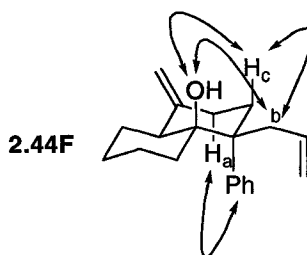
The relative stereochemistry of **2.43F'** was assigned by the coupling constant of H_a ($\delta = 2.84$, dd, $J = 5.9, 0.8$ Hz) which indicates an equatorial proton. In addition, the equatorial position of the methyl group was assigned based on its chemical shift of 0.71 ppm (d, $J = 6.6$ Hz) which corresponds to that of the equatorial methyl group in **2.43K'** ($\delta = 0.74$, d, $J = 6.6$ Hz) rather than the axial methyl group found in **2.43E'** ($\delta = 1.00$, d, $J = 7.3$ Hz).



The relative stereochemistry of **2.43K'** was assigned by the coupling constants for protons $H_a - H_d$: H_a ($\delta = 1.62-1.54$, m) was assigned as axial based on the large, vicinal coupling constant observed between it and axial proton H_b ($\delta = 0.86$, dd, $J = 13.1, 12.5$ Hz); H_c ($\delta = 2.58$, dd, $J = 12.9, 3.7$ Hz) was assigned as being axial based on the large vicinal coupling constant between it and axial proton H_d ($\delta = 2.00$, dddd, $J = 13.2, 13.2, 13.2, 4.4$ Hz).



Relative stereochemistry of **2.44E** assigned by default since the minor product was assigned as the **F** isomer.



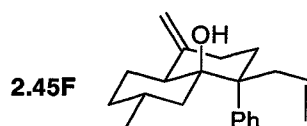
Key NOESY interactions for **2.44F**:

H_a ($\delta = 2.82$, ddd, $J = 14.1, 14.1, 5.8$ Hz) $\leftrightarrow$ H_{Ph} ($\delta = 7.60$ -7.58, m)

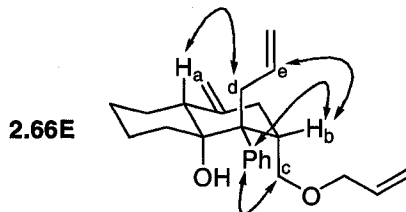
H_b ($\delta = 2.50$, dd, $J = 14.4, 8.8$ Hz) $\leftrightarrow$ H_{OH} ($\delta = 1.68$, d, $J = 1.7$ Hz)

H_b ($\delta = 2.50$, dd, $J = 14.4, 8.8$ Hz) $\leftrightarrow$ H_c ($\delta = 1.80$, ddd, $J = 14.4, 14.2, 6.2$ Hz)

H_c ($\delta = 1.80$, ddd, $J = 14.4, 14.2, 6.2$ Hz) $\leftrightarrow$ H_{OH} ($\delta = 1.68$, d, $J = 1.7$ Hz)



Relative stereochemistry of **2.45F** was assigned as being analogous to that of **2.14F** by virtue of their nearly identical ^1H NMR spectra.



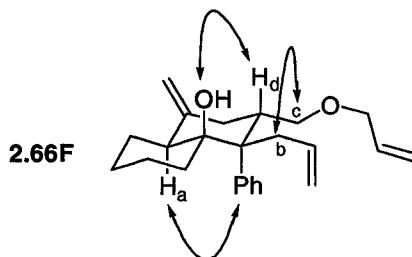
Key NOESY interactions for **2.66E**:

H_a ($\delta = 2.42$, dd, $J = 7.8, 7.4$ Hz) $\leftrightarrow$ H_d ($\delta = 3.03$, dd, $J = 16.3, 6.8$ Hz)

H_b ($\delta = 2.22$ -2.21, m) $\leftrightarrow$ H_e ($\delta = 5.82$ -5.75, m)

H_b ($\delta = 2.22$ -2.21, m) $\leftrightarrow$ H_{Ph} ($\delta = 7.98$, d, $J = 8.0$ Hz)

H_c ($\delta = 3.45$, dd, $J = 9.5, 7.2$ Hz) $\leftrightarrow$ H_{Ph} ($\delta = 7.98$, d, $J = 8.0$ Hz)

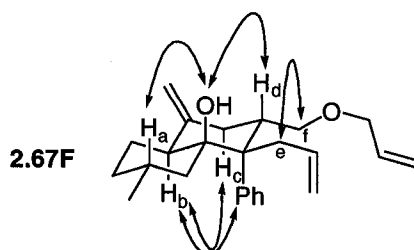


Key NOESY interactions for **2.66F**:

H_a ($\delta = 2.62$ - 2.60 , m) $\leftrightarrow$ H_{Ph} ($\delta = 7.59$, d, $J = 8.0$ Hz)

H_b ($\delta = 2.89$, dd, $J = 14.9, 7.9$) $\leftrightarrow$ H_c ($\delta = 3.53$, dd, $J = 9.3, 2.6$)

H_d ($\delta = 2.87$ - 2.75 , m) $\leftrightarrow$ H_{OH} ($\delta = 1.67$, s)



Key NOESY interactions for **2.67F**:

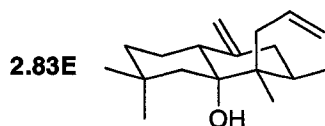
H_a ($\delta = 1.87$ - 1.85 , m) $\leftrightarrow$ H_{OH} ($\delta = 1.69$, s)

H_b ($\delta = 2.60$, d, $J = 10.3$ Hz) $\leftrightarrow$ H_c ($\delta = 2.84$, dd, $J = 14.0, 13.8$ Hz)

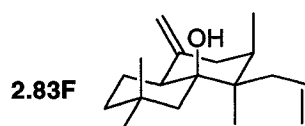
H_b ($\delta = 2.60$, d, $J = 10.3$ Hz) $\leftrightarrow$ H_{Ph} ($\delta = 7.60$, d, $J = 8.0$ Hz)

H_d ($\delta = 2.81$ - 2.75 , m) $\leftrightarrow$ H_{OH} ($\delta = 1.69$, s)

H_e ($\delta = 2.92$, dd, $J = 14.8, 8.1$ Hz) $\leftrightarrow$ H_f ($\delta = 3.54$, dd, $J = 9.3, 2.6$ Hz)



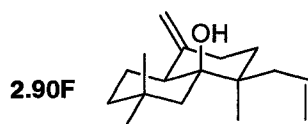
Relative stereochemistry of **2.83E** was assigned as being analogous to that of **2.10E** by virtue of their nearly identical ^1H NMR spectra.



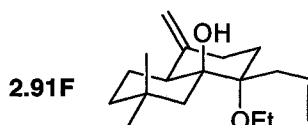
Relative stereochemistry of **2.83F** was assigned as being analogous to that of **2.10F** by virtue of their nearly identical ^1H NMR spectra.



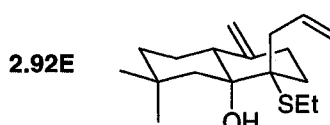
Relative stereochemistry of **2.90E** was assigned as being analogous to that of **2.4F** by virtue of their nearly identical ^1H NMR spectra.



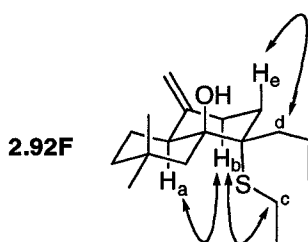
Relative stereochemistry of **2.90F** was assigned as being analogous to that of **2.4E** by virtue of their nearly identical ^1H NMR spectra.



Relative stereochemistry of **2.91F** was assigned as being analogous to that of **2.11F** by virtue of their nearly identical ^1H NMR spectra.



Relative stereochemistry of **2.92E** was assigned by default since the major product was assigned as the **F** isomer.

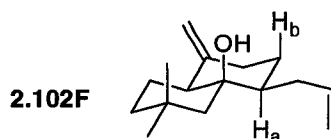


Key NOESY interactions for **2.92F**:

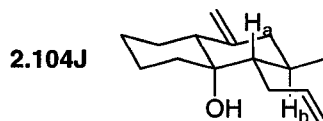
H_a ($\delta = 3.11$, dd, $J = 12.1, 1.5$ Hz) $\leftrightarrow$ H_b ($\delta = 2.45$, ddd, $J = 13.1, 13.1, 2.1$ Hz)

H_b ($\delta = 2.45$, ddd, $J = 13.1, 13.1, 2.1$ Hz) $\leftrightarrow$ H_c ($\delta = 2.27\text{--}2.21$, m)

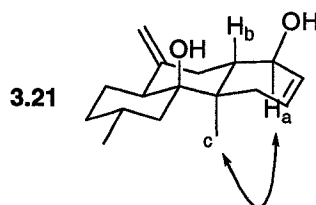
H_d ($\delta = 2.70\text{--}2.61$, m) $\leftrightarrow$ H_e ($\delta = 1.51$, ddd, $J = 13.8, 13.8, 4.2$ Hz)



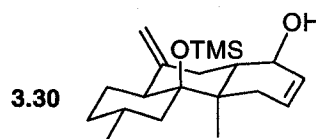
The allyl group in **2.102F** was assigned as equatorial based on the coupling constants of axial proton, H_b ($\delta = 0.99$, dddd, $J = 13.1, 13.1, 12.9, 4.3$ Hz), which indicate that H_a must also be axial.



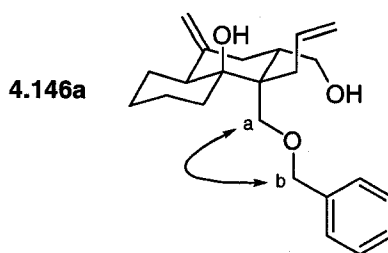
The allyl and methyl groups in **2.104J** were assigned as equatorial based on the coupling constants of H_a ($\delta = 0.78$, ddd, $J = 11.3, 4.5, 3.4$ Hz), indicating a diaxial relationship between it and H_b .



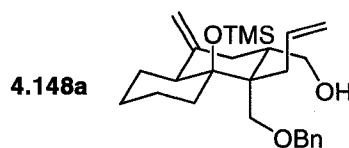
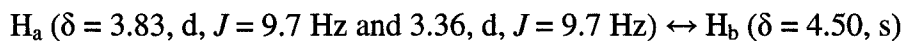
The secondary hydroxyl group in **3.21** was assigned as pseudo equatorial based on the coupling constant observed for proton H_a ($\delta = 3.82$, d, $J = 7.7$ Hz) which suggests a diaxial relationship between it and H_b . In addition, a weak NOE (1.5%) was observed between H_a and the adjacent methyl group (c).



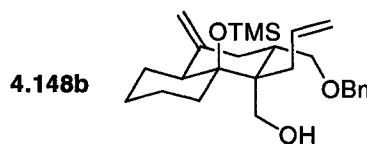
Relative stereochemistry of **3.30** was assigned as being analogous to that of **3.21** by virtue of their nearly identical ^1H NMR spectra.



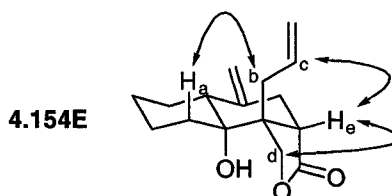
The position of the benzyl group in **4.146a** was assigned based on the following NOESY interactions:



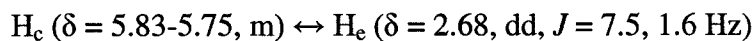
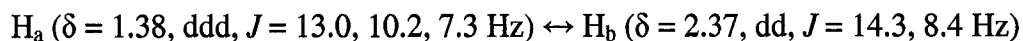
The position of the benzyl group in **4.148a** was assigned as being analogous to that of **4.146a** by virtue of their nearly identical ^1H NMR spectra.

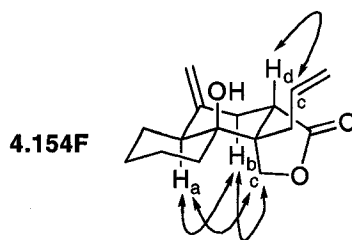


The position of the benzyl group in **4.148b** was assigned by default since the major product was assigned as **4.146a**.



Key NOESY interactions for **4.154E**:





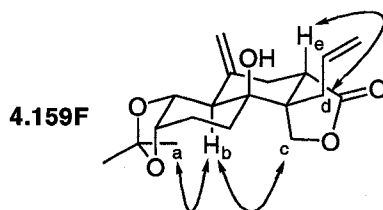
Key NOESY interactions for **4.154F**:

H_a ($\delta = 2.28$, dd, $J = 7.9, 7.5$ Hz) $\leftrightarrow$ H_b ($\delta = 2.14$, dd, $J = 13.2, 12.3$ Hz)

H_a ($\delta = 2.28$, dd, $J = 7.9, 7.5$ Hz) $\leftrightarrow$ H_c ($\delta = 4.38$, d, $J = 9.3$ Hz)

H_b ($\delta = 2.14$, dd, $J = 13.2, 12.3$ Hz) $\leftrightarrow$ H_c ($\delta = 4.38$, d, $J = 9.3$ Hz)

H_c ($\delta = 5.86$ - 5.78 , m) $\leftrightarrow$ H_d ($\delta = 2.51$, dd, $J = 12.1, 7.7$ Hz)

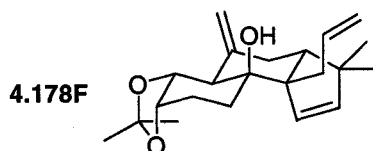


Key NOESY interactions for **4.159F**:

H_a ($\delta = 1.37$, s) $\leftrightarrow$ H_b ($\delta = 2.20$, d, $J = 8.6$ Hz)

H_b ($\delta = 2.20$, d, $J = 8.6$ Hz) $\leftrightarrow$ H_c ($\delta = 3.73$, d, $J = 9.4$ Hz)

H_d ($\delta = 2.13$, dd, $J = 14.3, 8.0$ Hz) $\leftrightarrow$ H_e ($\delta = 2.14$, dd, $J = 11.2, 7.5$ Hz)

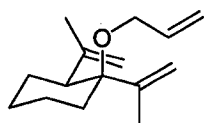


Relative stereochemistry of **4.178F** was proven by the single crystal X-ray crystallographic obtained for compound **4.192**.

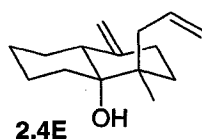
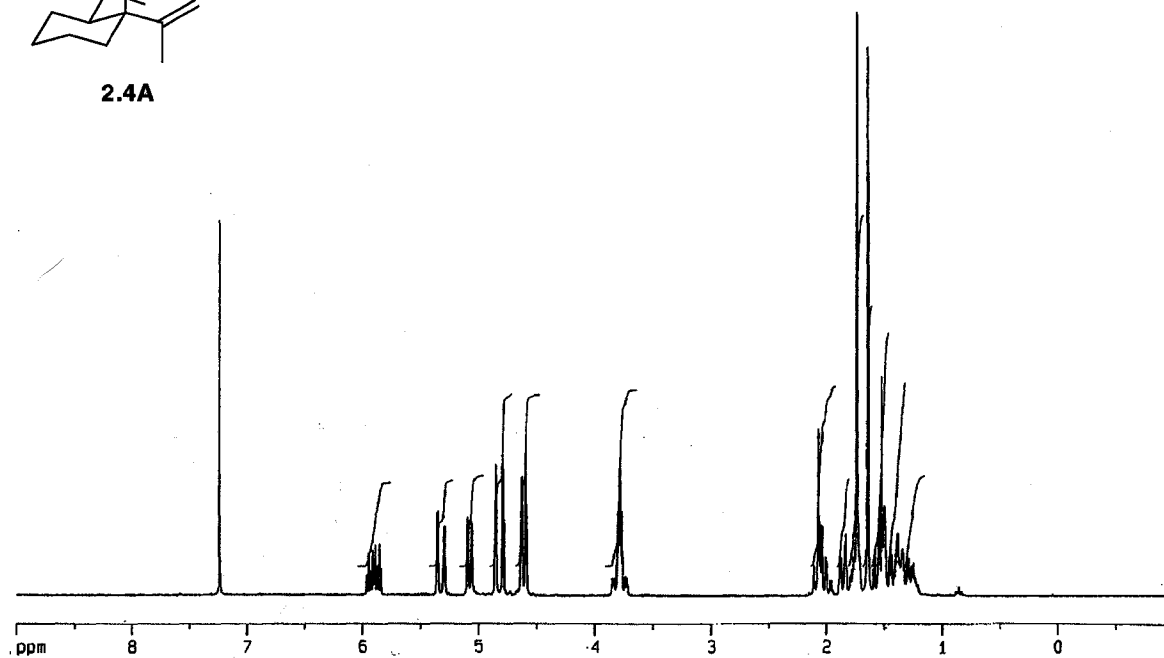
References

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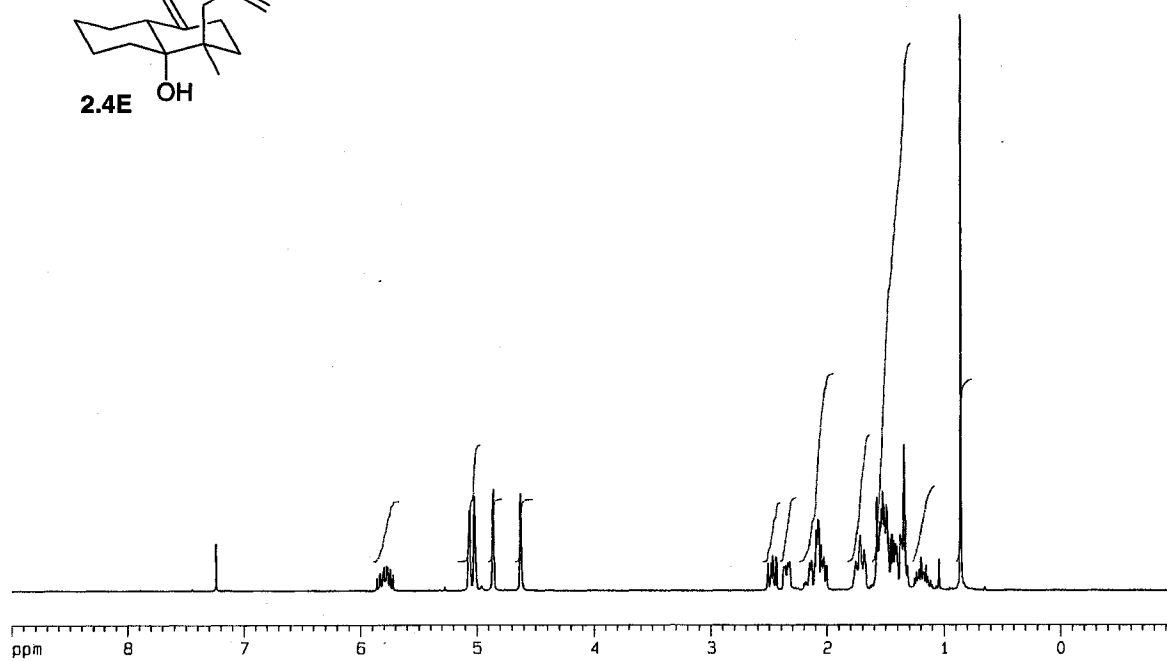
¹H NMR Spectra of New Compounds

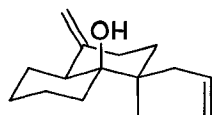


2.4A

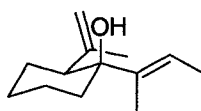
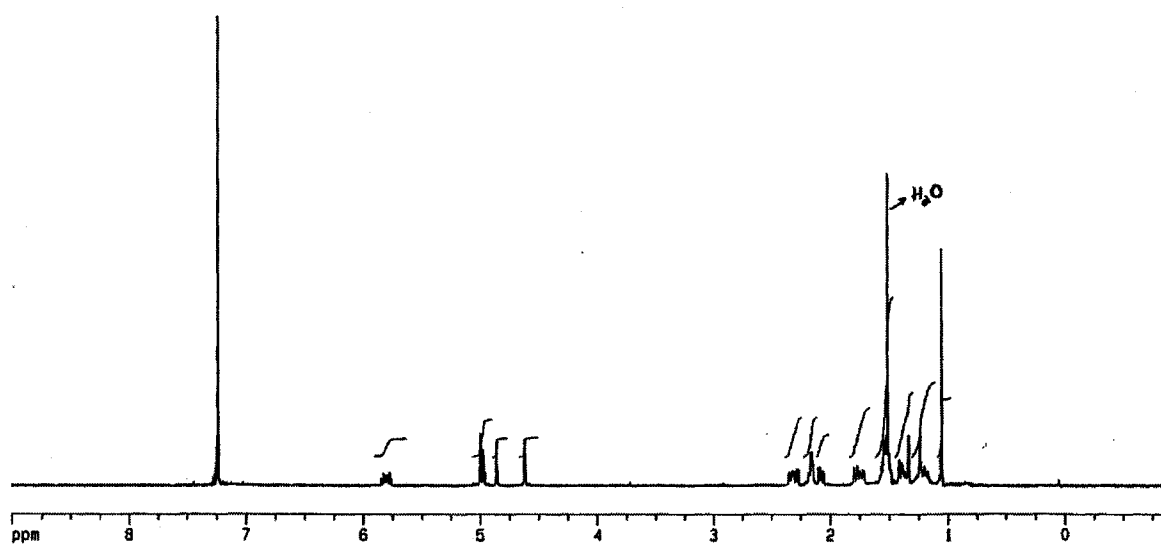


2.4E

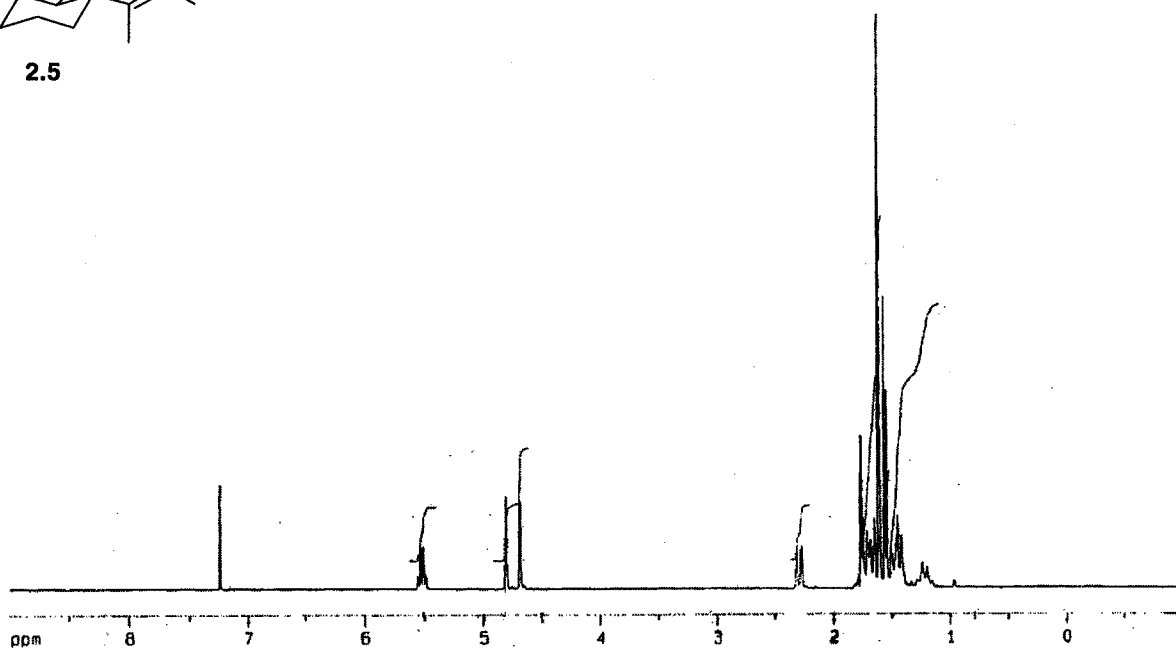


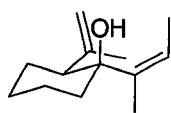


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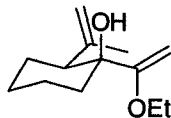
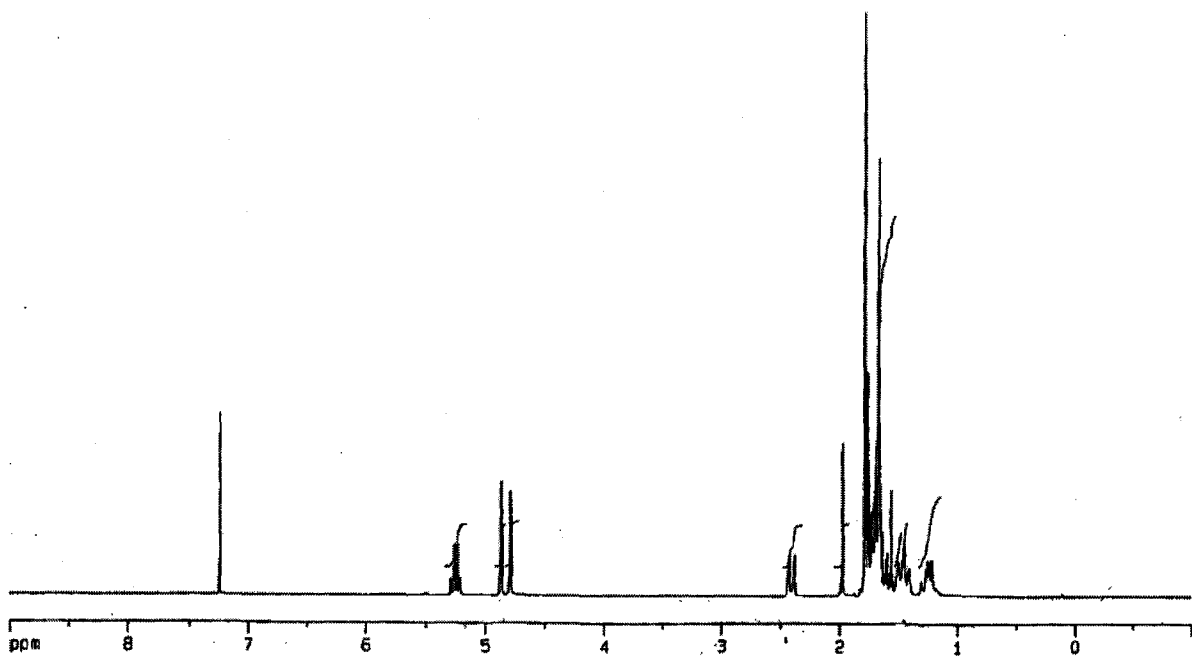


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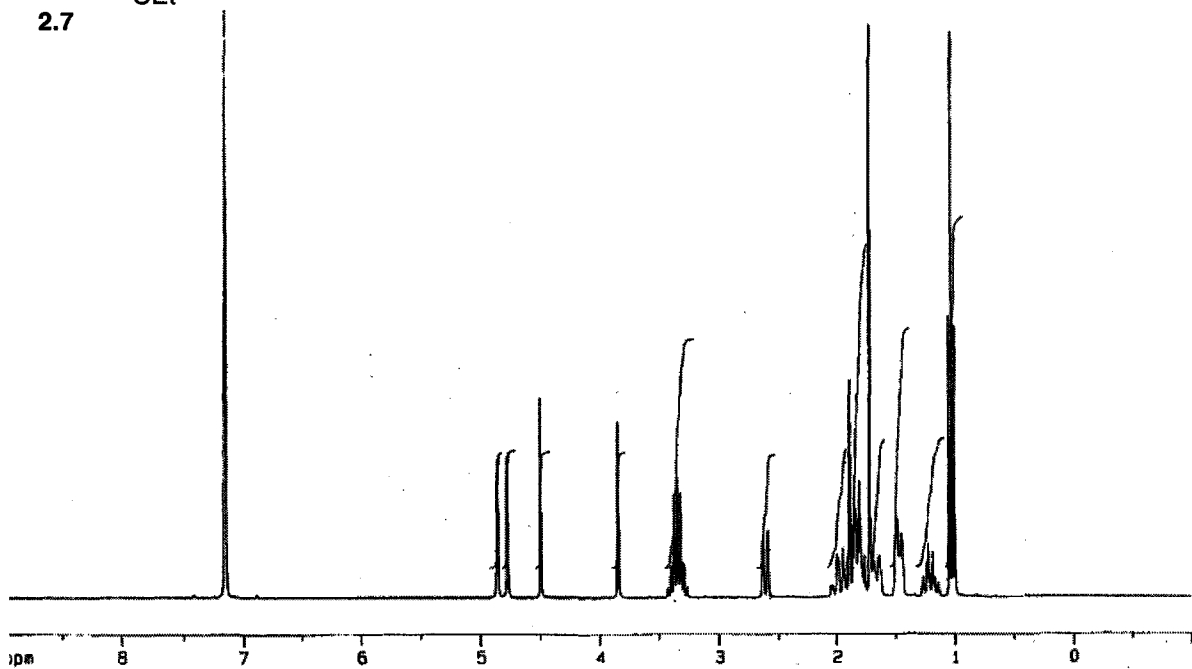


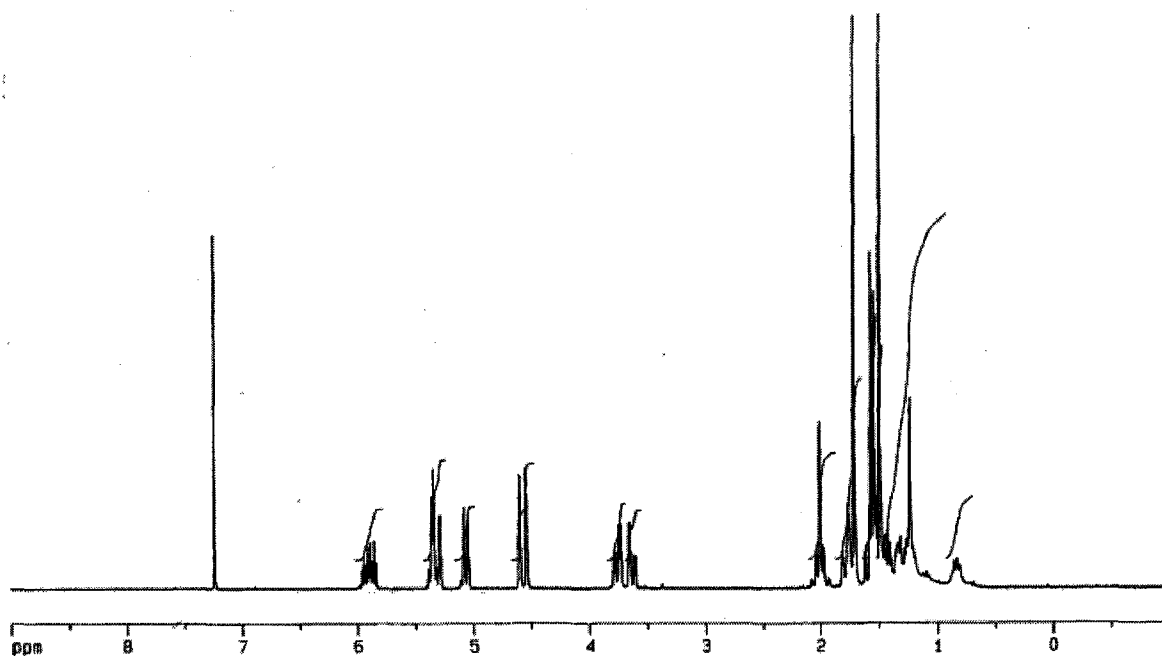
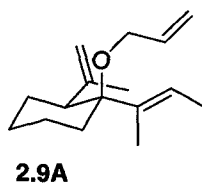
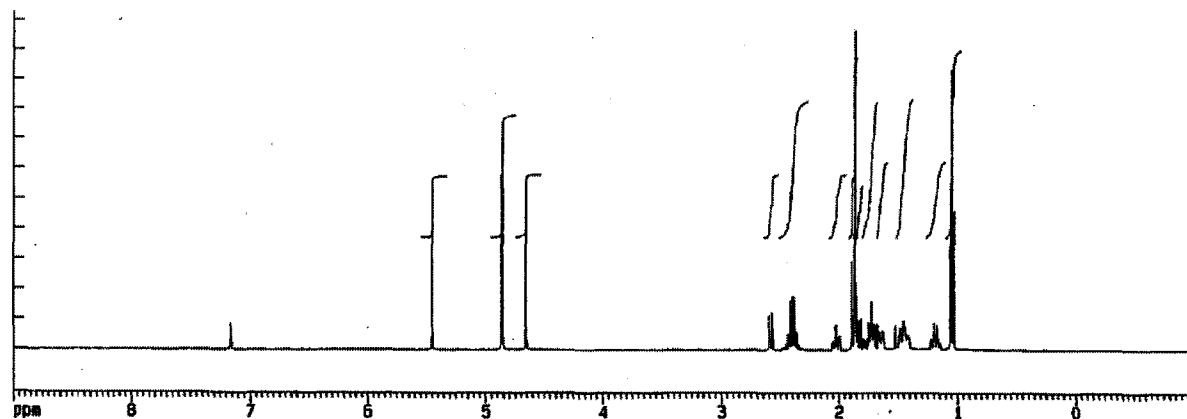
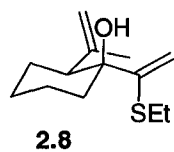


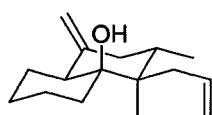
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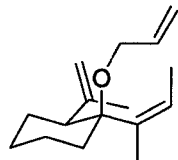
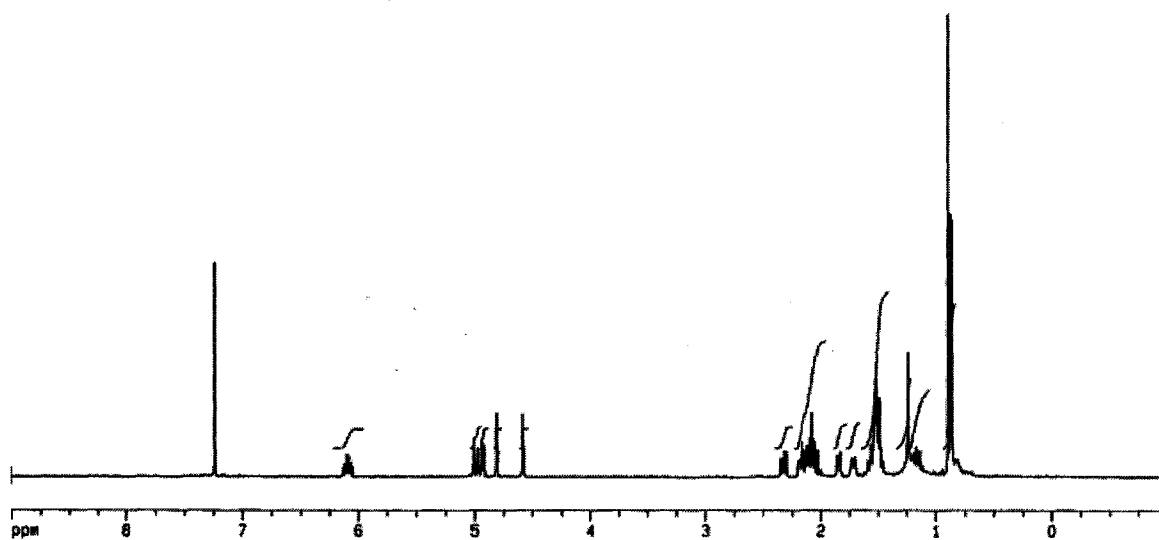
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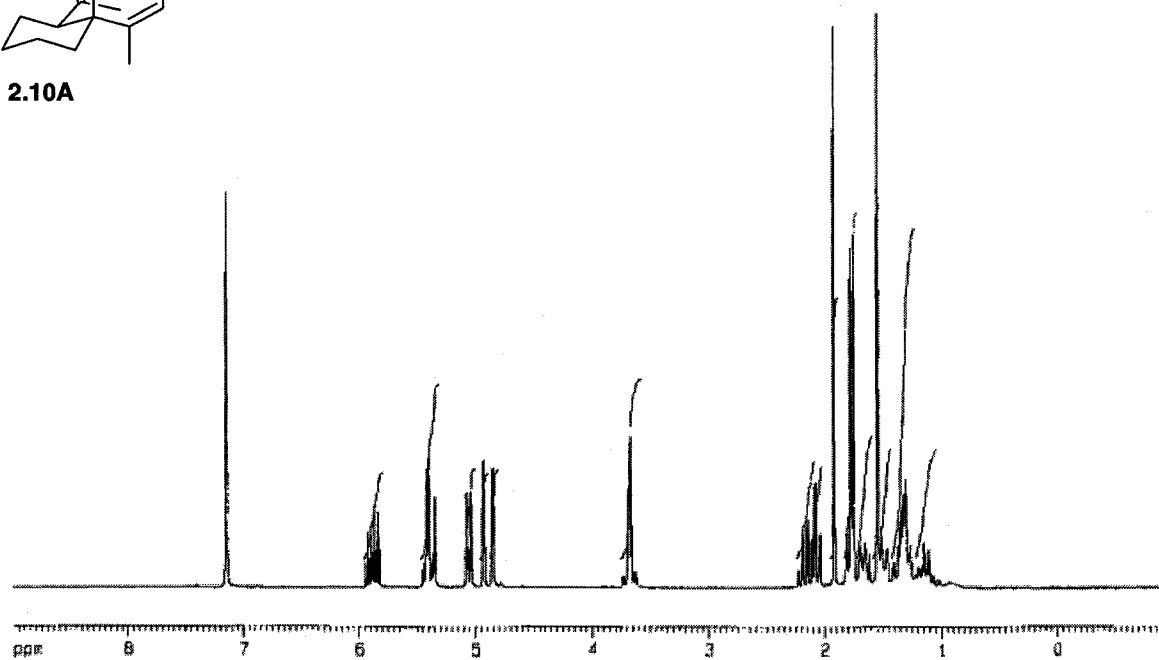


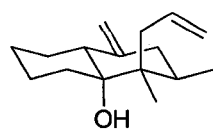


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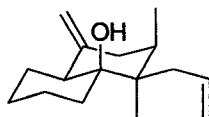
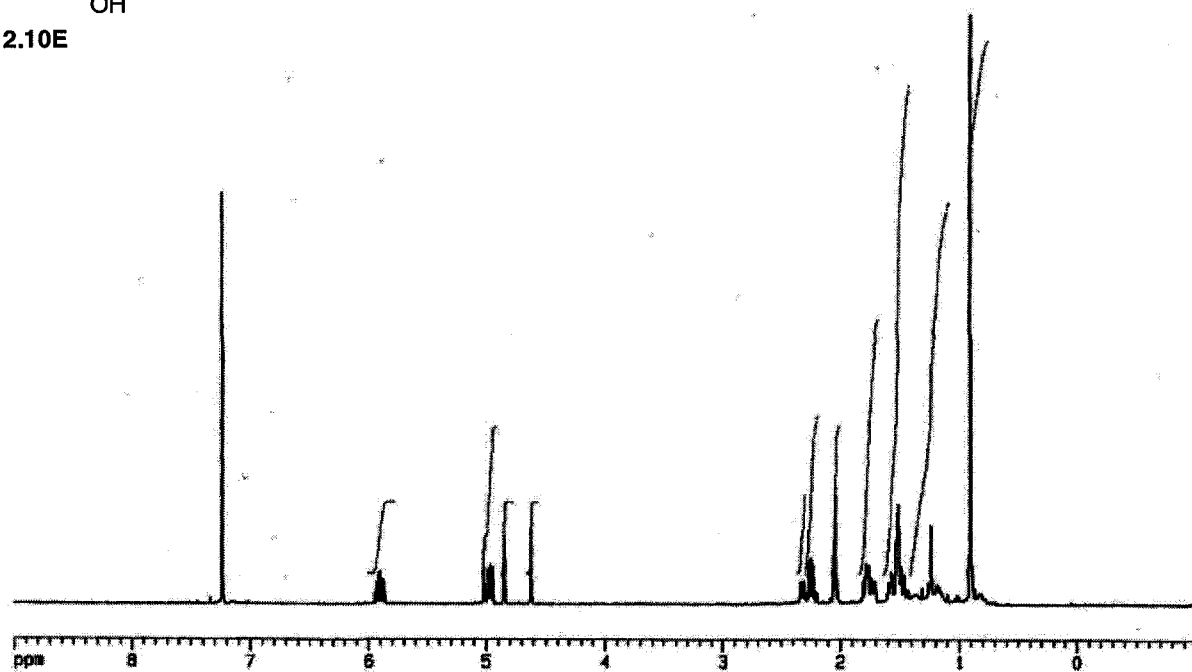


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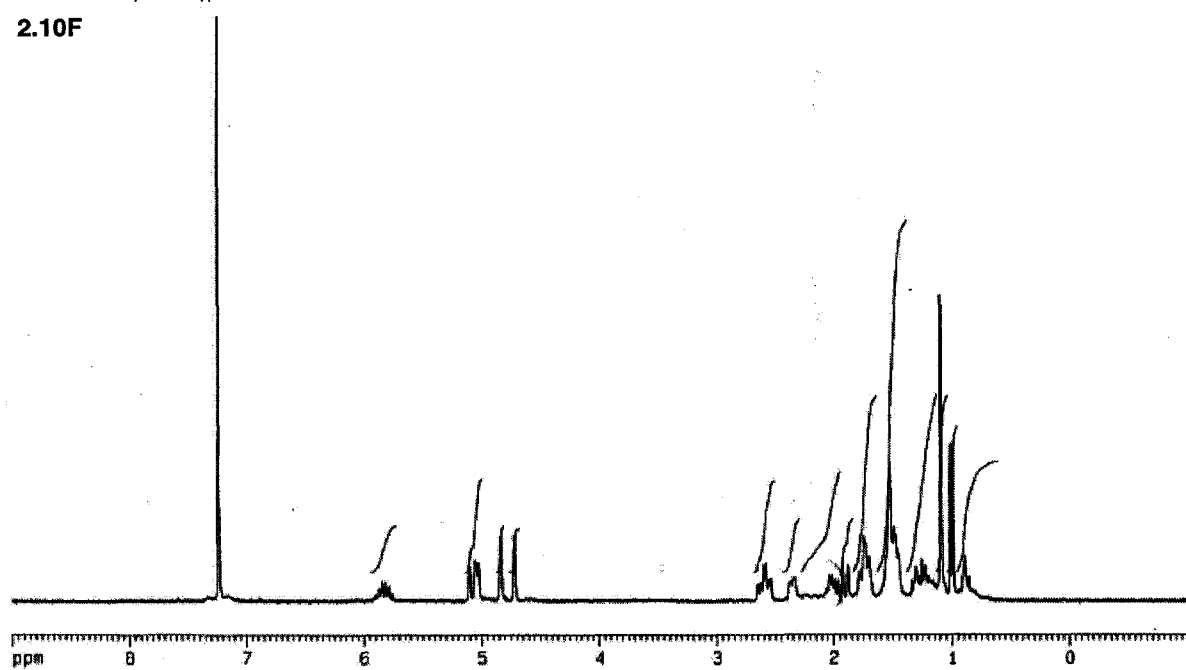


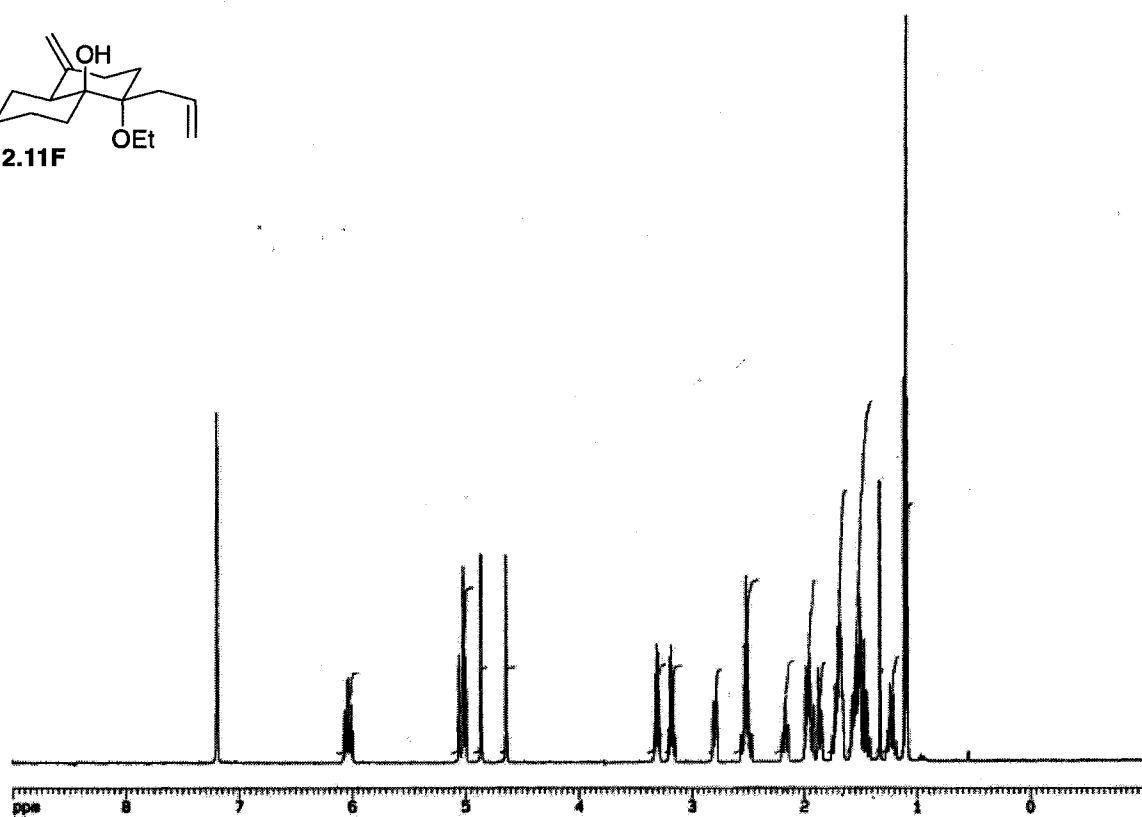
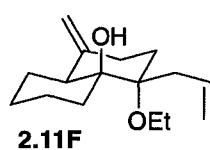
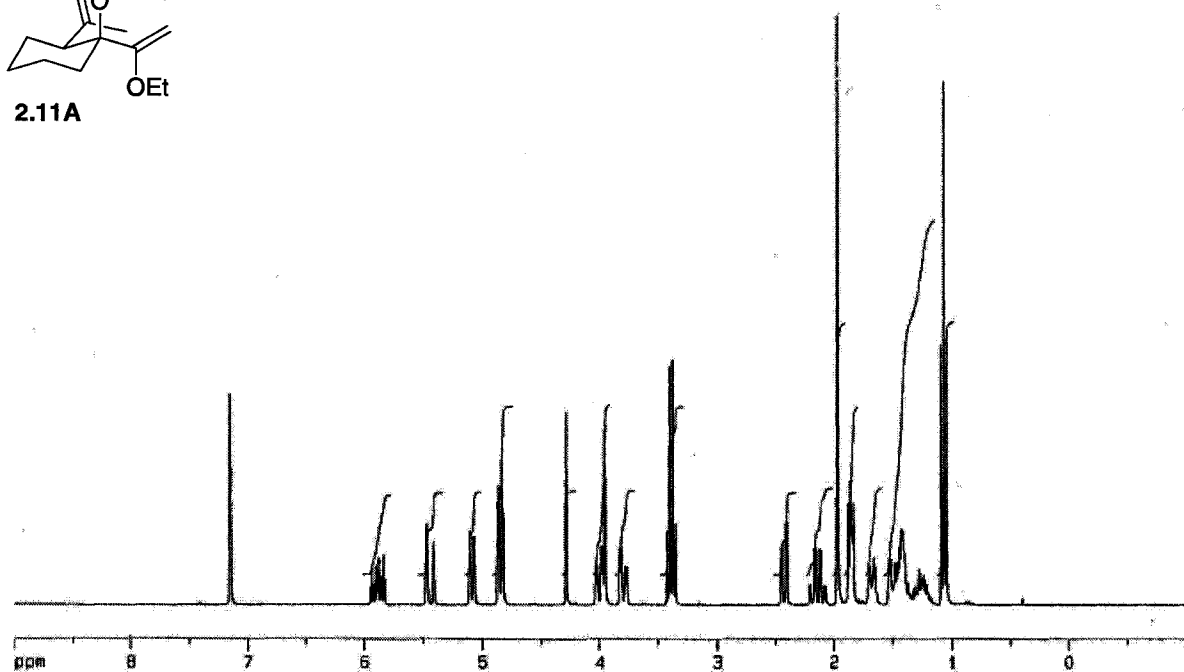
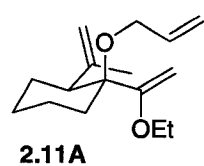


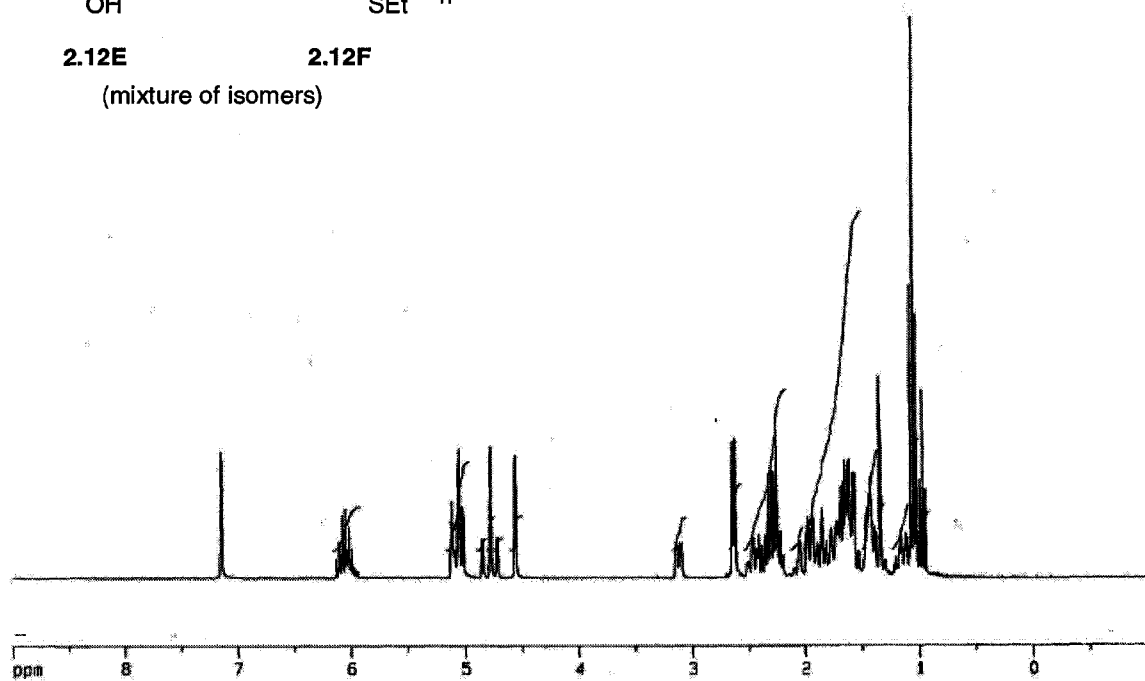
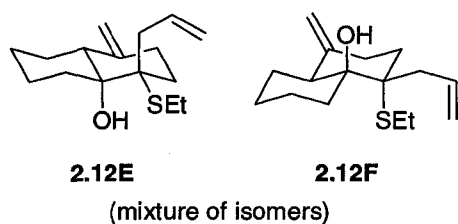
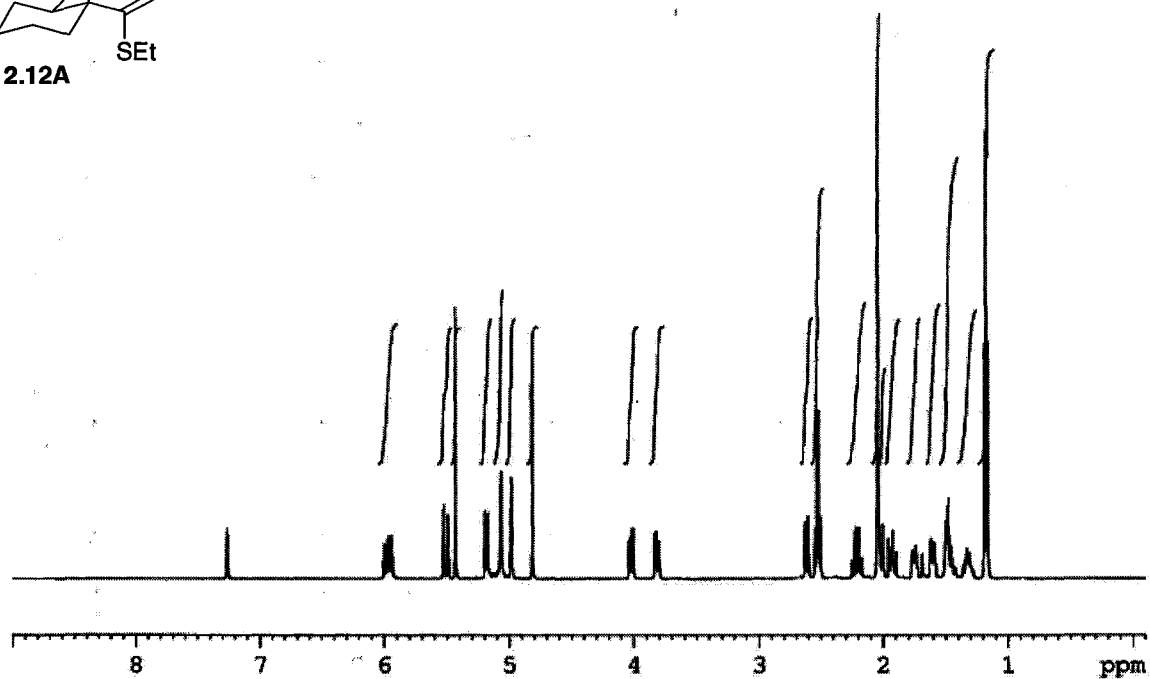
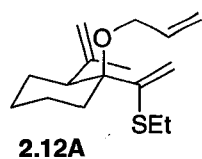
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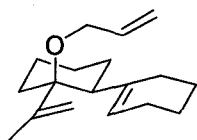


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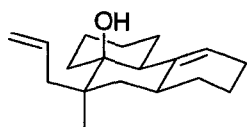
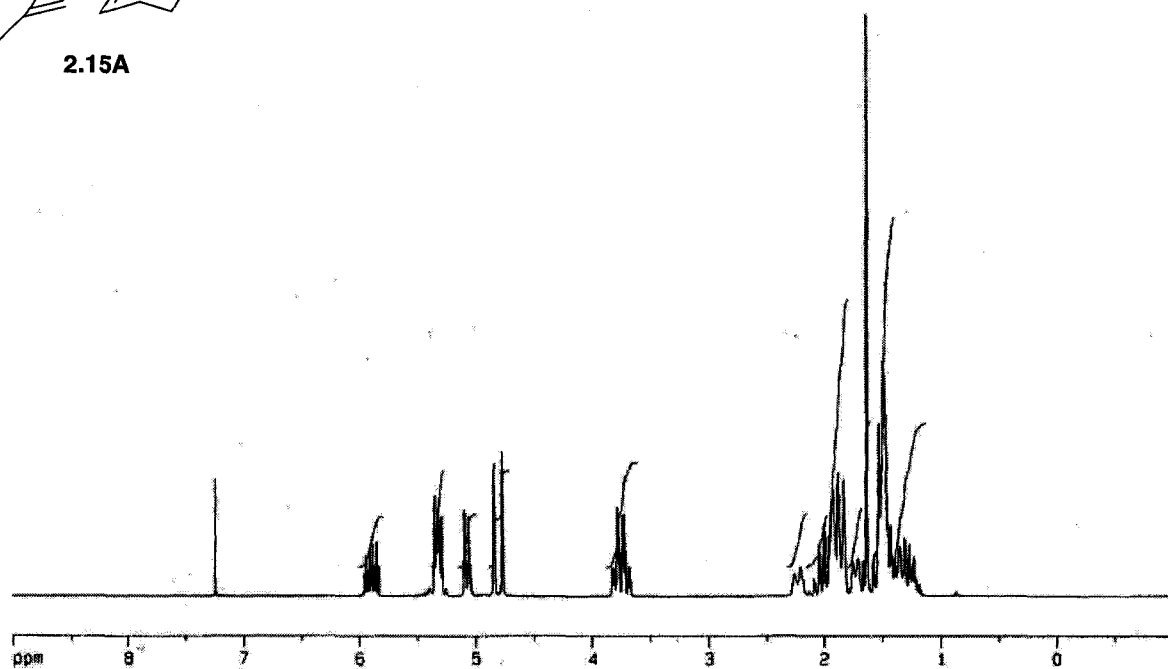




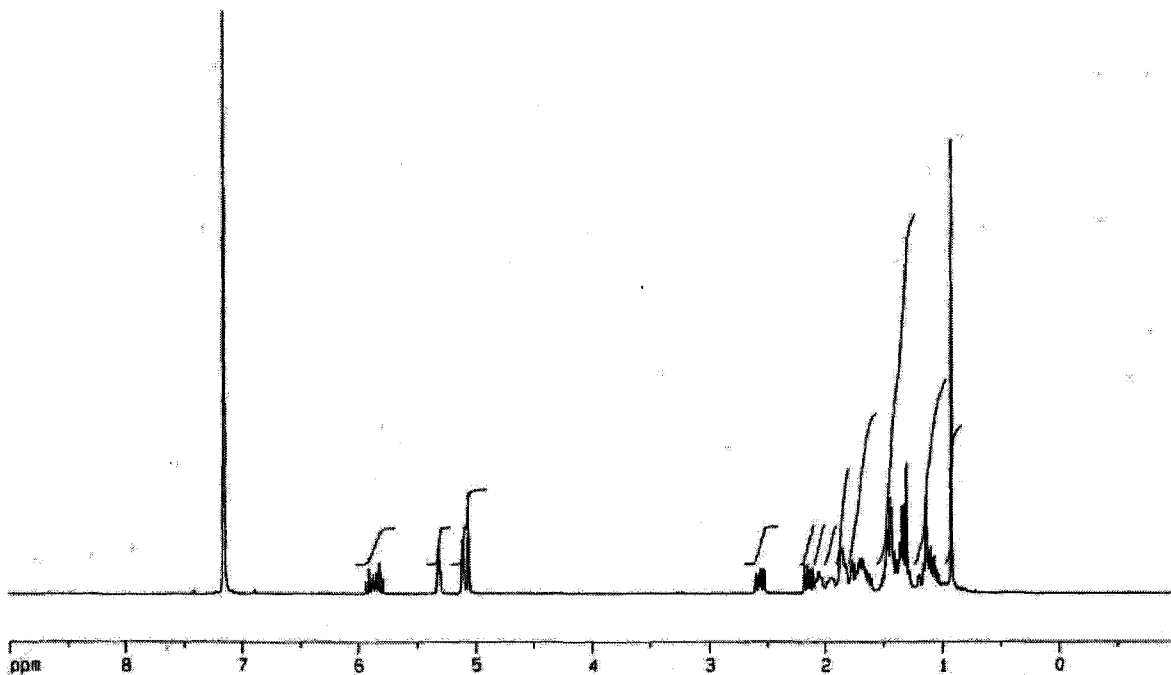


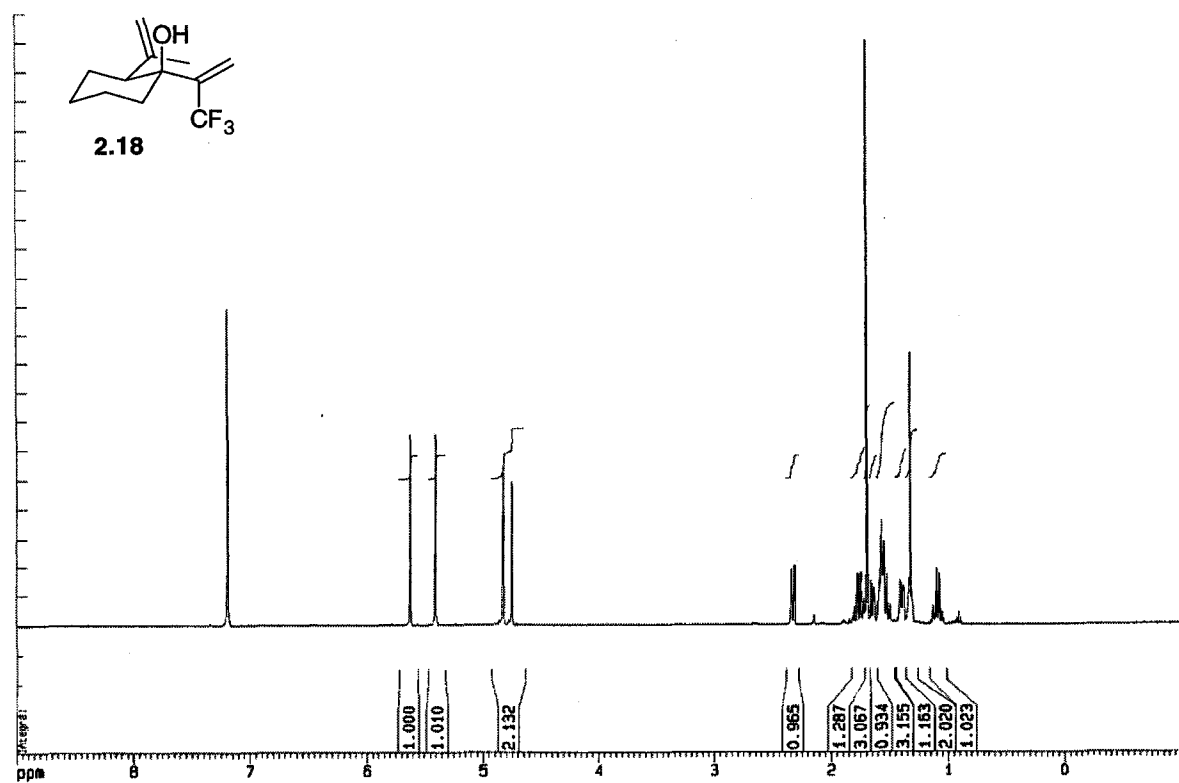
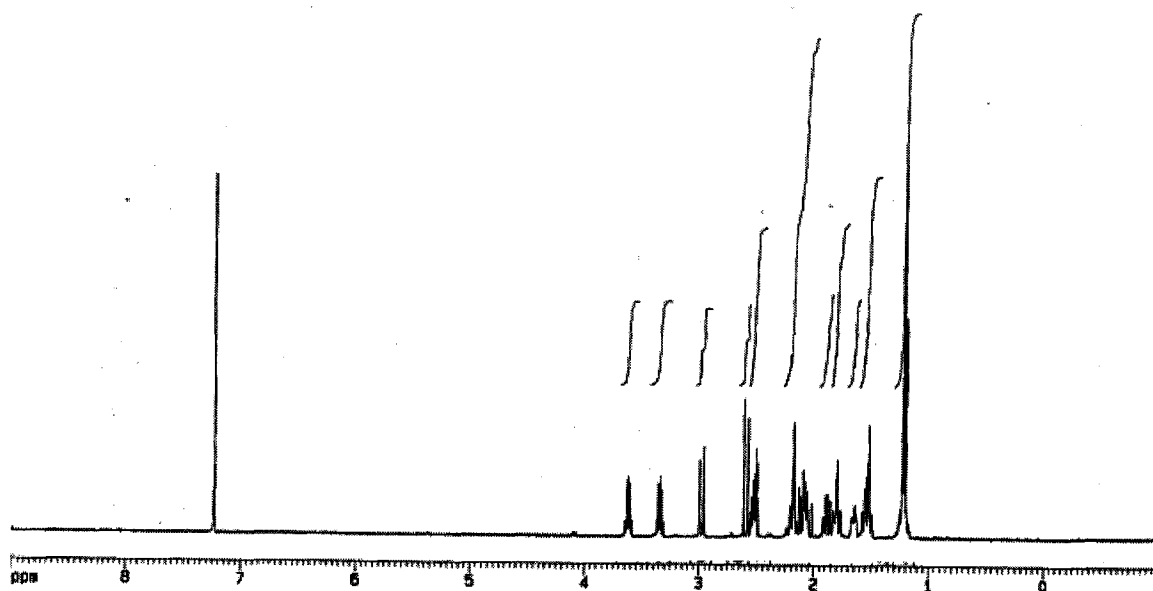
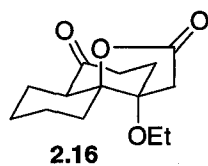


