uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

uOttawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Rachel Lynn Beingessner
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

Ph.D. (Chemistry)
GRADE / DEGREE

Department of Chemistry
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Application of the Hydroxy-Directed Diels-Alder Reaction Toward the Total Synthesis of Havellockate

TITRE DE LA THÈSE / TITLE OF THESIS

Louis Barriault
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Robert Ben

Jeffrey Manthorpe

Gregory Dake

William Ogilvie

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

Application of the Hydroxy-Directed Diels-Alder Reaction Toward the Total Synthesis of Havellockate

by

Rachel Lynn Beingessner

Thesis submitted to the

Faculty of Graduate and Postdoctoral Studies

In partial fulfillment of the requirements

For the PhD degree in Chemistry

Candidate

Rachel Lynn Beingessner

Supervisor

Prof. Louis Barriault

Ottawa-Carleton Chemistry Institute

Faculty of Science

University of Ottawa

Your file Votre référence
ISBN: 978-0-494-49329-8
Our file Notre référence
ISBN: 978-0-494-49329-8

This thesis is dedicated to Grandma Lucy

Abstract

This thesis describes our efforts into the synthesis of a natural product named havellockate, which was isolated from a soft coral in the Indian Ocean. This highly compact diterpenoid contains a *cis*-fused hydrindane core that bears eight stereogenic centers as well as a seco- and spiro-lactone.

The early part of this thesis details the application of the hydroxy-directed Diels-Alder reaction to provide rapid entry into the core of the molecule. The subsequent chapters describe the four approaches that were investigated for installing the side-chain of this natural product which contains a challenging stereogenic center. These approaches which include two different Claisen rearrangements, a Diels-Alder reaction as well as a cuprate addition onto an α,β-unsaturated carbonyl compound are presented in detail.

Acknowledgements

I would like to express my gratitude and appreciation to my supervisor Professor Louis Barriault, who throughout the course of this thesis provided much guidance and motivation. I have learned tremendously from him and for this, I am forever indebted.

I would like to thank my family for all of their love and support during my time here in Ottawa, especially during the most stressful moments.

I thank my husband for his unending patience and understanding during my studies. He was always there for me and has undoubtedly contributed to my success.

I would like to thank Lise-Anne Prescott for her contributions to this project. She was a joy to work with and I wish her well in her future endeavors.

I would also like to thank all of my colleagues in the laboratory, the department and the university for providing an enjoyable and stimulating environment.

Finally I would like to thank NSERC and OGSST for financial support during my Ph.D. studies.

Table of Contents

List of Figures

List of Schemes

List of Tables

Experimental index

List of Abbreviations

acac	acetylacetonate
Bn	benzyl
CSA	camphorsulfonic acid
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	methyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
Et	ethyl
Equiv.	equivalents
FTIR	fourier transform Infrared
h	hour
HDDA	hydroxy-directed Diels-Alder
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
LAH	lithium aluminum hydride
LDA	lithiumdiisopropylamide

LUMO	lowest occupied molecular orbital
Me	methyl
MHz	mega hertz
min	minute
MS	molecular sieves
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
O/N	overnight
PCC	pyridinium chlorochromate
Ph	phenyl
PPM	parts per million
pTSA	*para*-toluenesulfonic acid
PMBCl	4-methoxybenzyl chloride
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
rt	room temperature
SM	starting material
TBAF	tetrabutylammonium fluoride
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMSCl	trimethylsilyl chloride

TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPAP	tetrapropylammonium perruthenate

1

Introduction

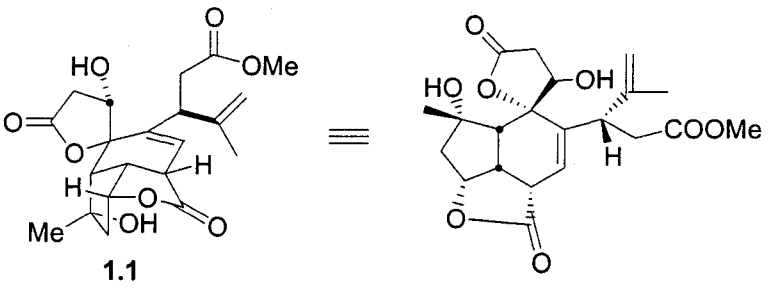
Marine organisms furnish a seemingly endless supply of novel compounds often containing complex carbon skeletons.[1] Soft corals for example, which belong in the family Alcyoniidae, produce large quantities of structurally diverse secondary metabolites in their tissues that are thought to have roles in defense, competition and reproduction of the organism.[2] Quite interestingly, within the family Alcyoniidae, a single genus such as *Sinularia* consists of almost 90 different species and the chemistry amongst this species is diversified; spanning the range of sesquiterpenes to diterpenes.[2]

Advances in chromatographic separation techniques, high-field NMR and X-ray crystallography have made it possible to elucidate the structure of many of these metabolites even though they are isolated in very small quantities. For synthetic organic chemists, these molecules offer unique synthetic challenges due the structural complexity and numerous stereocenters that are often present. Moreover, they provide an opportunity to learn new chemical transformations and patterns of reactivity in the course of reaching the objective of the total synthesis of the compound.

1.1 Havellockate

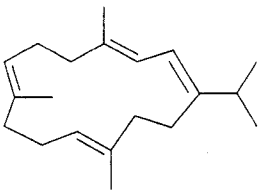
During their search for bio-active secondary metabolites, Anjaneyulu and coworkers discovered a novel diterpenoid in 1998 from the soft coral *Sinularia granosa* located on Havellock Island in the Indian Ocean.[3] The structure of this novel compound later named havellockate (**1.1**), was established without ambiguity by NMR spectroscopy and X-ray crystallography (Figure 1.1).

Figure 1.1: *Havellockate*



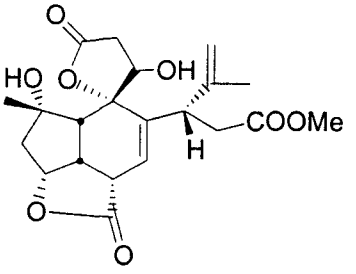
The key structural features of this molecule which pose a synthetic challenge include the *cis*-fused hydrindane core which bears eight stereogenic centers and the presence of both a seco- and spiro-lactone. As with the other known diterpenoids isolated from the *Sinularia* genus,[2] havellockate is believed to have been derived from the fourteen-membered carbocyclic cembrane nucleus shown in Figure 1.2.

Figure 1.2: *14-Membered cembrane nucleus*

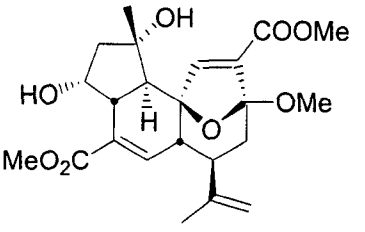


This natural product has structural components which are similar to those of other tetracyclic diterpenoids such as mandapamate (**1.2**)[4] and isomandapamate (**1.3**)[5] isolated from *Sinularia dissecta* and *Sinularia maxima* respectively as illustrated in Figure 1.3.

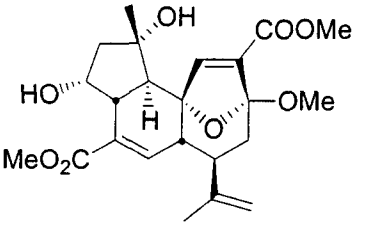
Figure 1.3: *Structure of havellockate (1.1), mandapamate (1.2) and isomandapamate (1.3)*



havellockate (**1.1**)



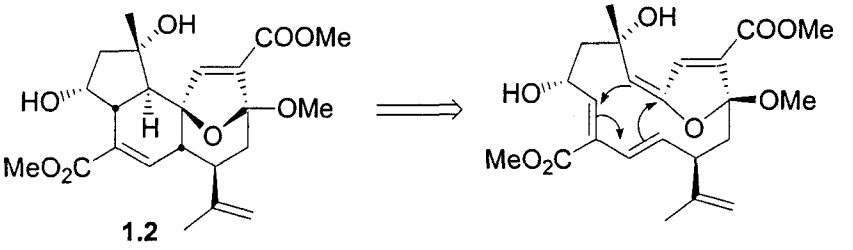
mandapamate (**1.2**)



isomandapamate (**1.3**)

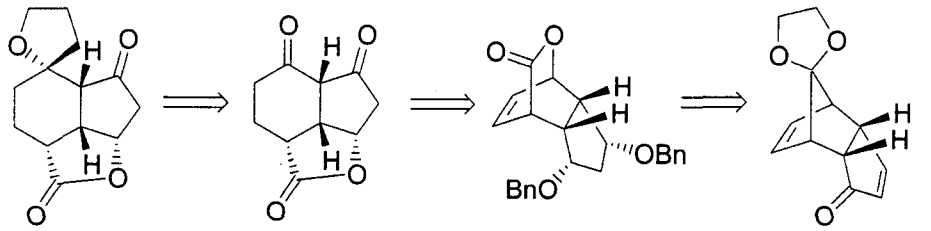
Furthermore, the tetracyclic skeleton of mandapamate is believed to originate biosynthetically from a transannular Diels-Alder reaction shown in Scheme 1.1. Thus, the application of a Diels-Alder reaction towards the synthesis of the core of havellockate seems an attractive and logical strategy.

Scheme 1.1: *Biosynthesis of 1.2 via a transannular Diels-Alder reaction*



Although havellockate is an interesting and challenging synthetic target, to the best our knowledge, only Mehta and Senthil Kumaran[6] have attempted its synthesis. In 2001, they published their approach to the core of the molecule **1.4**, which was accomplished in 20 steps from the endo [4+2] cycloadduct **1.7** shown in Scheme 1.2.

Scheme 1.2: *Mehta and Senthil Kumaran's approach to the core of havellockate*



1.4 **1.5** **1.6** **1.7**

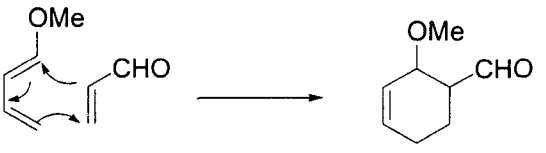
The purpose of this thesis was to design and implement a novel and more efficient synthetic strategy for the total synthesis of havellockate. We proposed that a hydroxy-directed Diels-Alder reaction developed in the Barriault lab,[7] could be used to rapidly access the *cis*-fused hydrindane core. The development of this Diels-Alder reaction as well as its potential application in the synthesis of this molecule are discussed in the following sections of this chapter.

1.2 The Diels-Alder Reaction

1.2.1 Diels-Alder reaction: Regioselectivity, Stereoselectivity and Facial selectivity

The Diels-Alder reaction has profoundly influenced the art of total synthesis.[8] In this six-electron [4+2] cycloaddition reaction, a 1,3-diene reacts with the π-bond of a dienophile to provide a six-membered ring product containing one π-bond (Scheme 1.3).

Scheme 1.3: *Example of a Diels-Alder reaction*

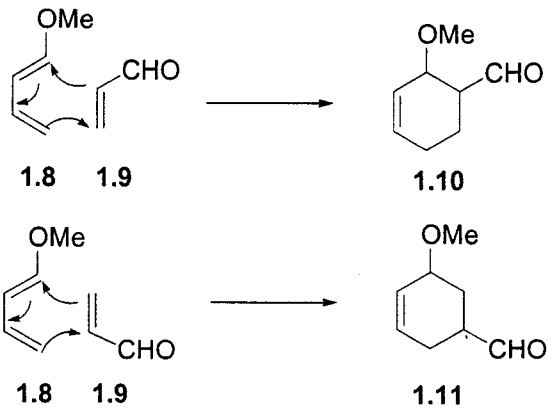


diene dienophile

1.8 **1.9** **1.10**

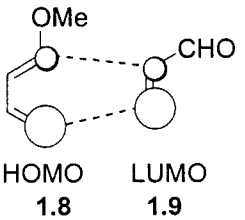
Although seemingly simple, the regiochemistry, stereoselectivity (*endo* vs *exo*) and facial selectivity of the reaction need to be addressed. For example in Scheme 1.4, dienophile **1.9** is shown to approach diene **1.8** with two possible orientations leading to **1.10** and **1.11**.

Scheme 1.4: *Regiochemical considerations of a Diels-Alder reaction*



The regiochemical outcome of this reaction can be determined by considering the coefficients of the atomic orbitals of the HOMO of the diene and the LUMO of the dienophile (Figure 1.4).[9] That is, the Diels-Alder reaction proceeds such that the diene terminus with the largest coefficient in the HOMO interacts with the terminus of the dienophile with the largest coefficient in the LUMO.

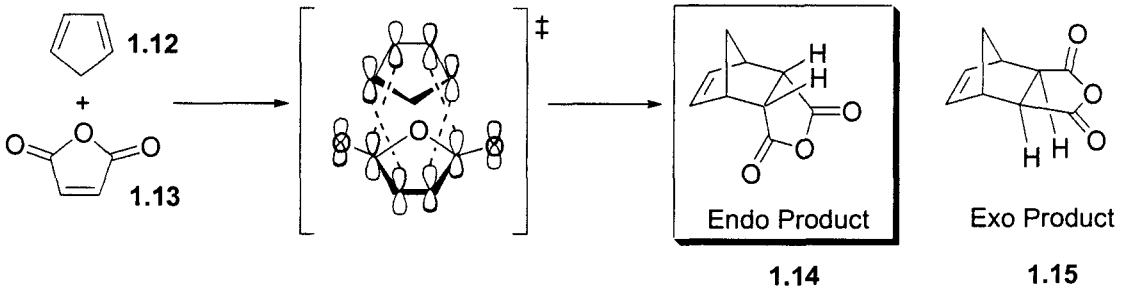
Figure 1.4: *HOMO of the diene reacting with the LUMO of the dienophile in a Diels-Alder reaction*



In a Diels-Alder reaction where the diene and dienophile are not sterically encumbered, the stereoselectivity of the cycloaddition is governed by electronic factors.[9] As illustrated in

Scheme 1.5, the reaction between cyclopentadiene (**1.12**) and maleic anhydride (**1.13**) can yield two products, **1.14** and **1.15**, which result from an *endo* and *exo* transition state respectively. The *endo* product **1.14** is the kinetic product of the reaction and is preferred due to the presence of secondary orbital interactions in the transition state that are represented by dashed lines. These orbital interactions are energetically favorable enough to counteract the steric interactions at the transition state, which results in this less thermodynamically stable *endo* adduct being the major product of the reaction.

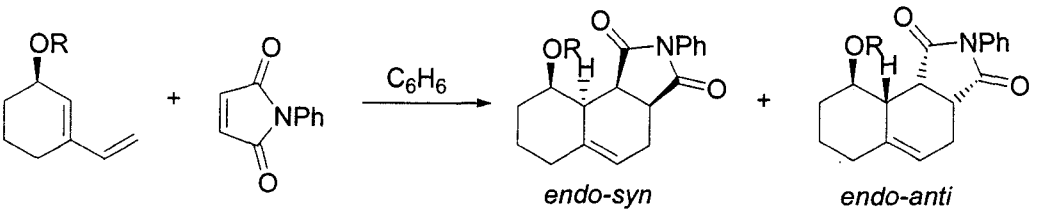
Scheme 1.5: *Stabilization of the endo transition state of a Diels-Alder reaction through secondary orbital overlap*



A third feature to consider in a Diels-Alder reaction is the facial selectivity (diastereoselectivity), which is important when either the dienophile or diene possess two different reactive faces due to the presence of at least one chiral center.[10] Franck and coworkers[11] have shown that heteroatoms present at the α-allylic position of semicyclic dienes can help control the diastereoselectivity. For example, the Diels-Alder reaction between the six-membered ring dienophile **1.16** and *N*-phenylmaleimide (**1.17**) furnished the *endo-syn* adduct **1.18** as the major product when R of **1.16** was hydrogen atom (Scheme 1.6). Alternatively, under the same reaction conditions, the *endo-anti* adduct **1.19** was favored when R of **1.16** was a methyl group. However, this selectivity was greatly influenced by the

choice of solvent. When DMF was used instead of benzene, the *endo-anti* adduct became the major product (83%) of the reaction when R was a hydrogen atom.

Scheme 1.6: *Endo-syn/anti selectivity of a Diels-Alder reaction using 6-membered ring dienes with α-allylic substituents*

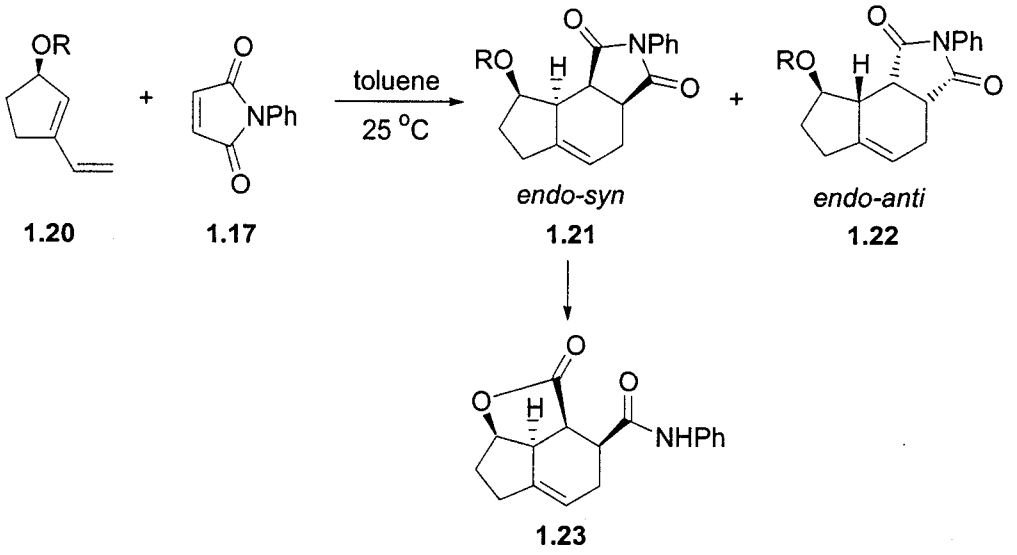


		endo-syn	endo-anti
1.16	**1.17**	**1.18**	**1.19**
R = H		63%	37%
R = CH_3		11%	89%

Similar studies were also conducted independently by Overman and Hehre using semi-cyclic 5-membered ring dienes.[12] As illustrated in Scheme 1.7, their observations followed those of Franck and coworkers. That is, the *endo-syn* adduct **1.23**, was the major product of the Diels-Alder reaction between diene **1.20** and dienophile **1.17** when R of **1.20** was a hydrogen atom. Alternatively, when R was a methyl group, the major product was the *endo-anti* adduct **1.22**. Once again, the diastereoselectivity of the reaction was dramatically affected by the choice of solvent.

Although both groups showed that the facial selectivity of the Diels-Alder reaction can be controlled by α-allylic heteroatomic substituents on the diene, the exact nature of their influence (i.e electronic vs steric) was debated.[13]

Scheme 1.7: *Endo-syn/anti selectivity of a Diels-Alder reaction using 5-membered ring dienes with α-allylic substituents*

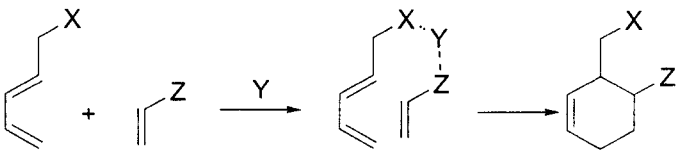


R = H	(**1.23**) 53%	28%
R = CH_3	(**1.21**) 23%	77%

1.2.2 Lewis Acids and Temporary Tethers

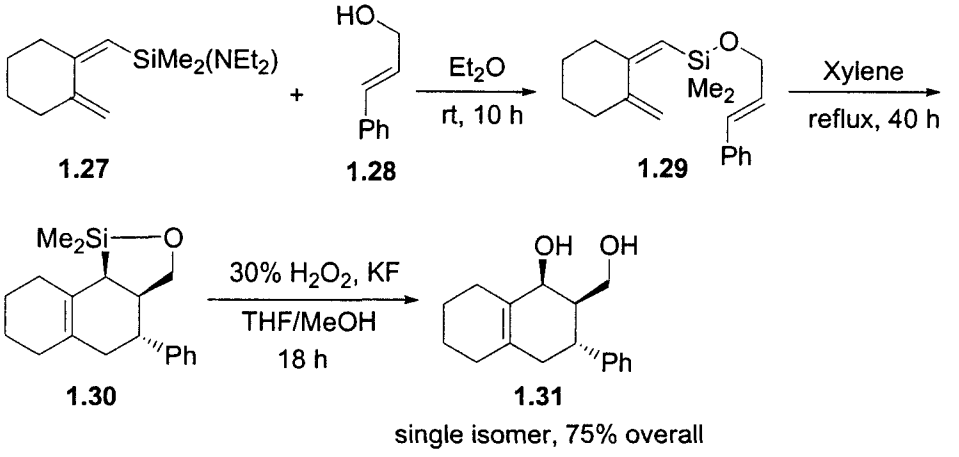
The use of temporary metal tethers in cycloaddition reactions is well established in the literature.[14] Of particular interest to this thesis is the use of metal tethers to link a dienophile and diene together in a Diels-Alder reaction (Figure.1.5).[7] The inherent constraining effects that result by transforming an intermolecular Diels-Alder reaction into an intramolecular process, help to control the regio- and π-facial selectivity of the reaction.

Figure 1.5: *Tethering a Diels-Alder reaction*



Tamao and Ito[15] were one of the first groups to establish the use of silicon as a disposable metal tether. By creating a silyl acetal linkage between diene **1.27** and dienophile **1.28**, they were able to perfectly control the regio- and stereoselectivity of the Diels-Alder reaction illustrated in Scheme 1.9. Perhaps the greatest limitation of this approach however, was that additional synthetic operations were required to introduce and then later remove the silicon tether.

Scheme 1.9: *Tamao and Ito's silicon tethered Diels-Alder reaction*



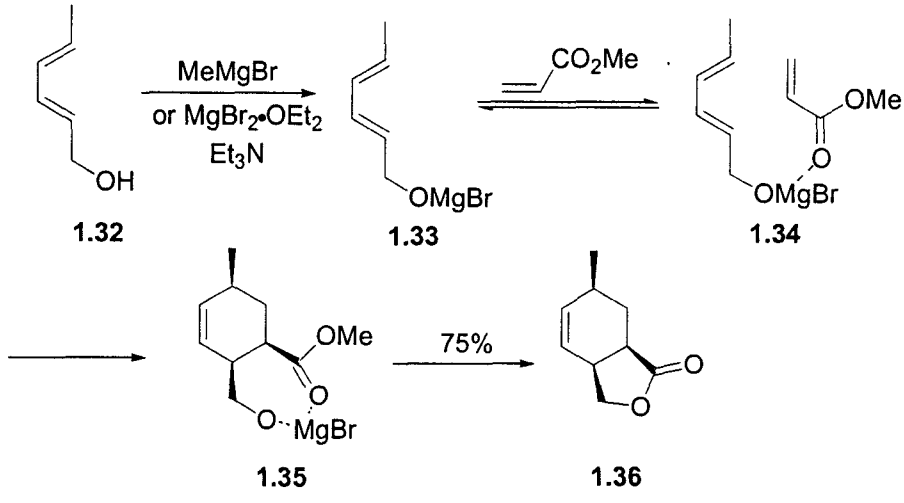
Other metal-based temporary tethers such as Al,[16] Zn,[17] and B[18] have also been effective in controlling the selectivity of the Diels-Alder reaction in the presence of nonactivated dienophiles. All of these reactions however, required harsh conditions and used dienes with primary alcohols (X = O in Figure 1.5) that participated in the tethering process.

A natural extension of this methodology would be to improve the selectivity *and* the reactivity of an intermolecular Diels-Alder reaction so that milder conditions could be employed. This could be accomplished by using a Lewis acid and an activated dienophile.

The Lewis acid would accelerate the rate of the reaction by coordinating to the dienophile[19] and enhance the selectivity by also tethering to the diene.

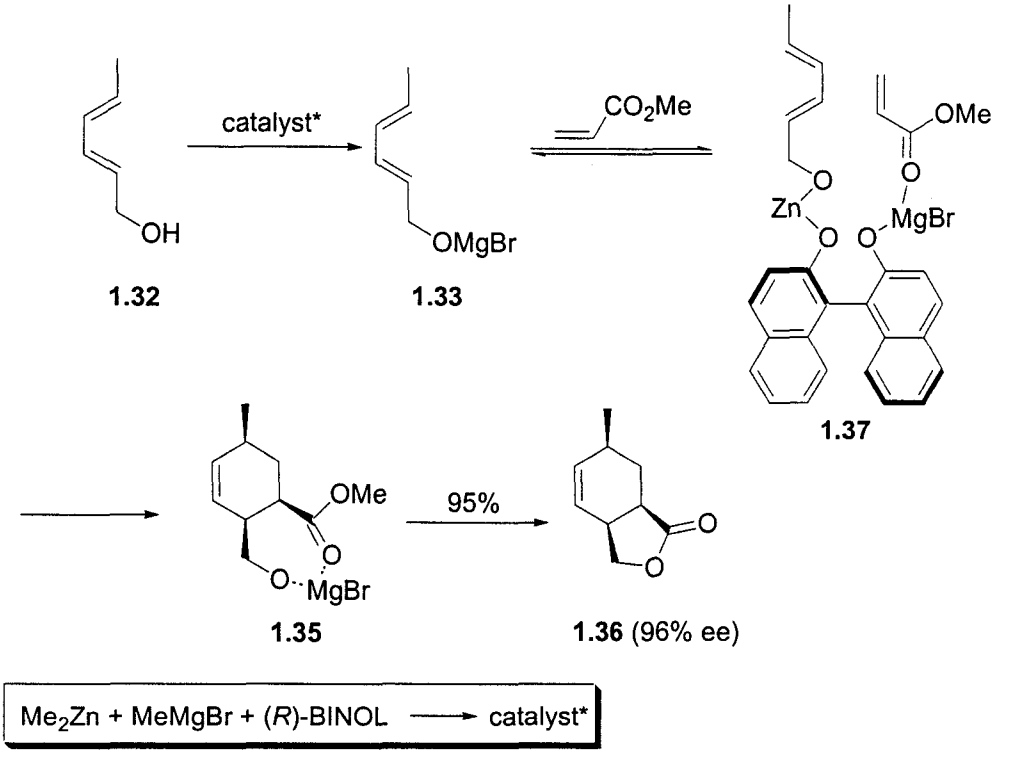
This concept was explored by Ward *et al.* in 2000.[20] They determined that the Diels-Alder reaction between **1.32** and methyl acrylate could proceed smoothly under mild conditions in the presence of $MgBr_2 \cdot OEt_2$ and triethylamine or methylmagnesium bromide, to provide **1.36** in 75% yield with excellent selectivity (Scheme 1.10).

Scheme 1.10: *Ward's use of magnesium as a tether and Lewis acid*



In 2005, Ward and Souweha[21] published a catalytic enantioselective version of this reaction. By coordinating diene **1.32** and methyl acrylate to a chiral bimetallic Lewis acid catalyst generated from Mg(II) and Zn(II) with BINOL, the regio-, diastereo-, and enantioselectivity of the reaction were well controlled to furnish a single adduct (Scheme 1.11).

Scheme 1.11: *Ward's catalytic enantioselective Diels-Alder reaction*



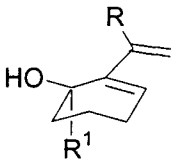
1.2.3 Hydroxy-Directed Diels-Alder Reaction (HDDA)

The work described by Ward *et al.* clearly demonstrates the reactivity and stereochemical benefits of a Lewis-acid catalyzed Diels-Alder reaction that is based on a self-assembled complex between the diene and dienophile. Unfortunately, this methodology was limited to dienes possessing primary alcohols.

To expand the scope of this reaction and make the methodology a truly powerful strategy for natural product synthesis, Barriault, Thomas and Clément in 2003 investigated the use of semicyclic dienes possessing secondary and tertiary alcohols in the Diels-Alder reaction.[7] Two types of dienes, defined as Type I and Type II were used for these studies as illustrated in Figure 1.6.

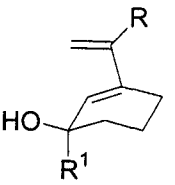
Figure 1.6: *Type I and Type II semicyclic dienes explored by Barriault and coworkers*

Type I



R = H, Me
R^1 = H, Ph, $C(CH_3)=CH_2$, $CH_2CH=CH_2$, $H_2C=CH_2$

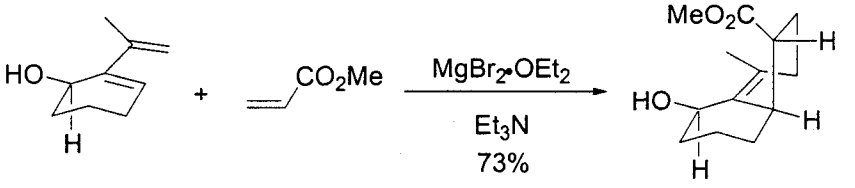
Type II



R = H, Me, Ph
R^1 = H, Ph, DHP, $C(CH_3)=CH_2$

Various Lewis acids such as $ZnBr_2$ and $AlMe_3$ were explored to promote the Diels-Alder reaction between a Type I or Type II diene and an unsymmetrical dienophile such as acrolein, methacrolein or methyl acrylate. After much optimization it was determined that magnesium Lewis acids, in particular PhMgBr or $MgBr_2 \cdot OEt_2$ and Et_3N provided the Diels-Alder adduct with the highest yields (30-89%) and greatest selectivity (dr>25:1). An example of a Diels-Alder reaction using a Type I diene is provided in Scheme 1.12.

Scheme 1.12: *Example of a hydroxy-directed Diels-Alder reaction using a Type I diene*

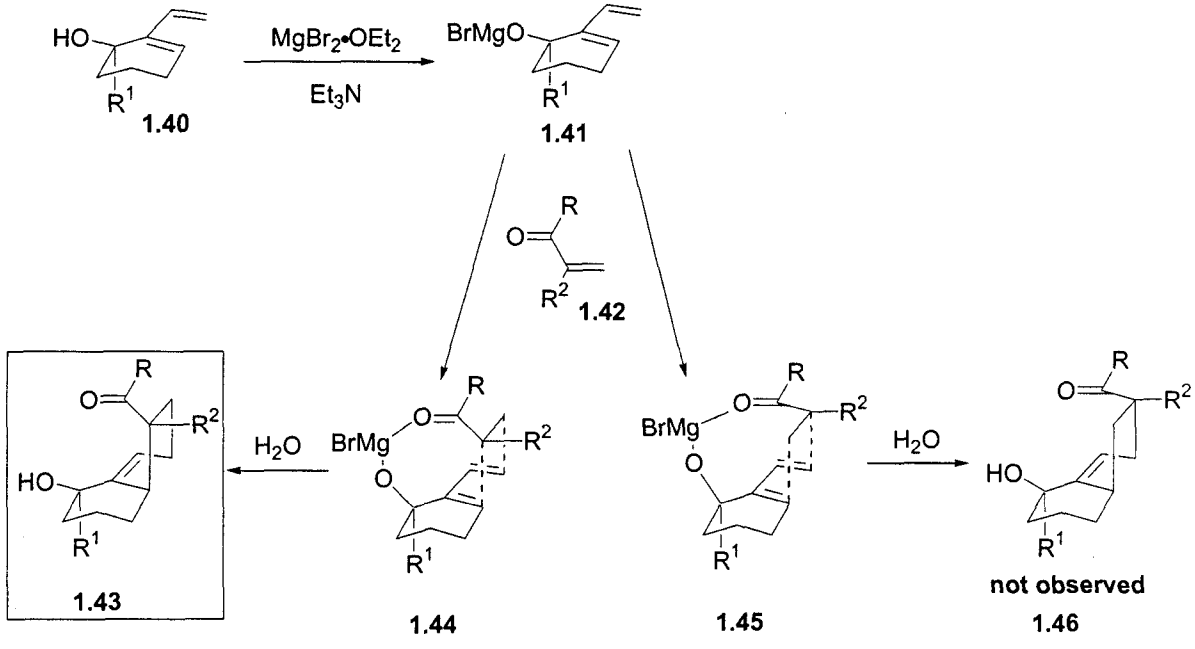


1.38 dr > 25:1 **1.39**

Barriault and coworkers rationalized the high regio- and stereoselectivity of the reaction according to Scheme 1.13 (for a general Type I diene). They proposed that the magnesium alkoxide species **1.41** that is generated from **1.40** in the presence of $MgBr_2 \cdot OEt_2$ and triethylamine complexes to the carbonyl group of dienophile **1.42.** This tethering facilitates an *endo* facial approach of the dienophile, *syn* to the tertiary alcohol (hence the

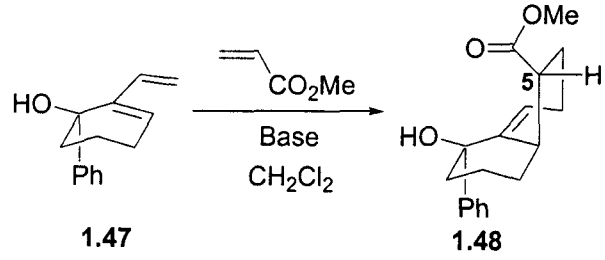
name hydroxy-directed Diels-Alder). In theory, this *endo* approach can occur via two possible transition states labeled **1.44** and **1.45,** which lead to an eight-membered ring intermediate and nine-membered ring intermediate respectively. However, since transition state **1.44** is favored for electronic reasons (i.e favorable overlapping of atomic orbitals) and because less strain is experienced when the dienophile approaches the diene, adduct **1.43** is exclusively observed. A similar justification was provided for the high selectivity observed with type II dienes as well.

Scheme 1.13: *Proposed mechanism for the hydroxy-directed Diels-Alder reaction*



It was also noted during the course of these studies that prolonged exposure (12 h) of **1.48** to $MgBr_2 \cdot OEt_2$ and triethylamine led to the epimerization at C5 as shown in Scheme 1.14. By changing the base to 2,6-lutidine, the diastereoselectivity was improved to 12:1.

Scheme 1.14: *Influence of base on the dr of the hydroxy-directed Diels-Alder reaction between* ***1.47*** *and methyl acrylate*

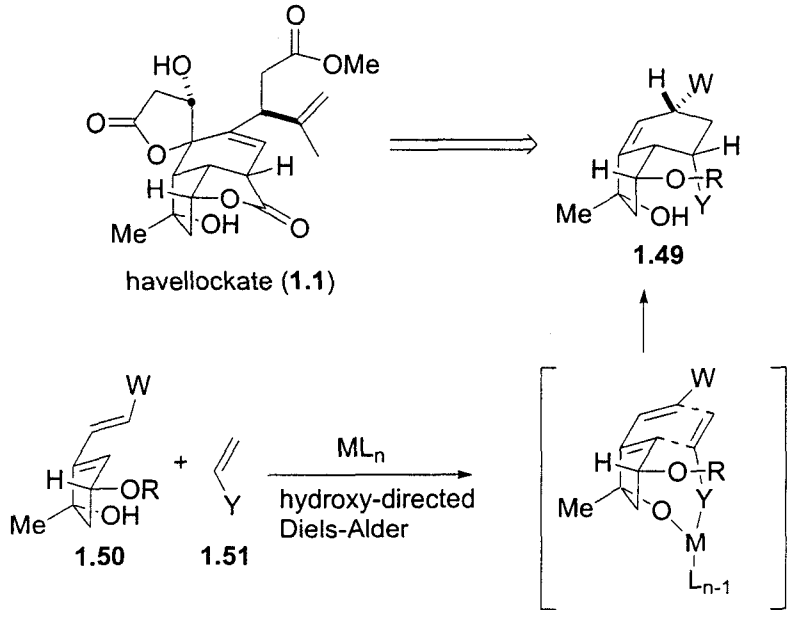


1.47 **1.48**

Base: Et_3N, 66% yield, dr 8:1 **or** 2,6-lutidine, 89% yield, dr 12:1

With the hydroxy-directed Diels-Alder reaction well established, it was now possible to demonstrate the power and utility of this reaction in natural product synthesis. It was proposed that the *cis*-fused hydrindane core present in havellockate could be rapidly obtained using this methodology (Scheme 1.15). The results of these studies are the focus of Chapter 2.

Scheme 1.15: *Application of the hydroxy-directed Diels-Alder reaction towards the synthesis of the core of havellockate*



References:

[1] Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17,* 1.

[2] Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *2,* 223.

[3] Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P.; Clardy, J.; Lobkovsky, E. *Tetrahedron Lett.* **1998**, *39*, 139.

[4] Venkateswarlu, Y.; Farooq Biabani, M. A.; Venkata Rami Reddy, M.; Prabhakar, Rao, T.; Kunwar, A. C.; Faulkner, D. J. *Tetrahedron Lett.* **1994**, *35,* 2249.

[5] Anjaneyulu, A. S. R.; Sagar, K. S.; Venugopal, M. J. R. V. *Tetrahedron* **1995,** *51,* 10997. Anjaneyulu, A. S. R.; Krishna Murthy, M. V. R.; Rao, G. V. *Tetrahedron* **1997**, *53,* 9301.

[6] Mehta, G.; Senthil Kumaran, R. *Tetrahedron Lett.* **2001**, *42*, 8097.

[7] Barriault, L.; Thomas, J. D. O. *J. Org. Chem.* **2003**, *68,* 2317.

[8] For a review see: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41,* 1668.

[9] For further information see: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions,* John Wiley & Sons, Trowbridge, 2000.

[10] Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, 876.

[11] Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chem. S.; Sihaed, A.. *J. Am. Chem. Soc.* **1990**, *112,* 8472.

[12] Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110,* 4625.

[13] Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109,* 663.

[14] Gauthier, D. R.; Zandi, K. S.; Shea, K. *Tetrahedron* **1998**, *54,* 2289.

[15] Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111,* 6478.

[16] Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117,* 6596.

[17] Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2,* 1283.

[18] Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121,* 450. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, A.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117,* 653. Shimada, S.; Osoda, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66,* 1254. Narasaka, K.; Shimada, K.; Osoda, N.; Iwasawa, N. *Synthesis* **1991**, 1171.

[19] Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960,** *82,* 4436.

[20] Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2,* 3937.

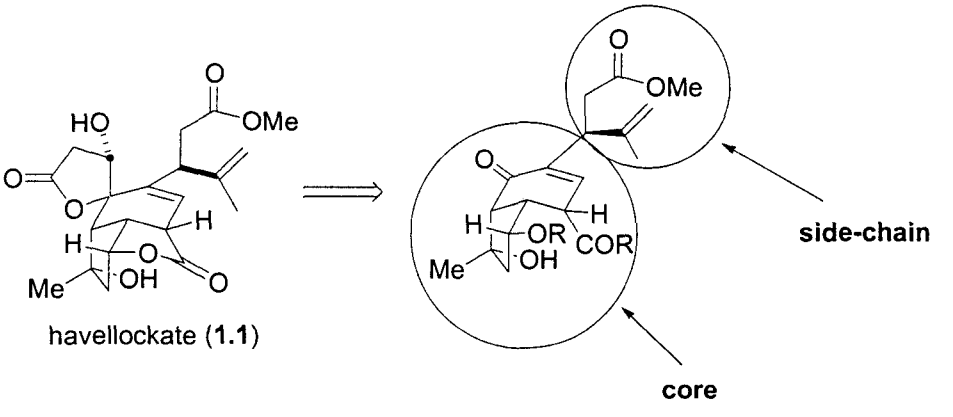
[21] Ward, D. E.; Souweha, M. S. *Org. Lett.* **2005**, *7,* 3533.

2

Synthesis of the Core

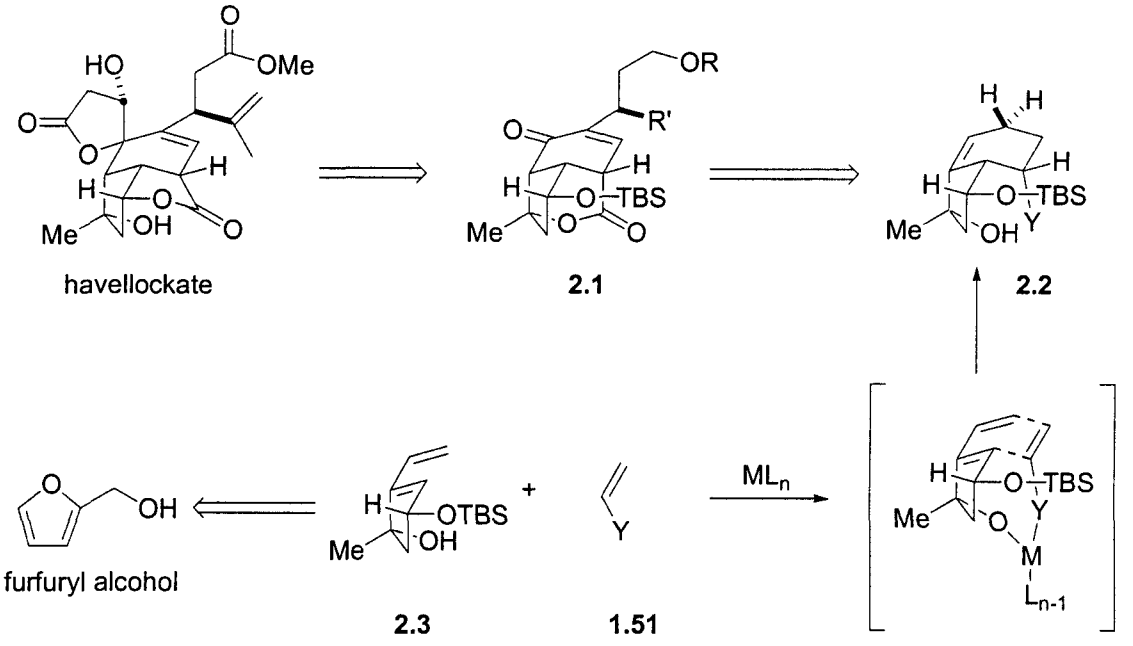
As discussed in Chapter 1, the goal of this project was to develop an efficient synthetic strategy for the total synthesis of havellockate. We recognized that the challenging aspects of this molecule were the *cis*-bicyclo[4.3.0]nonane core and the side-chain which contains a stereogenic center as shown in Scheme 2.1. The focus of this thesis was the construction of the side-chain which proved to be more challenging than anticipated. The synthesis of the core of the molecule, using an extension of the hydroxy-directed Diels-Alder (HDDA) reaction (Chapter 1) is credited to Julie Farand, a former M.Sc. student. The results of these studies are briefly summarized in this chapter along with improvements that were made to the original procedures published in her thesis in April 2004.