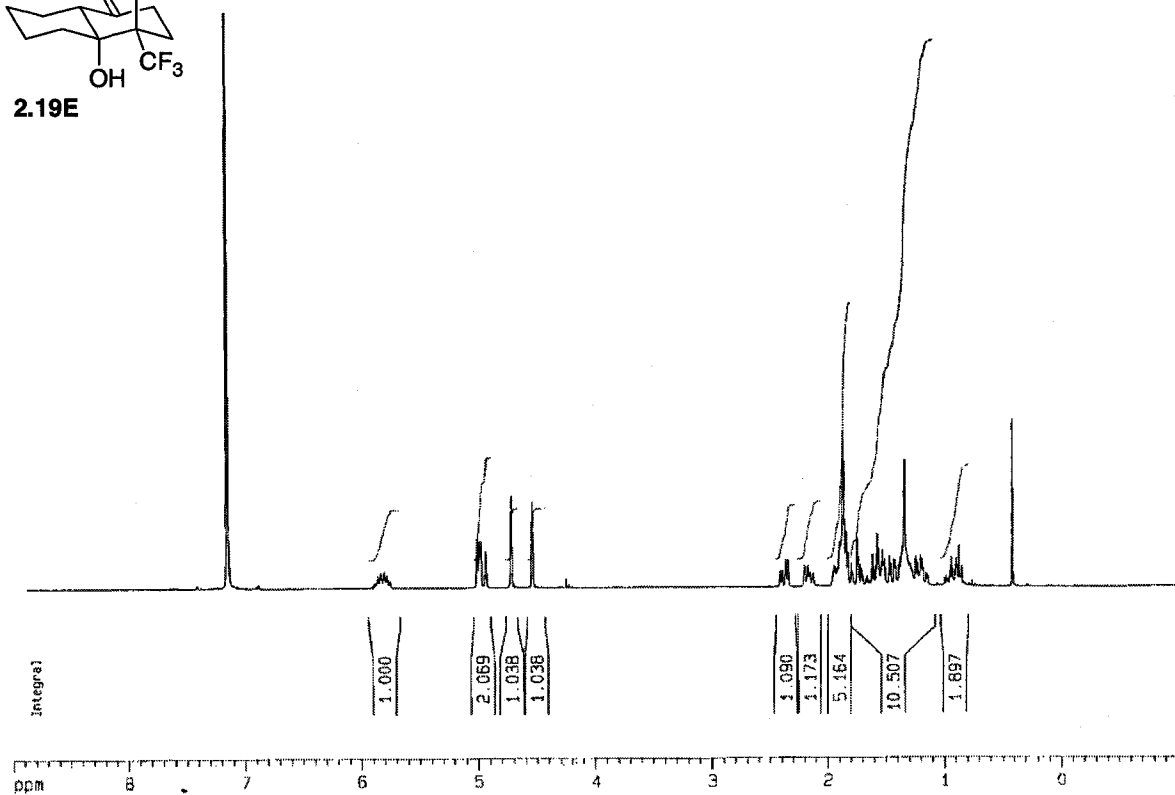
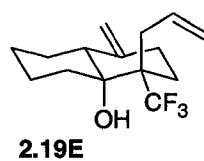
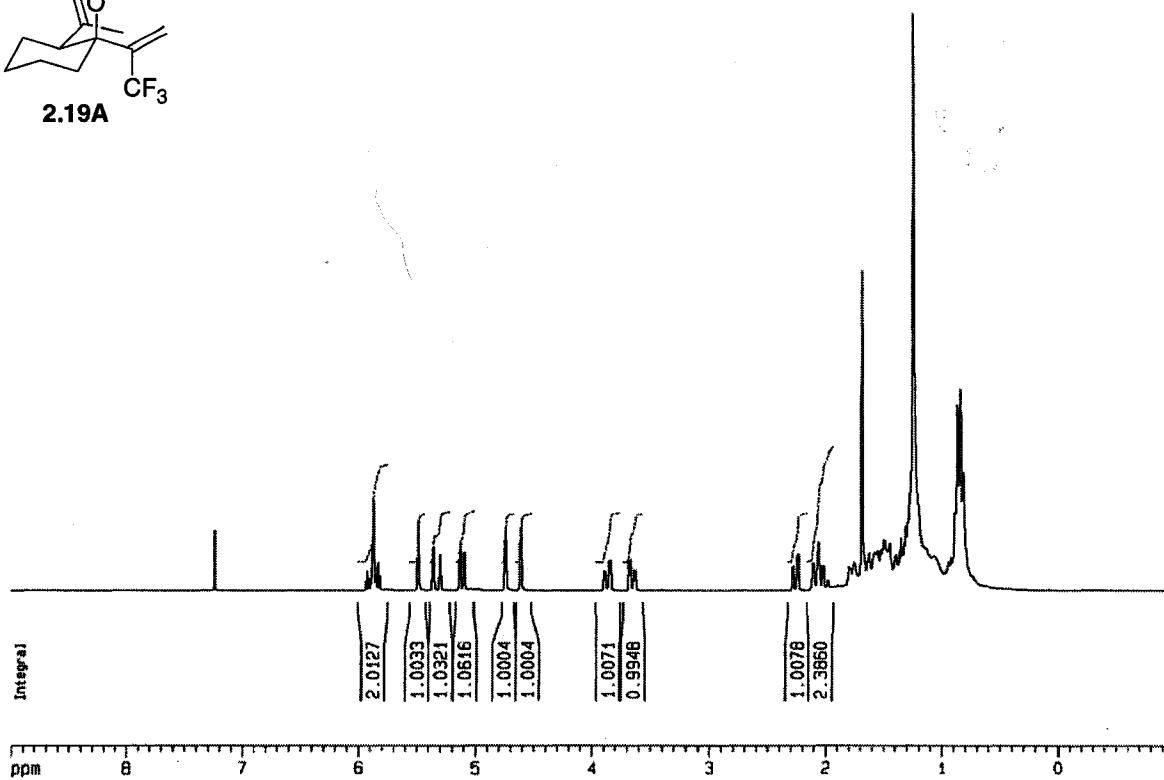
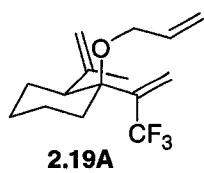
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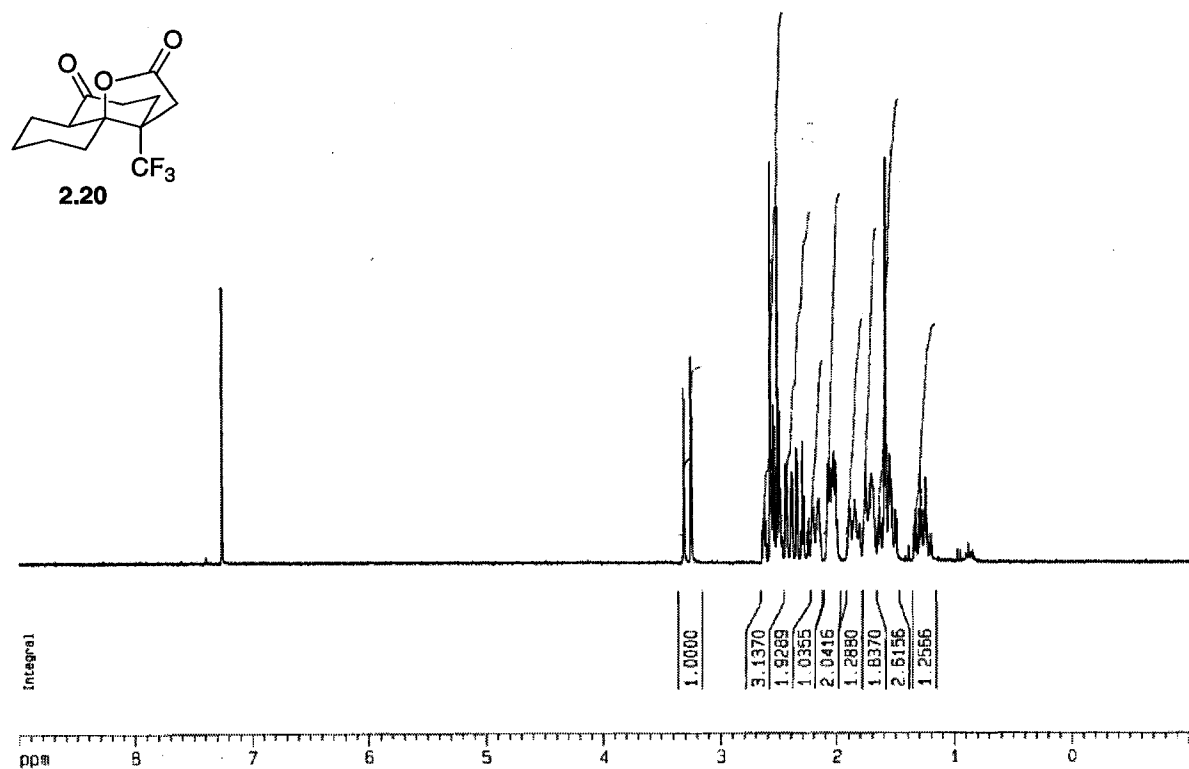
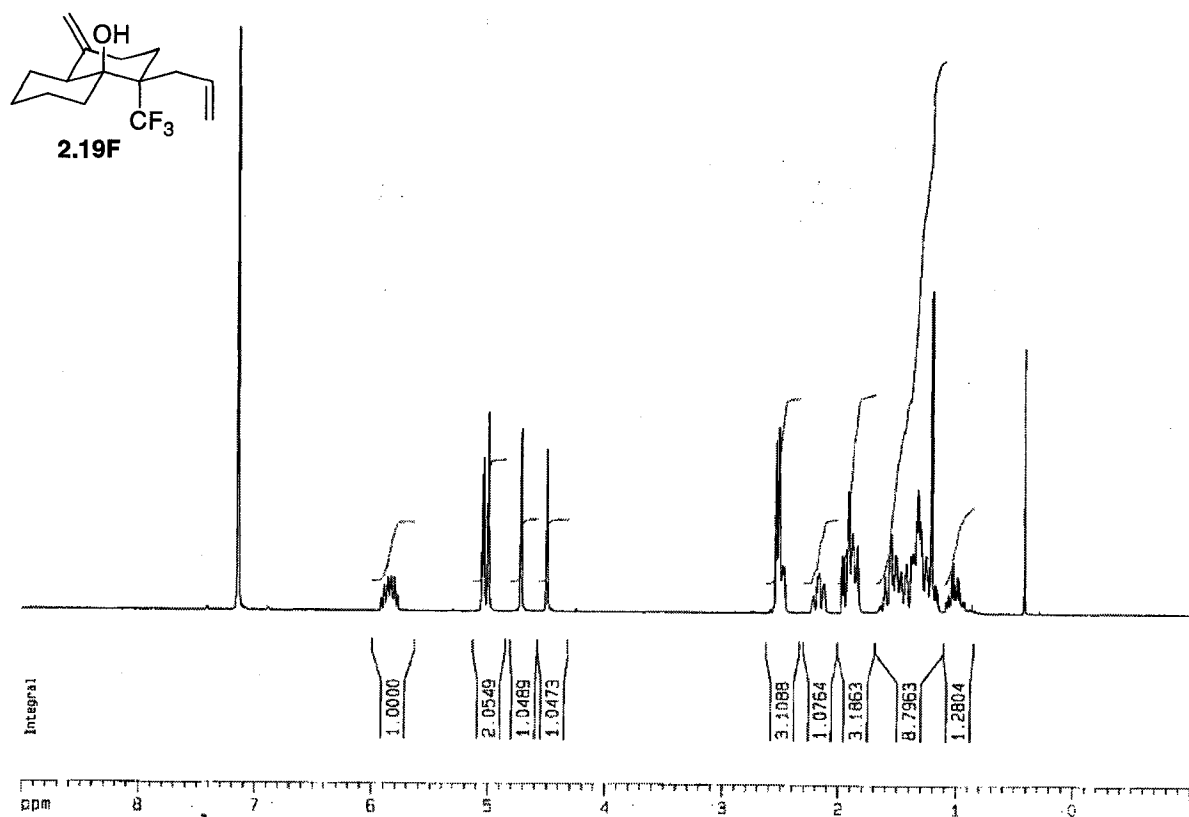


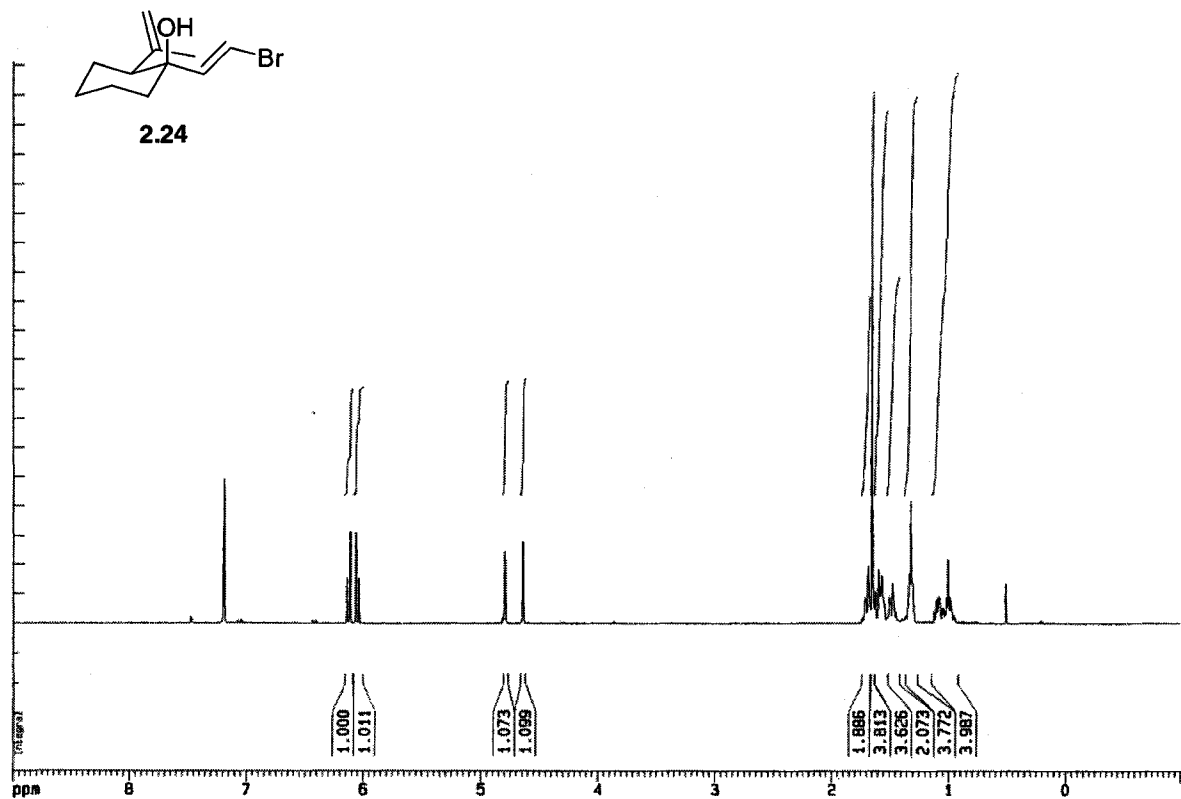
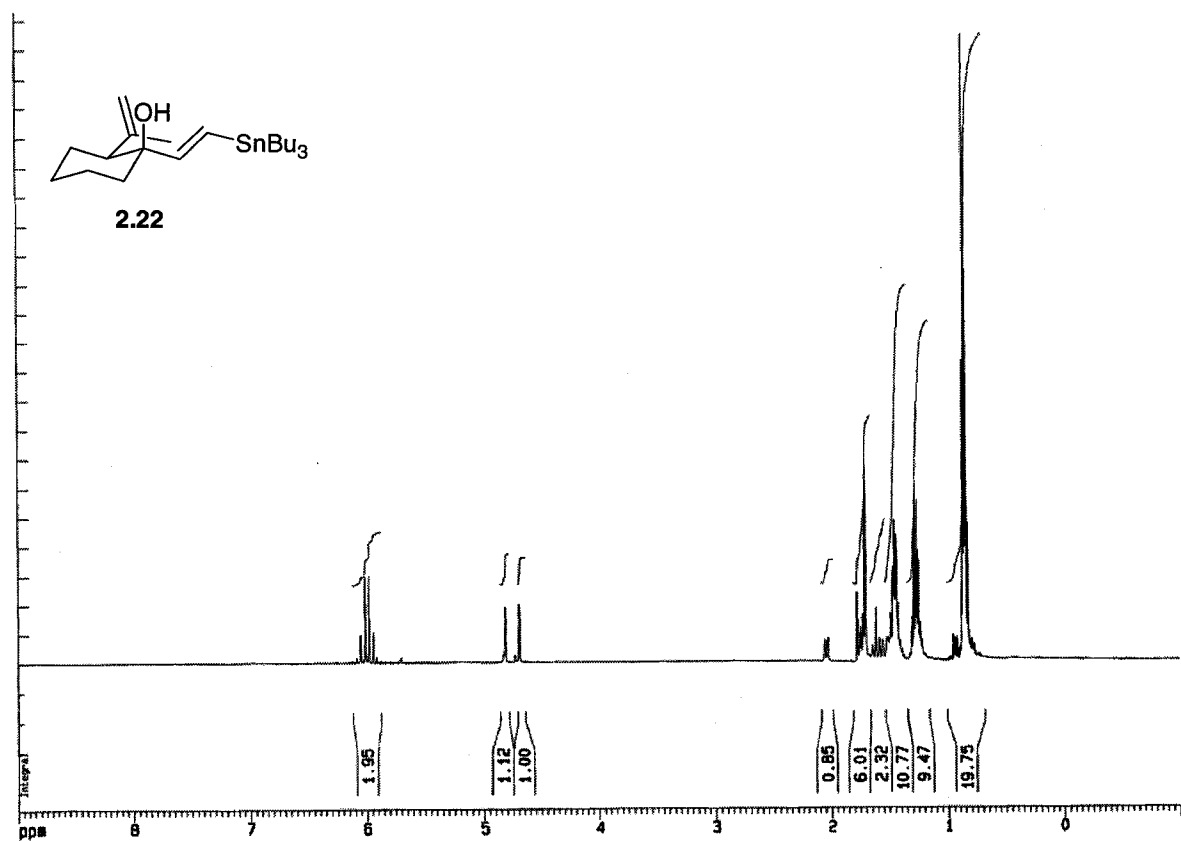
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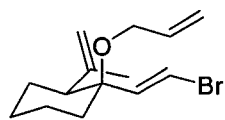




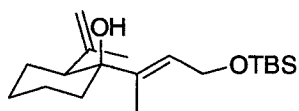
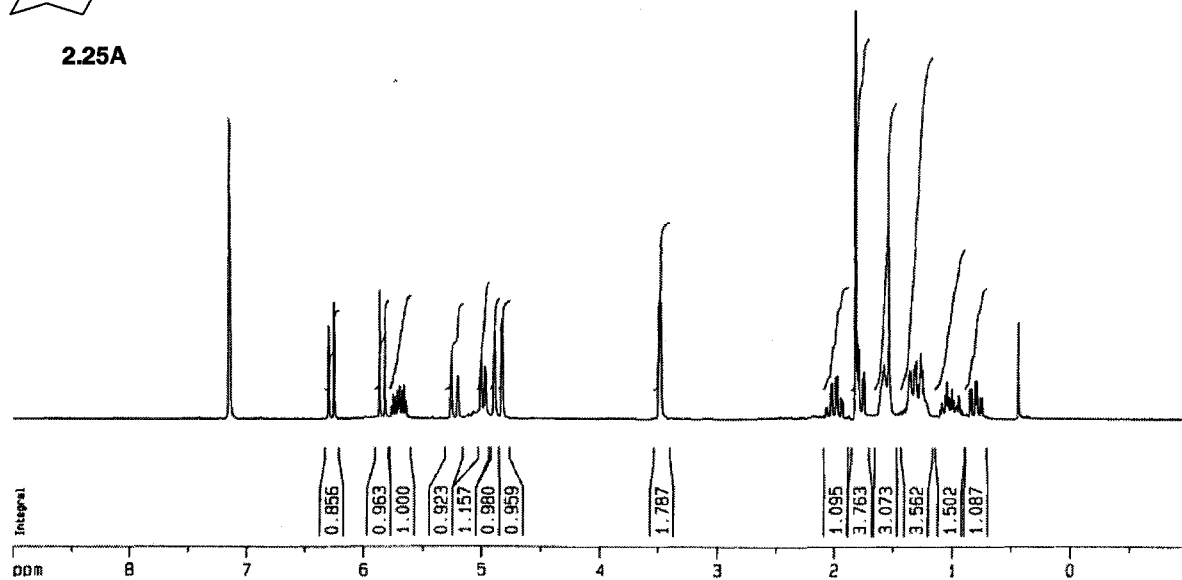




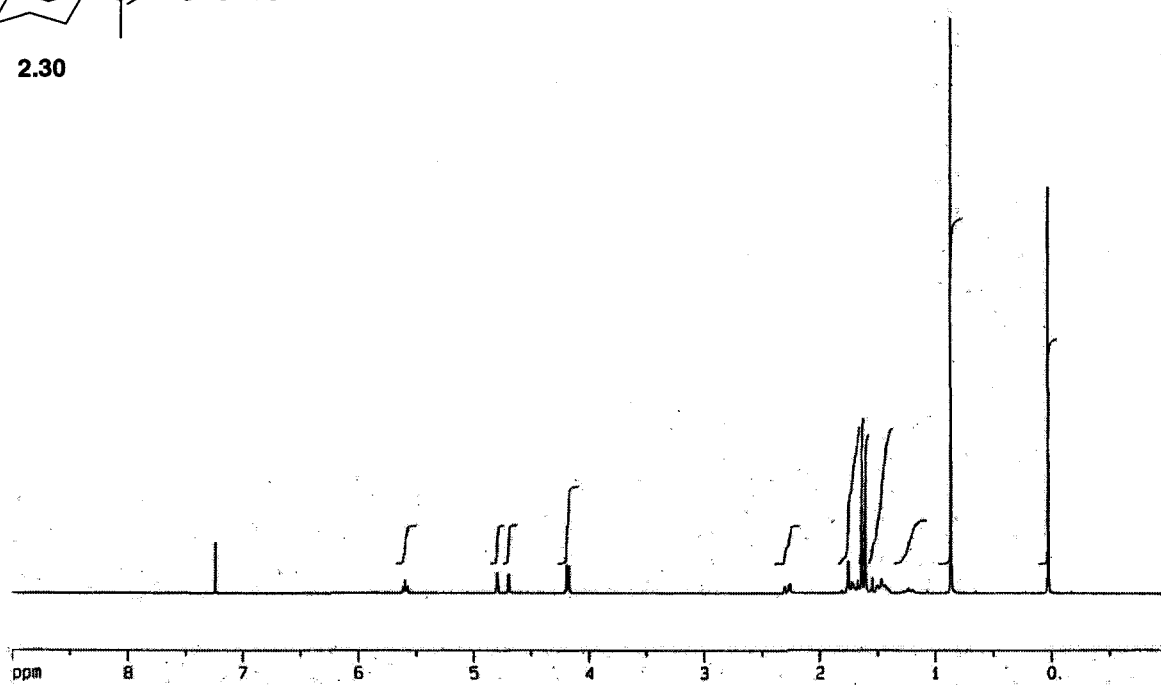


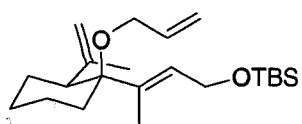


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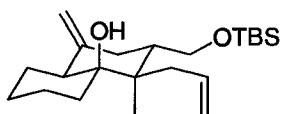
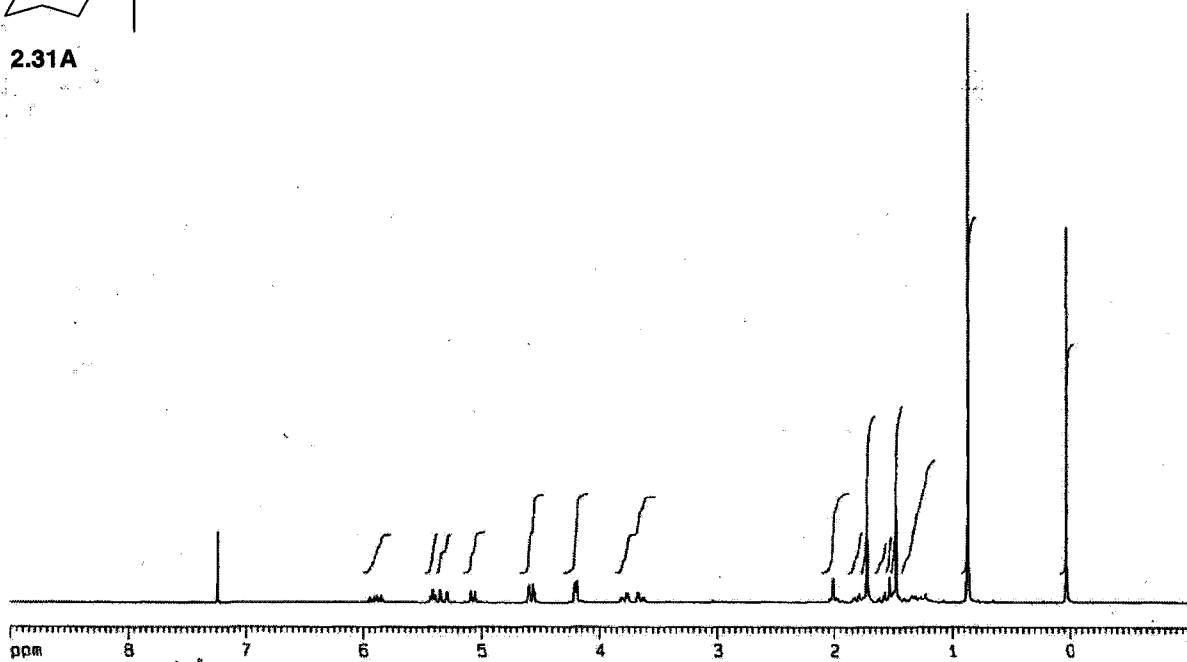


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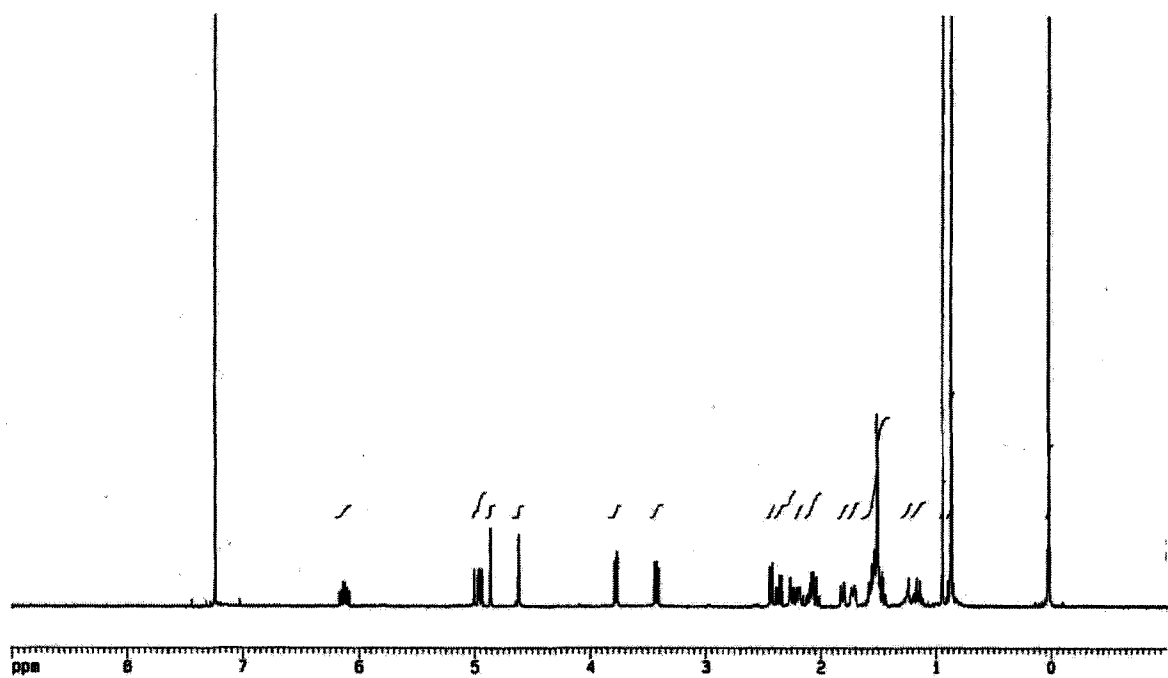


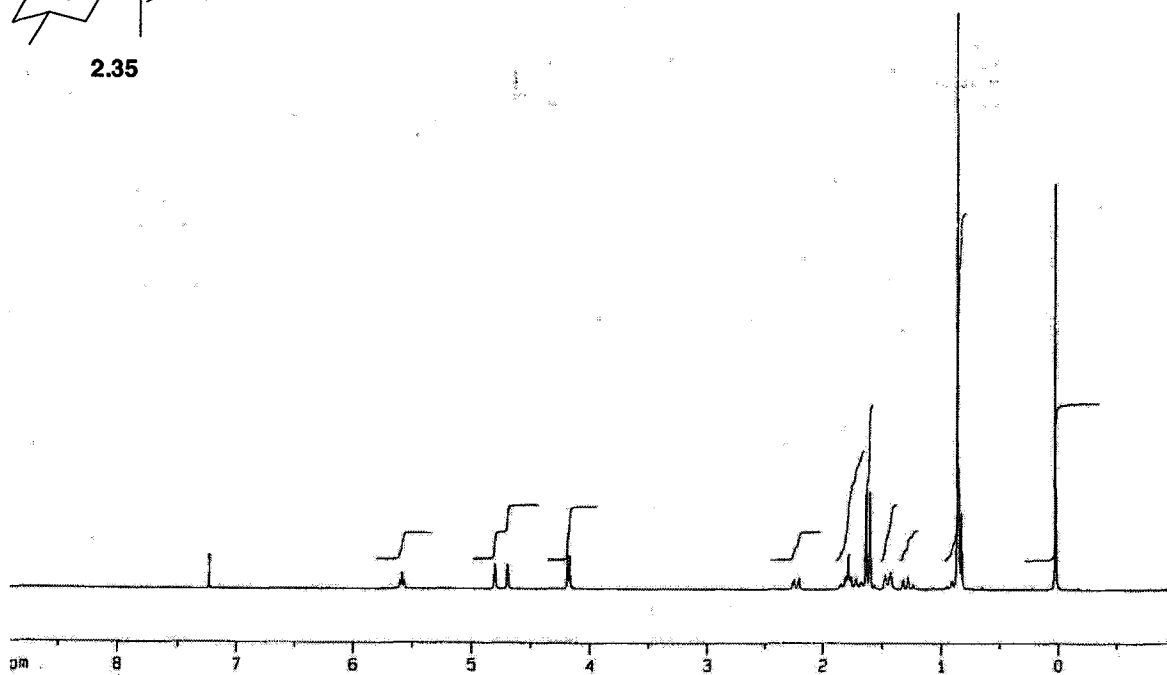
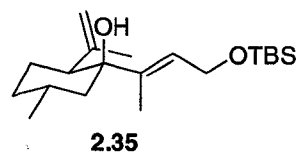
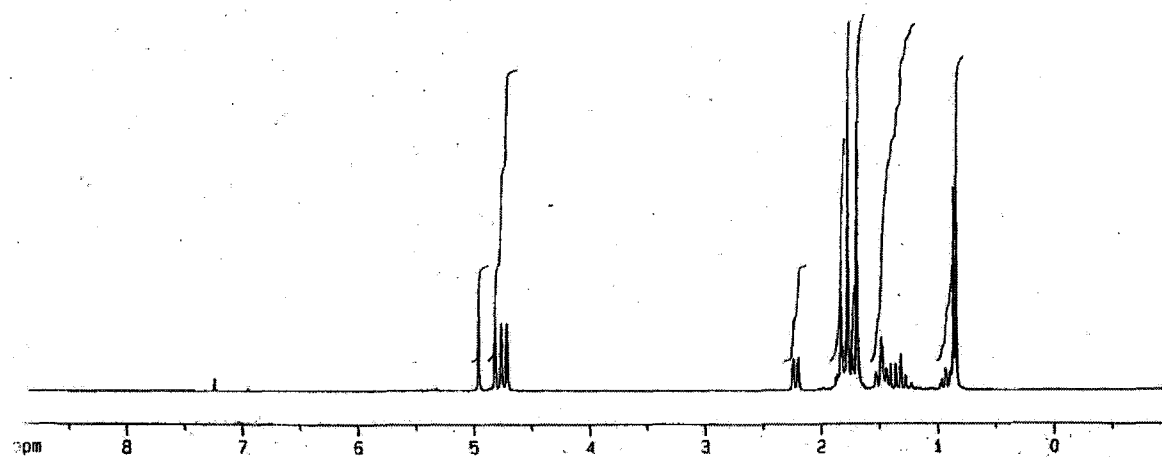
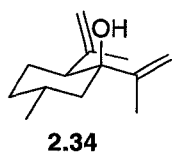


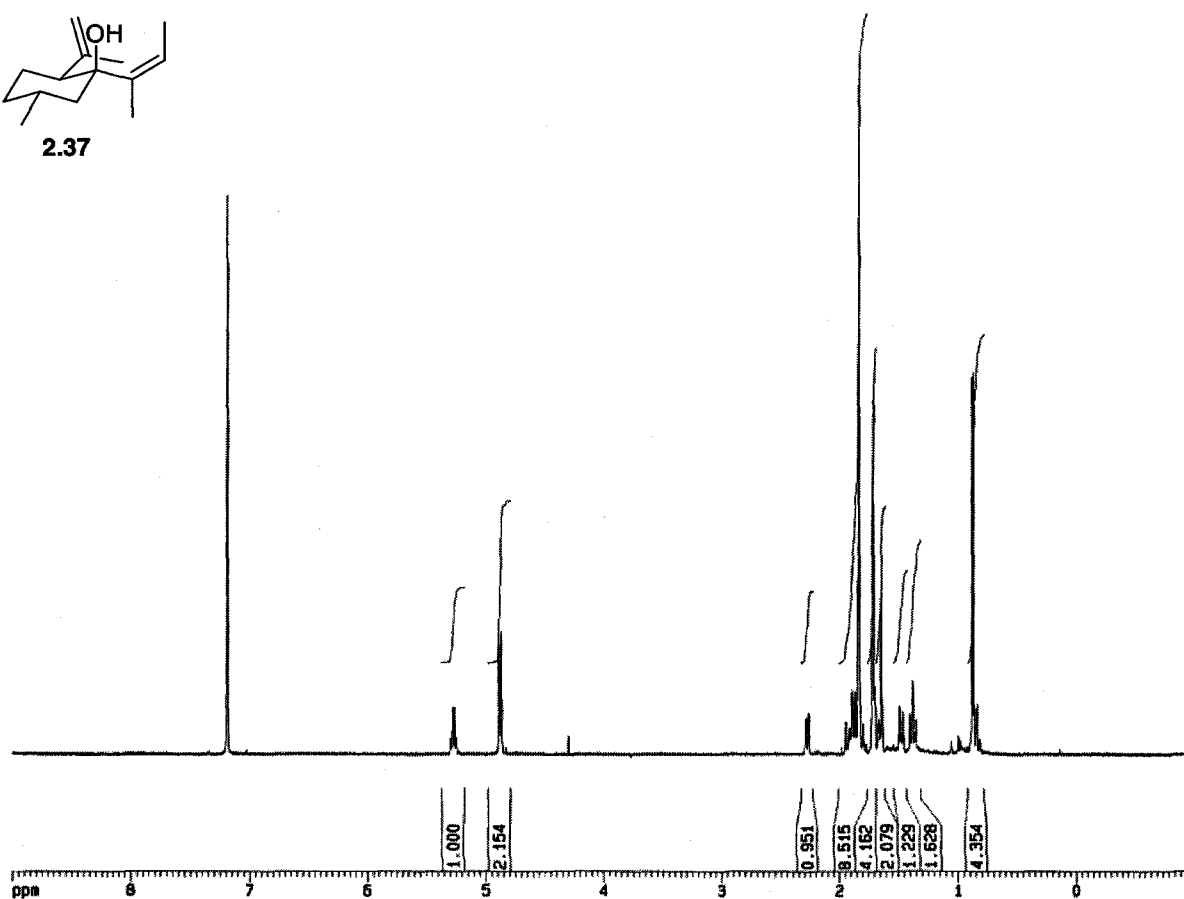
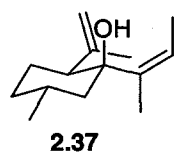
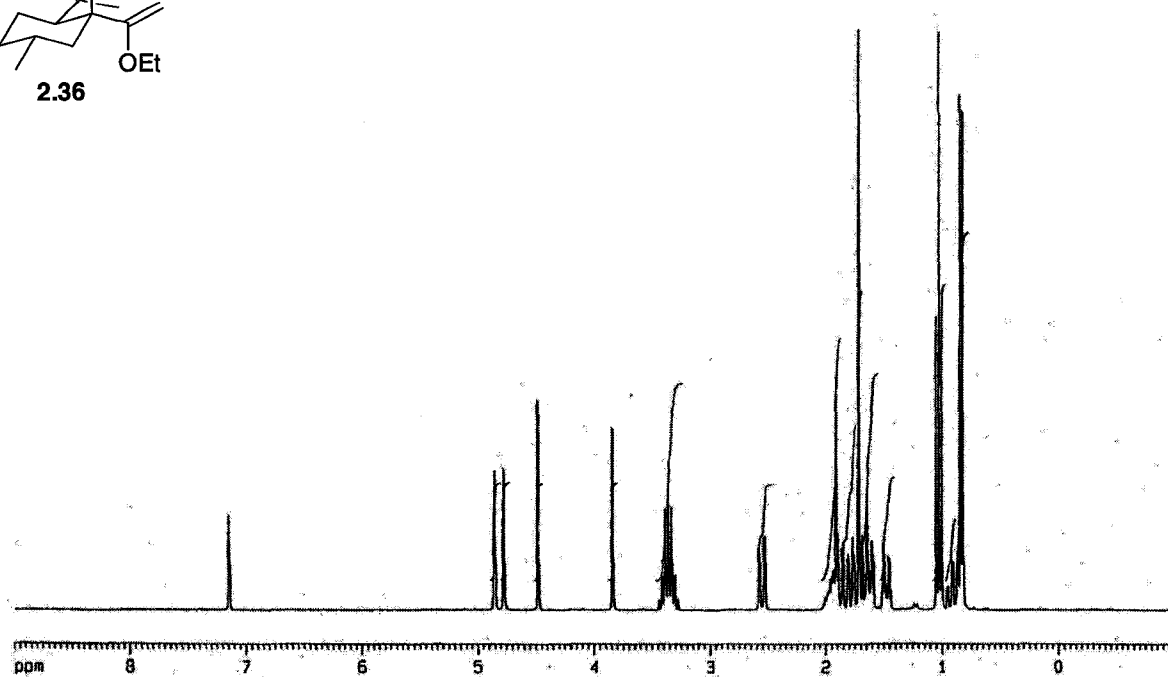
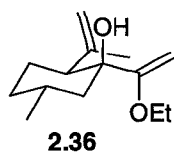
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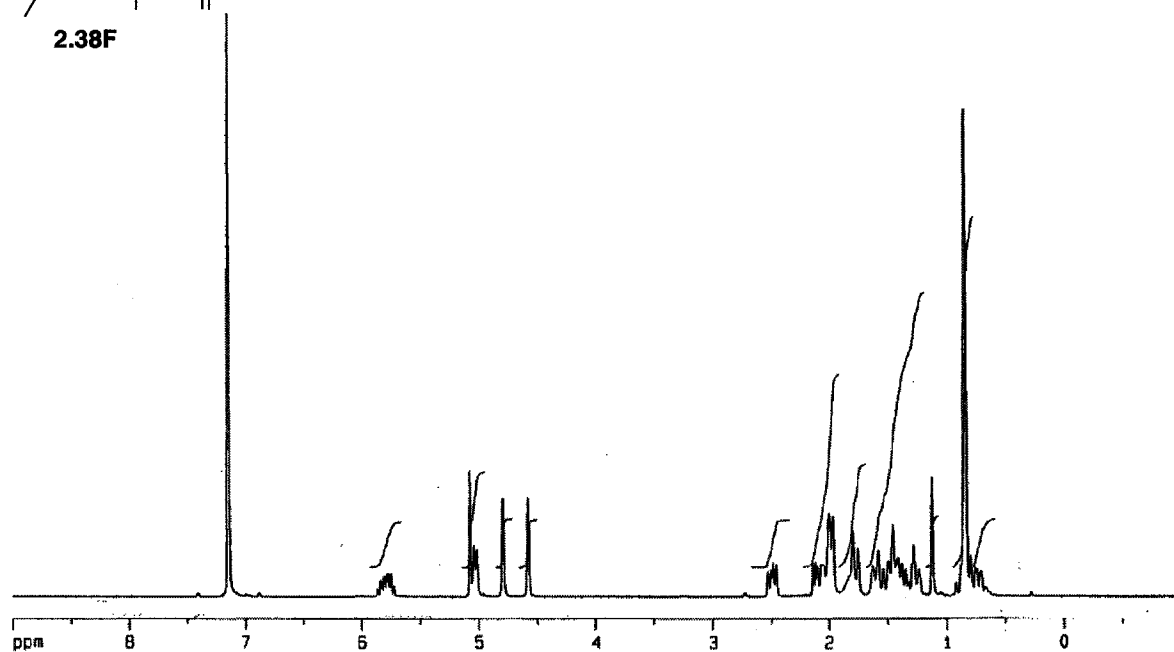
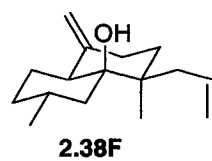
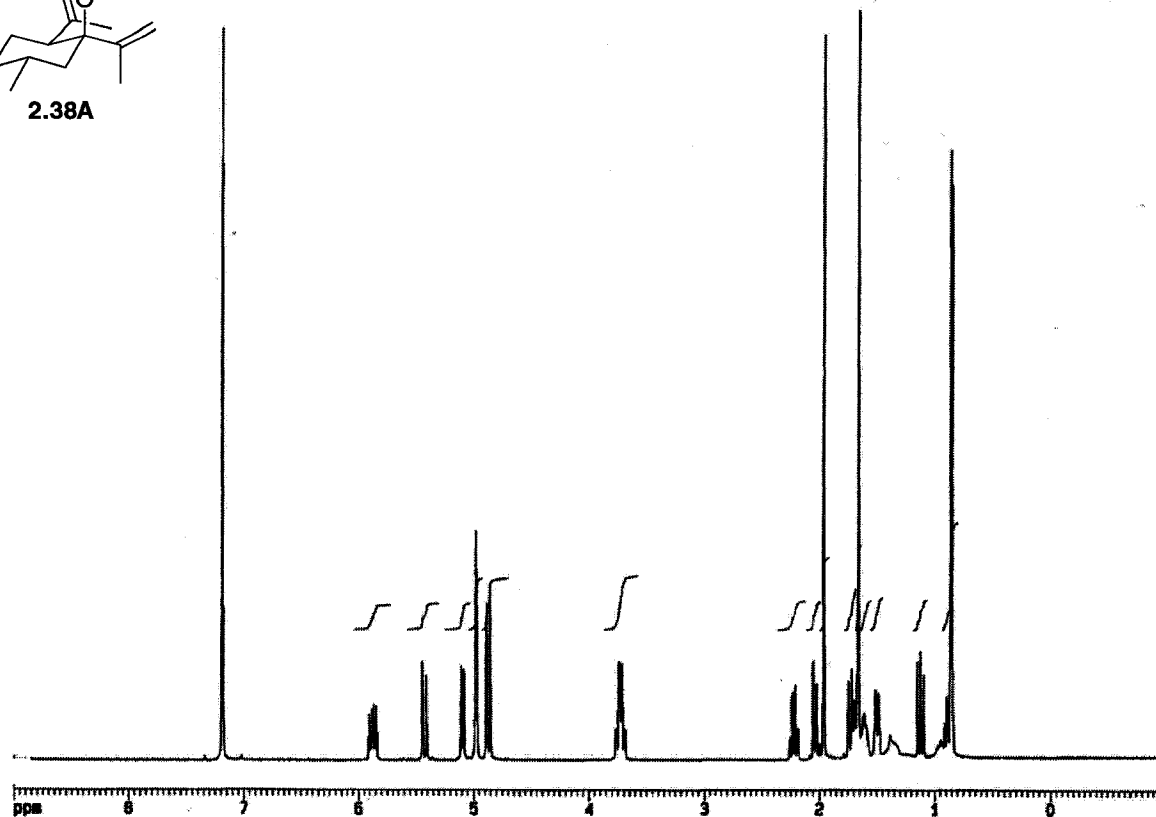
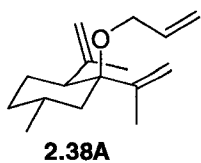


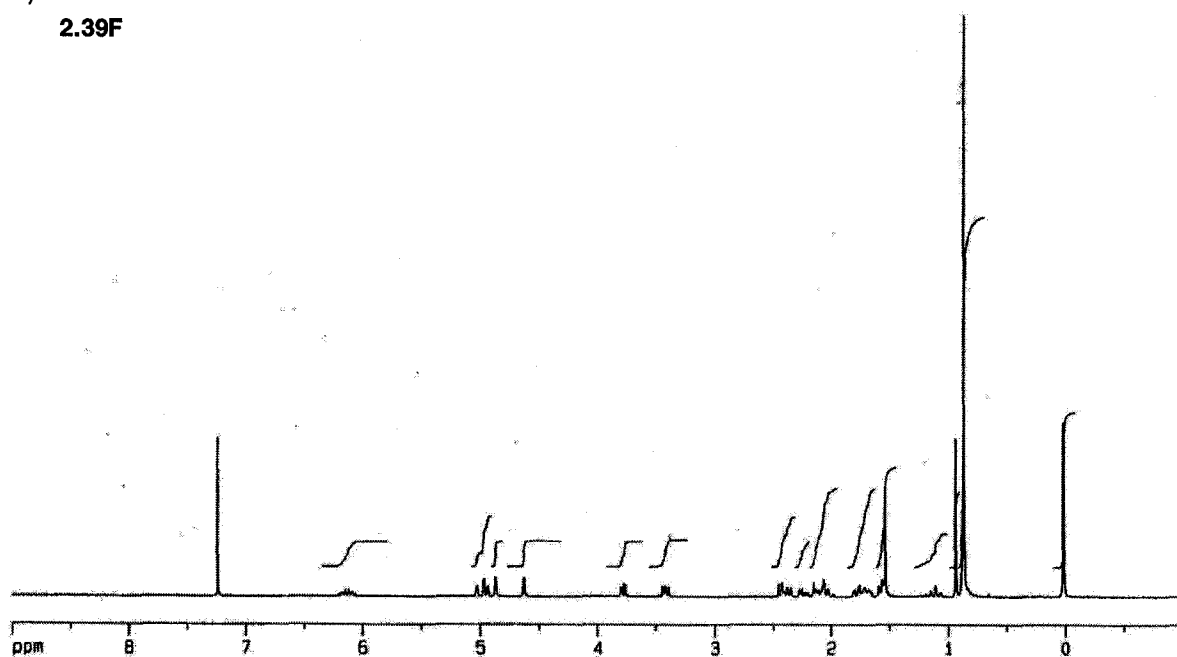
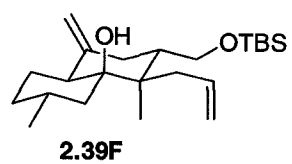
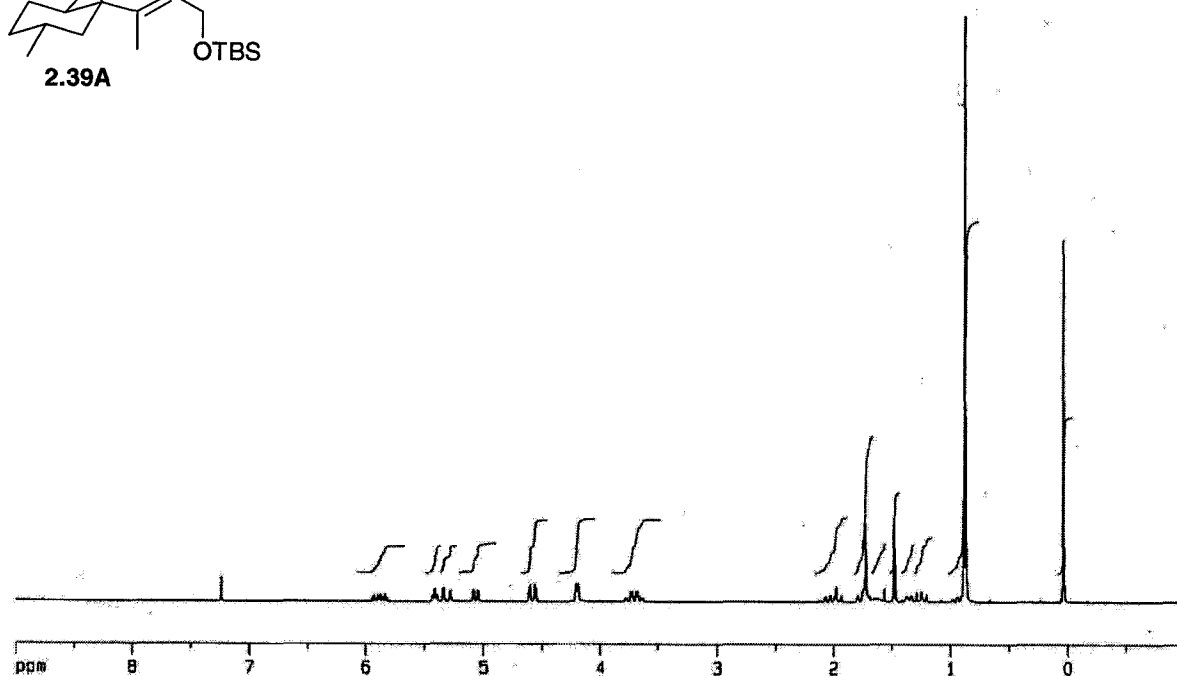
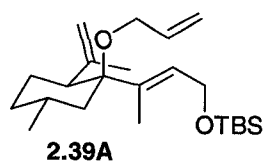
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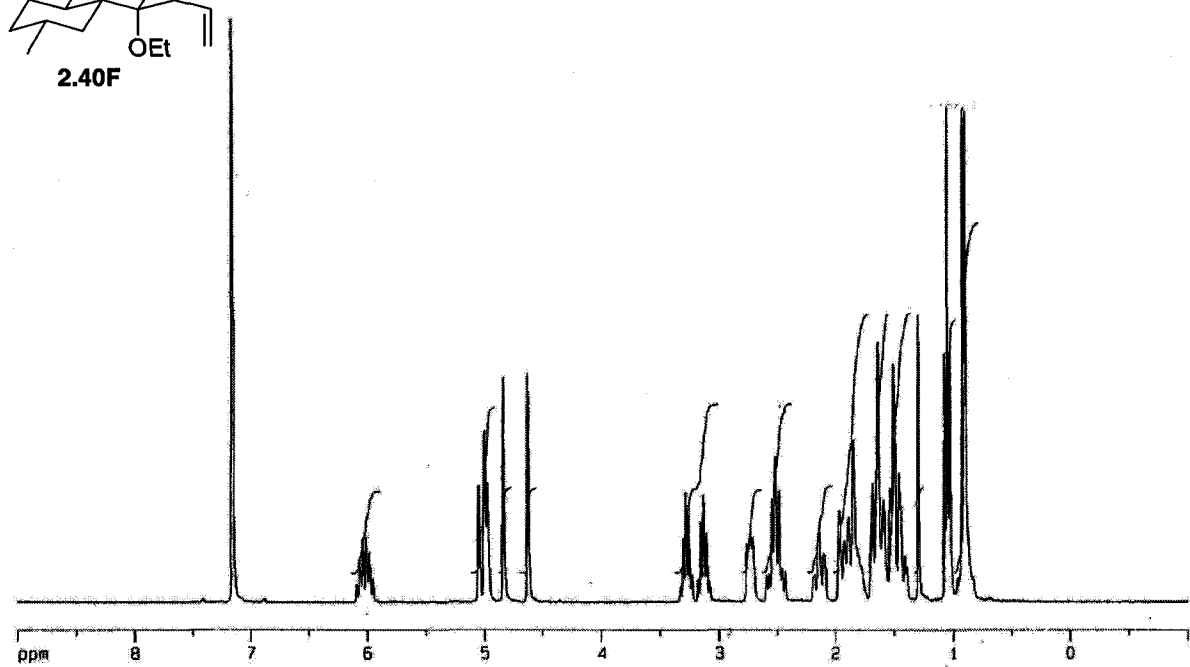
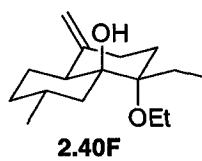
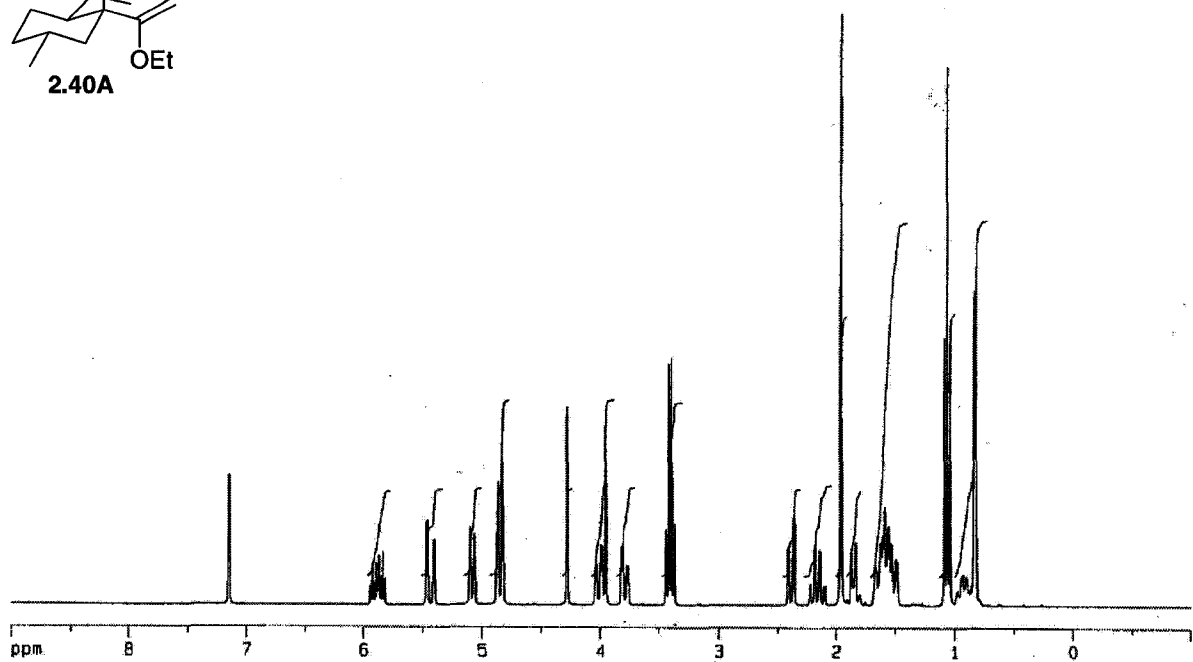
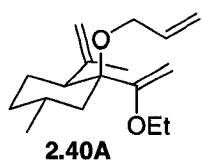


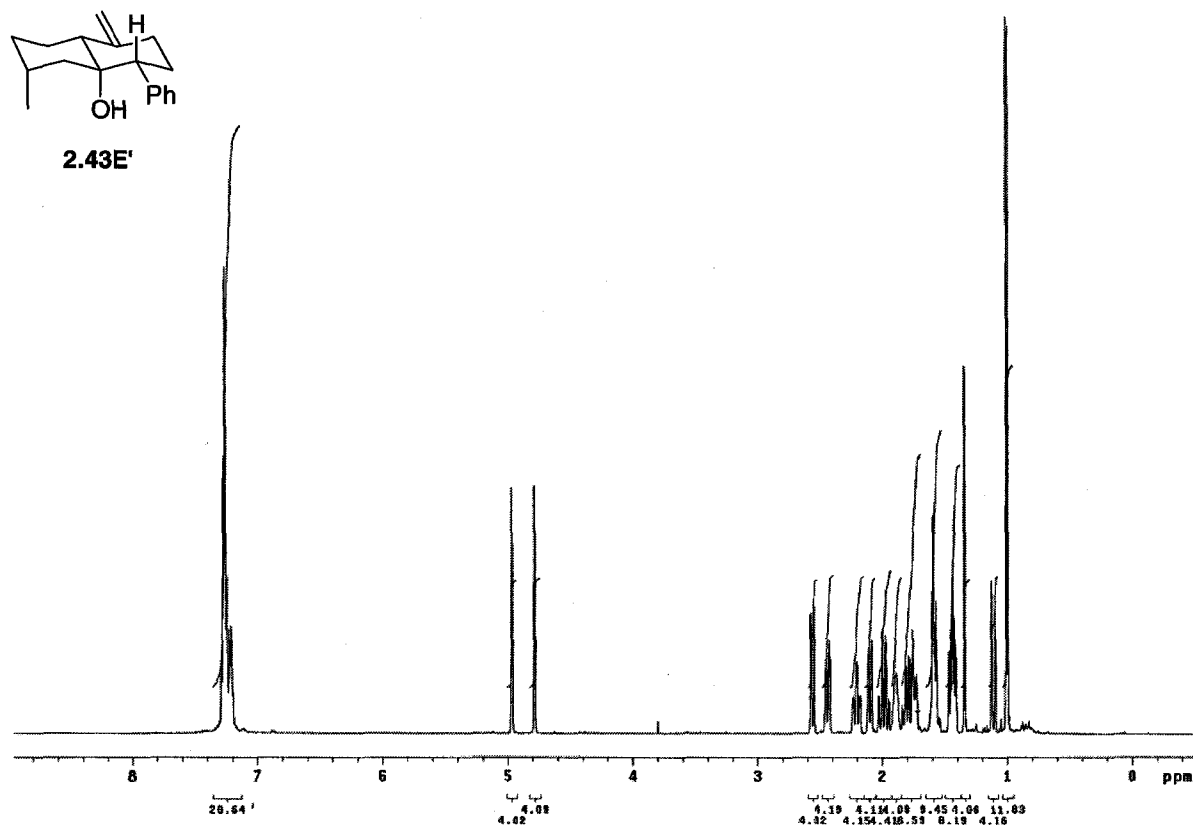
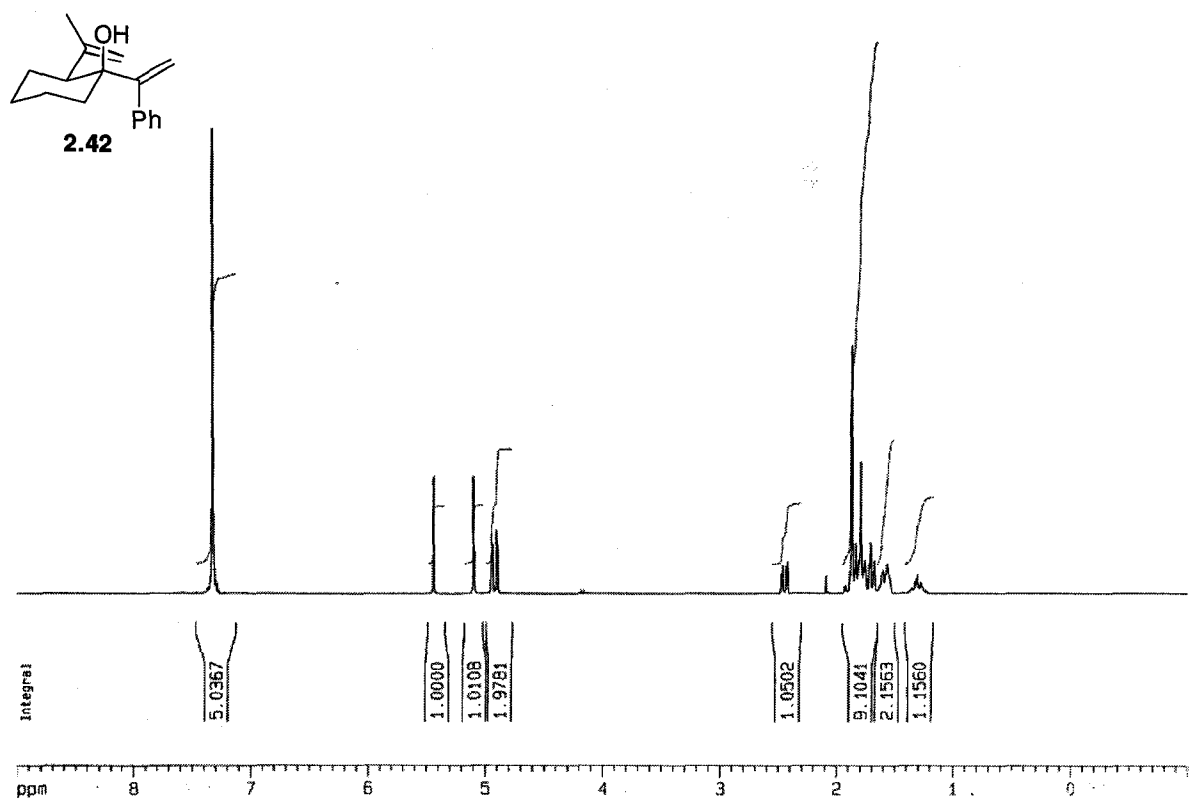


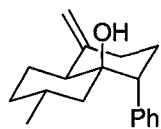




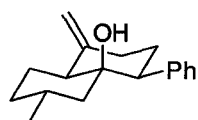
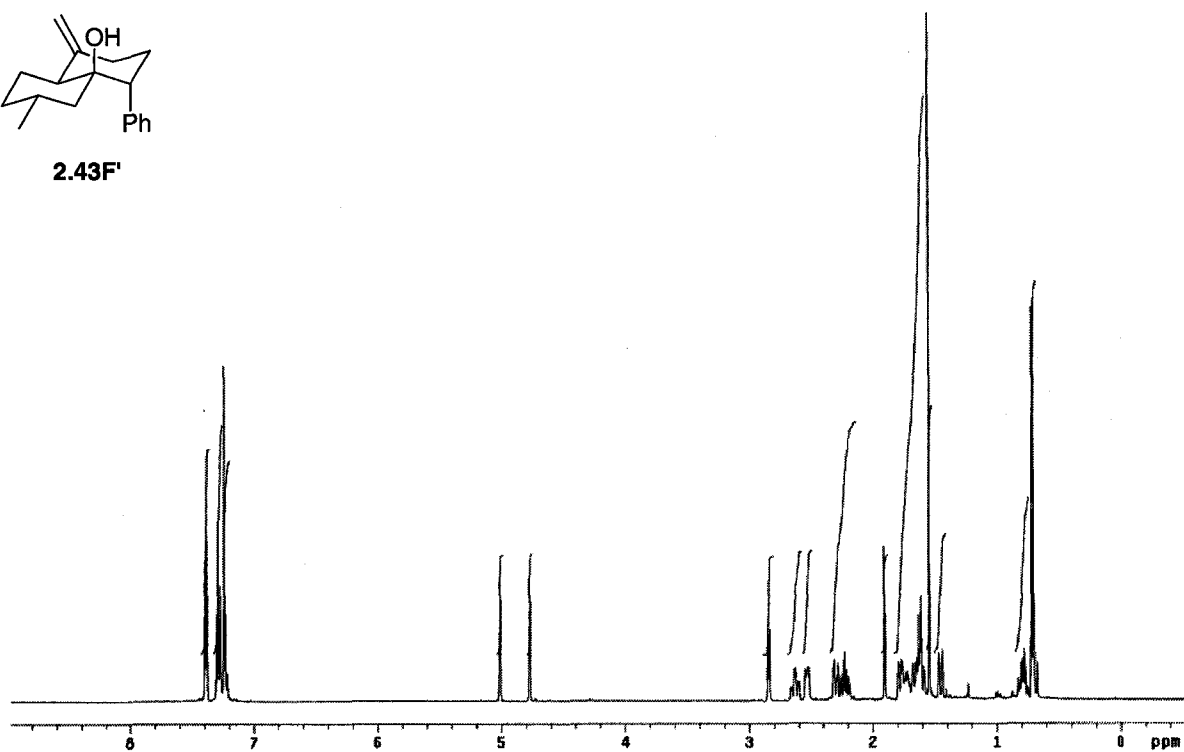




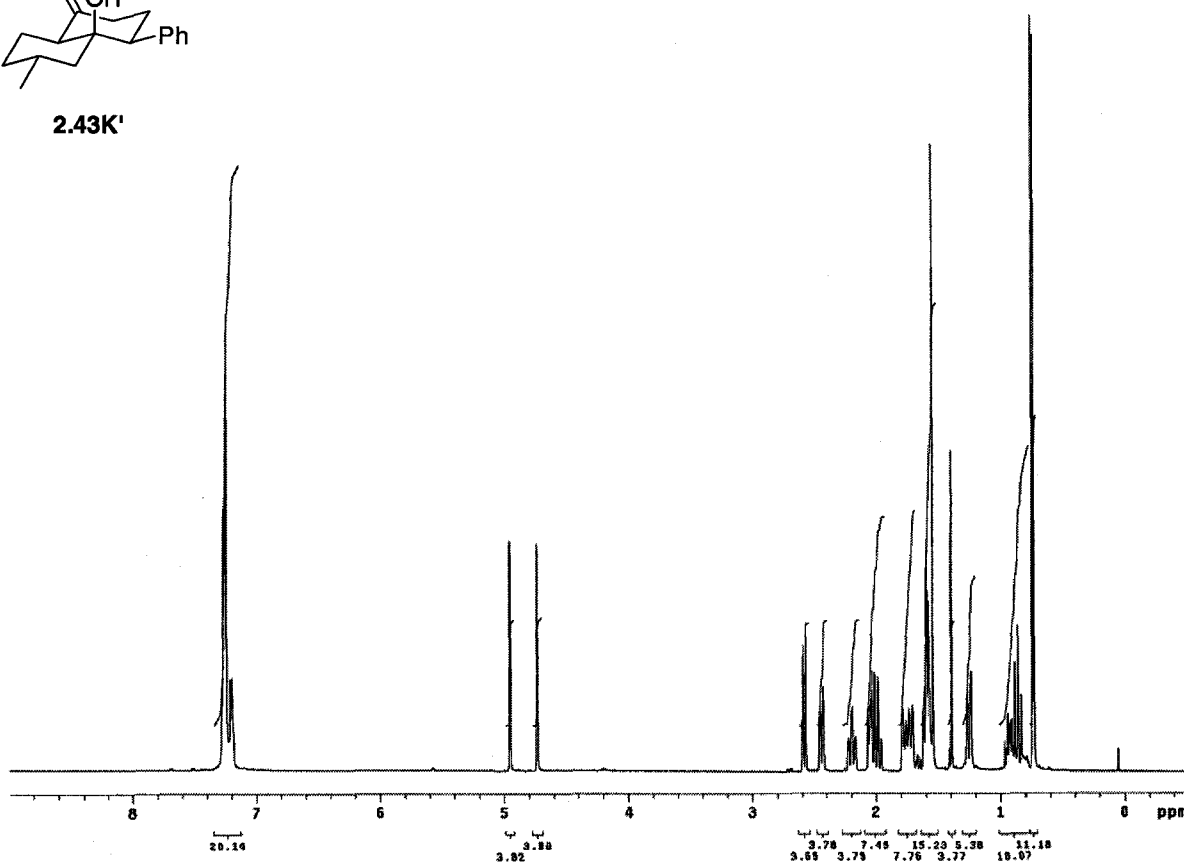


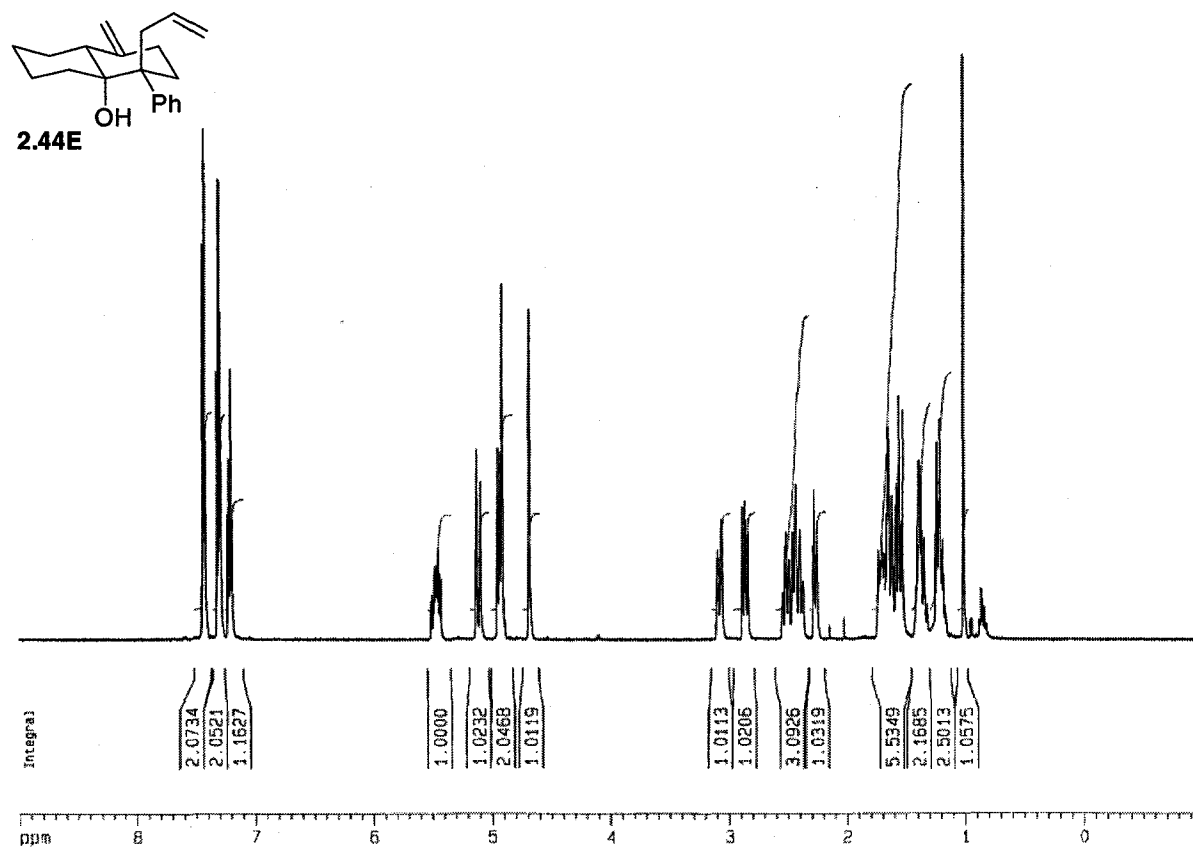
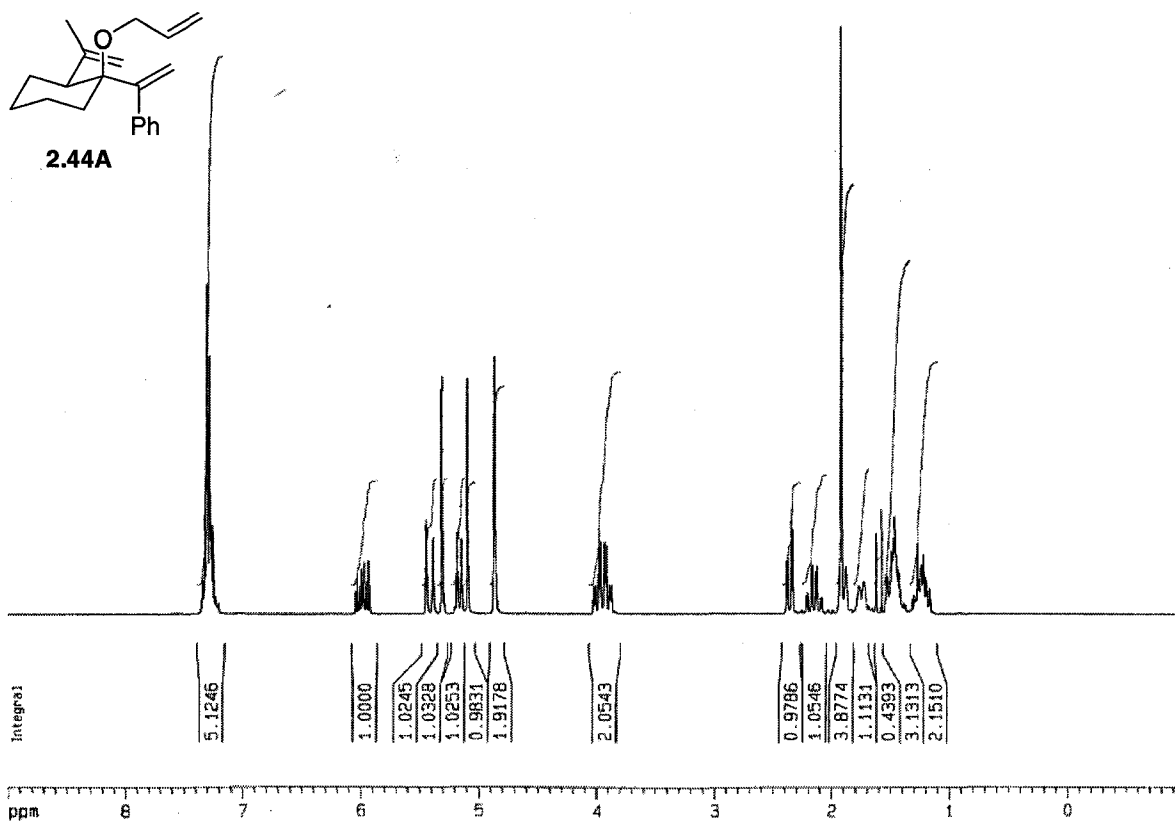


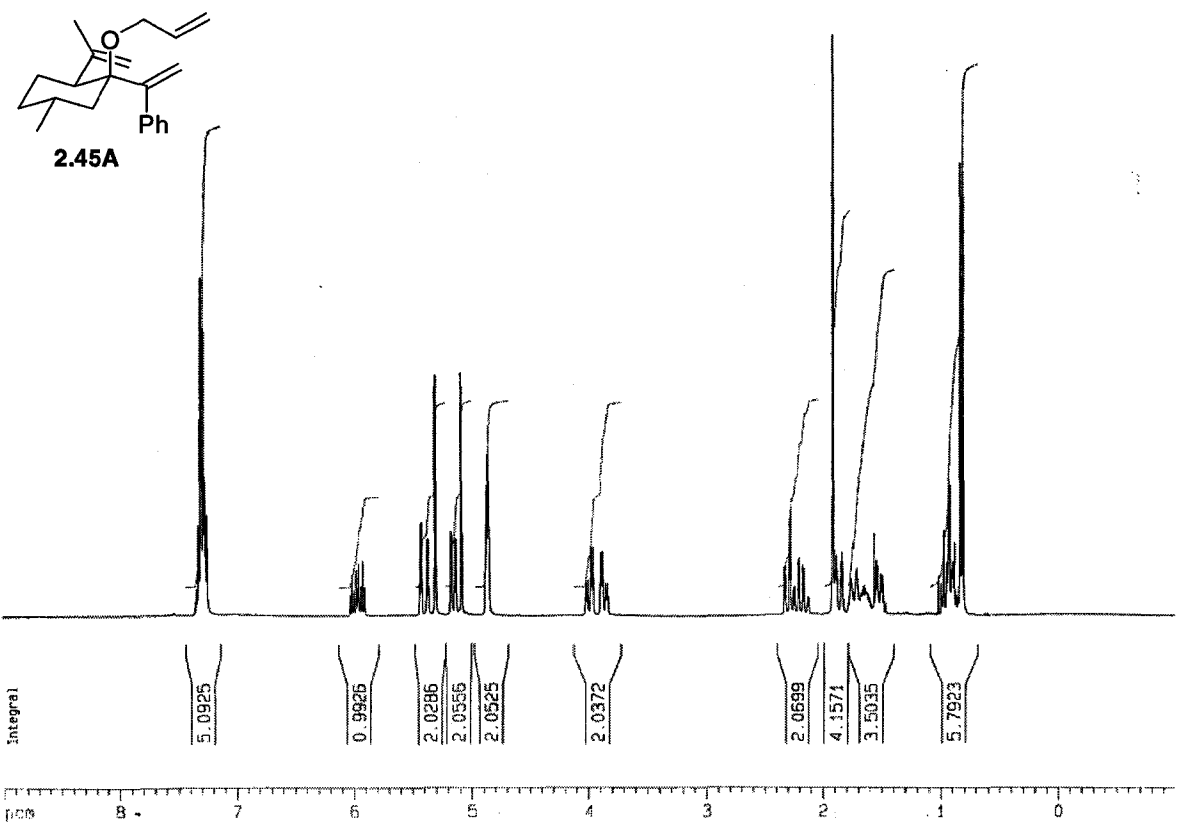
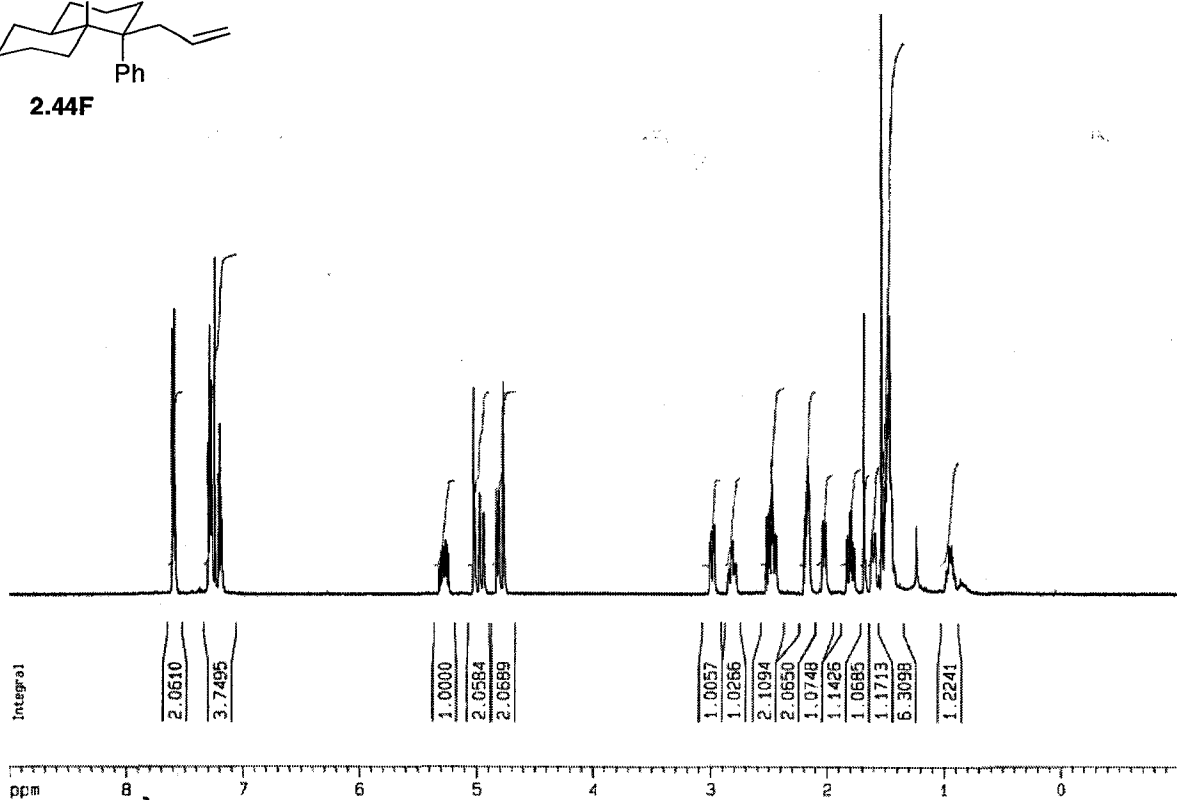
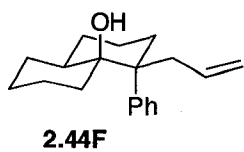
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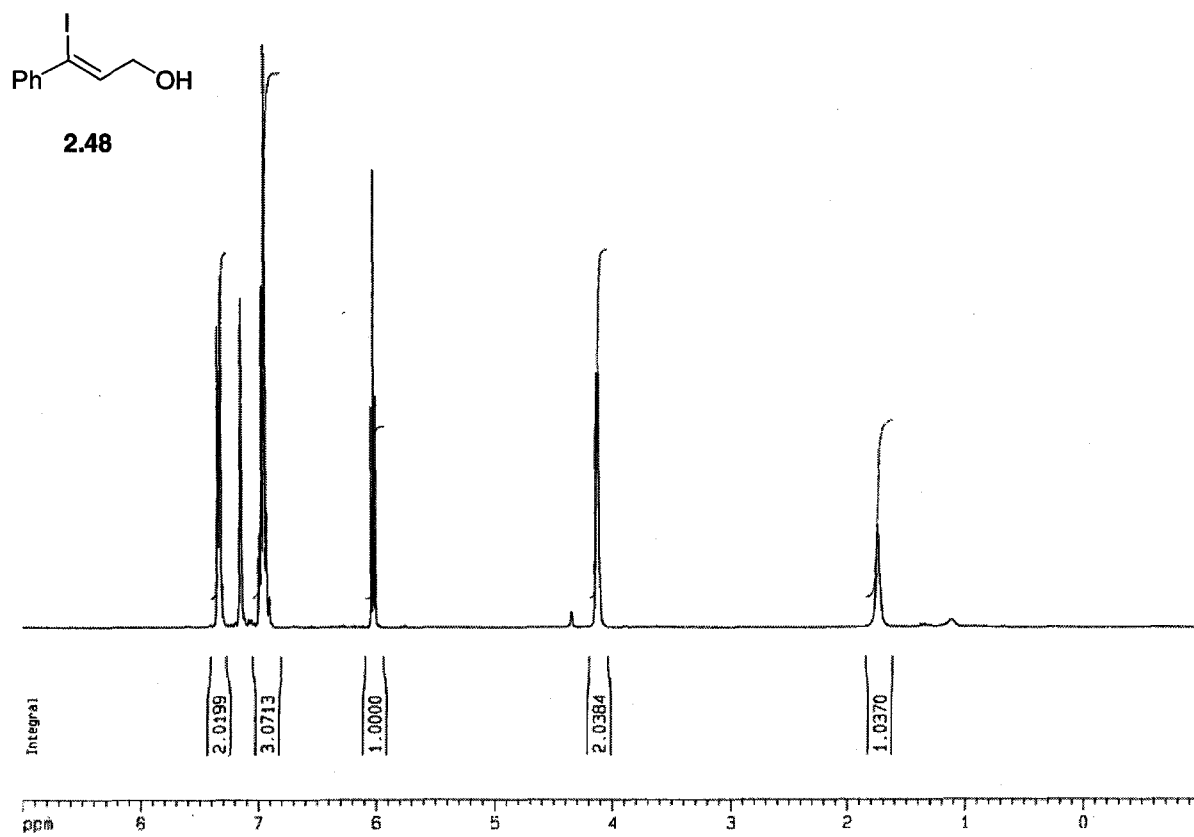
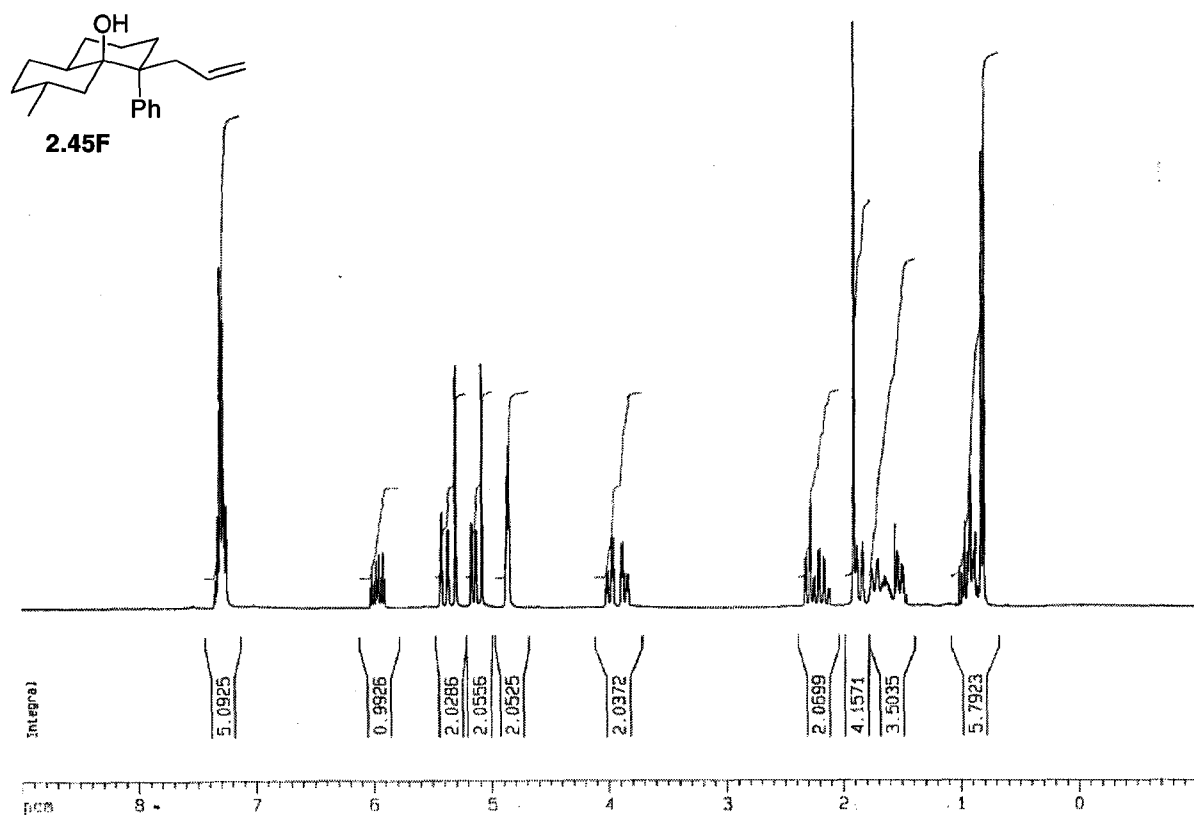


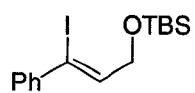
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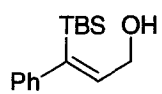
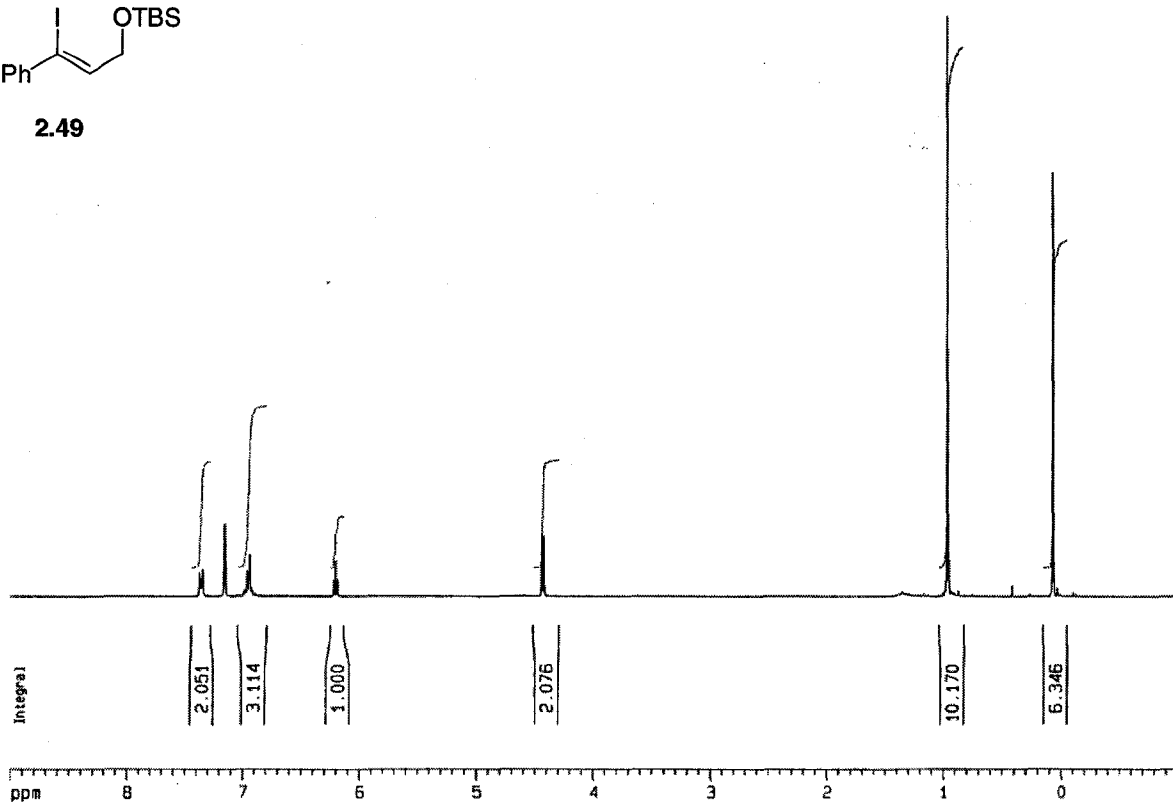




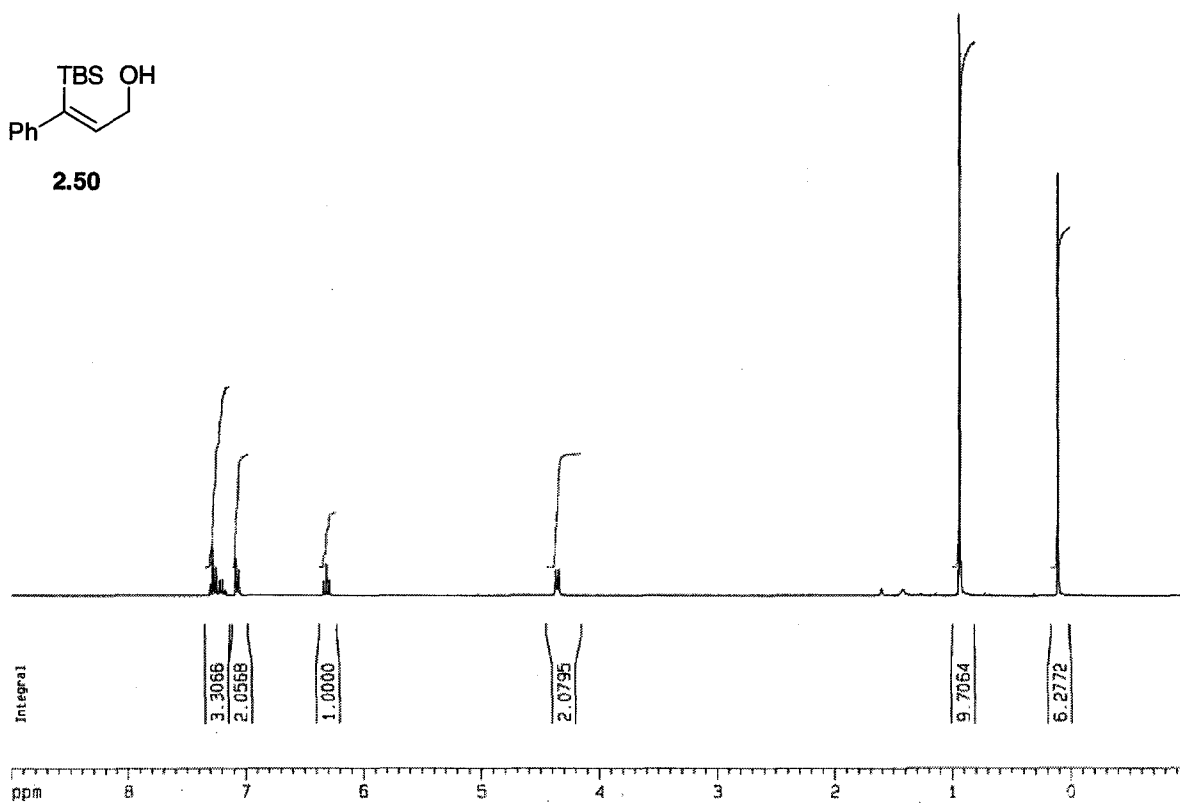


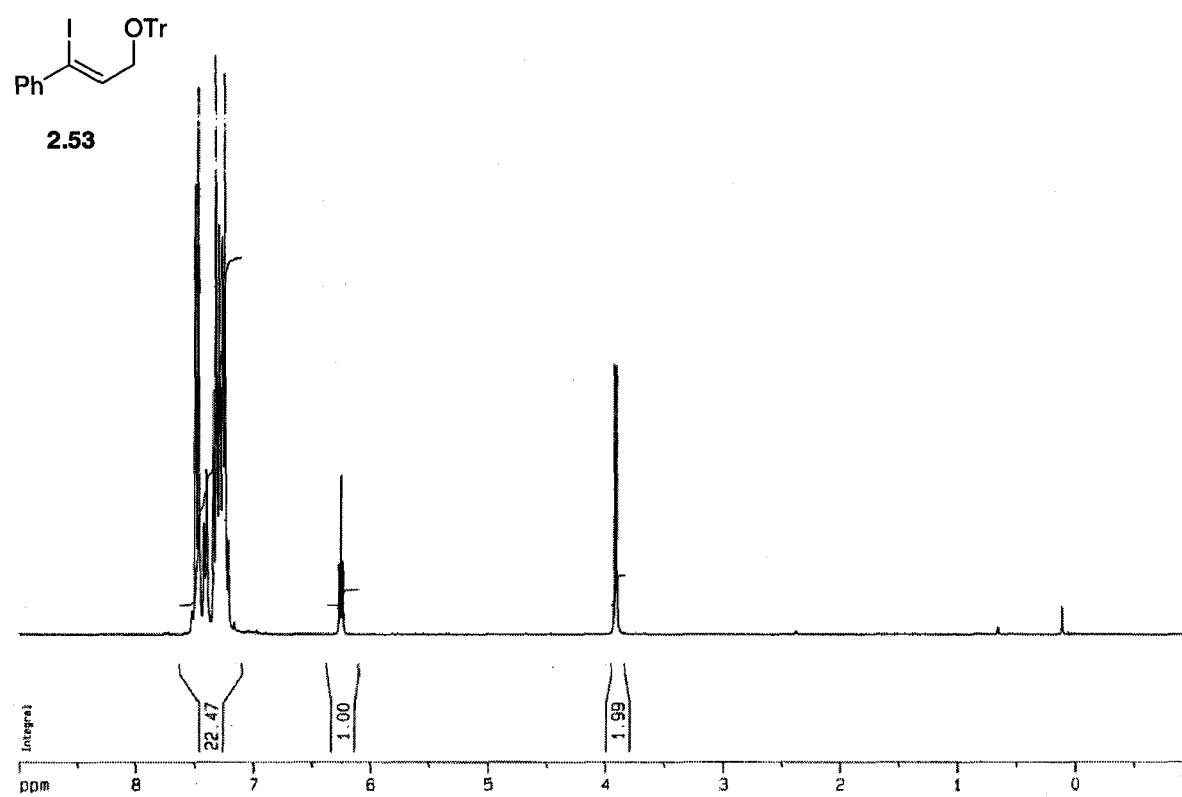
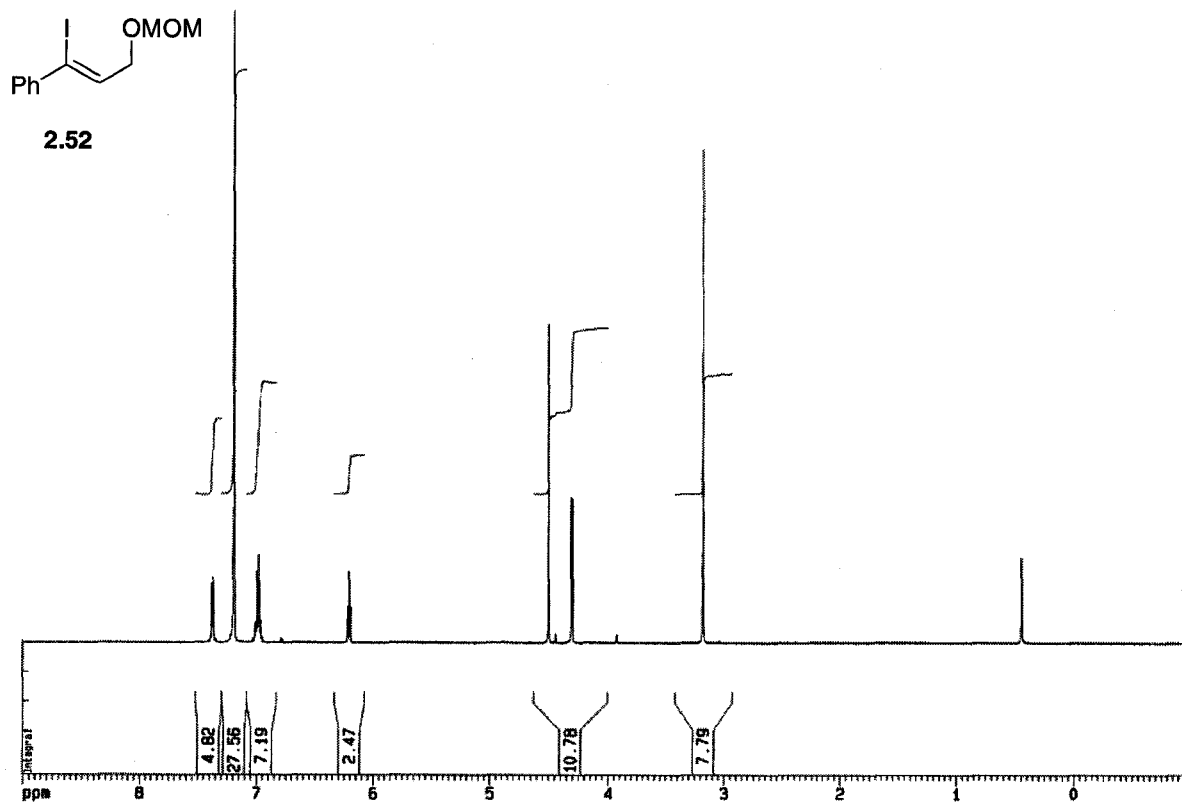


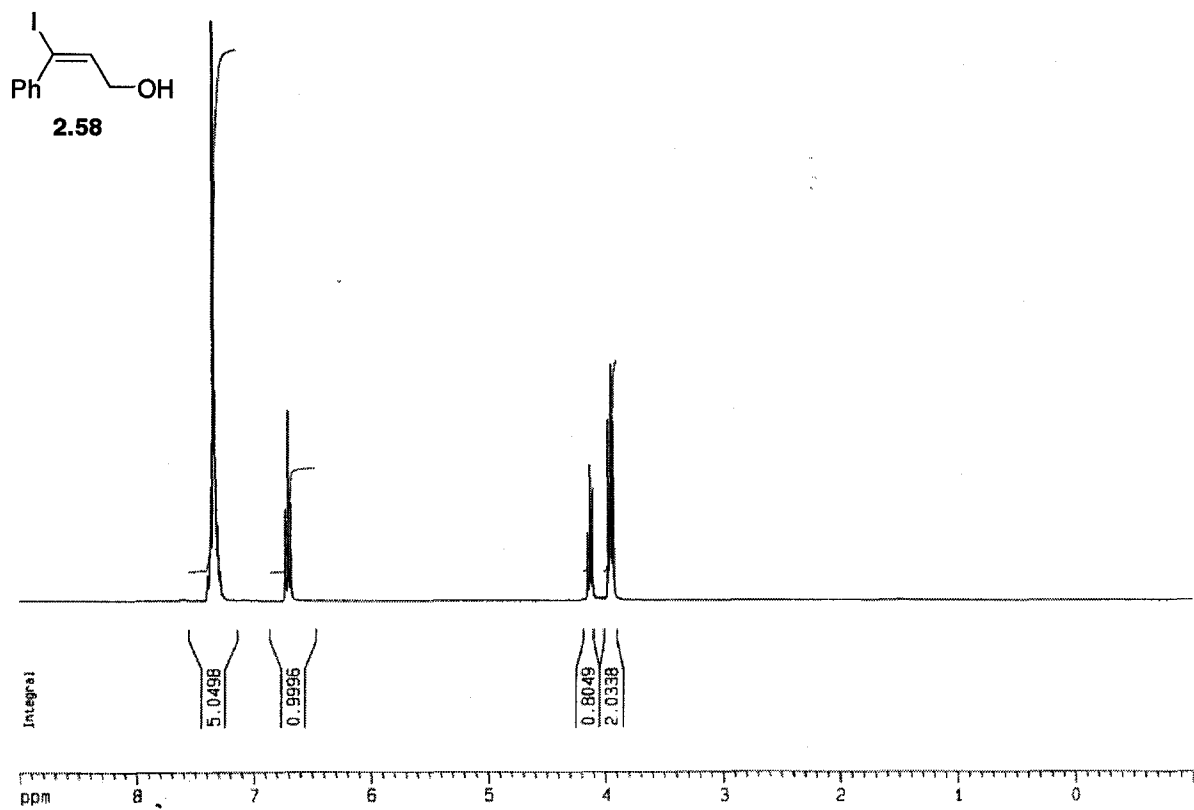
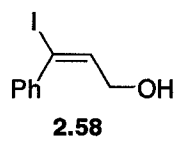
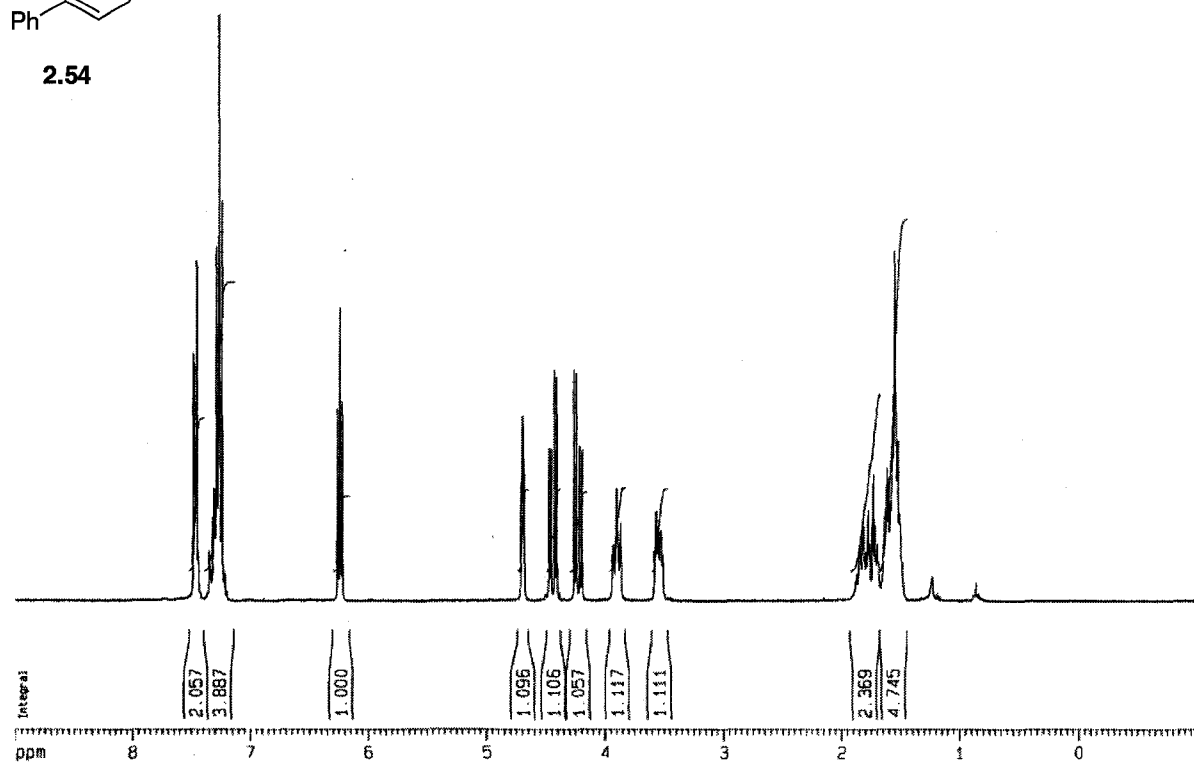
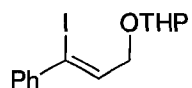
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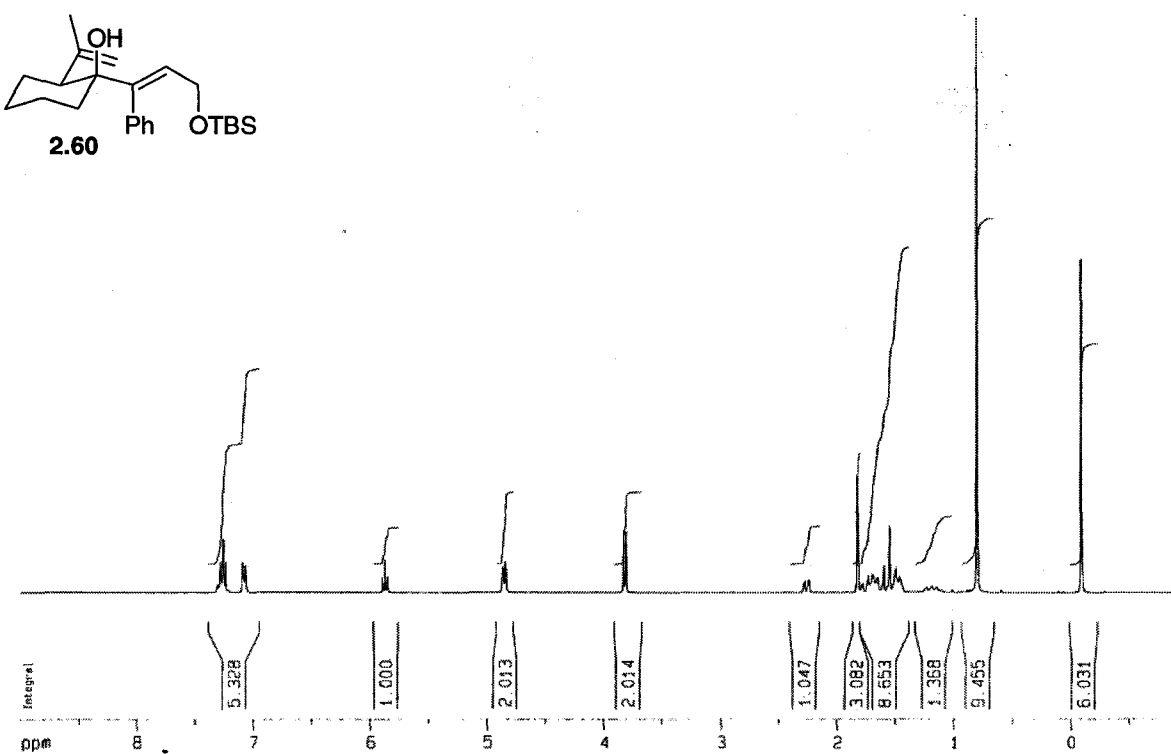
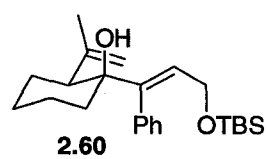
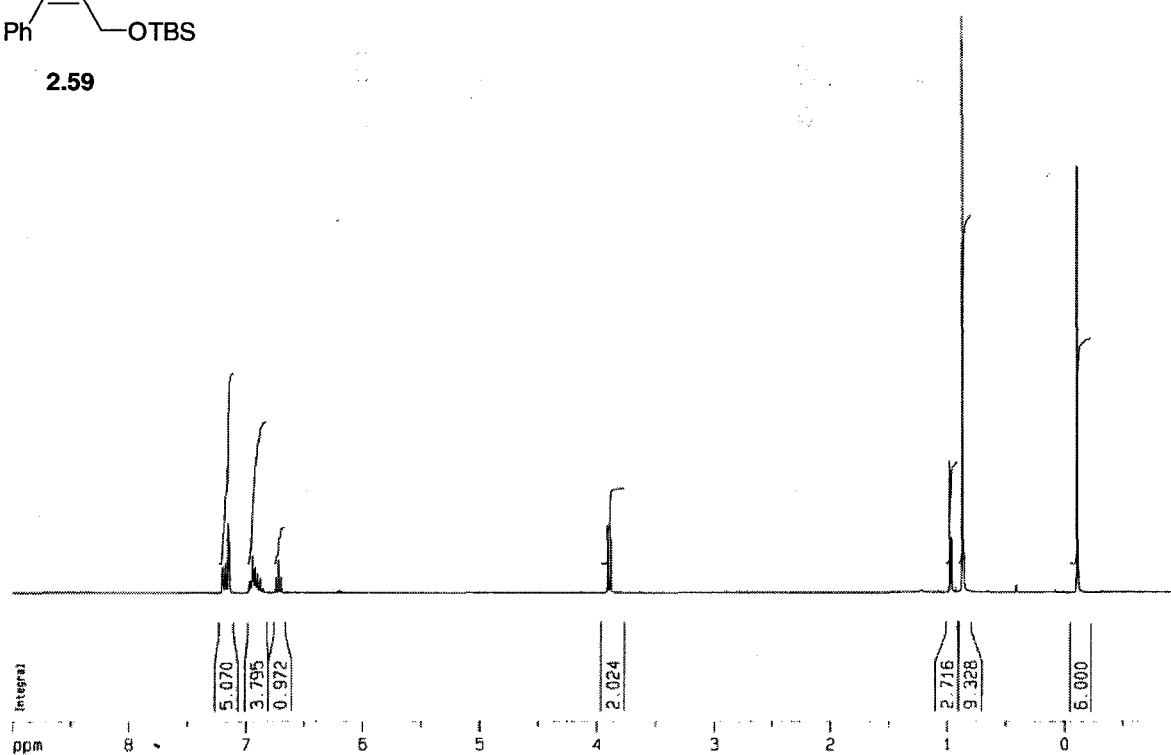
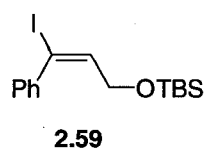


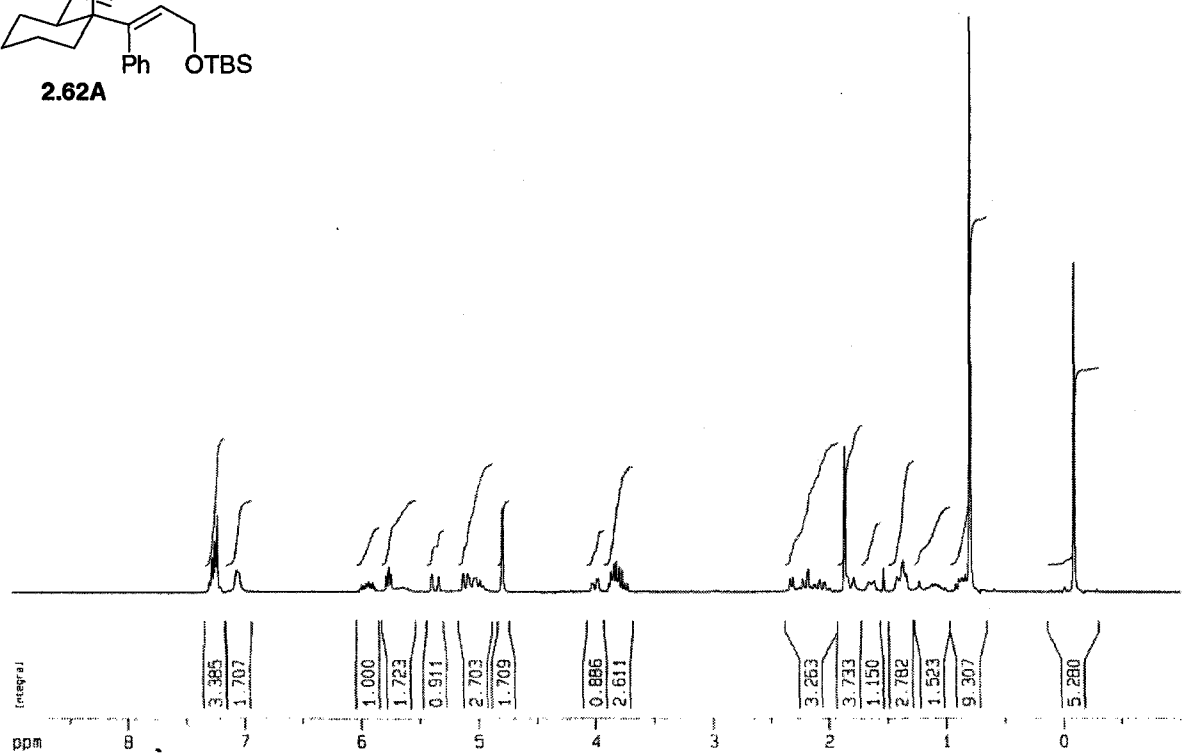
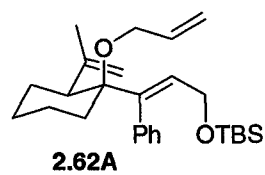
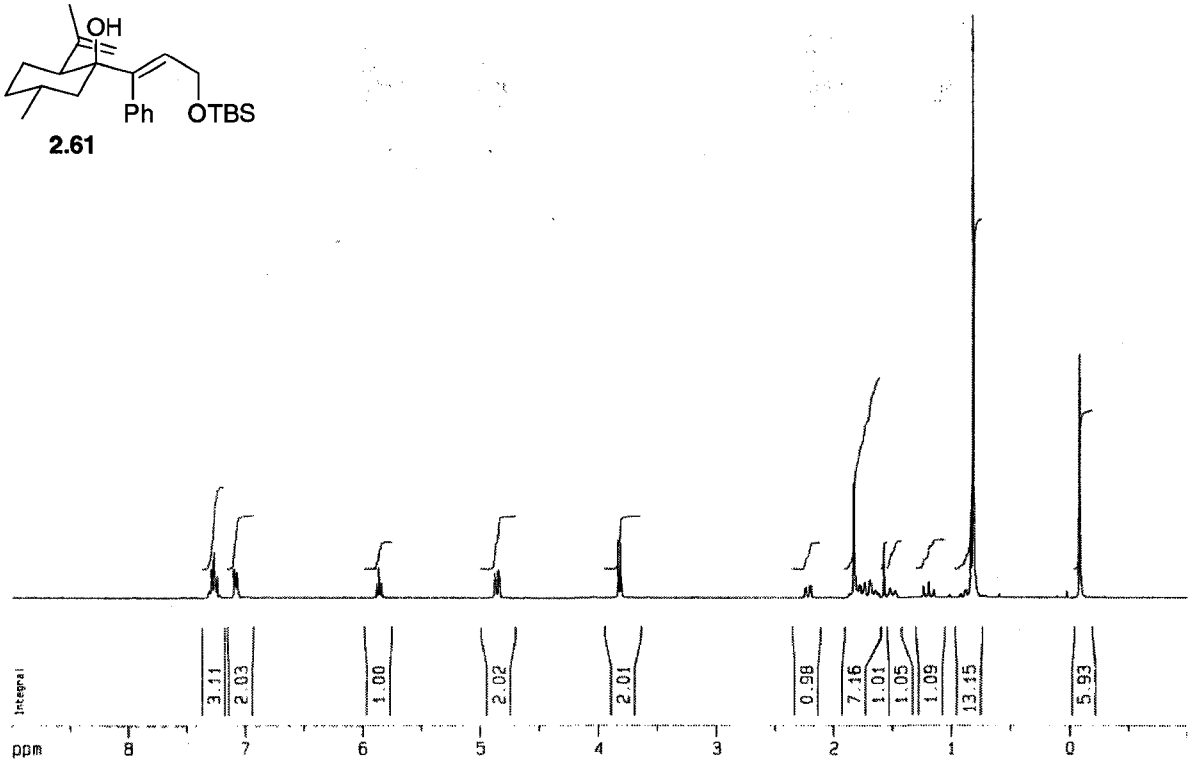
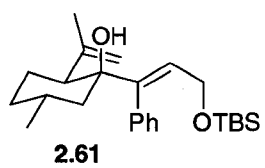
2.50

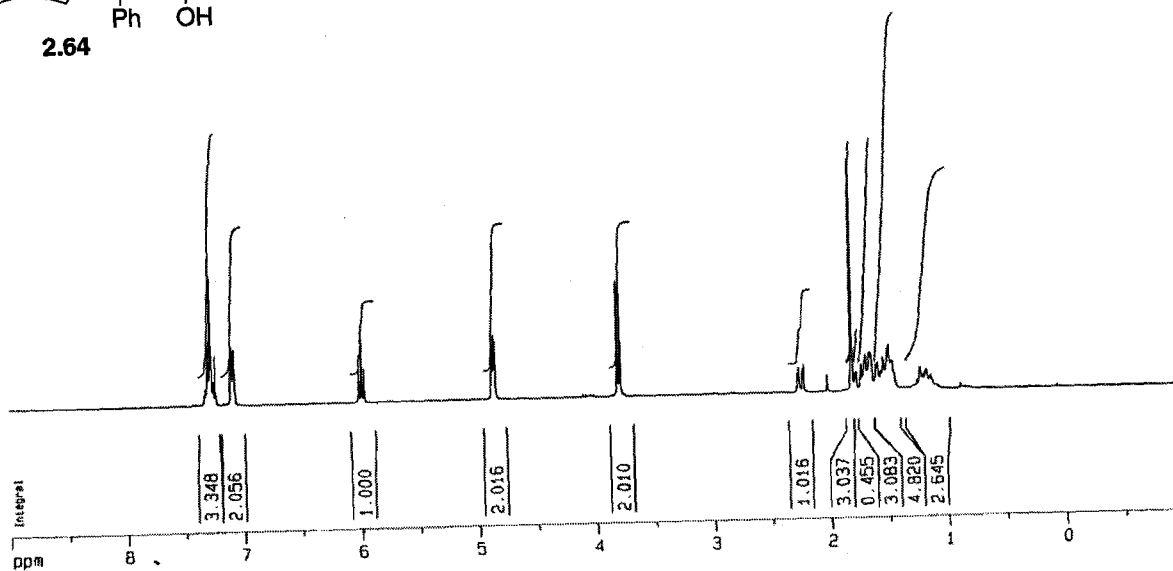
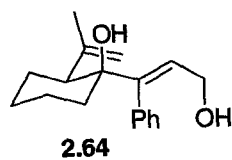
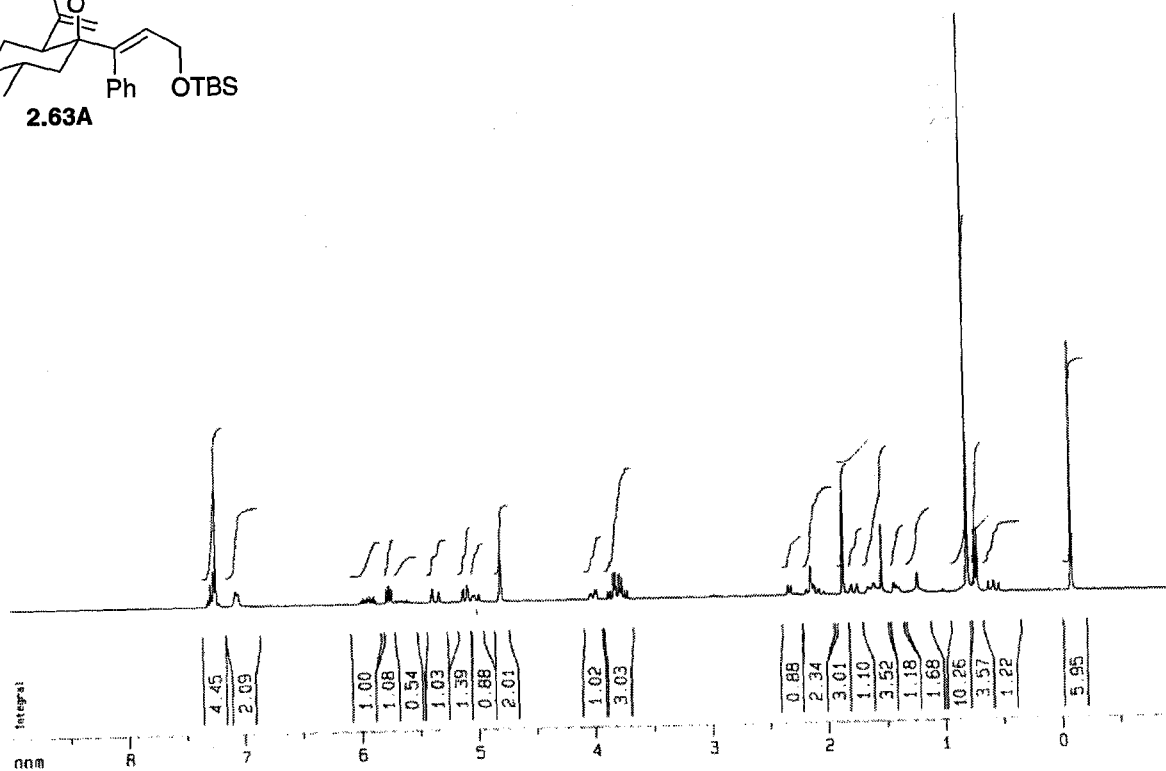
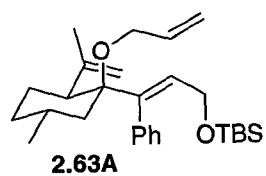


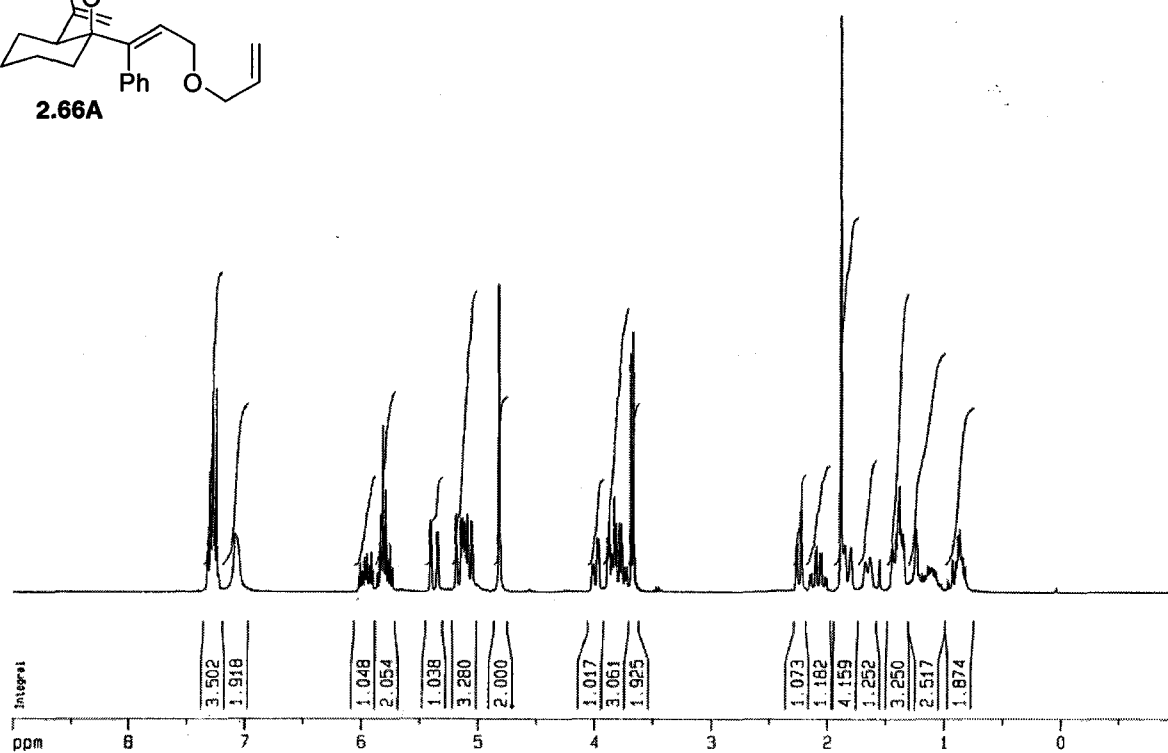
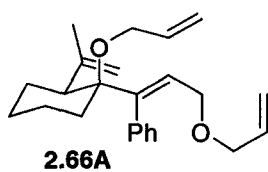
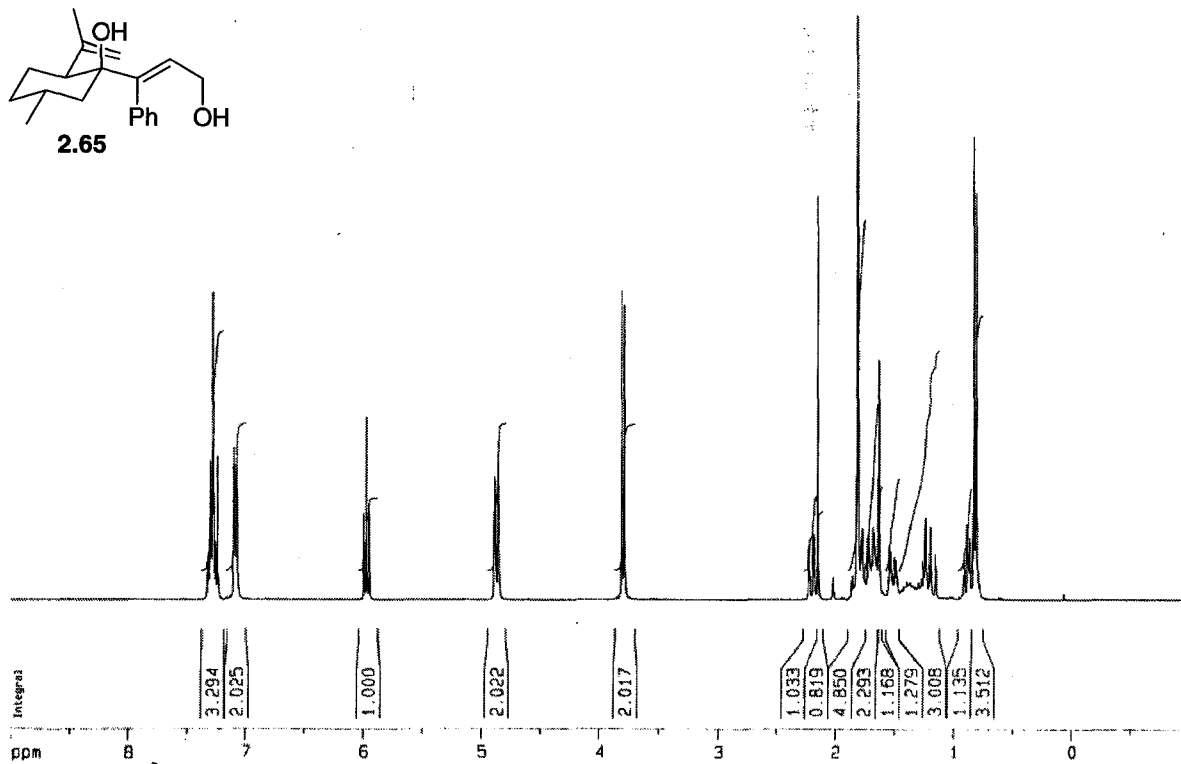
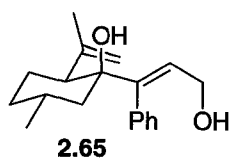


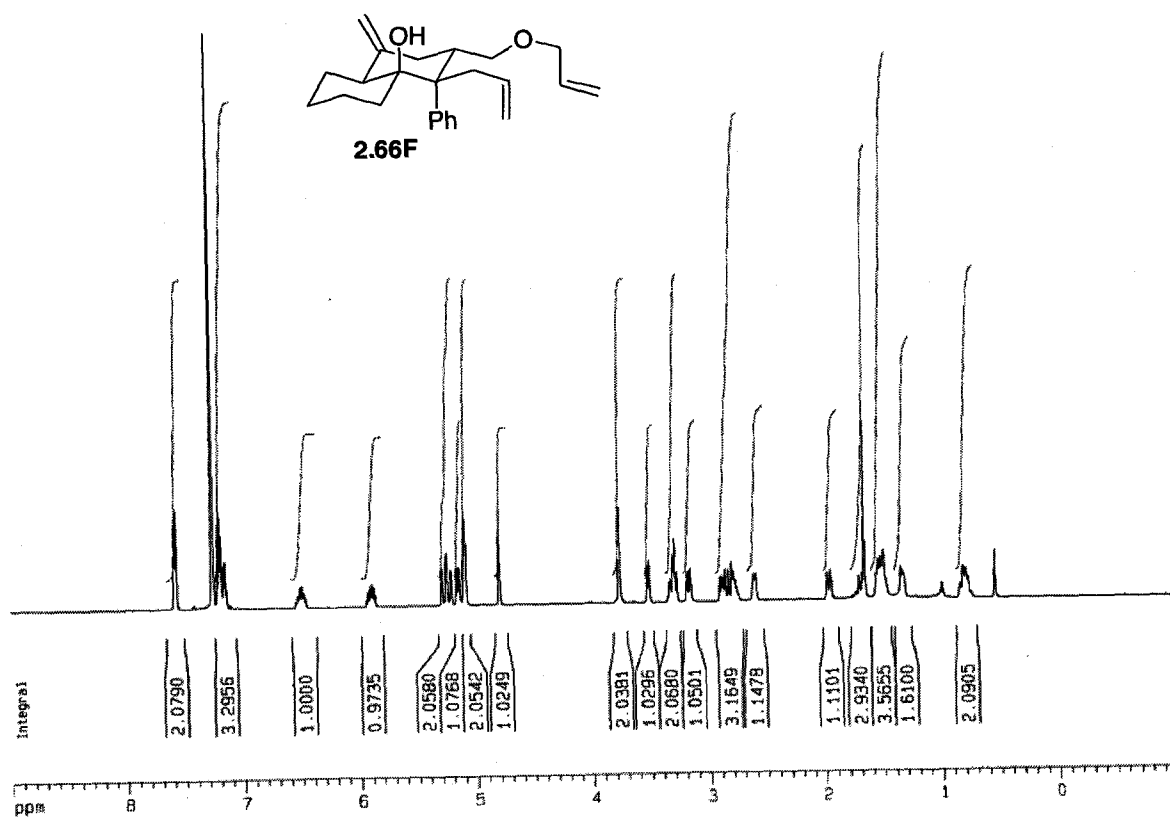
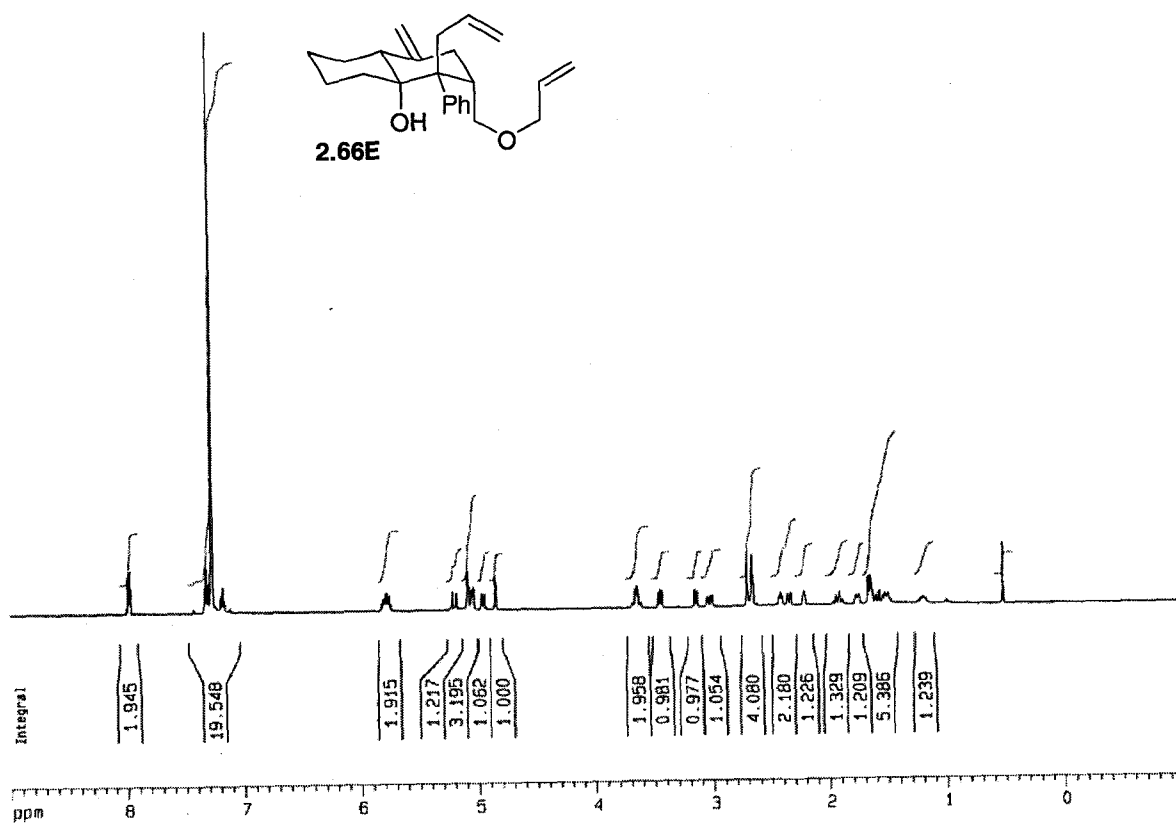


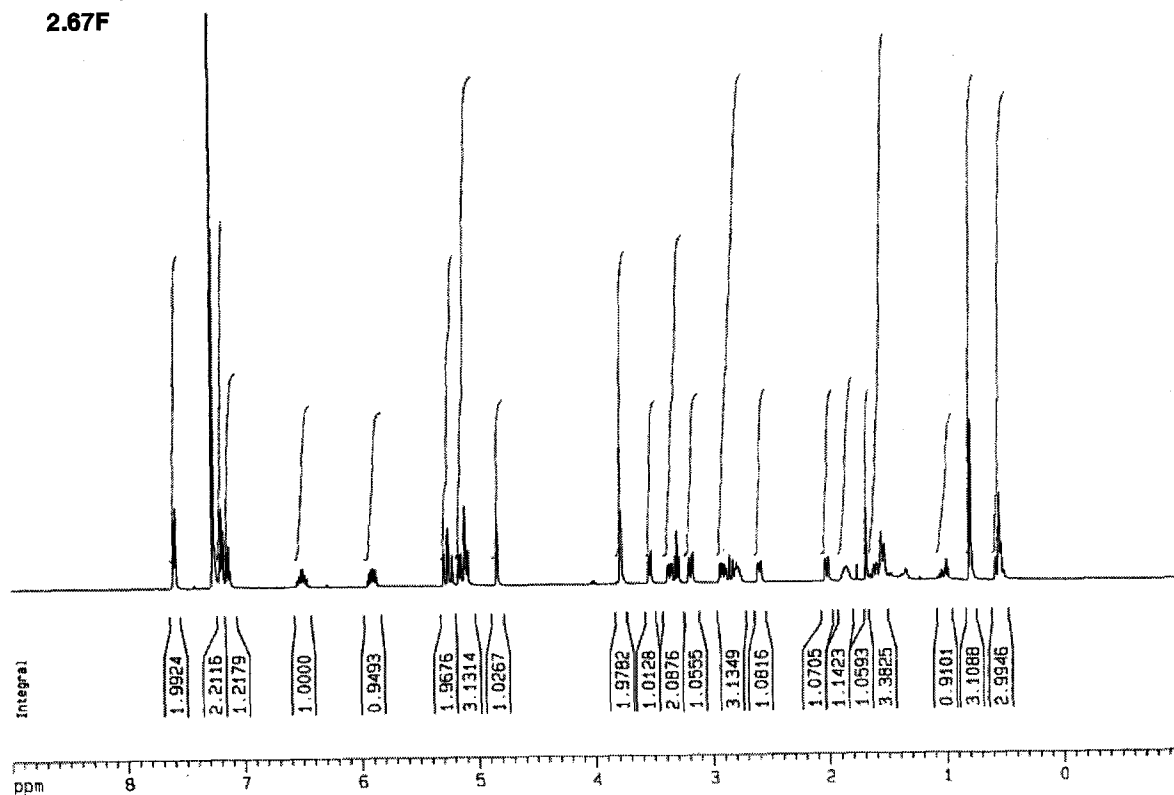
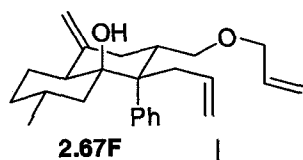
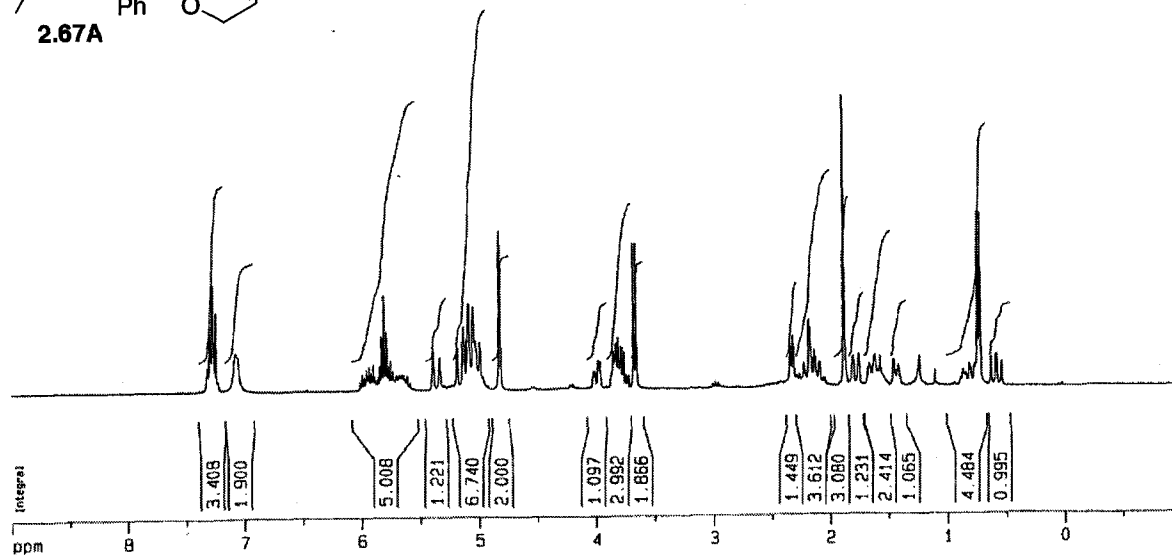
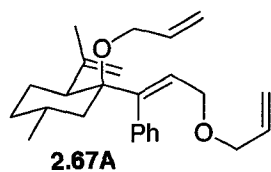