Scheme 2.1: *The cis-fused hydrindane core and side-chain of havellockate*



The synthesis commenced with the retrosynthetic analysis illustrated in Scheme 2.2. We proposed that havellockate could be readily generated from enone **2.1**. The bicyclo[4.3.0]nonane core **2.2** of the natural product could be accessed via a HDDA reaction between semicyclic diene **2.3** and dienophile **1.51**. Finally, diene **2.3** could be prepared from commercially available furfuryl alcohol.

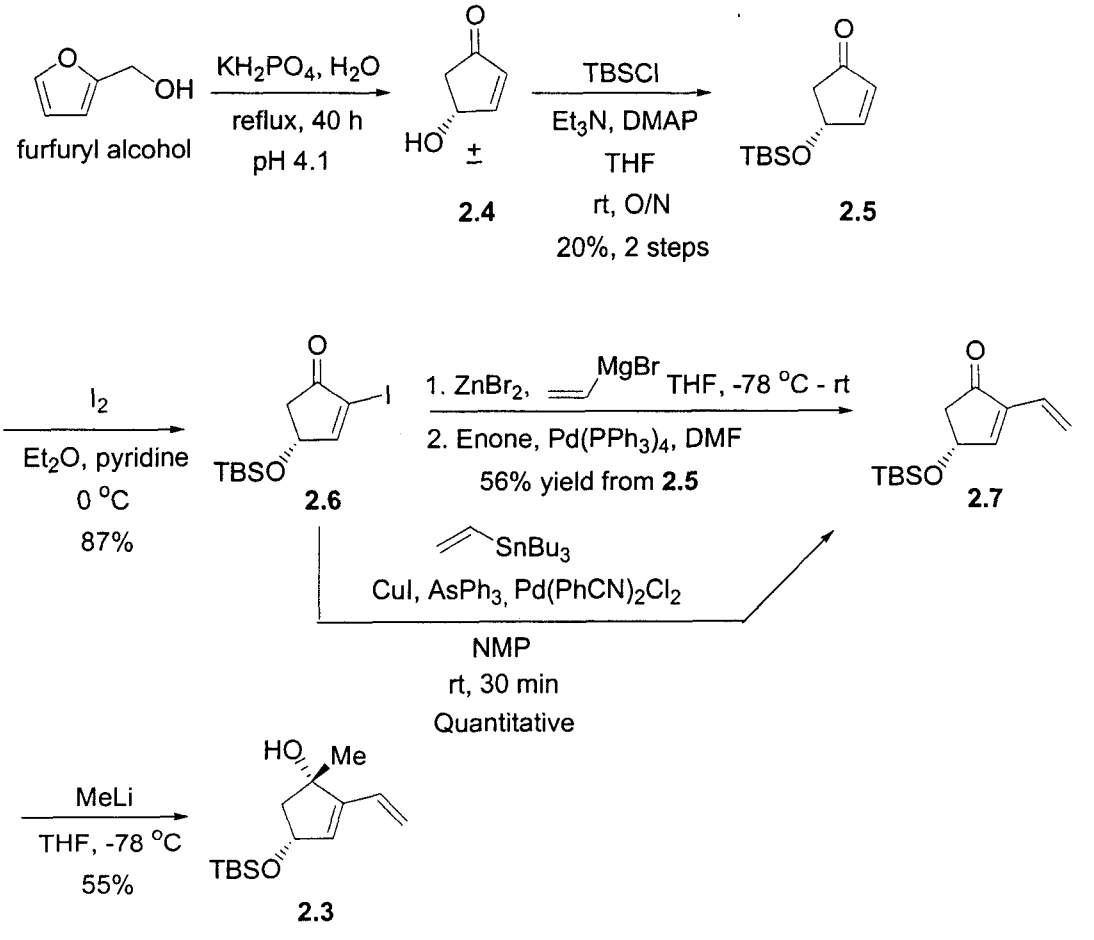
Scheme 2.2: *Retrosynthetic analysis of havellockate*



Our first objective was therefore to develop a concise route for the synthesis of diene **2.3**. This was accomplished according to Scheme 2.3. Furfuryl alcohol was refluxed in water at a pH of 4.10 for 40 h to provide **2.4**.[1] The secondary alcohol of the crude product **2.4** was then protected with TBSCl under standard conditions to afford **2.5** with a combined yield of 20% for the two steps. The resulting product was then treated with iodine in a mixture of ether and pyridine (1:1) at 0 °C to give α-iodoenone **2.6**.[2] The original protocol published in Julie Farand's thesis, was to use the crude oily product **2.6** for the subsequent Negishi[3] cross-coupling reaction. The combined yield for these two transformations (**2.5** to **2.7**) was 56%.

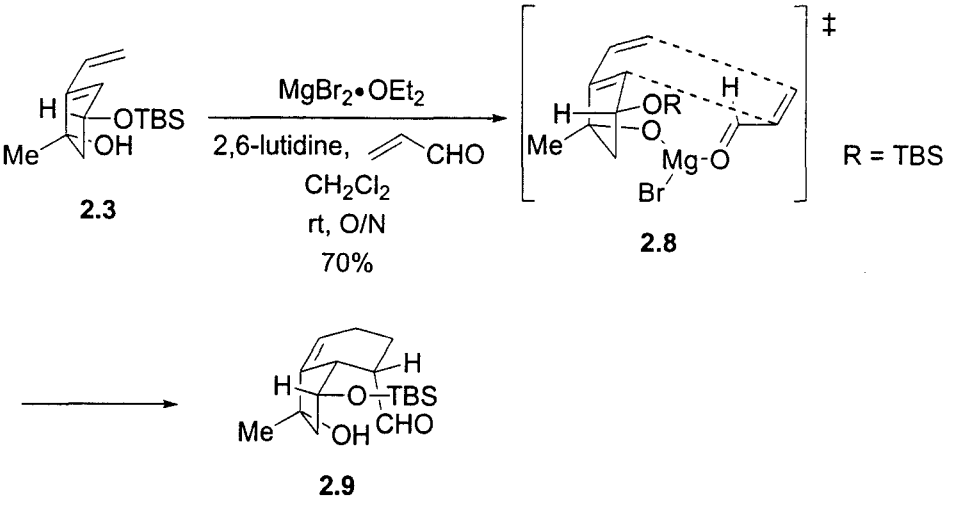
Fortunately, we later determined that **2.6** was quite stable (can be stored in the fridge for months!) and could be easily purified by silica gel flash chromatography to provide the product as a pale yellow solid in 87% yield. A Stille-cross coupling reaction of **2.6** with tributyl(vinyl)tin in the presence of triphenylarsine (10 mol%), copper iodide (10 mol%) and *bis*(benzonitrile)palladium(II) chloride (5 mol%) was much more reliable on larger scales and provided **2.7** in quantitative yield.[4] Finally, alkylation of the ketone with methyllithium furnished the desired diene **2.3** in 55% yield. We were now able to pursue the HDDA reaction using this diene to construct the hydrindane core of havellockate.

Scheme 2.3: *Synthesis of diene* ***2.3***



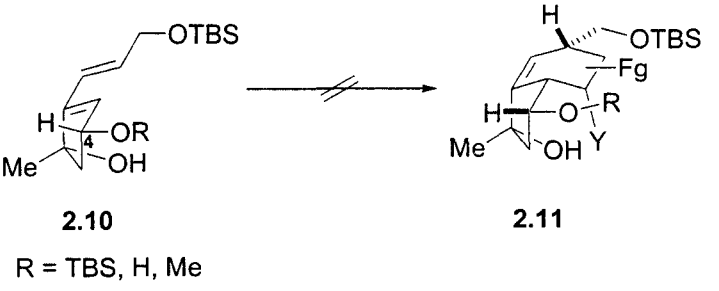
We were very pleased to observe the HDDA reaction between diene **2.3** and acrolein in the presence of $MgBr_2 \cdot OEt_2$ and 2,6-lutidine in dichloromethane was successful. Cycloadduct **2.9** was obtained in 70% yield as the sole regioisomer.

Scheme 2.4: *Hydroxy-directed Diels-Alder reaction between **2.3** and acrolein*



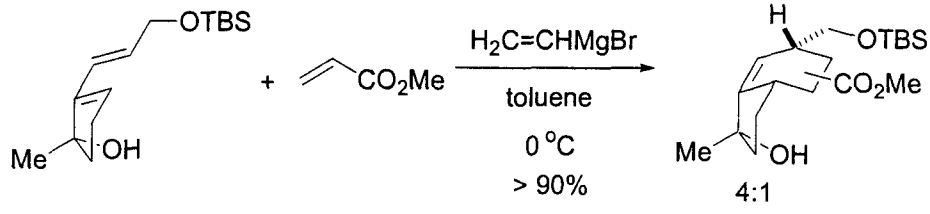
The HDDA reaction was also explored using diene **2.10**, with various R groups (TBS, H, Me)[5] so that a portion of the side-chain could be rapidly installed as shown in Scheme 2.5. These dienes were treated with activated dienophiles such as methyl acrylate, *N*-phenylmaleimide, dimethyl maleate or *cis*-3-bromo-2-propenoate in the presence $MgBr_2 \cdot OEt_2/Et_3N$ in dichloromethane or vinylmagnesium bromide in toluene. Unfortunately, the dienes were unreactive in these conditions and thus the corresponding cycloadducts **2.11** (R = TBS, H, Me) were not observed.

Scheme 2.5: *HDDA reaction using **2.10** and various dienophiles*



It was suspected that the alkoxy moiety at C4 and/or the $-CH_2OTBS$ group on diene **2.10** may be precluding the HDDA reaction. These suspicions were confirmed when a 90% yield of **2.13** was obtained from the cycloaddition reaction between methyl acrylate and diene **2.12**[5] which did not contain the alkoxy group at C4 (Scheme 2.6). The adduct was obtained as a mixture of regioisomers in a ratio of 4:1. It is possible that the lack of selectivity was caused by the electron withdrawing nature of the OTBS group on the diene which influences the coefficient size of the HOMO.

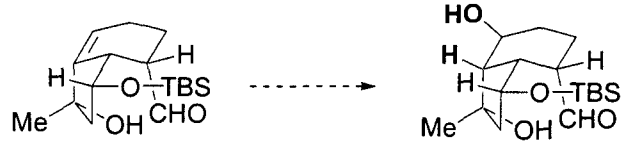
Scheme 2.6: *HDDA reaction using **2.12** and methyl acrylate*



2.12 **2.13**

Since the HDDA reactions using dienes **2.10** could not be realized, the synthesis was continued from the Diels-Alder adduct **2.9**. The next challenge was to install the *cis*-ring junction of the hydrindane core and a secondary alcohol as illustrated in Scheme 2.7.

Scheme 2.7: *Installation of the cis-ring junction and alcohol group*

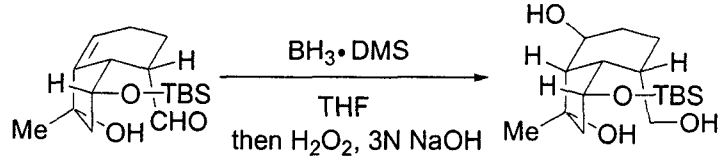


2.9 **2.14**

It was suspected that a hydroboration reaction could attain the desired transformation. The regioselectivity of the reaction would be dictated by the *anti*-Markovnikov addition of boron onto the less substituted carbon of the alkene. Furthermore, it was predicted that the facial selectivity would be controlled by sterics to afford the desired *cis* ring junction.

Following intensive optimization studies, it was established that treatment of **2.9** with BH_3·DMS in THF for 4 h at room temperature followed by an oxidative work-up with hydrogen peroxide and sodium hydroxide could provide the desired product **2.15** in 42% yield as the sole isomer (Scheme 2.8). As anticipated, the aldehyde was also reduced to the primary alcohol in these conditions.

Scheme 2.8: *Hydroboration of* ***2.9***



The primary and secondary alcohols in **2.15** were then oxidized with TPAP and NMO to provide **2.16** (Scheme 2.9). The close proximity of the tertiary alcohol to the aldehyde resulted in a cyclization reaction to form lactol **2.17**, which was further oxidized *in-situ* to provide ketone **2.18**. The relative stereochemistry of compound **2.18** was confirmed by X-ray crystallography (Figure 2.1).

Scheme 2.9: *Oxidation of* ***2.15***

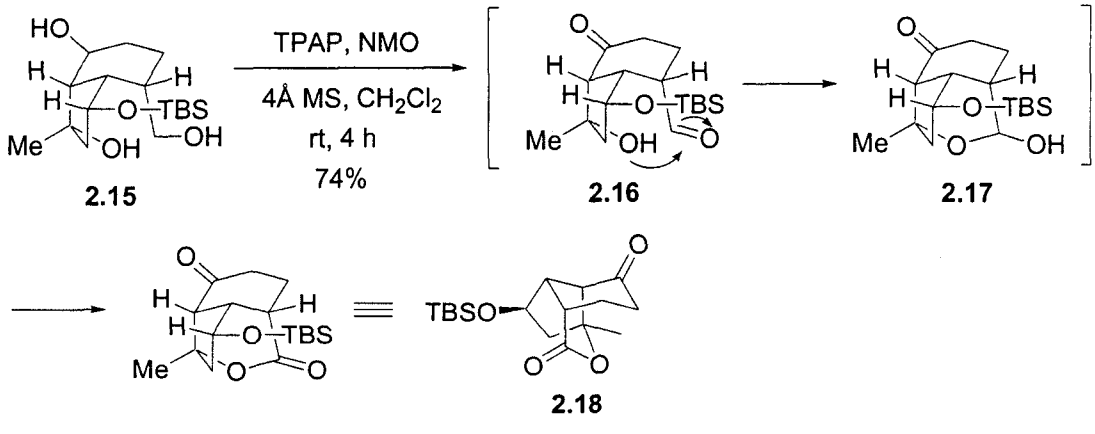
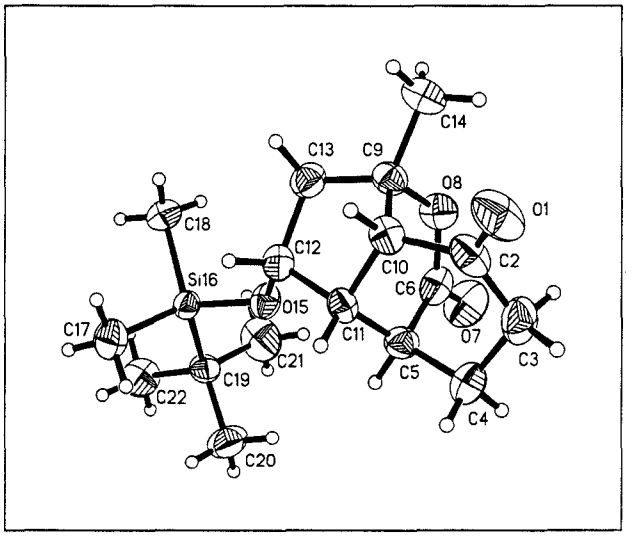
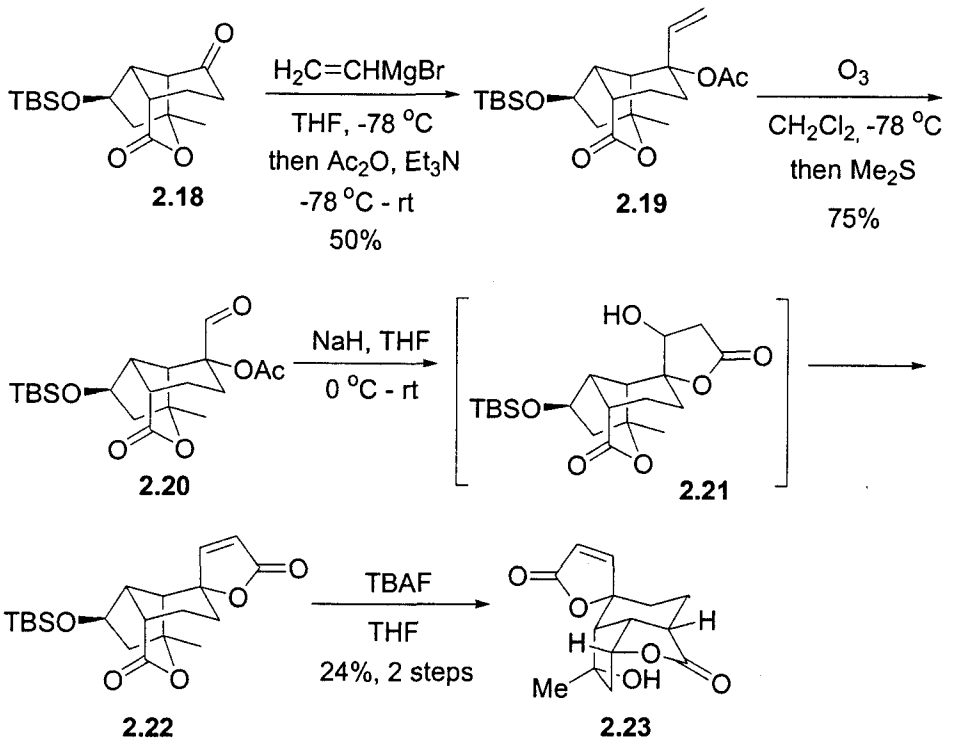


Figure 2.1: *X-ray crystal structure of* ***2.18***



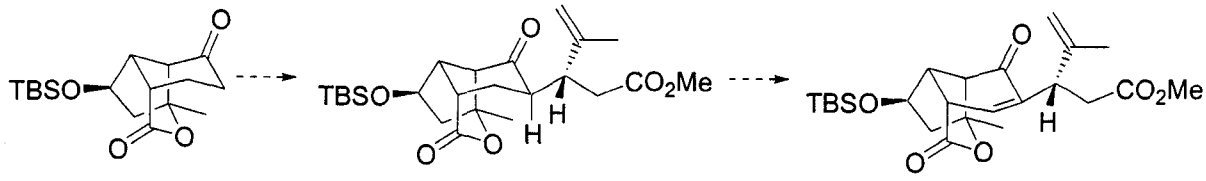
Prior to completing her M.Sc., Julie Farand constructed the spiro-lactone portion of the molecule as presented in Scheme 2.10. Ketone **2.18** was first treated with vinylmagnesium bromide at – 78 °C and the resulting magnesium alkoxide was then quenched with acetic anhydride in the presence of Et_3N to provide **2.19** in 53% yield. A solution of **2.19** in dichloromethane at -78 °C was then bubbled with ozone. Following the addition of dimethyl sulfide, the corresponding aldehyde **2.20** was obtained in 75% yield. Closure of the spiro-lactone was accomplished with NaH in THF. Unfortunately, it was observed that the aldol product **2.21** was very unstable and underwent rapid elimination to provide enone **2.22**. Finally, deprotection of the silyl ether with TBAF provided the free alcohol which then reacted with the 6-membered ring lactone to liberate the tertiary alcohol and establish the less strained 5-membered lactone **2.23** in 24% yield.

Scheme 2.10: *Synthesis of the spiro-lactone*



Two vital pieces of information had been acquired as a result of the synthesis of the core **2.23**. First, the facile elimination of the β-hydroxy group upon closure of the spirocycle, suggested that the side-chain should be installed prior to the formation of this β–hydroxy spiro-lactone. This approach was further encouraged since it was realized that the ketone of **2.18** could provide a handle to install this side-chain and the endocyclic double bond in the six-membered ring as illustrated in Scheme 2.11. Second, we had learned that the desired seco-lactone in havellockate could be established by simply deprotecting the secondary alcohol.

Scheme 2.11: *Synthesis of the side-chain and endocyclic double bond from* ***2.18***



2.18 **2.24** **2.25**

With this information in mind and the tricyclic core **2.18** in our hand, we began our explorations into the synthesis of the side-chain of havellockate.

References:

[1] Curran, T. T.; Hay, D.A.; Koegel, C. P.; Evans, J. C. *Tetrahedron* **1997**, *53,* 1983.

[2] Johnson, C. R.; Adams, J. P.; Matthew, P. B.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33,* 917.

[3] Pour, M.; Negishi, E. *Tetrahedron Lett.* **1996**, *37,* 4679. Negishi, E.; Owczarczyk, Z. R.; Swanson, D. *Tetrahedron Lett.* **1991**, *32*, 4453.

[4] Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.

[5] For the synthesis of diene **2.10** (R = TBS, H, Me) and diene **2.12** and subsequent attempts at the HDDA reactions see: Julie Farand, M.Sc. Thesis, 2004.

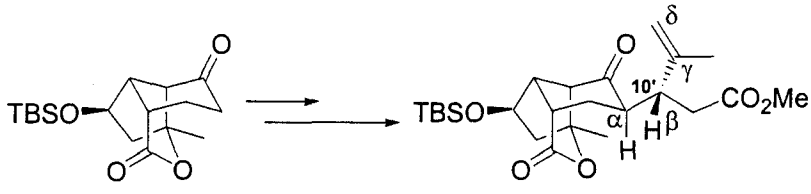
3

Construction of the Side-Chain

Part I: Claisen Rearrangement (A)

With the tricyclic core **2.18** of havellockate in-hand, the focus of the synthesis shifted to the construction of the side-chain which consists of a geminal di-alkyl substituted alkene as well as a methyl ester group (Scheme 3.1). The challenging aspect of this portion of the molecule is the stereogenic center at C10'.

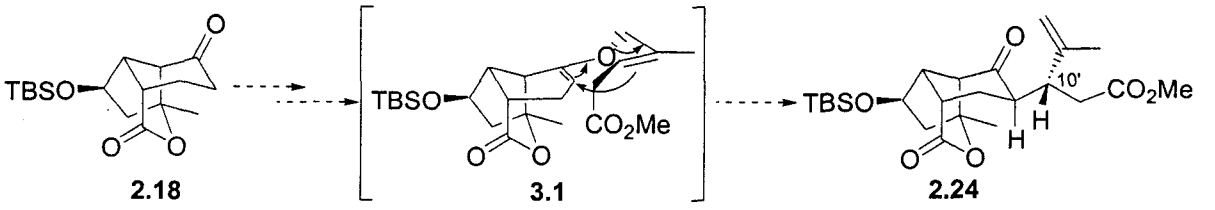
Scheme 3.1: *Installation of the side-chain from ketone* ***2.18***



2.18 **2.24**

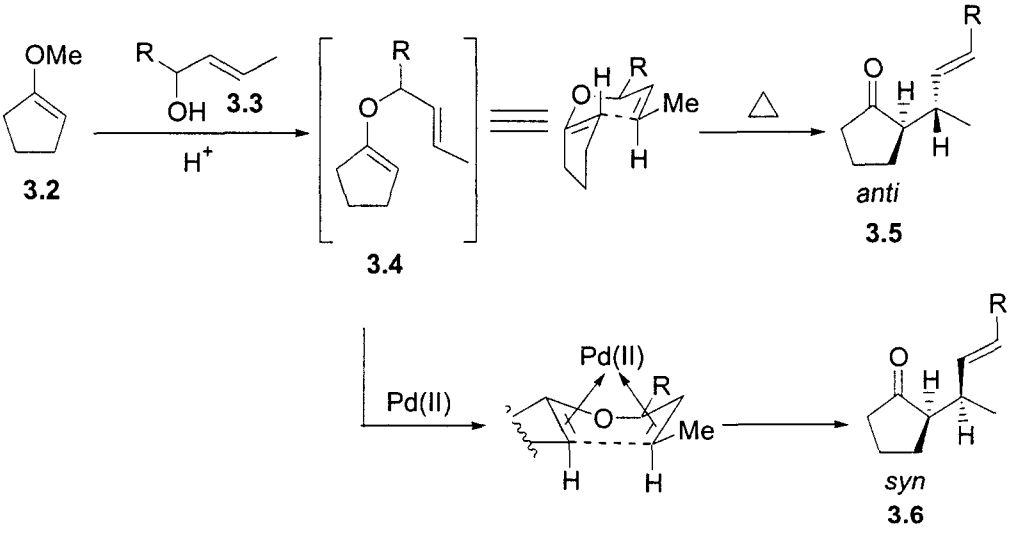
Upon closer inspection of compound **2.24** in Scheme 3.1, we recognized the presence of a γ,δ-unsaturated ketone. This type of molecular organization is characteristic of a Claisen rearrangement product of allyl vinyl ether **3.1** shown in Scheme 3.2.[1] We anticipated that a [3,3]-sigmatropic rearrangement of compound **3.1** would preferentially occur on the *si* face of the molecule via a chair-like transition state, due to the steric hindrance generated by the 6-membered ring lactone on the other face. This would afford the desired stereogenic center at C10'.

Scheme 3.2: *Proposed Claisen rearrangement for installing the side-chain*



For the Claisen rearrangement to be a viable approach, we needed to generate allyl vinyl ether **3.1**. While exploring the literature, we discovered a paper by Nakai and Sugiura,[2] which describes the *in-situ* enol ether exchange of methyl enol ether **3.2** with allylic alcohol **3.3** in the presence of a catalytic proton source (Scheme 3.3). A Claisen rearrangement of intermediate **3.4** then occurs via a chair-like transition state under thermal conditions to provide compound **3.5**, where the hydrogen atoms are *anti* to each other. If Pd(II) is introduced into the system, then the rearrangement proceeds though a boat-like transition state to yield the *syn* product **3.6**.

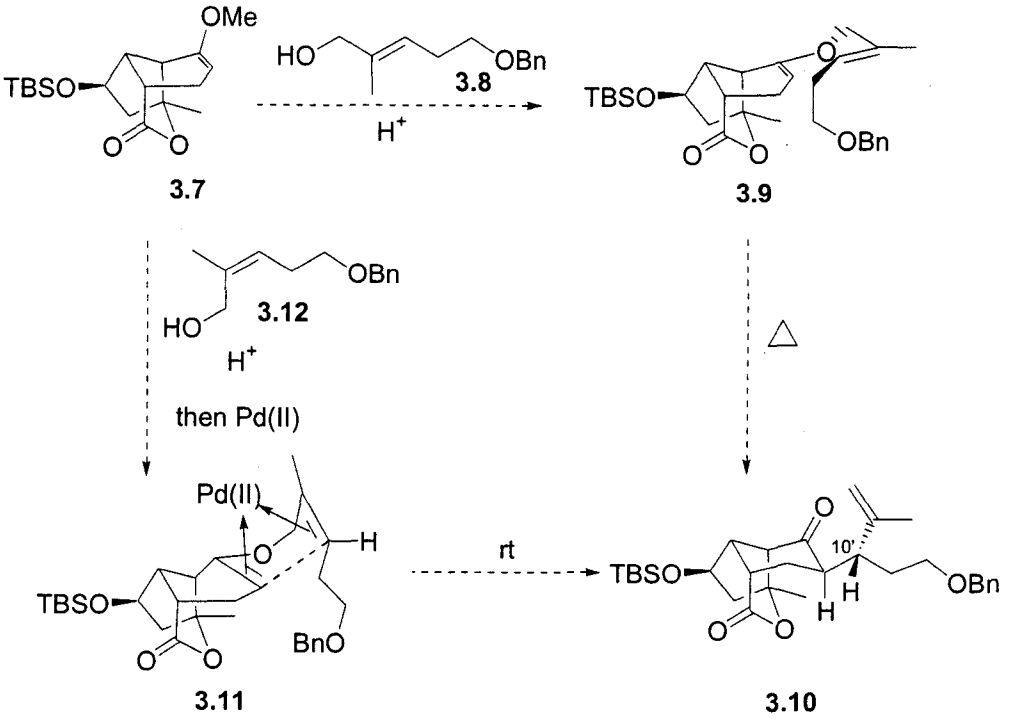
Scheme 3.3: *In-situ enol ether exchange/Claisen rearrangement by Nakai and Sugiura*



Applying this methodology to the synthesis of havellockate reveals that (*E*)-allylic alcohol **3.8** would be required in the case of a thermally-induced Claisen rearrangement, in

order to generate the correct stereochemistry at C10' (Scheme 3.4). Alternatively, (*Z*)-allylic alcohol **3.12** would be necessary for the Pd(II)-catalyzed reaction since it would proceed via a boat-like transition state.

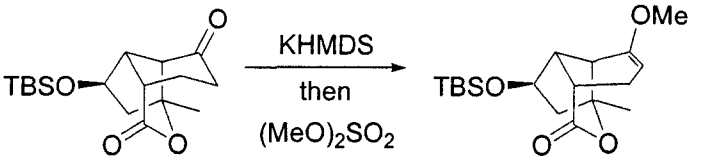
Scheme 3.4: *Proposed in-situ enol ether exchange/Claisen rearrangement to generate **3.10***



We opted to explore this methodology since intermediates **3.9** and **3.11** shown in Scheme 3.4 are generated *in-situ*. This alleviates any challenges that may be experienced while handling these potentially unstable intermediates. Before we could begin our studies however, we first needed to prepare methyl enol ether **3.7** as well as the allylic alcohol (**3.8** or **3.12**).

The synthesis of methyl enol ether **3.7** was accomplished by treating the enolate of **2.18** with freshly distilled dimethyl sulfate as illustrated in Scheme 3.5.

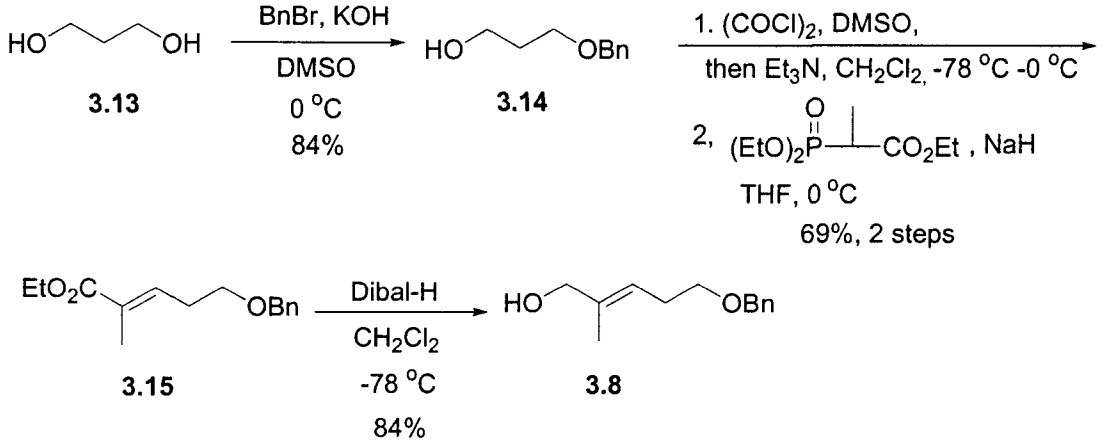
Scheme 3.5: *Synthesis of methyl enol ether* ***3.7***



2.18 **3.7**

(*E*)-allylic alcohol **3.8** was prepared as described in Scheme 3.6. Monoprotection of commercially available 1,3-propanediol (**3.13**) with benzyl bromide in the presence of KOH and DMSO at 0 °C provided **3.14** in 84% yield.[3] Swern oxidation of **3.14** followed by treatment of the crude aldehyde with the anion of triethyl 2-phosphonopropionate gave the desired ester **3.15** in 69% yield for the two steps. The ester was then reduced with Dibal-H to afford alcohol **3.8** in 84% yield.

Scheme 3.6: *Synthesis of allylic alcohol* ***3.8***

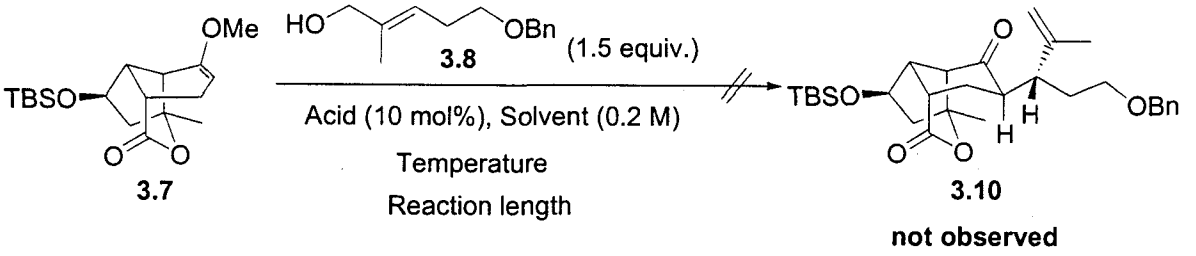


3.13 **3.14** **3.15** **3.8**

We commenced our studies by first exploring the thermally-induced Claisen rearrangement. A variety of acids such as *p*TSA, TFA, pivalic acid, CSA, HCl, phenol and 2,6-dimethylphenol were used to promote the *in-situ* enol ether exchange between **3.7** and **3.8** as illustrated in Scheme 3.7. Various solvents (CH_2Cl_2, PhMe or C_6H_6), temperatures (0 °C – reflux) and reaction lengths (1 – 48 h) were also scanned during the course of the study. Sadly however, under all of these conditions, the desired Claisen product nor the

intermediate allyl vinyl ether **3.9** were observed. The crude ^{1}H NMRs revealed the decomposition of **3.7** or the recovery of the hydrolyzed starting material, ketone **2.18**.

Scheme 3.7: *In-situ enol ether exchange/thermally-induced Claisen rearrangement studies*



Acid: *p*TSA, TFA, pivalic acid, CSA, HCl, phenol and 2,6-dimethylphenol

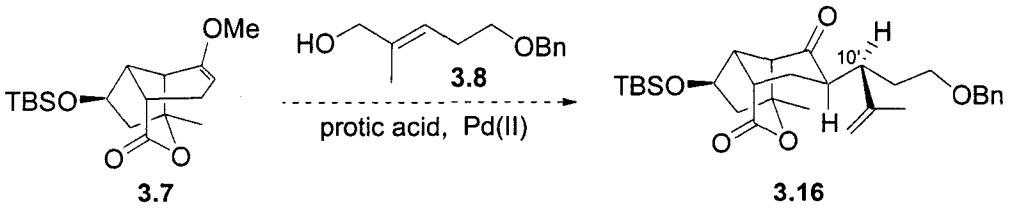
Solvent: CH_2Cl_2, PhMe, C_6H_6

Temperature: 0 °C - reflux

Reaction length: 1 - 48 h

We also investigated the Pd(II)-catalyzed Claisen rearrangement process. Since we had (*E*)-allylic alcohol **3.8** already prepared, we chose to use it for our studies even though the product of the reaction **3.16**, would have the wrong stereochemistry at C10' (Scheme 3.8). In the event that the Claisen rearrangement was successful, our intention was to repeat the reaction using (*Z*)-allylic alcohol **3.12** (see Scheme 3.4) in order to achieve the correct stereochemistry at the chiral center.

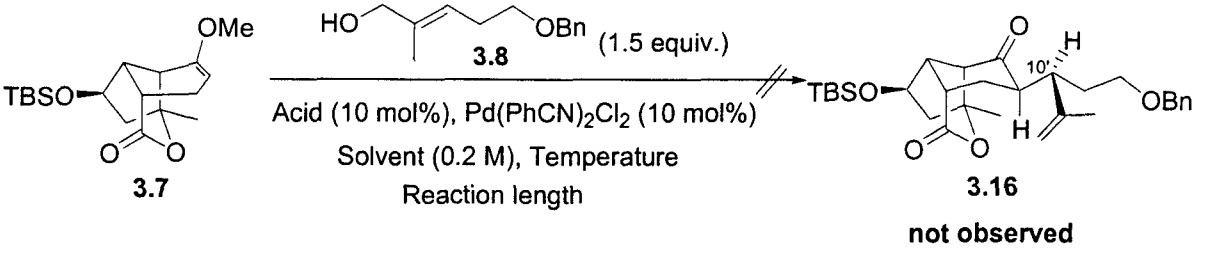
Scheme 3.8: *Proposed in-situ enol ether exchange/Pd(II)-catalyzed Claisen rearrangement in the presence of (E)-allylic alcohol **3.8***



Unfortunately, as illustrated in Scheme 3.9, we were never able to prepare the Claisen product **3.16**. Treatment of a solution of enol ether **3.7** and (*E*)-allylic alcohol **3.8** in either benzene or toluene with 10 mol% *bis*(benzonitrile)palladium(II) chloride and 10 mol% TFA,

pivalic acid, phenol or 2,6-dimethylphenol led to the decomposition of **3.7** or the recovery of ketone **2.18** at various temperatures (0 °C – reflux) and reaction lengths (1- 48 h).

Scheme 3.9: *In-situ enol ether exchange/Pd(II)-catalyzed Claisen rearrangement studies*



Acid: TFA, pivalic acid, phenol and 2,6-dimethylphenol

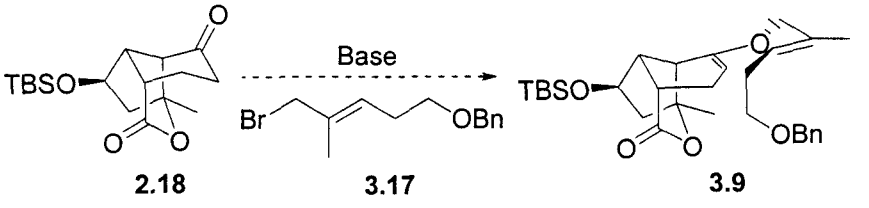
Solvent: PhMe, C_6H_6

Temperature: 0 °C - reflux

Reaction length: 1 - 48 h

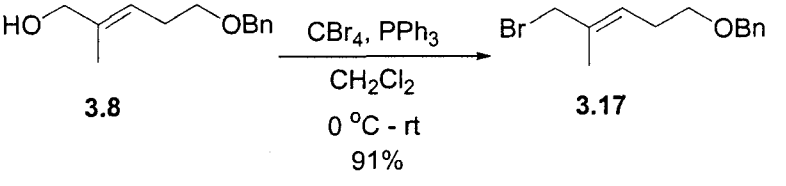
In order to overcome the difficulties associated with the acid-catalyzed process described above (i.e decomposition of the starting material), we decided to explore an *O*-alkylation reaction of an enolate derived from ketone **2.18** as an alternative method to prepare allyl vinyl ether **3.9** (Scheme 3.10).

Scheme 3.10: *Proposed O-alkylation strategy*



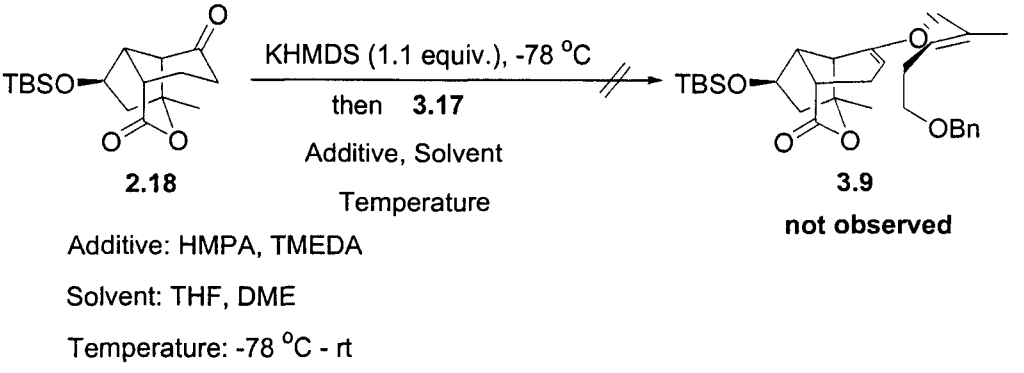
The requisite allyl bromide **3.17** for this reaction was generated by treating allylic alcohol **3.8** with CBr_4 and PPh_3 in CH_2Cl_2 (Scheme 3.11).

Scheme 3.11: *Synthesis of allyl bromide **3.17***



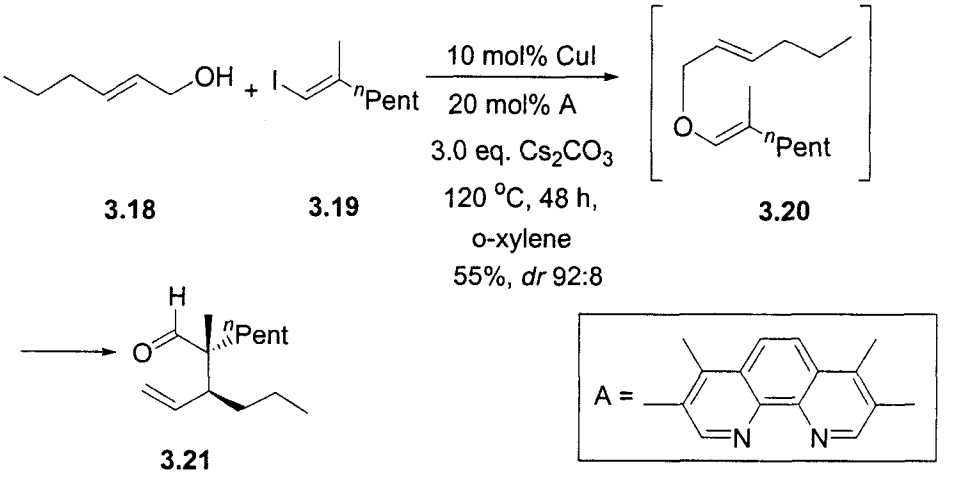
For all of the *O*-alkylation studies described in Scheme 3.12, the enolate of **2.18** was generated with KHMDS (1.1 equiv.) in either THF or DME prior to the addition of **3.17**. TMEDA and HMPA were employed as additives in the reactions since they are able to solvate cations which helps to promote the *O*-alkylation.[4,5] Although many temperatures (-78 °C – rt) and combinations of solvents and additives were explored, the *O*-alkylated product **3.9** was never observed by TLC or ^{1}H NMR. The *C*-alkylated product was not observed either. Starting material was recovered when the reaction was conducted at low temperatures (-78 °C to -20 °C) and decomposition occurred at temperatures higher than 0 °C.

Scheme 3.12: *O-alkylation investigations*



While exploring other possible strategies for preparing the allyl vinyl ether substrate **3.9** for the Claisen rearrangement, we came across the work of Nordmann and Buchwald.[6] In their communication they described the coupling of an allylic alcohol such as **3.18** with vinyl iodide **3.19** in the presence of CuI, Cs_2CO_3 and tetramethyl-1,10-phenanthroline (Scheme 3.13). The intermediate allyl vinyl ether **3.20** that is formed then proceeds through a Claisen rearrangement under thermal conditions to provide the γ,δ-unsaturated carbonyl compound **3.21**.

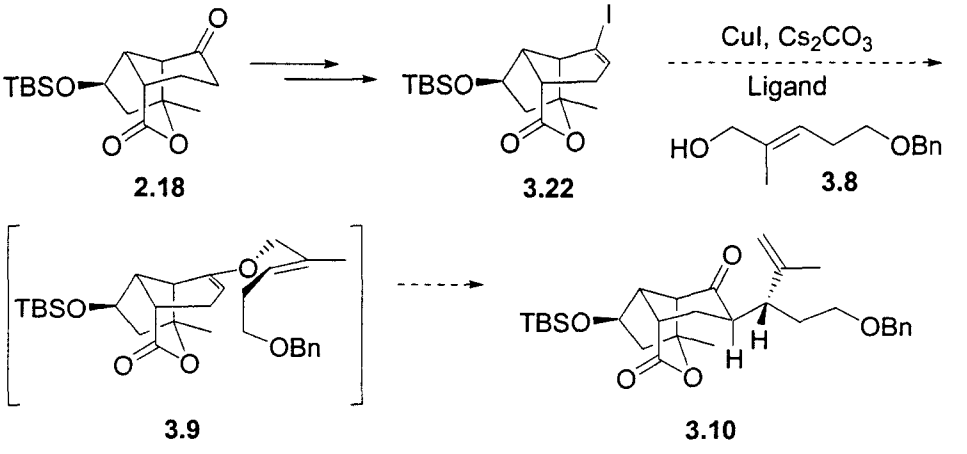
Scheme 3.13: *Domino Cu-catalyzed C-O coupling-Claisen rearrangement*



3.18 **3.19** **3.20** **3.21**

It was proposed that this domino strategy could be applied to the synthesis of havellockate provided that vinyl iodide **3.22** could be prepared (Scheme 3.14).

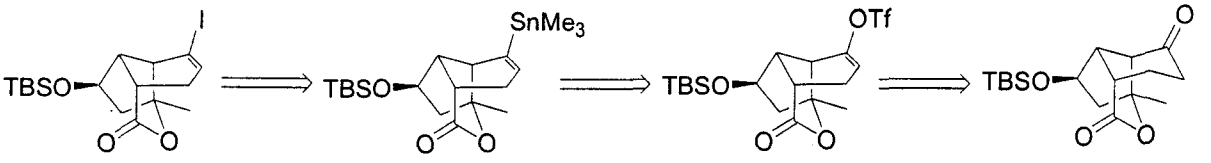
Scheme 3.14: *Proposed application of the domino Cu-catalyzed C-O coupling-Claisen rearrangement strategy to prepare* ***3.10***



2.18 **3.22** **3.8** **3.9** **3.10**

Thus a synthetic route for **3.22** was devised from ketone **2.18** which involved the preparation of intermediates **3.23** and **3.24** (Scheme 3.15).

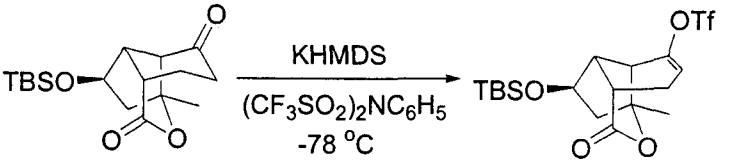
Scheme 3.15: *Retrosynthetic analysis of vinyl iodide* ***3.22***



3.22 **3.23** **3.24** **2.18**

The synthesis of vinyl triflate **3.24** was readily accomplished by *O*-alkylating the enolate of **2.18** with *N*-phenyltrifluoromethanesulfonimide[7] (Scheme 3.16). This product was found to be very stable and could be stored in the fridge for long periods of time (months) without degrading.

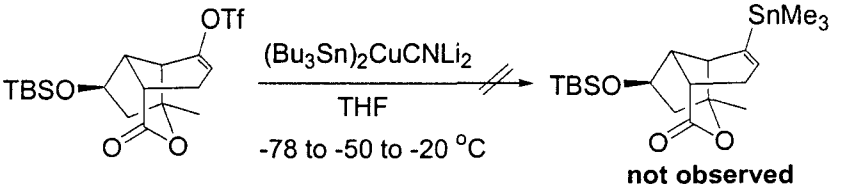
Scheme 3.16: *Synthesis of vinyl triflate* ***3.24***



2.18 **3.24**

The synthesis of vinyl stannane **3.23** was initially attempted by coupling compound **3.24** with a higher-order stannyl cuprate according to a literature procedure (Scheme 3.17).[8] This protocol was ineffective and only decomposition of vinyl triflate **3.24** was observed.

Scheme 3.17: *Attempted synthesis of vinyl stannane* ***3.23***



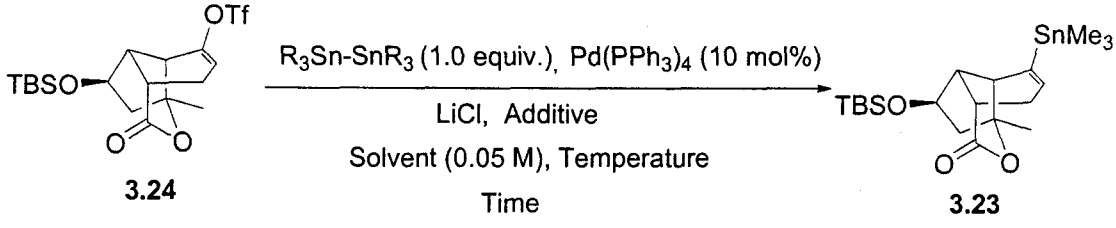
not observed

3.24 **3.23**

The second approach that was explored to prepare vinyl stannane **3.23** was a Pd-catalyzed cross-coupling reaction of triflate **3.24** with hexamethylditin or hexabutylditin. Many conditions were examined to effect this transformation, which are described in Table

3.1. As shown in entries 1-5, in the presence of 10 mol% $Pd(PPh_3)_4$, LiCl (5-7 equiv.) as well as other additives such as Li_2CO_3 (entry 4) and CuI (entry 5) in either THF or DMF, the Stille reaction failed to progress. However, when vinyl triflate **3.24** was treated with 10 mol% $Pd(PPh_3)_4$, hexamethylditin (1.0 equiv.) and LiCl (3.0 equiv.) in dioxane at 50 °C, the desired product **3.23** was obtained, although in only 28% yield after 24 h (entry 6). By increasing the temperature of the reaction to 75 °C, the yield of compound **3.23** was improved to 75% (entry 7).

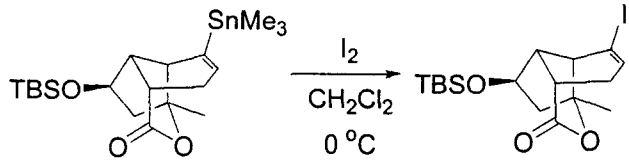
Table 3.1: *Stille-cross coupling results with vinyl triflate* ***3.24***



Entry	R	Equiv. LiCl	Additive (equiv.)	Solvent	Temp. (°C)	Time h	Result
1[8]	Bu	5	-	THF	Reflux	12	S.M.
2	Me	5	-	THF	Reflux	14	S.M.
3	Me	5	-	DMF	Reflux	24	S.M.
4[9]	Me	7	Li_2CO_3 (1.0)	THF	Reflux	20	S.M.
5	Me	6	CuI (5.0)	DMF	80	12	S.M.
6[10]	Me	3	-	Dioxane	50	24	28% yield
7	**Me**	**3**	**-**	**Dioxane**	**75**	**24**	**75% yield**

The subsequent formation of vinyl iodide **3.22** was readily accomplished in 83% yield by treating vinyl stannane **3.23** with a dilute solution of iodine in dichloromethane at 0 °C (Scheme 3.18).[8]

Scheme 3.18: *Synthesis of vinyl iodide* ***3.22***

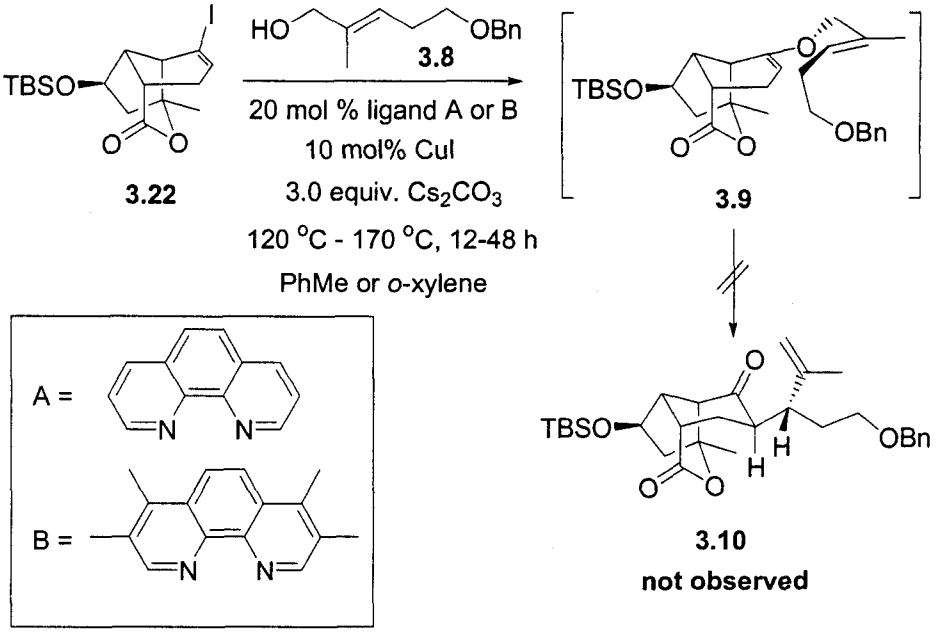


3.23 **3.22**

We were now able to investigate the copper(I)-mediated C-O coupling Claisen rearrangement strategy using vinyl iodide **3.22** and allylic alcohol **3.8**. All of the reactions for the study were conducted in the presence of 10 mol% CuI, 20 mol% 1,10-phenanthroline or tetramethyl-1,10-phenanthroline and 3.0 equivalents of Cs_2CO_3 as described in the original paper.[6] In addition, highly concentrated mixtures (0.5 mL of solvent/mmol vinyl halide) were prepared as this was deemed to be critical for the success of the reaction.

During the course of the study we noted that vinyl iodide **3.22** failed to react at temperatures ranging from 120 °C to 150 °C in the presence of either 1,10-phenanthroline or tetramethyl-1,10-phenanthroline (Scheme 3.19). As the temperature was increased beyond 150 °C, the vinyl iodide began to decompose which was evident by the presence of base-line material on the TLC. Furthermore, there was no evidence of the desired coupled product or the Claisen product in the ^1H NMR. At a temperature of 170 °C, the vinyl iodide had completely decomposed.

Scheme 3.19: *C-O Cu-coupling Claisen rearrangement attempts*



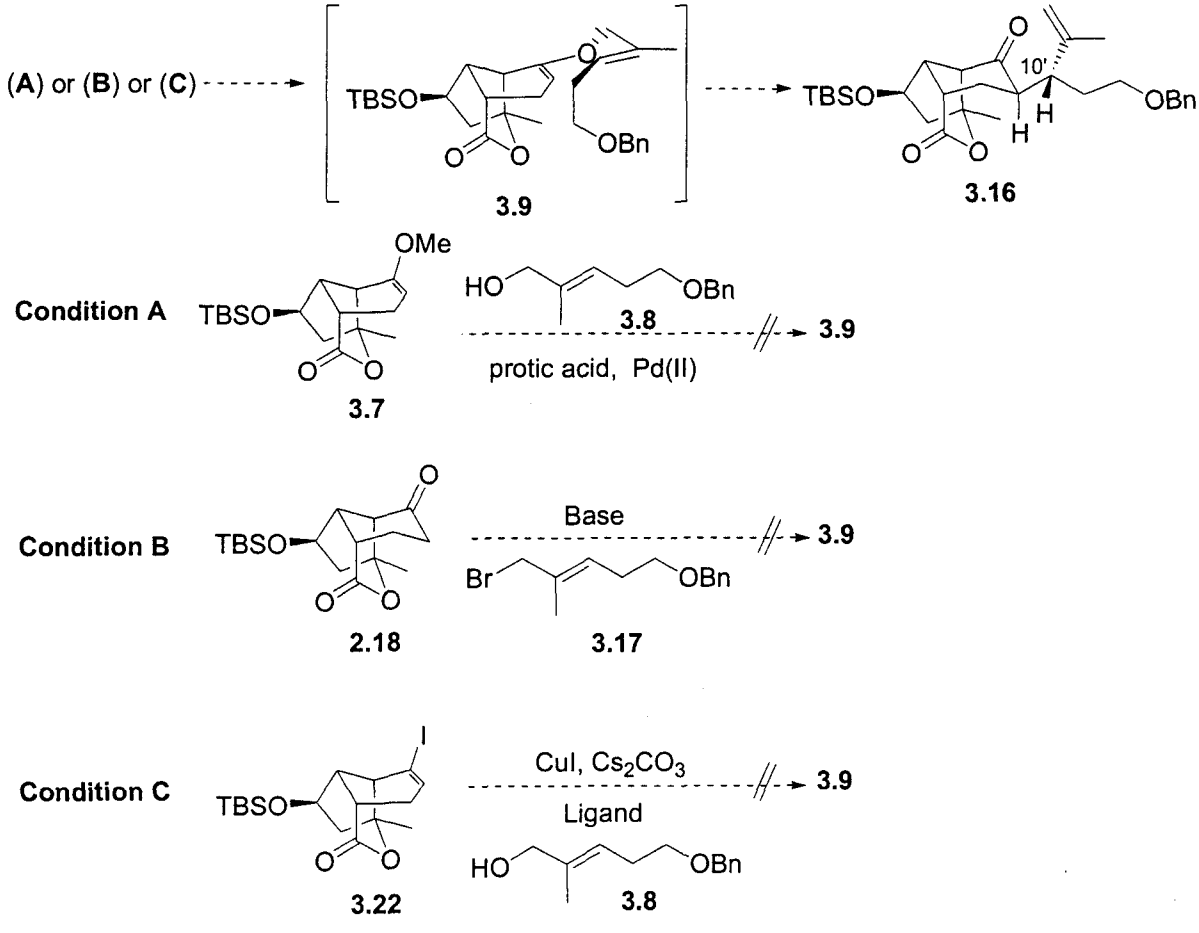
It was therefore evident that the C-O Cu-coupling Claisen rearrangement strategy was not a viable approach for our synthesis. One of the greatest challenges of this reaction was the demand for a highly concentrated mixture (0.5 mL of solvent/mmol vinyl halide) in order to promote the coupling process.[6] Since these test reactions were conducted on a small scale (10 mg of **3.22**) in order to conserve precious material, only 12 μL of *o*-xylene or toluene was required. The high reaction temperatures often led to the evaporation of the solvent and consequently the decomposition of the material.

Conclusions:

In this chapter we explored a Claisen rearrangement strategy as a means of installing the side-chain of havellockate with the correct stereochemistry at the chiral center (Scheme 3.20). Three approaches were investigated to prepare the intermediate allyl vinyl ether **3.9** for the rearrangement process. The first was an *in-situ* enol ether exchange of methyl enol ether **3.7** with allylic alcohol **3.8** (Condition A, Scheme 3.20).[2] This proved to be quite

challenging since the methyl enol ether **3.7** was prone to hydrolysis or decomposition. The second approach we explored was an *O*-alkylation reaction of an enolate prepared from **2.18** with allyl bromide **3.17** (Condition B, Scheme 3.20). This procedure was unable to generate **3.9**. The third and final strategy examined was a domino copper-catalyzed C-O coupling-Claisen rearrangement process (Condition C, Scheme 3.20).[6] Unfortunately, vinyl iodide **3.22** was prone to decomposition at high temperatures. It was therefore evident that an alternative strategy for installing this side-chain was required, which continued to be the focus of our synthesis.

Scheme 3.20: *Summary of the Claisen rearrangement attempts*



References:

[1] For review see: Castro, A. M. M. *Chem. Rev.* **2004**, *104,* 2939.

[2] Nakai, T.; Sugiura, M. *Tetrahedron Lett.* **1996**, *37,* 7991. Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28,* 5879.

[3] Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5,* 857.

[4] For reviews see: Parker, A. J. *Chem. Rev.* **1969**, *69,* 1. Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33,* 2737.

[5] Liotta, C. L.; Caruso, T. C. *Tetrahedron Lett.* **1985**, *26,* 1599.

[6] Nordmann, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

[7] Su, Z.; Paquette, L. A. *J. Org. Chem.* **1995**, *60,* 764.

[8] Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988,** *29,* 4795.

[9] Tius, M. A.; Kannangara, G. S. K.; Kerr, M. A.; Grace, K. J. S. *Tetrahedron* **1993,** *49,* 3291.

[10] Falck-Pedersen, M. L.; Rømming, C.; Undeheim, K. *Tetrahedron* **1999**, *55,* 8525.

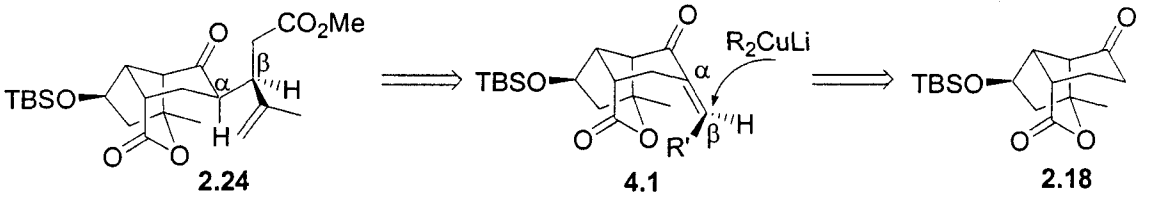
4

Construction of the Side-Chain Part II: 1,4-Addition & Diels-Alder Strategies

In light of the difficulties experienced with the Claisen rearrangement strategy described in Chapter 3, it was apparent that other carbon-carbon bond forming approaches needed to be explored to install the side-chain of havellockate.

Upon re-evaluating compound **2.24** shown in Scheme 4.1, we recognized that the stereogenic center of the side-chain was located at the β-position of the ketone. Thus, it was conceivable that carbon-carbon bond formation could be attained at the β-position via a 1,4-addition of a carbon nucleophile onto α,β-unsaturated ketone **4.1**.

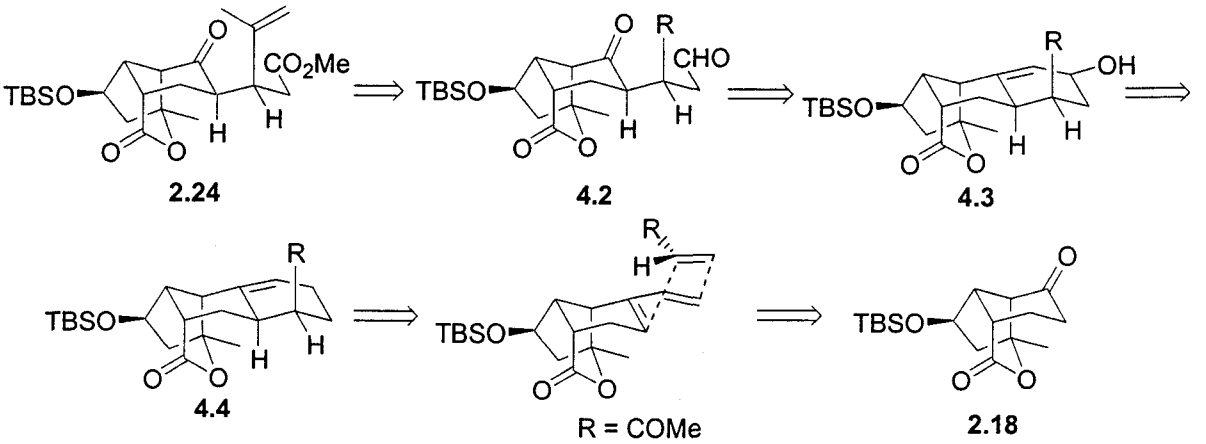
Scheme 4.1: *1,4-Addition strategy to prepare* ***2.24***



We also envisioned an alternative approach to construct the side-chain of havellockate which is illustrated in Scheme 4.2. In this strategy, we proposed that **2.24** could be generated from compound **4.2**. Cleavage of the olefin in **4.3** would provide aldehyde **4.2**. Allylic alcohol **4.3** in-turn, could originate from **4.4** which is a Diels-Alder adduct formed between a

diene prepared from ketone **2.18** and a commercially available dienophile such as methyl vinyl ketone.

Scheme 4.2: *Diels-Alder strategy to prepare compound* ***2.24***

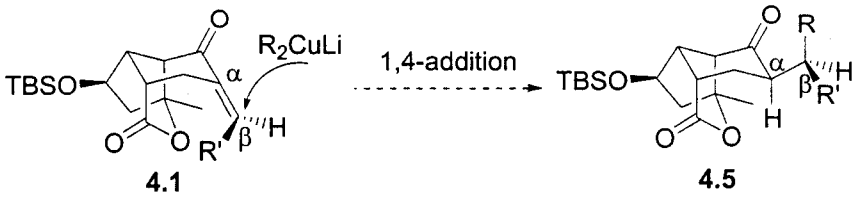


Both of the synthetic approaches described in Scheme 4.1 and 4.2 were studied concurrently. Section 4.1 of this chapter will focus on the results of the 1,4-addition strategy and will be followed by the results of the Diels-Alder strategy in Section 4.2.

4.1. 1,4-Addition Strategy

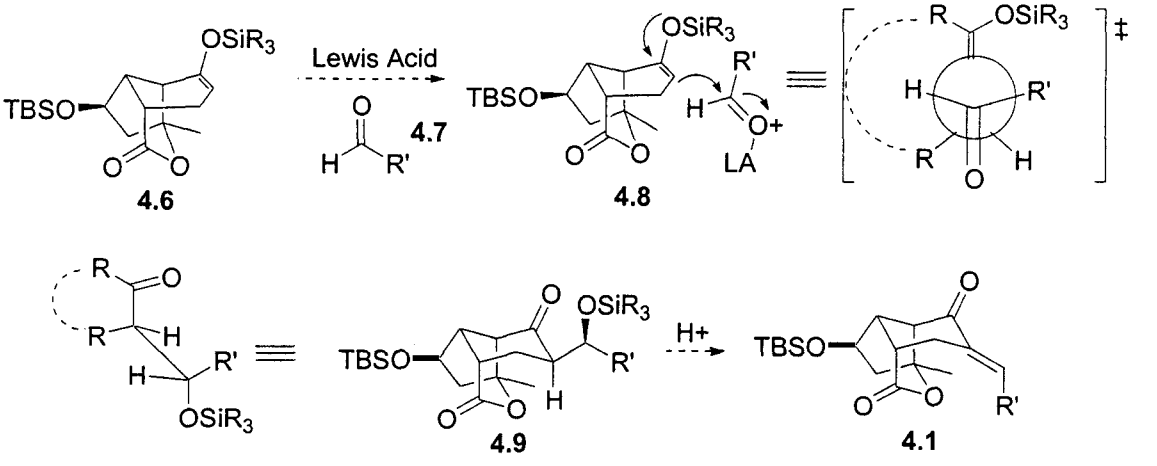
The conjugate addition of an alkyl or alkenyl cuprate to an α,β-unsaturated ketone is a well developed strategy for creating carbon-carbon bonds.[1] This approach, illustrated in Scheme 4.3, offered substantial promise for the synthesis of the side-chain of havellockate, since it could be used to install the challenging chiral centre.

Scheme 4.3: *Proposed 1,4-addition of an alkyl or alkenyl cuprate to install the chiral center of the side-chain*



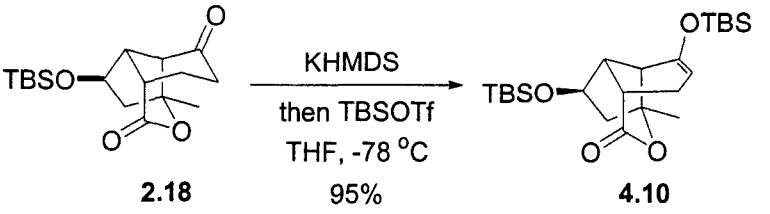
Before determining the conditions for the cuprate addition, we first had to prepare α,β-unsaturated ketone **4.1**, which we imagined could be achieved using a Mukaiyama aldol reaction.[2] As illustrated in Scheme 4.4, this reaction would involve a nucleophilic attack of a Lewis acid-activated aldehyde by silyl enol ether **4.6** via an open transition state.[3] We predicted that aldehyde **4.7** would approach on the *si* face of the molecule for steric reasons, resulting in the formation of **4.9**. Elimination of water under acidic conditions was expected to generate the thermodynamically more stable (*E*)-α,β-unsaturated ketone **4.1**.[4]

Scheme 4.4: *Proposed Mukaiyama aldol reaction*



Before exploring the Mukaiyama aldol reaction, we needed to generate silyl enol ether **4.6**. Although the TMS derivative could not be prepared due to its tendency to hydrolyze back to ketone **2.18**, TBS enol ether **4.10** was isolated in 95% yield as illustrated in Scheme 4.5.

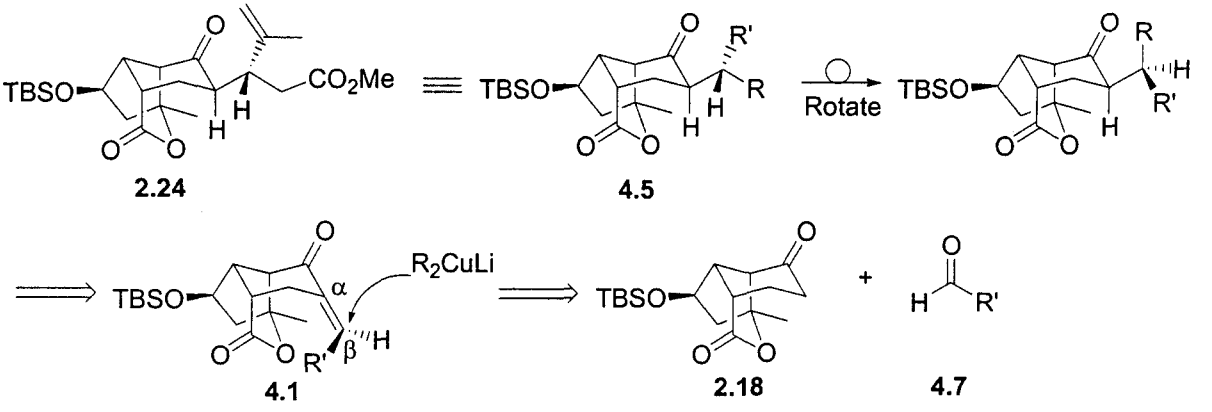
Scheme 4.5: *Synthesis of silyl enol ether* ***4.10*** *from ketone* ***2.18***



2.18 **4.10**

The aldehyde (**4.7**) that would serve as the electrophilic partner in the aldol reaction was also necessary to prepare. In order to choose an appropriate R' group for this aldehyde, we thoroughly examined Scheme 4.6. By assuming that the *(E)*-α,β-unsaturated ketone **4.1** would be generated from the aldol reaction and that the subsequent 1,4-addition would occur on the *si* face of **4.1** for steric reasons, this implied that the R' group of **4.7** would represent the isopropenyl moiety in compound **2.24**.

Scheme 4.6: *Detailed retrosynthetic analysis of the conjugate addition reaction*

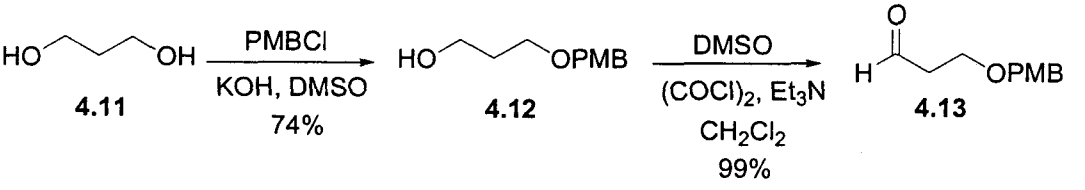


2.24 **4.5** **4.1** **2.18** **4.7**

With this knowledge, some flexibility was gained in choosing an R' group provided it could be transformed into the isopropenyl group shown in compound **2.24**. Our main concern initially was simply finding the conditions to promote the aldol reaction. Upon optimization, various R' groups could be explored that may be more efficiently transformed into the desired olefin.

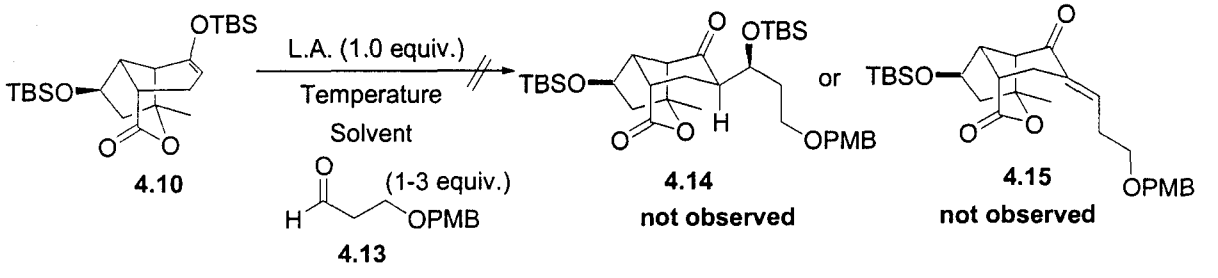
Aldehyde **4.13** was the electrophile chosen for the studies and was prepared in two steps from commercially available 1,3-propanediol (**4.11**) as outlined in Scheme 4.7.[5]

Scheme 4.7: *Synthesis of aldehyde* ***4.13***



A variety of Lewis acids such as $AlMe_3$, $TiCl_4$,[2] $SnCl_4$ as well as freshly distilled $BF_3{\cdot}OEt_2$[6] were examined to promote the aldol reaction between enol ether **4.10** and aldehyde **4.13** (Scheme 4.8). Unfortunately, a combination of hydrolysed material (i.e ketone **2.18**) and decomposition products were observed with temperatures ranging from -78 °C to -0 °C. The addition of a proton scavenger, 2,6-di-*tert*-butyl-4-methylpyridine (4 equivalents) did prevent the hydrolysis of **4.10** in the presence of $BF_3{\cdot}OEt_2$ at -78 °C, however the aldol reaction did not proceed. Slowly increasing the temperature only promoted the decomposition of enol ether **4.10**. Perhaps most concerning was the degradation of aldehyde **4.13** in all of the conditions.

Scheme 4.8: *Mukiayma aldol attempts between enol ether* ***4.10*** *and aldehyde* ***4.13***



L.A. = $AlMe_3$, $TiCl_4$, $SnCl_4$, $BF_3{\bullet}OEt_2$

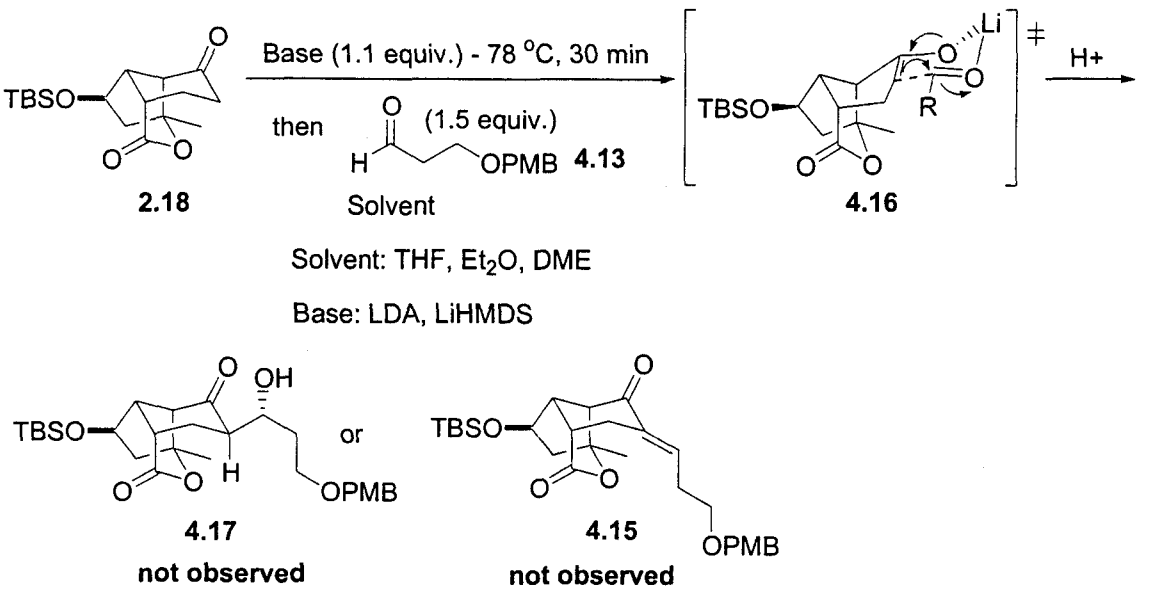
Temperature = -78 °C to 0 °C

Solvent = CH_2Cl_2 or CH_2Cl_2/Et_2O (9:1)[10]

Although the decomposition of aldehyde **4.13** was initially puzzling, we discovered many examples in the literature demonstrating the removal of a PMB group in the presence of a Lewis acid.[7] It is therefore possible that the primary alcohol of **4.13** was deprotected in the reaction conditions, which may have initiated other decomposition pathways, ultimately leading to the demise of enol ether **4.10** and aldehyde **4.13**.

Since the Mukaiyama aldol conditions (i.e Lewis acid) were not compatible with aldehyde **4.13**, a mixed aldol condensation using a lithium enolate was next explored (Scheme 4.9). This reaction was expected to proceed via a chair-like transition state (Zimmerman-Traxler[8] transition state), due to the chelating effect of the lithium cation.[9,10] Once again, we predicted that the reaction would occur on the *si* face of the molecule for steric reasons to generate **4.17** or **4.15** after the elimination of water. As illustrated in Scheme 4.9, LDA (1.1 equiv.) or LiHMDS (1.1 equiv.) were used to prepare the enolate of **2.18** in THF, Et_2O or DME, prior to the addition of aldehyde **4.13** (1.5 equiv.). To our surprise, all of these conditions were incapable of effecting the desired transformation. The aldehyde had again decomposed and although ketone starting material **2.18** was evident in the crude ^1H NMR spectrum, there seemed to be other unidentified side products originating from **2.18** as well.

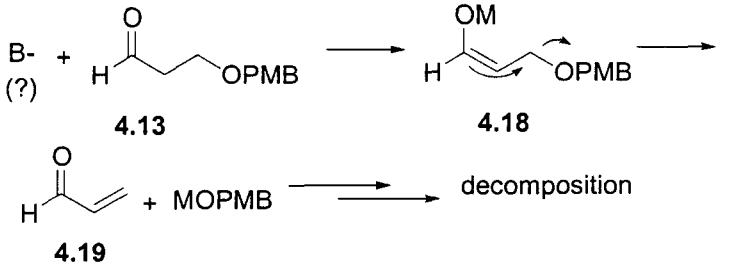
Scheme 4.9: *Mixed aldol reaction between the lithium enolate of ketone* ***2.18*** *and aldehyde* ***4.13***



We also repeated the aldol reactions using a potassium enolate prepared from ketone **2.18** and KHMDS in THF, Et_2O or DME. Unfortunately, mixtures of decomposition products or recovered ketone **2.18** were obtained as previously observed in Scheme 4.9.

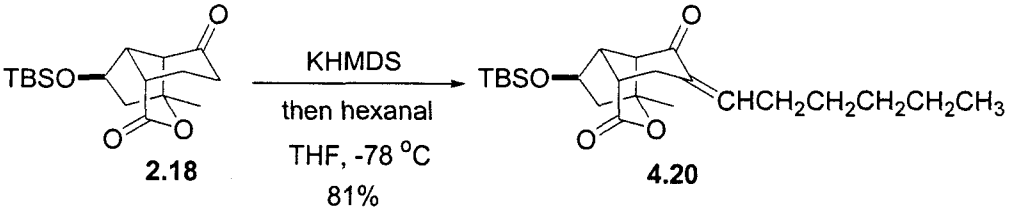
The tendency of aldehyde **4.13** to decompose into multiple products was quite unsettling. The presence of 4-methoxybenzyl alcohol in some of the crude ^1H NMRs suggested that **4.13** was eliminating the OPMB group, perhaps by an E1cb mechanism, and then further decomposing in the reaction conditions.

Scheme 4.10: *Possible decomposition pathway of* ***4.13***



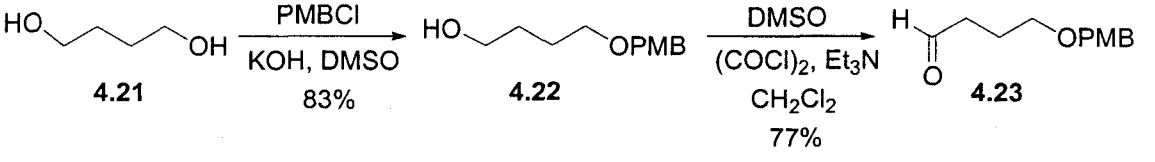
We therefore decided to perform an aldol reaction between commercially available hexanal and the enolate of **2.18** generated with KHMDS (Scheme 4.11). We were delighted to observe that the α,β-unsaturated ketone **4.20** was isolated in 81% yield. The geometry of the double bond could not be determined by NMR.

Scheme 4.11: *Synthesis of* ***4.20***



With this encouraging result, we opted to use an aldehyde that was similar to **4.13** but that contained an additional methylene group. Thus, aldehyde **4.23** was prepared in two steps beginning from commercially available 1,4-butanediol (**4.21**) as shown in Scheme 4.12.

Scheme 4.12: *Synthesis of aldehyde* ***4.23***



As anticipated, deprotonation of ketone **2.18** with KHMDS in THF at -78 °C followed by the addition of aldehyde **4.23** provided α,β–unsaturated ketone **4.24** in 82% yield (Scheme 4.13). Based on the 2D-NMR data, (Figure 4.1), it was established that the *(E)*-alkene had been formed as the sole isomer. A detailed analysis of the NMR data is found in Chapter 7.

Scheme 4.13: *Synthesis of α,β–unsaturated ketone* ***4.24***

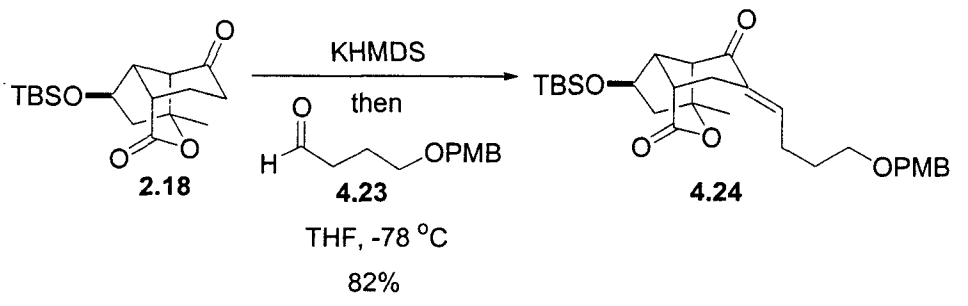
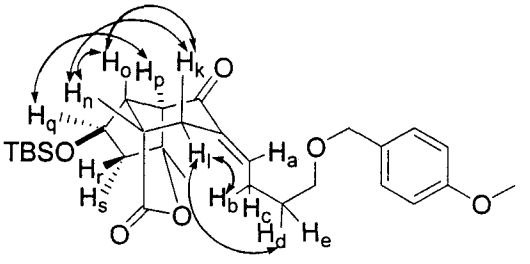
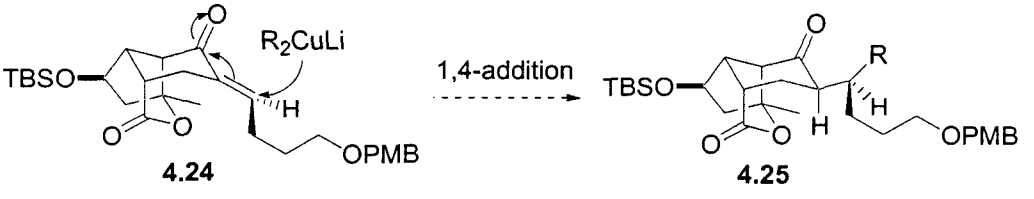


Figure 4.1*: NOESY correlations for* ***4.24***



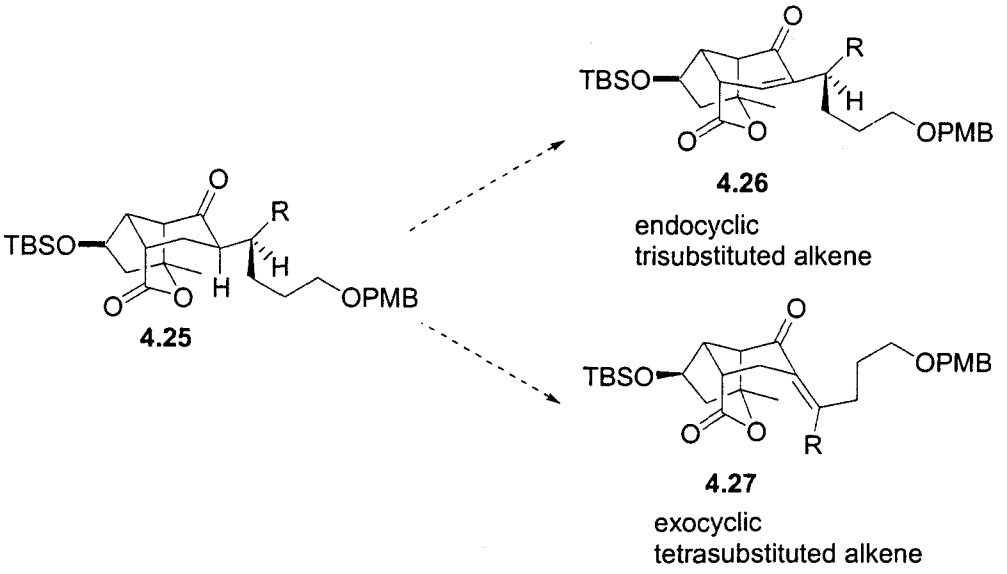
With the aldol adduct **4.24** prepared, it was now possible to explore the conjugate addition reaction to install the stereogenic center of the side-chain (Scheme 4.14). The efficiency of this synthetic route depended on the 1,4-addition occurring exclusively from the *si* face of *(E)*-α,β-unsaturated ketone **4.24** so that compound **4.25** would be generated as a single diastereomer.