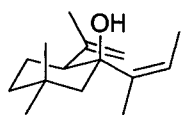




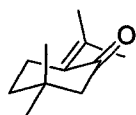
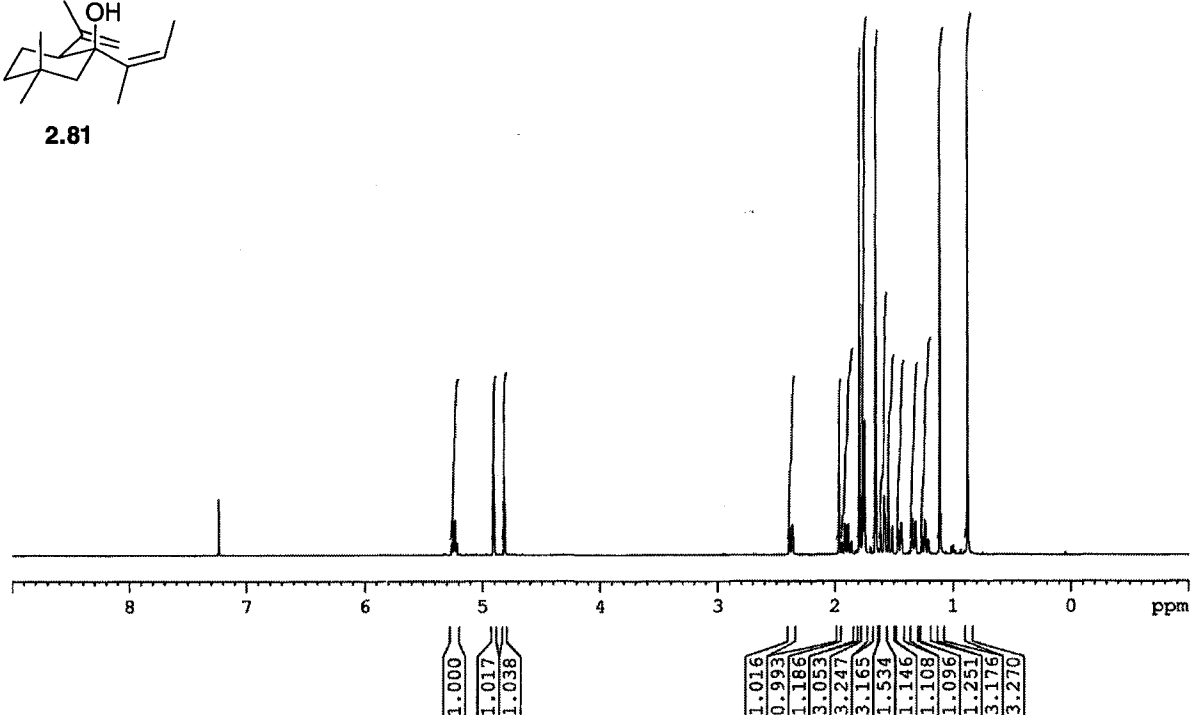




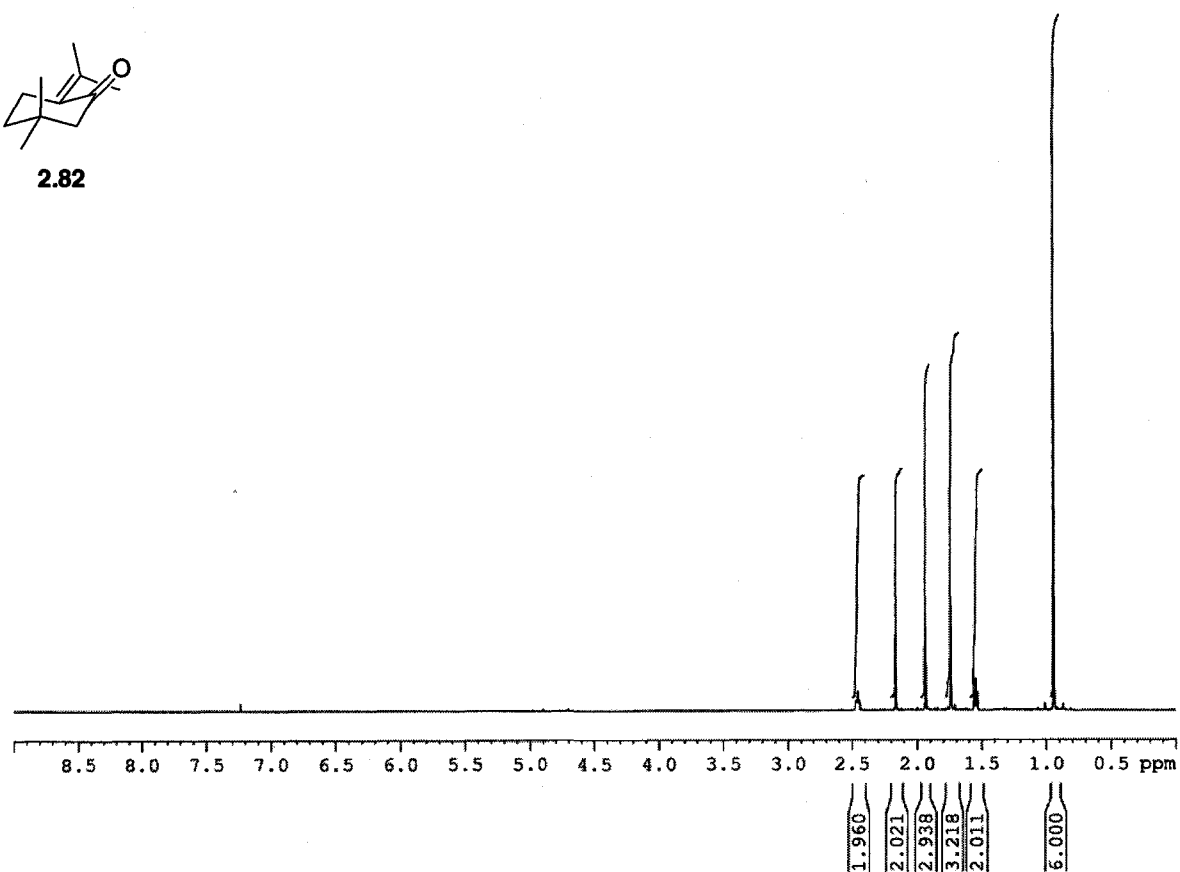


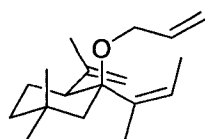


2.81

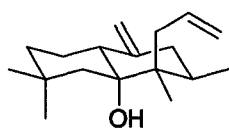
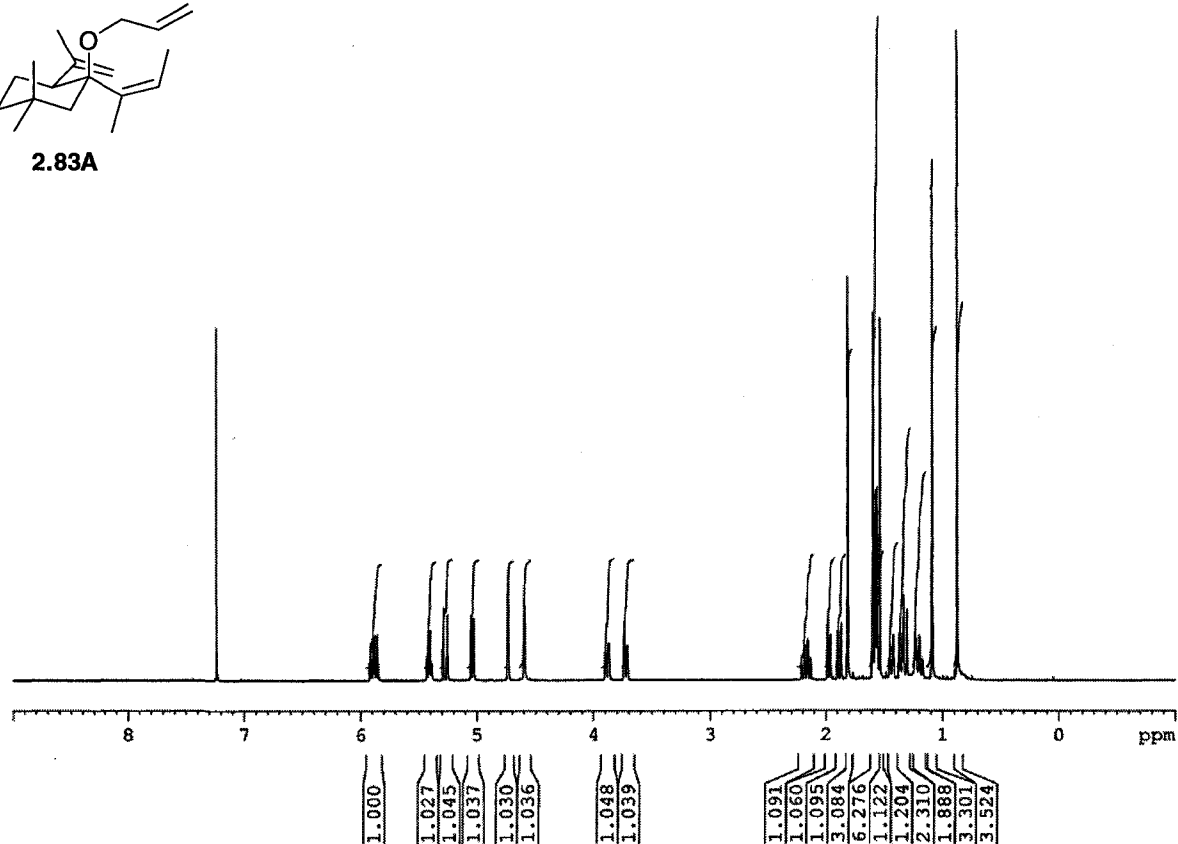


2.82

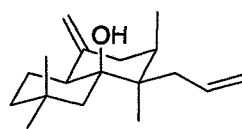




2.83A

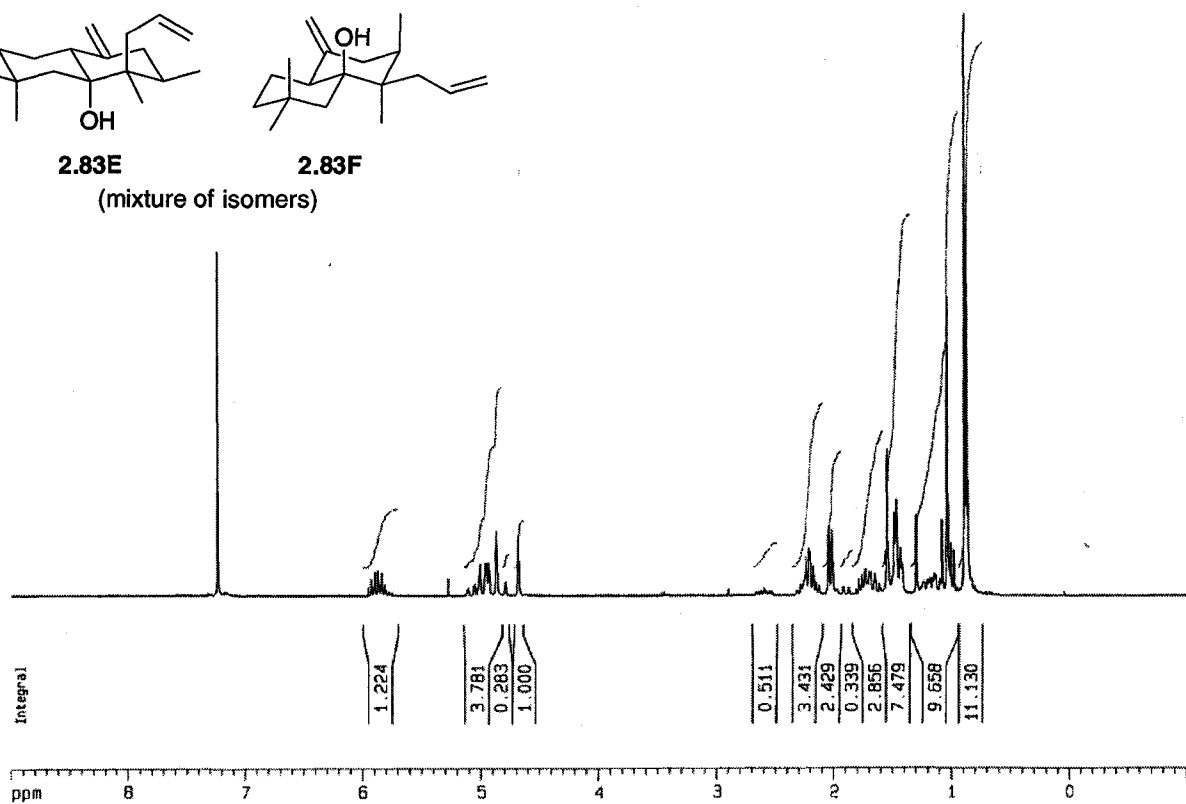


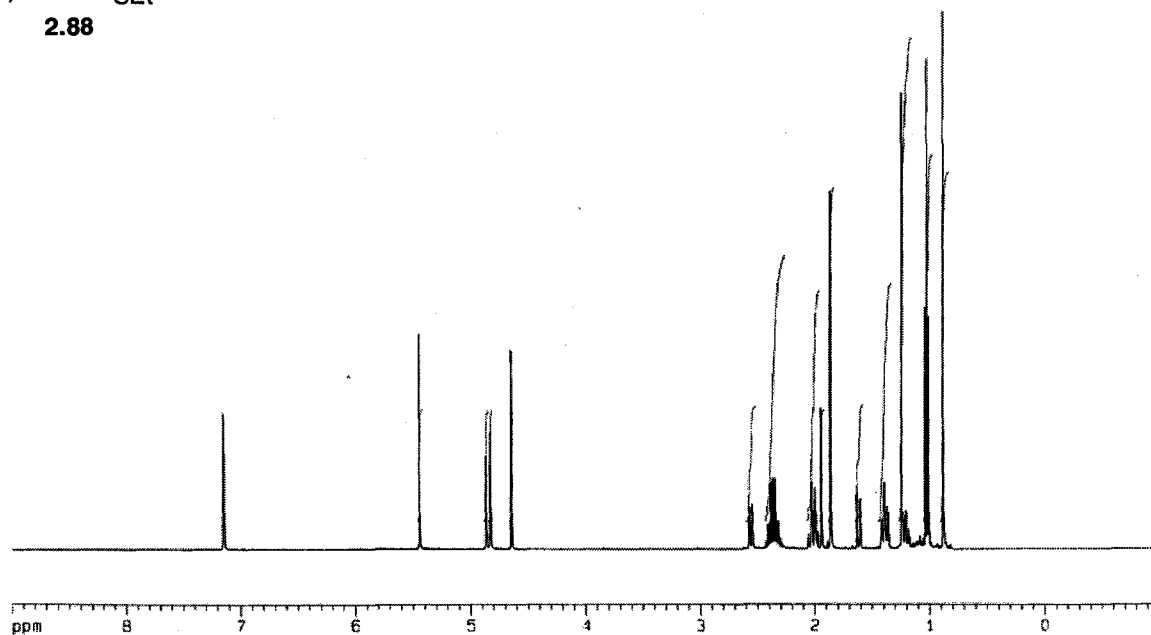
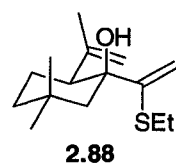
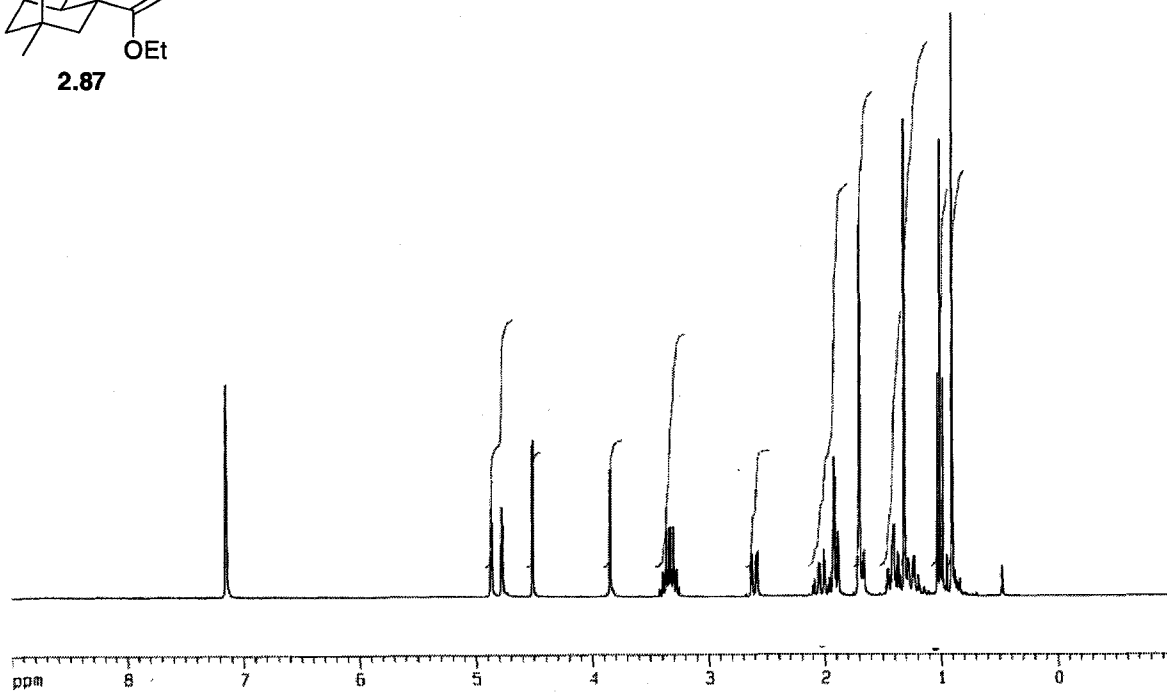
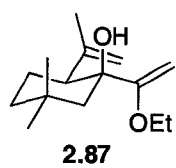
2.83E

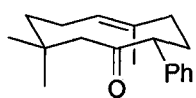


2.83F

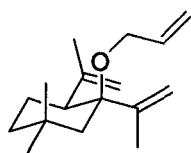
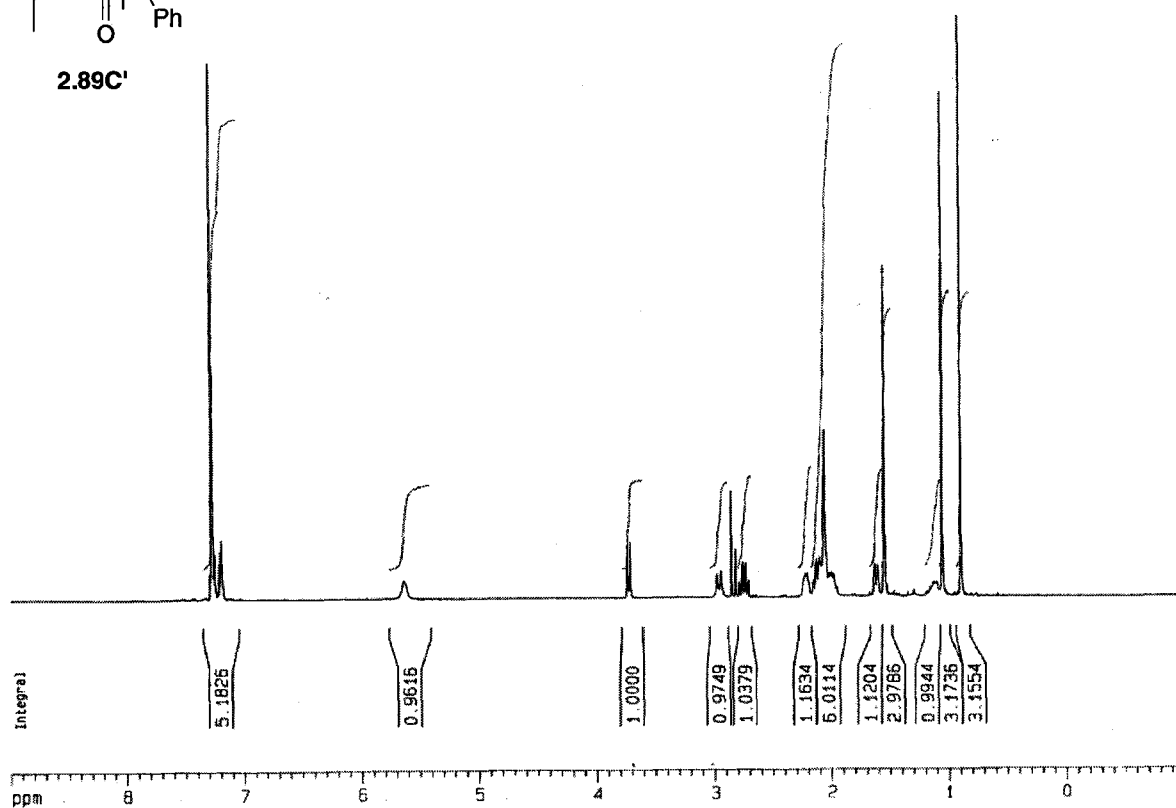
(mixture of isomers)



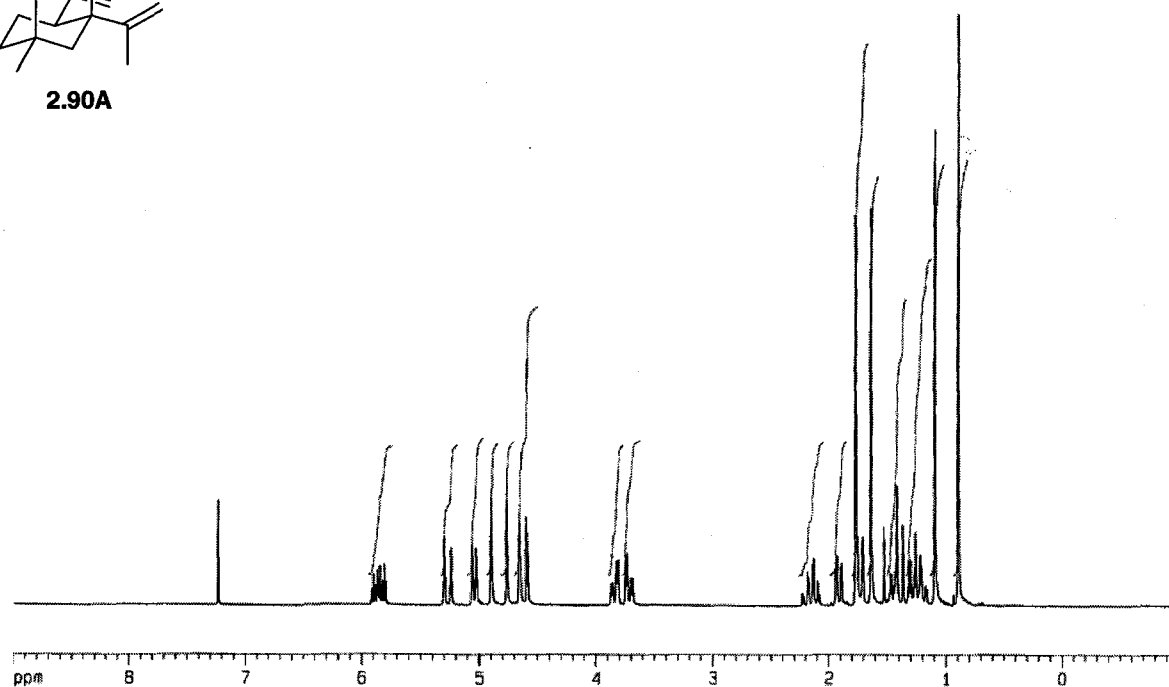


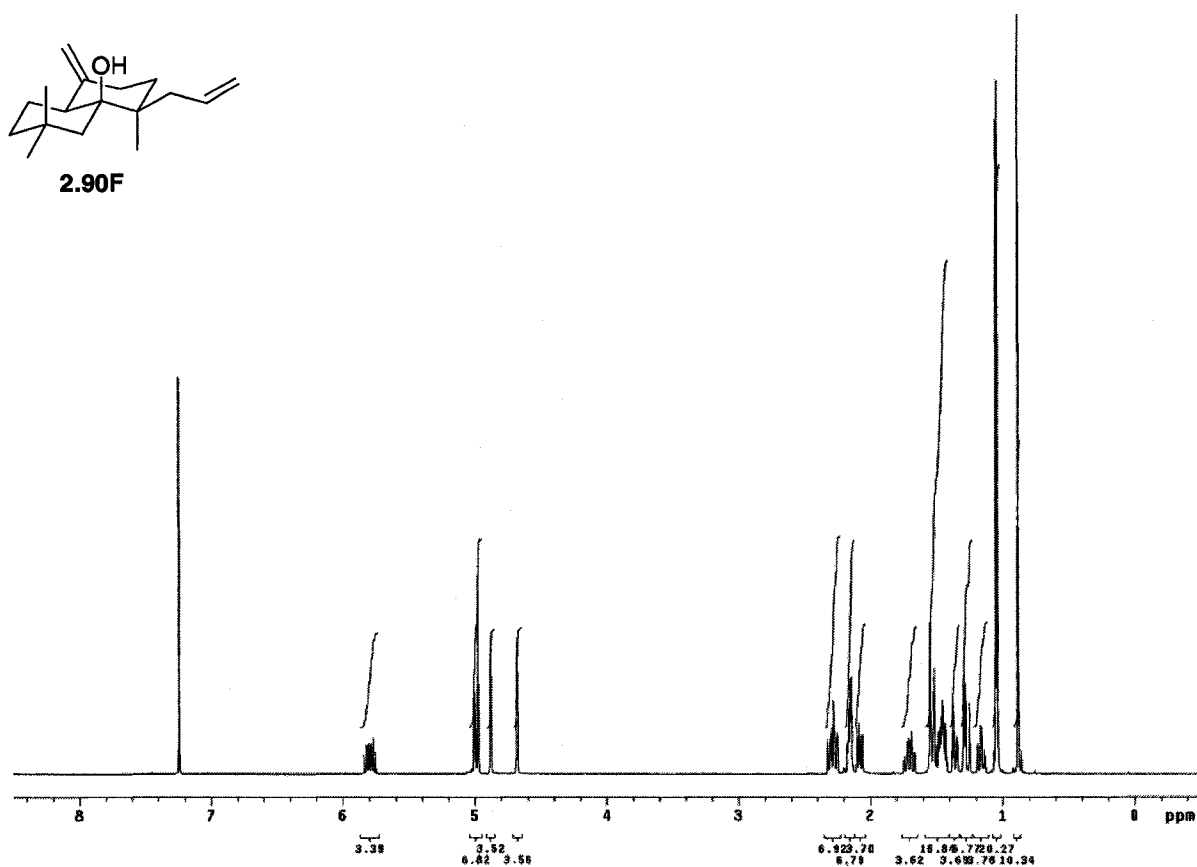
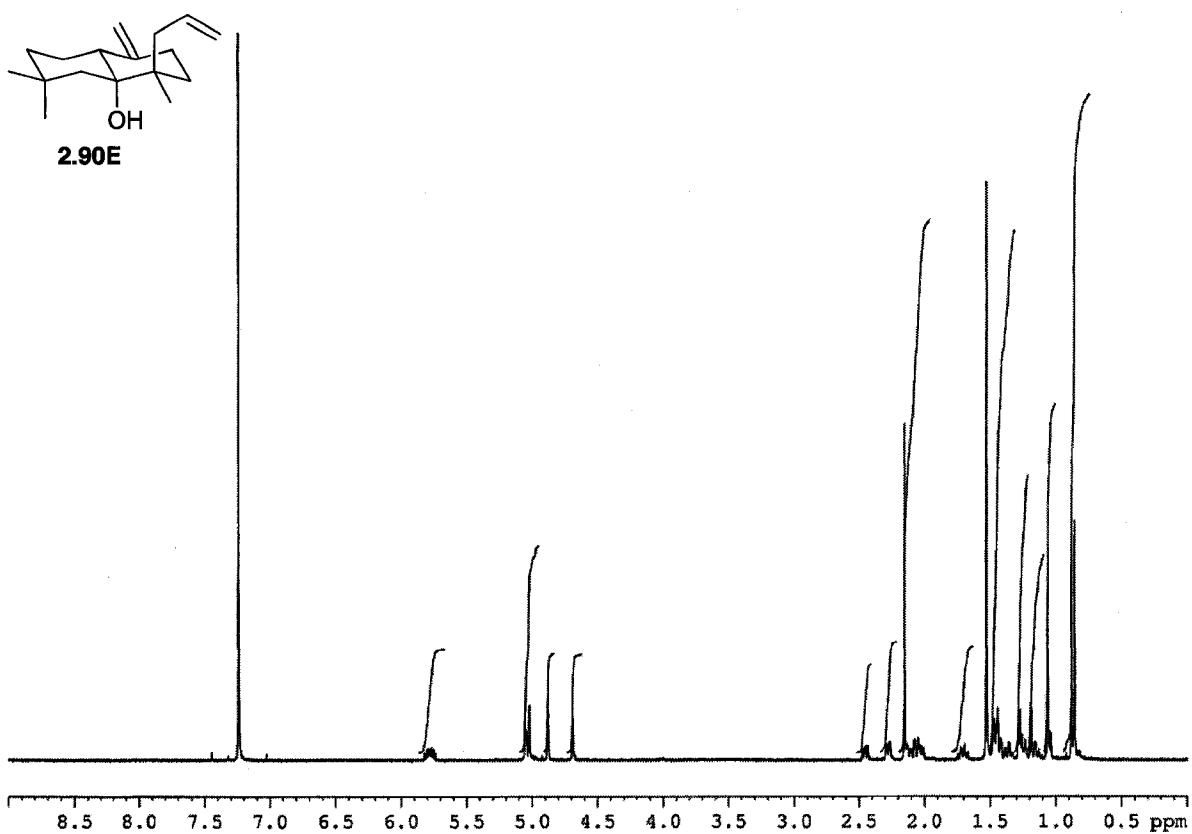


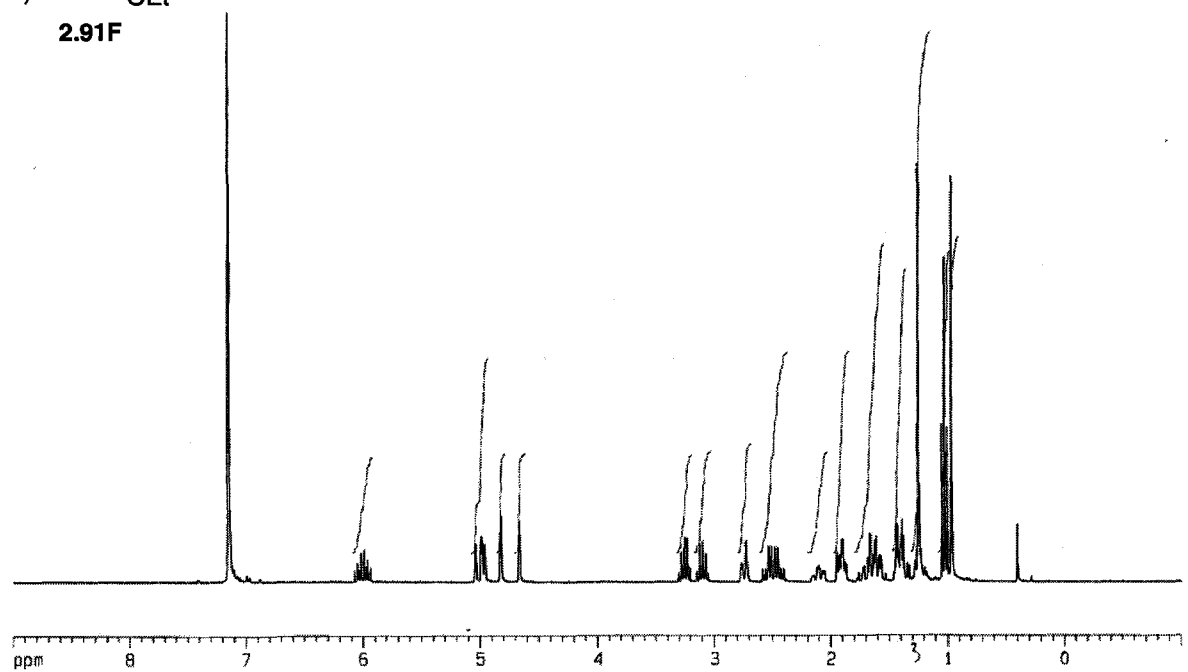
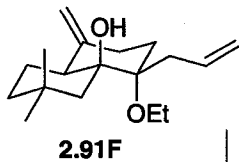
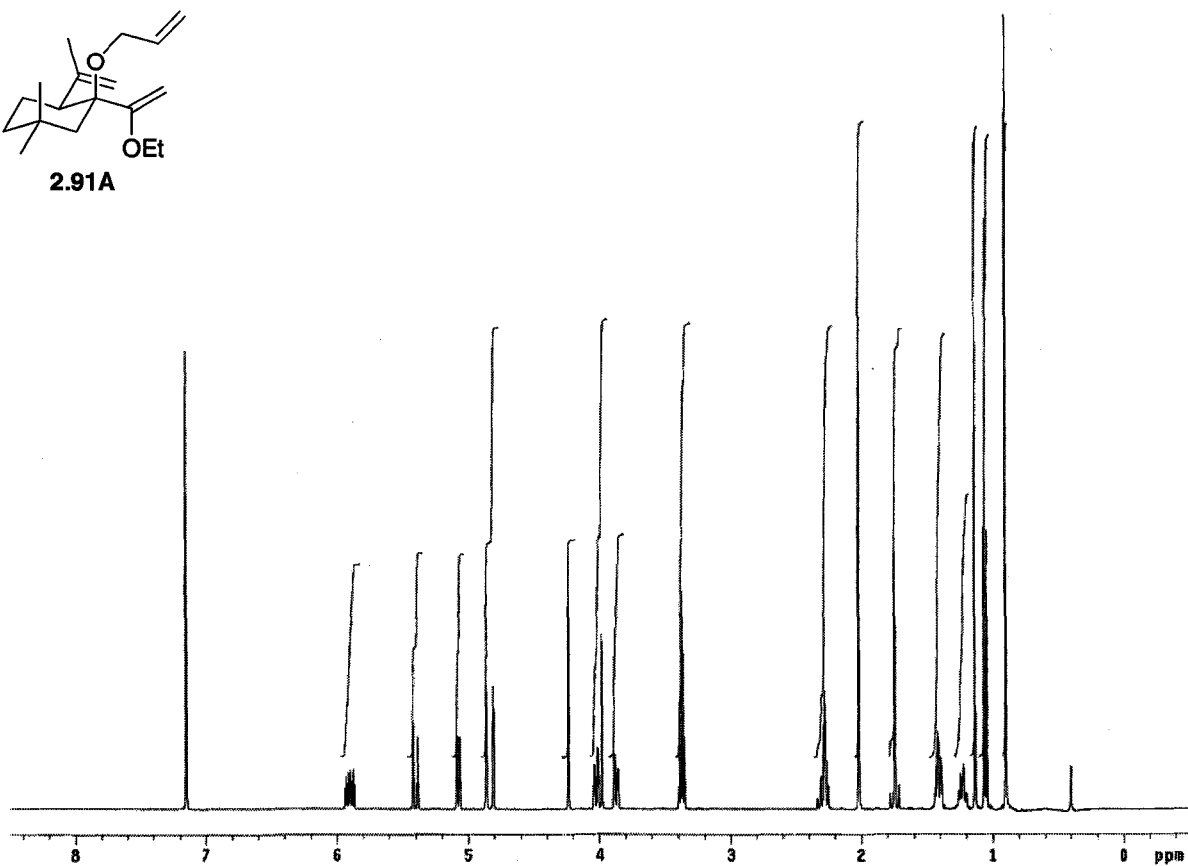
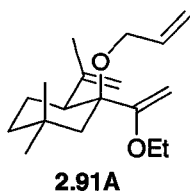
2.89C'

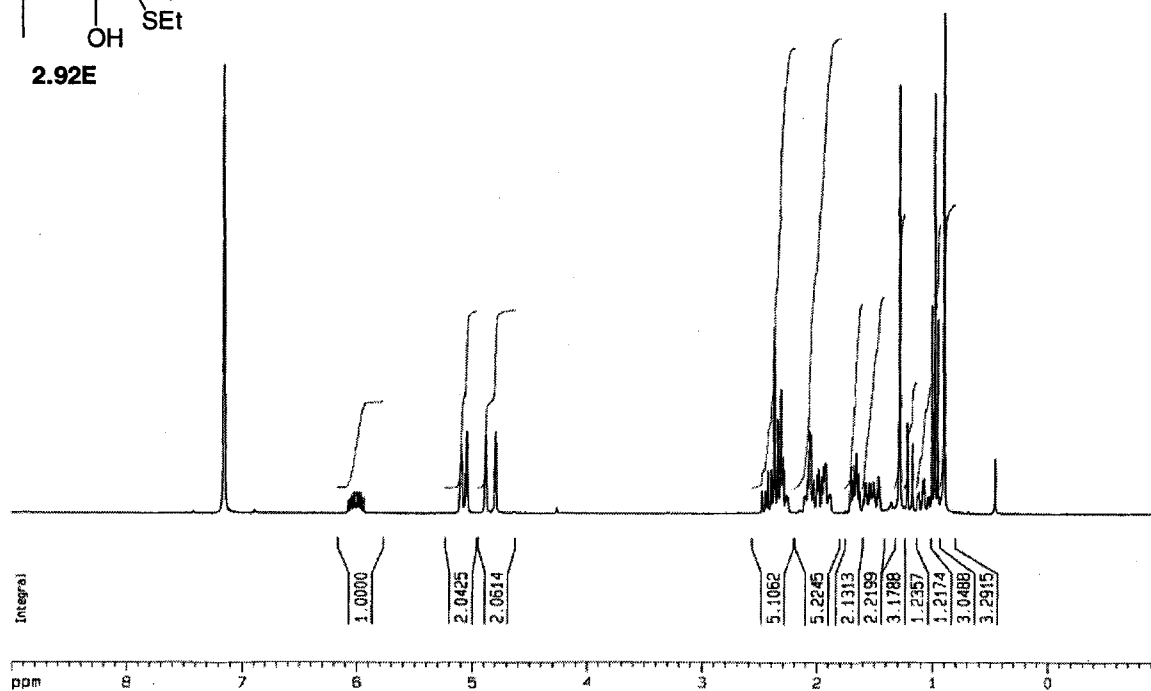
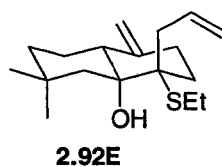
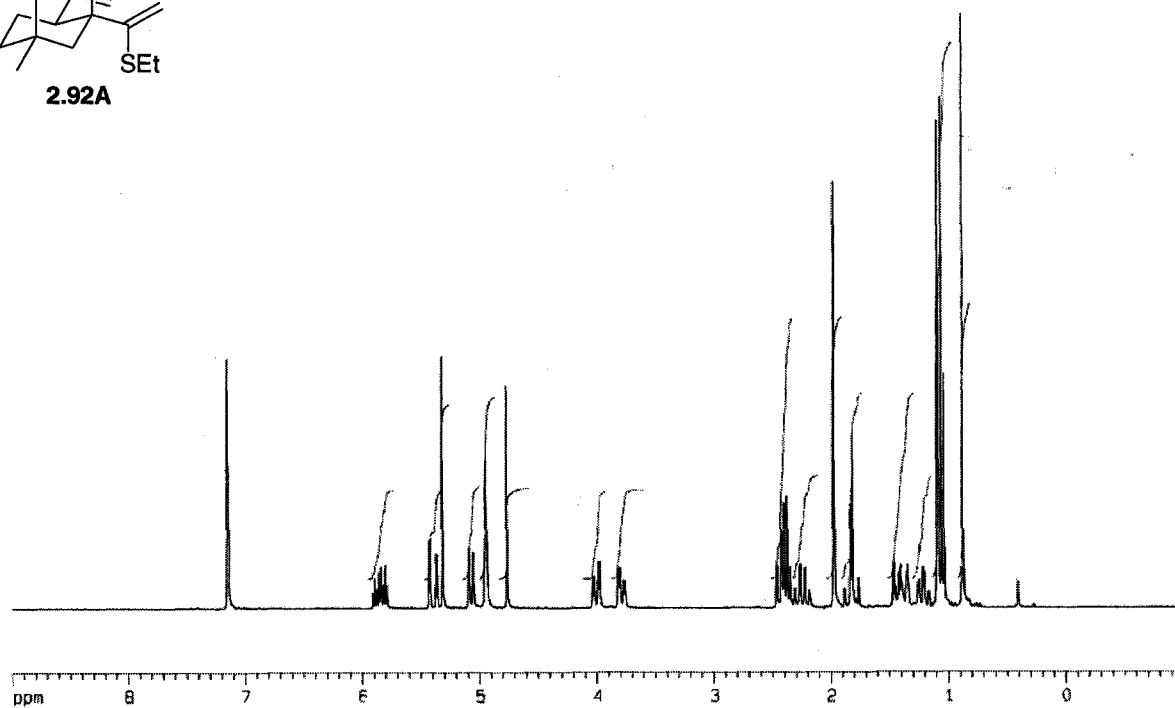
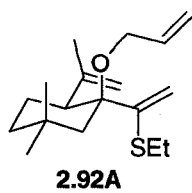


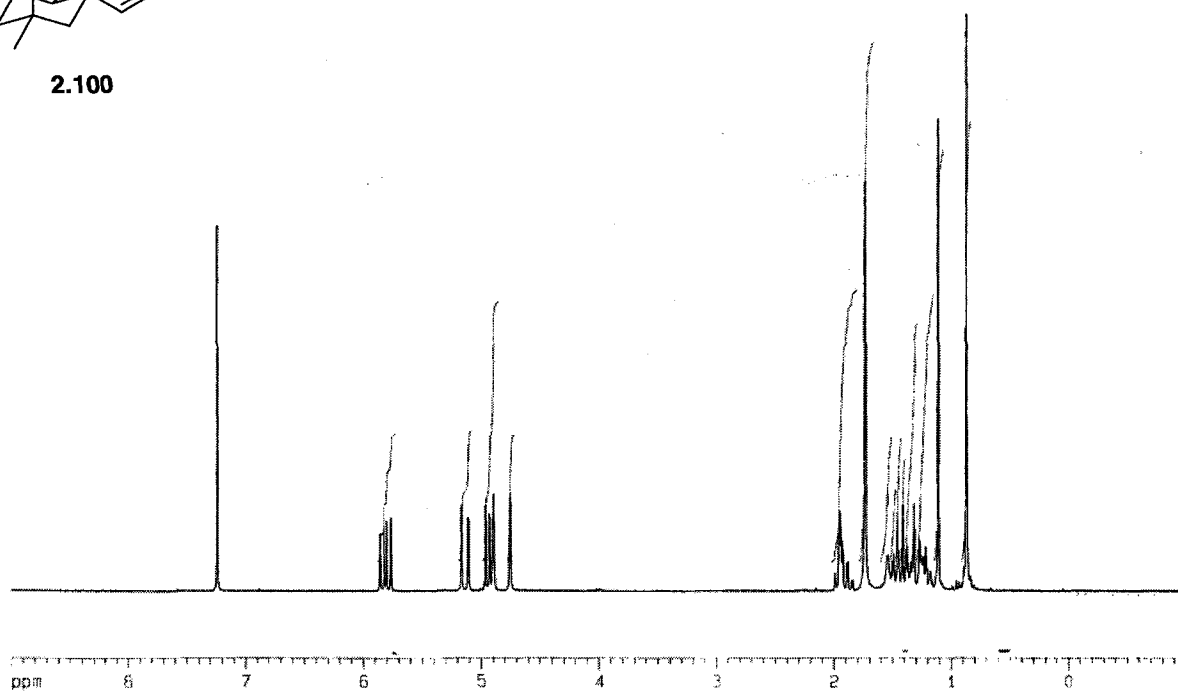
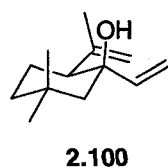
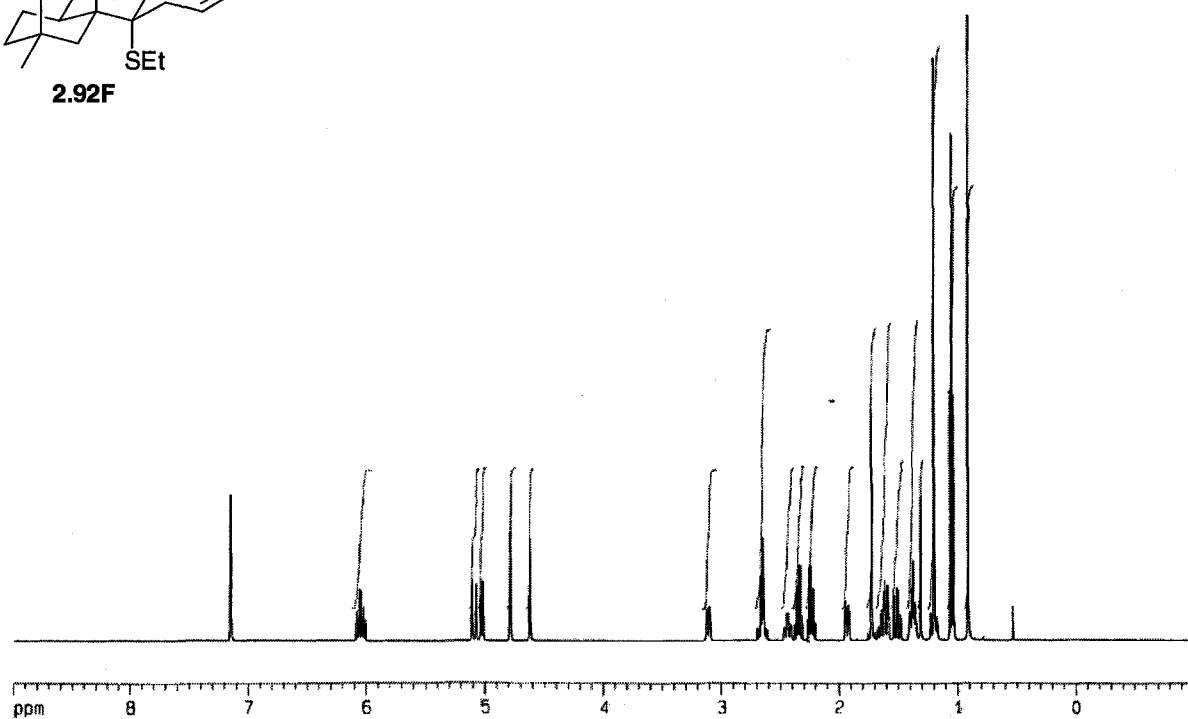
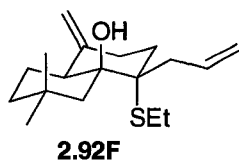
2.90A

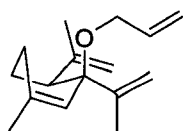




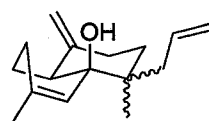
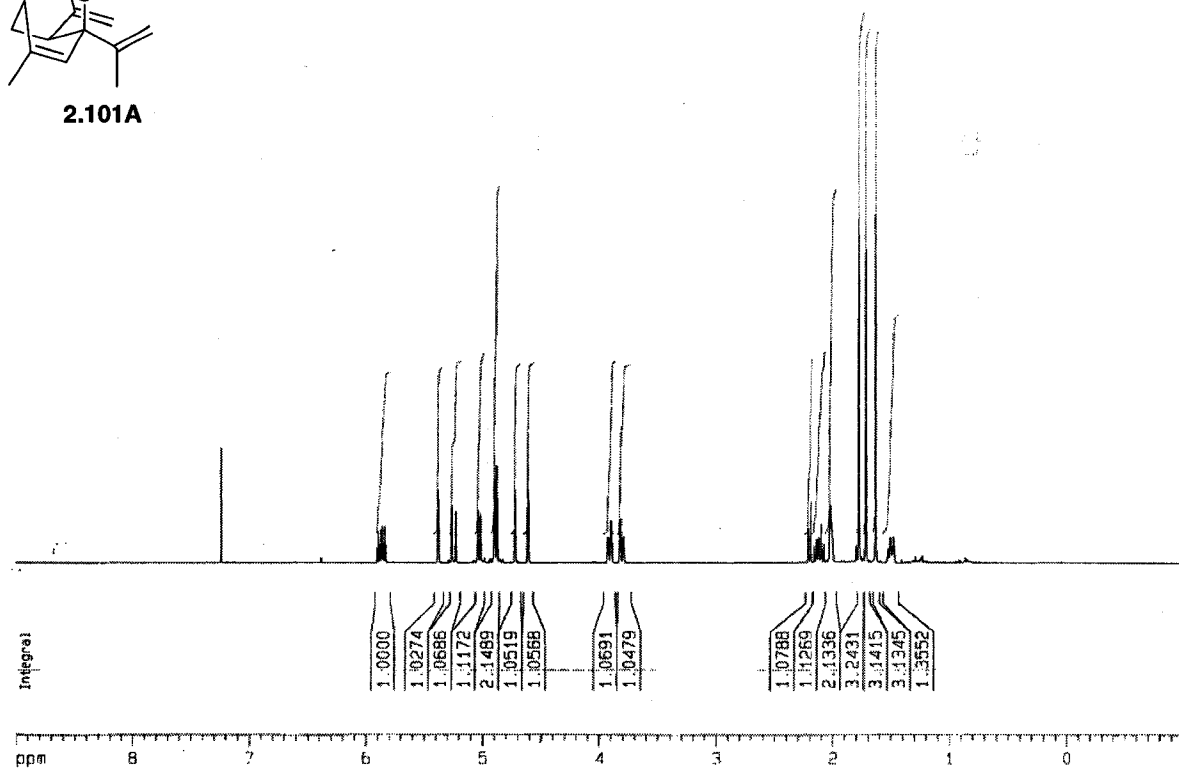




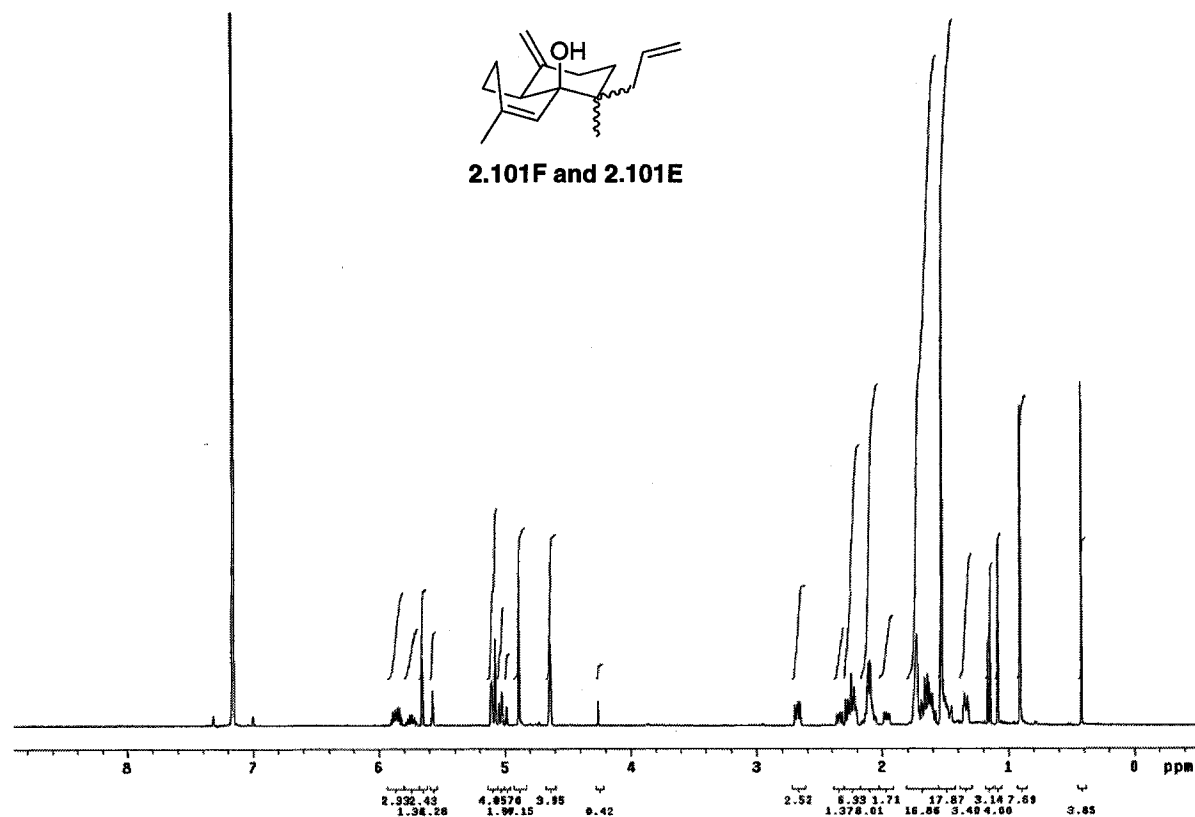


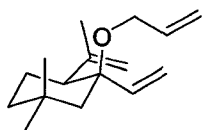


2.101A

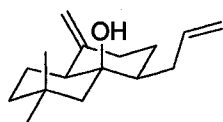
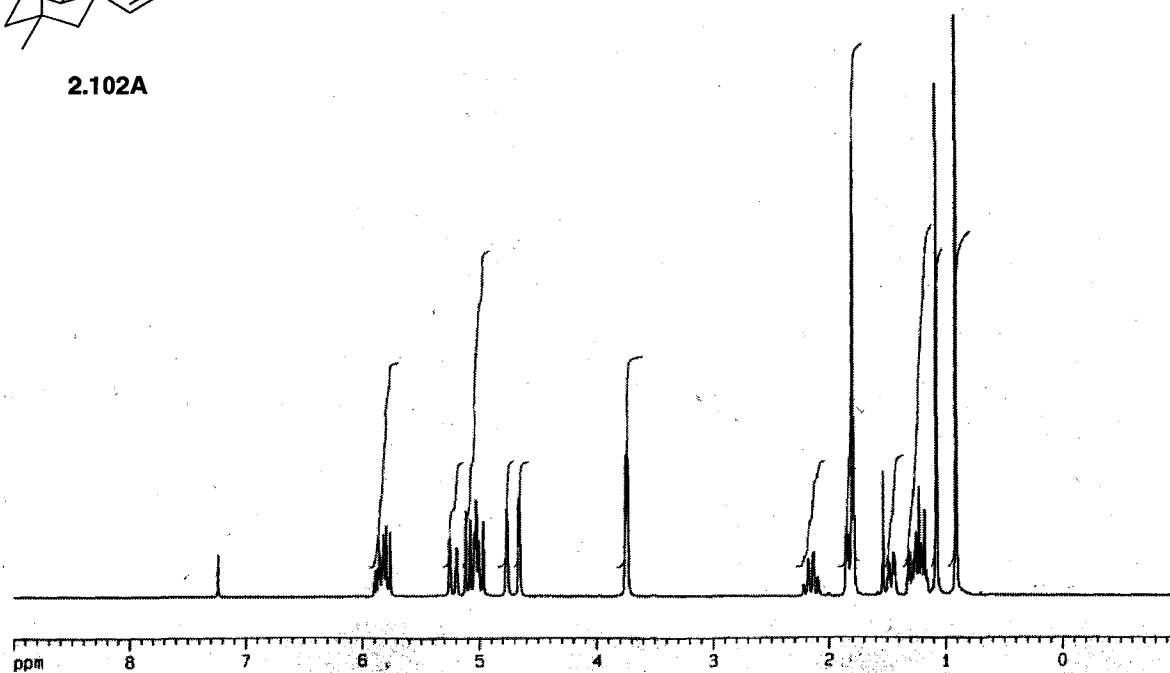


2.101F and 2.101E

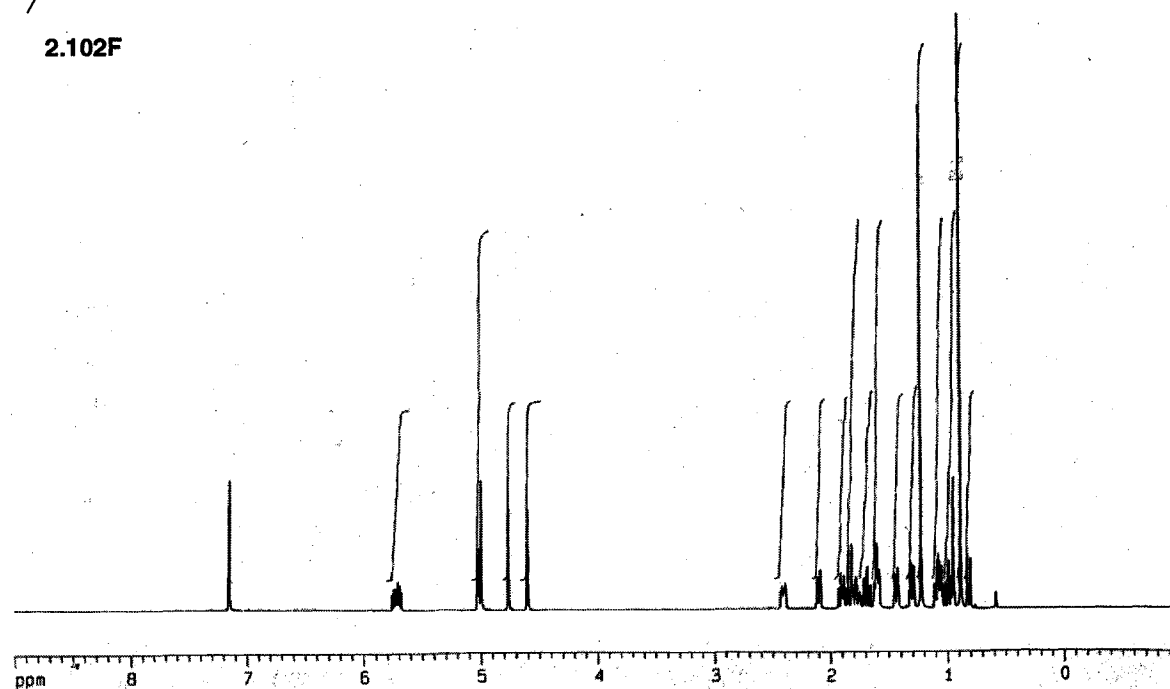


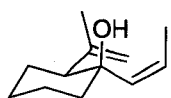


2.102A

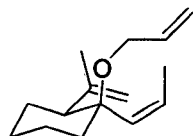
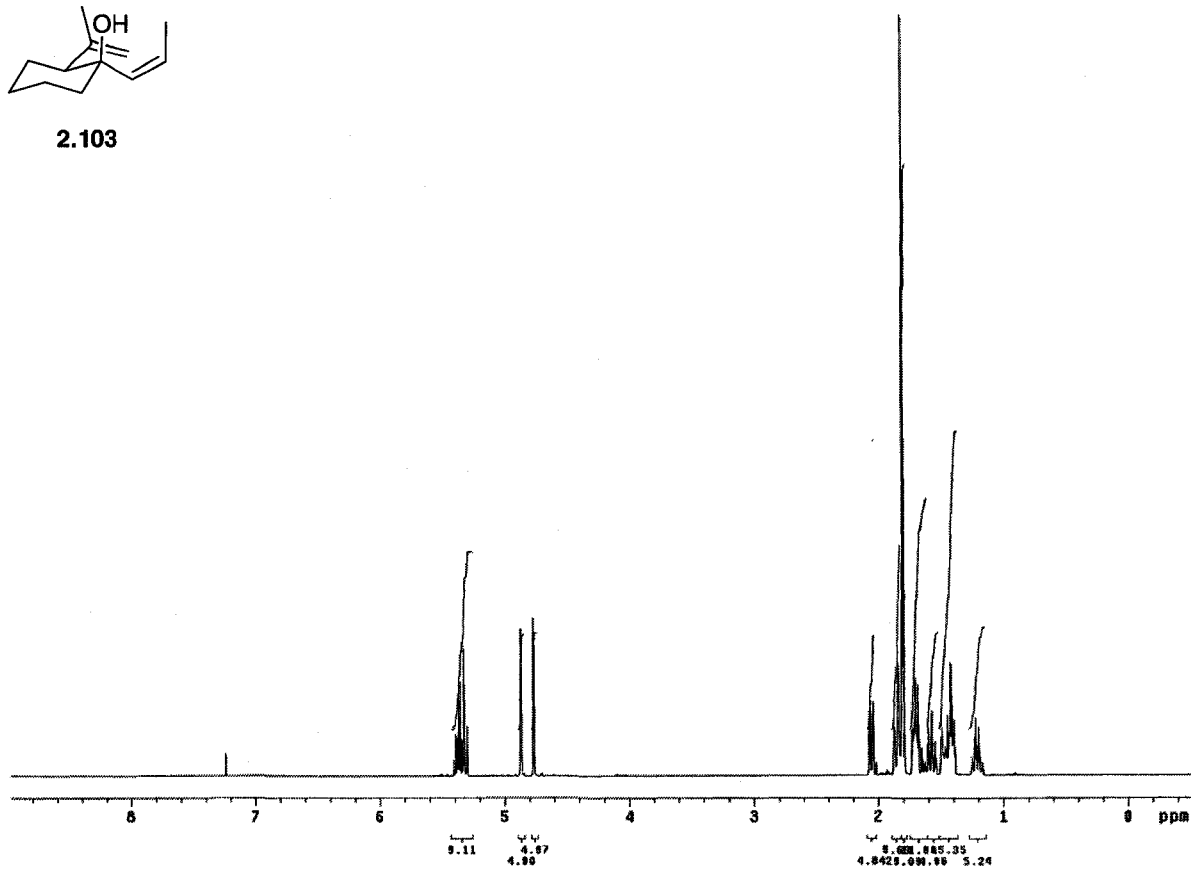