Scheme 4.14: *Proposed conjugate addition from the si face of* ***4.24***



Following the cuprate addition, we would begin the task of installing the endocyclic trisubstituted double bond in the six-membered ring (i.e **4.26**) via a β-hydrogen elimination reaction (Scheme 4.15). We recognized that this task may be difficult since the undesired tetrasubstituted alkene **4.27** could also be generated. More details regarding this transformation will be discussed in Section 4.3 of this chapter: Installation of the Endocyclic Alkene.

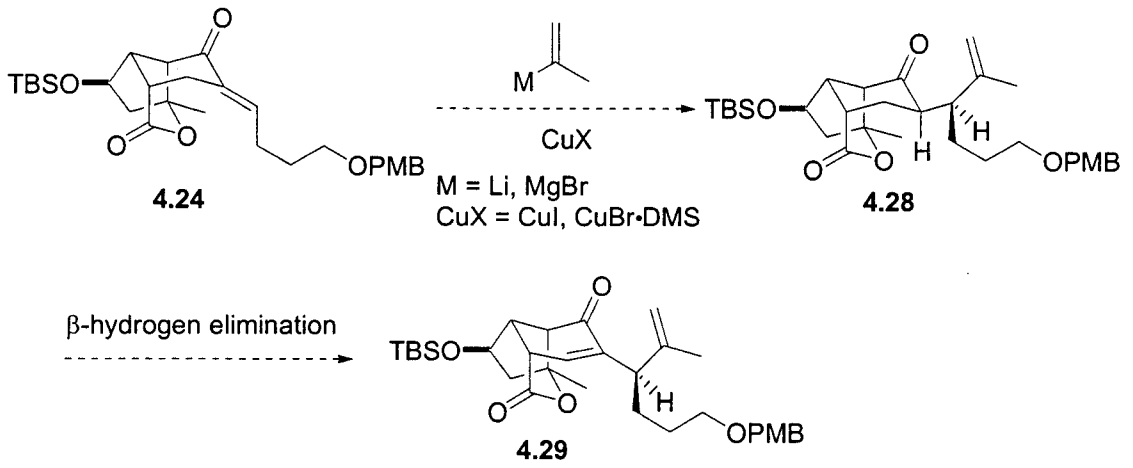
Scheme 4.15: *Endocyclic vs exocyclic double bond formation*



In view of this possible challenge, we decided to perform the conjugate addition reaction with an isopropenyl group to prepare **4.28** (Scheme 4.16). In doing so, the core of the side-chain would be complete, although with the incorrect stereochemistry at the stereogenic center, if the addition occurred from the *si* face as expected. Regardless of the stereochemistry, compound **4.28** would be a sufficient model in which to explore various β–hydrogen elimination procedures to prepare **4.29**. Provided that the endocyclic trisubstituted alkene could be installed, the aldol and cuprate addition reactions would be

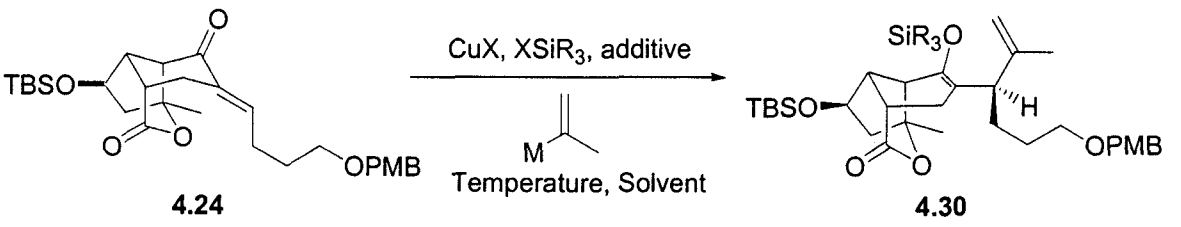
repeated using an R' for the aldehyde and R group for the cuprate that would access the side-chain in the most efficient manner (see Scheme 4.6).

Scheme 4.16: *Proposed conjugate addition of an isopropenyl cuprate nucleophile onto enone* ***4.24***



As shown in Table 4.1, a variety of conditions were investigated to promote the conjugate addition reaction. Copper sources such as CuBr·DMS and CuI and nucleophiles such as isopropenyl magnesium bromide and the lithium equivalent were used. Various additives such as HMPA, nBu_3P, TMEDA or LiCl were also explored in the reaction. After many attempts, we were very pleased to observe complete conversion of the starting material to one major product in the presence of CuI (2 equiv.), TMSCl (10 equiv.), LiCl (4 equiv.) and isopropenyl magnesium bromide (10 equiv.) in THF at 0 °C (entry 10, Table 4.1).[16]

Table 4.1: *Conditions explored for the 1,4-addition reaction of* ***4.24***



4.24 **4.30**

Entry	CuX	Additive	$XSiR_3$	M	Temp. (° C)	Solvent	Conversion (%)
1[11]	CuBr·DMS	-	Me_3SiCl	MgBr	-78	THF	SM
2	CuBr·DMS	HMPA	Me_3SiCl	MgBr	-78	THF	SM
3	CuBr·DMS	HMPA	Me_3SiCl	MgBr	78 to rt	THF	SM
4	CuBr·DMS	-	Me_3SiCl	Li	-78	THF	SM
5	CuBr·DMS	-	-	MgBr	0 to -78	THF	SM
6	CuBr·DMS	HMPA	Me_3SiCl	MgBr	-78	Et_2O	SM
7[12]	CuI	nBu_3P	TBSOTf	Li	-78 to -40	Et_2O	Decomp.
8[13]	CuI	-	-	MgBr	0	THF	SM
9[14]	CuI	TMEDA	Me_3SiCl	MgBr	-78	THF	SM
10[15]	**CuI**	**LiCl**	**Me_3SiCl**	**MgBr**	**0**	**THF**	**100**

The single diastereomer obtained from the reaction was determined to be ketone **4.28** (Scheme 4.17). Strong nOe signal between H_f and H_o, Me_e and H_a as well as between H_b and H_r confirmed that the 1,4-addition had indeed occurred on the *si* face of the molecule to provide **4.28** (Figure 4.2). A detailed analysis of the NMR data is found in Chapter 7.

Scheme 4.17: Synthesis of ***4.28***

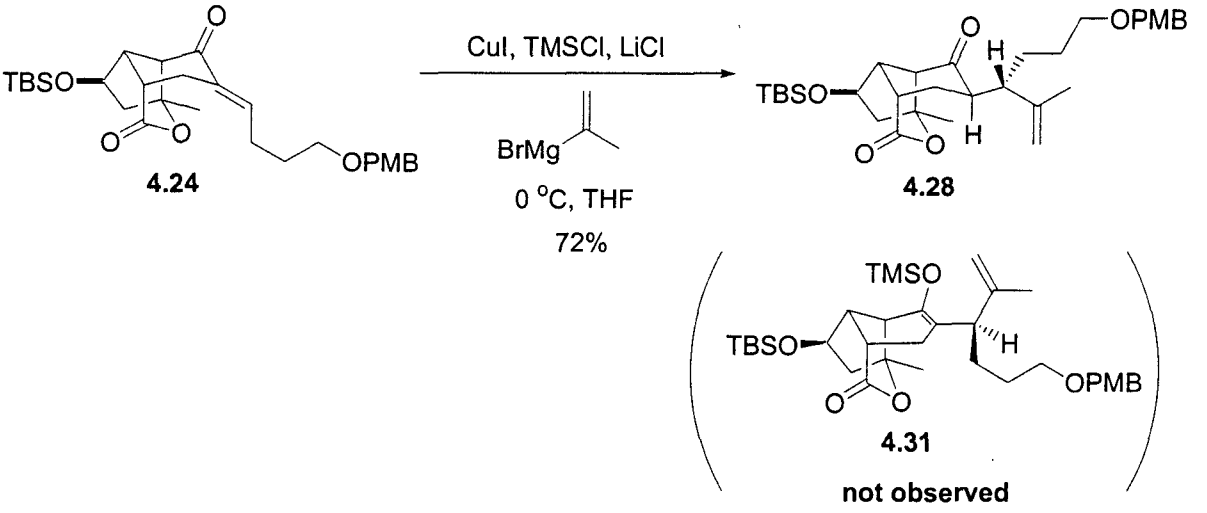
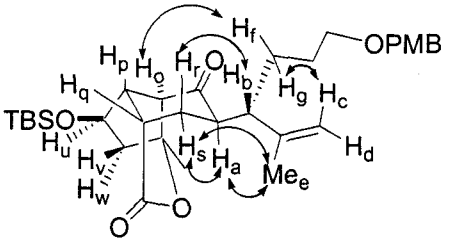


Figure 4.2: *NOESY correlations for* ***4.28***

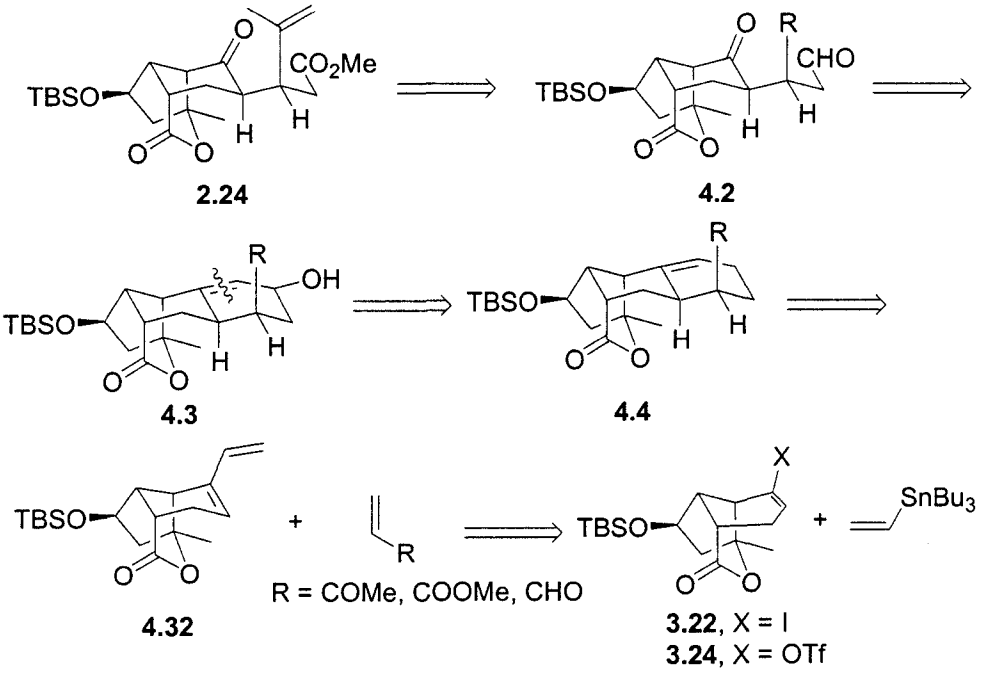


Using **4.28**, we next embarked on installing the endocyclic olefin positioned in the six-membered ring. The results of these studies are discussed in Section 4.3 of this chapter: Installation of the Endocyclic Alkene.

4.2 Diels-Alder Strategy

While exploring the 1,4-addition strategy for installing the side-chain of havellockate, we also envisioned a novel approach, described in Scheme 4.18, in which **2.24** could be accessed from compound **4.2**. The ketone and aldehyde functional groups in compound **4.2** could arise from an alkene cleavage reaction of allylic alcohol **4.3**. The secondary alcohol in **4.3** could be installed via an allylic oxidation of alkene **4.4**, which is the adduct of a Diels-Alder reaction between diene **4.32** and a commercially available dienophile. Finally, the diene could be prepared via a Stille cross-coupling reaction between tributyl(vinyl)tin and vinyl iodide **3.22** or vinyl triflate **3.24** (Chapter 3).

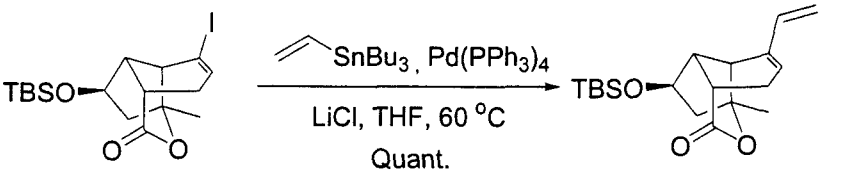
Scheme 4.18: *Synthesis of* ***2.24*** *via a Diels-Alder reaction*



The exploration of this strategy thus commenced with the synthesis of diene **4.32**. Since vinyl iodide **3.22** was available from our previous studies in Chapter 3, a Stille cross-coupling reaction was attempted using this coupling partner.[16] We were pleased to observe

that the reaction proceeded smoothly to provide the desired product **4.32** in quantitative yield (Scheme 4.19).

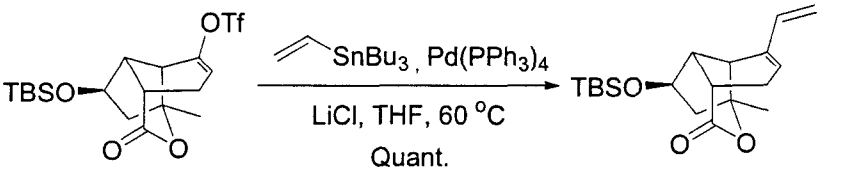
Scheme 4.19: *Synthesis of diene* ***4.32*** *from vinyl iodide* ***3.22***



3.22 **4.32**

The Stille reaction was later attempted with vinyl triflate **3.24** since it was more convenient to prepare. Diene **4.32** was again provided in quantitative yield (Scheme 4.20).

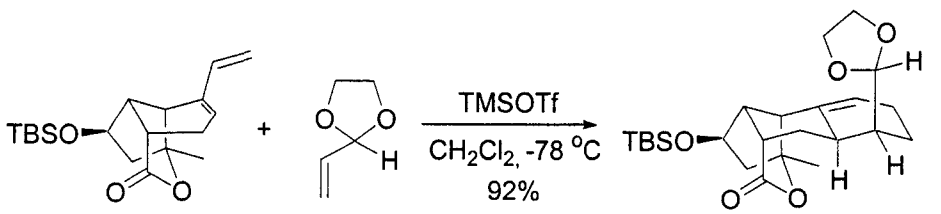
Scheme 4.20: *Synthesis of diene* ***4.32*** *from vinyl triflate* ***3.24***



3.24 **4.32**

Conditions for the Diels-Alder reaction were explored following the synthesis of the diene. A variety of Lewis acids such as $MgBr_2 \cdot OEt_2$, $MeAlCl_2$, $SnCl_4$ and $BF_3 \cdot OEt_2$ were used to promote the reaction between diene **4.32** and acrolein, methyl vinyl ketone or methyl acrylate. In these conditions however, only starting material was observed. An alternative Gassman-type dienophile, 2-vinyl-1,3-dioxolane (**4.33**) was next employed in the Diels-Alder reaction.[17] We were delighted to observe that treatment of **4.32** with this dienophile and TMSOTf at – 78 °C, furnished the desired adduct **4.34** in 92% yield (Scheme 4.21).

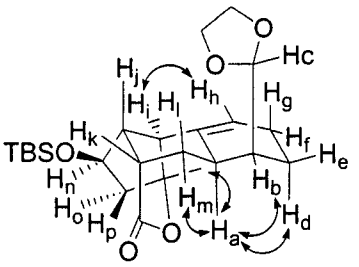
Scheme 4.21: *Diels-Alder reaction between* ***4.32*** *and 2-vinyl-1,3-dioxolane (****4.33****)*



4.32 **4.33** **4.34**

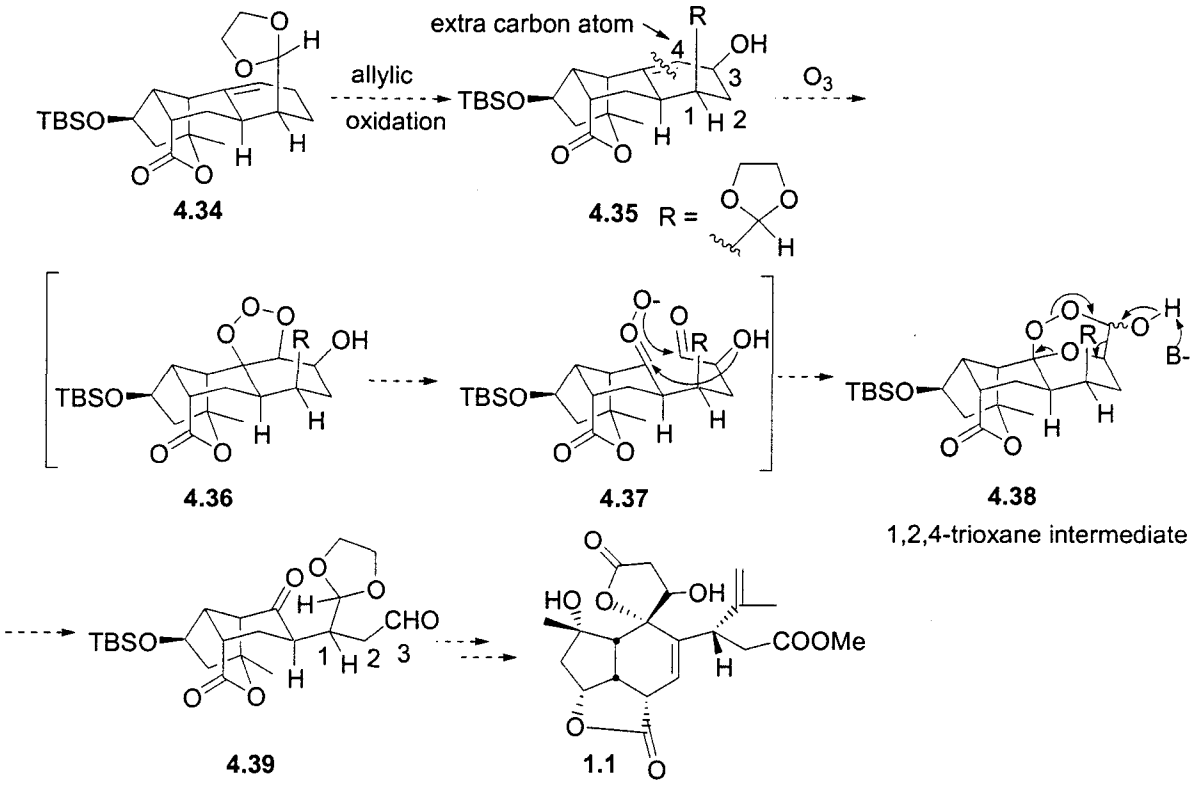
Srong nOe signals between H_a and H_d, H_a and H_b and finally H_a and H_m confirmed the stereo- and regiochemistry of the Diels-Alder adduct **4.34** as shown in Figure 4.3. A detailed analysis of the nOe and COSY data can be found in Chapter 7.

Figure 4.3: *nOe correlations for* ***4.34***



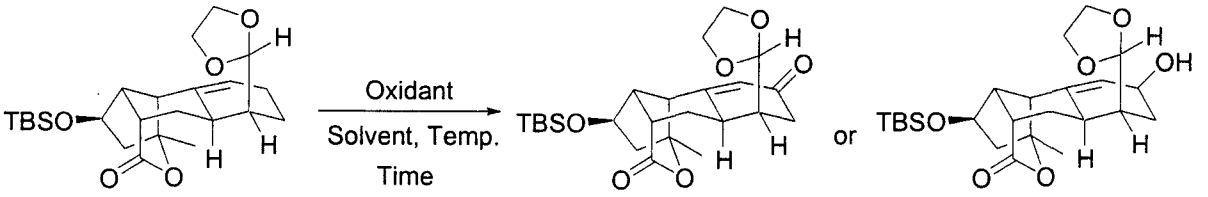
The allylic oxidation reaction to prepare allylic alcohol **4.35** from alkene **4.34** was next investigated (Scheme 4.22). This newly installed secondary alcohol would provide a handle in which to remove the extraneous carbon atom to provide the three-carbon chain present in the natural product (**1.1**). For example, by subjecting compound **4.35** to ozonolysis conditions, a 1,2,4-trioxane intermediate **4.38** would be generated during the course of the reaction, due to the participation of the allylic alcohol.[18] In the presence of a base, this intermediate would fragment to ketone **4.39.** Thus the overall process would lead to the cleavage of the double bond and the adjacent single bond.

Scheme 4.22: *Proposed allylic oxidation of* ***4.34*** *and subsequent ozonolysis*



We examined some common procedures for the allylic oxidation reaction of **4.34** involving selenium dioxide[19] (entries 1-6, Table 4.2) to form **4.35** or **4.40** (or mixtures of both) depending on the conditions. Initially a catalytic amount of selenium dioxide (5 mol%) in the presence of a stoichiometric amount of *tert*-butyl hydroperoxide was investigated to facilitate the oxidation reaction.[20] At room temperature (entries 1 and 2) starting material **4.34** was observed and at higher temperatures (40 °C), **4.34** simply degraded (entries 3 and 4). The addition of acetic acid to prevent the formation of enone **4.40** also failed to produce the desired allylic alcohol **4.35** (entry 5).[22] Conducting the reaction with a stoichiometric amount of SeO_2 in dioxane at 40 °C decomposed **4.34** (entry 6). A variety of chromium trioxide oxidation procedures were also examined as illustrated in entries 7-12, but **4.34** was quite resistant to even refluxing conditions.

Table 4.2: *Allylic oxidation attempts of* ***4.34***

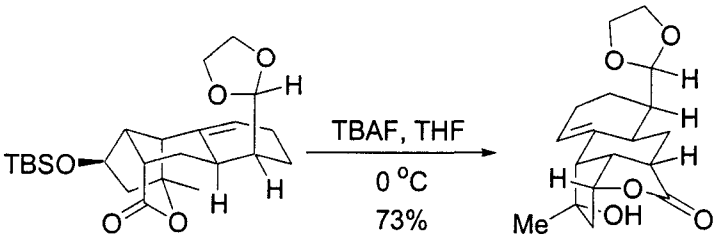


4.34 **4.40** **4.35**

Entry	Oxidant	Solvent	Temp. (° C)	Time (h)	Result
1[21]	SeO_2, *t*BuOOH (70% in H_2O)	CH_2Cl_2	0 to rt	72	SM
2	SeO_2, *t*BuOOH (in decane)	CH_2Cl_2	0 to rt	72	SM
3	SeO_2, *t*BuOOH (70% in H_2O)	CH_2Cl_2	40	2	Decomp.
4	SeO_2, *t*BuOOH (in decane)	CH_2Cl_2	40	2	Decomp.
5[22]	SeO_2, *t*BuOOH (70% in H_2O), H_2O, AcOH	CH_2Cl_2	0 to rt	24	Decomp.
6[23]	SeO_2	dioxane	40	1	Decomp.
7[24]	CrO_3·2Py	CH_2Cl_2	rt	4	SM
8	CrO_3·2Py	CH_2Cl_2	reflux	4	SM
9[25]	CrO_3, pyridine, Celite	CH_2Cl_2	rt	72	SM
10	CrO_3, pyridine, Celite	CH_2Cl_2	reflux	72	SM
11[26]	CrO_3, 3,5-dimethylpyrazole	CH_2Cl_2	-78 to reflux	2	SM
12[27]	CrO_3·2Py, NaOAc, Celite	PhH	reflux	4	SM

We were suspicious that the conformation of the molecule may be influencing the reactivity of the double bond. Thus, the secondary alcohol of **4.34** was deprotected with TBAF at 0 °C, to provide **4.41** in 73% yield (Scheme 4.23).

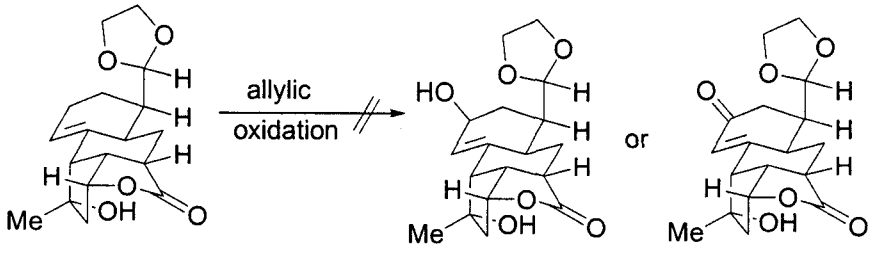
Scheme 4.23: *Synthesis of* ***4.41*** *via deprotection of the secondary alcohol*



4.34 **4.41**

The allylic oxidation protocols described in Table 4.2 were repeated with **4.41**, but the oxidized products **4.42** and/or **4.43** were never obtained (Scheme 4.24).

Scheme 4.24: *Allylic oxidation attempts of* ***4.41***

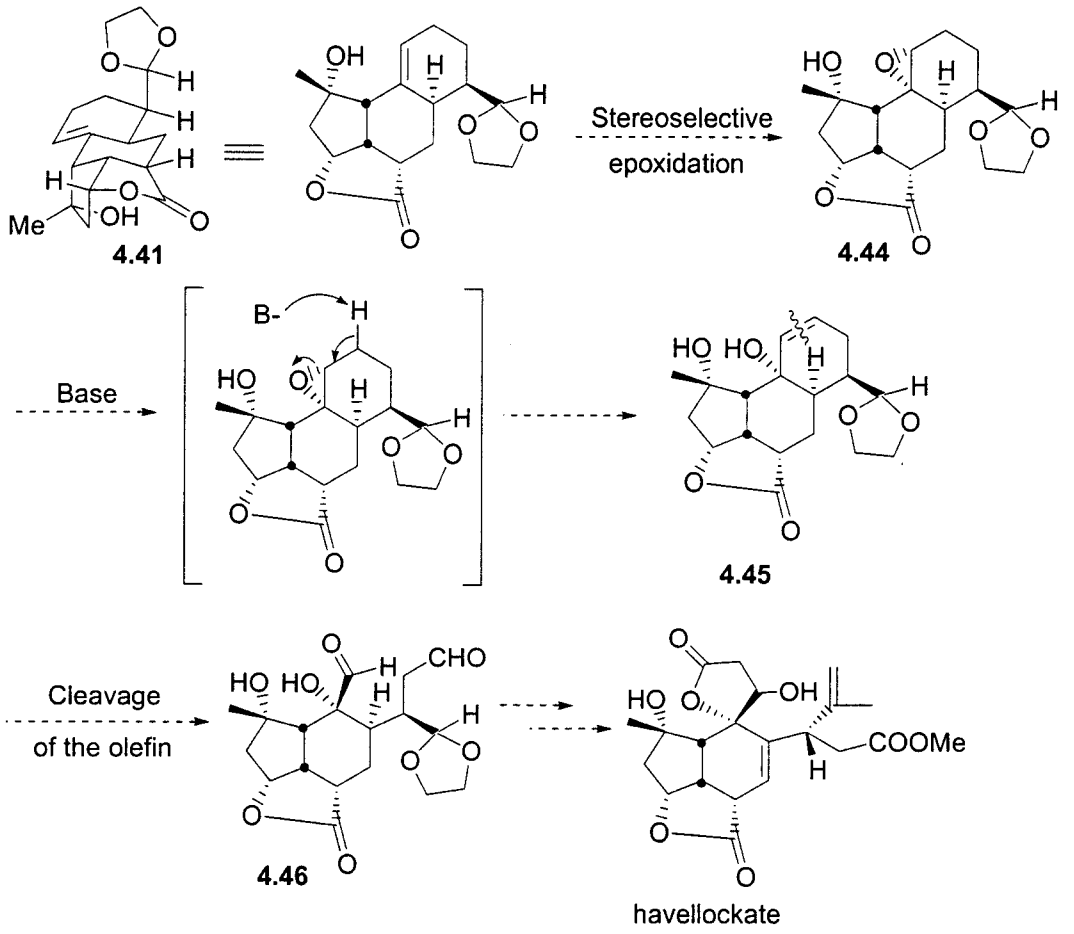


4.41 **4.42** **4.43**

not observed **not observed**

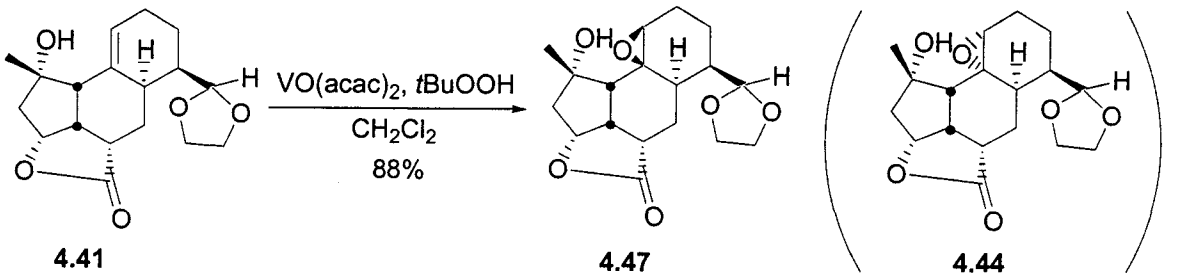
We recognized that the free hydroxyl group in **4.41** could be used to perform a stereoselective epoxidation reaction to provide **4.44** as illustrated in Scheme 4.25. Allylic alcohol **4.45** could then be formed via a base[28] induced rearrangement of the oxirane. With this approach, a portion of the spirocycle with the correct stereochemistry would be readily constructed and the side-chain would contain the correct number of carbon atoms following cleavage of the endocyclic olefin.

Scheme 4.25: *Alternative approach to installing the side-chain from* ***4.41***



The stereoselective epoxidation reaction was thus conducted by treating **4.41** with a mixture of $VO(acac)_2$ and *tert*-butyl hydroperoxide in CH_2Cl_2 at room temperature as illustrated in Scheme 4.26.[29] Although the reaction proceeded smoothly, closer inspection of the NMR data revealed a strong nOe signal between H_h and H_b (Figure 4.4), which indicated that the epoxide was *anti* to the tertiary alcohol (i.e. **4.47**). Thus, the complex must have formed on the convex face of the molecule for steric reasons instead of being directed by the tertiary alcohol of **4.41.** A detailed analysis of the 2D-NMR data is found in Chapter 7.

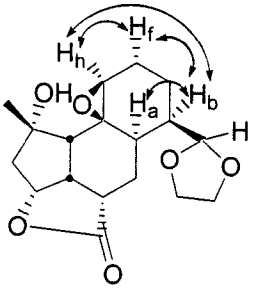
Scheme 4.26: *Epoxide formation from* ***4.41***



4.41 **4.47** **4.44**

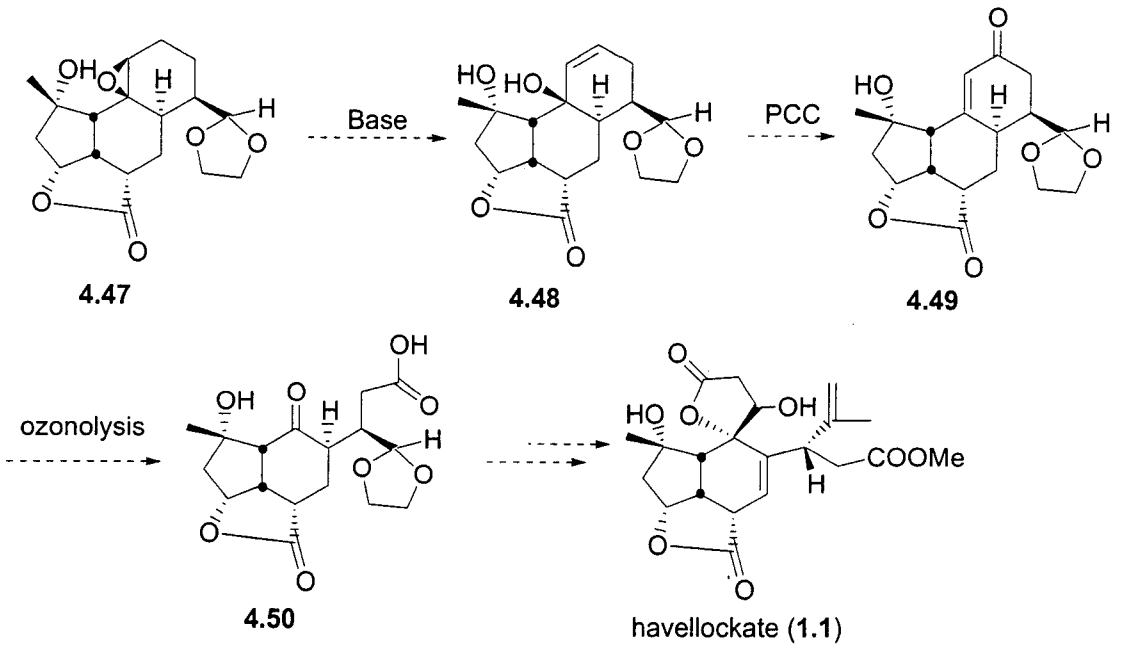
not observed

Figure 4.4: *NOESY correlations of* ***4.47***



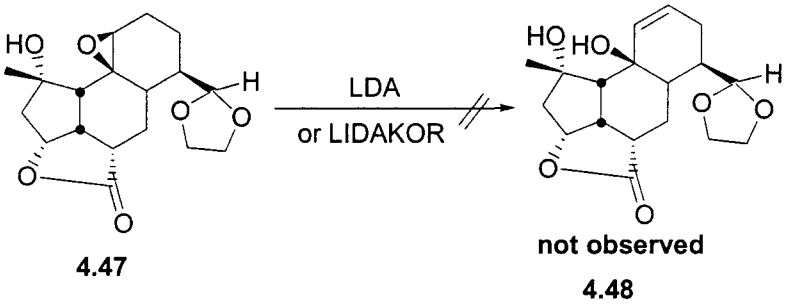
Although epoxide **4.47** did not have the stereochemistry that was intended, it was still a very useful intermediate for our synthesis. Base-induced opening of epoxide **4.47**, for example, would provide allylic alcohol **4.48,** which could undergo an allylic transposition reaction in the presence of PCC to generate α,β-unsaturated ketone **4.49** (Scheme 4.27). Cleavage of the olefin in **4.49** would provide ketone **4.50**. This ketone could act a handle for installing the endocylic double bond in the six-membered ring of havellockate and could be used to generate the spirocylic portion of the molecule.

Scheme 4.27: *Proposed synthetic route to havellockate from epoxide* ***4.47***



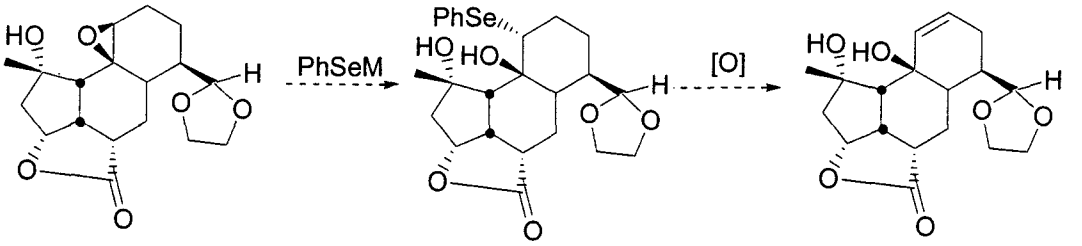
The base-induced opening of **4.47** was thus attempted with LDA[30] and LIDAKOR (LDA and KO*t*-Bu).[31] Unfortunately, these conditions could not generate the desired allylic alcohol **4.48** (Scheme 4.28).

Scheme 4.28: *Base induced opening of epoxide* ***4.47***



The use of a selenium anion generated *in-situ* to open the epoxide of **4.47** was also examined (Scheme 4.29).[32] Following the oxidation of the selenium atom in **4.51**, a *syn*-elimination reaction was expected to occur to provide allylic alcohol **4.48**.

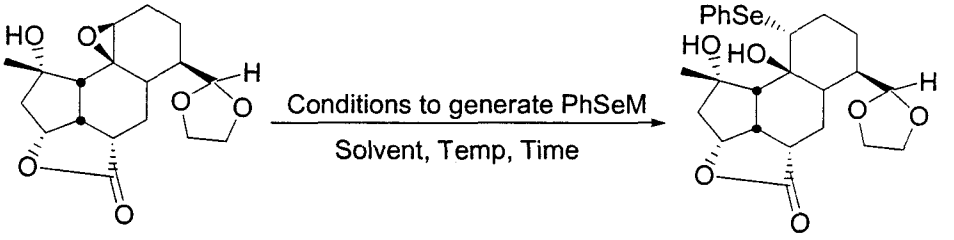
Scheme 4.29: *Proposed opening of epoxide* ***4.47*** *using a selenium anion followed by oxidation and syn elimination*



4.47 **4.51** **4.48**

As shown in Table 4.3, numerous conditions were explored to generate the selenide anion and open the epoxide, but the desired product **4.51** was not observed.

Table 4.3: *Epoxide opening of* ***4.47*** *with a selenide anion*

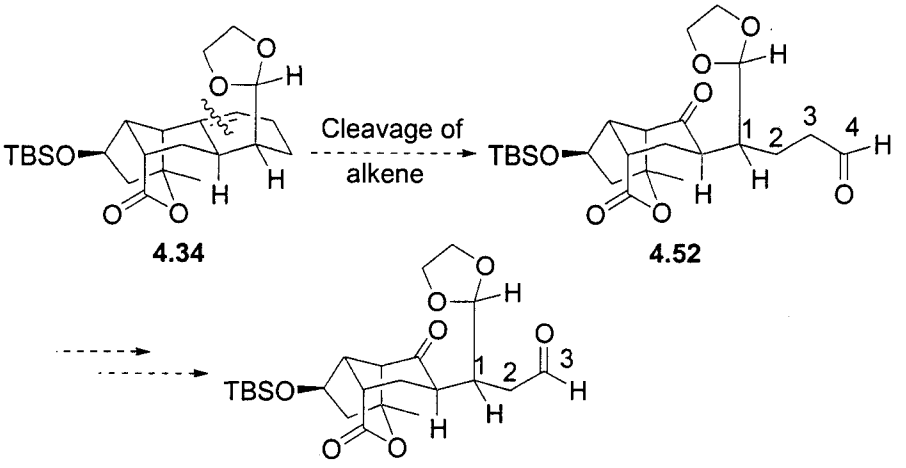


4.47 **4.51**

Entry	Conditions to generate $PhSe^-$	Solvent	Temp (°C)	Time (h)	Result
1	$LiBH_4$/PhSeSePh[32]	EtOH	rt	2	S.M.
2	$LiBH_4$/PhSeSePh[32]	EtOH	0	2	S.M.
3	$LiBH_4$/PhSeSePh[32]	EtOH/THF	rt	2	S.M.
4	$NaBH_4$/PhSeSePh[33]	EtOH	rt	1.5	S.M.
5	LAH/PhSeSePh[34]	Dioxane	rt	3	Decomp.

It was evident that we needed to consider other options beginning from the Diels-Alder adduct **4.34** since both the allylic oxidation and oxirane opening attempts were unproductive. We decided to investigate methods to simply cleave the endocyclic alkene as illustrated in Scheme 4.30. Even though this would lead to a side-chain containing one extra carbon atom (i.e **4.52**), we were confident this could be removed to generate **4.39**.[35]

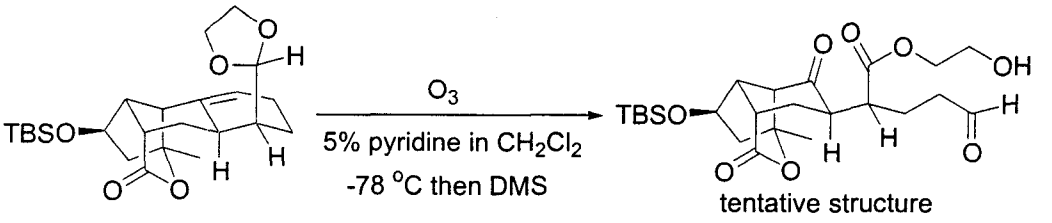
Scheme 4.30: *Cleavage of alkene* ***4.34***



4.34 **4.52** **4.39**

Although we examined many different conditions to cleave the olefin in **4.34** such as diol formation using OsO_4/NMO followed by treatment with $NaIO_4$,[36] the most promising results was obtained by performing an ozonolysis reaction. After optimization studies, we observed the best outcome by bubbling ozone in a flask containing **4.34** dissolved in a 5% solution of pyridine in CH_2Cl_2 at – 78 °C followed by a methyl sulfide work-up. Although the crude ^1H NMR seemed to reveal that the alkene had been cleaved, we also suspected the formation of a hydroxy-ester (Scheme 4.31).