2.102F

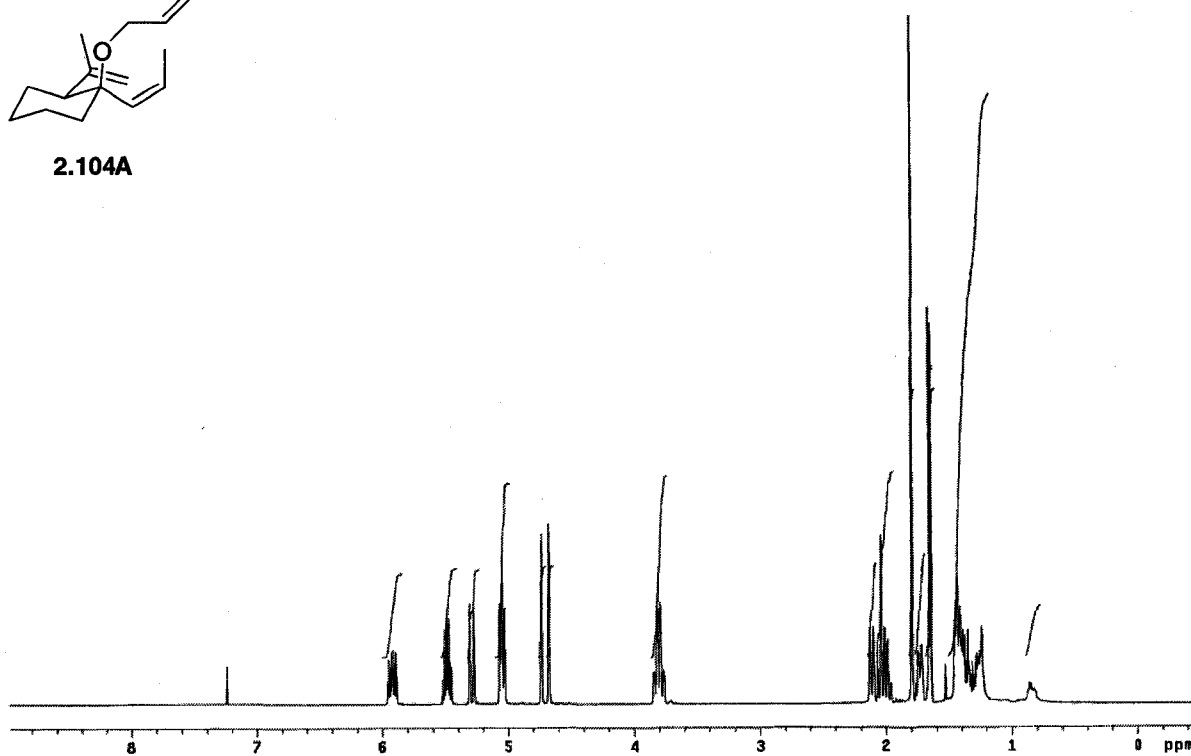


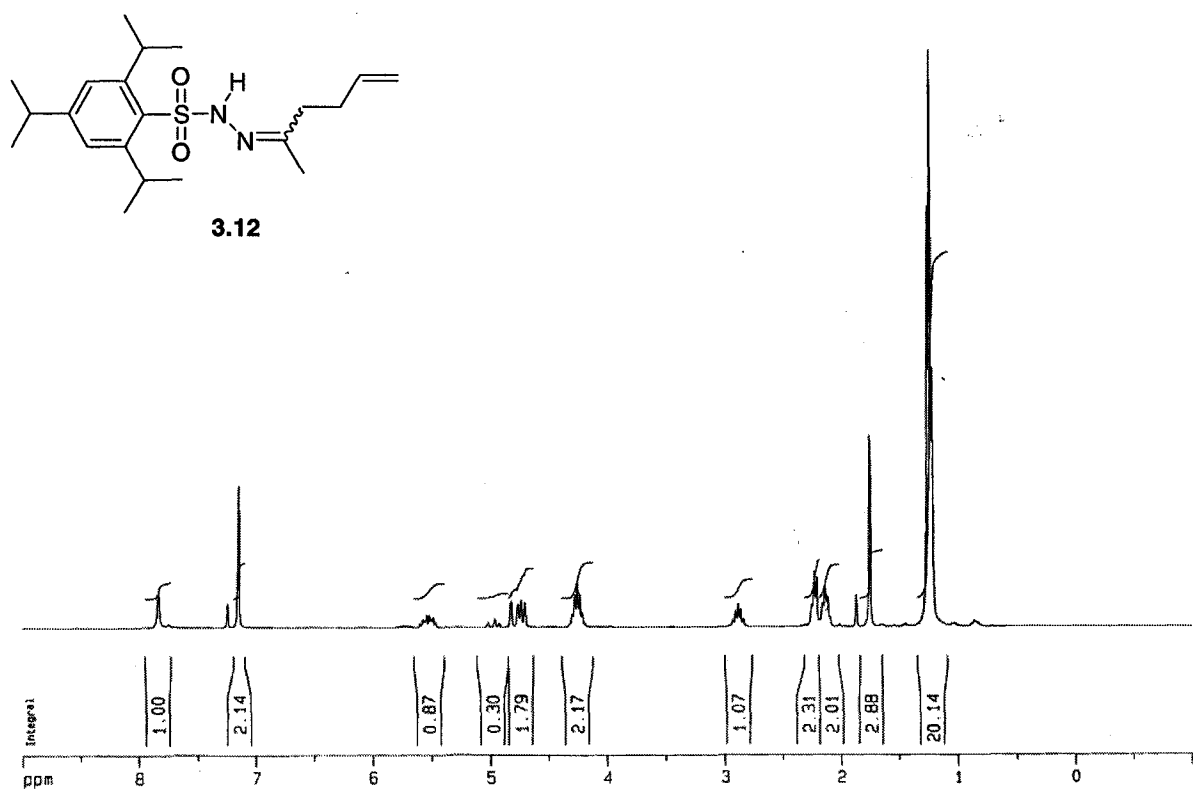
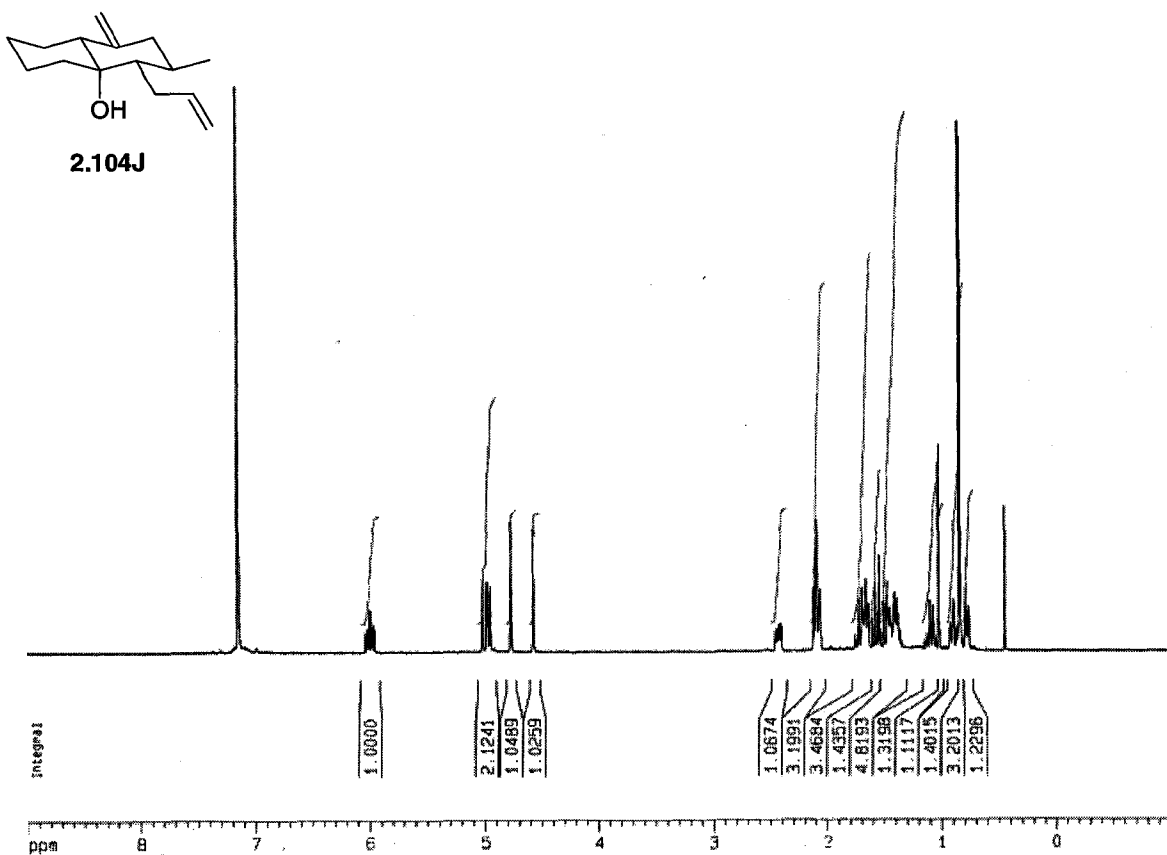


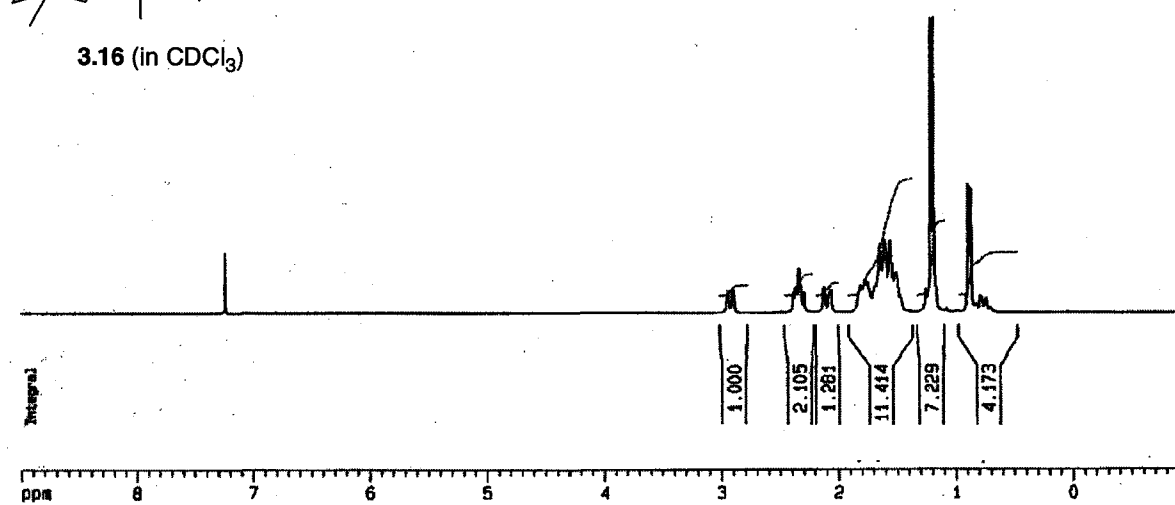
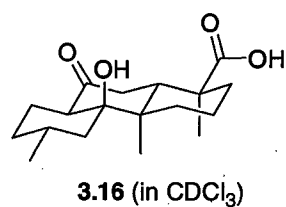
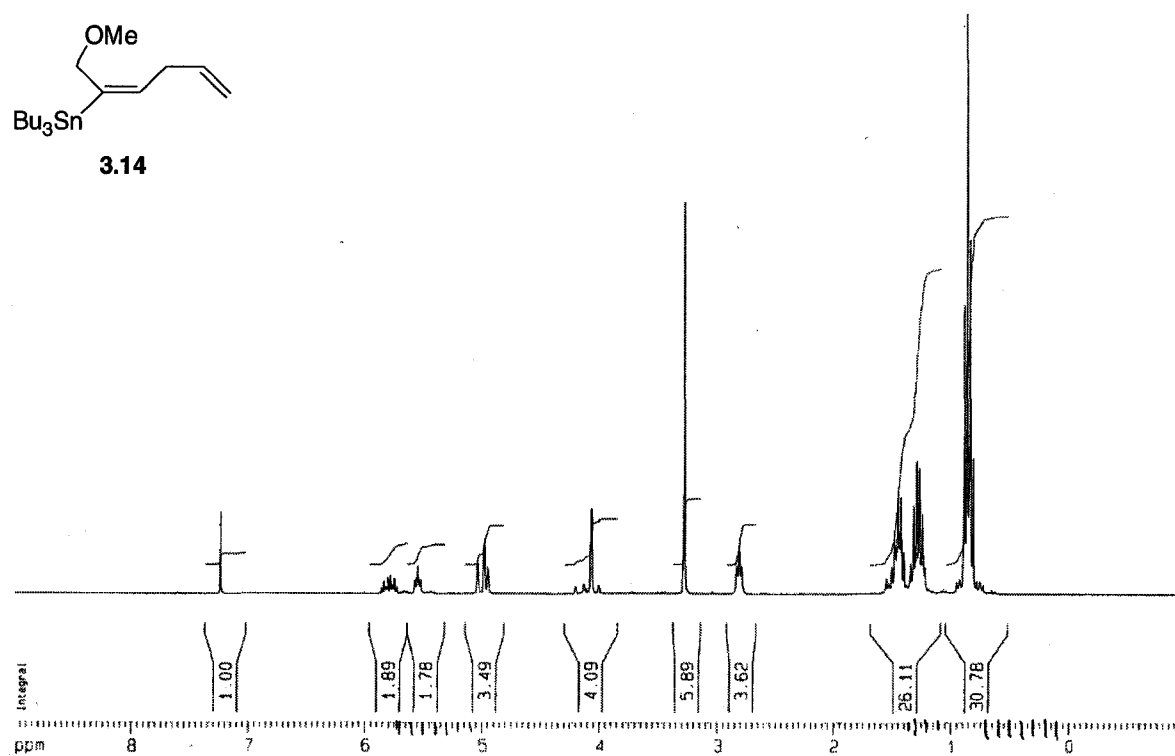
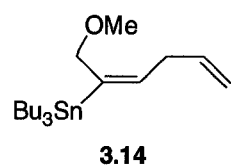
2.103

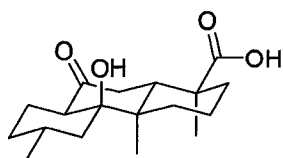


2.104A

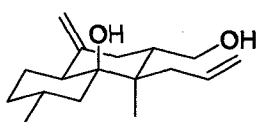
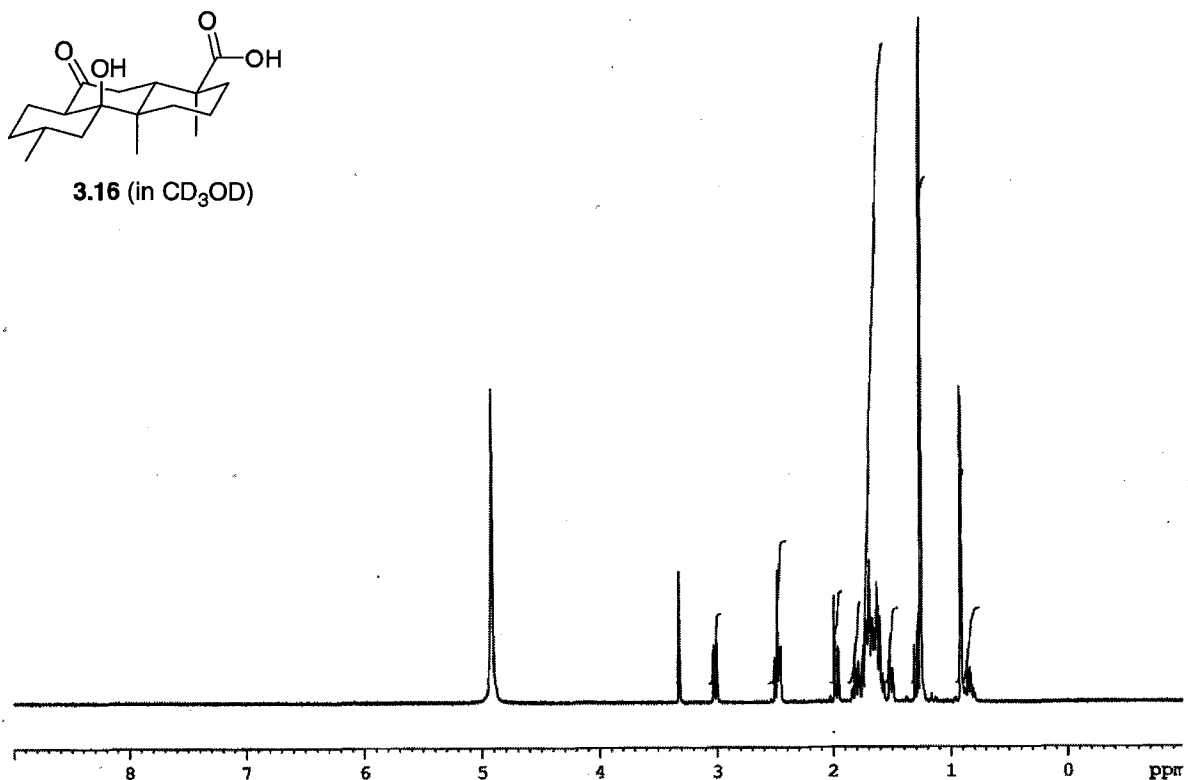




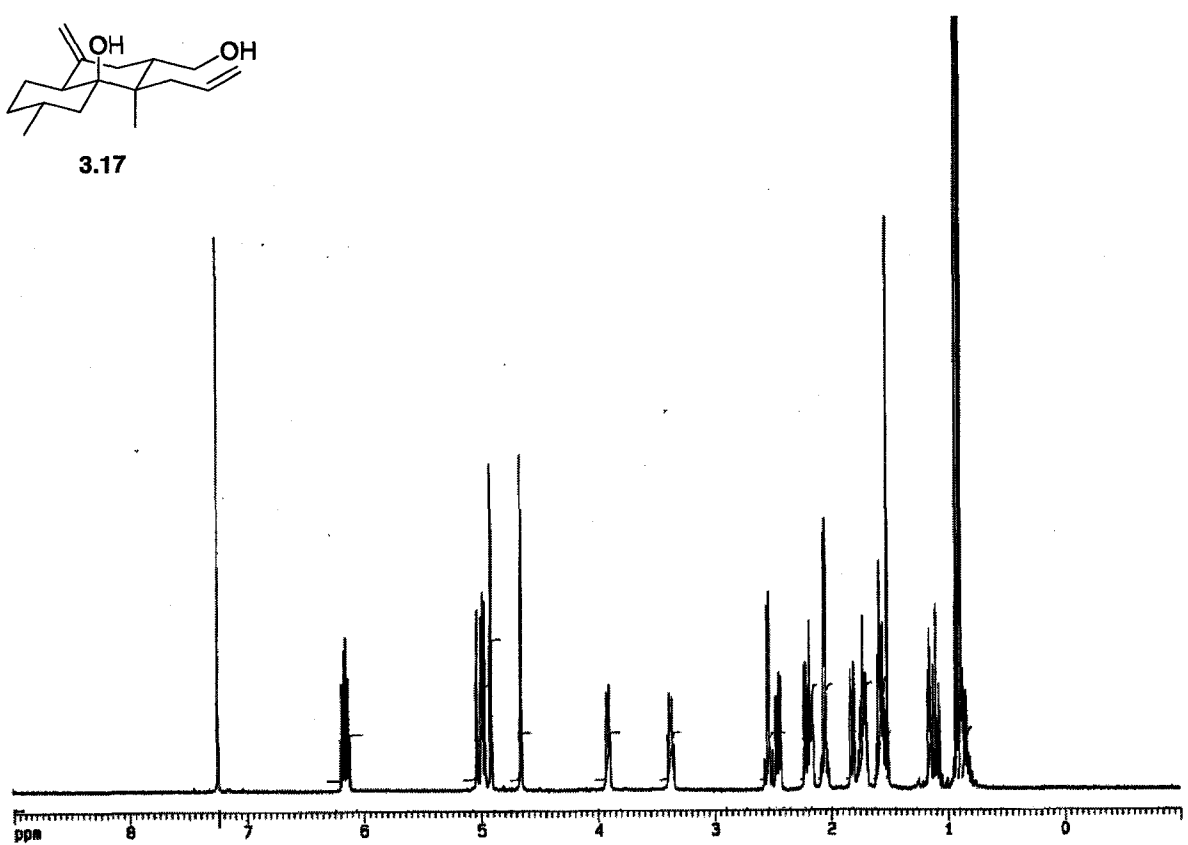


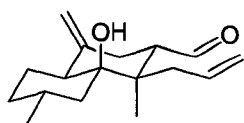


3.16 (in CD₃OD)

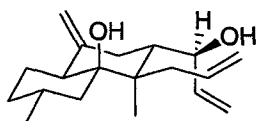
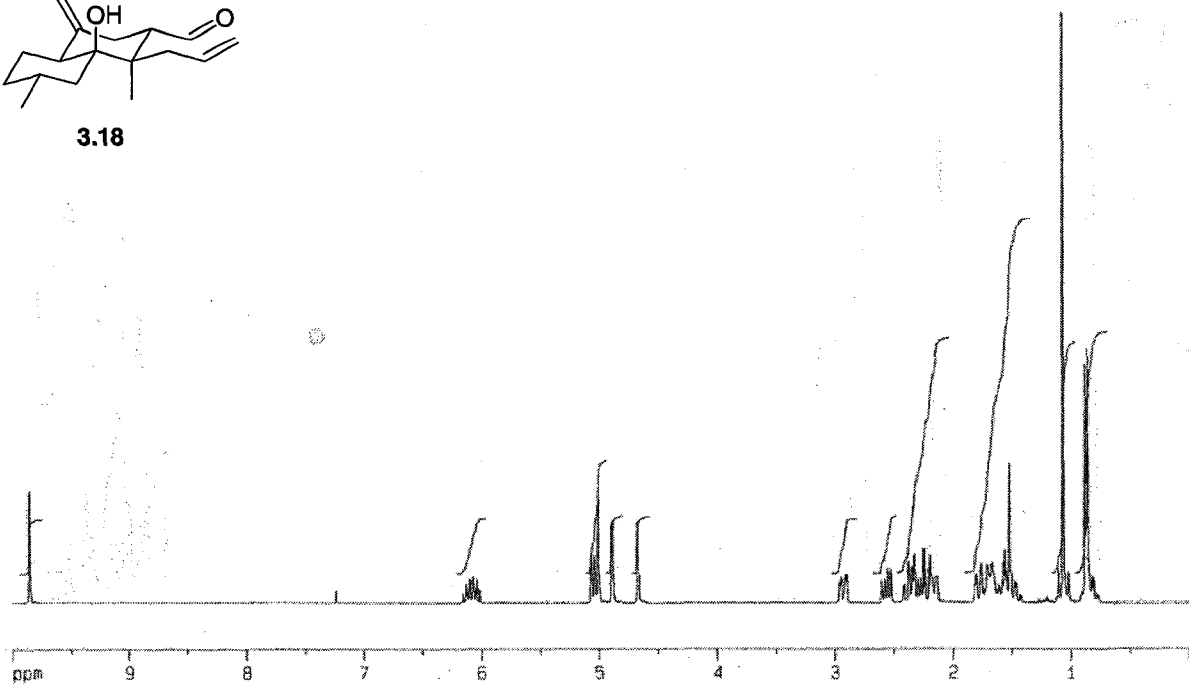


3.17

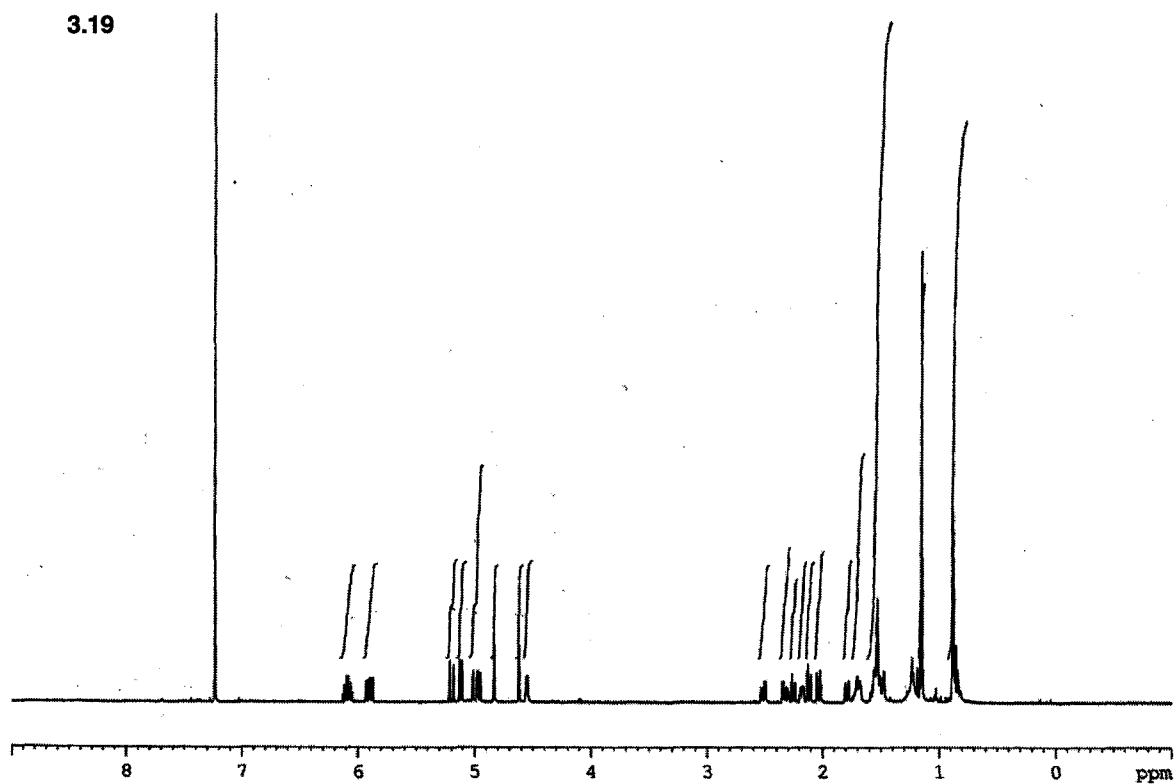


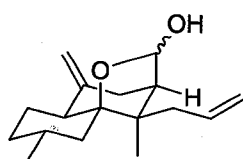


3.18

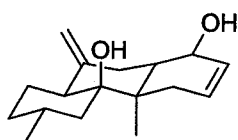
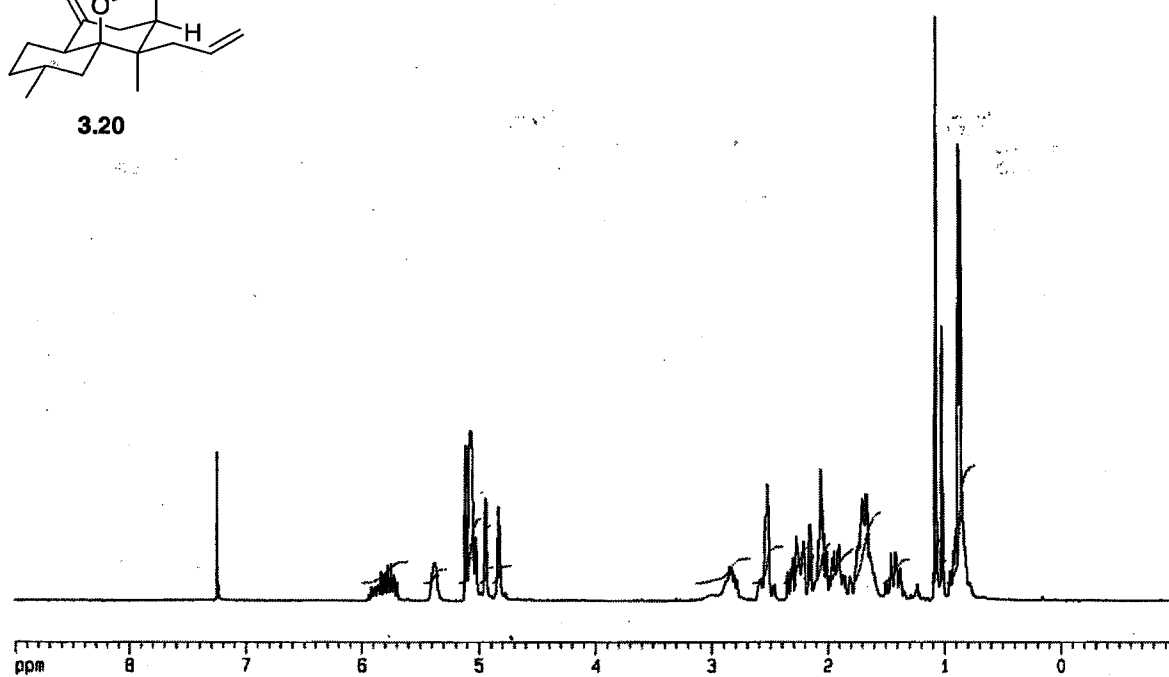


3.19

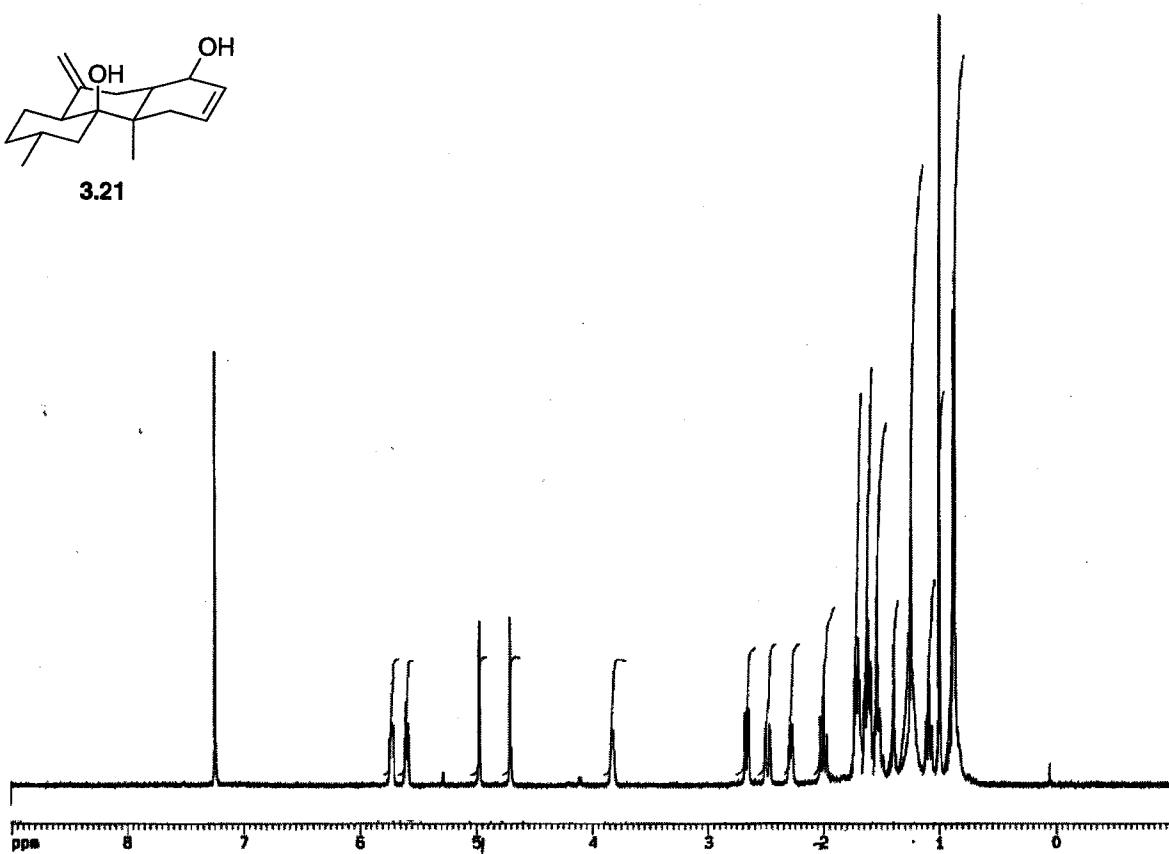


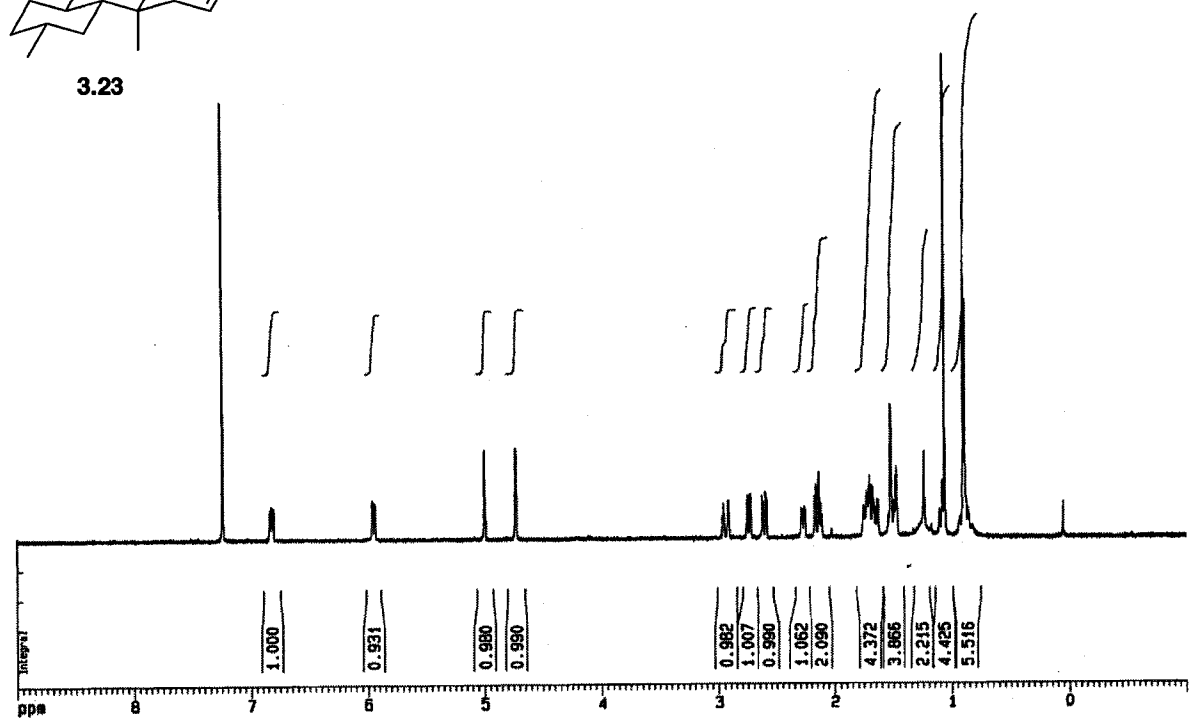
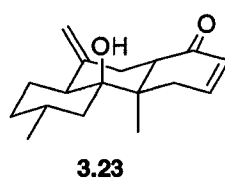
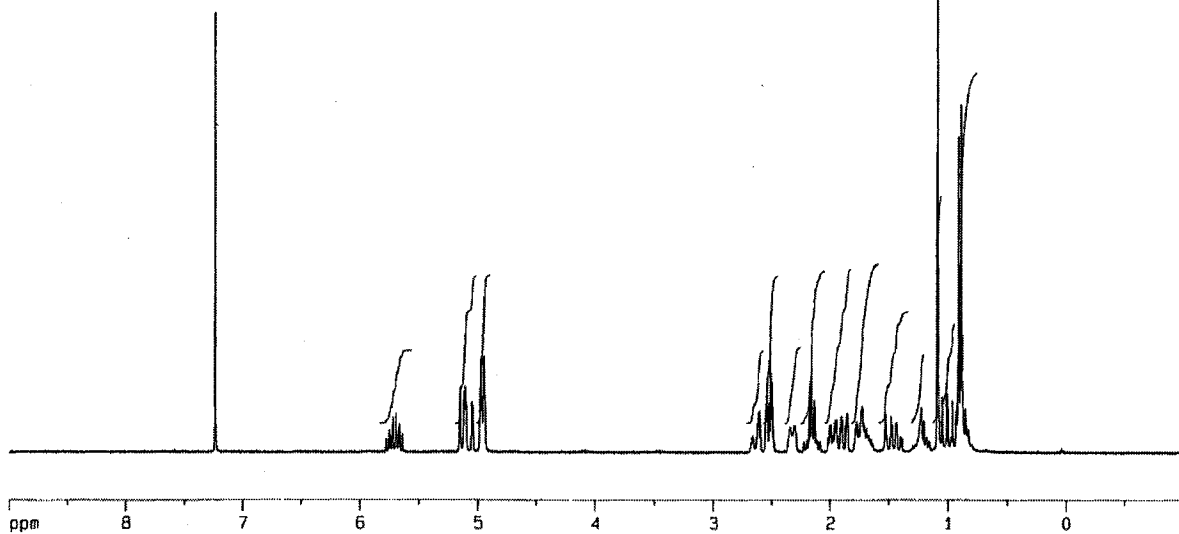
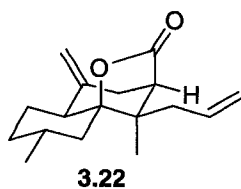


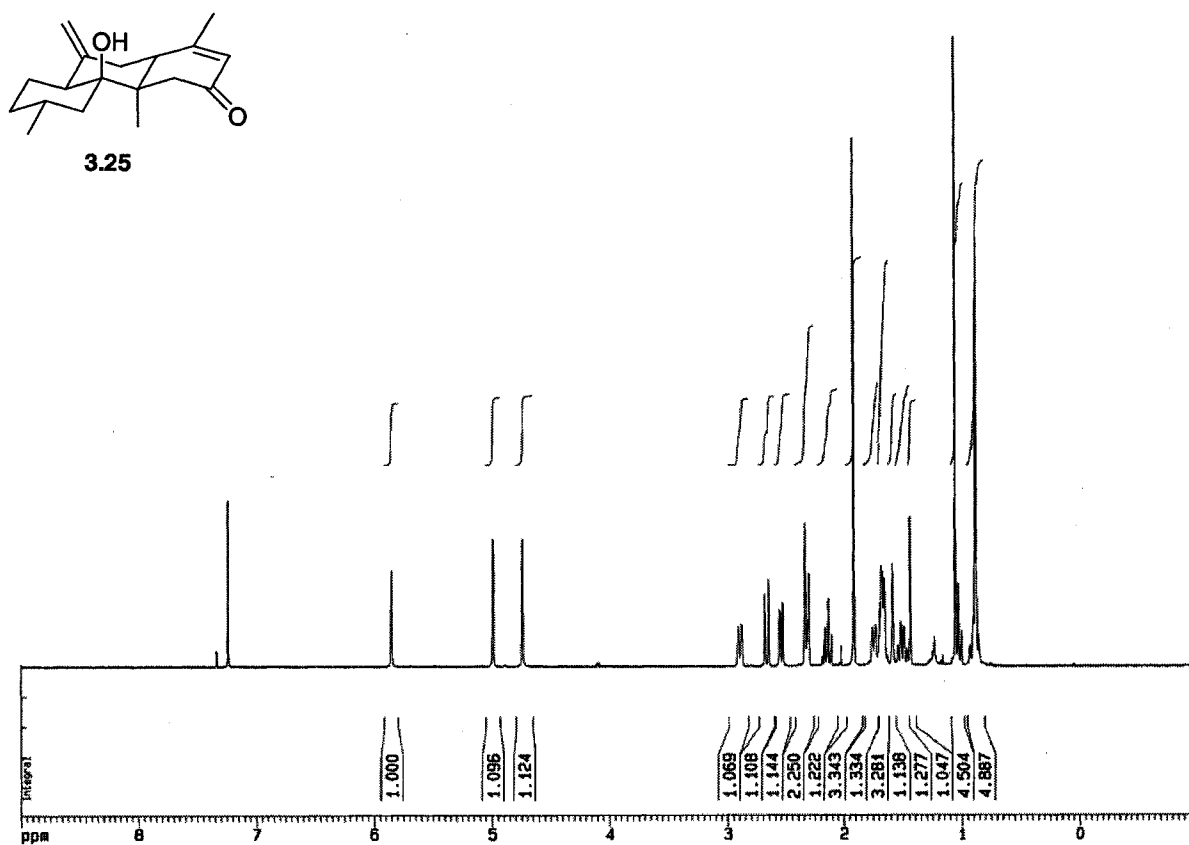
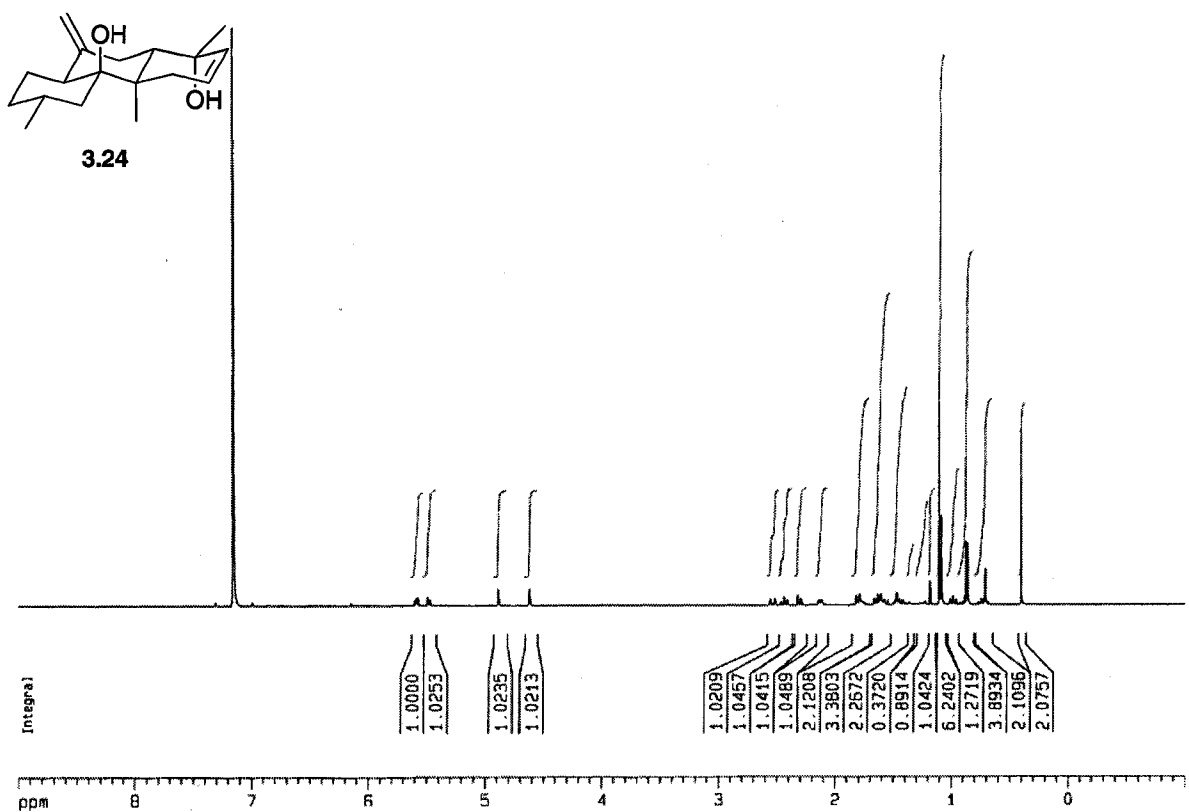
3.20

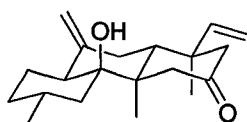


3.21

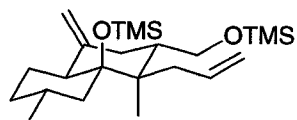
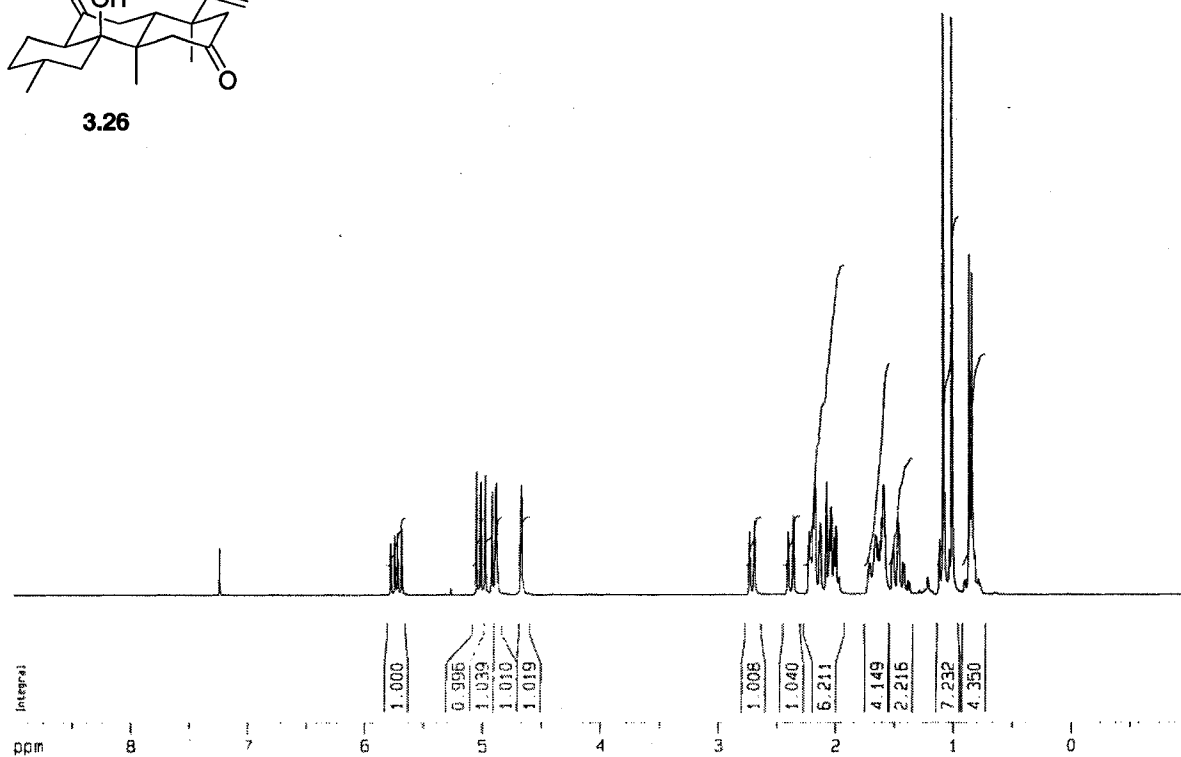




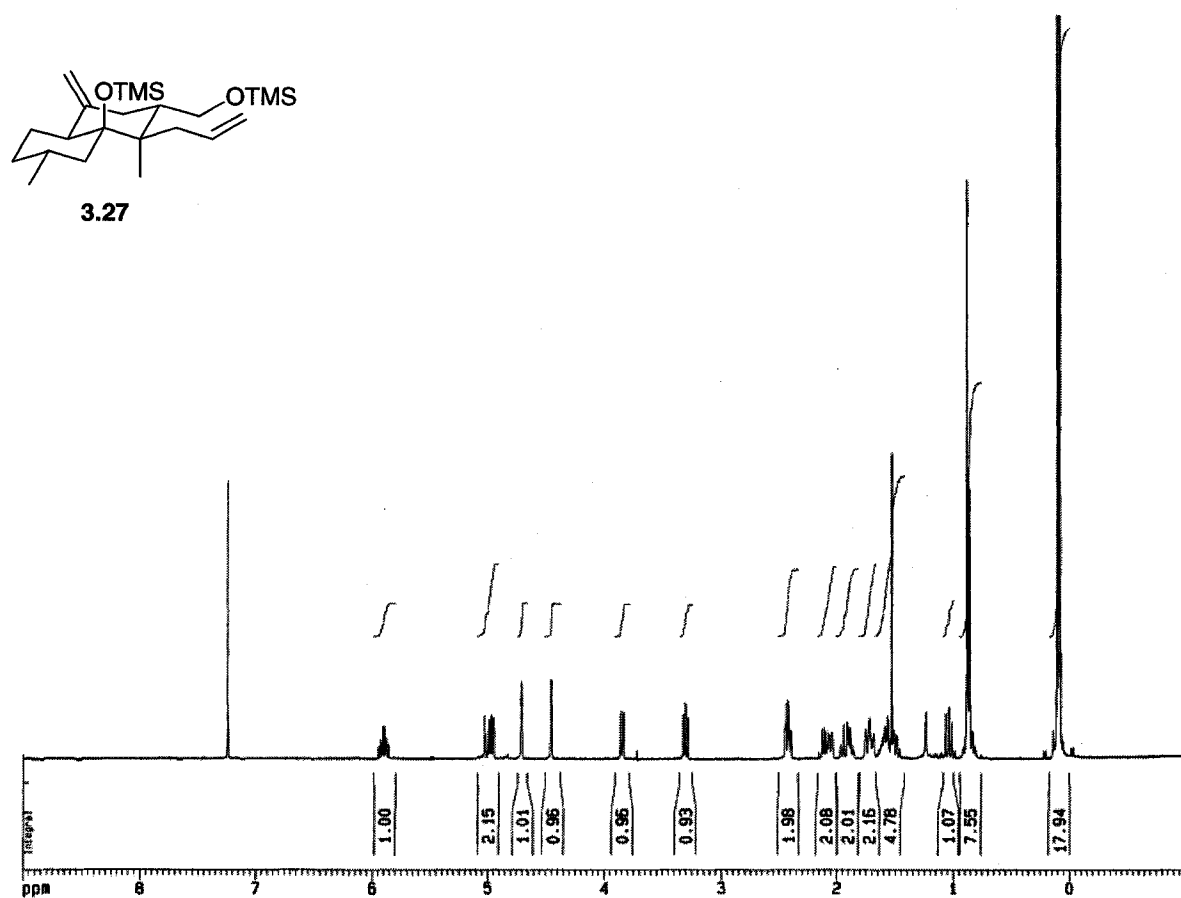


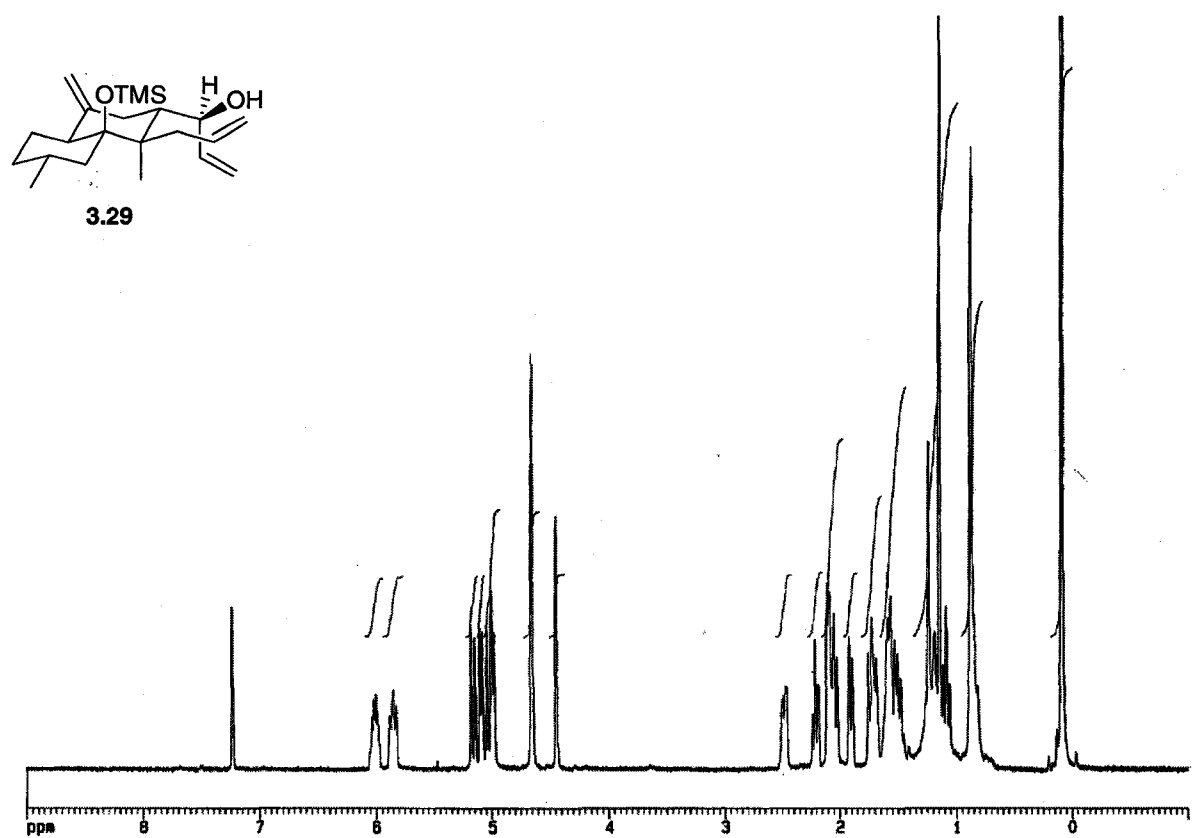


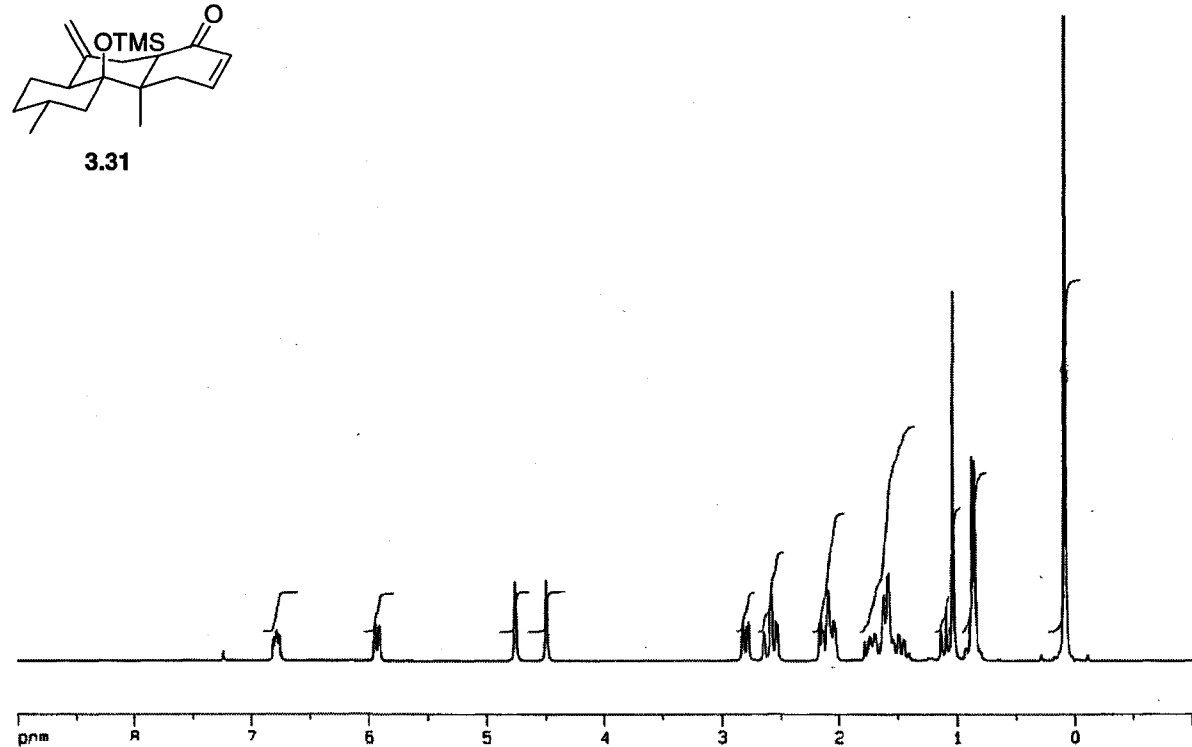
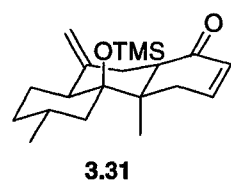
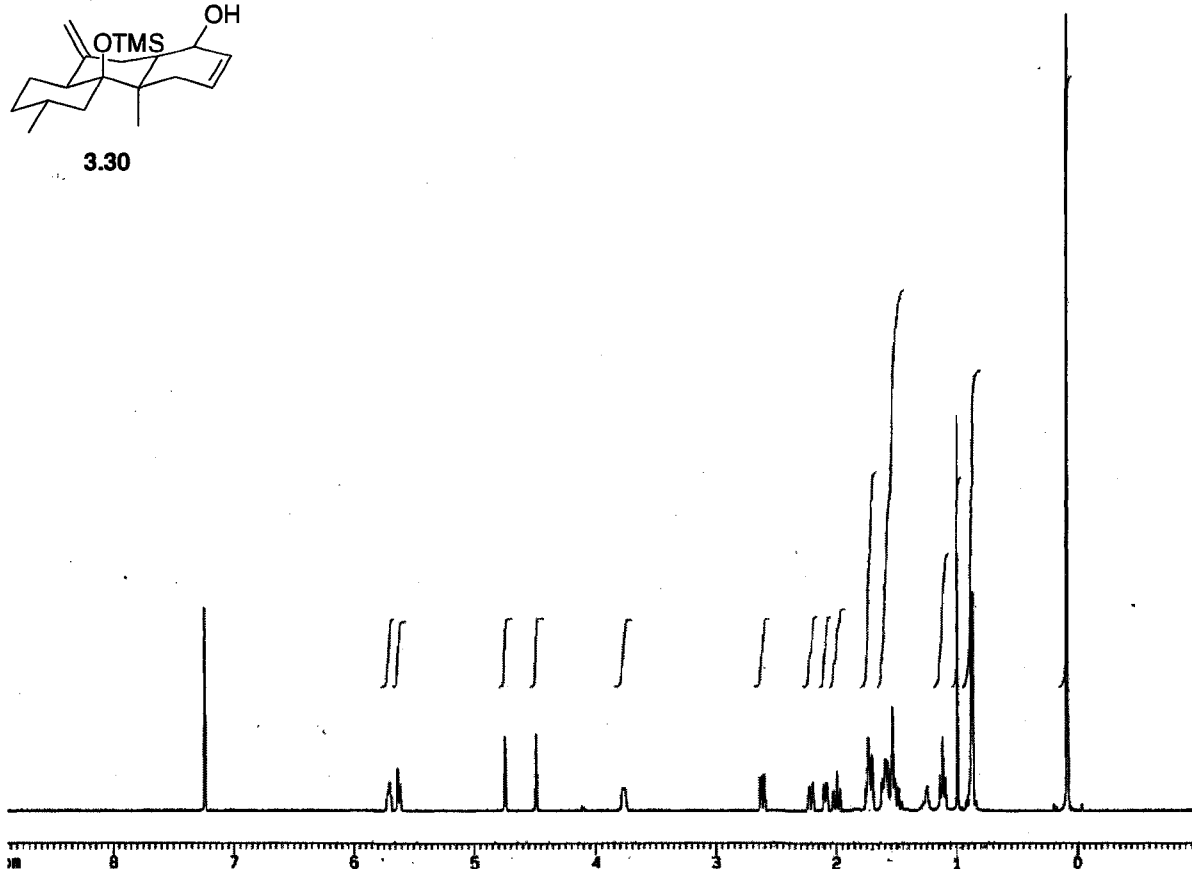
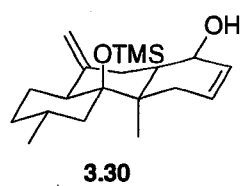
3.26

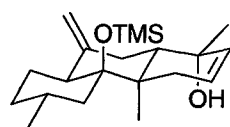


3.27

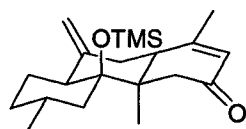
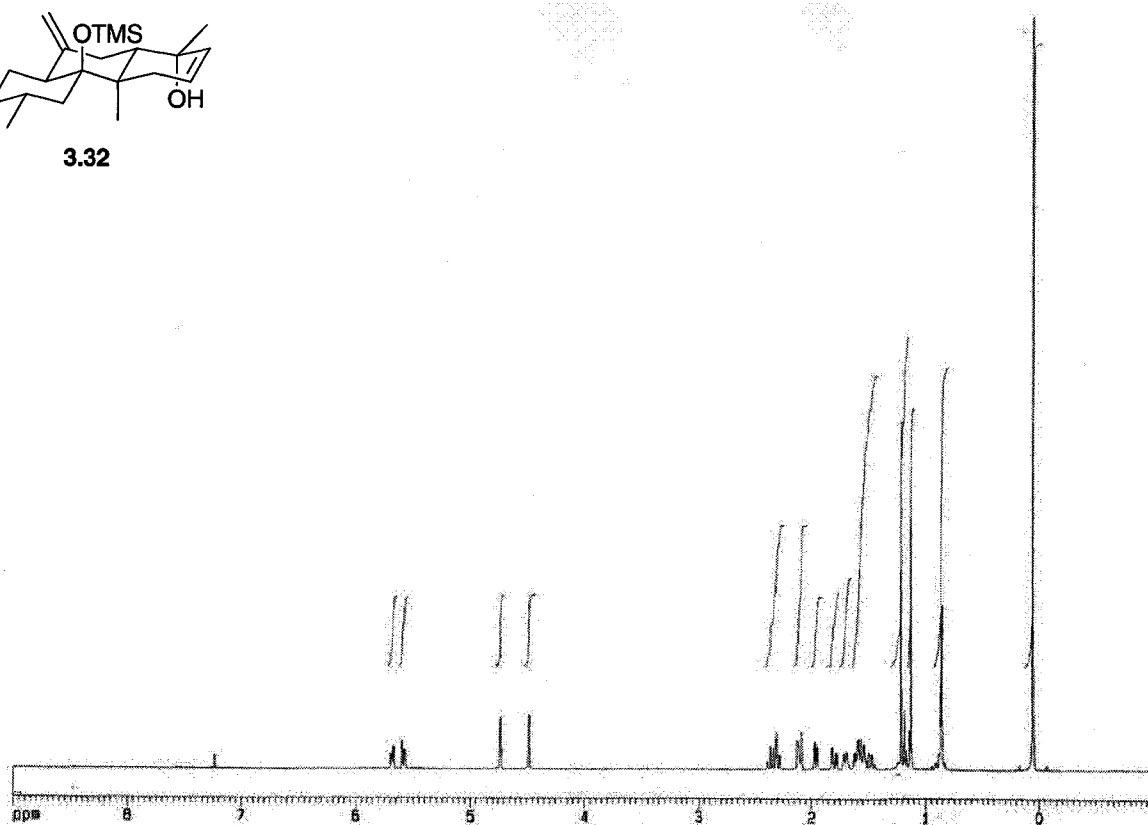




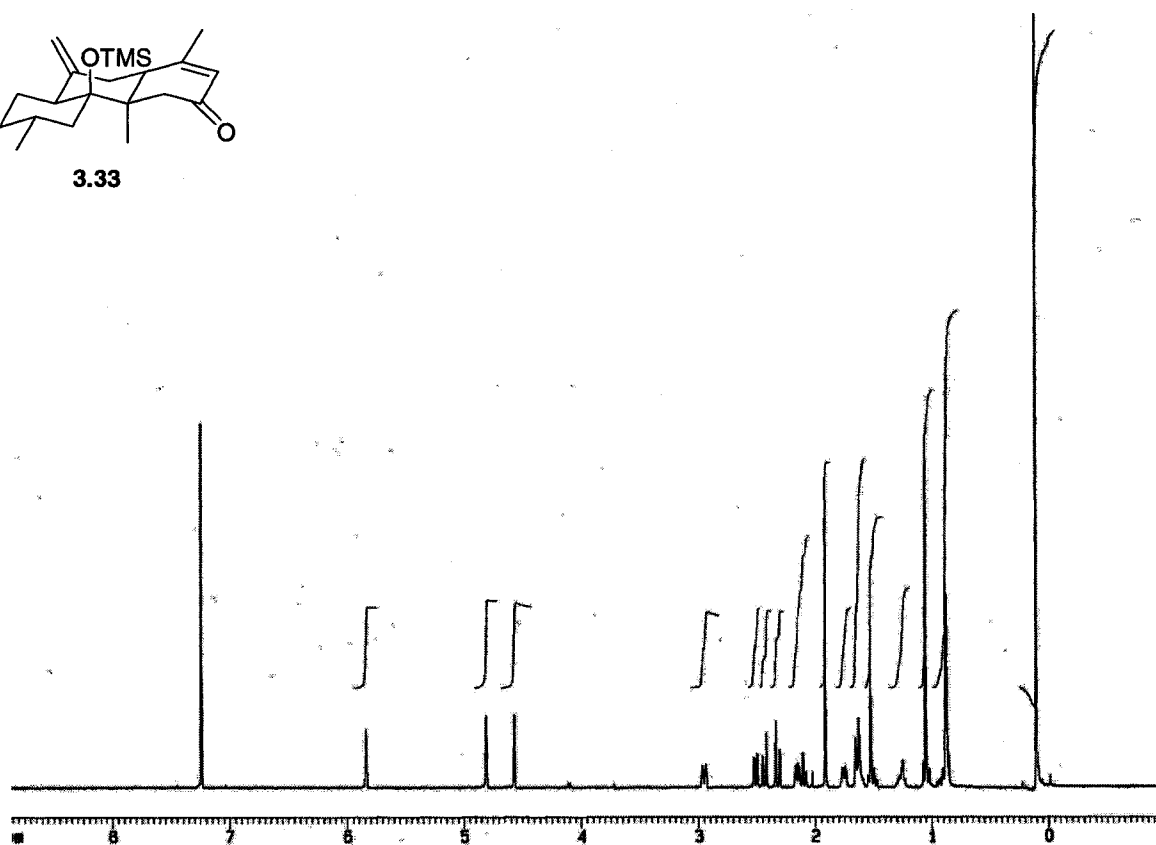


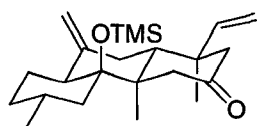


3.32

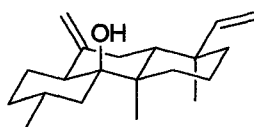
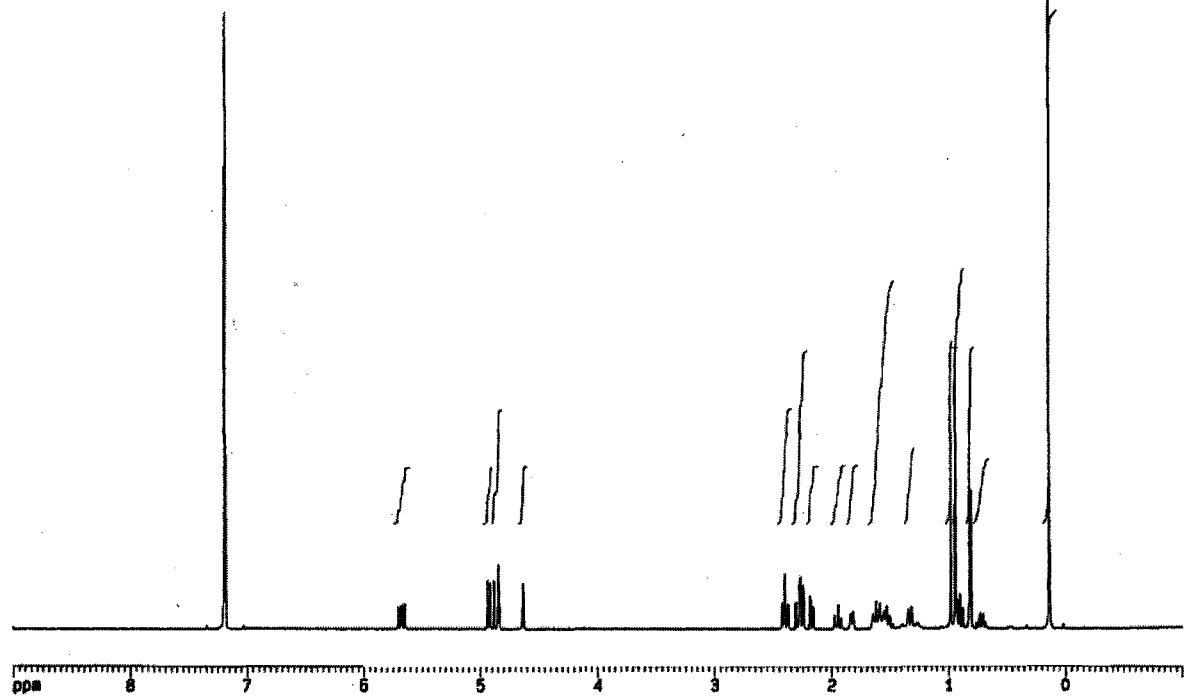


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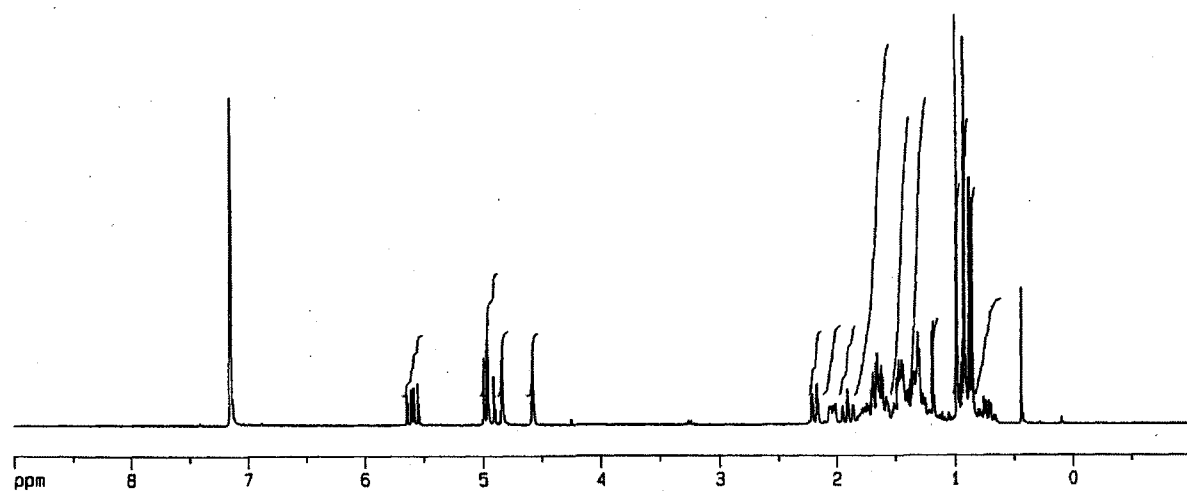