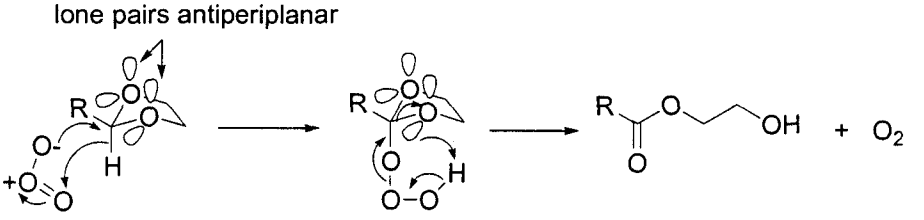
Scheme 4.31: *Ozonolysis of* ***4.34***



4.34 **4.53**

This latter observation can be readily explained by considering the stereoelectronic nature of the cyclic acetal as illustrated in Scheme 4.32.[37] Each oxygen atom of the acetal contains a lone pair of electrons that are antiperiplanar to the C-H bond, which increases the electron density and makes this bond more susceptible to attack by ozone. Once ozone is inserted, the resulting hydrotrioxide intermediate **4.55** can be cleaved to form the hydroxy ester **4.56**.[24]

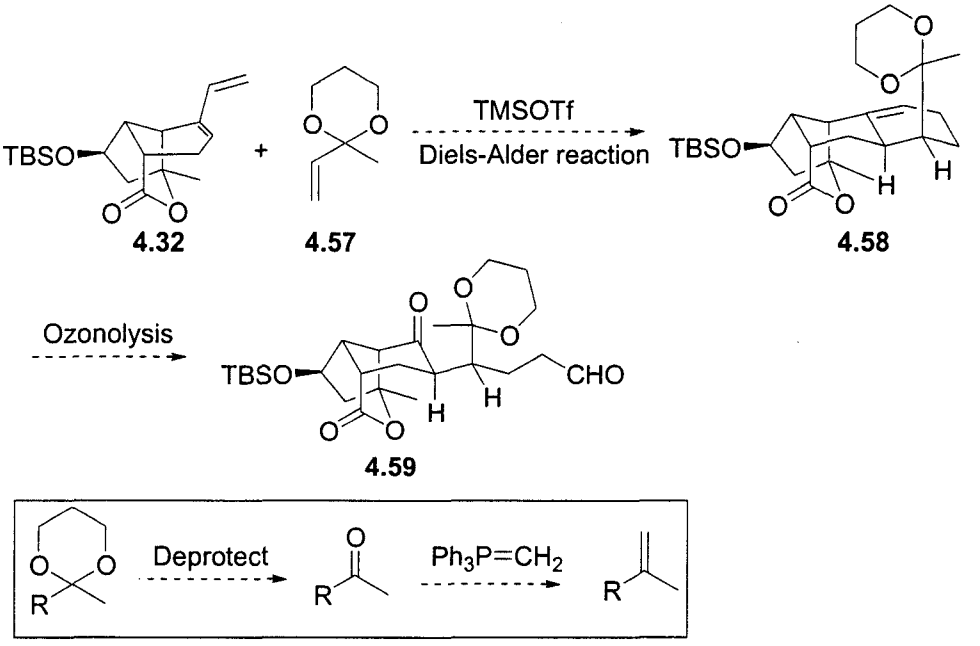
Scheme 4.32: *Stereoelectronic explanation for the opening of an acetal by ozone*



4.54 **4.55** **4.56**

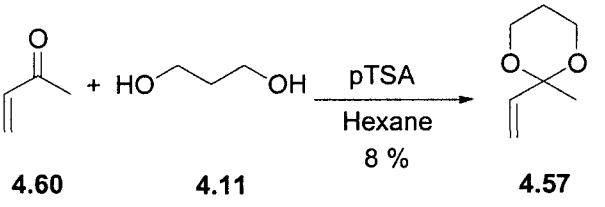
We proposed that this undesirable side-reaction could be avoided if the reactive hydrogen atom in the acetal was replaced with a methyl group (Scheme 4.33). In order to satisfy this demand, the Diels-Alder reaction would need to be repeated using a dienophile such as **4.57**, which was actually very favorable for our synthesis since the ketal could be easily transformed into the 1,1-disubstituted alkene found in the natural product.

Scheme 4.33: *Proposed Diels-Alder reaction and subsequent ozonolysis*



Before commencing with the Diels-Alder reaction, 2-methyl-2-vinyl-1,3-dioxane **4.57** was prepared from methyl vinyl ketone (**4.60**) and 1,3-propanediol (**4.11**) (Scheme 4.34).[38] Although the yield for this reaction was very low (8%), **4.57** was easily prepared on large scale.

Scheme 4.34: *Synthesis of dienophile **4.57***



The Diels-Alder reaction was then conducted between dienophile **4.57** and diene **4.32** in the presence of TMSOTf in CH_2Cl_2 at -78 °C. The desired adduct **4.58** was obtained in 89% yield (Scheme 4.35). The nOe signals between H_b and H_l, H_c and H_b as well as between H_a and H_l confirmed the regio- and stereochemistry of **4.58** as depicted in Figure 4.5. A detailed analysis of the 2D-NMR data is found in Chapter 7.

Scheme 4.35: *Synthesis of* ***4.58*** *via a Diels-Alder reaction between* ***4.32*** *and* ***4.57***

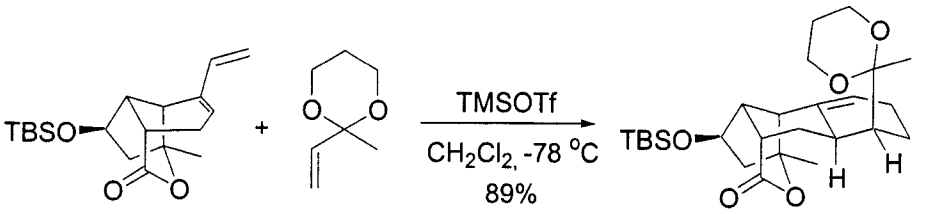
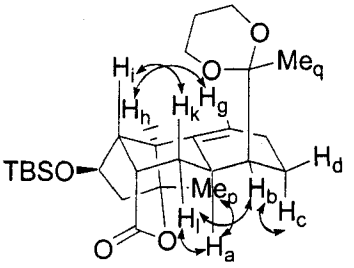
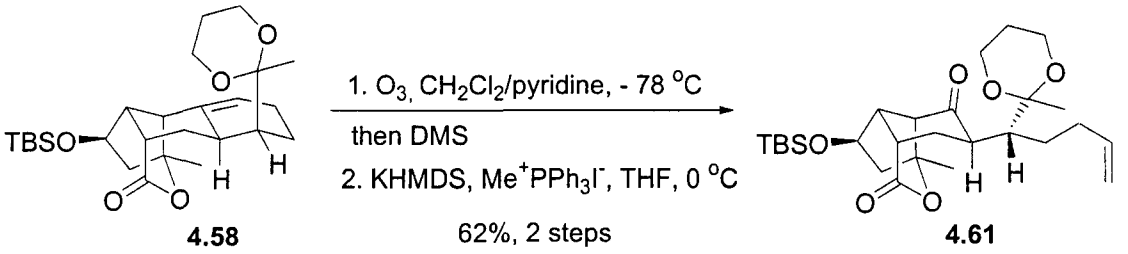


Figure 4.5: *NOESY correlations for* ***4.58***



The olefin present in **4.58** was then cleaved in the presence of ozone using the same conditions described in Scheme 4.31. Although the product was evident by NMR, it co-spotted with an impurity. By transforming the aldehyde into an alkene using Wittig conditions,[39] we were able to separate the impurity and characterize **4.61**. The overall yield for the two steps was 62% (Scheme 4.36).

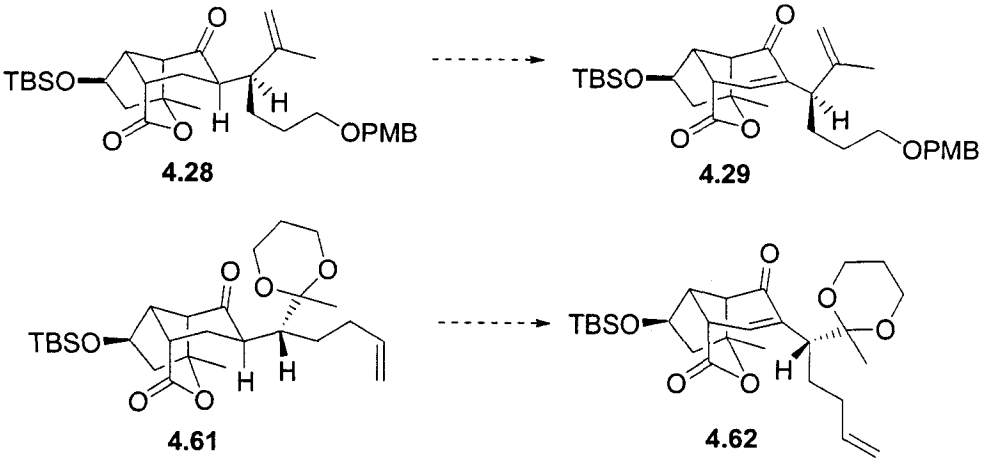
Scheme 4.36: *Cleavage of the olefin in the Diels-Alder adduct* ***4.58***



4.3 Installation of the Endocyclic Alkene

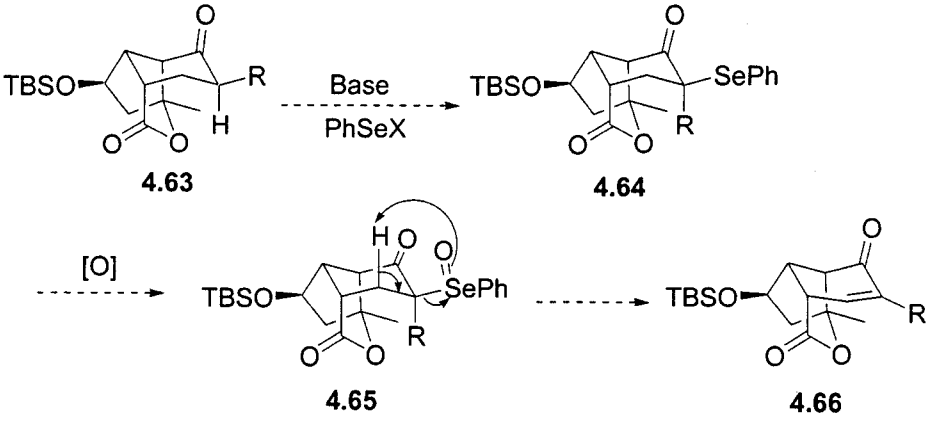
Before continuing with the synthesis of the side-chain from adducts **4.28** and **4.61** which had been prepared as described in Section 4.1 (mixed aldol condensation followed by 1,4-addition) and Section 4.2 (Diels-Alder reaction) respectively, we wanted to establish the conditions to install the endocyclic double bond within the six-membered rings (Scheme 4.37).

Scheme 4.37: *Installation of the endocyclic olefin in* ***4.28*** *and* ***4.61***



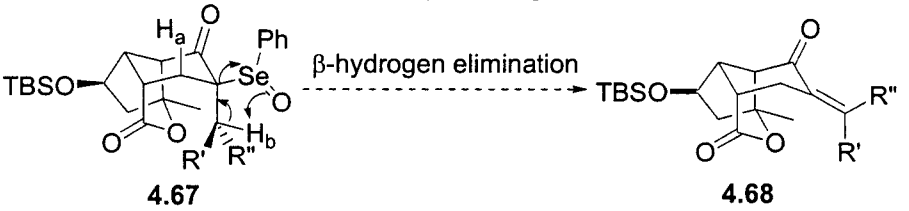
We initially explored the preparation of enones **4.29** and **4.62**, using a *syn*-elimination reaction.[40] This two-step process required the *C*-alkylation of an enolate with a selenium electrophile, XSePh (X = Cl, Br) as illustrated in Scheme 4.38. Under oxidizing conditions, the resulting selenoxide **4.65** would undergo a β-hydrogen elimination reaction in a *syn* fashion to generate the α,β-unsaturated carbonyl compound **4.66**.

Scheme 4.38: *Proposed syn-elimination reaction*



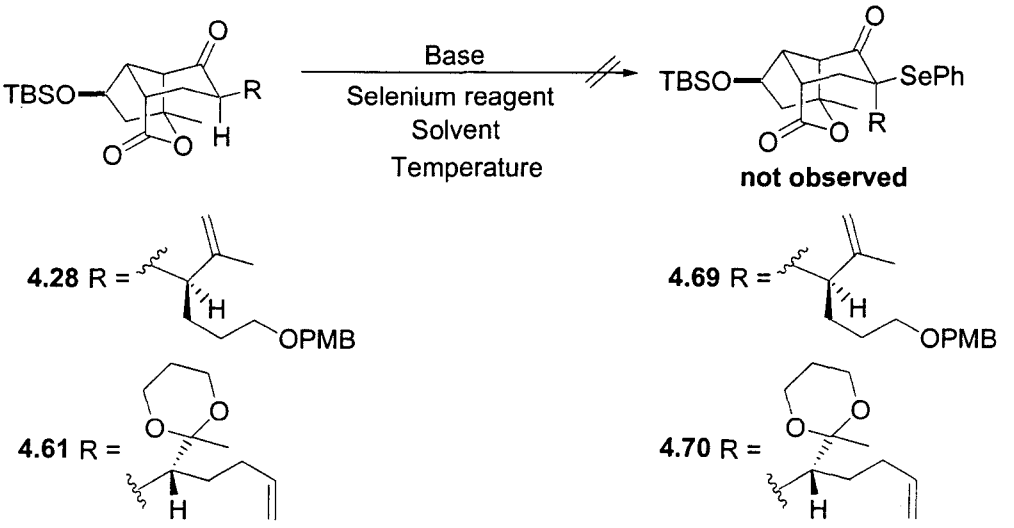
We were aware that both **4.28** and **4.61** contained a β-hydrogen atom (H_b) at the stereogenic center of the side-chain that could also eliminate to form the undesired tetrasubstituted exocyclic double bond (Scheme 4.39). A mixture of products arising from the elimination of both H_a and H_b (for both **4.28** and **4.61**) would clearly affect the efficiency of the synthesis.

Scheme 4.39: *Possible undesired β-hydrogen elimination reaction*



Although our initial concern was the β-hydrogen elimination process, we quickly learned that the *C*-alkylation reactions of enolates derived from **4.28** and **4.61** with a selenium electrophile was very difficult (Scheme 4.40). Regardless of the base (LDA, LiHMDS, KHMDS and KH), solvent (THF or Et_2O), electrophile (PhSeSePh, PhSeBr or PhSeCl) or temperature of the reaction (-78 °C or -20 or 0 °C), the alkylated products (**4.69** or **4.70**) could not be obtained. It is likely that the enolate formation and/or alkylation reactions with the bulky electrophiles at the tertiary carbon were prevented because of the surrounding steric congestion.

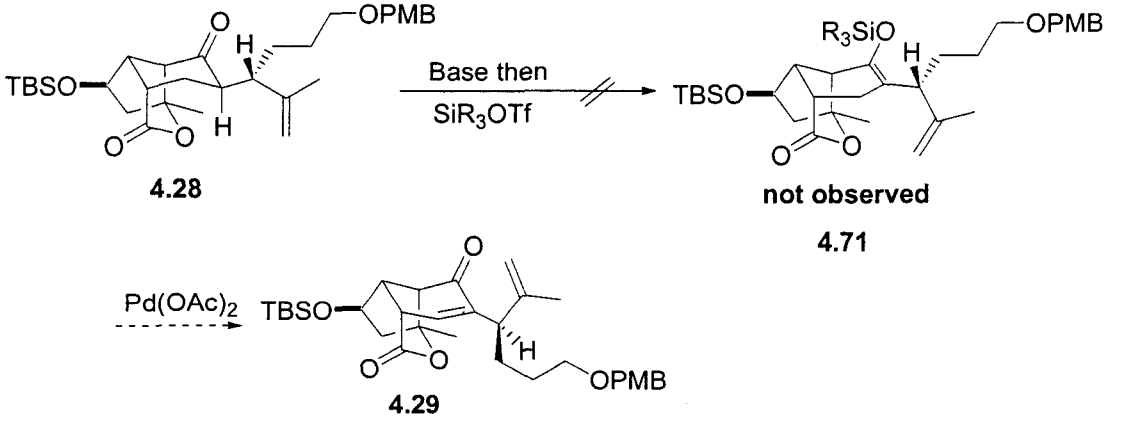
Scheme 4.40: *Attempts to form the α-selenide compound from* ***4.28*** *and* ***4.61***



Base: LDA, LiHMDS, KHMDS, KH
Selenium reagent: PhSeSePh, PhSeCl, PhSeBr
Solvent: THF, Et_2O
Temperature: -78 °C to - 20 °C to 0 °C

We also considered a Saegusa oxidation[41] as illustrated in Scheme 4.41. However, our attempts to prepare the TMS enol ether or the TBS enol ether from **4.28** did not prevail and thus the β-hydrogen elimination reaction using $Pd(OAc)_2$ could not be examined.

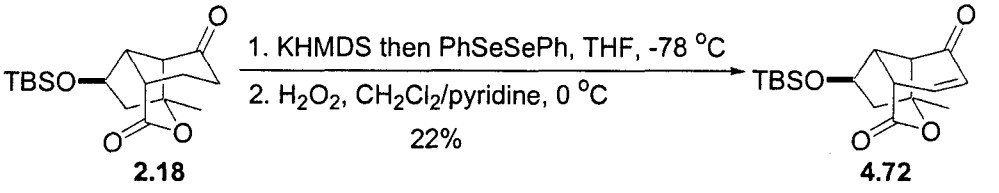
Scheme 4.41: *Attempted synthesis of enol ether* ***4.71*** *for the Saegusa oxidation*



Given the difficulties we encountered, we were curious to learn how facile the enone

formation would be using ketone **2.18** which contained a more accessible secondary carbon atom alpha to the ketone. Thus, the enolate of **2.18** was prepared using KHMDS and treated with PhSeSePh (Scheme 4.42). Although we were pleased to observe the formation of the desired product, the reaction failed to go to completion. The crude selenide was then oxidized with hydrogen peroxide in a solution of CH_2Cl_2/pyridine (1:1) to provide **4.72** in 22% yield (for the 2 steps).

Scheme 4.42: *Synthesis of enone 4.72*



2.18 **4.72**

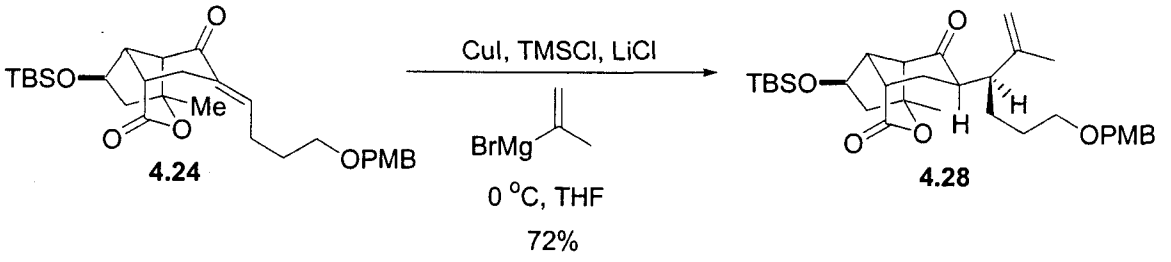
It was evident from the low yield of **4.72** that the enone formation was not a trivial transformation even in the absence of the side-chain. We therefore made the decision to discontinue our current strategies and develop a new synthetic approach which installed the endocyclic double bond prior to the alkyl side-chain. The details of this strategy are discussed in Chapter 5.

Conclusions:

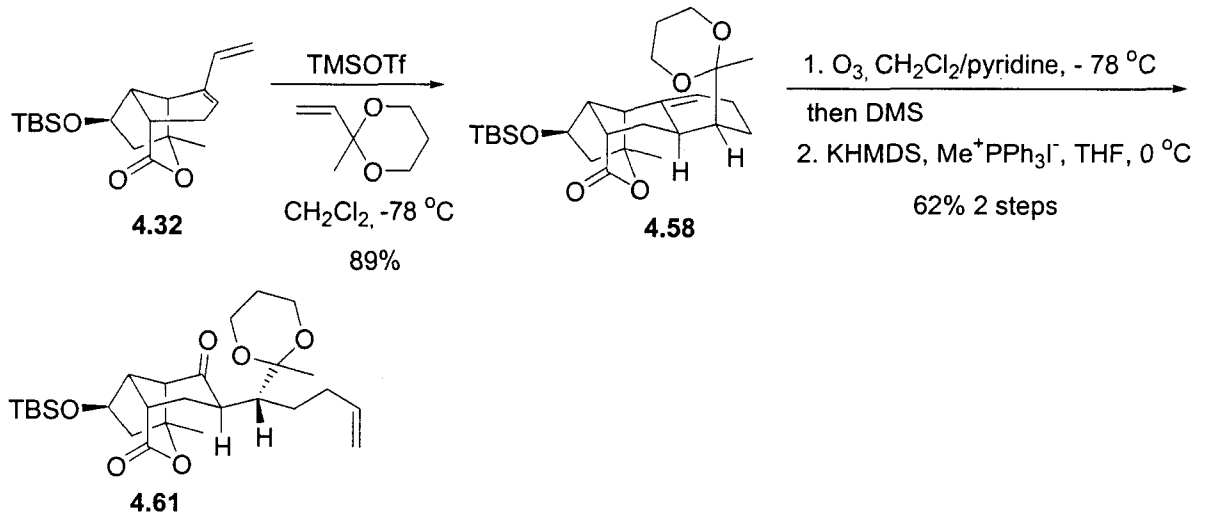
In this chapter we explored two very different approaches for installing the side-chain of havellockate. The first strategy described in Section 4.1 was a 1,4-addition of a carbon nucleophile onto α,β-unsaturated ketone **4.24** (Scheme 4.43) The second strategy described in Section 4.2, accessed the side-chain from Diels-Alder adduct **4.58** formed between a Gassman-type dienophile and diene **4.32** (Scheme 4.43).

Scheme 4.43: *Summary of 1,4-addition and Diels-Alder strategies*

1,4-Addition Strategy



Diels-Alder Strategy



Although both of these strategies offered great potential, we later discovered that the endocyclic double bond in the six-membered ring was difficult to install. Thus, we decided that a more promising synthetic strategy would be to establish the olefin prior to the side-chain.

References:

[1] House, H. O. Respess, W. L. Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. Schwartz, R. H.; Filippo, J. S. *J. Org. Chem.* **1979**, *44*, 2705. Marshall, J. A.; Cohen, G. M. *J. Org.*

Chem. **1971**, *36,* 877. Alvarez, F. S.; Wren, D.; Prince, A. *J. Am. Chem. Soc.* **1972**, *94,* 7823.

[2] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96,* 7503.

[3] Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44,* 4259. Gennari, C.; Beretta, M.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1886**, *42,* 893. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51,* 3027.

[4] de la Puente, M. L.; Ley, S. V.; Simmonds, M. S. J.; Blaney, W. M. *J. Chem. Soc. Perkin Trans. 1,* **1996**, 1523.

[5] Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5,* 857.

[6] Adhikari, S.; Caille, S.; Hanbauer, M.; Ngo, V. X.; Overman, L. E. *Org. Lett.* **2005**, *7,* 2795.

[7] Bouzide, A.; Sauvé, G. *Syn Lett.* **1997**, 1153. Akiyama, T.; Shima, H.; Ozaki, S. *Synlett.* **1992**, 415. Onoda, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1998**, *38,* 1143. Cappa, A.; Marcantoni, E.; Torregiani, E. *J. Org. Chem.* **1999**, *64,* 5696.

[8] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79,* 1920.

[9] Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol 3, Chapter 2, and references cited therein.

[10] Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16,* 1. Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry, 3rd Ed. Part B.* Plenum Press: New York. 1990; pg 55-74.

[11] Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27,* 4025.

[12] Kawabata, T.; Grieco, P. A.; Sham, H. L.; Kim, H.; Yan Jaw, J.; Tu, S. *J. Org. Chem.* **1987**, *52,* 3346.

[13] House, H. O.; Latham, R. A.; Slater, C. D. *J. Org. Chem.* **1966**, *31,* 2267.

[14] Johnson, C. R.; Marren, T. J. *Tetrahedron. Lett.* **1987**, *28,* 27.

[15] Reetz, M. T.; Kindler, A. *J. Organometallic Chem.* **1995**, *502,* C5.

[16] Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108,* 3033.

[17] Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1994,** *59,* 6890. Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998,** *120*, 1615. Gassman, P.G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. J. *J. Am. Chem. Soc.* **1987,** *109,* 2182.

[18] DiNinno, M. P. *J. Am. Chem. Soc.* **1995**, *117,* 9927.

[19] Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94,* 7154.

[20] Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99,* 5526.

[21] Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123,* 3369.

[22] Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.

[23] Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69,* 7802.

[24] Dauben, W. G.; Lorber, M.; Fullerton, D. *J. Org. Chem.* **1969**, *34,* 3587.

[25] Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Yan Jaw, J.; Tu, S. *J. Org. Chem.* **1987**, 52, 3346.

[26] Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43,* 2057.

[27] Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1994**, *116,* 1591.

[28] Crandall, J. K. Apparu, M. *Org. React.* **1983**, *29,* 345.

[29] Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95,* 6136.

[30] Barriault, L.; Warrington, J. "Literature update for LDA". *Electronic Encyclopedia of*

Reagents for Organic Synthesis. John Wiley & Sons, 2003.

[31] Mordini, A.; Pecchi, S.; Capozzi, G. Capperucci, A.; Deg'Innocenti, A.; Reginato, R.; Ricci, A. *J. Org. Chem.* **1994**, *59,* 4784.

[32] Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973,** *95,* 2697.

[33] Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124,* 12416.

[34] Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *J. Org. Chem.* **1991**, *56,* 5401.

[35] Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41,* 1485.

[36] Schroder, M. *Chem. Rev.* **1980**, *187,* 187.

[37] Deslongchamps, P. Stereoelectronic Effects in Organic Chemistry. Pergamon Press, New York. 1983. Pg 45 and 85.

[38] Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58,* 1449.

[39] For a review see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89,* 863.

[40] Trost, B. M. *Chem. Rev.* **1978**, *78,* 363. Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97,* 5434.

[41] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43,* 1011.

5

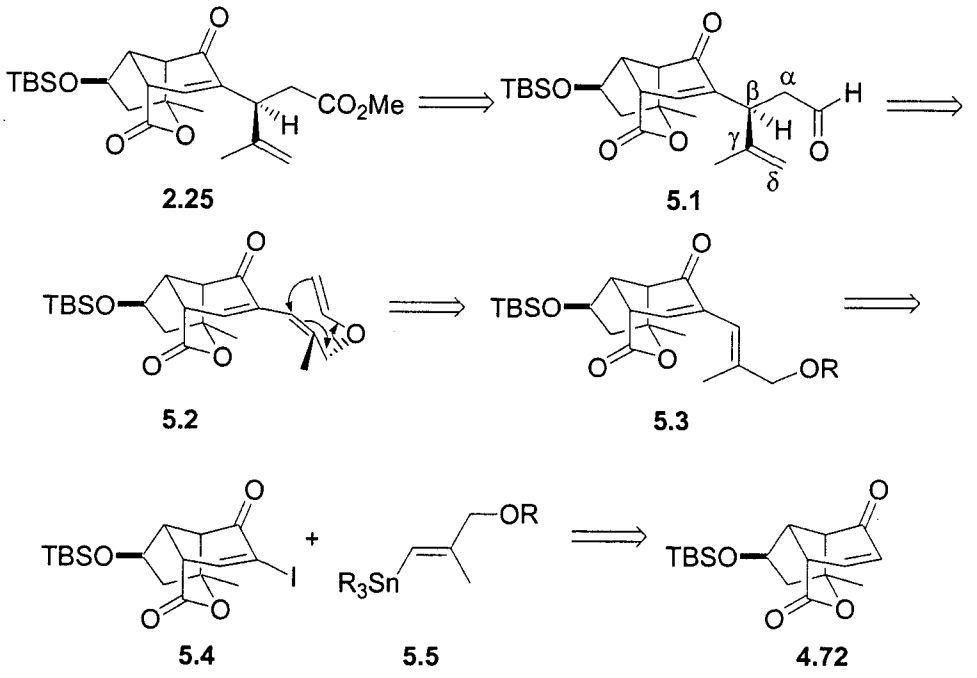
Construction of the Side-Chain

Part III: Claisen Rearrangement (B)

In Chapter 4, two approaches for constructing the side-chain of havellockate were discussed. These included a 1,4-addition of a carbon nucleophile as well as a Diels-Alder reaction followed by a cleavage of the newly generated double bond. Unfortunately, the downfall of both of these strategies was the endocyclic double bond in the six-membered ring, which could not be installed under various conditions.

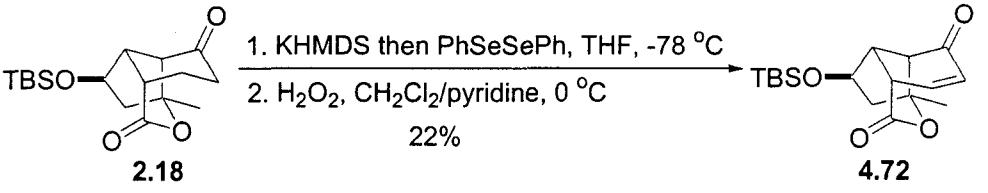
Given our experiences, it was clear that the endocyclic double bond needed to be installed prior to the side-chain. A fourth synthetic approach was therefore developed and is described in the retrosynthetic analysis in Scheme 5.1. We envisioned that compound **2.25** could be readily prepared from **5.1** via an oxidation of the aldehyde to the carboxylic acid followed by an esterification. Enone **5.1** contains a γ,δ-unsaturated aldehyde, which could arise from a Claisen rearrangement of allyl vinyl ether **5.2**. Compound **5.2** could originate from allylic alcohol **5.3**, which in-turn could be prepared via a Stille cross-coupling reaction between vinyl iodide **5.4** and vinyl stannane **5.5**. Finally **5.5** could be prepared from enone **4.72** via an α-iodination reaction.

Scheme 5.1: *Retrosynthetic analysis of* ***2.25***



As previously discussed in Chapter 4, our first attempt to prepare compound **4.72** using a *syn* elimination reaction provided the enone in only 22% yield (Scheme 5.2). This low yield is attributed to the alkylation step failing to go to completion and the oxidation conditions causing significant decomposition of the material.

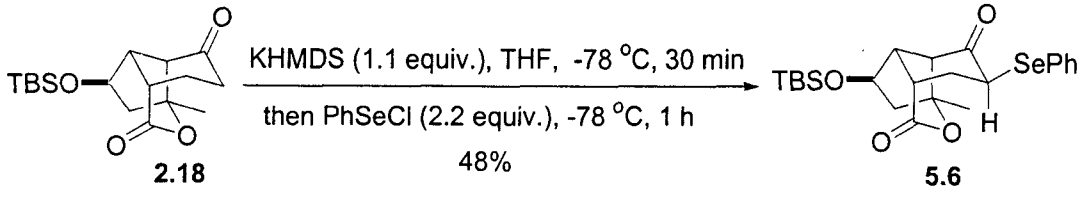
Scheme 5.2: *β-hydrogen elimination reaction to prepare* ***4.72***



The yield of compound **4.72** was clearly unacceptable for the synthesis and thus our studies of this new approach commenced by optimizing both the alkylation and oxidation step of the *syn*-elimination reaction.

We predicted that more reactive selenium electrophiles such as PhSeCl or PhSeBr would significantly improve the yield of the alkylation step. Unfortunately, the highest yield obtained of **5.6** was only 48% (72% based on recovered starting material) in the presence of 2.2 equivalents of PhSeCl as illustrated in Scheme 5.3.

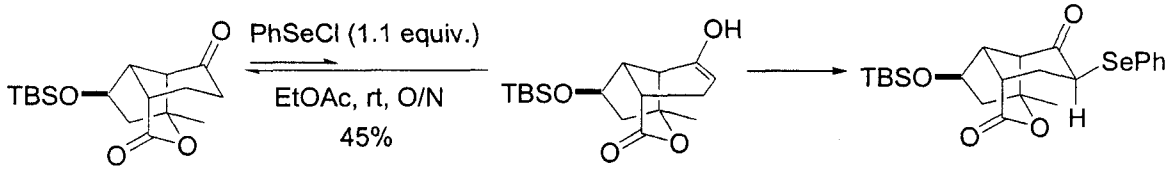
Scheme 5.3: *Alkylation of the enolate generated from* ***2.18*** *with 2.2 equiv. PhSeCl*



2.18 **5.6**

We also examined the alkylation of enol **5.7** with PhSeCl in a solution of EtOAc (Scheme 5.4).[1] Following substantial optimization studies, we determined that 1.1 equivalents of PhSeCl in a 0.16 M solution of freshly distilled EtOAc could provide **5.6** in 45% yield (82% based on recovered starting material).

Scheme 5.4: *Alkylation of enol* ***5.7*** *with 1.1 equiv. PhSeCl*



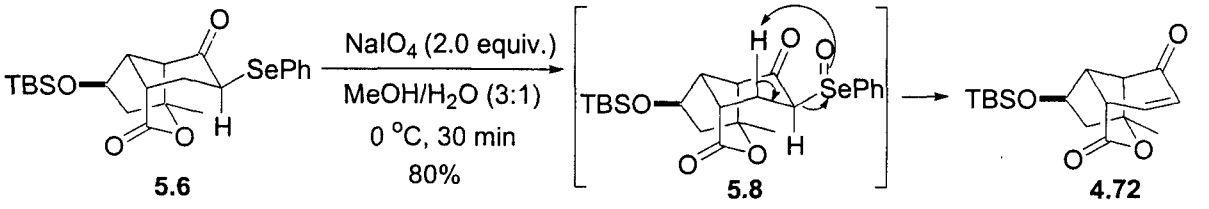
2.18 **5.7** **5.6**

A similar alkylation protocol to the one described in Scheme 5.4 was also investigated using $PhSeNMe_2$[2] in a solution of CH_2Cl_2. However, this selenium electrophile was very difficult to prepare and often decomposed upon distillation. Even when sufficiently pure $PhSeNMe_2$ was obtained, the yield of **5.6** was a mere 22% (68% recovered starting material).

We decided to accept the optimized yield of 48% for **5.6** (Scheme 5.3) and focus on improving the subsequent oxidation-elimination step of the reaction. In addition to H_2O_2

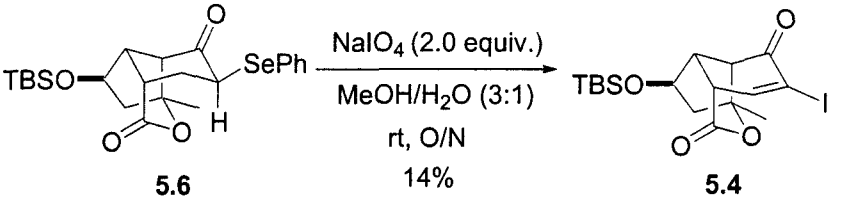
(Scheme 5.2), we also examined the use of $NaIO_4$ in an aqueous methanolic solution to form the intermediate selenoxide **5.8** from compound **5.6** as illustrated in Scheme 5.5.[3] We were pleased to observe that there was very little decomposition of **5.6** in these conditions and after stirring for 30 min at 0 °C, the desired product **4.72** was obtained in 80% yield.

Scheme 5.5: *Oxidation of* ***5.6*** *with* $NaIO_4$ *in an aqueous methanolic solution*



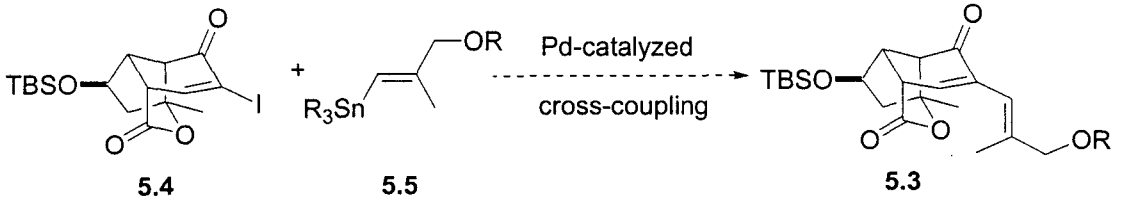
In one occasion, the reaction was stirred overnight at room temperature. We were surprised to see in the morning that there was no trace of enone **4.72** by TLC. Quite interestingly though, vinyl iodide **5.4** was obtained in 14% yield (Scheme 5.6)

Scheme 5.6: *Direct formation of* ***5.4*** *from* ***5.6*** *with* $NaIO_4$ *in an aqueous methanolic solution at room temperature, overnight*



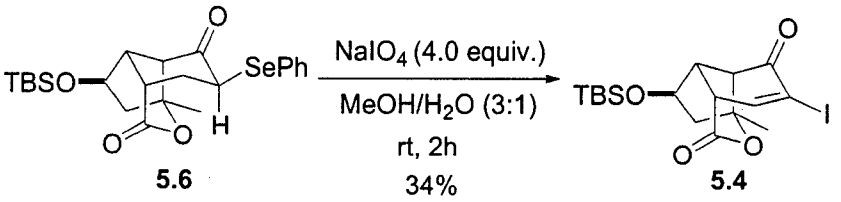
This initial result was very exciting, because vinyl iodide **5.4** was required for the subsequent palladium-catalyzed cross coupling reaction (Scheme 5.7).

Scheme 5.7: *Proposed palladium-cross coupling of vinyl iodide* ***5.4*** *and vinyl stannane* ***5.5***



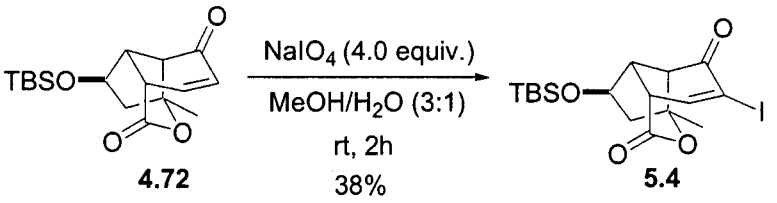
After conducting optimization studies, we were able to improve the yield of **5.4** to 34% by treating **5.6** with four equivalents of $NaIO_4$ for 2 h at room temperature (Scheme 5.8).

Scheme 5.8: *Direct formation of **5.4** from **5.6** with $NaIO_4$ in an aqueous methanolic solution at room temperature for 2 h*



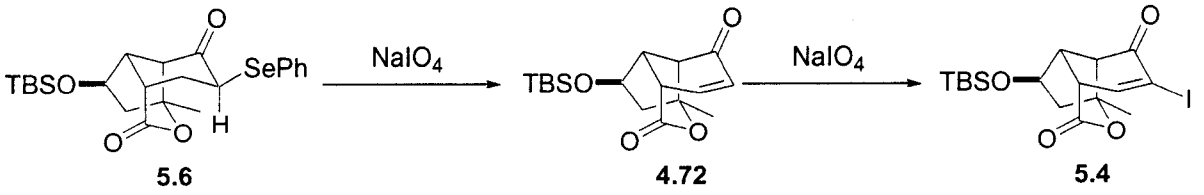
Furthermore, we noted that treating enone **4.72** with the same oxidizing conditions described in Scheme 5.8, lead to the formation of α-iodoenone **5.4** in 38% yield (Scheme 5.9).

Scheme 5.9: *Formation of **5.4** from **4.72** in the presence of $NaIO_4$ in an aqueous methanolic solution at rt for 2 h*



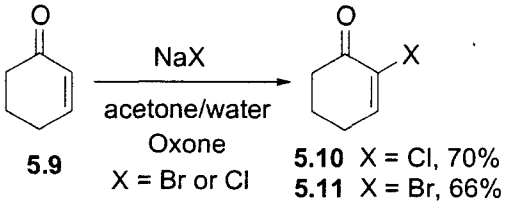
Given the above observation, it was conceivable that the reaction was occurring via a two-step process that included intermediate **4.72** as illustrated in Scheme 5.10.

Scheme 5.10: *Proposed two-step sequence for the synthesis of **5.4***



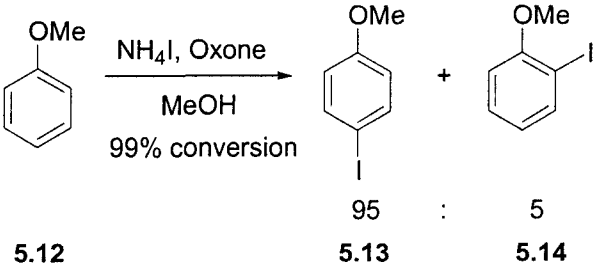
We examined the literature to determine if similar transformations had been mentioned. To the best of our knowledge, there are no other reports of a tandem oxidation-*syn* elimination-α-iodination sequence using $NaIO_4$. We did uncover an interesting example however, illustrated in Scheme 5.11, where cyclohexenone (**5.9**) was treated with NaCl or NaBr in the presence of Oxone®.[4] In these conditions, molecular chlorine or bromine were produced *in-situ* which then reacted with enone **5.9**. The corresponding α-halides **5.10** (X = Cl) and **5.11** (X = Br) were obtained in 70% and 66% yield respectively.

Scheme 5.11: *Oxy-halogenation of cyclohexenone*



A similar oxyhalogenation reaction was observed when methoxyphenol (**5.12**) was treated with NH_4I and Oxone® (Scheme 5.12).[5] The electrophilic iodine that was generated *in-situ* reacted with the aromatic compound to provide a mixture of **5.13** and **5.14**.

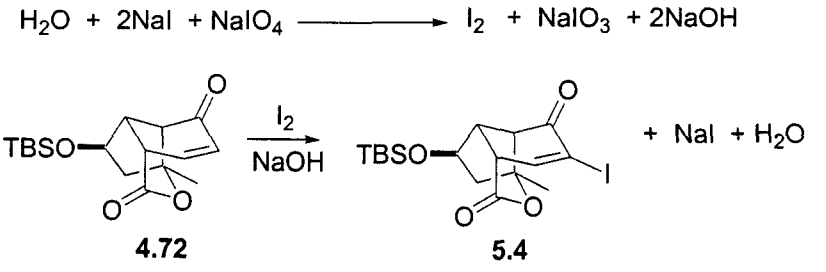
Scheme 5.12: *Oxyiodination of methoxyphenol with NH_4I and Oxone®*



Based of these accounts in the literature, we questioned whether the old bottle of $NaIO_4$ that was being used for these reactions was contaminated with NaI. If this were indeed the

case, then as illustrated in Scheme 5.13, I_2 could be generated *in-situ*, which would then immediately react with **4.72** to form **5.4**.