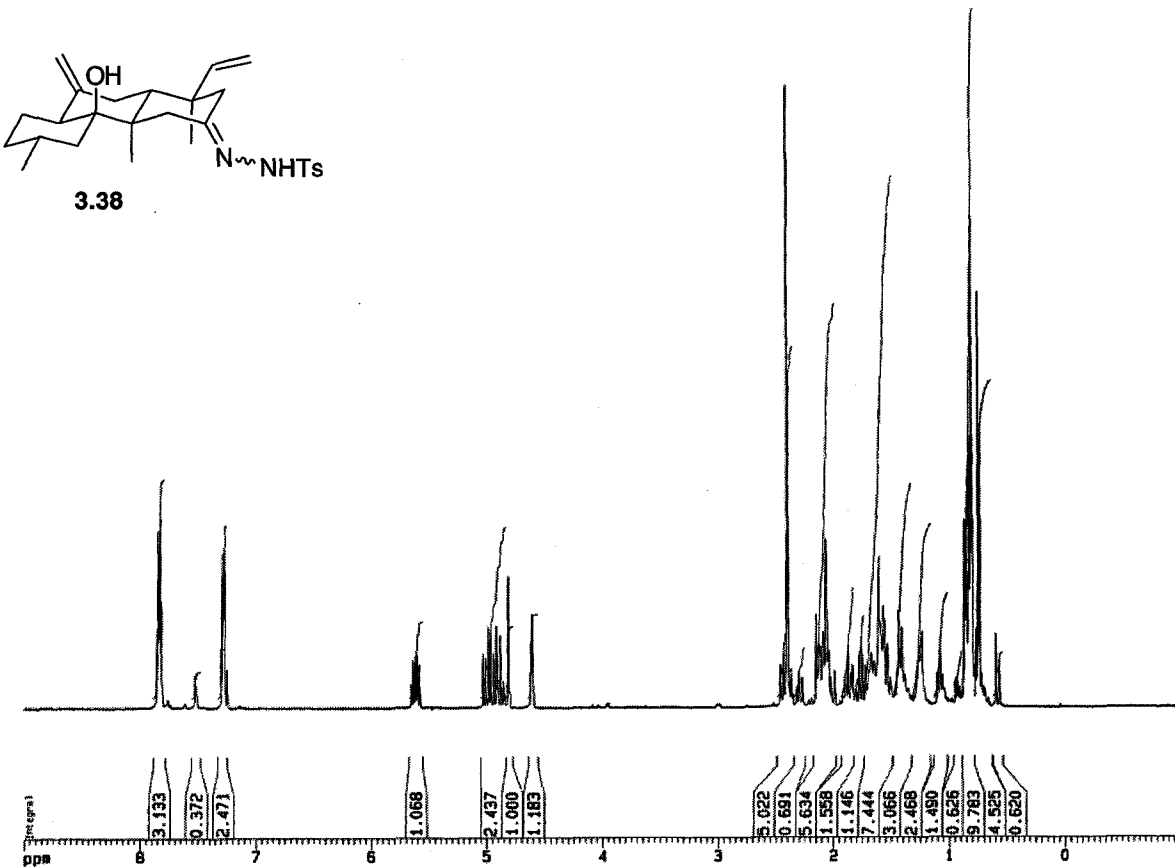


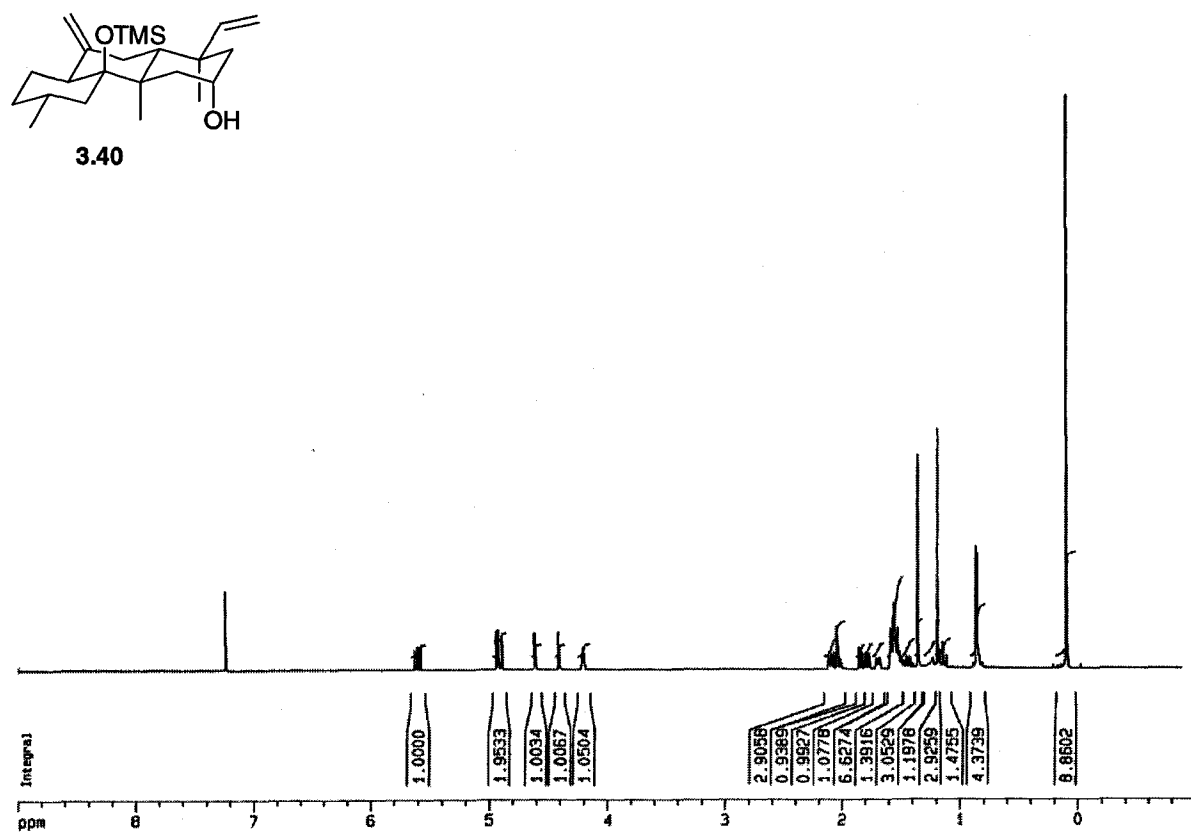
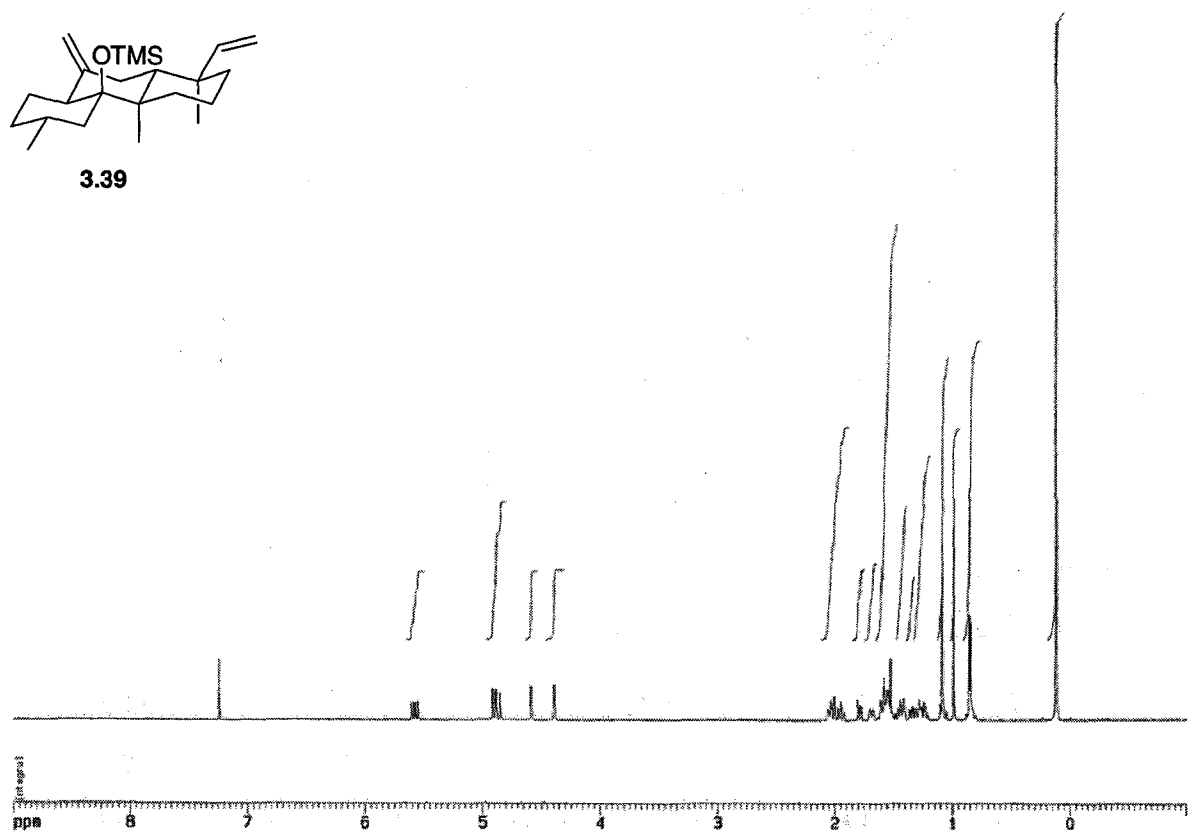
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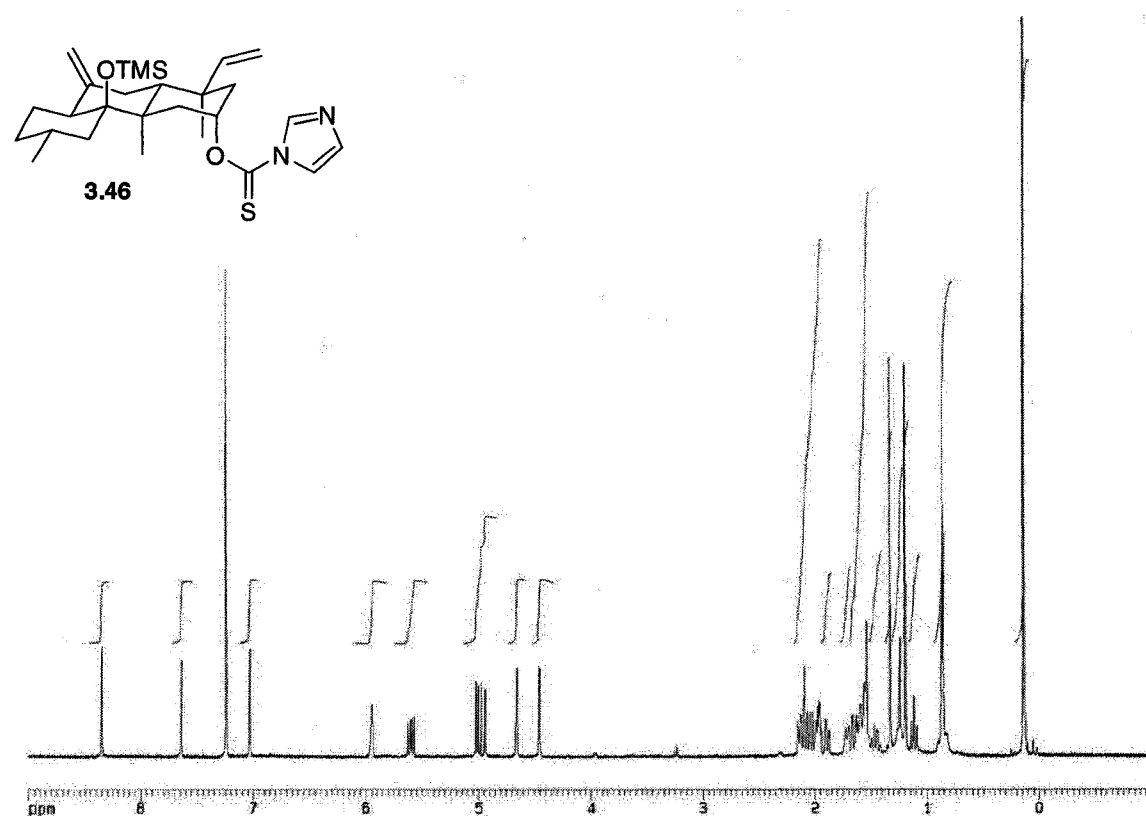
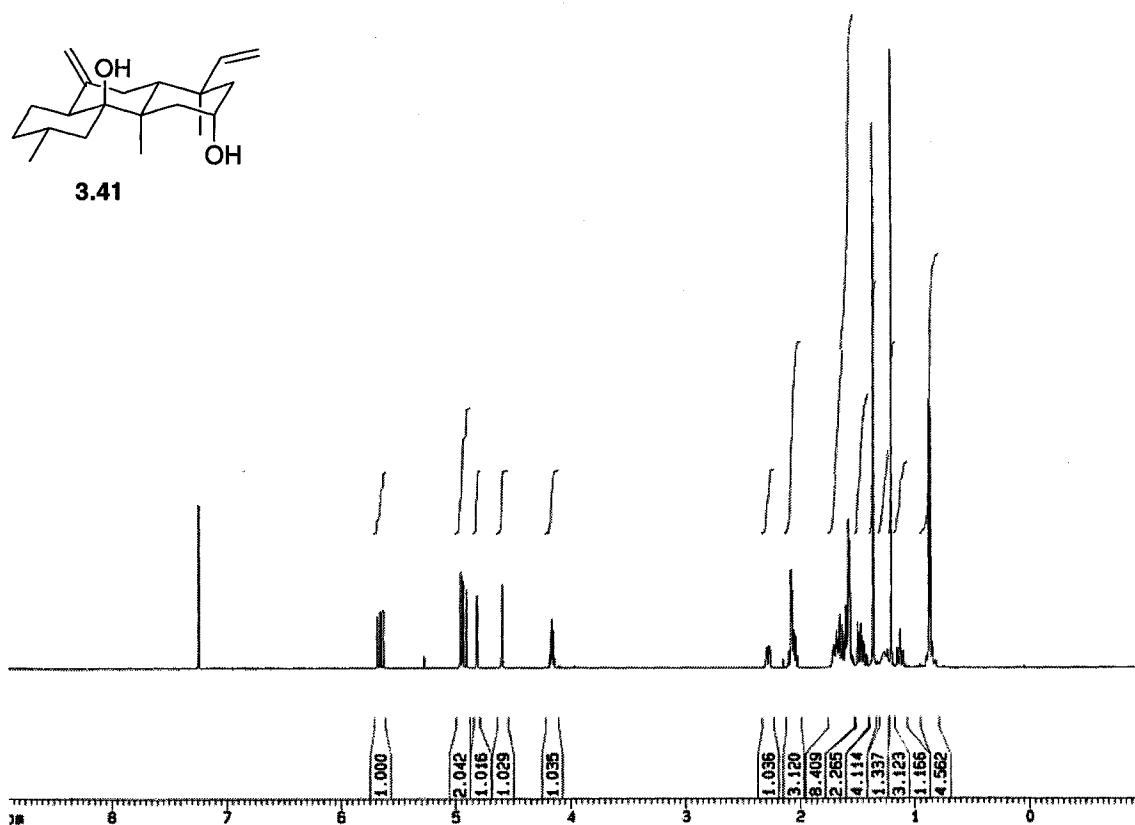


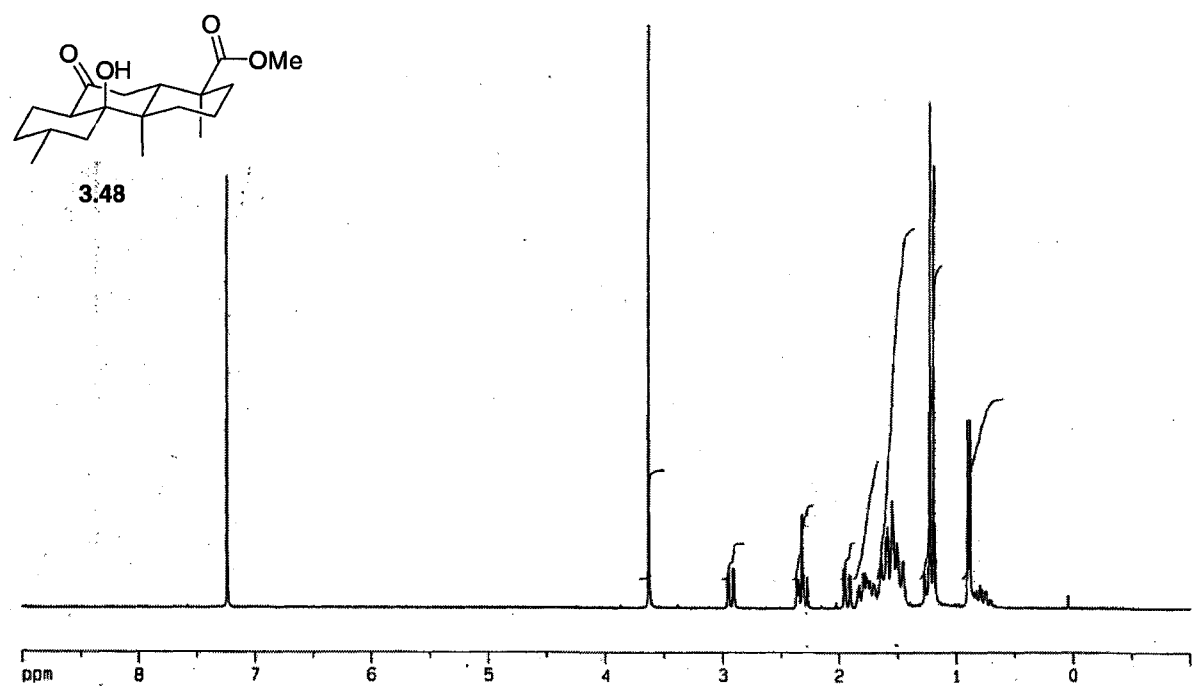
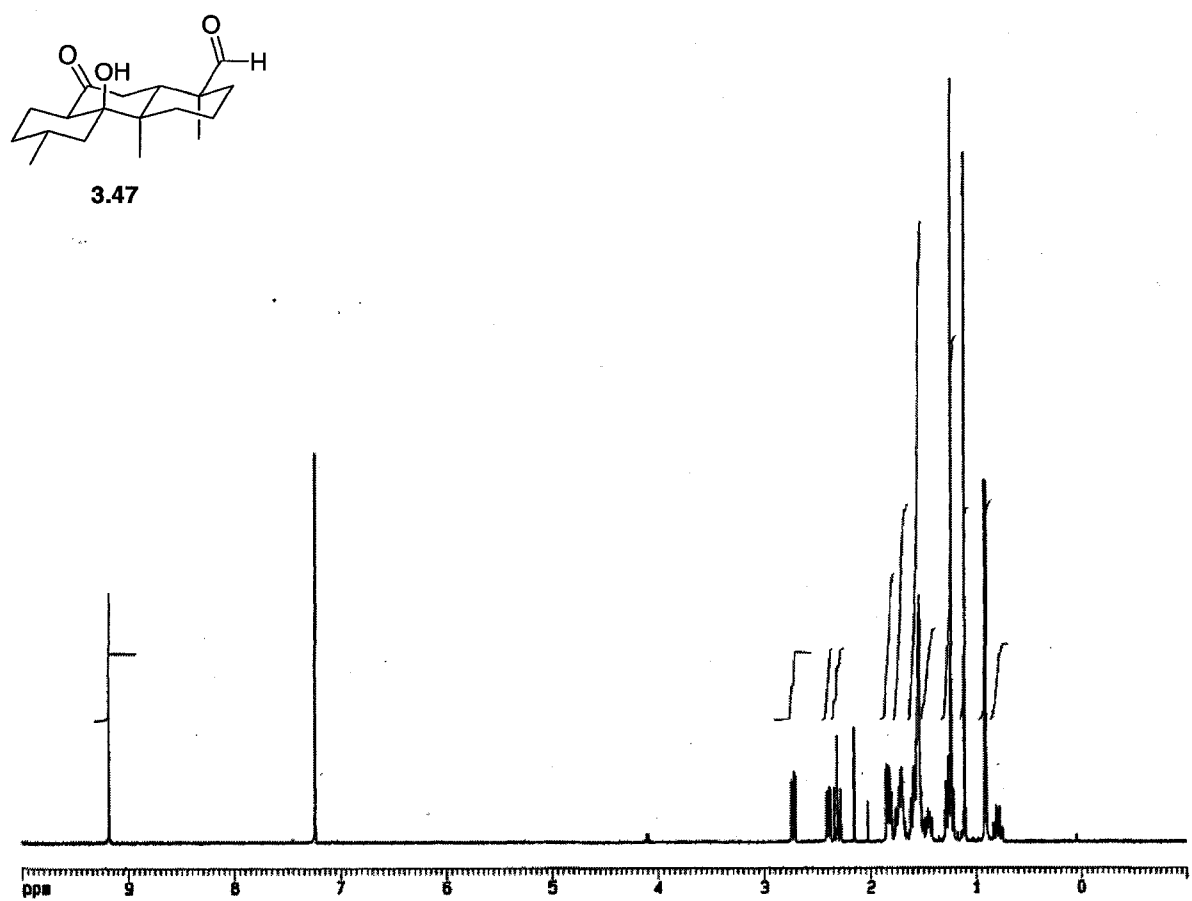
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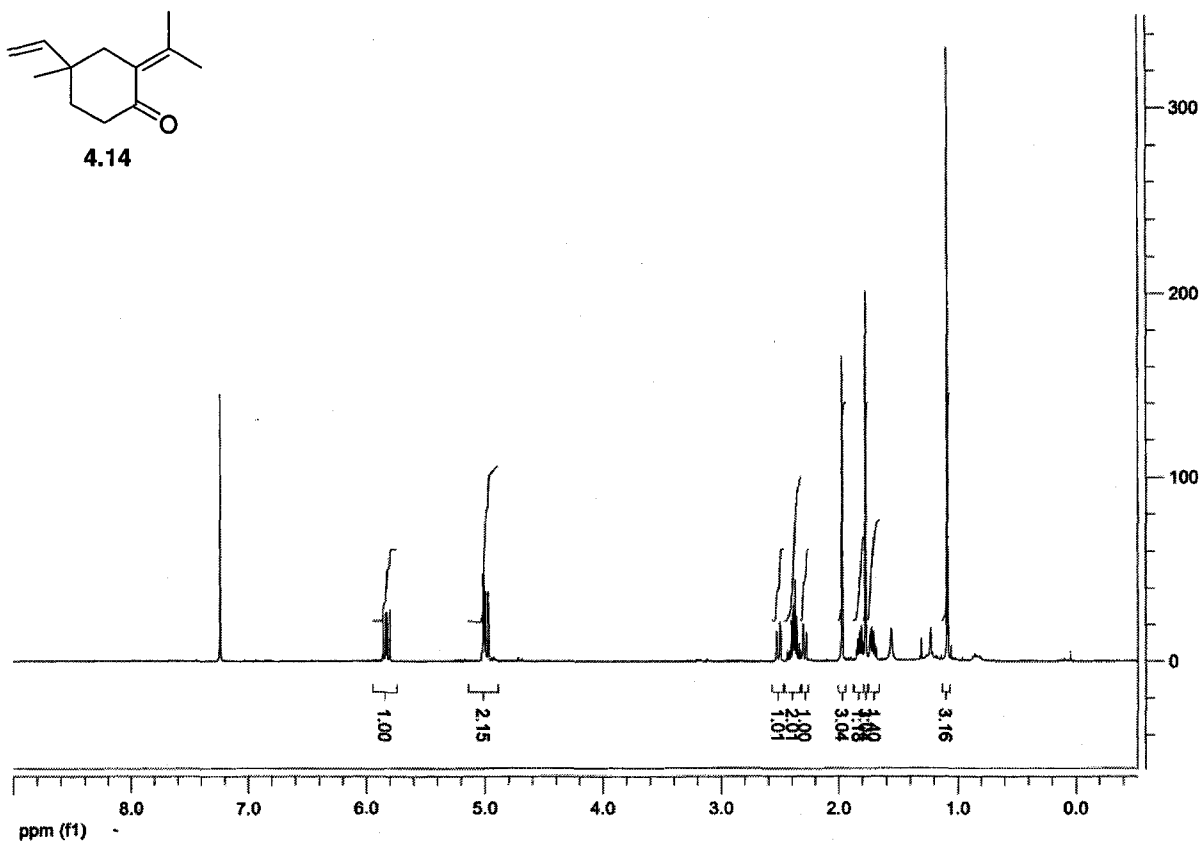
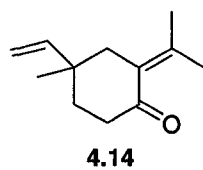
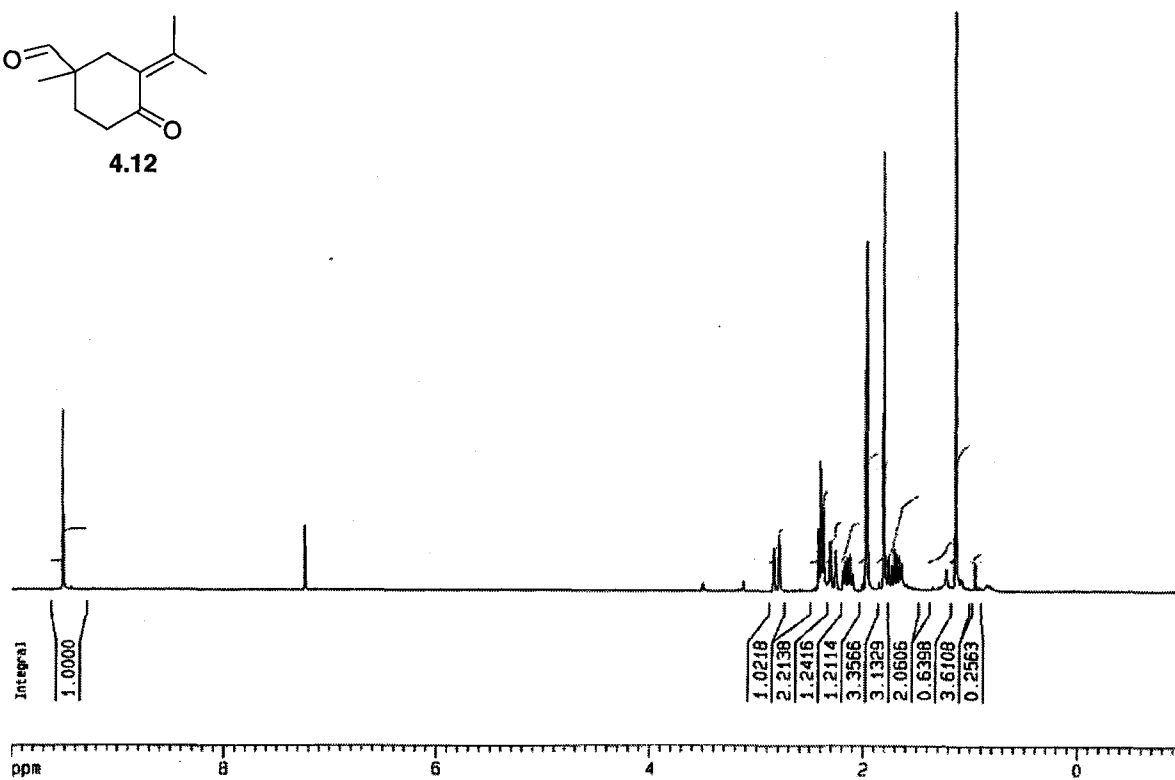
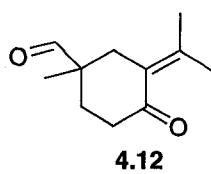


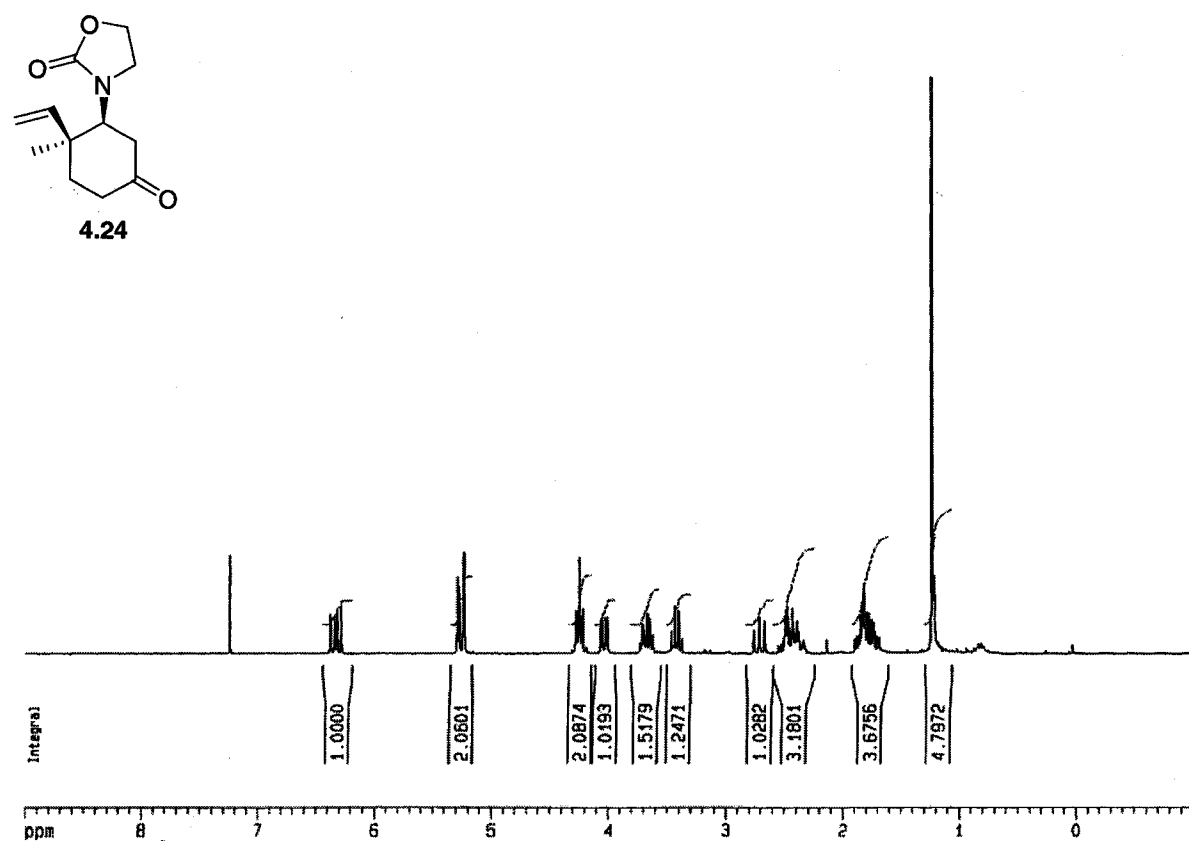
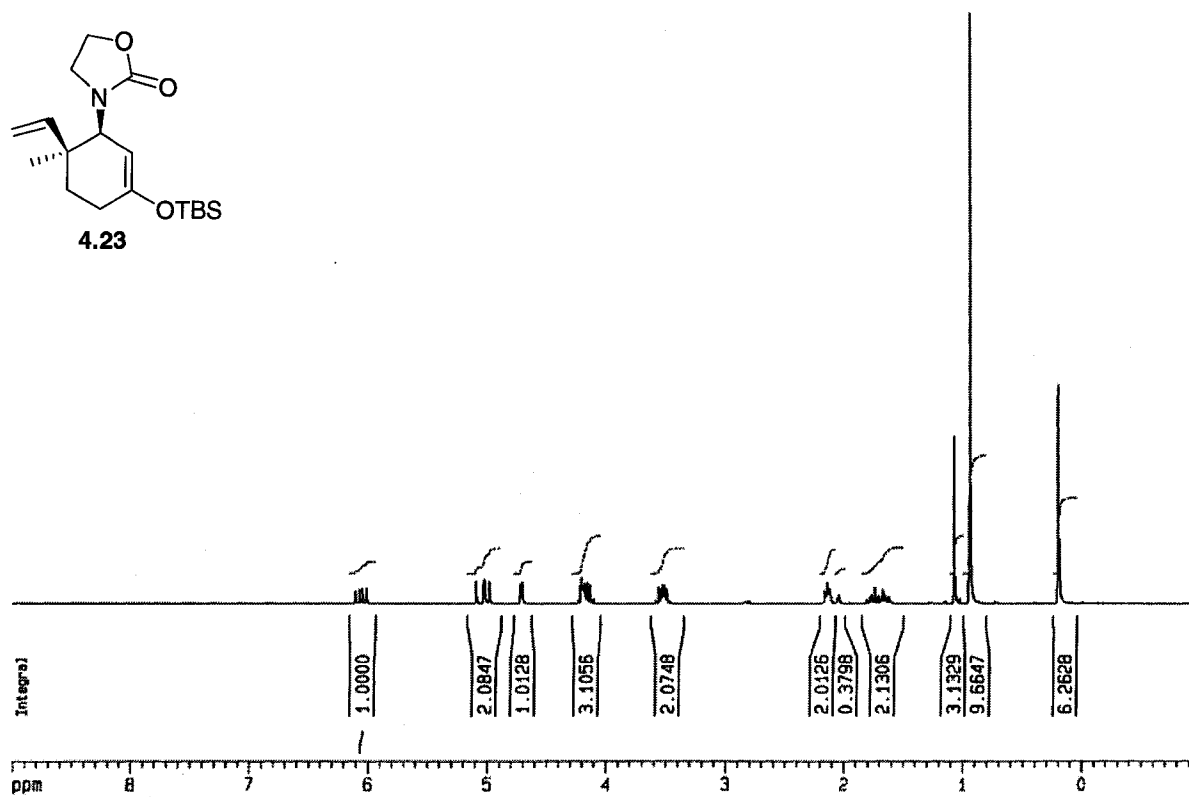


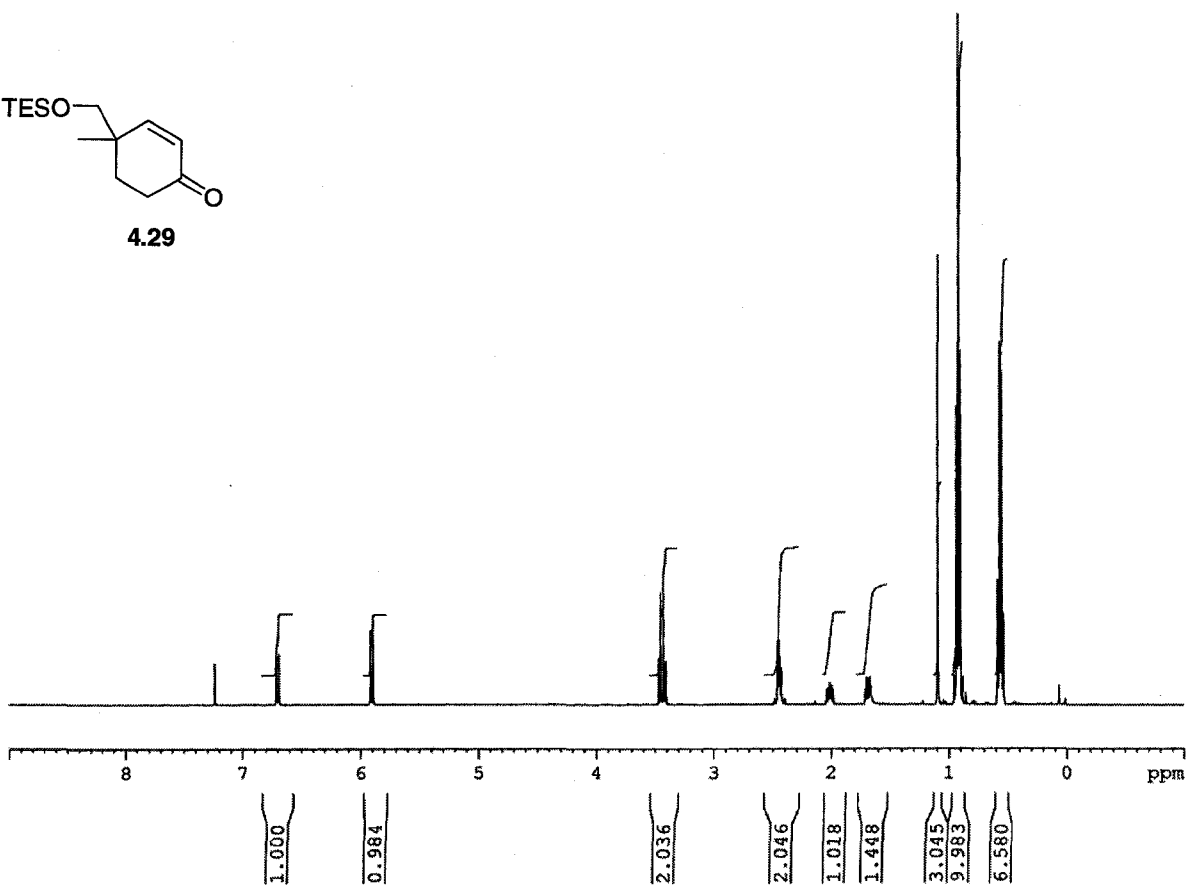
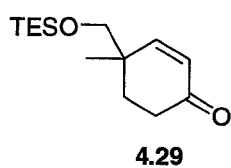
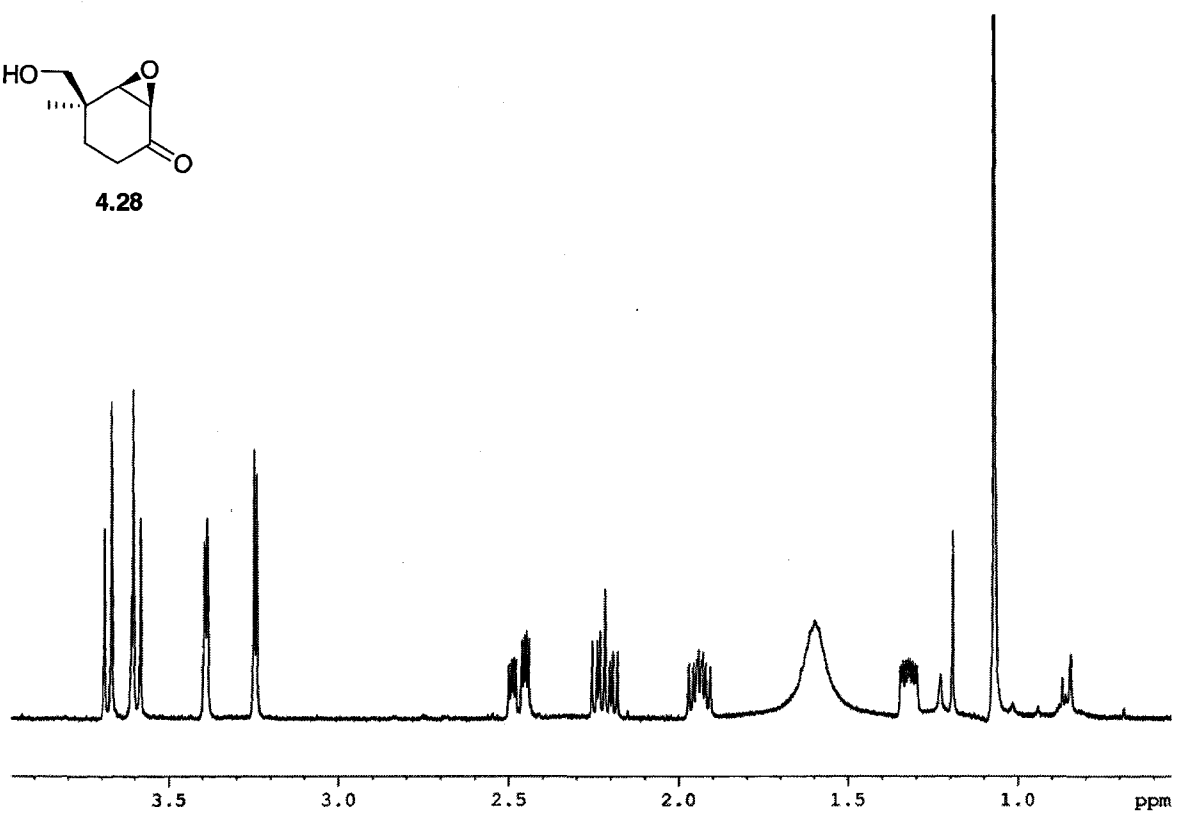
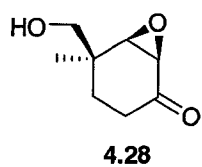




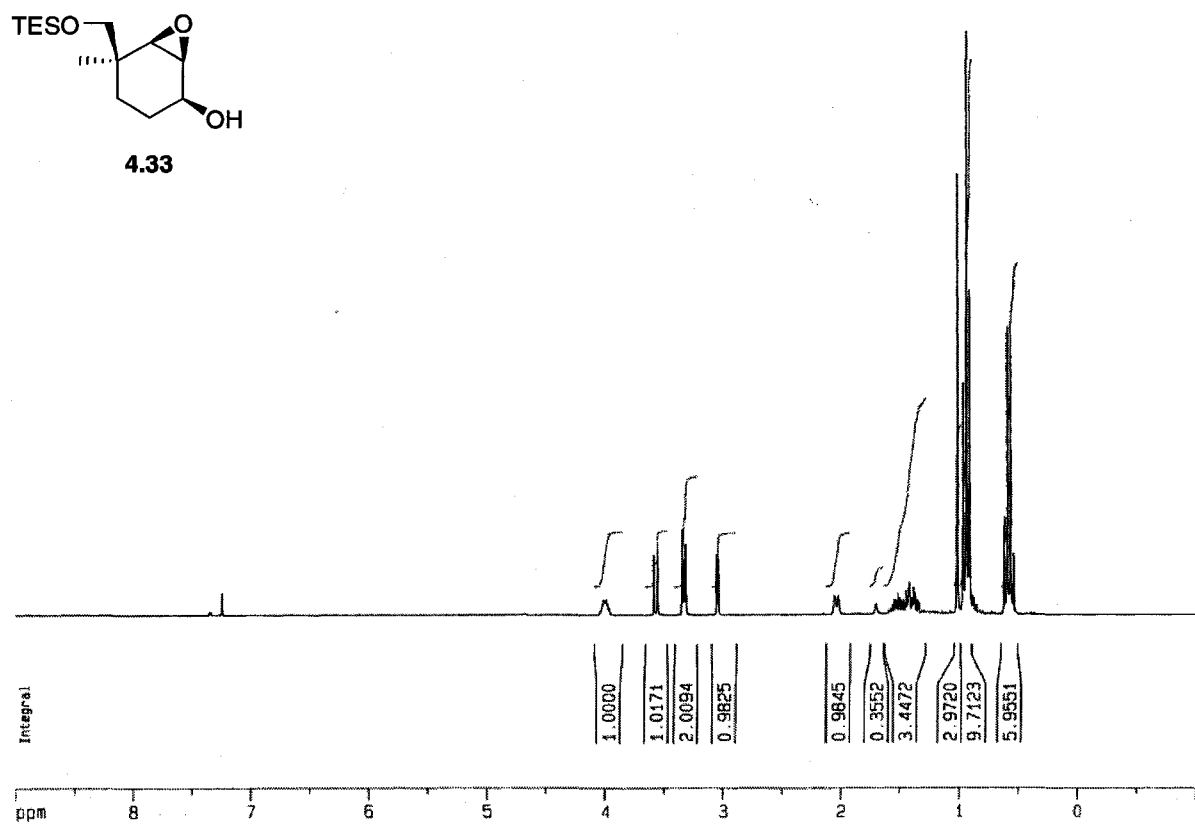
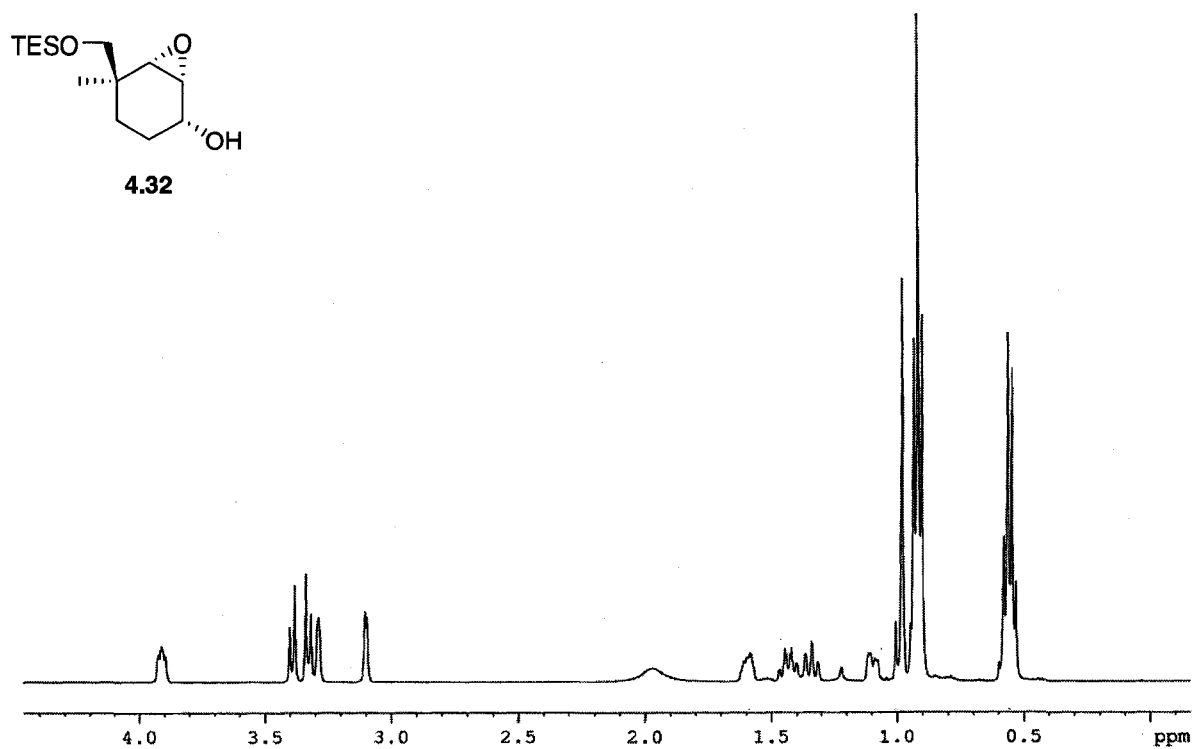


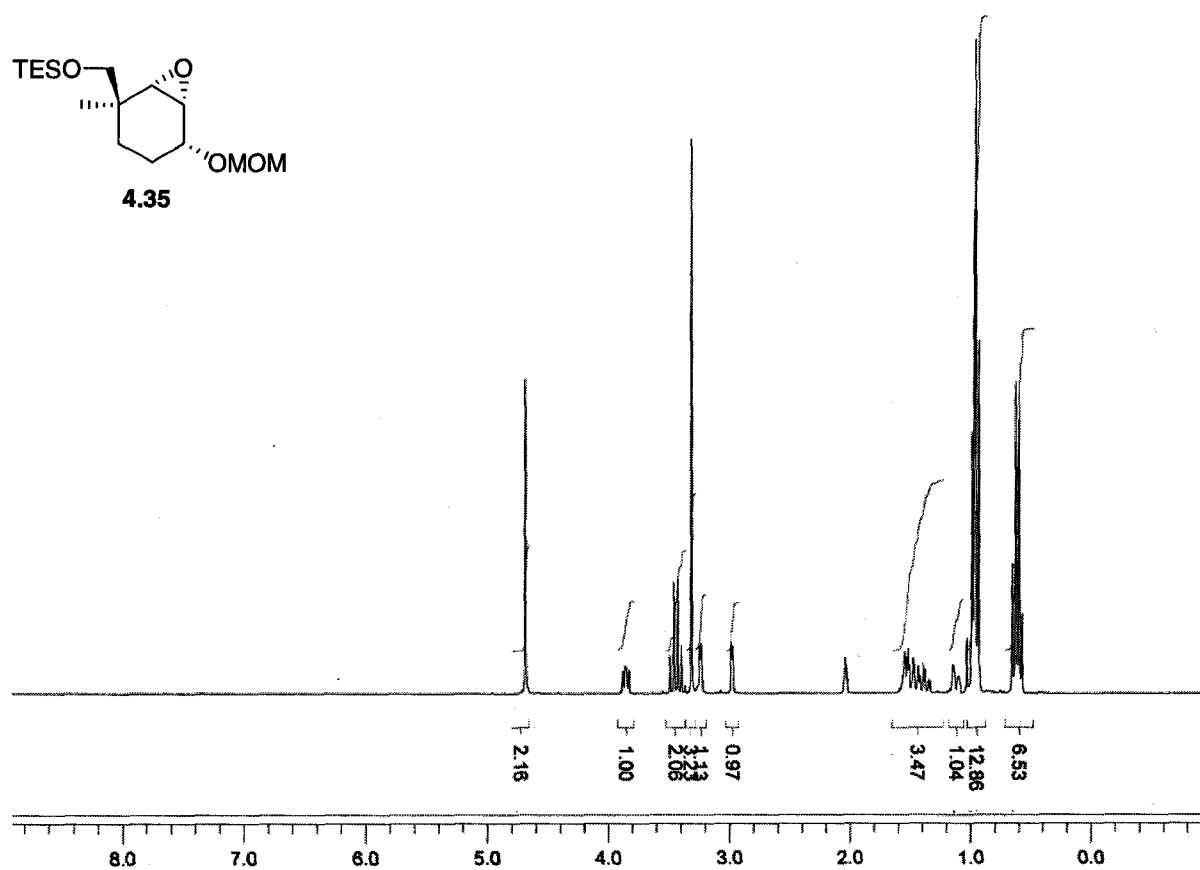
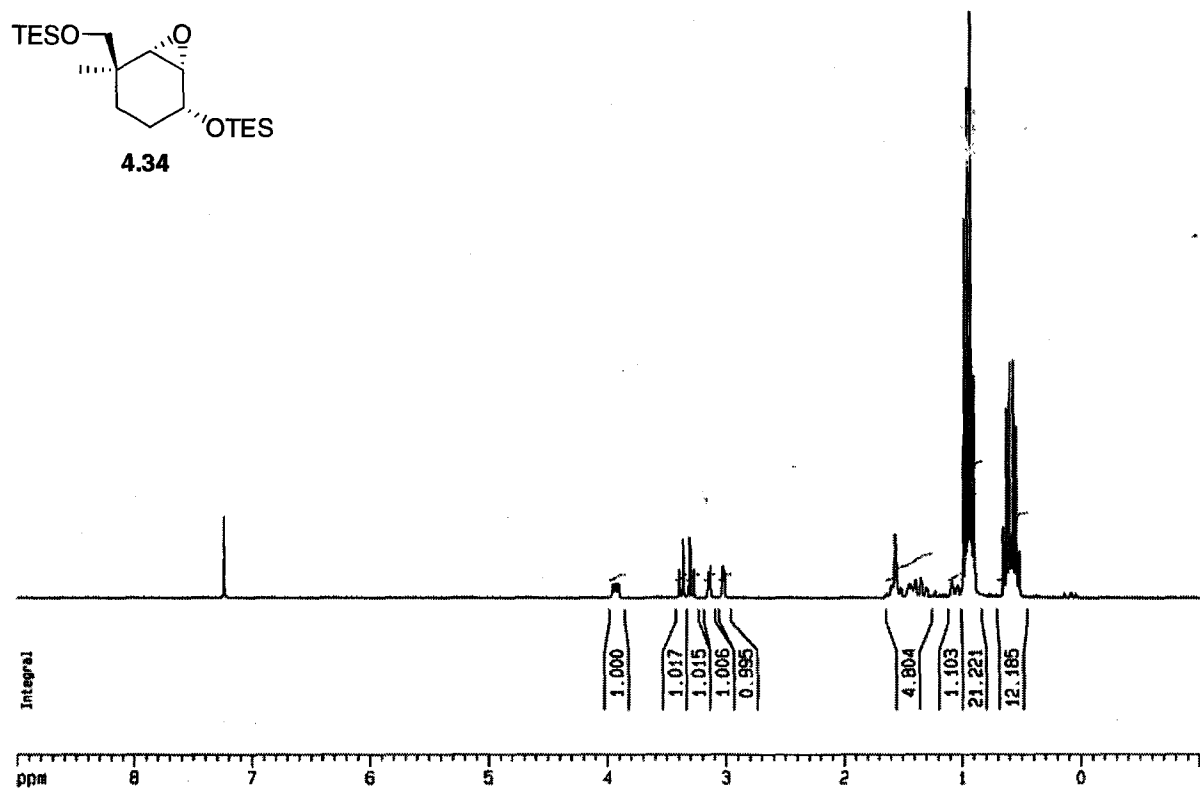


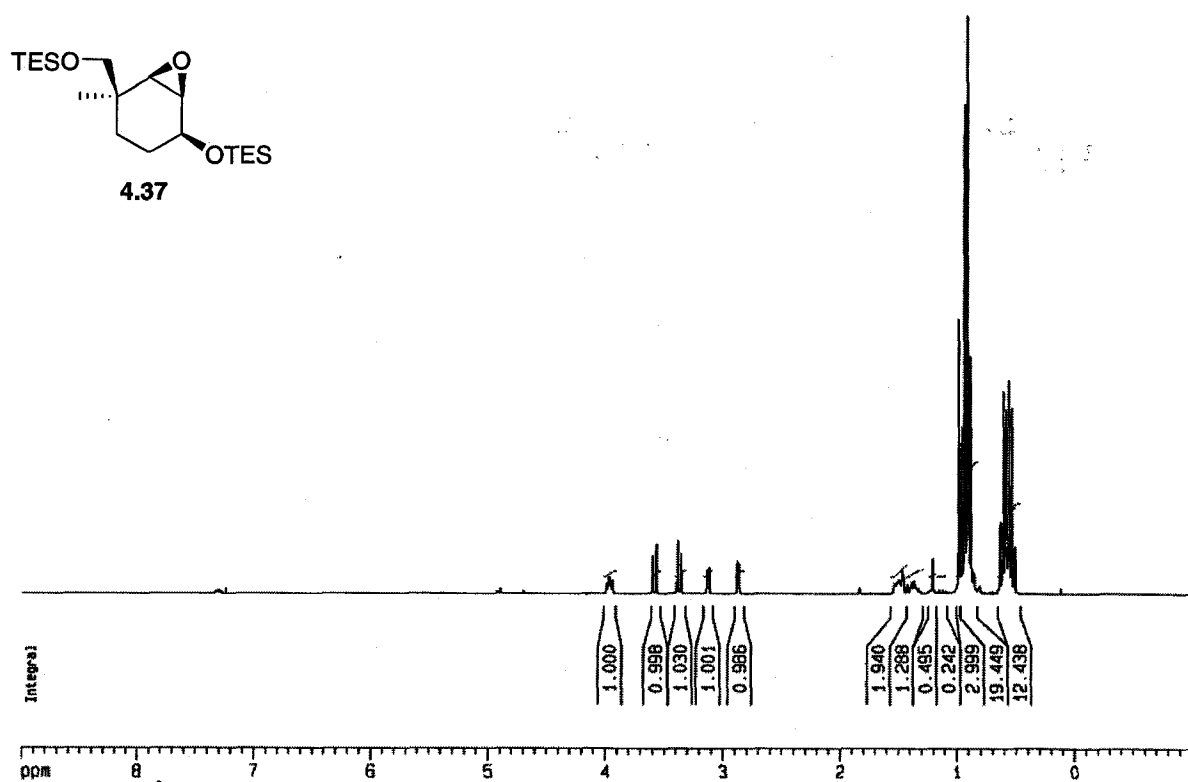
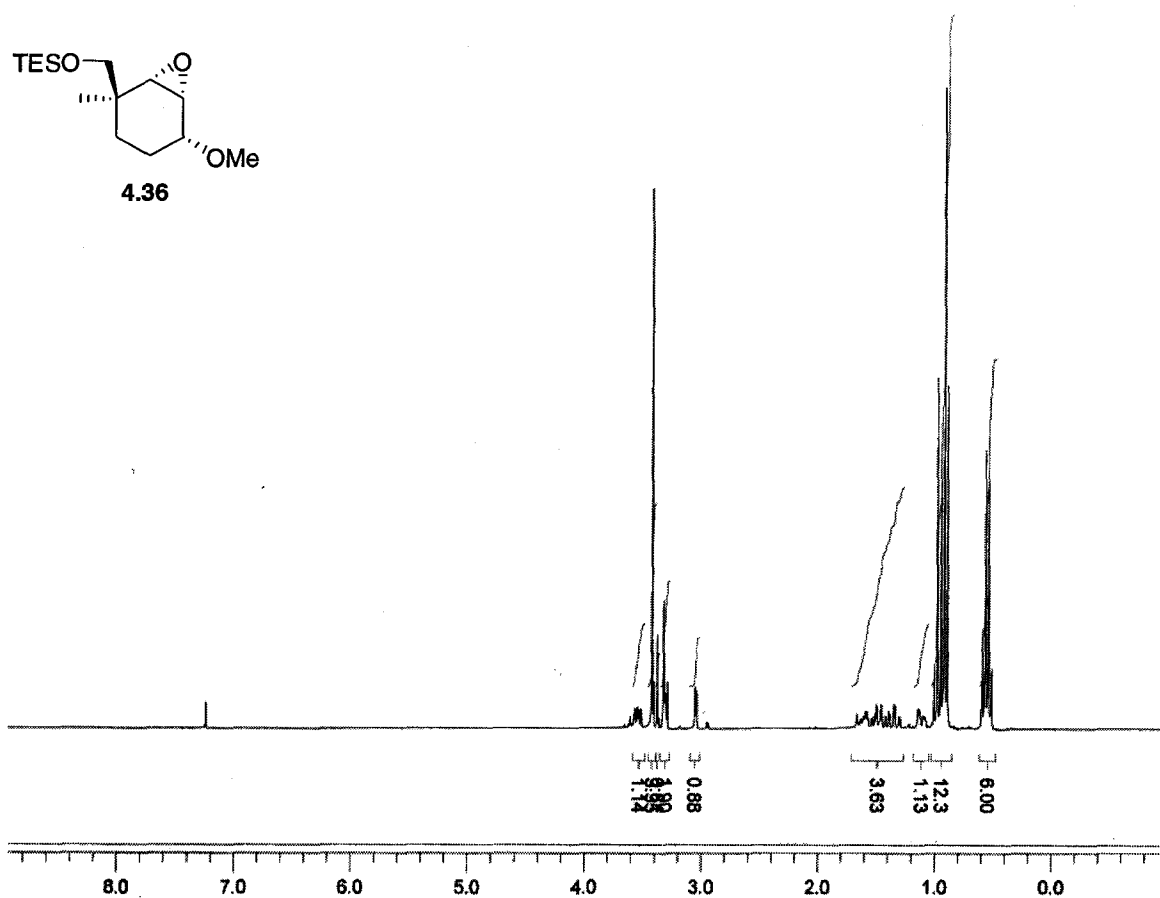


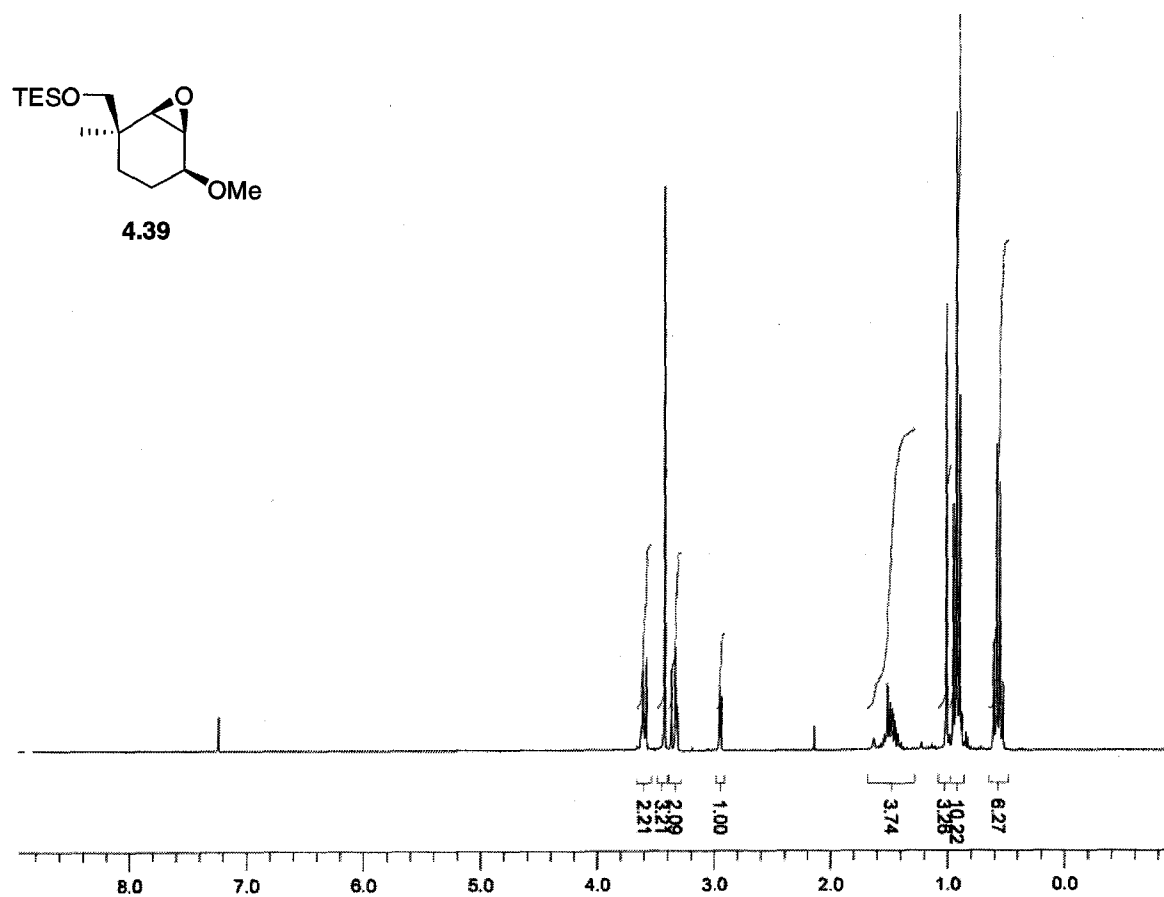
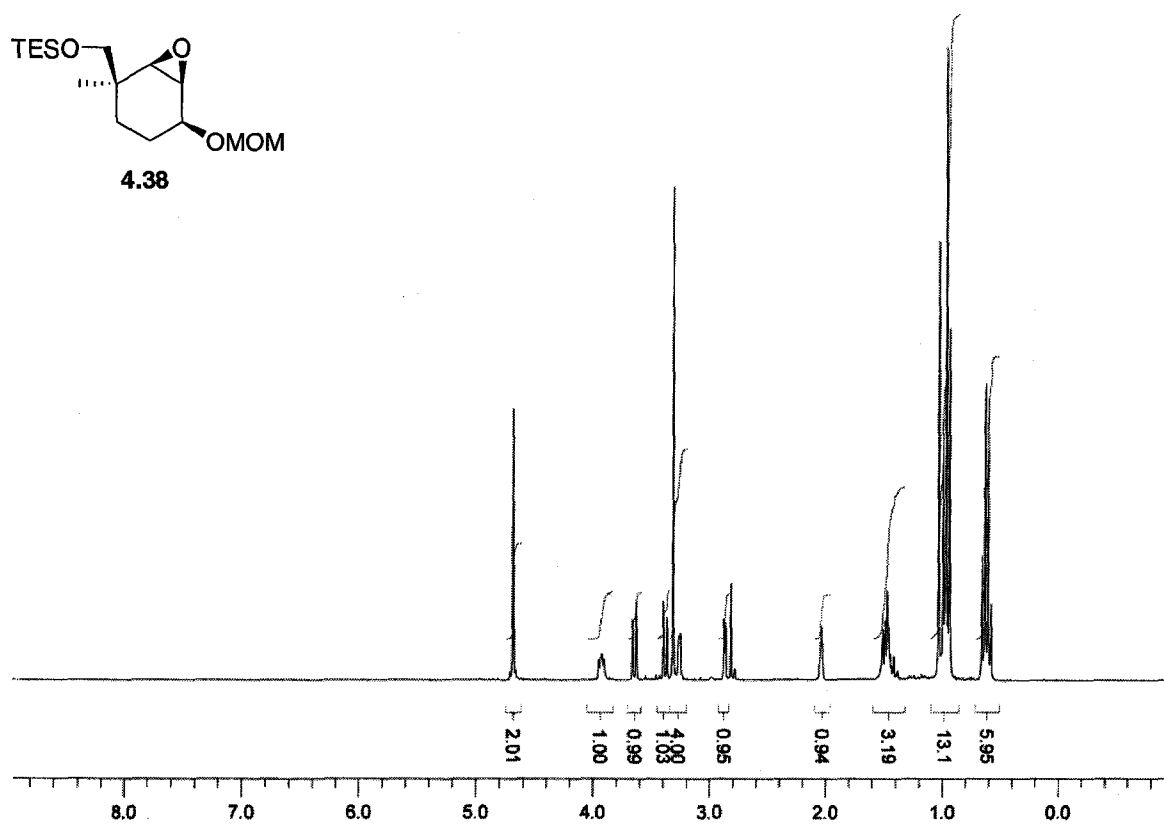


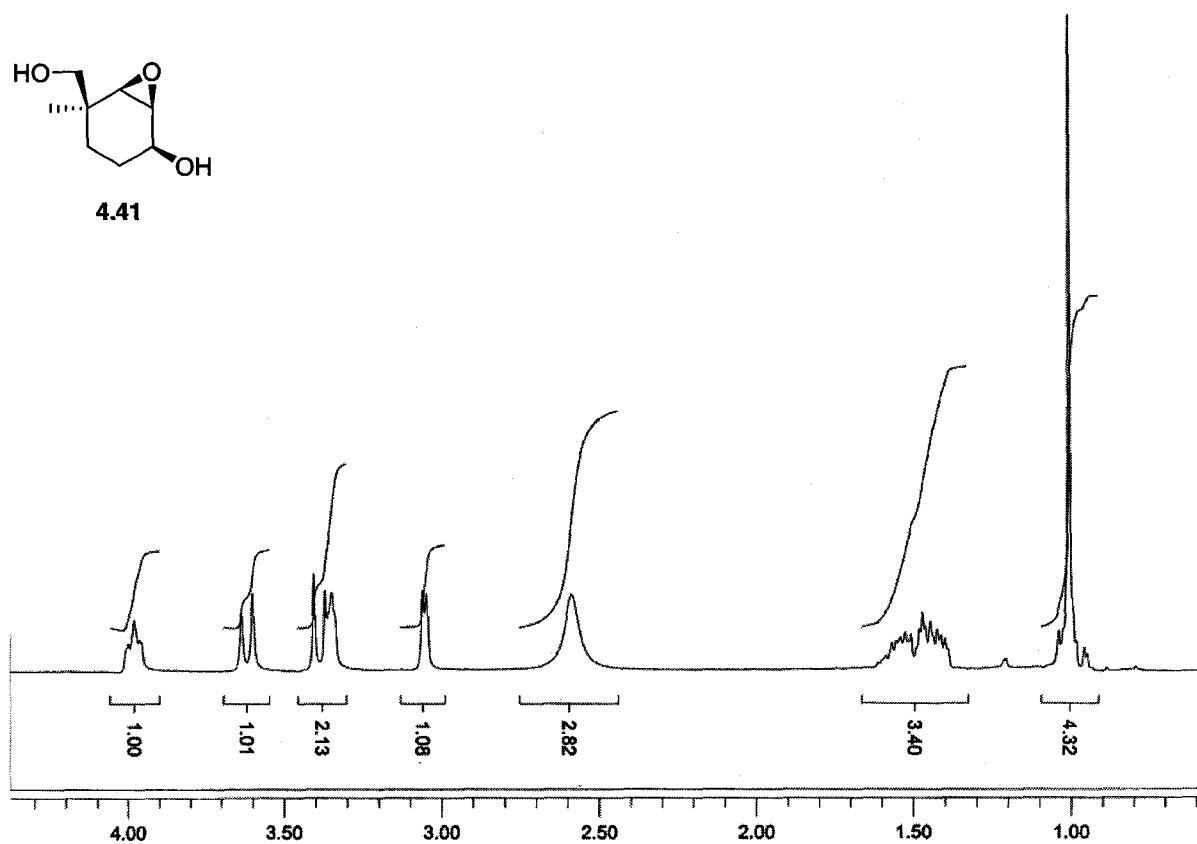
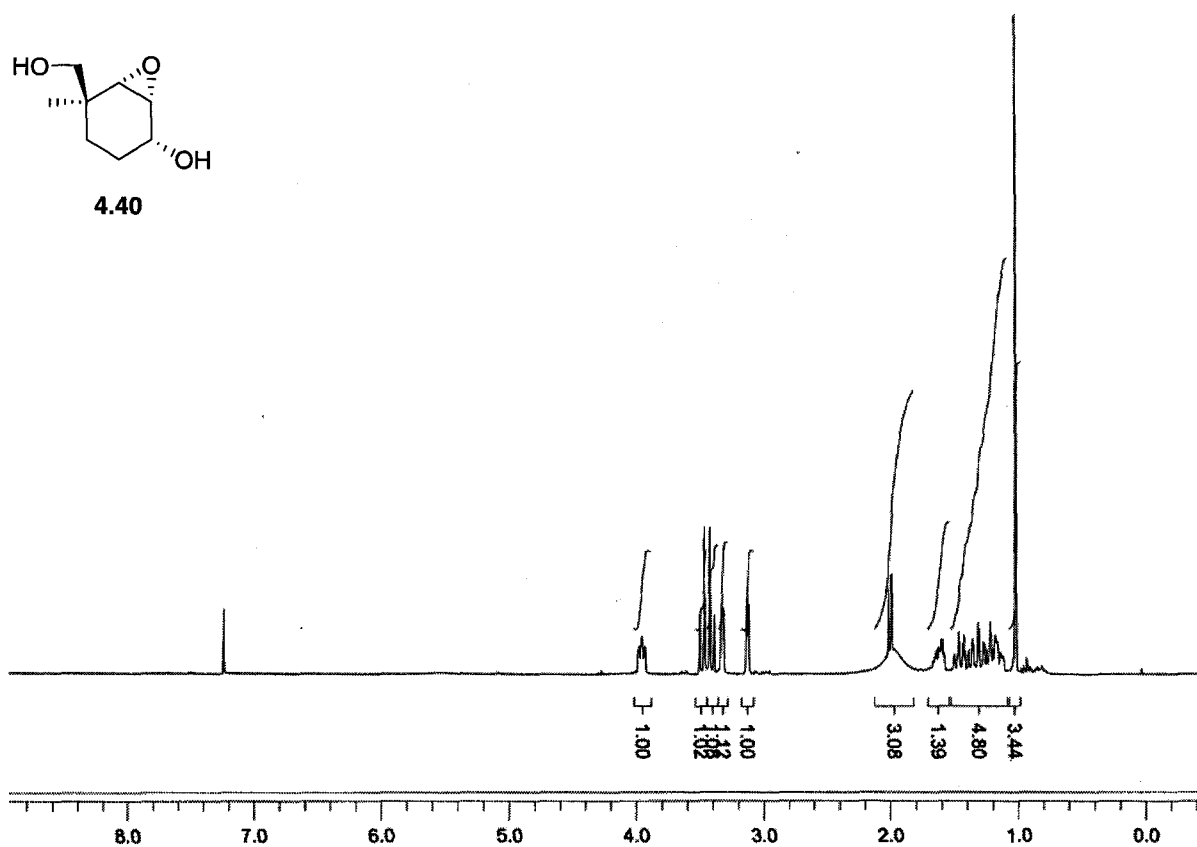


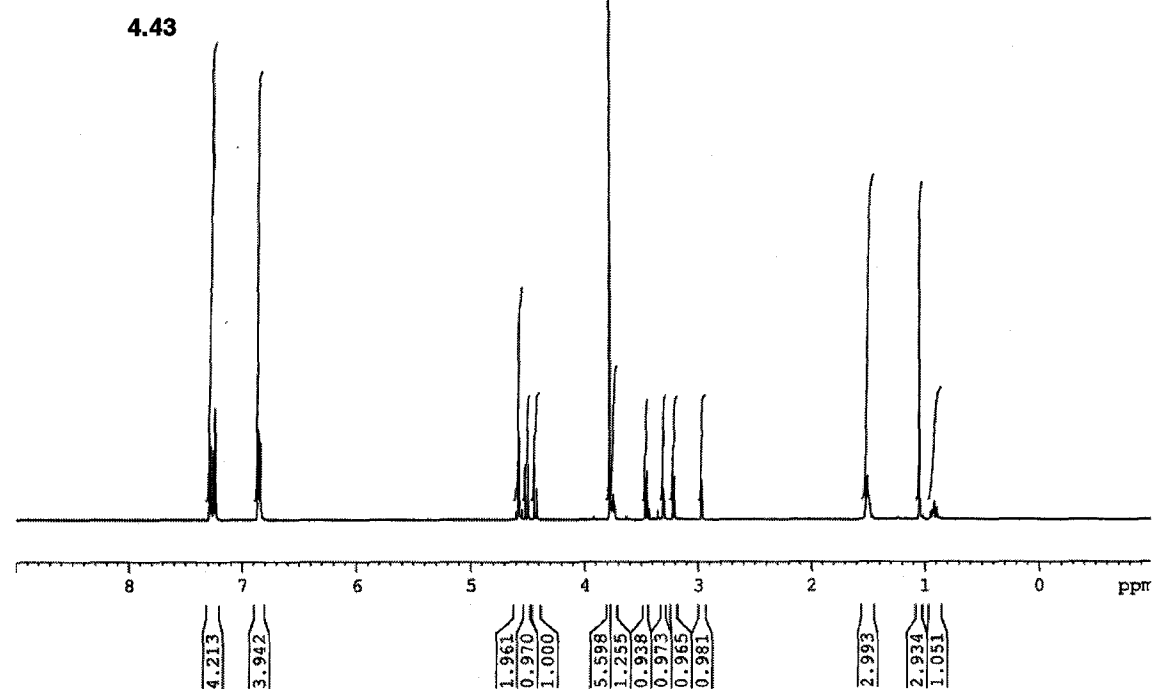
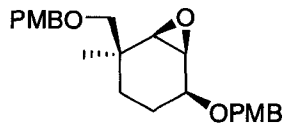
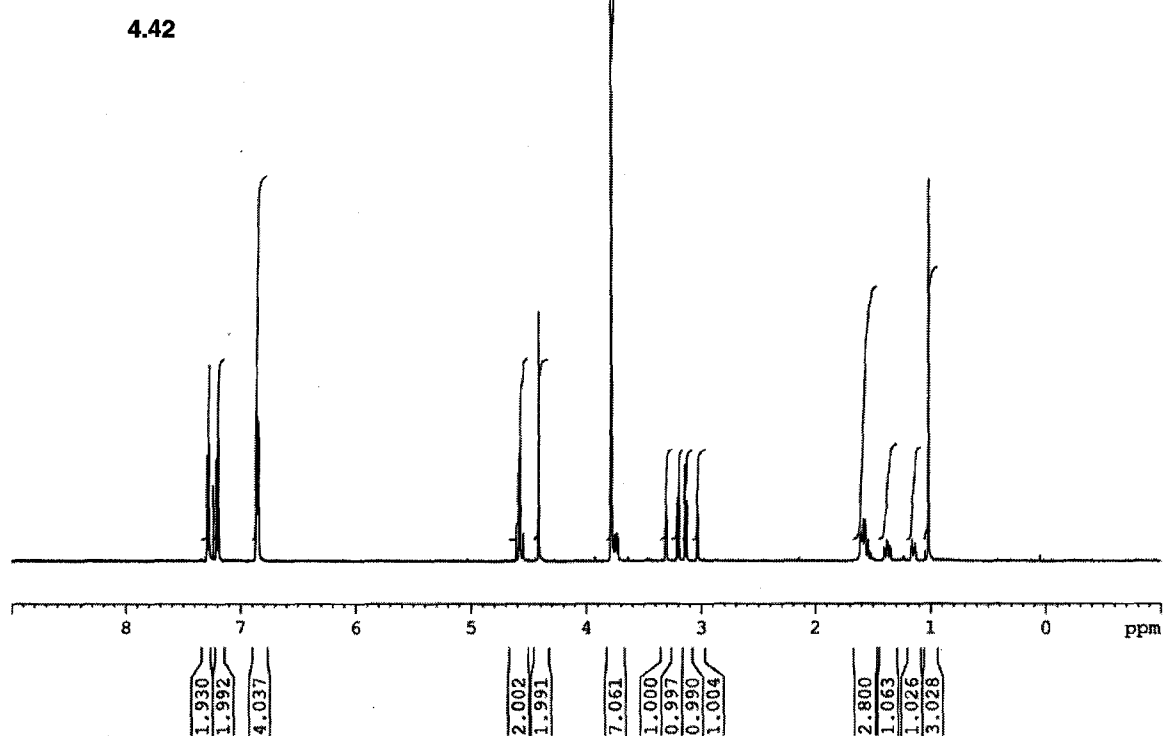
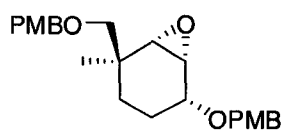


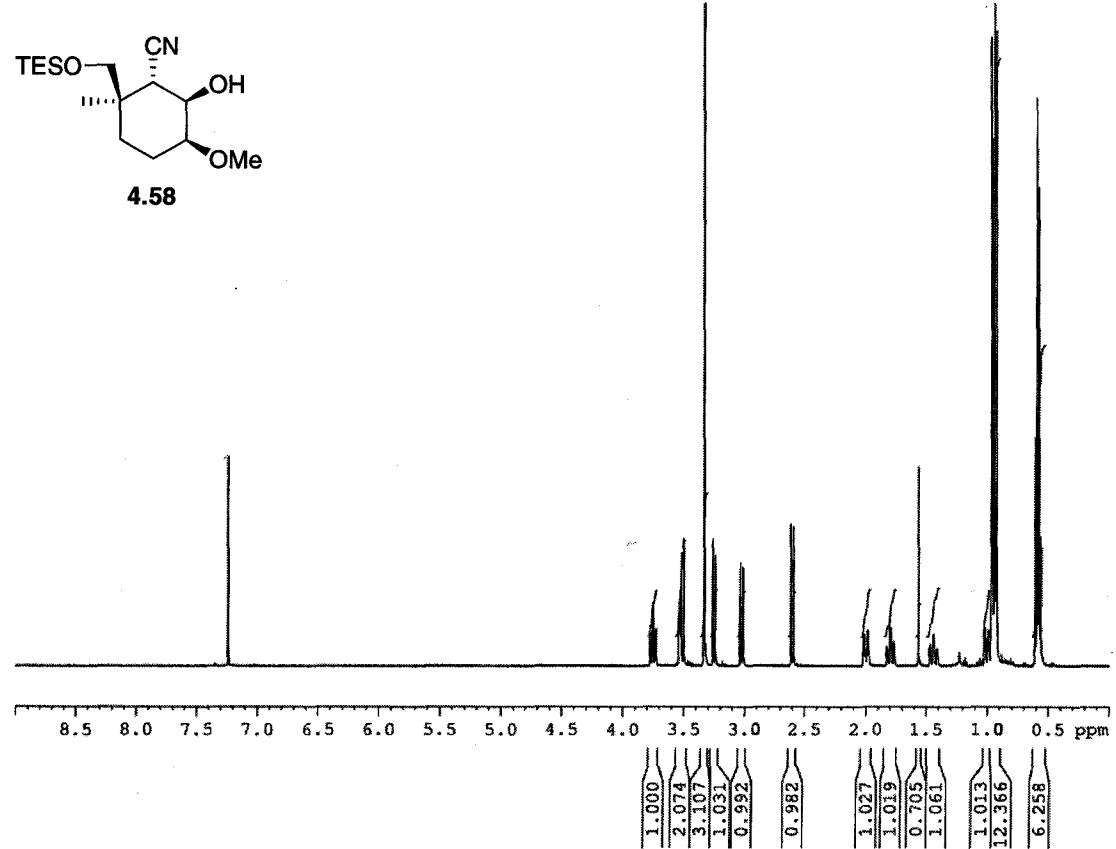


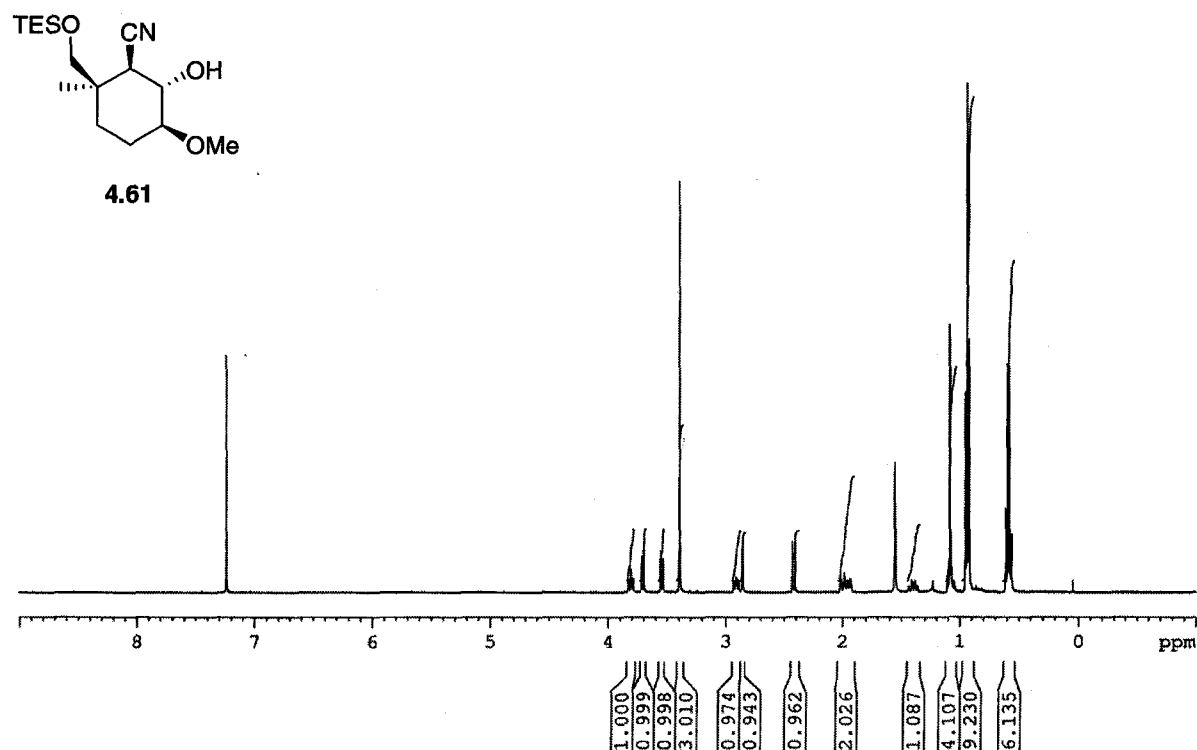
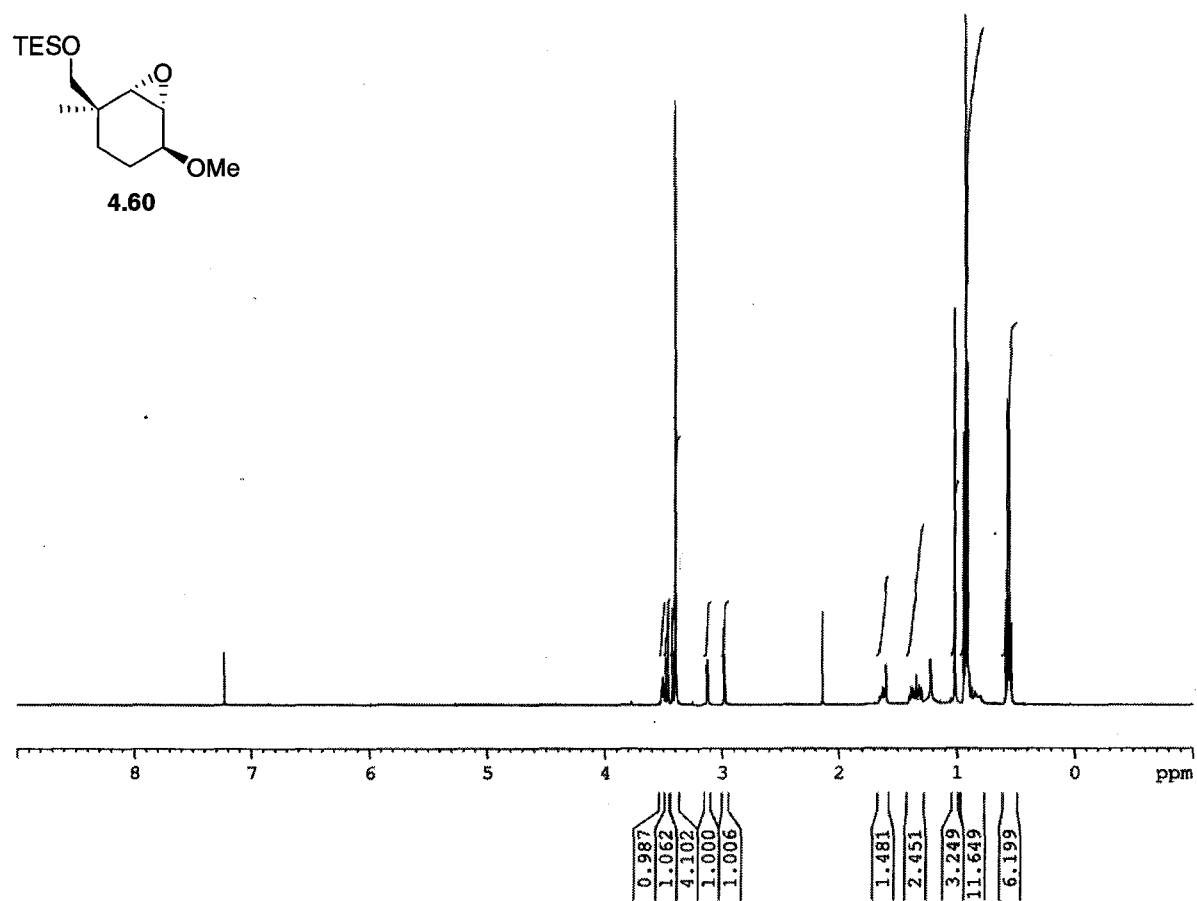


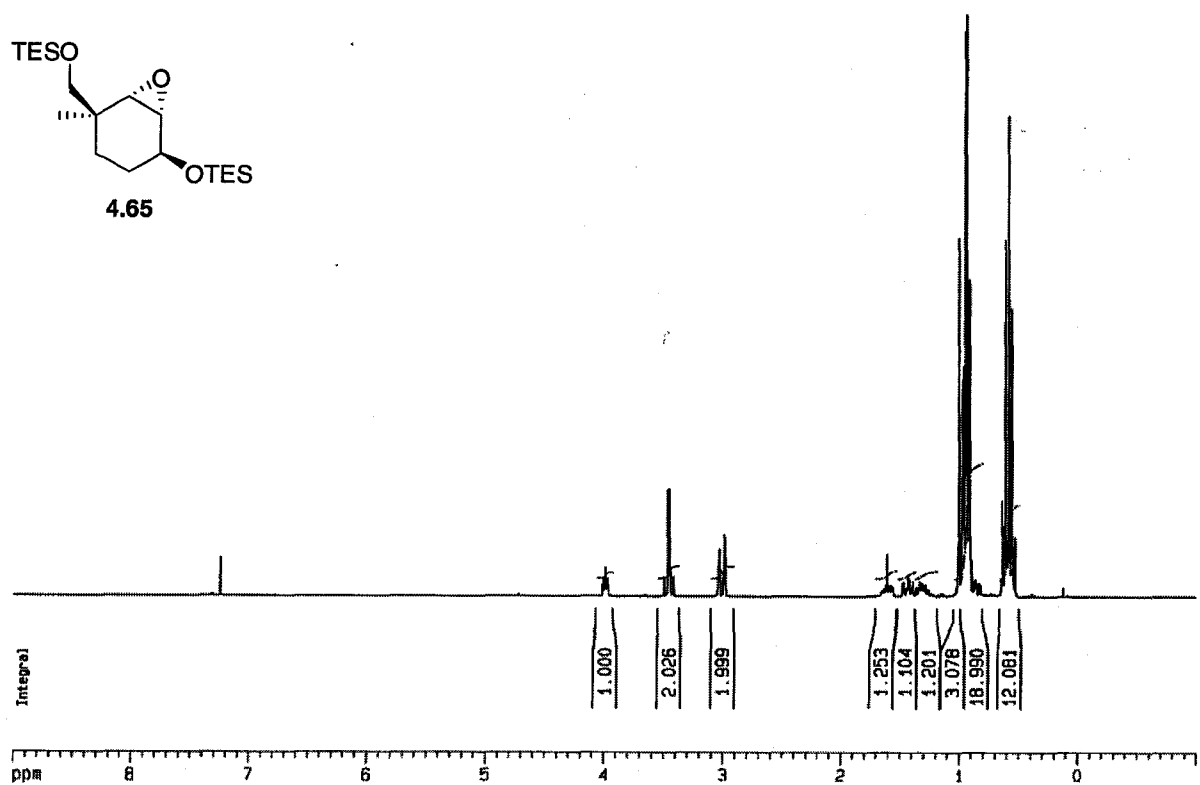
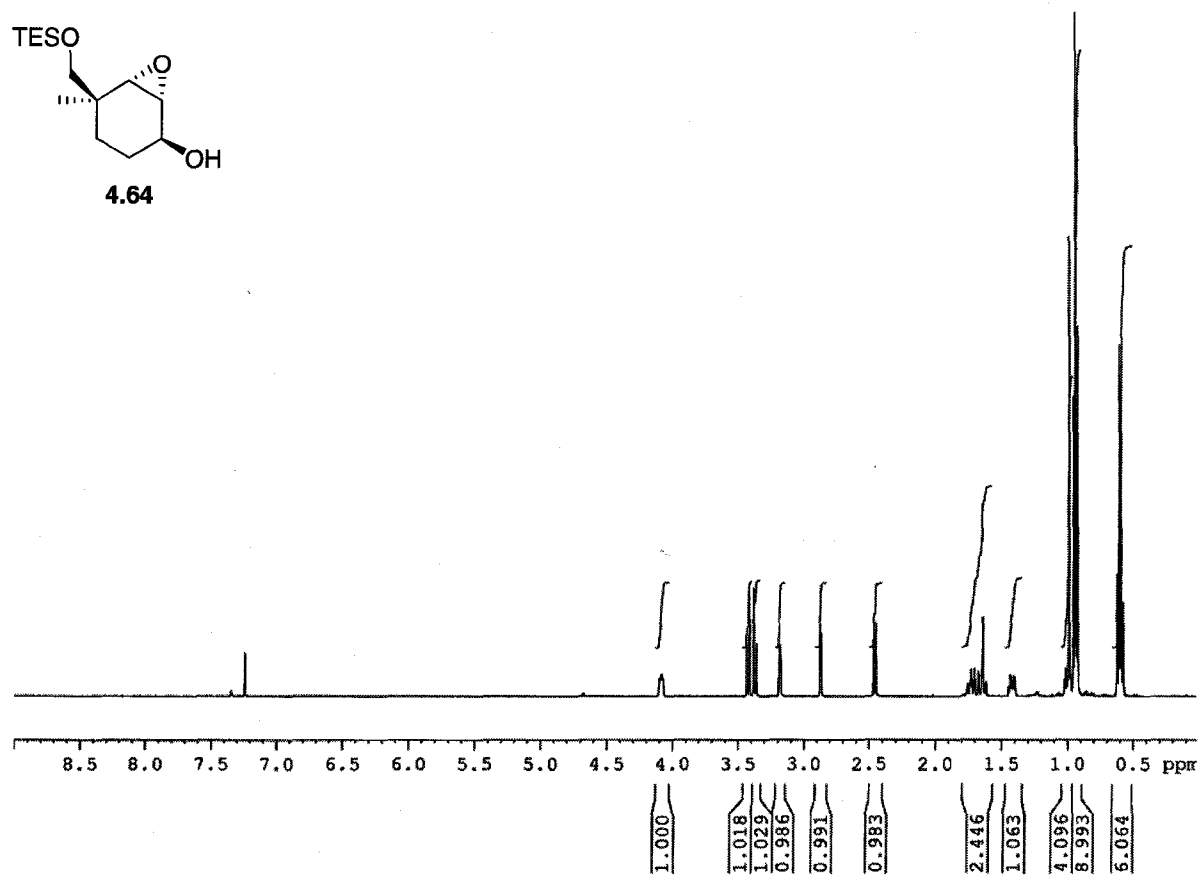


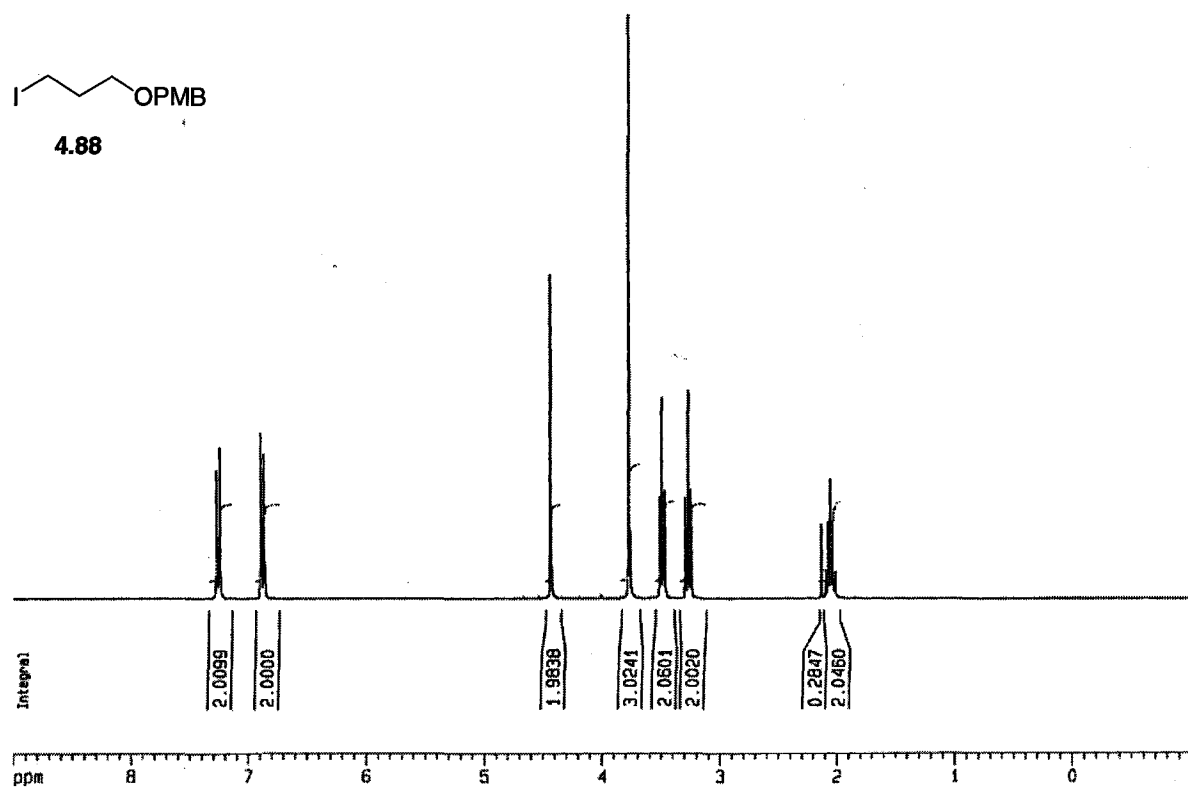
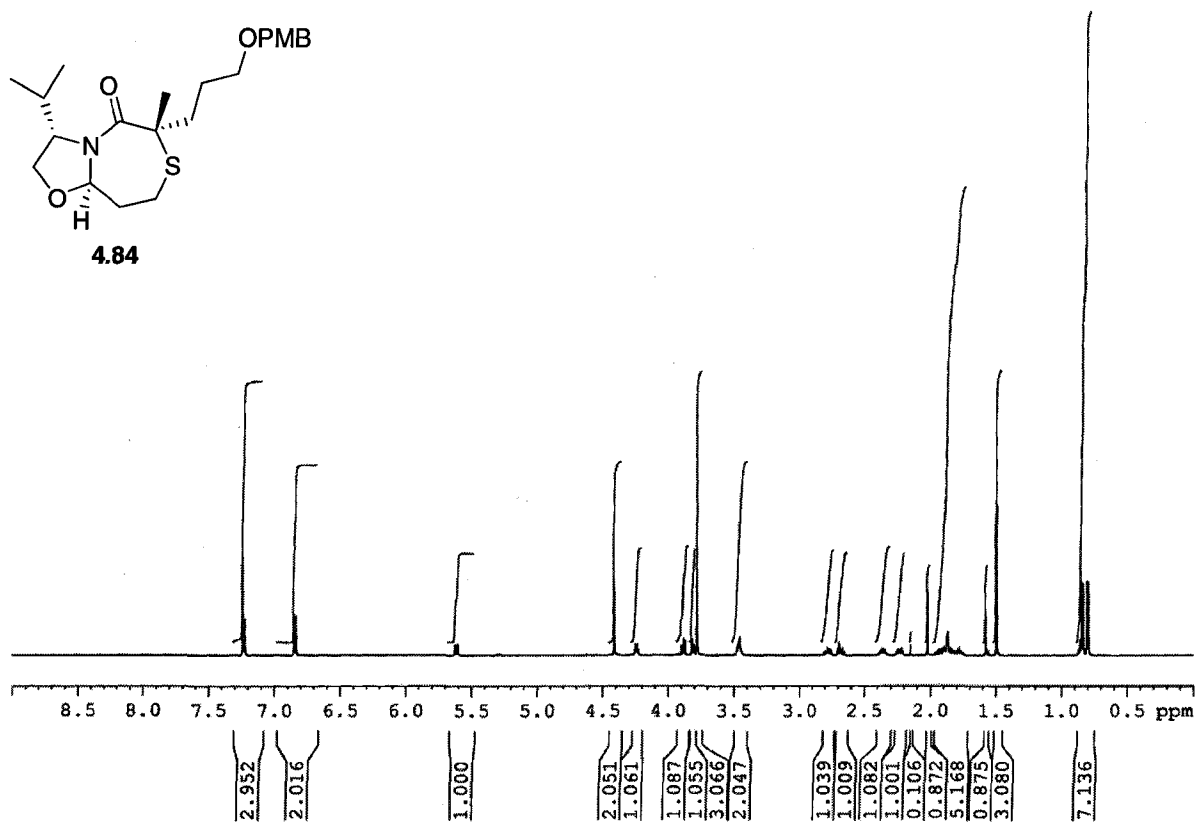


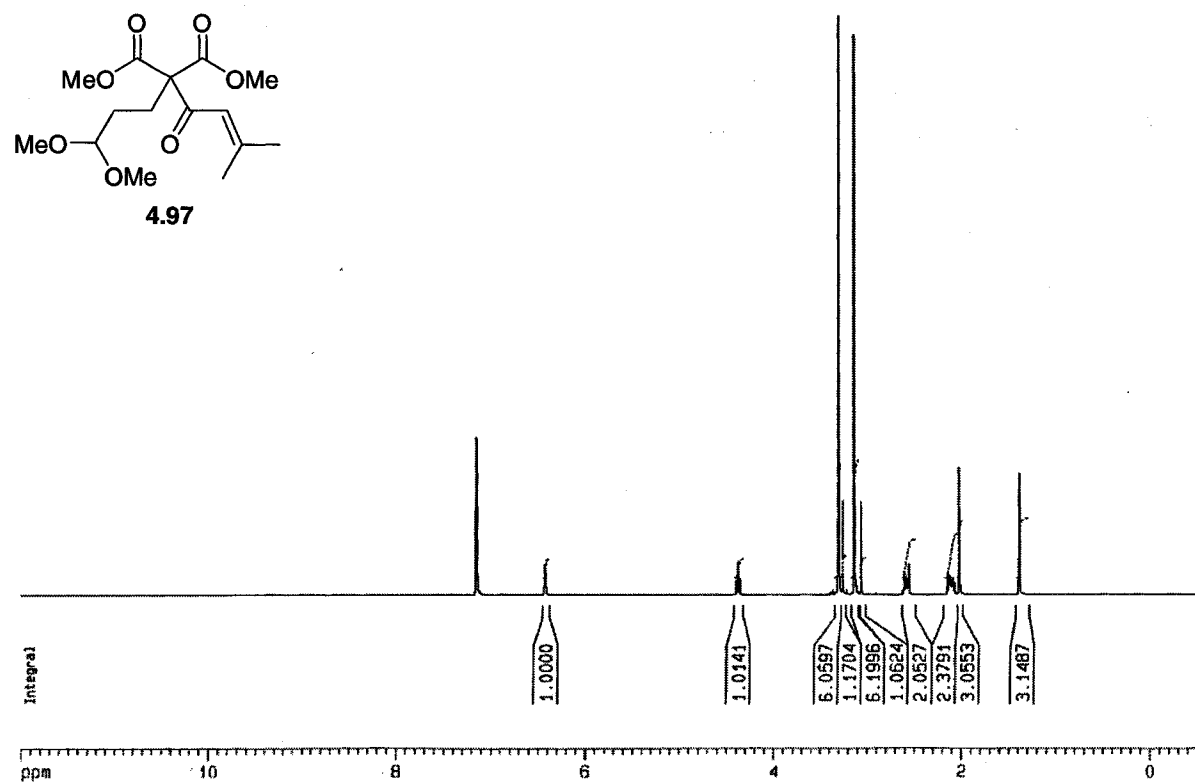
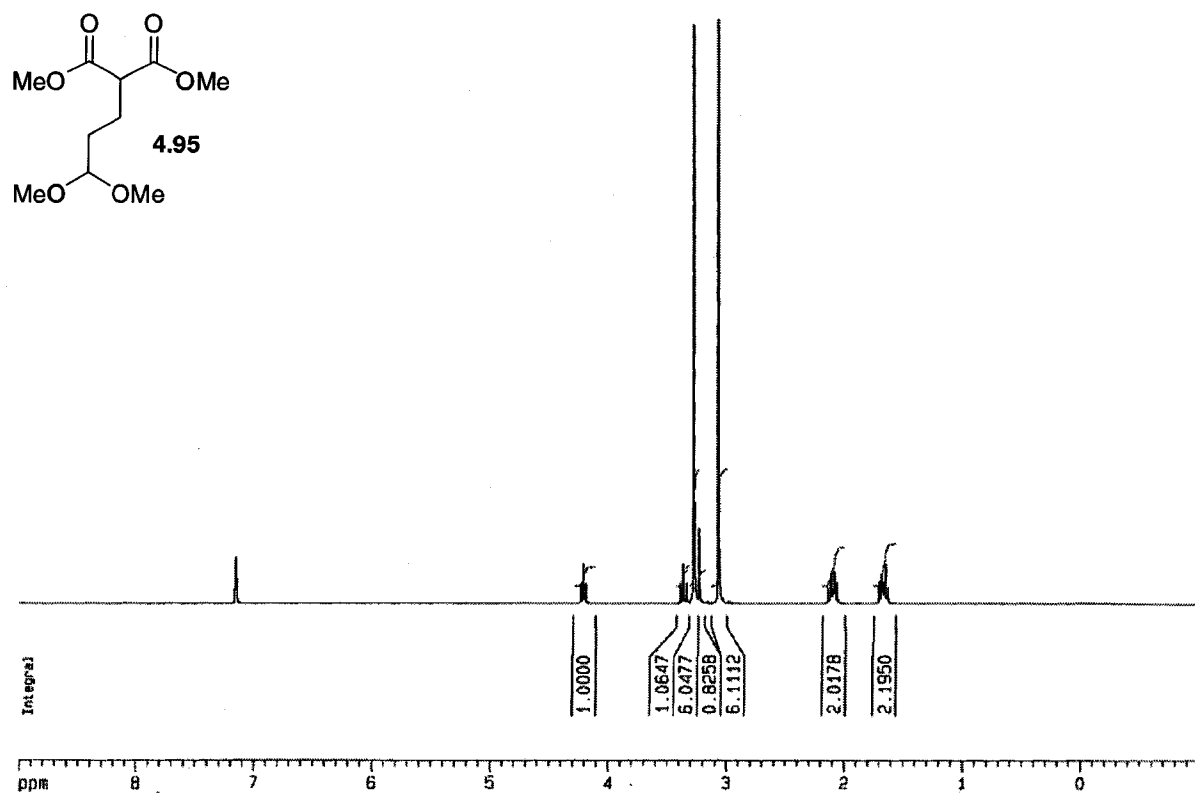


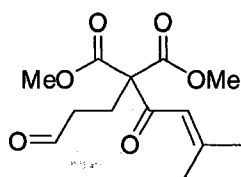




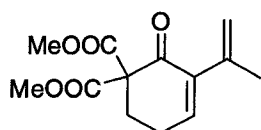
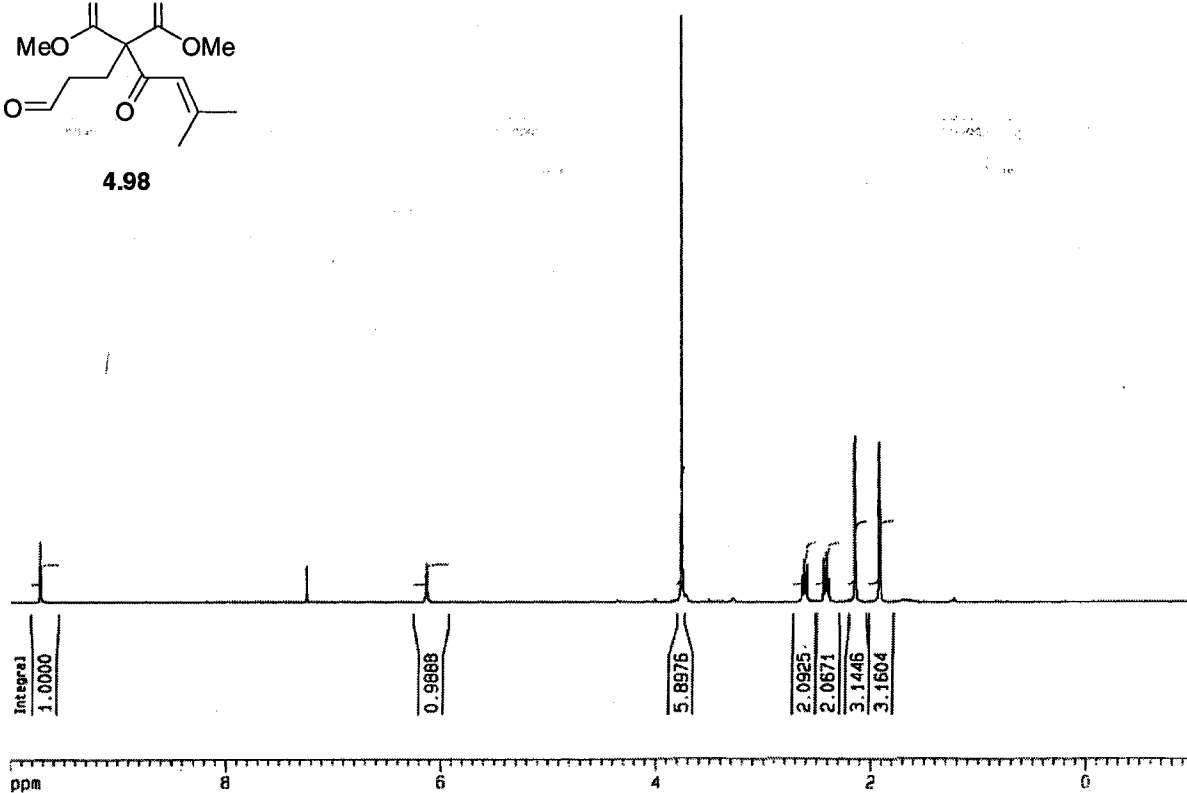




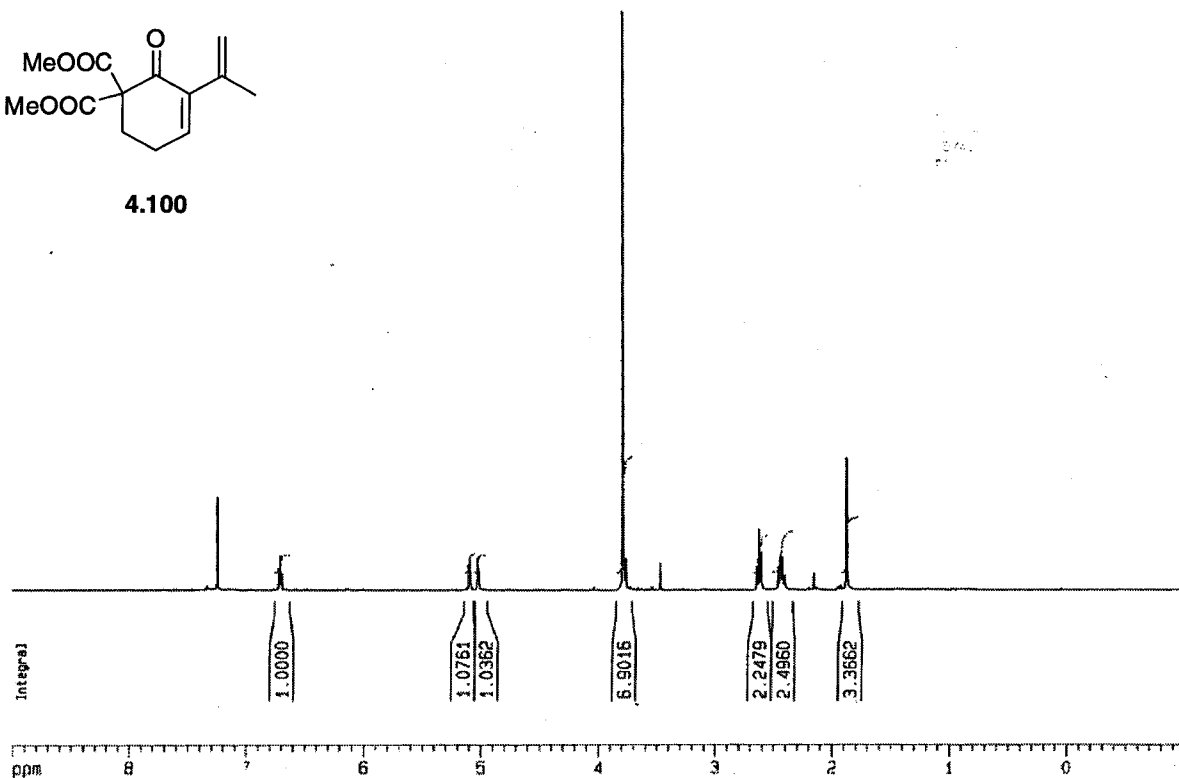


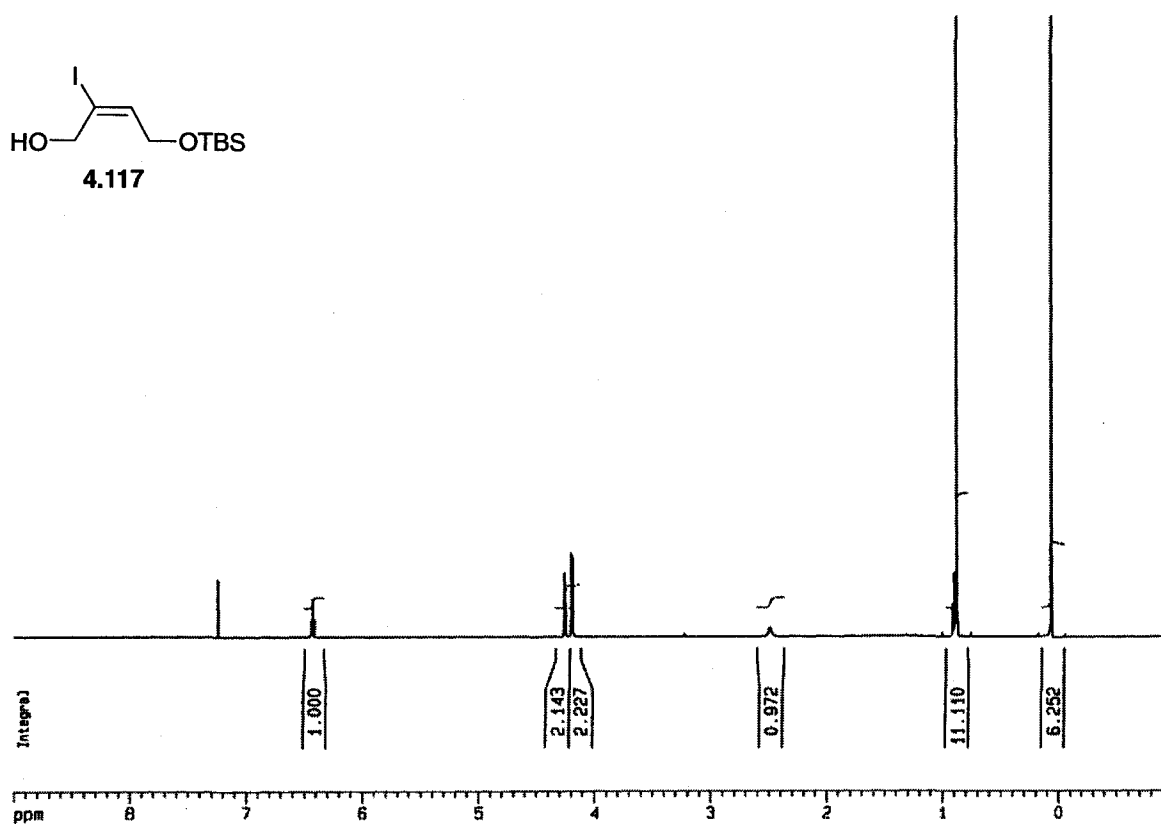


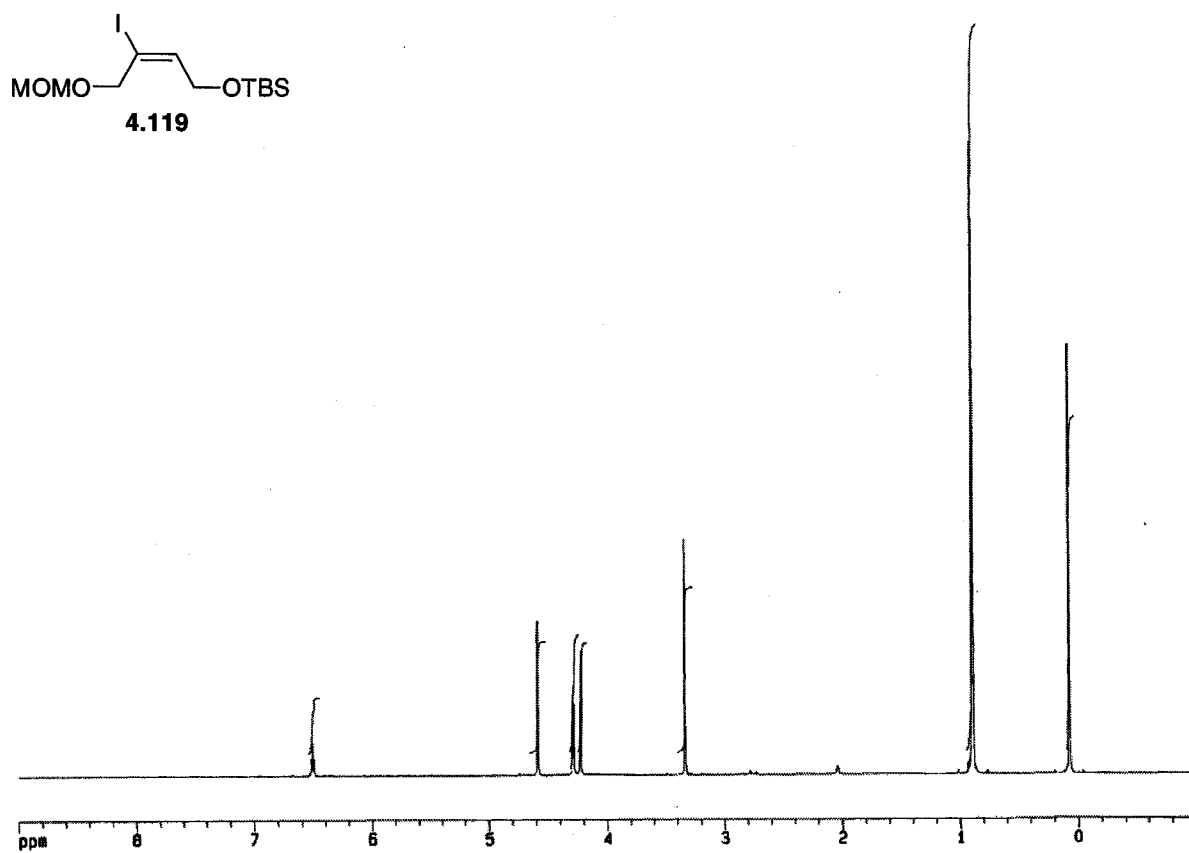
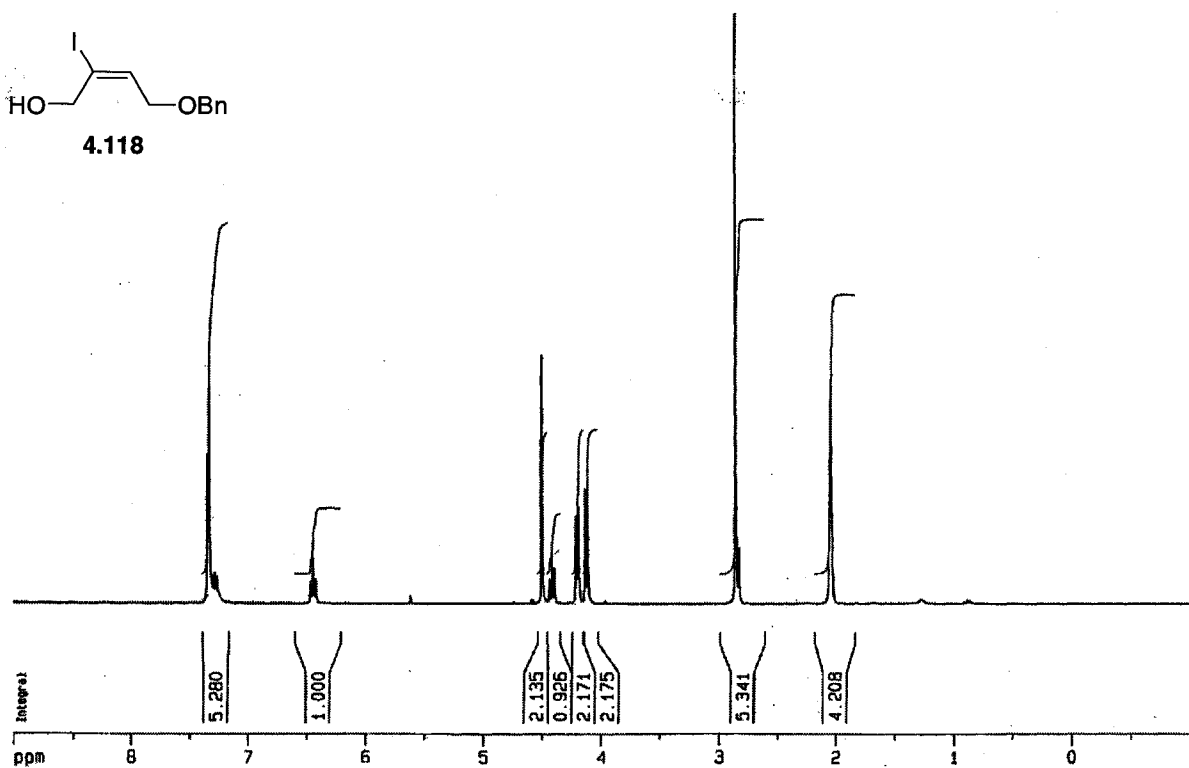
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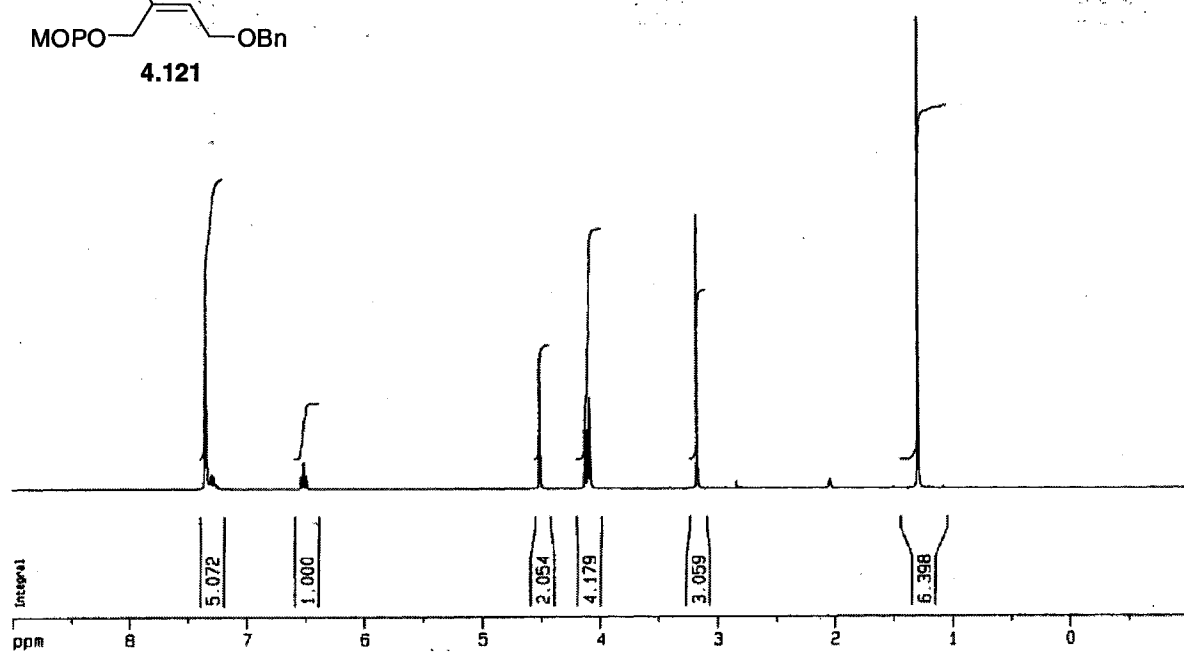
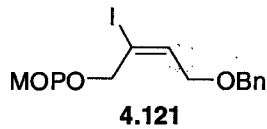
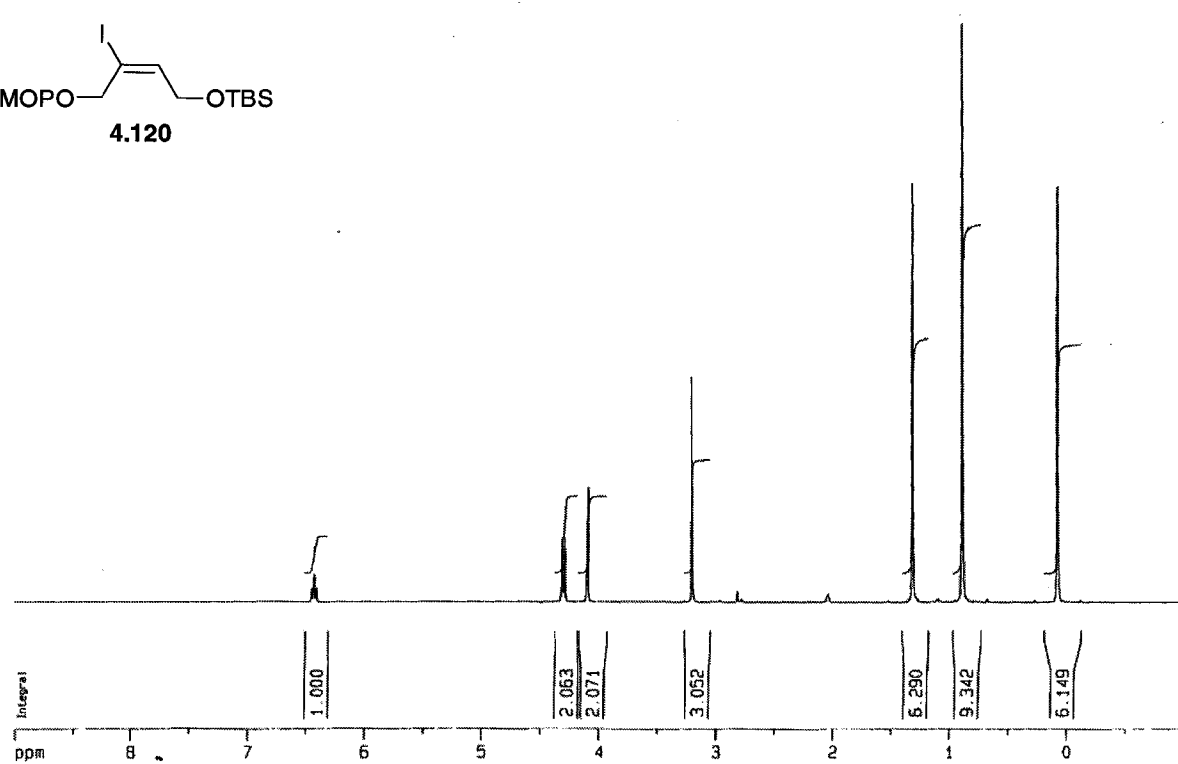


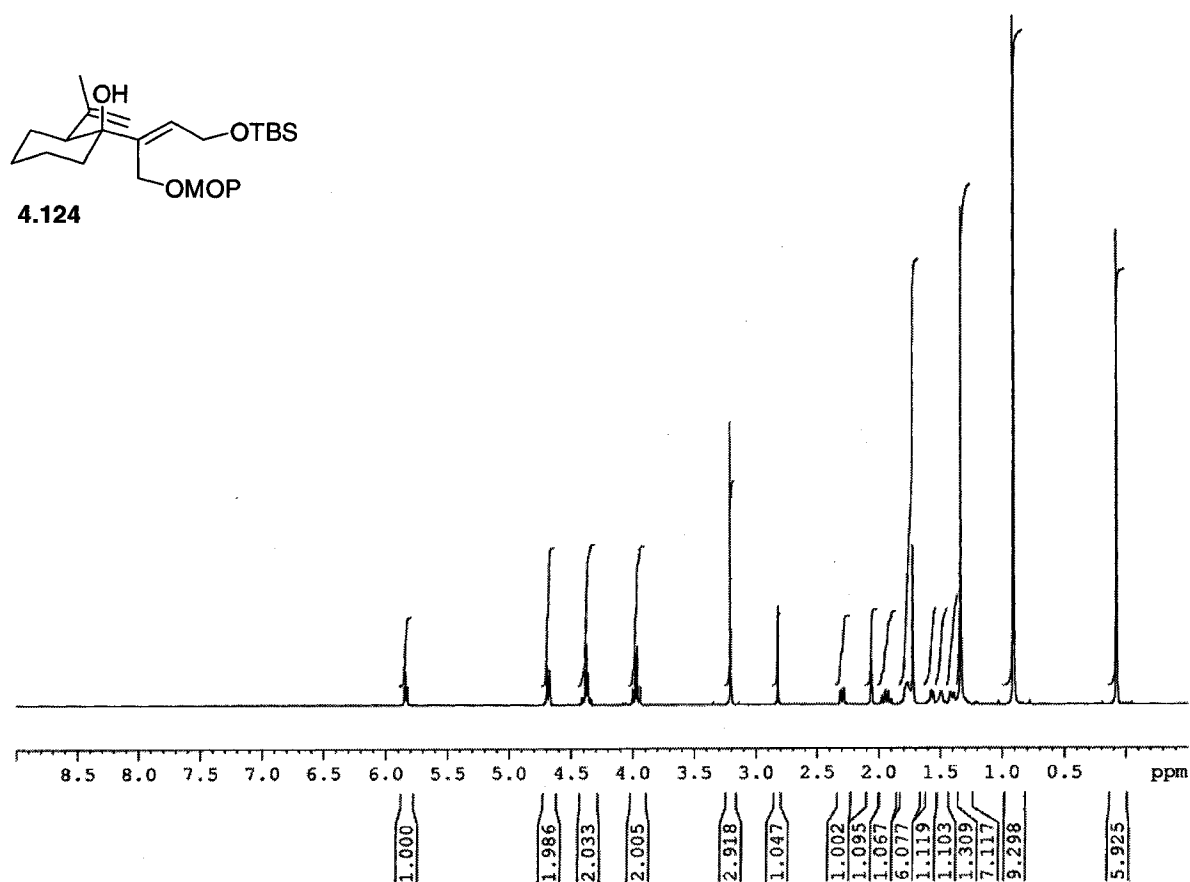
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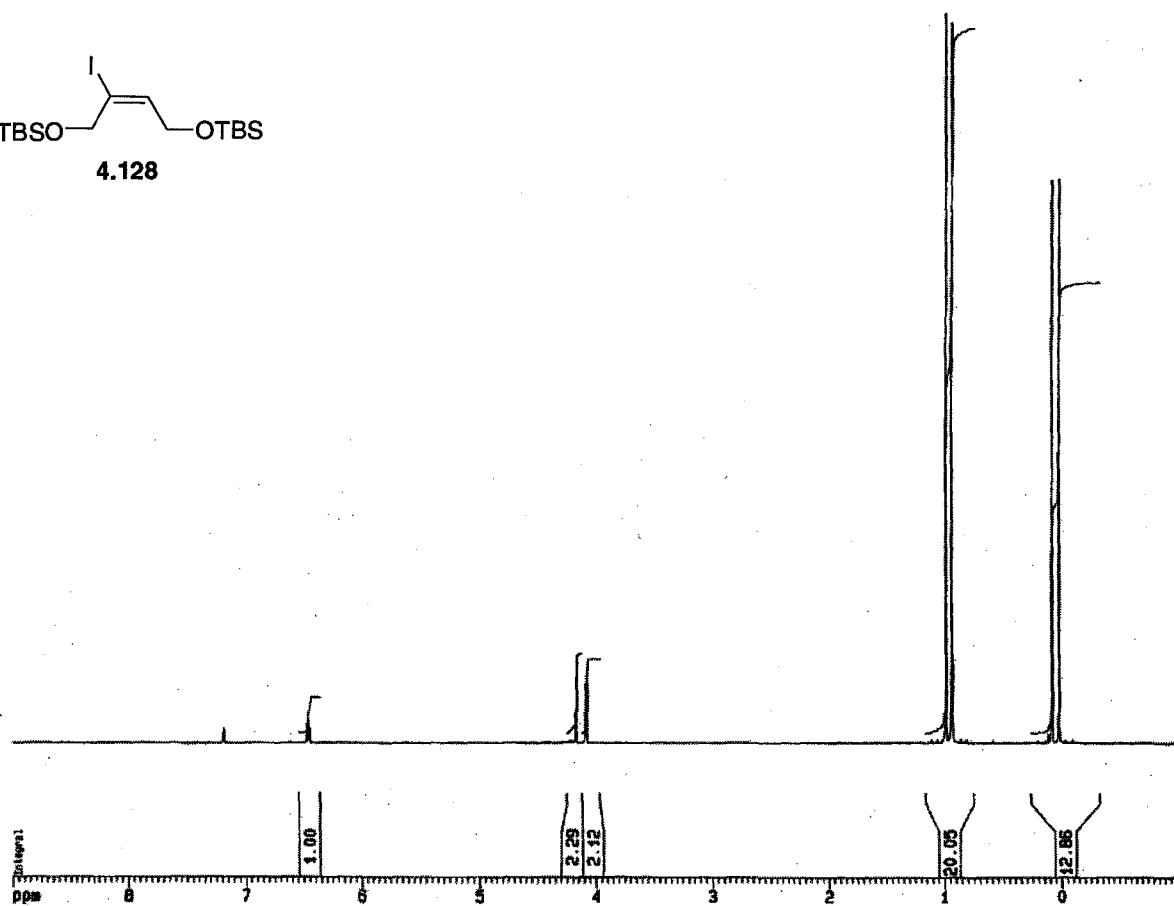
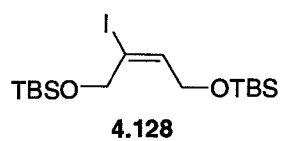
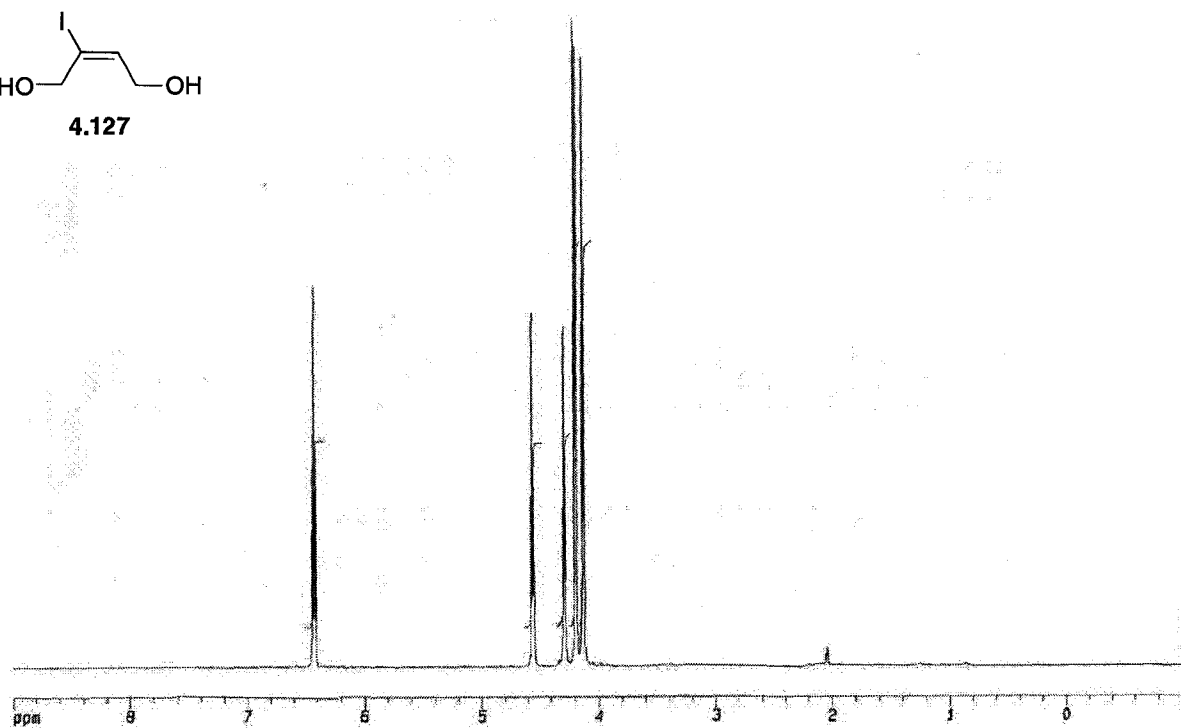
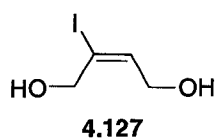