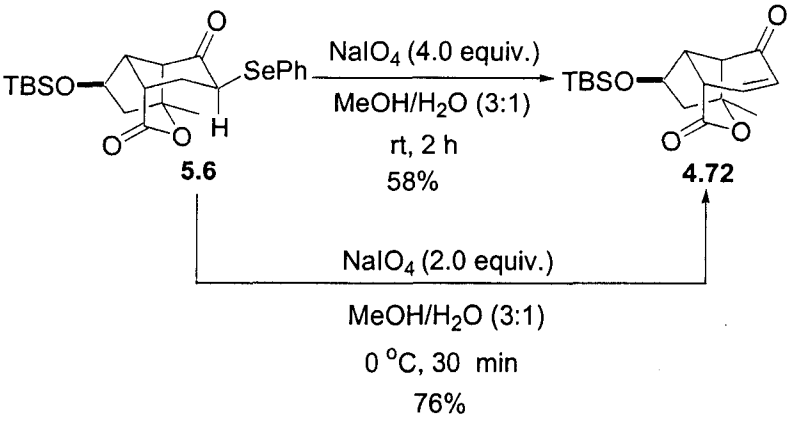
Scheme 5.13: *In-situ generation of I_2 and reaction with **4.72***



Thus, a new bottle of $NaIO_4$ was purchased* and the reactions were repeated. As expected, treatment of **5.6** with 4.0 equivalents of the oxidizing agent at room temperature for 2 hours provided **4.72** in 58% yield, without any trace of **5.4** (Scheme 5.14). When the reaction was conducted at 0 °C for 30 min, the yield of **4.72** remained essentially the same (80% vs 76%) as that previously described in Scheme 5.5. It was therefore evident that the new bottle of $NaIO_4$ was free of the contaminant (i.e NaI) present in the older bottle, which was responsible for the formation of **5.4**.

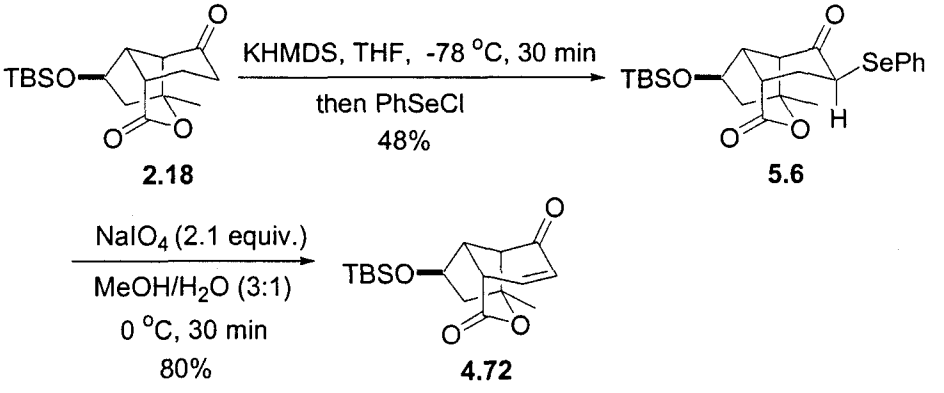
* Purchased from Sigma-Aldrich

Scheme 5.14: *Oxidation-syn elimination of* ***5.6*** *using a newly purchased bottle of* $NaIO_4$



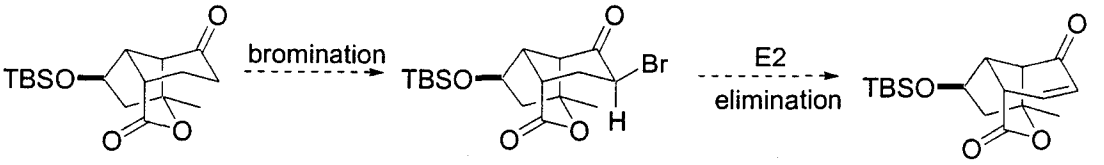
Prior to observing this peculiar oxy-iodination reaction, our goal was to improve the yield of enone **4.72**. Our efforts thus far, had only resulted in a maximum combined yield of 38% for the alkylation and oxidation-*syn*-elimination steps (Scheme 5.15).

Scheme 5.15: *Summary of the alkylation and oxidation steps for the synthesis of* ***4.72*** *from ketone* ***2.18***



We therefore continued our quest to find conditions that would provide **4.72** in an acceptable yield. As shown in Scheme 5.16, we next explored an E2 elimination reaction of bromide **5.15**.[6]

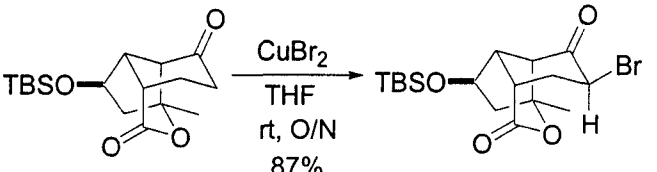
Scheme 5.16: *Proposed E2 elimination of* ***5.15*** *to prepare* ***4.72***



2.18 **5.15** **4.72**

The synthesis of **5.15,** was readily accomplished from ketone **2.18** in the presence of $CuBr_2$ in THF (Scheme 5.17).[7] The product was obtained in 87% yield.

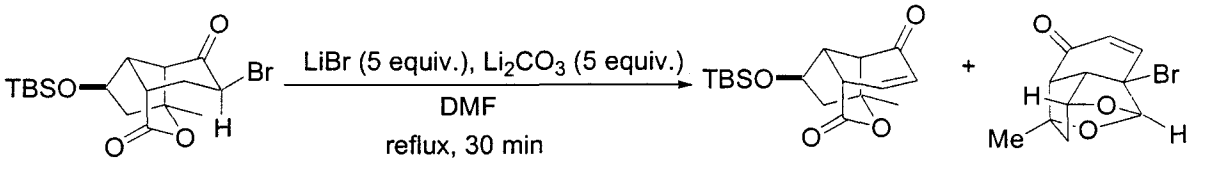
Scheme 5.17: *Synthesis of* ***5.15***



2.18 **5.15**

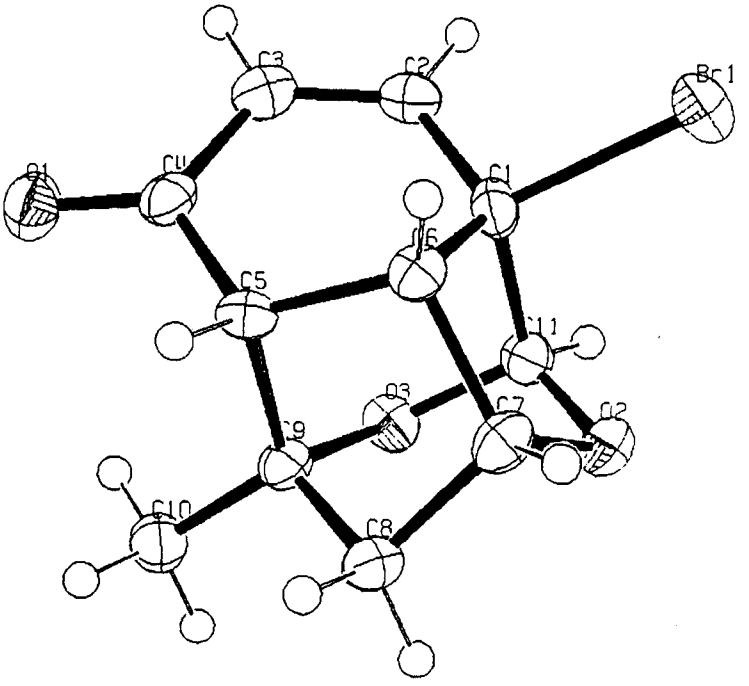
The following E2 elimination reaction was promoted by refluxing **5.15** in a mixture of LiBr and Li_2CO_3 in freshly distilled DMF for 30 minutes according to a literature procedure.[8] The desired product, enone **4.72**, was isolated in 39% yield. Unfortunately, an undesired side-product **5.16**, was also obtained in 43% yield. The structure of this molecule was identified by 1D and 2D-NMR and confirmed by X-ray crystallography (crystal formed by slow evaporation in CH_2Cl_2/hexanes) as shown in Figure 5.1.

Scheme 5.18: *E2 elimination of* ***5.15*** *conducted in DMF in the presence of* Li_2CO_3*/ LiBr*



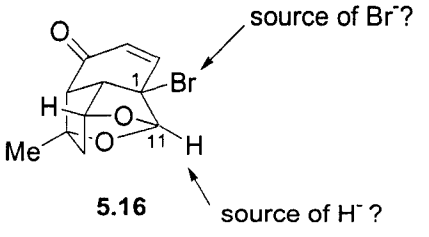
5.15 **4.72** 39% **5.16** 43%

Figure 5.1: *X-ray crystal structure of* ***5.16***



Closer examination of this undesired acetal **5.16**, revealed a hydrogen atom at C11 and bromine atom at C1. (Figure 5.2). We contemplated whether the reagents and solvent were contributing to the synthesis of **5.16**. In particular, it was possible that the excess amount of LiBr (5 equivalents) used in the reaction was providing the source of bromine at C1.

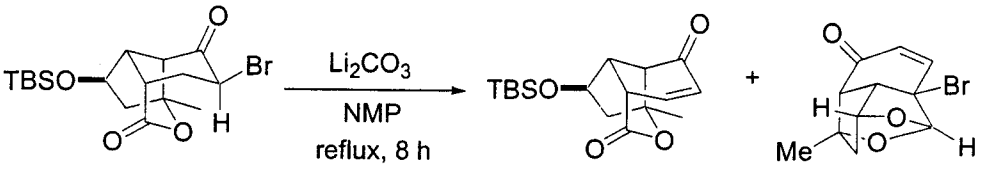
Figure 5.2: *Closer inspection of* ***5.16***



Thus, the E2 elimination reaction was repeated using only Li_2CO_3 and NMP as a solvent. Although the yield of **4.72** improved greatly (63%) in these reaction conditions, **5.16**

was still present. This suggested that the atoms at C1 and C11 were derived from the starting material **5.15**.

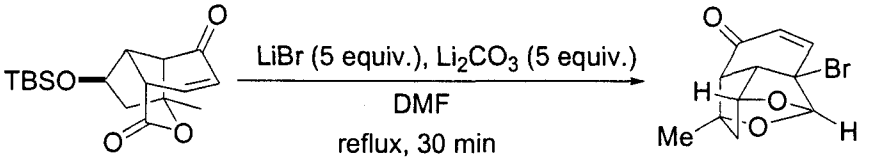
Scheme 5.19: *E2 elimination of* ***5.15*** *conducted in NMP in the presence of* Li_2CO_3



5.15 → **4.72** (63%) + **5.16** (22%)

In a subsequent experiment, a mixture of **4.72**, LiBr and Li_2CO_3 were refluxed in freshly distilled DMF for 30 minutes as illustrated in Scheme 5.20. Compound **5.16** was obtained in 28% yield.

Scheme 5.20: *Formation of* ***5.16*** *in the presence of* Li_2CO_3*/ LiBr*

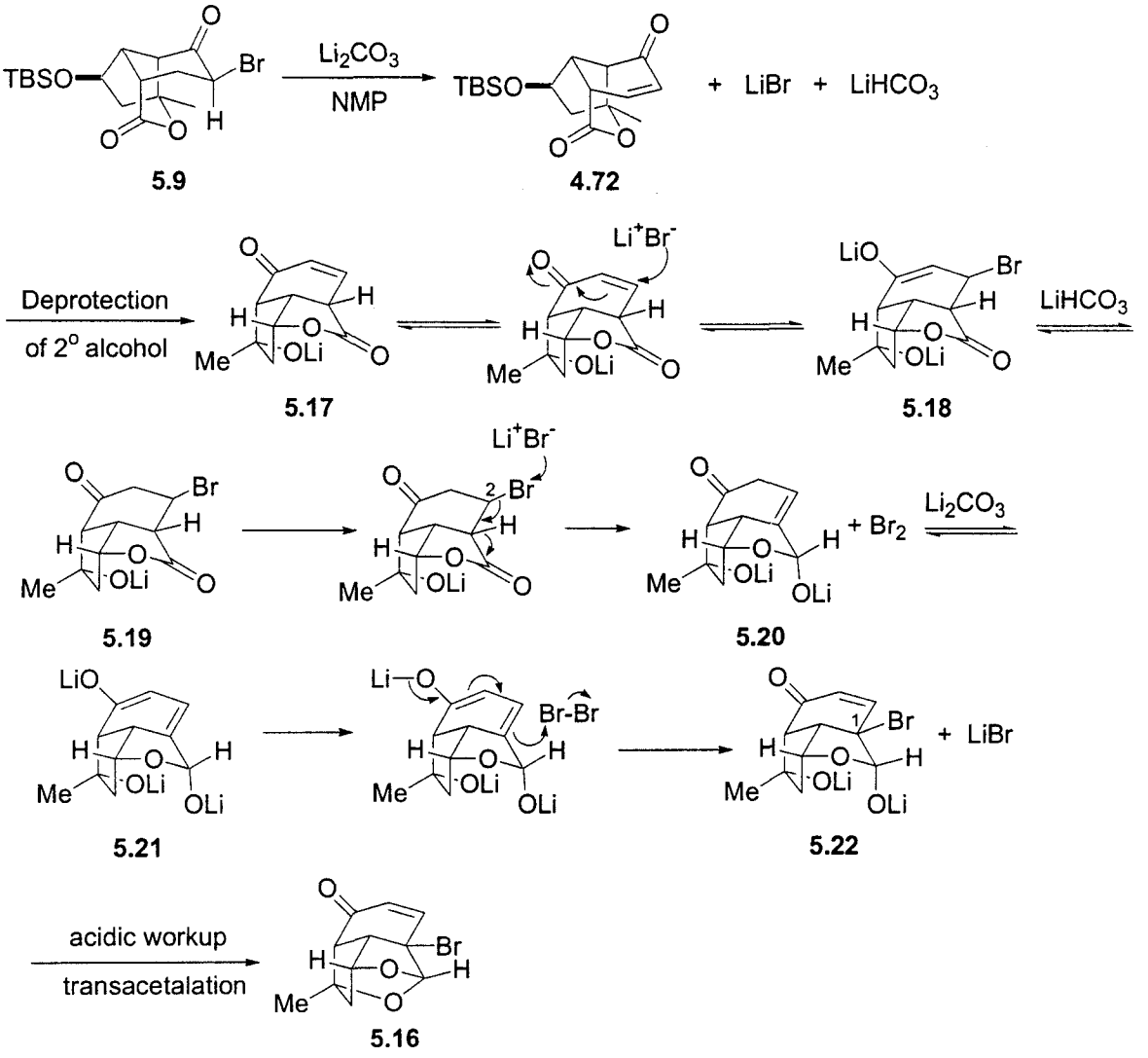


4.72 — 28% — **5.16**

Based on the result in Scheme 5.20, it is likely that the LiBr which was being produced *in-situ* from the E2 elimination reaction of **5.15** in the presence of Li_2CO_3 (Scheme 5.19), was further reacting with enone **4.72** to generate the undesired product **5.16**. A mechanism was proposed for the synthesis of **5.16** and is illustrated in Scheme 5.21. Following the elimination of the bromine atom to form **4.72**, the secondary TBS alcohol may be deprotected to form **5.17**.[9] A 1,4-addition of a bromide ion onto the enone could then take place to provide **5.18** which is in equilibrium with **5.19**. In the presence of an additional

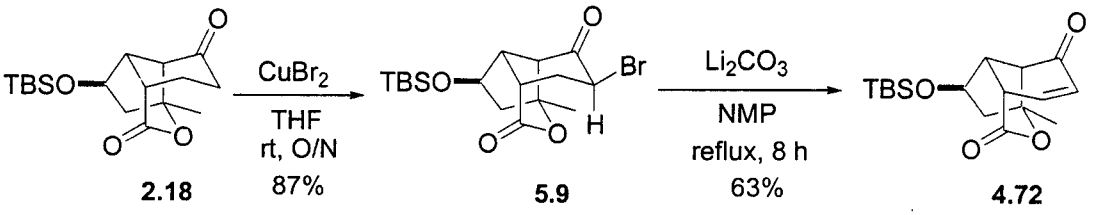
equivalent of LiBr, a *syn* elimination of the bromine at C2 may occur along with a 1,2-hydride shift which reduces the lactone to the lactol to form **5.20**. Compound **5.21** could then react with the bromine formed *in-situ* to establish the carbon-bromide bond at C1. Upon workup under acidic conditions, a transacetalation reaction would generate the acetal of **5.16**.

Scheme 5.21: *Proposed mechanism for the synthesis of* ***5.16***



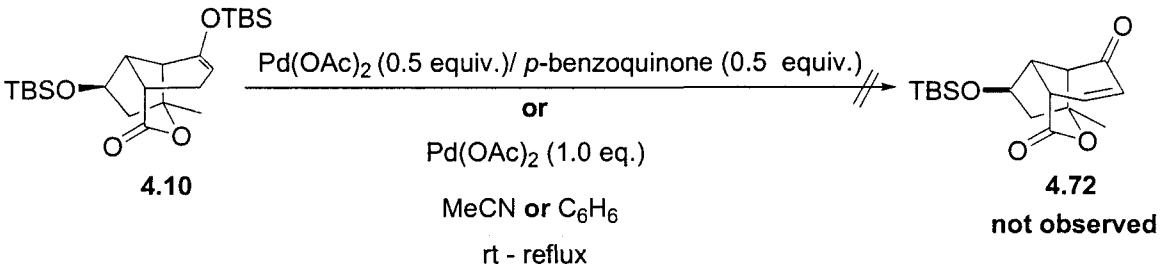
In summary, even though the yield of the E2 elimination reaction of **5.9** had been improved to 63%, the overall yield for the synthesis of enone **4.72** from ketone **2.18** was only 55% as illustrated in Scheme 5.22.

Scheme 5.22: *Summary of the E2 elimination strategy to generate **4.72***



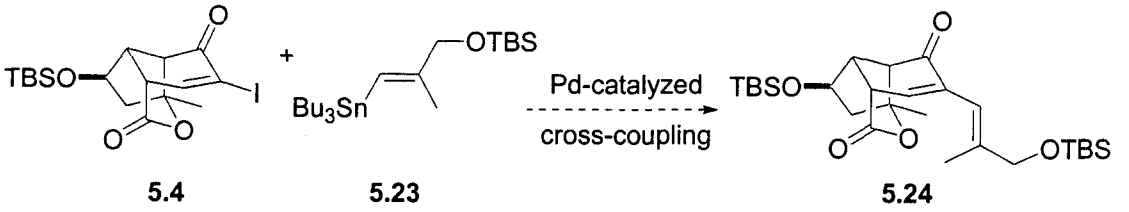
We therefore investigated one final strategy to generate enone **4.72** which was the Saegusa oxidation reaction using TBS enol ether **4.10** (cheme 5.23). Unfortunately, in the presence of a stoichiometric amount of $Pd(OAc)_2$ or 0.5 equivalents of $Pd(OAc)_2$ and *p*-benzoquinone in MeCN or C_6H_6 at room temperature, no reaction was observed and enol ether **4.10** as recovered. When the mixture was heated to the refluxing temperature, the enol ether hydrolyzed to ketone **2.18**.

Scheme 5.23: *Attempts at the Saegusa oxidation to form **4.72***



A decision was therefore made to continue with the synthesis and begin the preparation of vinyl iodide **5.4** and vinyl stannane **5.23** so that diene **5.24** could be generated via a Stille-cross coupling reaction (Scheme 5.24).

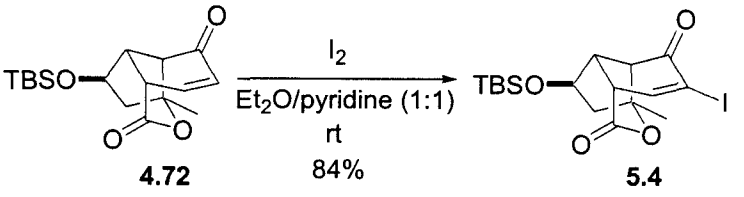
Scheme 5.24: *Proposed Stille-cross coupling reaction between vinyl iodide* ***5.4*** *and vinyl stannane* ***5.23***



5.4 **5.23** **5.24**

We were very pleased to observe that vinyl iodide **5.4** could be obtained in 84% yield by treating **4.72** with I_2 in a 1:1 solution of Et_2O/pyridine at room temperature (Scheme 5.25).

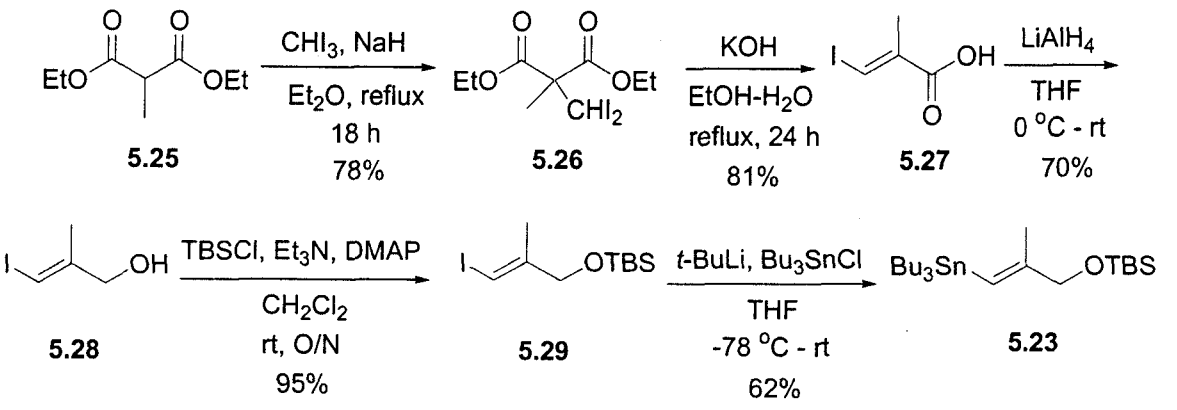
Scheme 5.25: *Synthesis of iodo-enone* ***5.4***



4.72 **5.4**

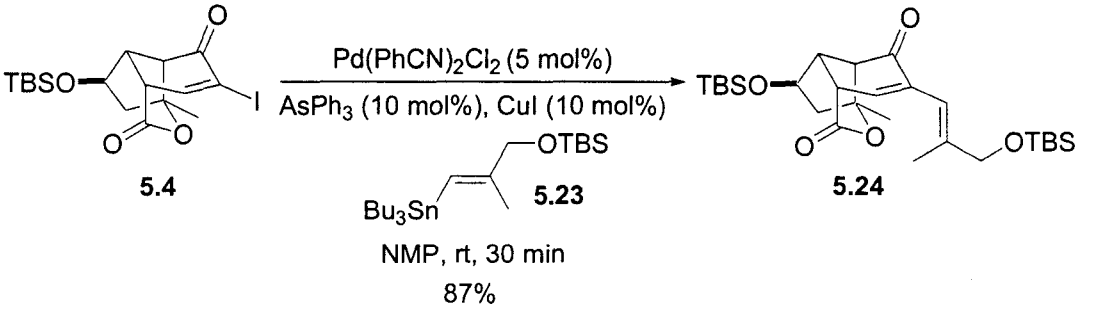
The vinyl stannane coupling partner **5.23** was prepared as described in Scheme 5.26.[10] Diethyl methylmalonate (**5.25**) was treated with di-iodocarbene in refluxing Et_2O to provide diethyl di-iodomethylmethylmalonate (**5.26**) in 78% yield. Conversion of **5.26** to *(E)*-3-iodo-2-methyl-2-propenoic acid (**5.27**) was accomplished in the presence of KOH in a solution of EtOH-water in 81% yield. Reduction of the acid with LAH provided allylic alcohol **5.28** which was protected with TBSCl under standard conditions to provide **5.29**. Finally, vinyl iodide **5.29** was treated with *t*-BuLi at – 78 °C and the resulting vinyl lithium species was trapped with Bu_3SnCl to provide **5.23** in 62% yield.[11]

Scheme 5.26: *Synthesis of vinyl stannane* ***5.23***



The Stille cross-coupling reaction which followed between vinyl stannane **5.23** and vinyl iodide **5.4** in the presence of 5 mol% *bis*(benzonitrile)palladium(II) chloride, 10 mol% copper iodide and 10 mol% triphenylarsine in NMP at room temperature, furnished the desired product **5.24** in 87% yield (Scheme 5.27).

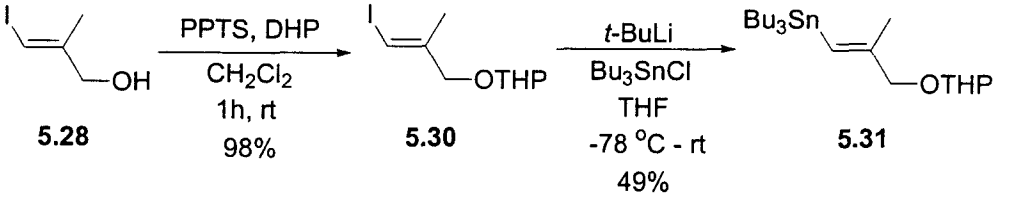
Scheme 5.27: *Synthesis of* ***5.24*** *via a Stille cross-coupling reaction*



We were delighted that the conditions for the Stille cross-coupling reaction were realized in such a timely manner. However, we were concerned by the fact that the primary and secondary alcohol in **5.24** contained the same TBS protecting group. Although there are conditions to selectively remove the TBS group on the primary alcohol, we wanted to eliminate as many future challenges as possible.[12]

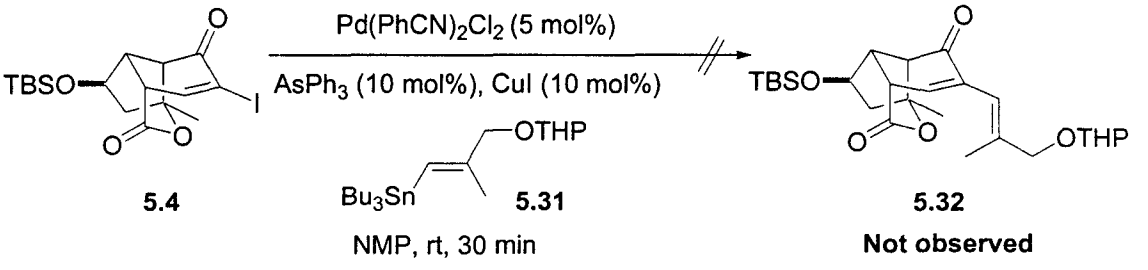
Therefore, the vinyl stannane coupling partner was modified to contain a THP protecting group as shown in Scheme 5.28.

Scheme 5.28: *Synthesis of vinyl stannane* ***5.31***



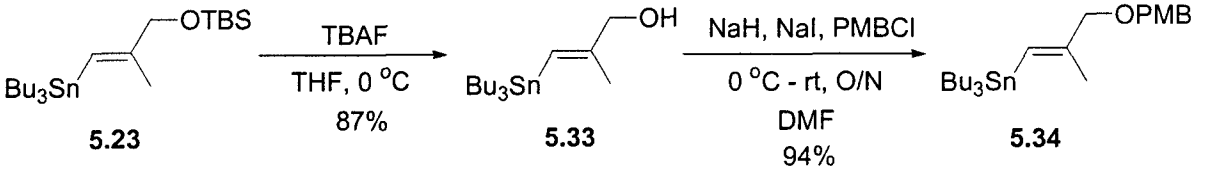
The Stille reaction was repeated using vinyl stannane **5.31** and vinyl iodide **5.4** (Scheme 5.29). Unfortunately, this reaction generated many unidentified products, none of which appeared to be the desired coupled compound.

Scheme 5.29: *Attempted Stille reaction between vinyl iodide* ***5.4*** *and vinyl stannane* ***5.31***



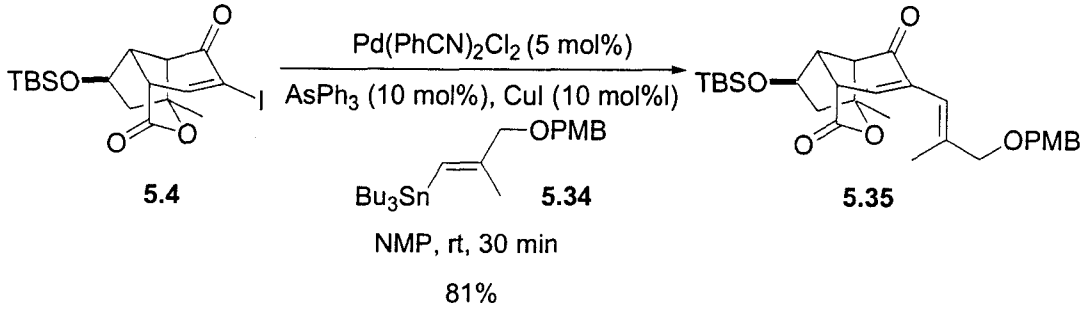
A third protecting group, PMB (*p*-methoxybenzyl), was therefore chosen for the primary alcohol of the vinyl stannane and was installed on allylic alcohol **5.33** in 94% yield according to Scheme 5.30.[13]

Scheme 5.30: *Synthesis of vinyl stannane* ***5.34***



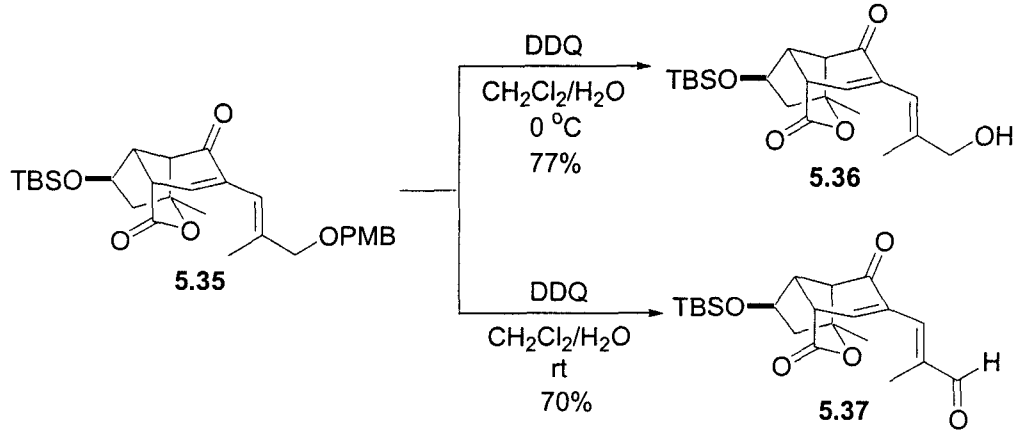
The Stille cross-coupling reaction was then performed between vinyl iodide **5.4** and the newly formed vinyl stannane **5.34**. The reaction proceeded smoothly to provide **5.35** in 81% yield as shown in Scheme 5.31.

Scheme 5.31: *Synthesis of* ***5.35*** *via a Stille cross-coupling reaction*



The primary alcohol of **5.35** was subsequently revealed using DDQ at 0 °C in a biphasic mixture of CH_2Cl_2/H_2O (Scheme 5.32).[14] If the reaction was conducted at room temperature rather than 0 °C, allylic aldehyde **5.37** was obtained instead.

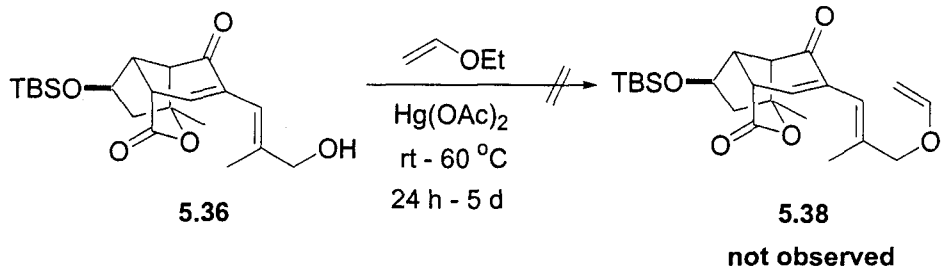
Scheme 5.32: *Deprotection of the primary alcohol in* ***5.35*** *using DDQ*



With **5.36** in-hand, the synthesis of the Claisen rearrangement precursor, allyl vinyl ether **5.38** was next attempted (Scheme 5.33). This proved to be more challenging than expected. The desired product **5.38** was never observed in the presence of ethyl vinyl ether

and $Hg(OAc)_2$.[15] At lower temperatures (room temperature to 40 °C) starting material **5.36** was recovered and at higher temperatures degradation products were observed.

Scheme 5.33: *Attempted synthesis of* ***5.36***

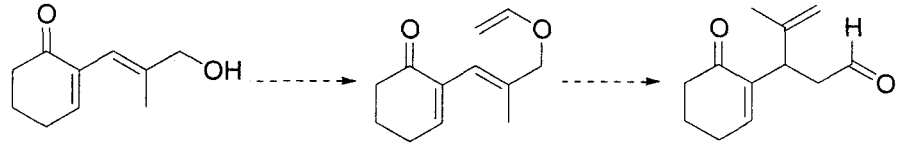


5.36 **5.38**

not observed

Since allylic alcohol **5.36** was quite precious, a model substrate **5.39** (Scheme 5.34) was used to investigate other methods to prepare the allyl vinyl ether compound **5.38** and explore conditions for the subsequent Claisen rearrangement. This model compound was designed to contain an α,β-unsaturated ketone (like **5.36**) in order to understand how it influenced the synthesis of the Claisen precursor as well as the rearrangement. These studies were conducted with the assistance of Lise-Anne Prescott who was an undergraduate student completing her 4th year honors project.[16]

Scheme 5.34: *Model substrate used to investigate the Claisen rearrangement*

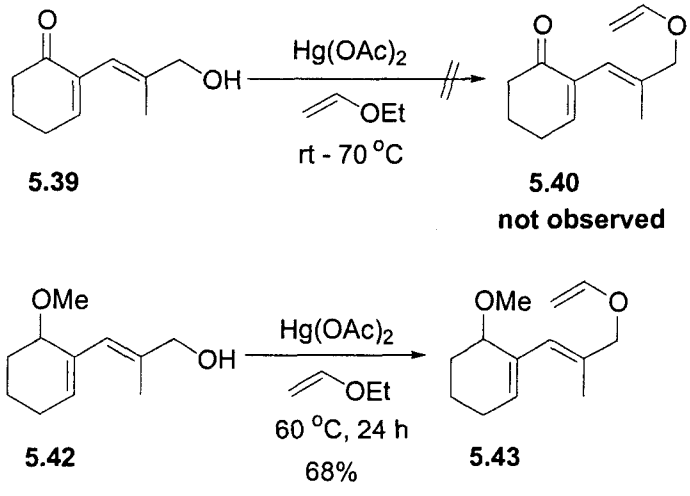


5.39 **5.40** **5.41**

Interestingly, the synthesis of the Claisen precursor **5.40** could not be achieved from allylic alcohol **5.39** (Scheme 5.35) using the same conditions described in Scheme 5.33 for the attempted synthesis of allyl vinyl ether **5.38**. However, once the ketone in **5.39** was

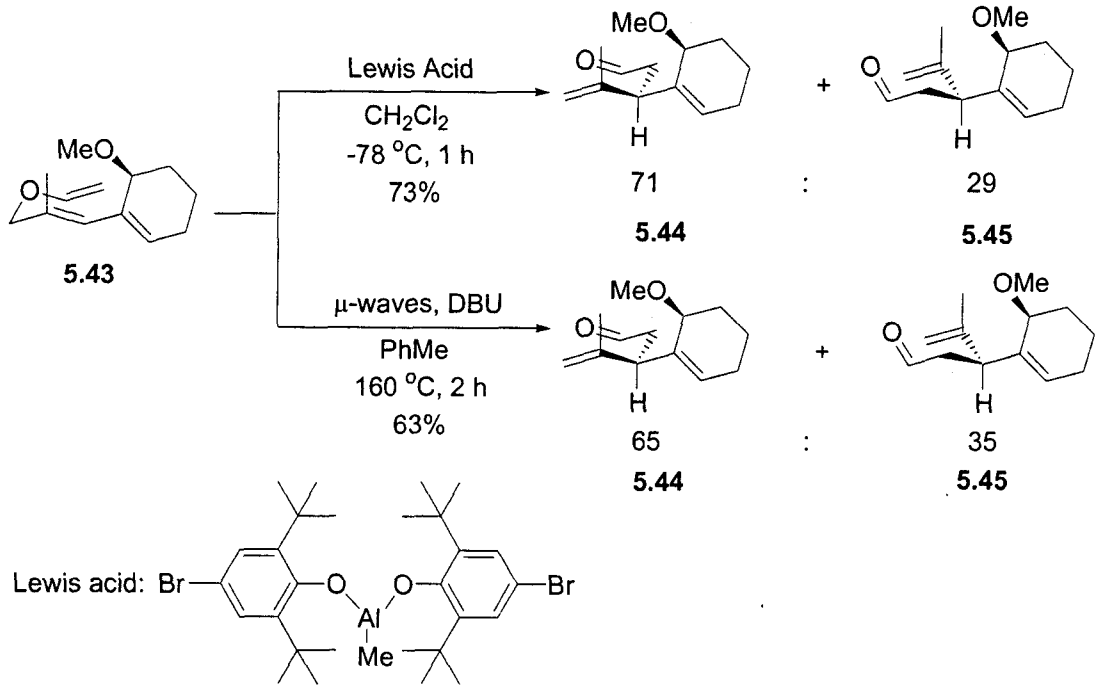
reduced (and the alcohol protected, i.e **5.42**), the Claisen precursor **5.43** was readily prepared in the presence of $Hg(OAc)_2$ and freshly distilled ethyl vinyl ether. It is therefore possible that the electron-withdrawing nature of the ketone in **5.36** and **5.39** decreased the reactivity of the allylic alcohols and thus prevented the formation of the desired products.

Scheme 5.35: *Synthesis of the Claisen rearrangement precursor using the model substrate*



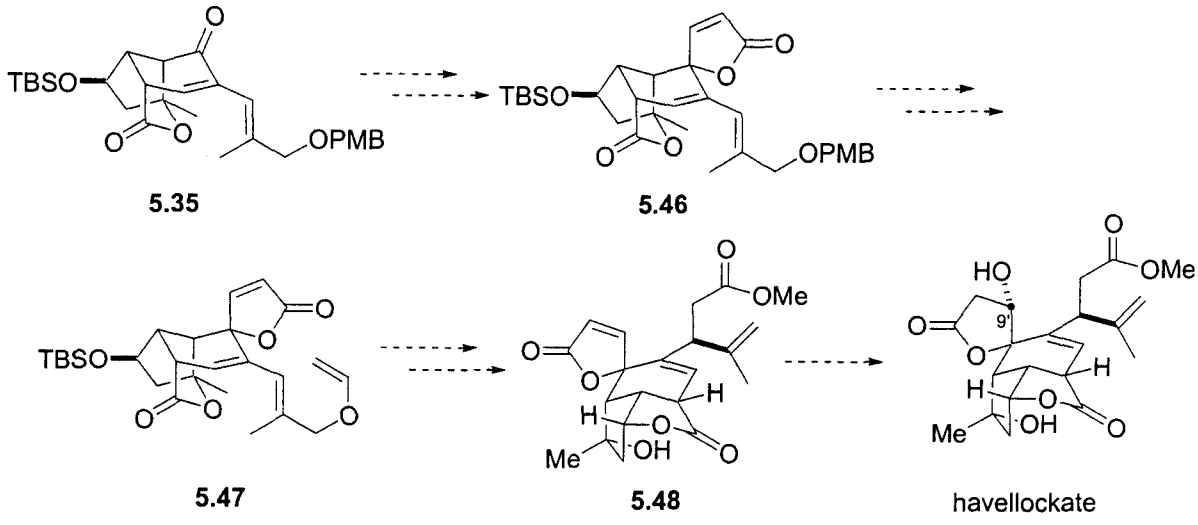
Various conditions were then explored to promote the Claisen rearrangement of allyl vinyl ether **5.43** (Scheme 5.36). We were very pleased to observe that both microwaves (160 °C, toluene, DBU) and a Lewis acid[17] were capable of effecting the desired transformation. For both of the reactions, the product was obtained as a mixture of diastereomers (**5.44** and **5.45**) with a good yield.

Scheme 5.36: *Claisen rearrangement of* ***5.43***



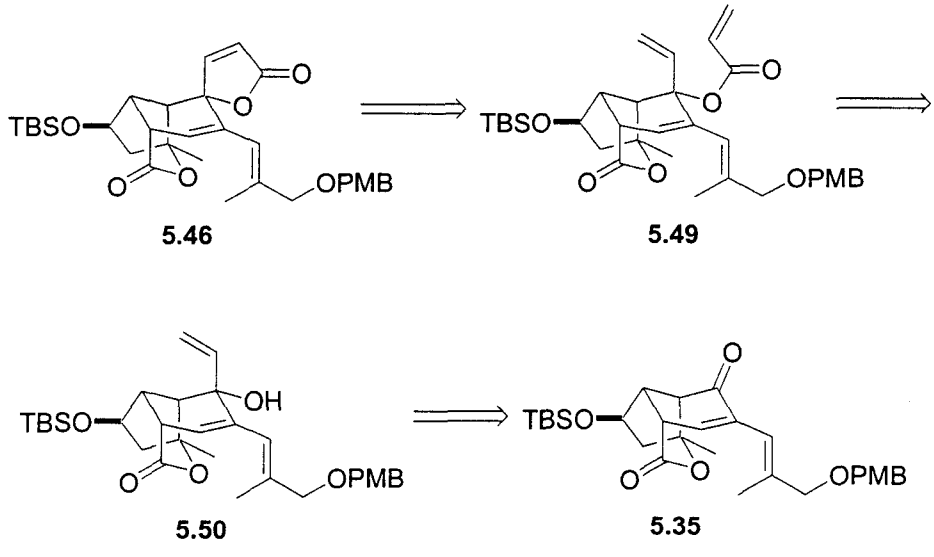
The results from the model studies suggested that the difficulties associated with the synthesis of the allyl vinyl ether substrate **5.38** (Scheme 5.33) may be remedied by reducing the ketone to an alcohol. However, since this ketone was the handle for installing the spiro-lactone in havellockate, it was logical to construct this portion of the natural product and then commence with the Claisen rearrangement as illustrated in Scheme 5.37. Furthermore it was decided that the secondary alcohol at C9′ of the lactone would be best installed at the end of the synthesis due to its tendency to eliminate under basic and acidic conditions as discussed in Chapter 2. Our initial focus was therefore the preparation of **5.46** from **5.35**.