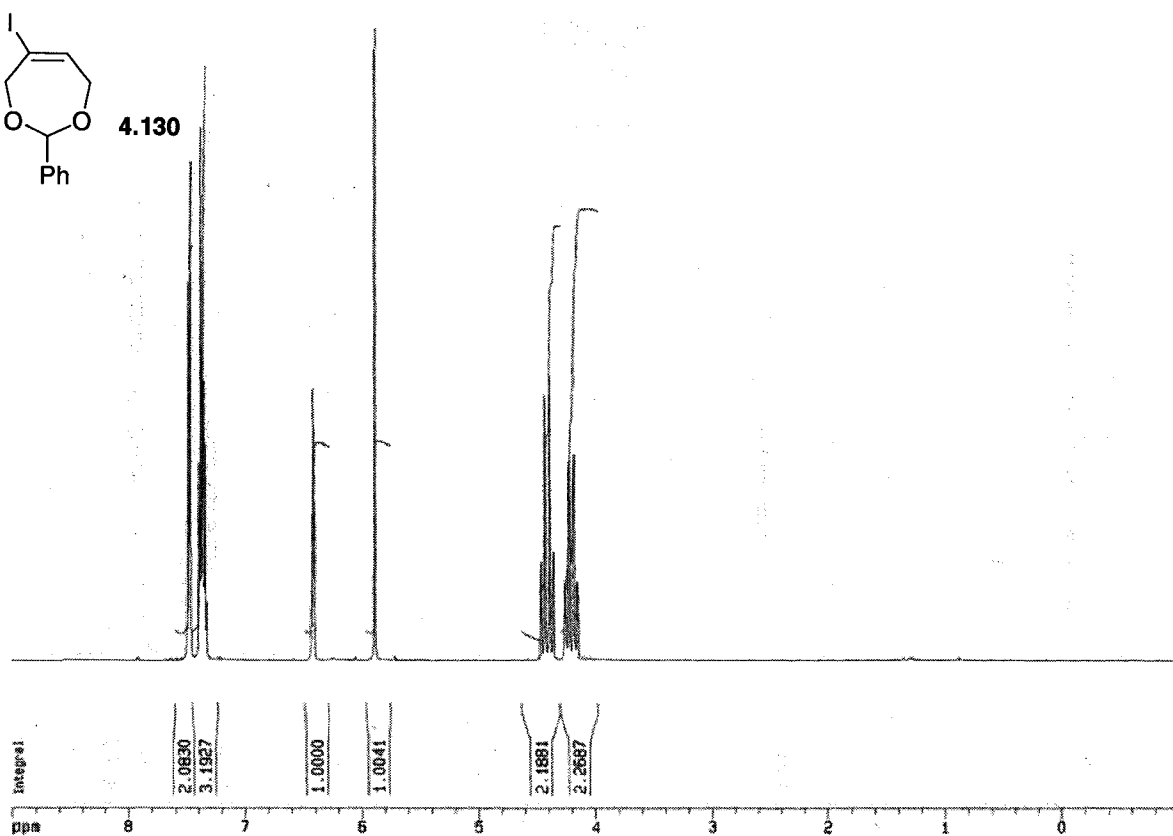
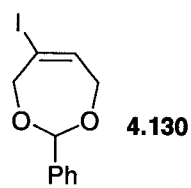
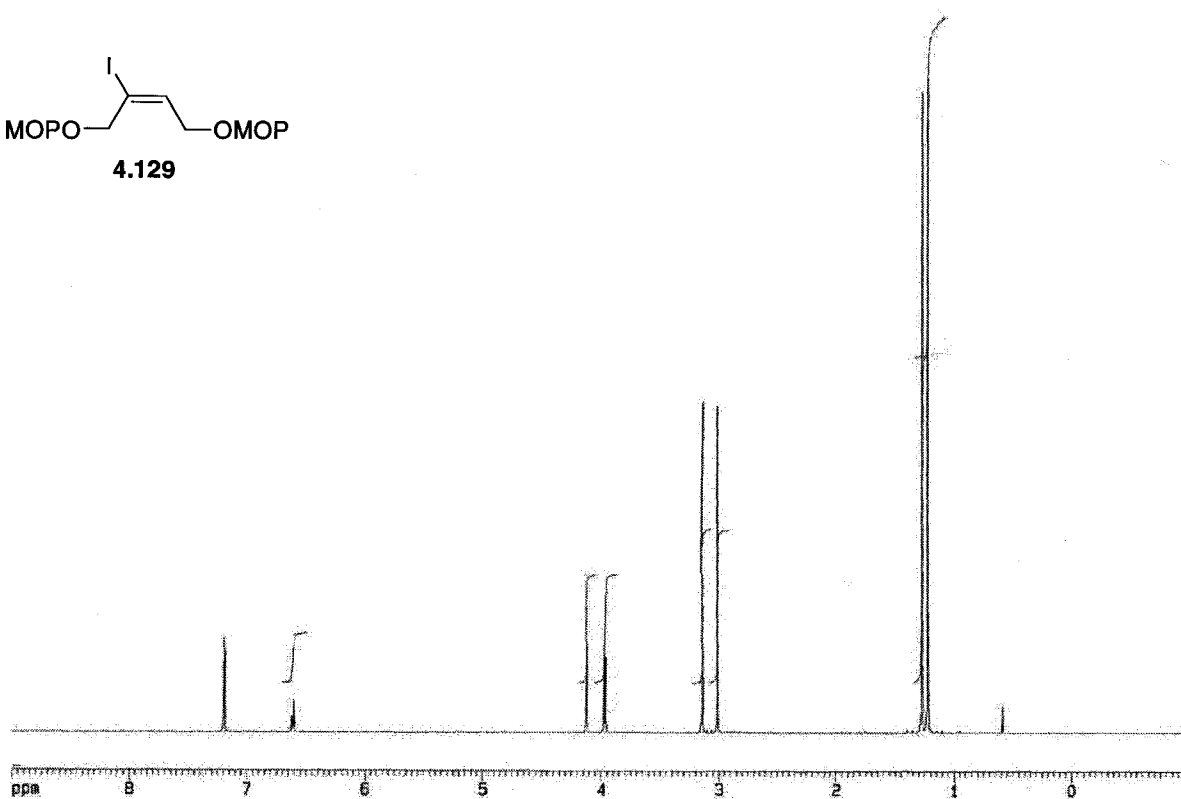
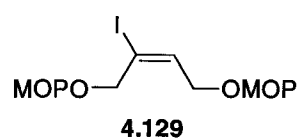


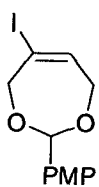




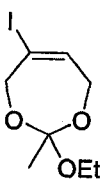
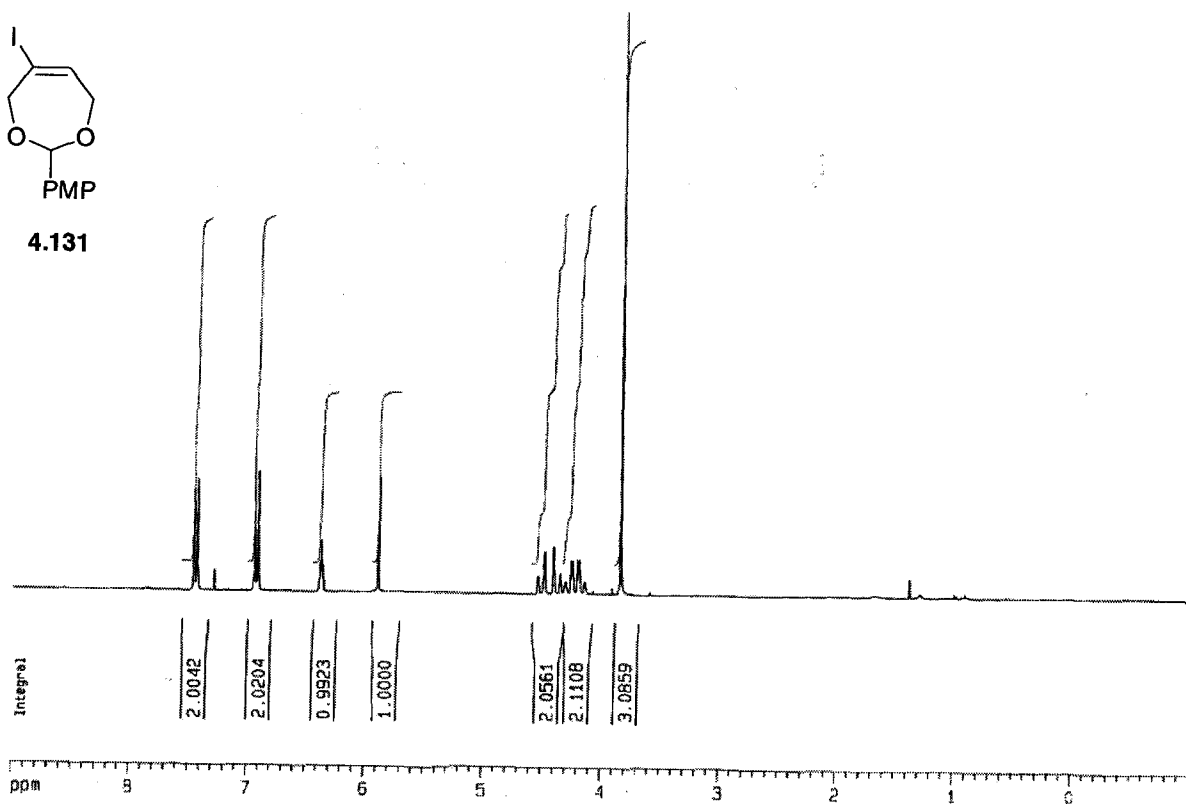




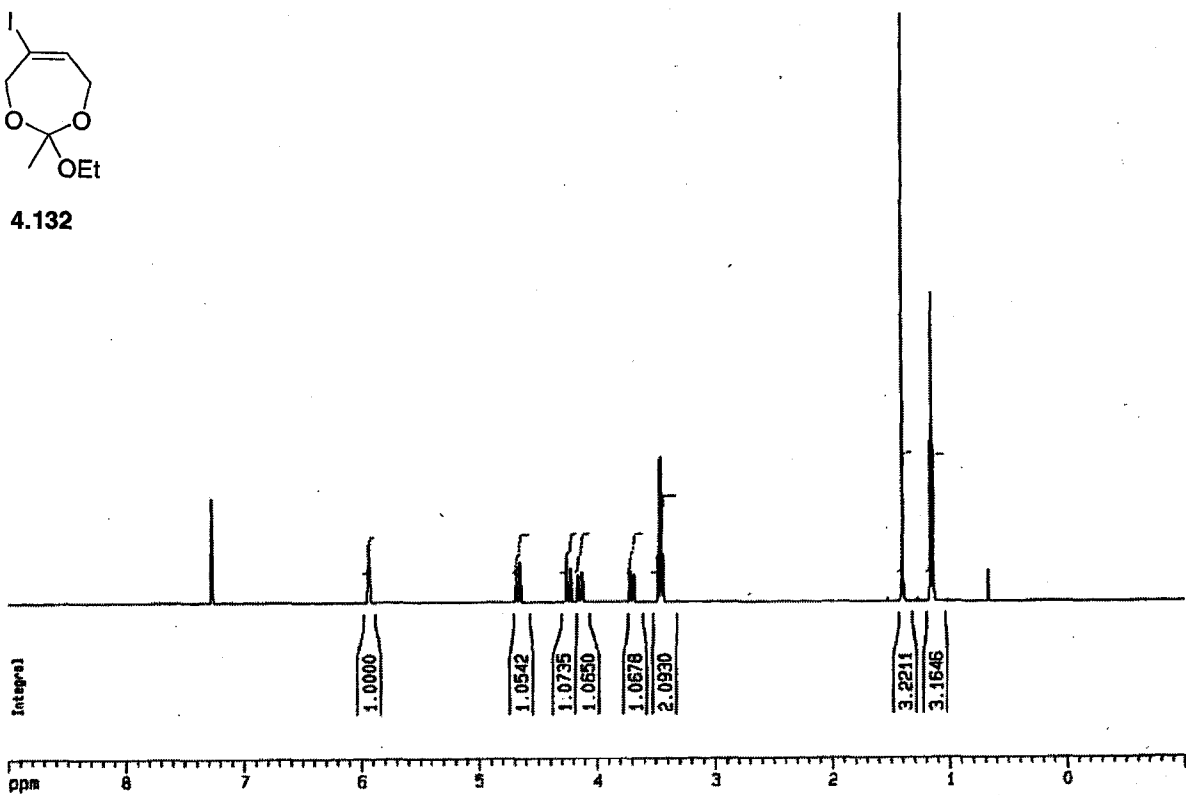


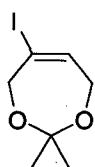


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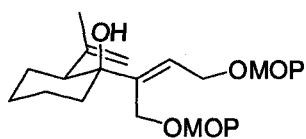
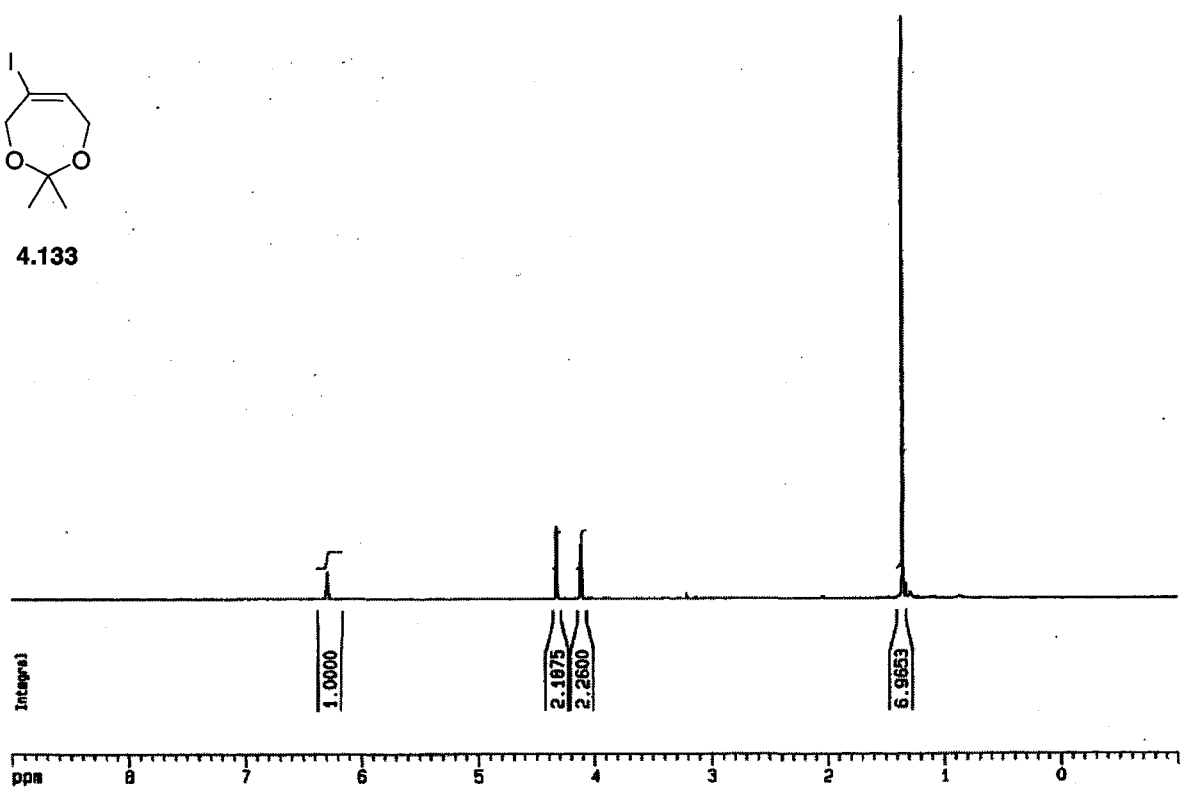


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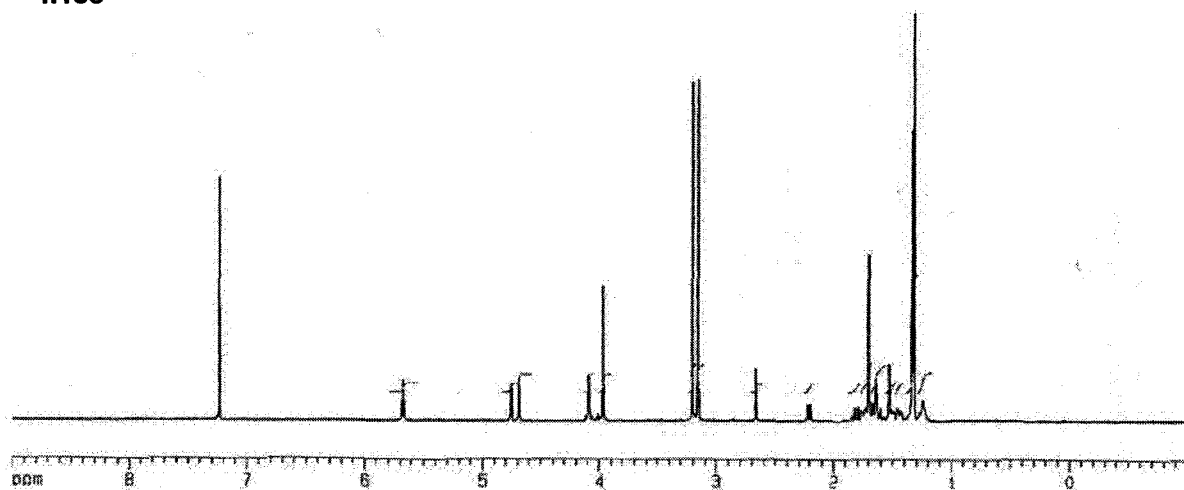


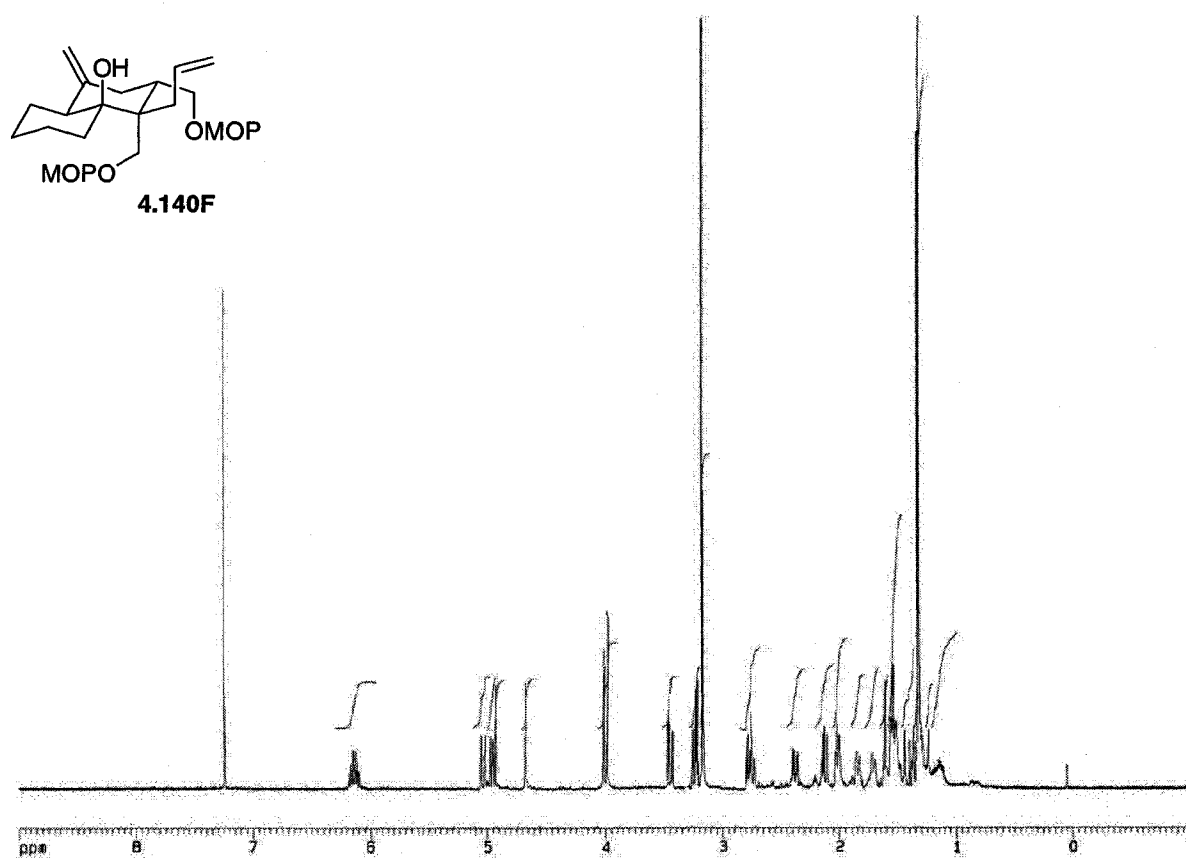
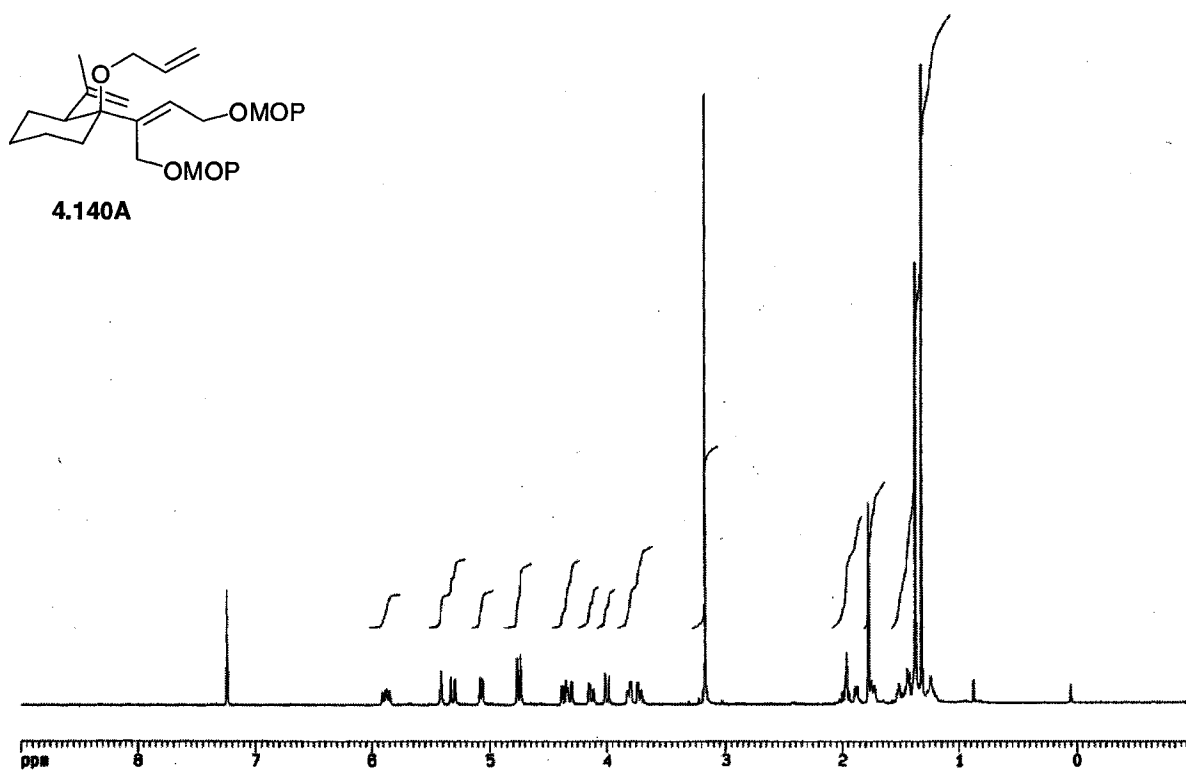


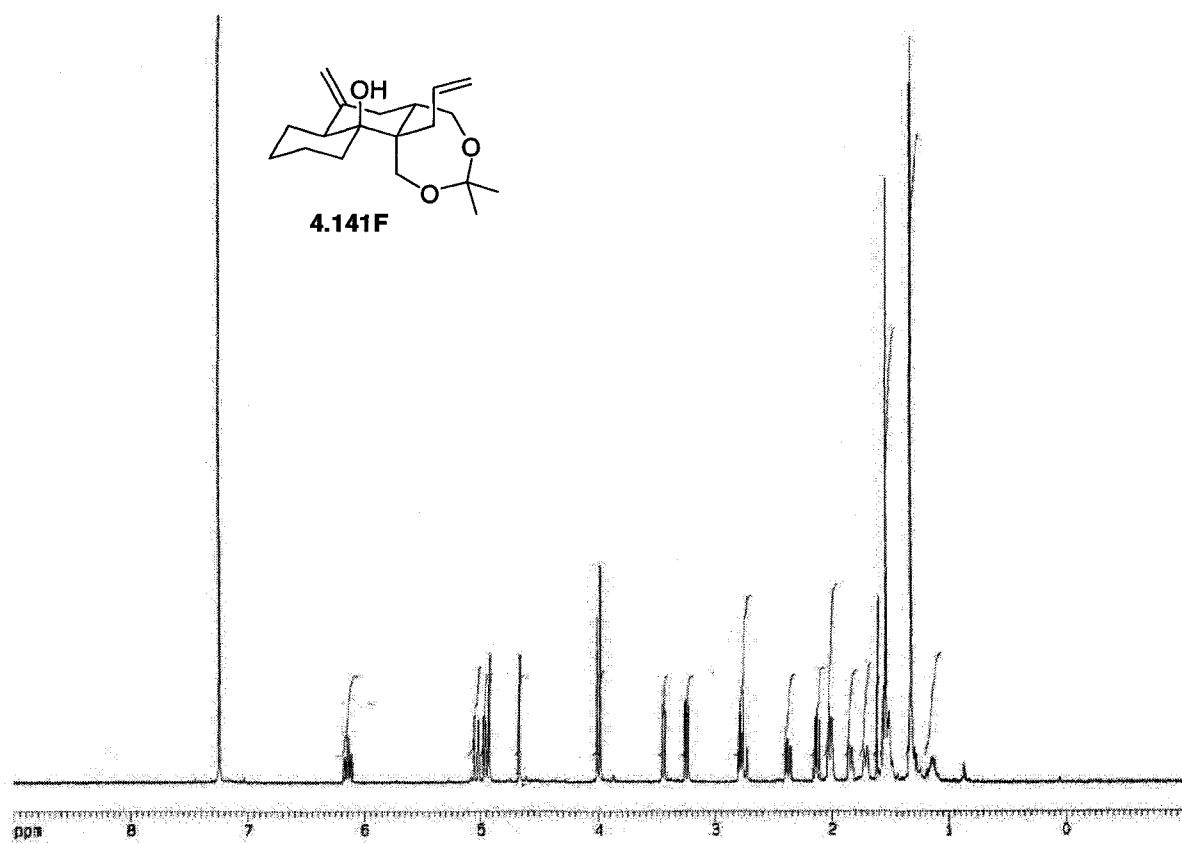
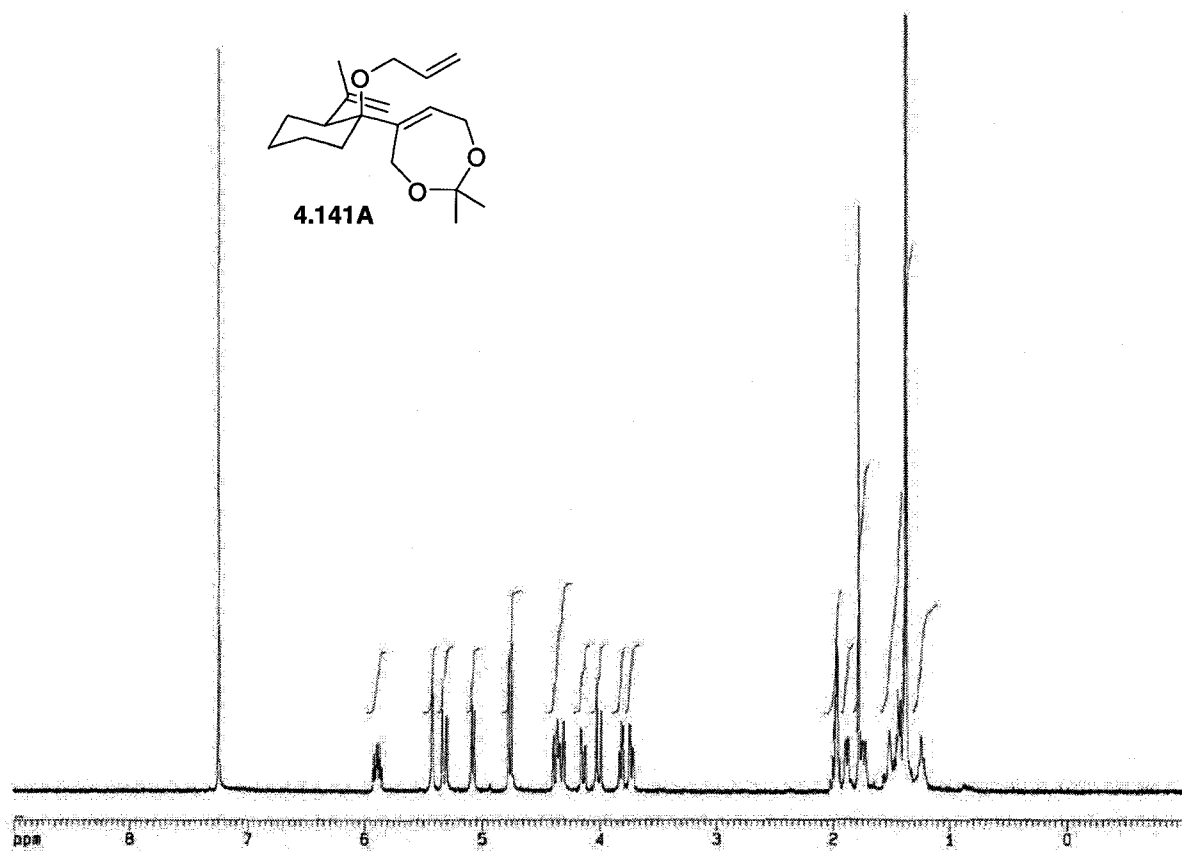
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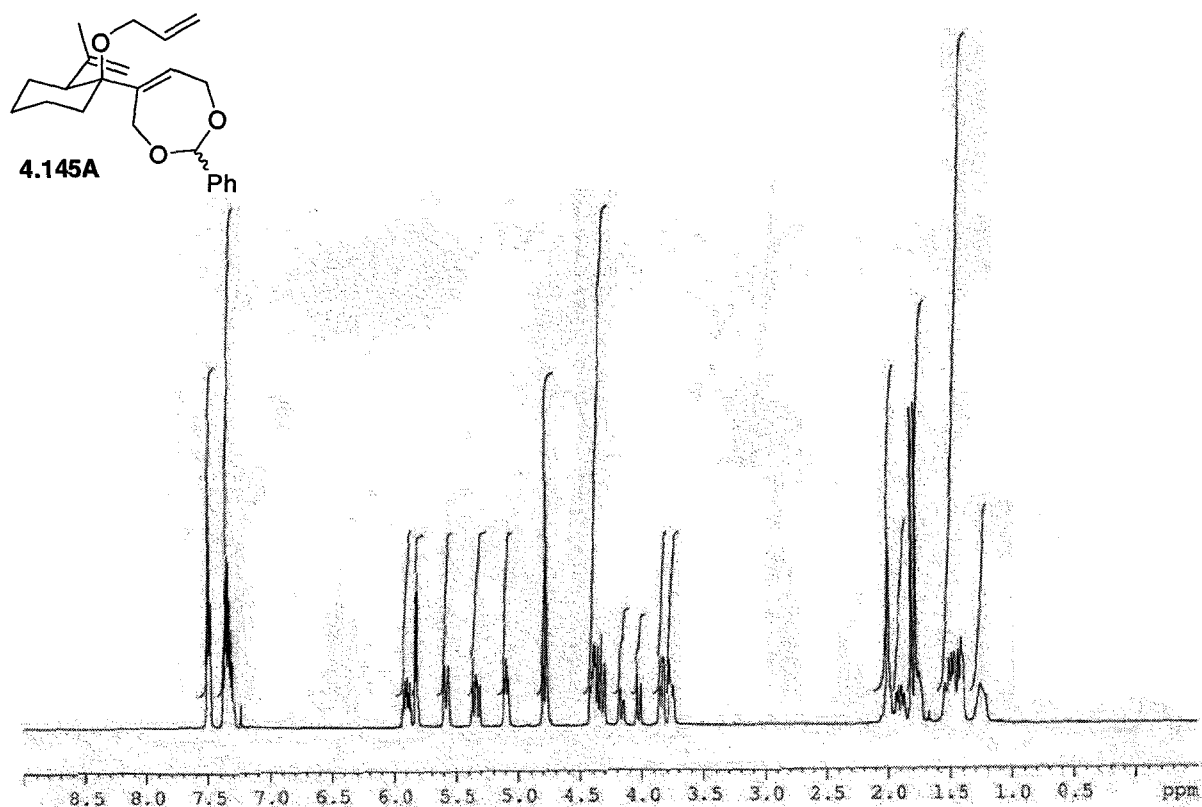
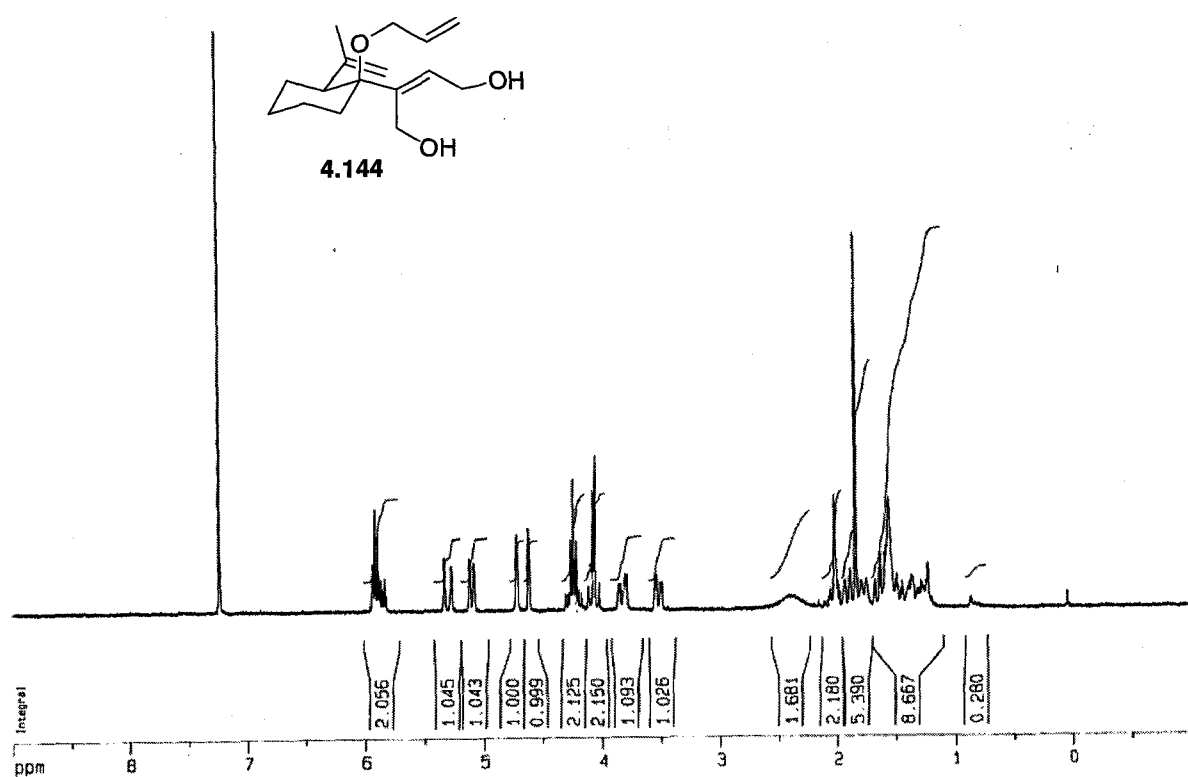


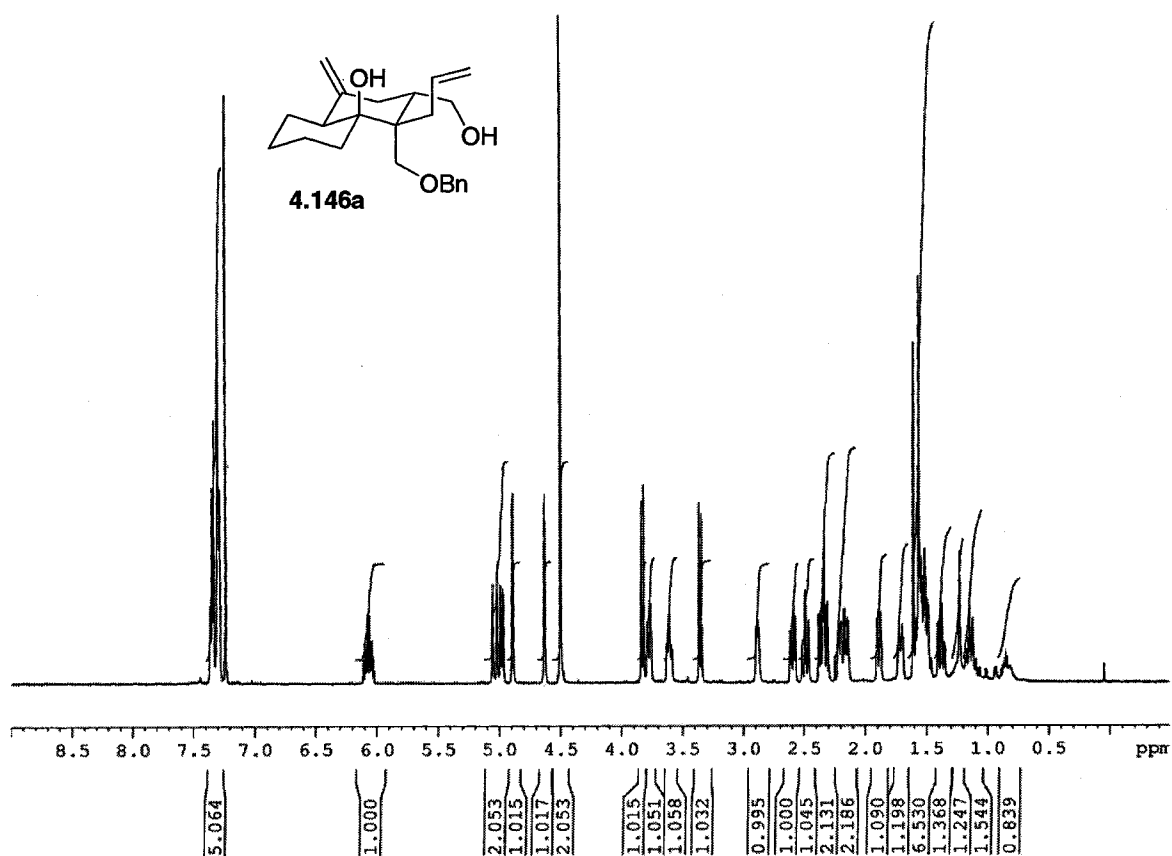
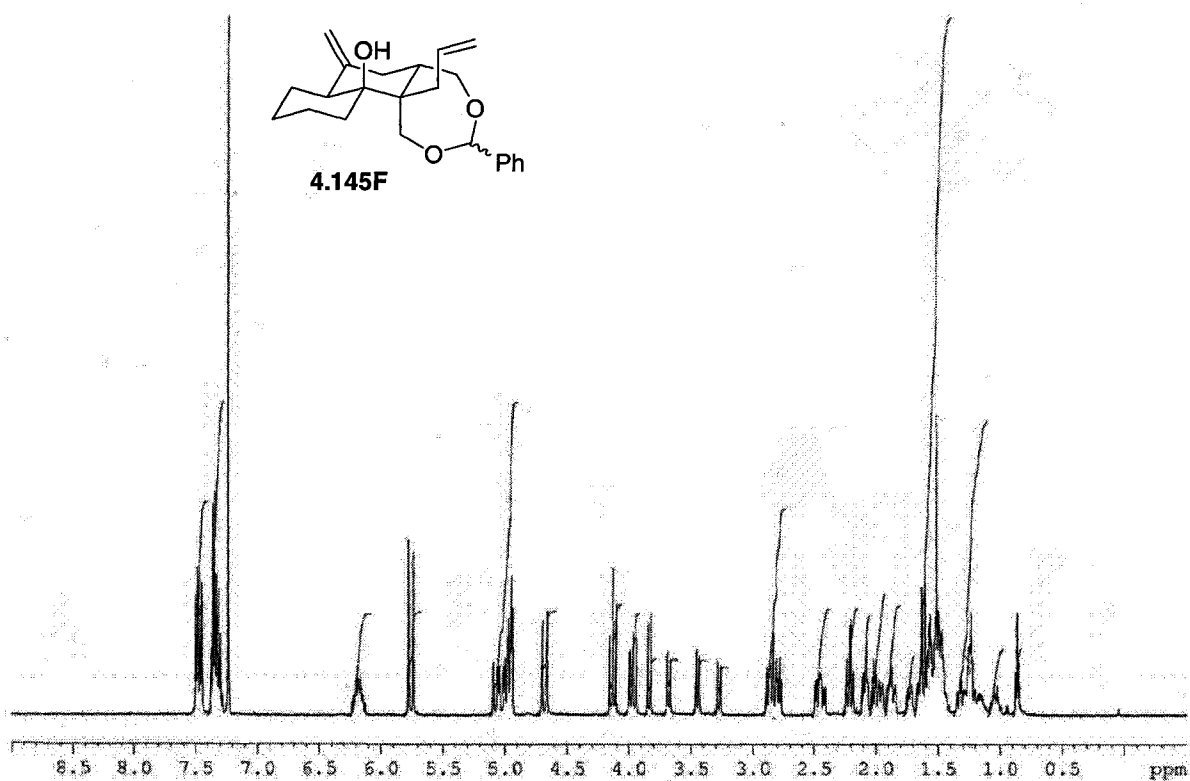
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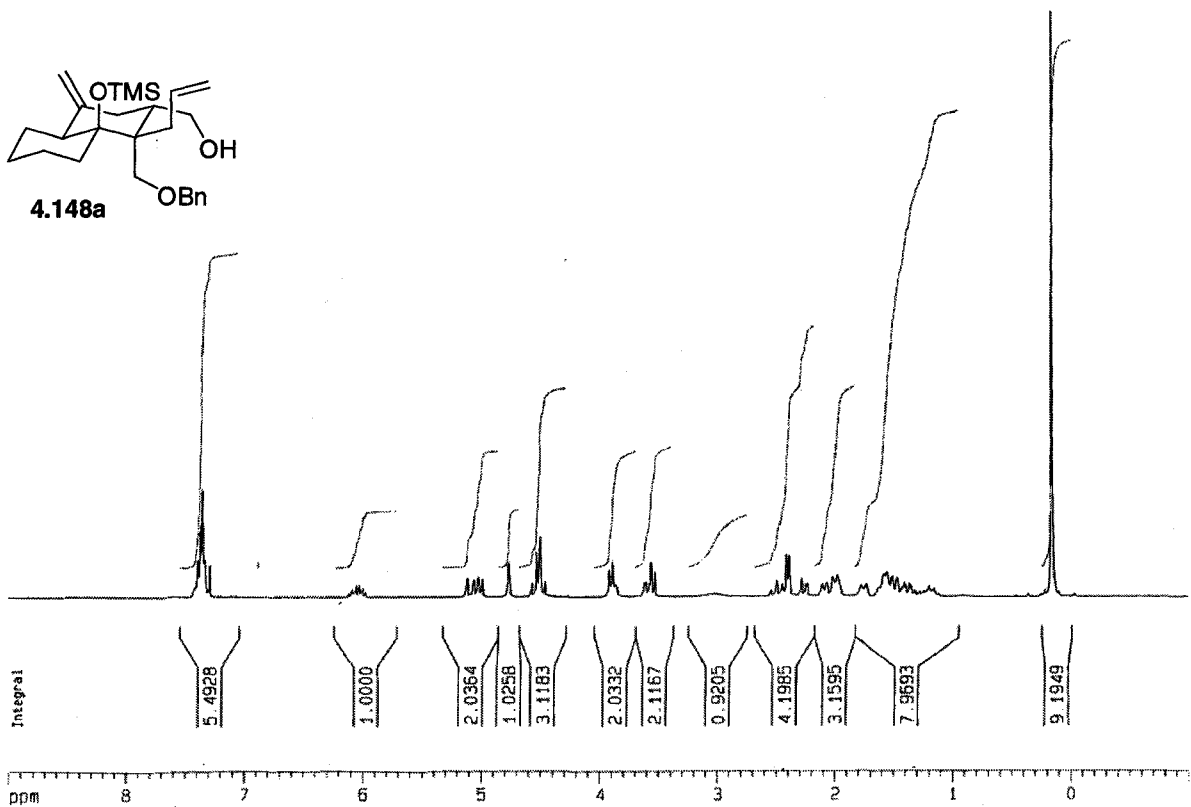


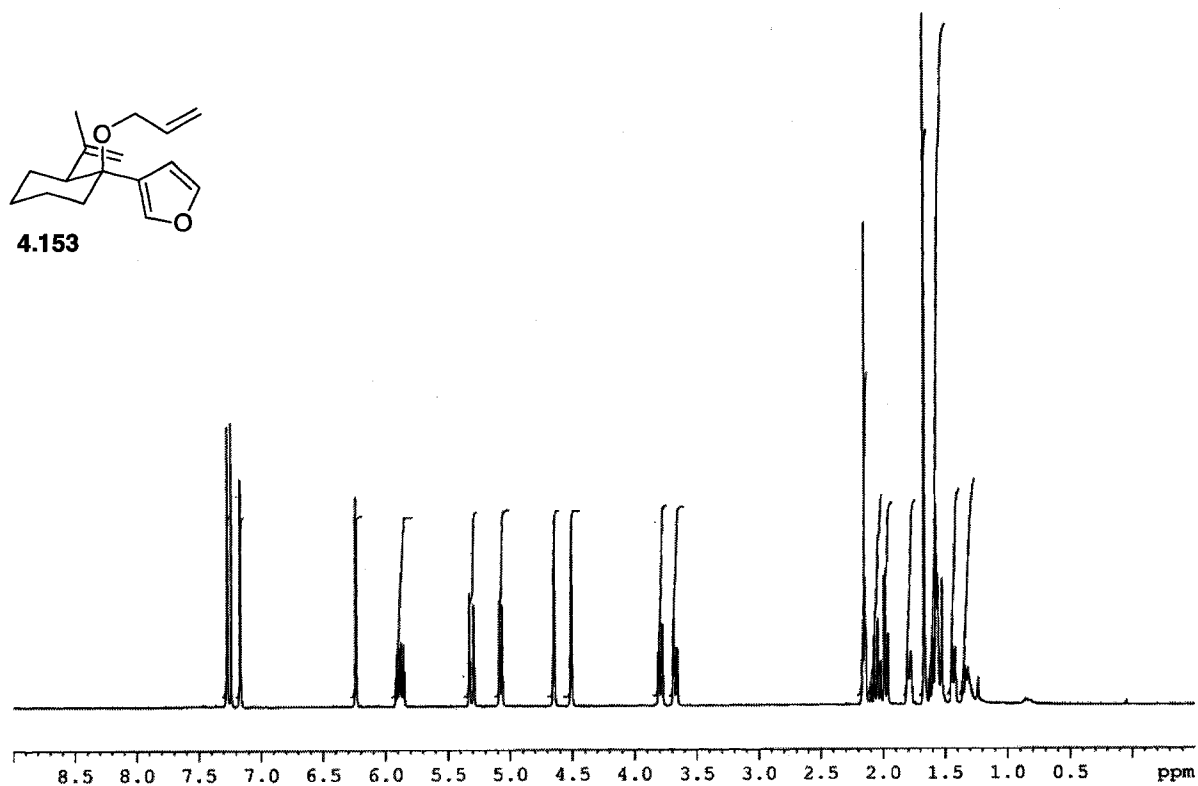
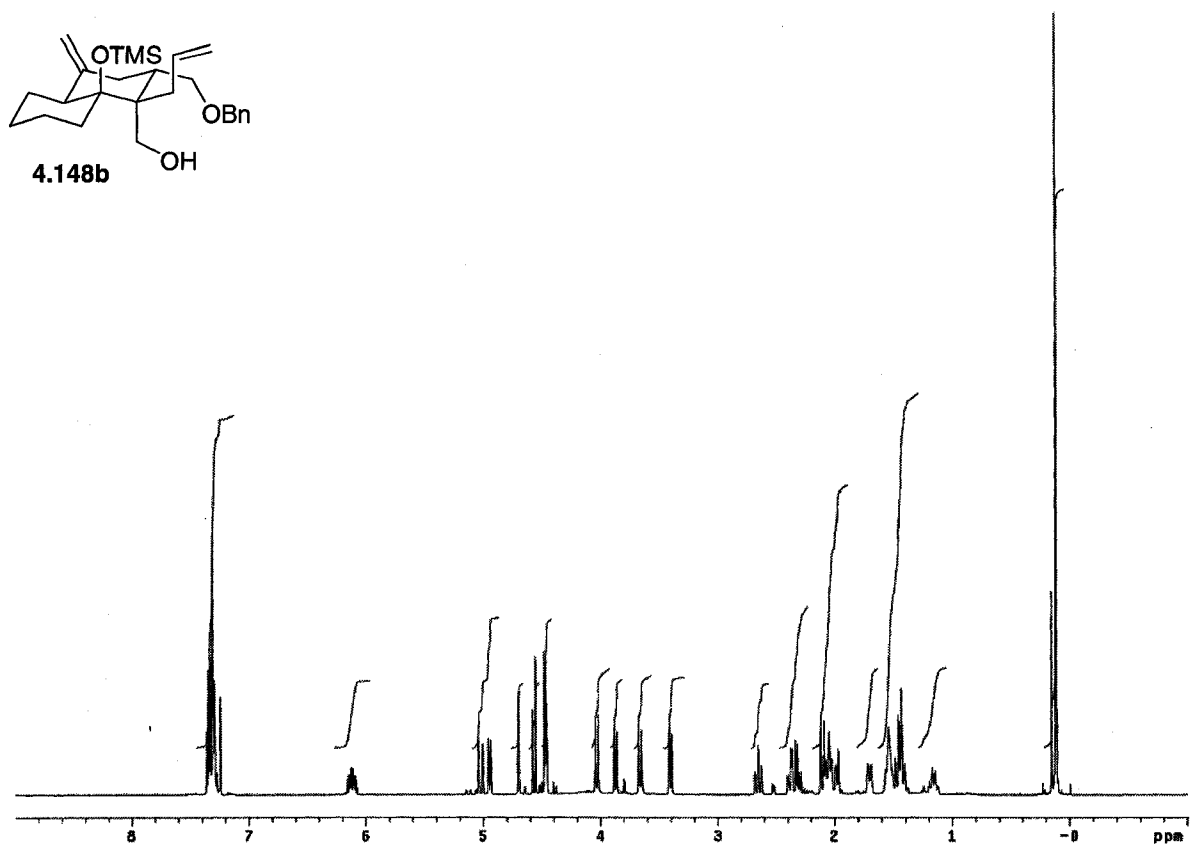


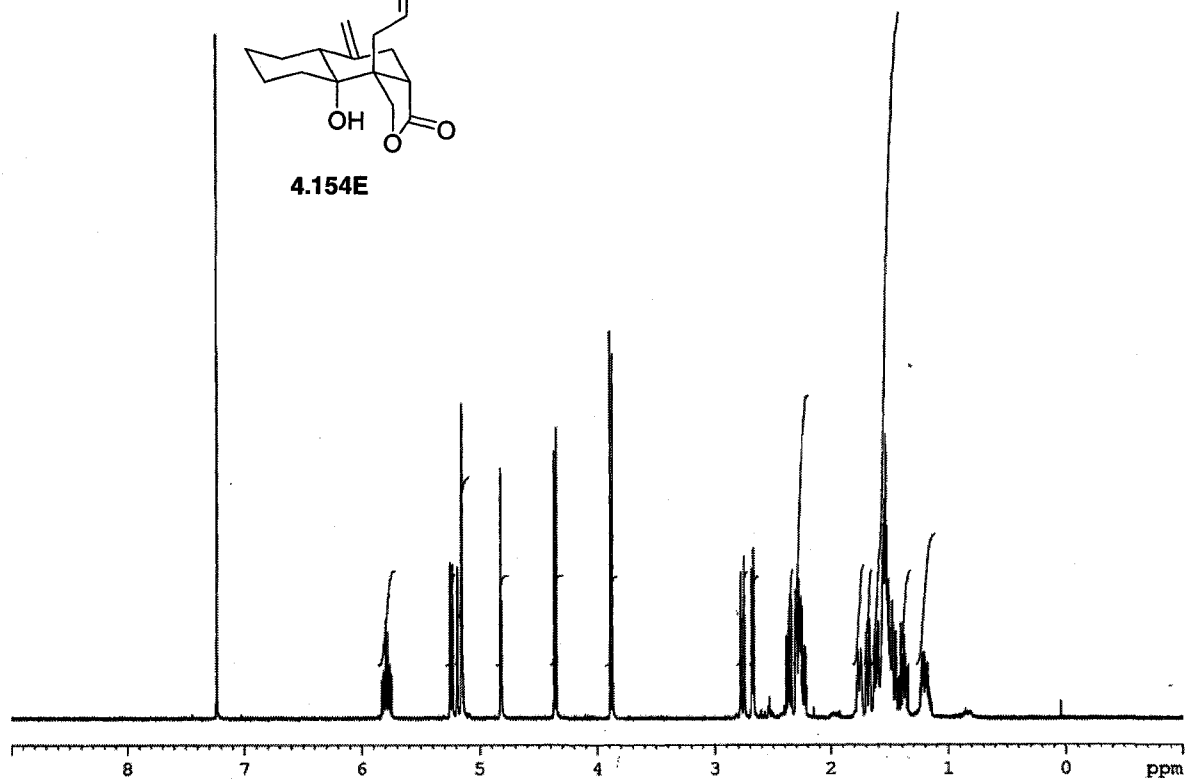
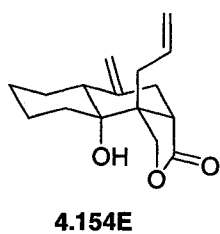
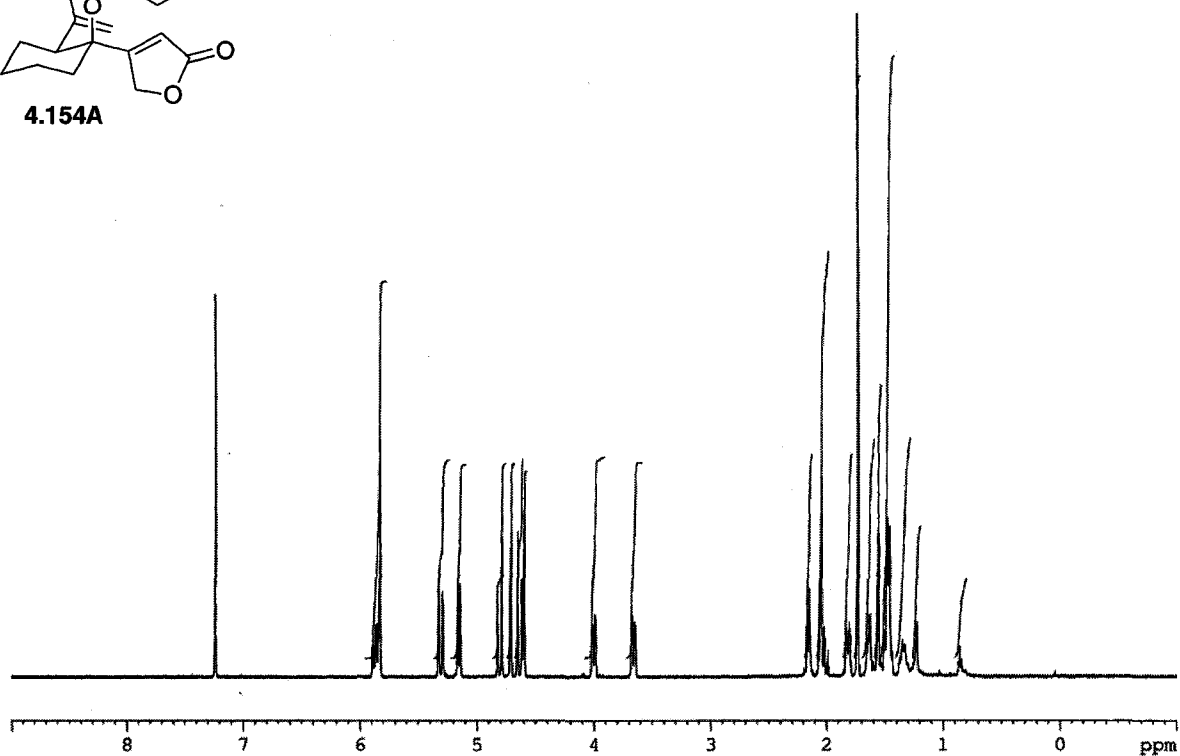
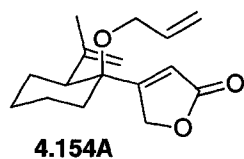


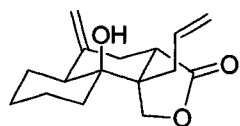




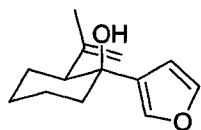
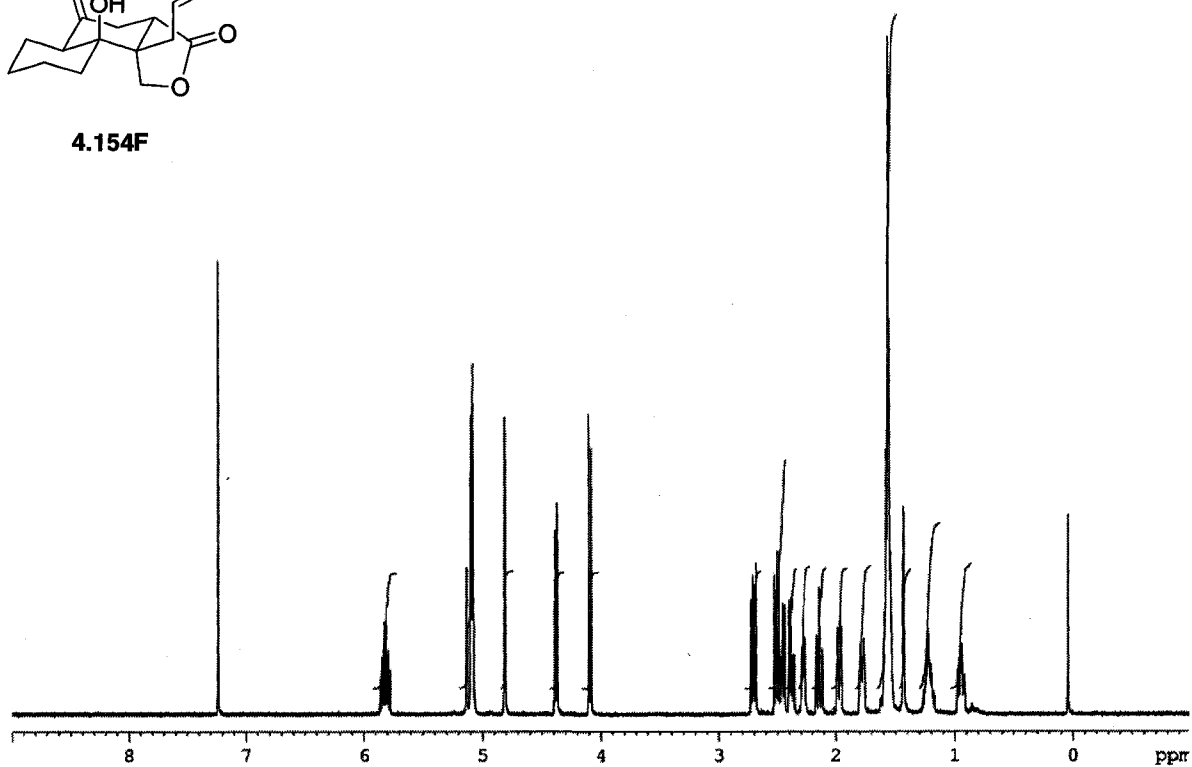




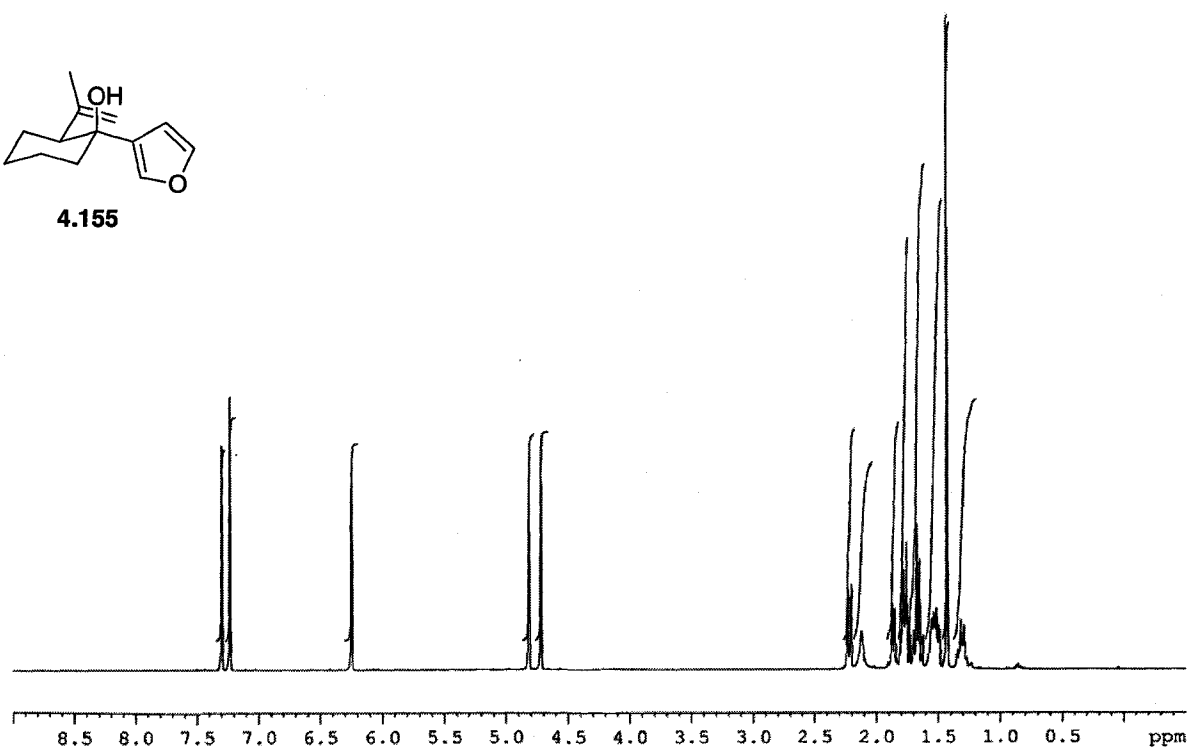


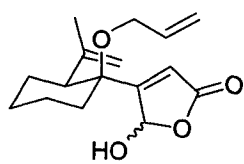


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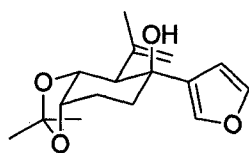
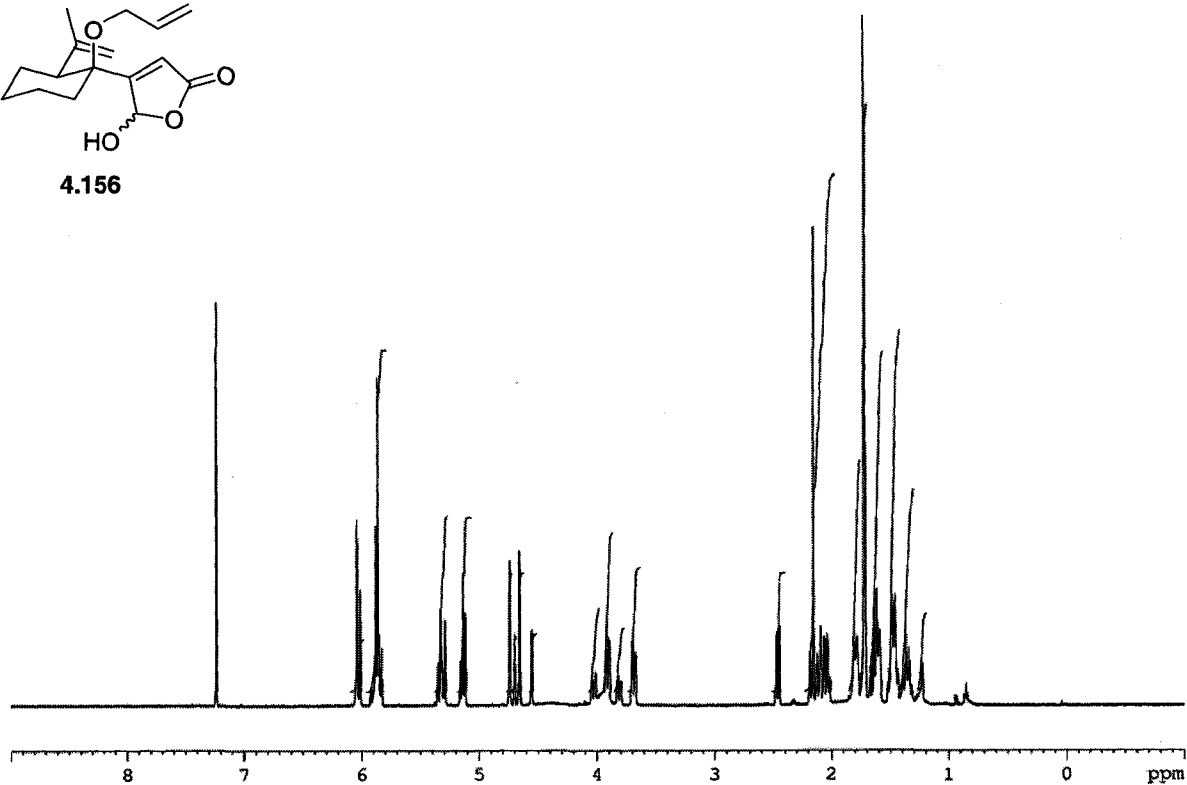


4.155





4.156



4.157a