Scheme 5.37: *Proposed installation of the spiro-lactone prior to the Claisen rearrangement*



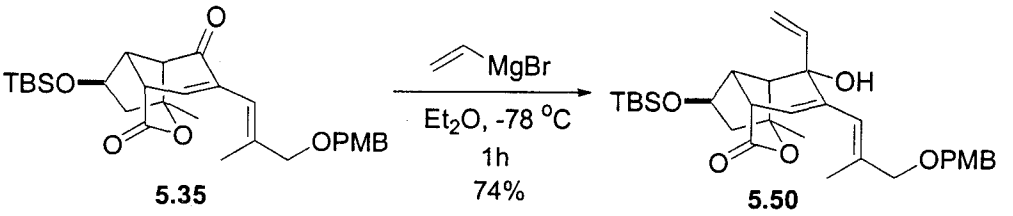
As shown in Scheme 5.38, we proposed that **5.46** could arise from a ring closing metathesis reaction[18] (RCM) of **5.49**. Compound **5.49** could be formed via an acylation of **5.50**, which in-turn is the alkylated product of **5.35**.

Scheme 5.38: *Retrosynthetic analysis of* ***5.46***



The synthesis of the spiro-lactone thus began with the alkylation of ketone **5.35** with vinyl magnesium bromide in Et_2O at -78 °C. The product **5.50** was obtained in 74% yield.

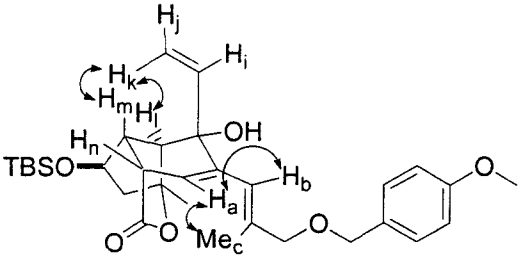
Scheme 5.39: *Alkylation of* ***5.35*** *with vinyl magnesium bromide*



5.35 **5.50**

The stereochemistry of the alkylated product **5.50** was determined by 2D-NMR analysis. Strong nOe signals between H_k and H_l and H_m (Figure 5.3) confirmed that the alkylation occurred on the *re* face to provide **5.50** as shown. A detailed analysis of the 2D-NMR data is found in Chapter 7.

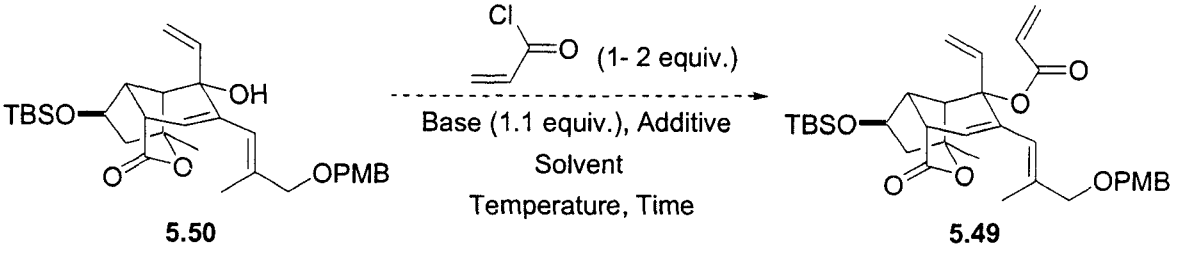
Figure 5.3*: NOESY correlations of compound* ***5.50***



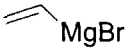
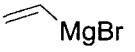
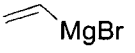
We next proceeded with the acylation of the tertiary alcohol of **5.50** using acroloyl chloride to form the RCM precursor **5.49**. Unfortunately, this transformation was very difficult to achieve. As illustrated in Table 5.1, entries 1-10, **5.50** was treated with 1.1 equivalents of a strong base (i.e KH, NaH, LDA, vinylmagnesium bromide, *n*-BuLi) in either THF, DME or Et_2O at the noted temperature, prior to the addition of 1-2 equivalents of freshly distilled acryloyl chloride. HMPA was also added as shown in entries 3 and 6 to form a more reactive alkoxide by dissociating the potassium or lithium cations. All of these conditions however, resulted in the recovery (entries 1-5, 8 and 10) or the decomposition of the starting material **5.50** (entries 6, 7 and 9). The acylation reaction was also unsuccessful in

the presence of a catalytic amount of DMAP, acryloyl chloride and either Et_3N, or iPr_2NEt at room temperature (entries 11-12).

Table 5.1: *Acylation attempts of* ***5.50*** *with acroloyl chloride*

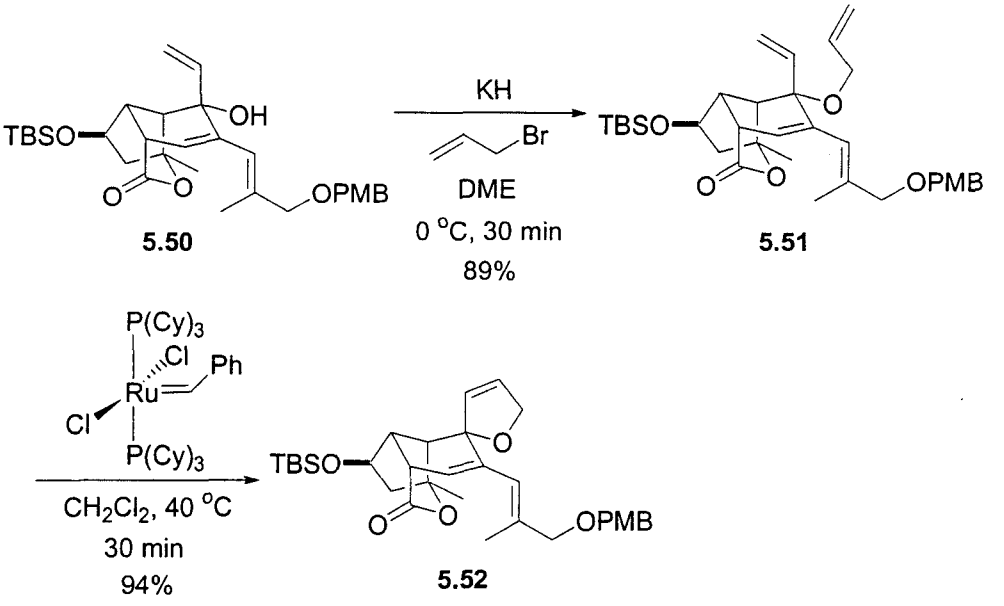


5.50 **5.49**

Entry	Base	Additive	Solvent	Temp (°C)	Time (h)	Result
1	KH	-	THF	0 to rt	14	SM
2	KH	-	DME	0 to rt	14	SM
3	KH	HMPA (20 equiv.)	THF	0 to rt	14	SM
4	NaH	-	THF	0 to rt	14	SM
5	LDA	-	THF	-78	2	SM
6	LDA	HMPA (20 equiv.)	THF	-78 to -20	5	Decomp
7	*n*-BuLi	-	Et_2O	-78 to -20	0.5	Decomp.
8		-	Et_2O	-78	5	SM
9		-	Et_2O	-78 to rt	0.5	Decomp.
10		-	THF	-78	5	SM
11	Et_3N	DMAP (5 mol%)	CH_2Cl_2	0 to rt	24	SM
12	iPr_2NEt	DMAP (5 mol%)	CH_2Cl_2	0 to rt	24	SM

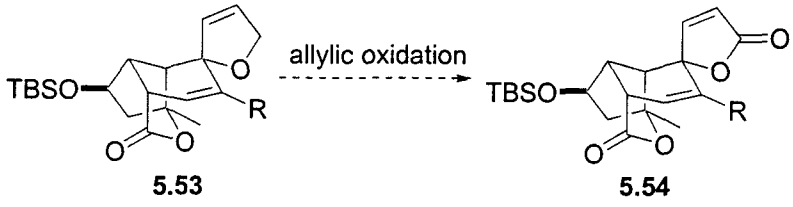
Since the tertiary alcohol of **5.50** could not be acylated with acryloyl chloride, more reactive electrophiles were examined. Fortunately, compound **5.50** could be allylated in 89% yield in the presence of KH, allyl bromide and DME as illustrated in Scheme 5.40. Following the synthesis of **5.51**, the ring closing metathesis reaction was examined. The desired transformation was realized in 94% yield in the presence of Grubbs' 1st generation catalyst[19] (10 mol%), in a 0.1 M solution of CH_2Cl_2 at 40 °C for 30 min (Scheme 5.40).

Scheme 5.40: *Allylation of* ***5.50*** *and subsequent RCM reaction*



Even though compound **5.52** did not contain the spirocycle that we had originally intended to construct (i.e. **5.46** Scheme 5.38), we were hopeful that an allylic oxidation reaction executed at a later stage of the synthesis would be able to install the carbonyl moiety and form the desired α,β-unsaturated lactone **5.54** illustrated in Scheme 5.41.

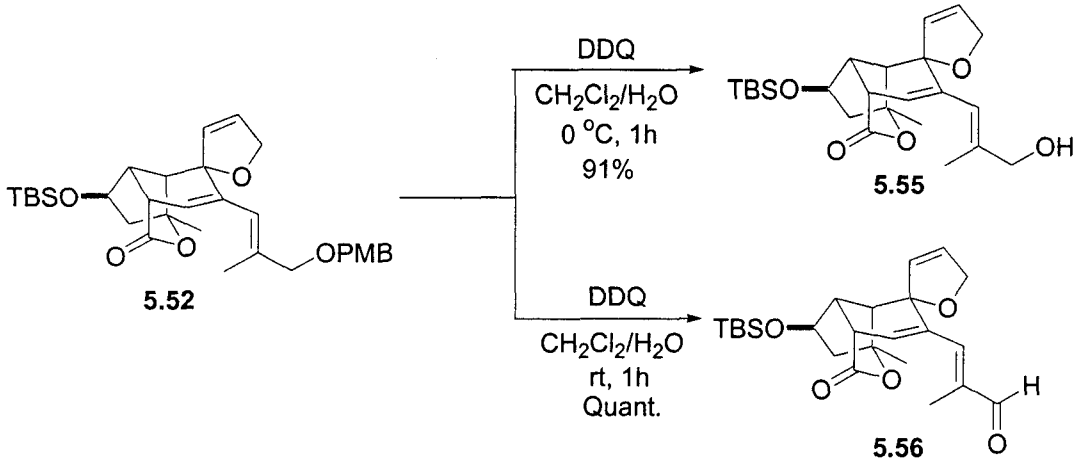
Scheme 5.41: *Proposed allylic oxidation to form the α,β-unsaturated ketone*



5.53 **5.54**

With the core of the spirocycle complete, we continued to work on the side-chain with the eventual goal of performing a Claisen-rearrangement. As illustrated in Scheme 5.42, treatment of **5.52** with DDQ in a biphasic mixture of CH_2Cl_2/H_2O at 0 °C provided allylic alcohol **5.55.** By permitting the reaction to warm to room temperature, the deprotected alcohol was oxidized to aldehyde **5.56** in quantitative yield.

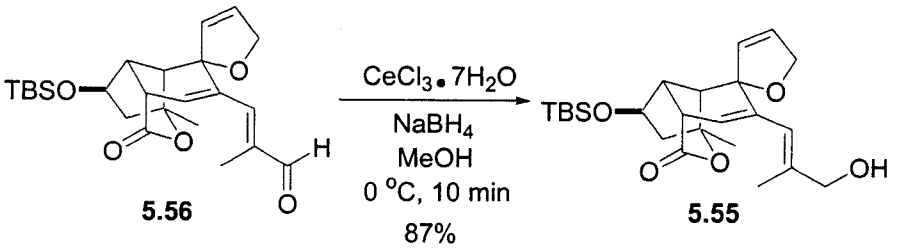
Scheme 5.42: *Deprotection of **5.52** in the presence of DDQ*



5.52 **5.55** **5.56**

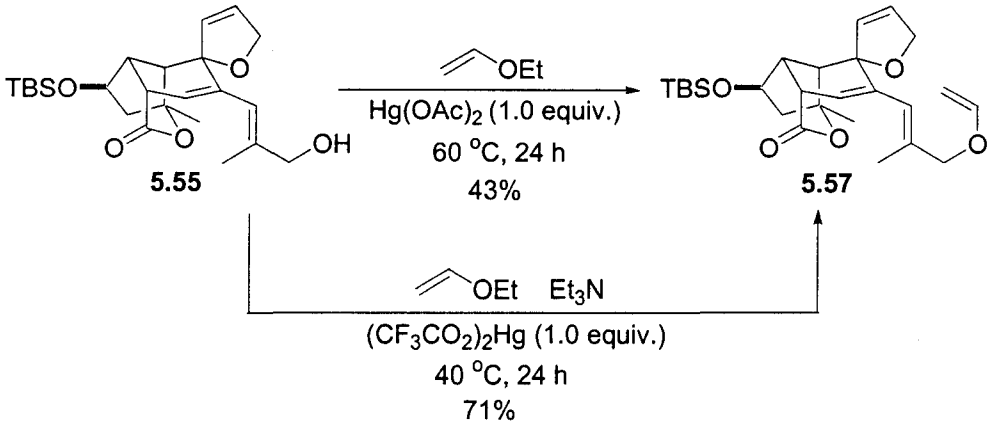
The over-oxidized product **5.56** was salvaged by performing a 1,2-reduction of the aldehyde using sodium borohydride in combination with cerium chloride (Luche reduction).[20] Alcohol **5.55** was obtained in 87% yield (Scheme 5.43).

Scheme 5.43: *Luche reduction of* ***5.56***



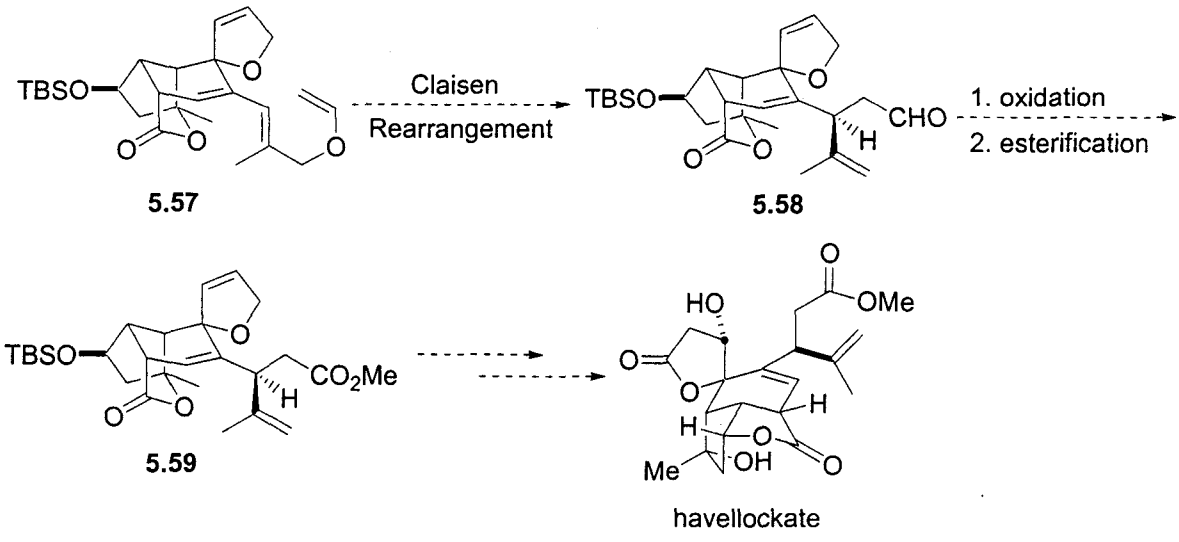
The synthesis of allyl vinyl ether **5.57** from allylic alcohol **5.55** was next explored as illustrated in Scheme 5.44. It was determined that this Claisen precursor could be prepared in 43% yield in the presence of $Hg(OAc)_2$ (1.0 equiv.) and ethyl vinyl ether at 60 °C for 24 h. The yield of **5.57** was further improved to 71% by treating **5.55** with mercury trifluoroacetate (1.0 equiv.), Et_3N and ethyl vinyl ether at 40 °C for 24 h.[21]

Scheme 5.44: *Synthesis of allyl vinyl ether* ***5.57*** *from allylic alcohol* ***5.55***



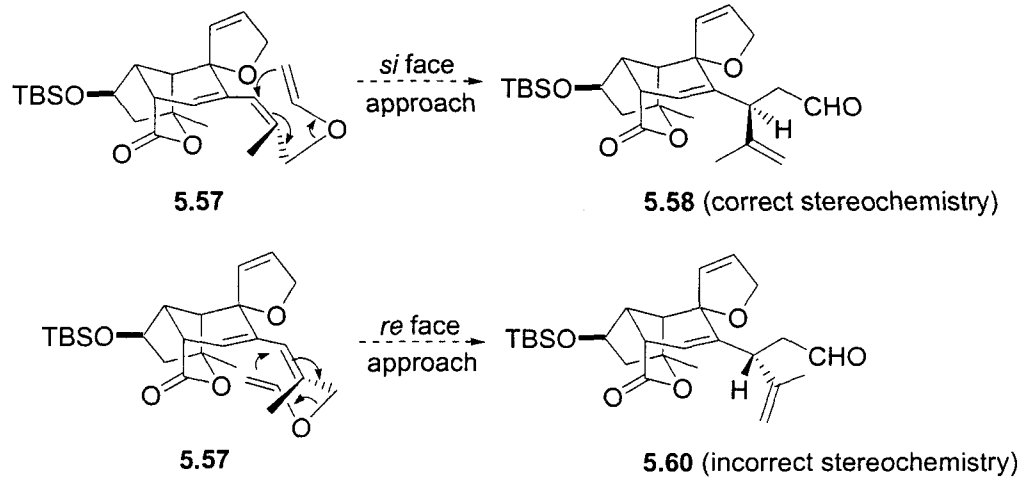
We were finally at the position in the synthesis where the conditions for the Claisen rearrangement could be determined. This reaction would generate a side-chain which bared the required isopropenyl group as well as an aldehyde moiety that could be easily transformed into the methyl ester found in the natural product as illustrated in Scheme 5.45.

Scheme 5.45: *Proposed synthetic route to* ***5.59***



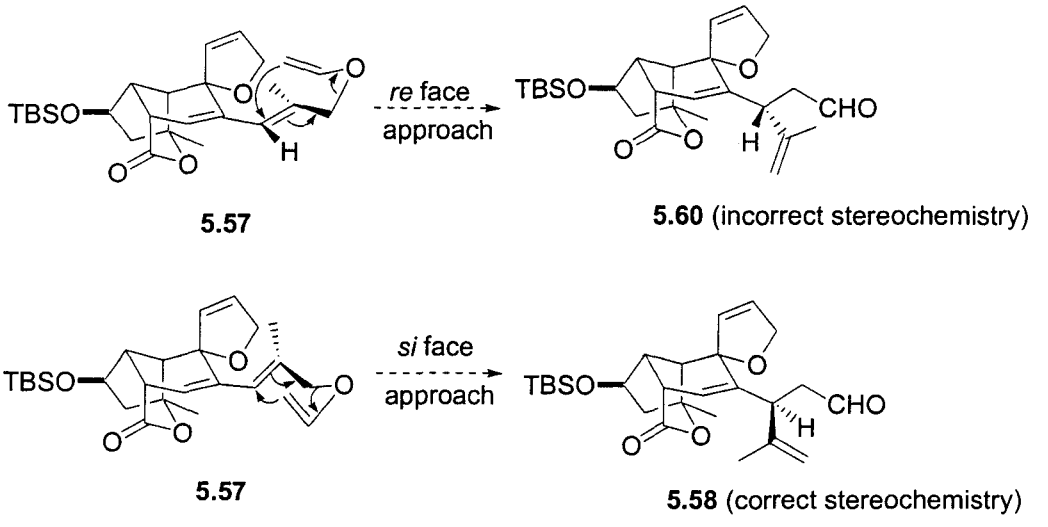
We recognized however, that it would be difficult to predict any facial selectivity in this rearrangement. For example, if the reaction occurred via a chair-like transition state, involving the s-*cis*, conjugated configuration of diene **5.57**, then either a *si* or *re* facial approach of the terminal alkene seemed possible, which would result in a mixture of diastereomers (Scheme 5.46).

Scheme 5.46: *Si and re facial approach of the alkene with the s-cis, conjugated configuration of the diene*



Alternatively, the s-*trans,* conjugated configuration of the diene could also experience a *re* and *si* facial approach of the terminal alkene. Only the *si* facial approach of the olefin in this case would lead to the correct stereochemistry at the chiral center (Scheme 5.47).

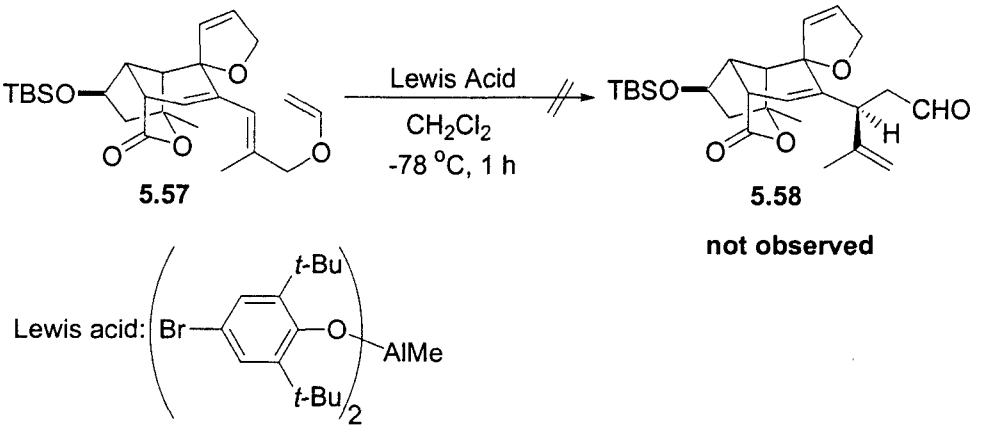
Scheme 5.47: *Re and si facial approach of the terminal alkene with the s-trans, conjugated configuration of the diene*



In addition, both facial approaches (i.e. *re* and *si*) of the olefin seemed likely in the case where the diene of **5.57** was de-conjugated (i.e the two π-bonds of the olefins were orthogonal to each other) at the transition state.

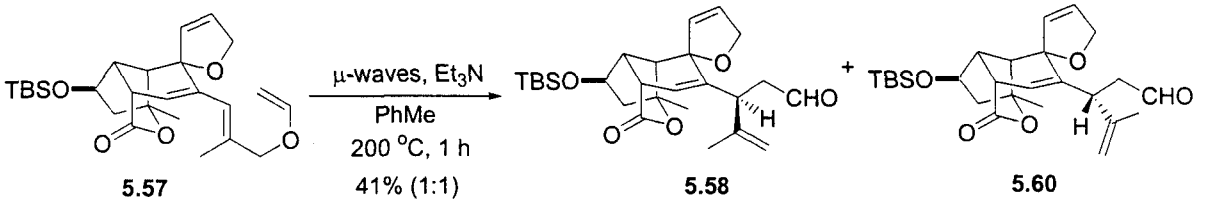
The highly anticipated Claisen rearrangement of allyl vinyl ether **5.57** was attempted in the presence of the Lewis acid, methylaluminium *bis*(4-bromo-2,6-di-*tert*-butylphenoxide)[18] (Scheme 5.48). Much to our disappointment however, only starting material **5.57** was recovered.

Scheme 5.48: *Attempted Claisen rearrangement of* ***5.57*** *in the presence of a Lewis acid*



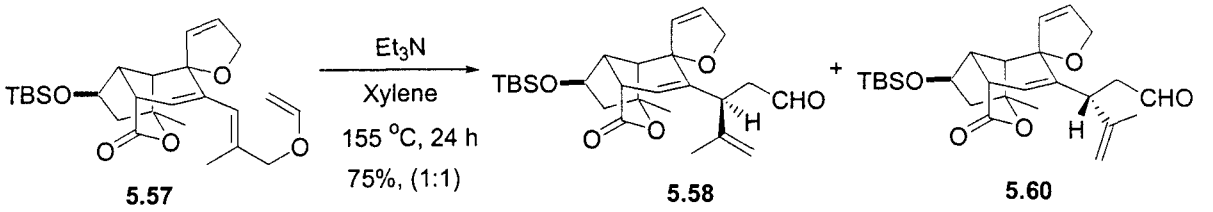
A microwave-assisted Claisen rearrangement of **5.57** was subsequently explored as illustrated in Scheme 5.49. We were delighted to observe that the rearrangement had occurred at 200 °C. The crude ^{1}H NMR confirmed the presence of a 1:1 mixture of diastereomers (**5.58** and **5.60**) as we had expected.

Scheme 5.49: *Microwave assisted Claisen rearrangement of* ***5.57***



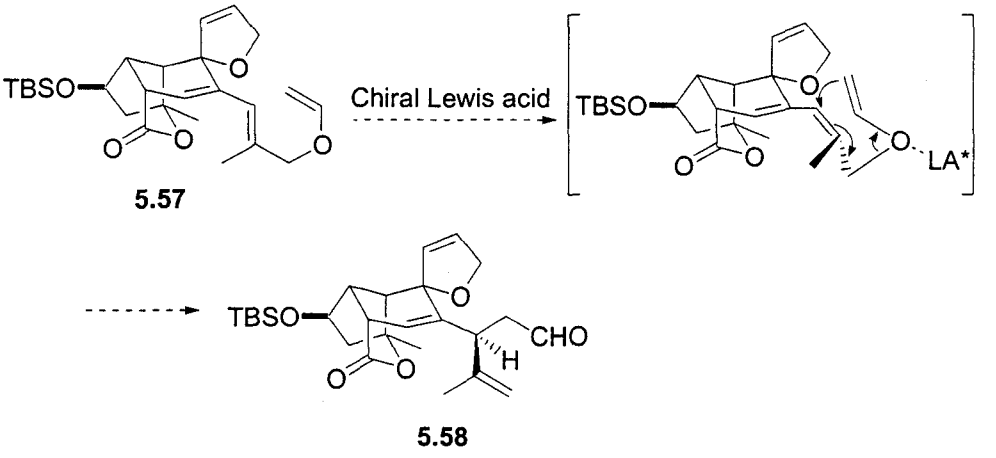
The yield of the rearrangement reaction was further improved to 75% under thermal conditions (155 °C, 24 h) as depicted in Scheme 5.50. Once again, a 1:1 mixture of diastereomers were obtained.

Scheme 5.50: *Thermal-induced Claisen rearrangement of* ***5.57***



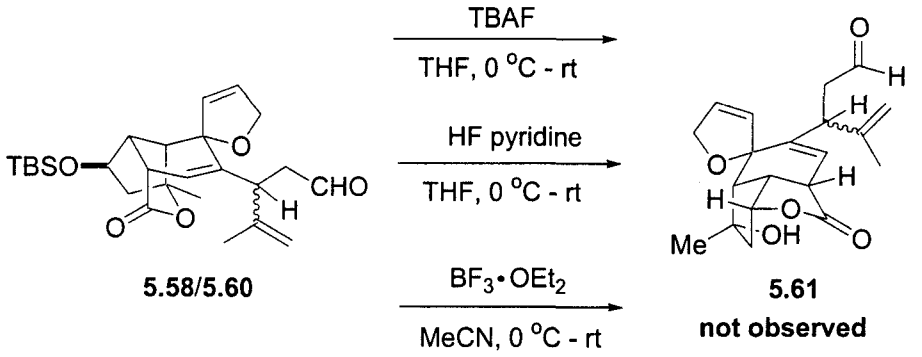
Despite this mixture, the Claisen rearrangement was proven to be an effective strategy for constructing the side-chain. Most importantly, this synthetic approach had allowed for the endocyclic double bond within the six-membered ring to be installed. It would be wise in the future to use a chiral Lewis acid[22] to help control the facial selectivity of the rearrangement so that **5.58** could be formed as the major product (Scheme 5.51).

Scheme 5.51: *Use of a chiral Lewis acid to control the facial selectivity of the Claisen rearrangement*



With the small amount of remaining material (i.e **5.58** and **5.60**), three conditions were examined for the deprotection of the secondary alcohol. As shown in Scheme 5.52 this deprotection was not accomplished under the conditions presented. In all cases, the starting material completely decomposed.

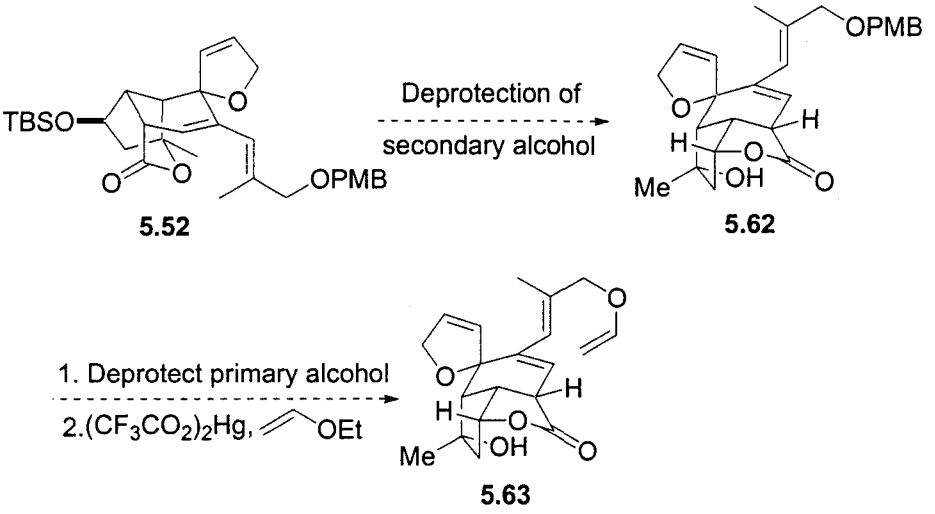
Scheme 5.52: *Attempted deprotection of the Claisen product*



5.58/5.60 **5.61 not observed**

The rather unfortunate finale to this thesis may be averted in the future if **5.52** shown in Scheme 5.53 were deprotected prior to the formation of the Claisen precursor **5.63**.

Scheme 5.53: *Attempted deprotection of the Claisen product*



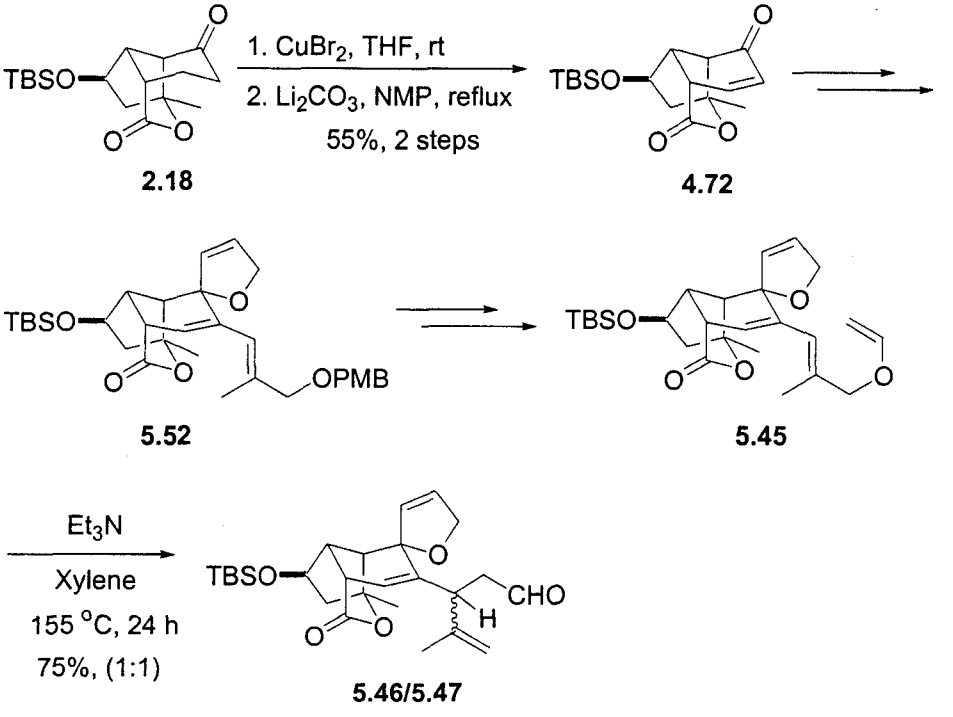
5.52 **5.62** **5.63**

Conclusions:

In the beginning of this chapter we explored a variety of methods to install the endocyclic double bond within the six-membered ring. The optimum approach, an E2 elimination of a bromine atom provided the product in 55% yield (Scheme 5.54). During the course of the synthesis, it was revealed that the spirocyclic portion of the natural product should be established prior to the Claisen rearrangement. Although the α,β-unsaturated

spiro-lactone **5.46** could not be generated due to difficulties with the acylation reaction, the core of the spirocycle (i.e **5.52**, Scheme 5.54) was still obtained. We then proceeded with the Claisen rearrangement using allyl vinyl ether **5.45** and observed that thermal conditions could induce the rearrangement to provide a 1:1 mixture of diastereomers. The future work needed to complete the synthesis of havellockate as well as some suggestions to improve upon the current synthetic approach are provided in Chapter 6.

Scheme 5.54: *Summary of the Claisen rearrangement approach*



References:

[1] Ihara, M.; Makita, K.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59,* 6008.

[2] Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54,* 4345.

[3] Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97,* 5434.

[4] Dieter, R. K.; Nice, L. E.; Velu, S. E. *Tetrahedron Lett.* **1996**, *37,* 2377.

[5] Krishna Mohan K. V. V.; Narender, N.; Kulkarni, S. J. *Tetrahedron Lett.* **2004**, *45,* 8015.

[6] Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50,* 4173. Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45,* 4077.

[7] Berkowitz, W. F.; Wilson, P. J. *J. Org. Chem.* **1991**, *56,* 3097.

[8] Jackman, L. M.; Webb, R. L.; Yick, H. C. *J. Org. Chem.* **1982**, *47,* 1824.

[9] TBS deprotection is known to occur in the presence of LiBr. Tandon, M.; Begley, T. P. *Synth. Commun.* **1997**, *27,* 2953.

[10] Baker, D.; Castro, J. L. *J. Chem. Soc. Perkin Trans 1.* **1990**, *1*, 47.

[11] Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61,* 6139.

[12] Kawai, A.; Hara, O.; Hamada, Y.; Shiari, T. *Tetrahedon Lett.* **1988**, *29,* 6331. Crich, D.; Herman, F. *Tetrahedron Lett.* **1993**, *34,* 3385.

[13] Friesen, R. W.; Trimble, L. A. *J. Org. Chem.* **1996**, *61,* 1165.

[14] Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42,* 3021.

[15] Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79,* 2828.

[16] For a full explanation of results and experimental data see: Lise-Anne Prescott, 4th year Honors Thesis, 2006.

[17] Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112,* 316.

[18] For an example see: Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115,* 10998. Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115,* 3800.

[19] Fu, G. C.; Nguyen, S. B. Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115,* 9856.

[20] Luche, J. -L.; *J. Am. Chem. Soc.* **1978**, *100,* 2226. Luche, J.-L.; Rodrequez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

[21] Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347.

[22] Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112,* 7791. Corey, E. J.; Lee, D. –H. *J. Am. Chem. Soc.* **1991**, *113,* 4026. Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed. Engl.*, **1995**, *34,* 2012.

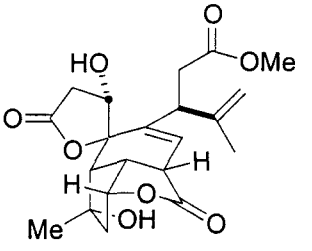
6

Summary and Outlook

6.1 Summary

Detailed in this thesis was our journey into the synthesis of a diterpenoid natural product named havellockate (Figure 6.1). This molecule contains a *cis*-fused hydrindane core which bears eight stereogenic centers as well as a seco- and spiro-lactone.

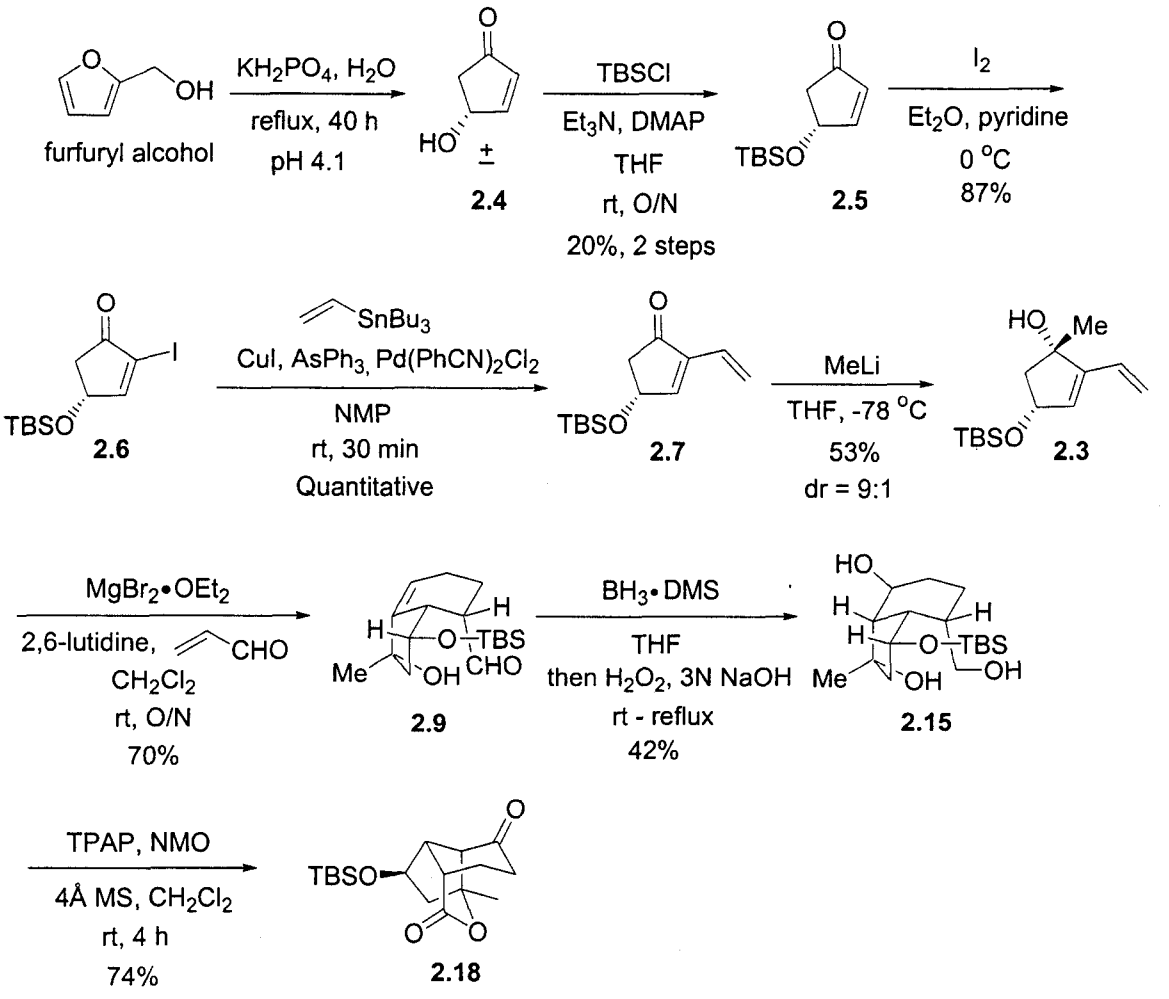
Figure 6.1: *Havellockate*



havellockate (**1.1**)

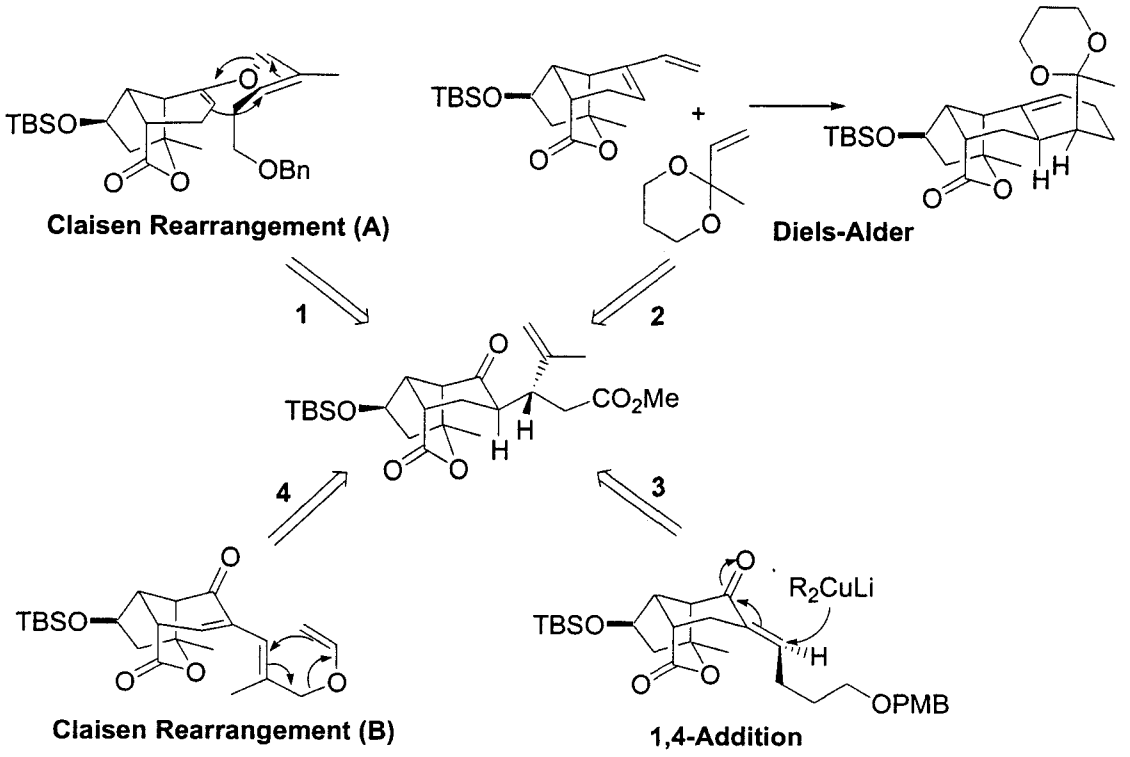
By applying the hydroxy-directed Diels-Alder reaction in our synthesis, we were able to access the core of the molecule **2.18** in only eight synthetic steps, which clearly highlights the efficiency and utility of this reaction in natural product synthesis (Scheme 6.1).

Scheme 6.1: *Summarized synthetic route for the core* ***2.18*** *of havellockate*



Beginning from **2.18**, we next explored four approaches for installing the side-chain which is summarized in Scheme 6.2. The challenging aspect of this mission was clearly the stereogenic center.

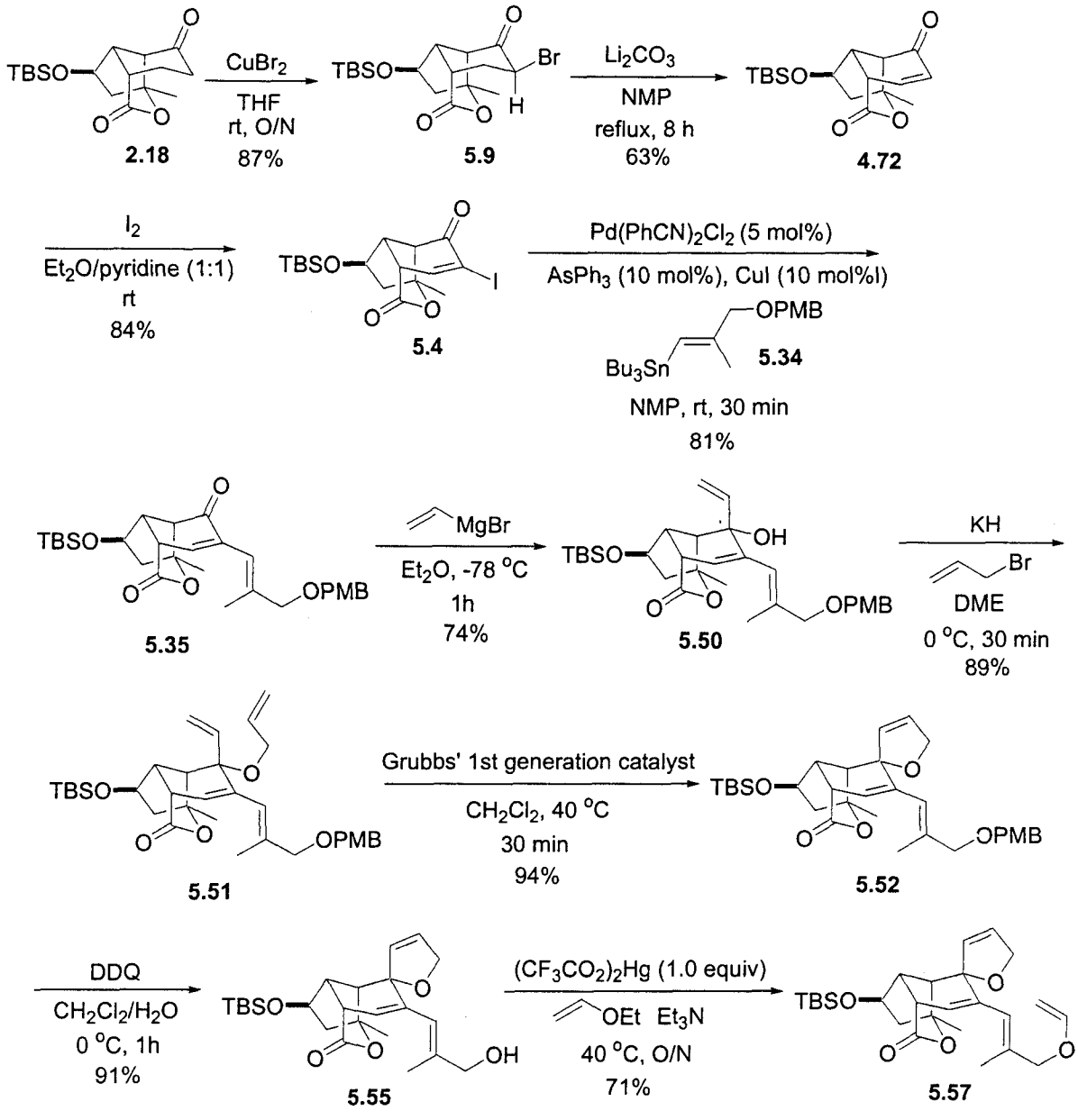
Scheme 6.2: *Summary of synthetic approaches for installing the side-chain*



Although the Claisen rearrangement (A) was a promising approach on paper, the allyl vinyl ether precursor could not be prepared and thus this rearrangement was never realized. Both the Diels-Alder and 1,4-addition strategies however, proved to be viable routes for constructing the core functionality of the chain. Unfortunately, it became apparent that the endocyclic double bond within the six-membered could not be established once this chain was installed. We therefore abandoned these two approaches and explored our fourth and final strategy which was the Claisen rearrangement (B) (Scheme 6.2). This novel approach solved the endocyclic double bond dilemma by establishing the alkene prior to the side-chain.

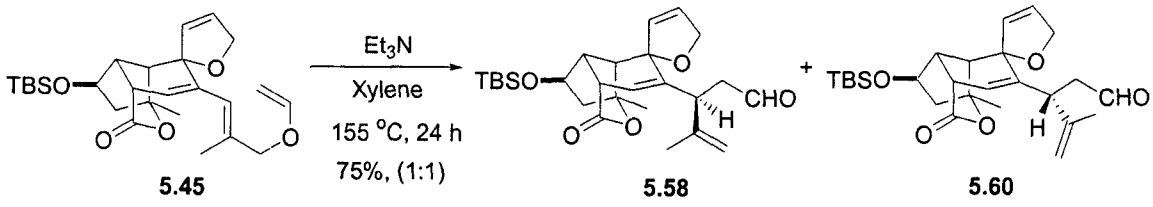
As shown in Scheme 6.3 below, this new approach began from ketone **2.18** and in nine linear steps the Claisen precursor was prepared.

Scheme 6.3: *Summary of synthetic route for installing the side-chain*



Using **5.57**, various conditions for promoting the rearrangement were studied. We were quite satisfied to observe that under thermal conditions the reaction proceeded well to provide the product in 75% yield as a 1:1 mixture of diastereomers (Scheme 6.4).

Scheme 6.4: *Summary of Claisen rearrangement under thermal conditions*



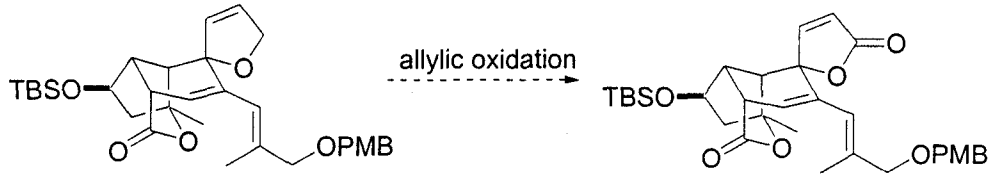
5.45 **5.58** **5.60**

6.2 Outlook

As a result of our studies, we have learned that the best approach for the synthesis of havellockate is the Claisen-rearrangement strategy described above. It has allowed us to install the endocyclic double bond and has provided the side-chain with the correct number of carbon atoms as well as the isopropenyl group and the aldehyde moiety which can be easily converted to the methyl ester at a later point.

For the synthesis of havellockate to reach its conclusion we need to first address the spirocycle. More specifically, the carbonyl moiety needs to installed to form the α,β-unsaturated lactone **5.46** (Scheme 6.5). This could be accomplished via an allylic oxidation reaction.

Scheme 6.5: *Allylic oxidation of* ***5.52***

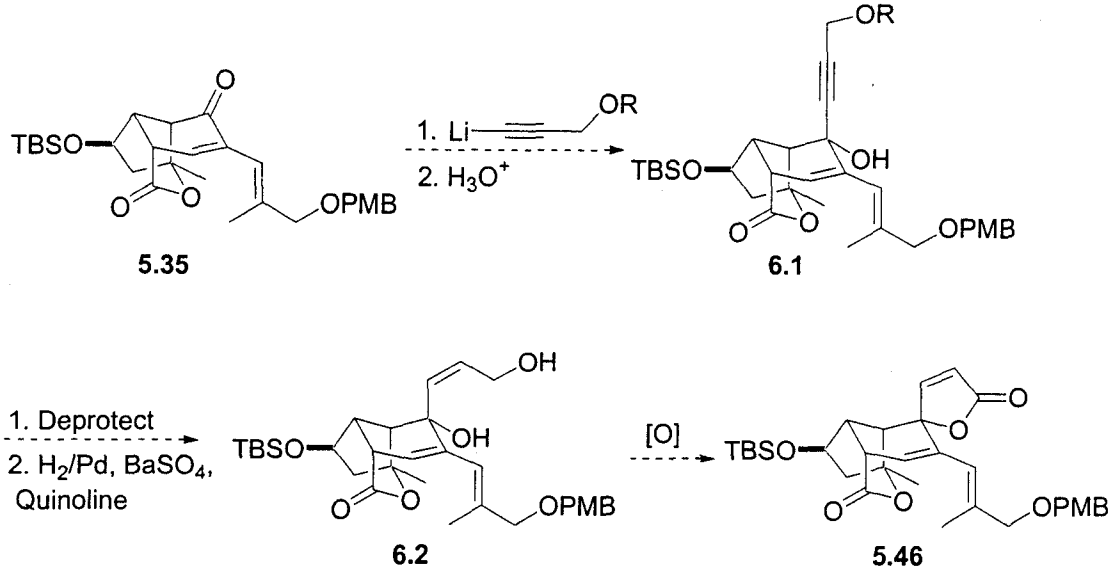


5.52 **5.46**

If difficulties are experienced with the above transformation due to the presence of the olefin in the side-chain, an alternative strategy illustrated in Scheme 6.6 below could be

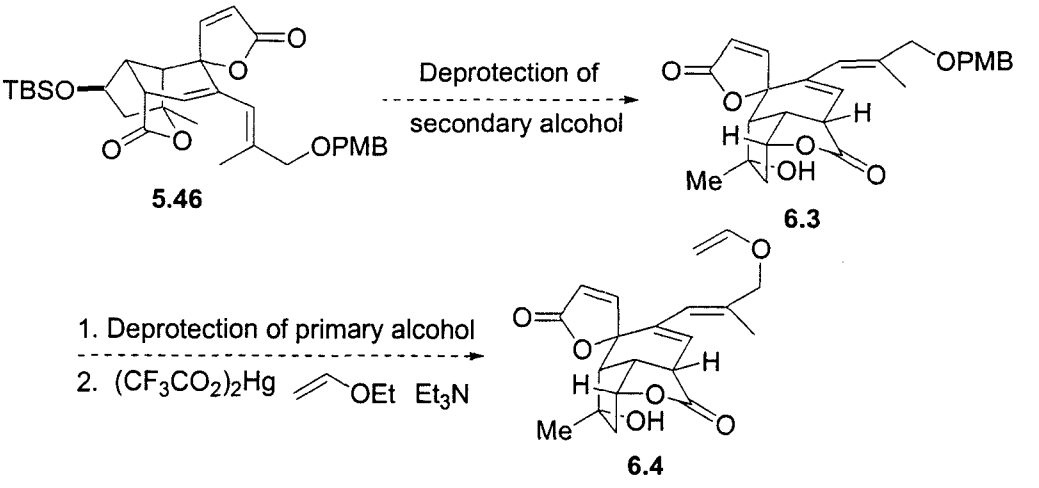
studied as well. Alkylation of the ketone of **5.35** with lithio propargyl alcohol (protected) would furnish in **6.1**. Following deprotection, hydrogenation and oxidation, the spiro-lactone would be complete.

Scheme 6.6: *Alternative strategy to the spiro-lactone*



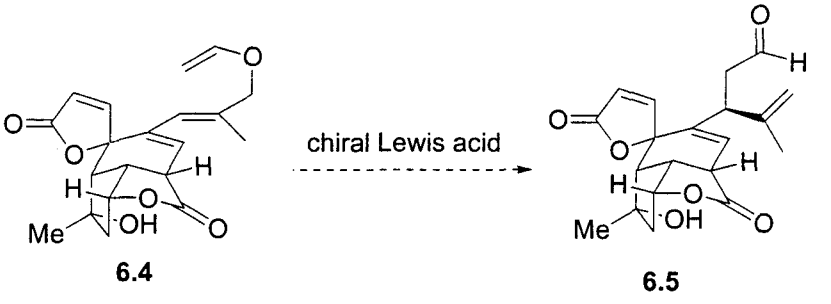
Since we were unable to deprotect the secondary TBS alcohol after the Claisen-rearrangement, this step should occur prior to the synthesis of the allyl vinyl ether substrate **6.4** (Scheme 6.7).

Scheme 6.7: *Deprotection of the TBS alcohol and subsequent generation of the Claisen precursor*



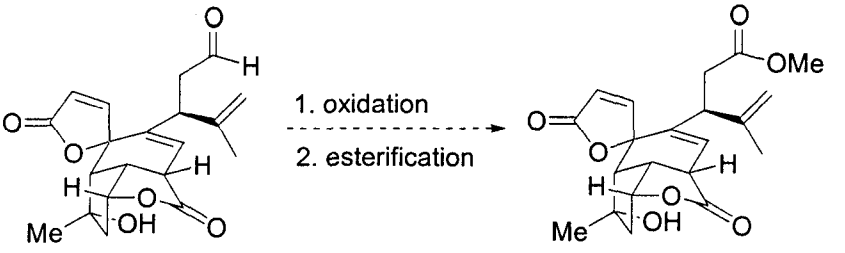
With **6.4** we could explore the use of a chiral Lewis acid as mentioned in Chapter 5, to improve the diastereoselectivity of the [3,3]-sigmatropic rearrangement (Scheme 6.8).

Scheme 6.8: *Claisen rearrangement in the presence of a chiral Lewis acid*



Once the Claisen product **6.5** is obtained, an oxidation followed by a methylation reaction would complete the side-chain (Scheme 6.9).

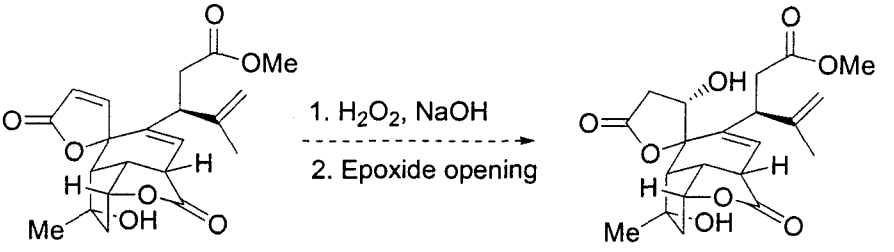
Scheme 6.9: *Completion of the side-chain*



6.5 **6.6**

The grand-finale would entail an epoxidation of the spiro-lactone followed by a cleavage of the oxirane (via PhSeNa for example)[1] to generate the β-hydroxy-lactone and thus complete the natural product.

Scheme 6.10: *Completing the synthesis of havellockate*



6.6 havellockate (**1.1**)

References:

[1] Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4294.

Final Comments

When a synthetic route for a natural product is proposed in a linear sequence on paper the approach as well as the conditions for each reaction seem simple and logical. In practice though, many unforeseen challenges often arise while attempting to execute this route in the laboratory. Havellockate was certainly no exception.

The side-chain and endocyclic alkene of this natural product for example, offered a substantially greater challenge than we had anticipated. In-fact, only our fourth synthetic approach was capable of accomplishing both of these challenges.

Despite the fact that we did not complete the synthesis of havellockate, much was learned about the reactivity of the intermediates along the way. As a result, we have a clearer understanding of how to approach this molecule and with a little patience we believe that the synthesis will be completed in the near future.

Claims to Original Research

1. Optimized some of the reaction conditions previously developed in the lab to prepare the tricyclic core of havellockate

2. Studied four approaches for generating the side-chain of the natural product

3. Discovered that a thermally-induced Claisen-rearrangement could provide the core of the side-chain as a 1:1 mixture of diastereomers

4. Investigated and optimized the reaction conditions for installing the endocyclic double bond within the six-membered ring as well as the spirocyclic portion of the molecule

Posters:

Studies Toward the Total Synthesis of Havellockate, August 2006, Synthesis Day 2006, Ottawa, Ontario; Beingessner, R., Farand, J., Prescott, L.A. and Barriault, L.

Studies Toward the Total Synthesis of Havellockate, June 2006, AstraZeneca Chemistry Symposium, St-Laurent, Quebec; Beingessner, R., Farand, J. and Barriault, L.

Toward the Total Synthesis of Havellockate, April 2005, International Symposium on Organic and Organometallic Synthesis at Université de Montréal, Montréal, Quebec; Beingessner, R., Farand, J. and Barriault, L.

Toward the Total Synthesis of Havellockate, November 2004, Quebec-Ontario Mini-Symposium in Synthetic and Bioorganic Chemistry, Hull, Quebec; Beingessner, R., Farand, J. and Barriault, L.

Studies Toward the Total Synthesis of Havellockate, May 2004, Synthesis Day 2004, University of Ottawa, Ottawa, Ontario; Beingessner, R., Farand, J. and Barriault, L.

Presentations:

Application of the Hydroxy-Directed Diels-Alder Reaction Toward the Total Synthesis of Havellockate, November 2005, 16th Quebec-Ontario Mini-Symposium in Synthetic and Bioorganic Chemistry, St. Adèle, Quebec; Beingessner, R., Farand, J., and Barriault L.

Application of the Hydroxy-Directed Diels-Alder Reaction Toward the Total Synthesis of Havellockate, May 2005, Ottawa-Carleton Chemistry Institute Day, Ottawa, Ontario; Beingessner, R., Farand, J. and Barriault, L.

7

Experimental

General Experimental:

All reactions were performed under an atmosphere of argon in flame-dried glassware equipped with a magnetic stirbar and rubber septum unless otherwise stated. Solvents were freshly distilled prior to use: ether, THF, 1,2-dimethoxyethane over sodium and benzophenone; dichloromethane, toluene, DMF and Et_3N over calcium hydride. All other commercial reagents were used without purification unless otherwise stated.

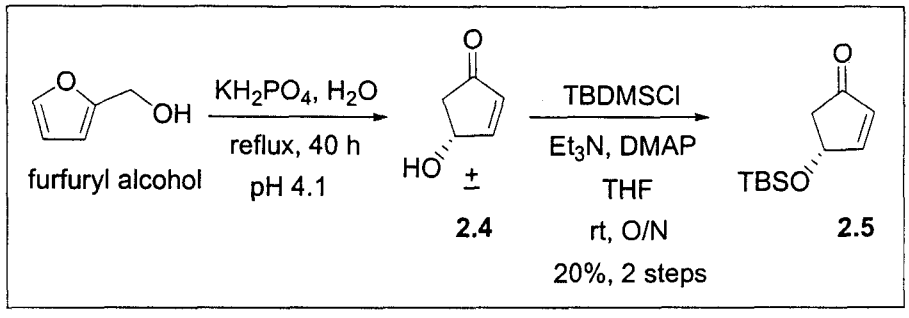
Reactions were monitored by TLC analysis using glass plates pre-coated (250 μm thickness) with silica gel 60 F_{254} (E. Merck). TLC plates were viewed using UV light, *para*-anisaldehyde staining solution or potassium permanganate staining solution. Flash chromatography was carried out on 230-400 mesh silica gel 60.

Microwave reactions were performed in a CEM Discover microwave oven. The reaction vessel was a quartz tube and in each case a carboflon^{TM} was used to aid in the absorption of microwave radiation.

^1H and ^{13}C NMR spectra were recorded on a Brucker Avance 300 MHz or Brucker Avance 500 MHz spectrometer in the specified deuterated solvent. Residual ^1H shifts in $CDCl_3$ (7.27 ppm), C_6D_6 (7.16 ppm) and Acetone-d_6 (2.05 ppm) were used as the internal references where stated for ^1H NMR. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, brs = broad singlet. $CDCl_3$ (77.23 ppm), C_6D_6 (128.39 ppm) and Acetone-d_6 (29.92) were

used as the internal references for ^{13}C NMR as stated. The carbon atoms were assigned based on information provided from DEPT 135 and HMQC experiments.

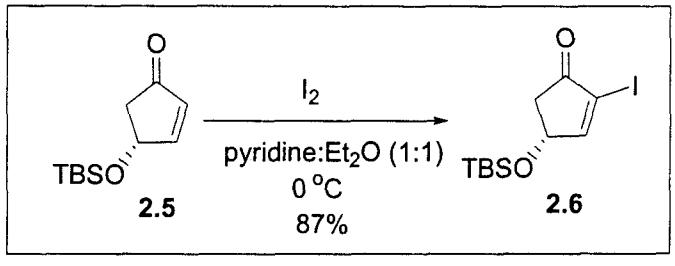
IR spectra were recorded on a Bomen Michaelson 100 FT-IR spectrometer. The following abbreviations were used to describe the intensity of the vibrations: s = strong, m = medium, w = weak. HRMS spectra were obtained using a Kratos Analytical Concept spectrometer, and melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus.



(+/-)-(*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-2-enone (2.5). Potassium dihydrogenphosphate (2.25 g, 136 mmol) was added to a solution of furfuryl alcohol (45.1 g, 460 mmol) in H_2O (1350 mL). The pH was adjusted to 4.10 using KOH or H_3PO_4 and the solution was heated to reflux for 40 h. Adequate stirring must be maintained throughout the length of the reaction to prevent the formation of a viscous red polymer. After cooling to room temperature, a saturated aqueous solution of NaCl (300 mL) was added and the biphasic mixture was separated into 5 portions. Each of those portions was extracted with EtOAc (3x100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to provide 20.7 g of **2.4** as a crude viscous red oil. The product was subsequently dissolved in THF (200 mL) and cooled to 0 °C. Et_3N (47.1 mL, 338 mmol) and DMAP (258 mg, 2.11 mmol) were added followed by TBDMSCl (28.6 g, 190 mmol) portion-wise. The contents of the flask were warmed to room temperature and

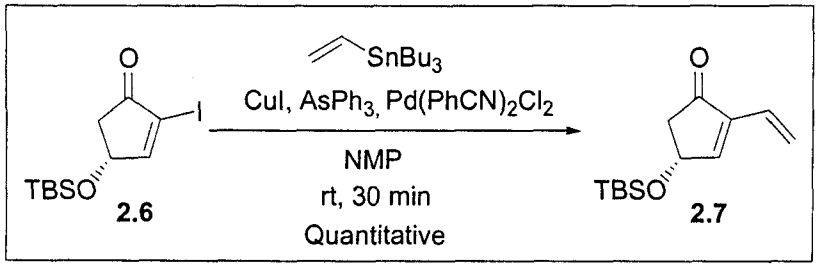
stirred O/N. The reaction was quenched with a 0.5 N solution of HCl (200 mL) and the aqueous phase was extracted with Et_2O (3x150 mL). The combined organic extracts were washed with a saturated aqueous solution of NaCl (250 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (100% hexanes) provided 19.5 g of **2.5** (20%) as a viscous red oil.

Spectral data of **2.5** is in accordance with the literature data: Curran, T. T.; Hay, D.A.; Koegel, C. P.; Evans, J. C. *Tetrahedron* **1997**, *53,* 1983.



(+/-)-(*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-iodo-cyclopent-2-enone (2.6). Iodine (1.2 g, 4.7 mmol) was dissolved in a 1:1 solution of Et_2O/pyridine (10 mL) and slowly added to a 0 °C solution of **2.5** (1.0 g, 4.7 mmol) also in a 1:1 solution of Et_2O/pyridine (20 mL). After warming to room temperature, the reaction was stirred for 1 h. The mixture was diluted with Et_2O (30 mL) and washed successively with 1N HCl (3x25 mL), H_2O (25 mL) and a 20% aqueous solution of $Na_2S_2O_3$ (25 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) provided 1.66 g of **2.6** (87%) as a pale yellow solid.

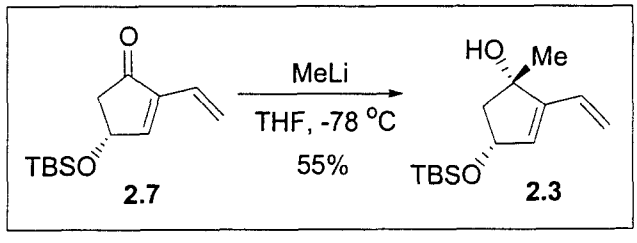
Spectral data of **2.6** is in accordance with the literature data: Johnson, C. R.; Adams, J. P.; Matthew, P. B.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33,* 917.



(+/-)-(*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-vinylcyclopent-2-enone (2.7).

Triphenylarsine (1.21 g, 10 mol%, 3.96 mmol), $Pd(PhCN)_2Cl_2$ (760 mg, 5 mol%, 1.98 mmol) and CuI (755 mg, 10 mol%, 3.96 mmol) were weighed in the glove box and placed into a flame-dried round bottom flask. A solution of enone **2.6** (13.4 g, 39.6 mmol) in NMP (80 mL) was then added followed by tributyl(vinyl)tin (12.7 mL, 43.6 mmol). The reaction was stirred for 30 min before the contents of the flask were poured into H_2O (50 mL). The product was extracted with Et_2O (3x20 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes: EtOAc) provided 9.4 g of **2.7** (quantitative) as a clear colorless oil.

Spectral data of **2.7** is in accordance with Julie Farand's M.Sc. Thesis, April 2004, University of Ottawa.

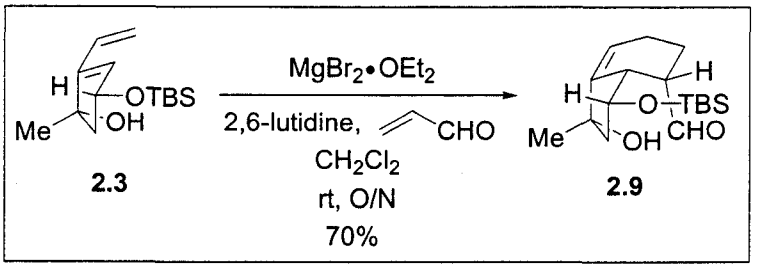


(+/-)-(1*S*,4*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-2-vinylcyclopent-2-enol (2.3).

Ketone **2.7** (8.2 g, 34 mmol) was placed into a flame-dried round bottom flask and diluted with THF (50 mL). After cooling to -78 °C, MeLi (86.0 mL, 1.6 M in Et_2O, 138 mmol) was added drop-wise and the mixture was stirred for 2 h at -78 °C. The reaction was then

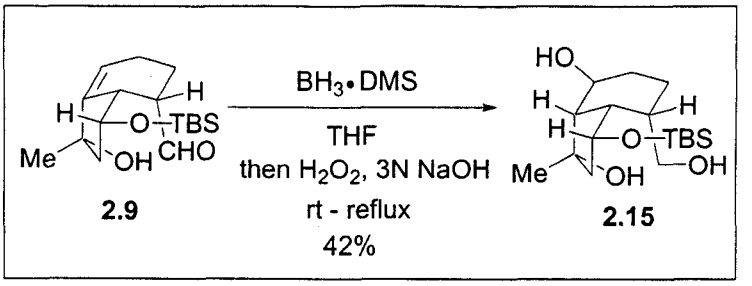
quenched with water (75 mL) at 0 °C and the aqueous layer was extracted with Et_2O (3x50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (4:1 hexanes:Et_2O) provided 4.8 g of **2.3** (55%) as a clear colorless oil.

Spectral data of **2.3** is in accordance with Julie Farand's M.Sc. Thesis, April 2004, University of Ottawa.



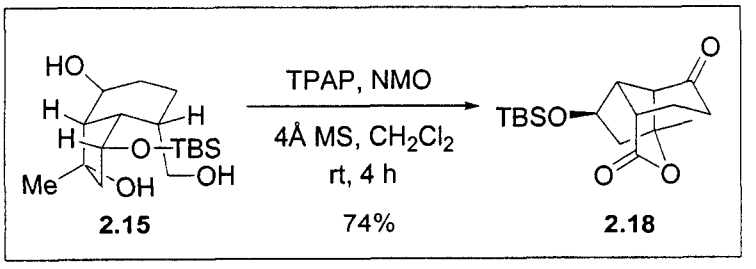
(+/-)-(1*S*,3*R*,3a*S*,4*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-1-methyl-2,3,3a,4,5,6-hexahydro-1*H*-indene-4-carbaldehyde (2.9). A mixture of $MgBr_2 \cdot OEt_2$ (18.0 g, 69.6 mmol) in CH_2Cl_2 (100 mL) at room temperature under an atmosphere of argon was treated with 2,6-lutidine (13.5 mL, 116 mmol). After stirring for 20 min, a solution of diene **2.3** (5.9 g, 23 mmol) in CH_2Cl_2 (20 mL) was added. Following an additional 20 min, acrolein (7.75 mL, 116 mmol) was added and stirring continued for 14 h. The reaction was then quenched with H_2O (50 mL) the product was extracted with CH_2Cl_2 (5x50 mL). The combined organic layers were washed with a saturated aqueous solution of brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by silica gel flash chromatography on silica gel basified with Et_3N (10:1 hexane:Et_2O) provided 5.1 g of **2.9** (70%) as a clear colorless oil.

Spectral data of **2.9** is in accordance with Julie Farand's M.Sc. Thesis, April 2004, University of Ottawa.



(+/-)-(1*S*,3*R*,3a*S*,4*S*,7*S*,7a*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-4-hydroxymethyl-1-methyl-octahydro-indene-1,7-diol (2.15). BH_3·DMS (610 μL, 6.43 mmol) was added to a solution of **2.9** (670 mg, 2.14 mmol) in THF (10 mL) at room temperature. After stirring for 4 h, the viscous jelly was cooled to 0 °C. A condenser was placed on the round bottom flask and the borane was then oxidized by drop-wise addition of 30% H_2O_2 (4 mL) and 3N NaOH (4 mL) (alternating between both). *Caution*: on a large scale, the reaction is very vigorous! The ice bath was removed and the mixture was refluxed for 2 h. After cooling to room temperature, H_2O (20 mL) was added and the product was extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (1:1 EtOAc:hexanes) provided 373 mg of **2.15** (42%) as a white solid.

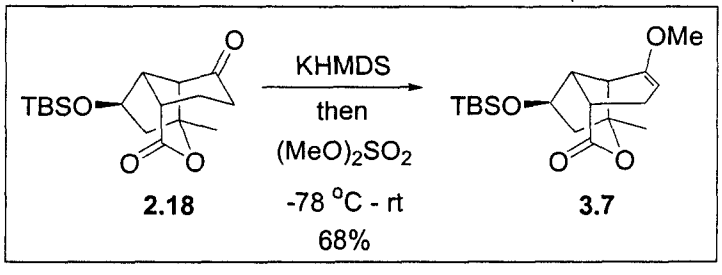
Spectral data of **2.15** is in accordance with Julie Farand's M.Sc. Thesis, April 2004, University of Ottawa.



(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo-[5.4.0.0^{4,8}]undecane-2,9-dione (2.18). Molecular sieves (4 Å) (550 mg, 500 mg/mmol of

alcohol) were flame-dried under vacuum in a round bottom flask. After cooling to room temperature, the flask was filled with argon and a solution of triol **2.15** (456 mg, 1.10 mmol) in CH_2Cl_2 (25 mL) was added, followed by NMO (451 mg, 3.85 mmol) and TPAP (19 mg, 0.055 mmol). The dark green solution was stirred for 4 h at room temperature and was then filtered through a pad of silica gel, eluting with 5% MeOH in EtOAc. The organic solvent was removed *in vacuo* and the crude product was purified by silica gel flash chromatography (5:1 hexanes:Et_2O) to provide 264 mg of **2.18** (74%) as a white solid.

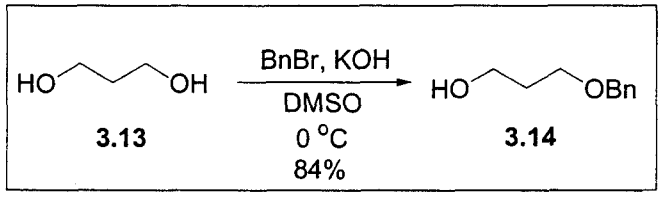
Spectral data of **2.18** is in accordance with Julie Farand's M.Sc. Thesis, April 2004, University of Ottawa.



2.18 **3.7**

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-butyl-dimethyl-silanyloxy)-9-methoxy-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-9-en-2-one (3.7). Ketone **2.18** (133 mg, 410 mmol) was dissolved in THF (3 mL) and slowly cannulated into a mixture of KHMDS (164 mg, 820 mmol) in THF (3 mL) at – 78 °C. After stirring for 30 min, freshly distilled dimethyl sulfate (78 mg, 0.82 mol) was added and the flask was warmed to room temperature over a period of 30 min. The reaction was quenched with H_2O (5 mL) and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) basified with Et_3N provided 94 mg of **3.7** (68%) as a white solid.

Spectral data of **3.7** is in accordance with Julie Farand's M.Sc. Thesis, April 2004, University of Ottawa.



3-(Benzyloxy)propan-1-ol (3.14). Benzyl bromide (3.9 mL, 66 mmol) was added to a solution of 1,3-propanediol (5.0 g, 66 mmol) and KOH (ground powder) (7.72 g, 138 mmol) in DMSO (26 mL) at 0 °C. The solution was stirred for 2 h before being quenched with a saturated aqueous solution of NH_4Cl (30 mL). The product was extracted with Et_2O (3 x50 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (1:1 hexanes: EtOAc) provided 8.4 g of **3.14** (84%) as a clear colorless oil.

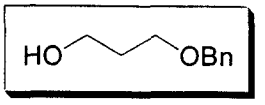
Data for **3.14:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.36 - 7.28 (m, 5H), 4.50 (s, 2H), 3.78 (t, J = 5.7 Hz, 2H), 3.64 (t, J = 5.8 Hz, 2H), 2.50 (s, 1H), 1.84 (quint, J = 5.8 Hz, 2H)

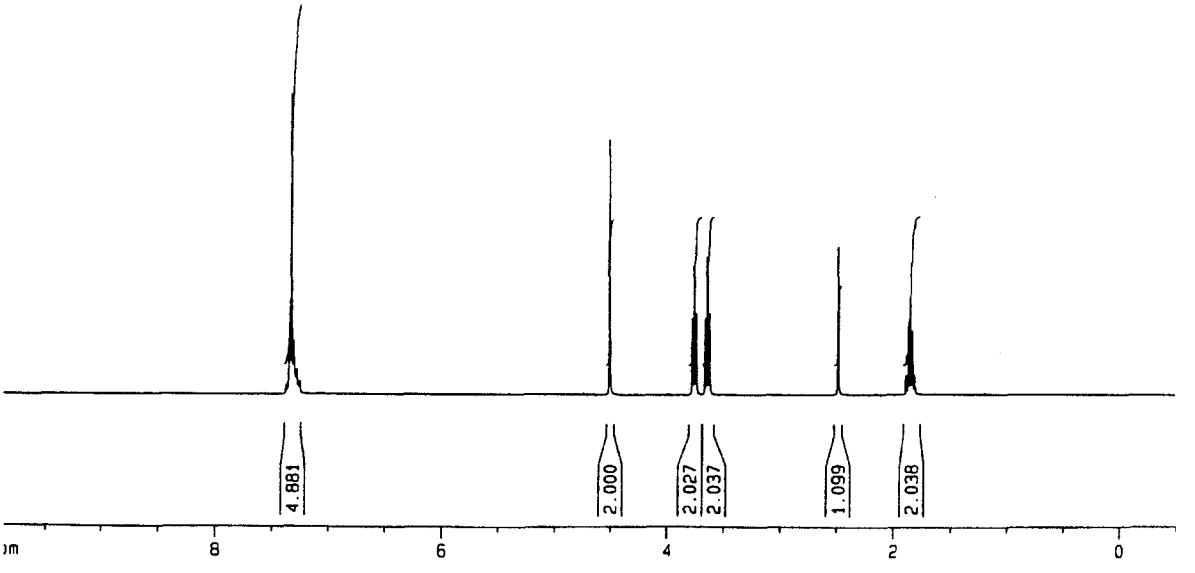
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 138.0 (C_4), 128.4 (CH), 127.6 (CH), 127.6 (CH), 73.2 (CH_2), 69.2 (CH_2), 61.6 (CH_2), 32.0 (CH_2)

FTIR (neat, cm^{-1}) 3399 (brs), 2945 (s), 2866 (s), 1454 (s), 1366 (s), 1090 (s)

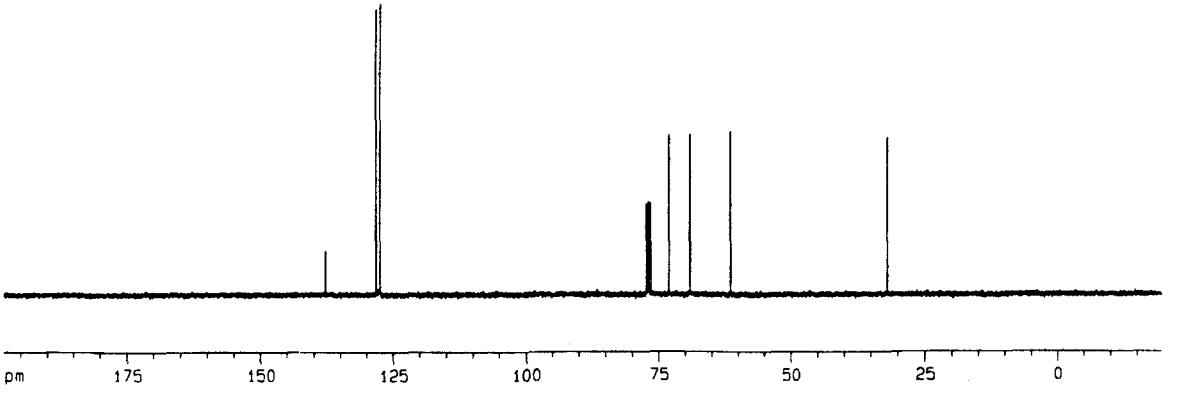
HRMS (EI, m/z) Expected for $C_{10}H_{14}O_2$ [$(M)^+$]: 166.0994, found: 166.0999 (2.18%)

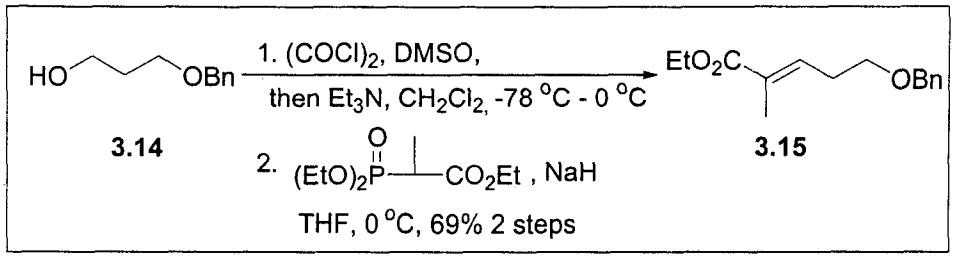


^{1}H NMR (300 MHz, $CDCl_3$)



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





(*E*)-Ethyl 5-(benzyloxy)-2-methyl-pent-2-enoate (3.15). DMSO (560 μL, 7.88 mmol) was added drop-wise (note: gas evolution observed) to a solution of oxalyl chloride (344 μL, 3.94 mmol) in CH_2Cl_2 (32 mL) at -78 °C. After stirring for 20 min, a solution of alcohol **3.14** (500 mg, 3.29 mmol) in CH_2Cl_2 (5 mL) was cannulated into the flask and the contents were stirred for 1.5 h at -78 °C. Et_3N (2.29 mL, 16.4 mmol) was then added and the flask was warmed to 0 °C and stirred for an additional 20 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the product was extracted with CH_2Cl_2 (3x25 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was used without further purification. In a separate flask, triethyl 2-phosphonopropionate (845 μL, 3.94 mmol) was added drop-wise to a mixture of NaH (197 mg, 60% dispersion in oil, 4.92 mmol) in THF (20 mL) at 0 °C. After stirring for 1 h, the crude aldehyde (from above) was added and the mixture was stirred for an additional 1 h at 0 °C. The reaction was then quenched with a saturated aqueous solution of NH_4Cl and the product was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes: Et_2O) provided 530 mg of **3.15** (69%) as a clear colorless oil.

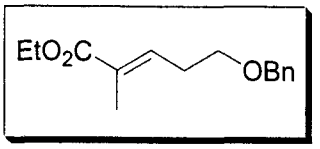
Data for **3.15:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.33 – 7.29 (m, 5H), 6.81 - 6.76 (m, 1H), 4.51 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.55 (t, J = 6.7 Hz, 2H), 2.51 – 2.45 (m, 2H), 1.84 – 1.83 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H)

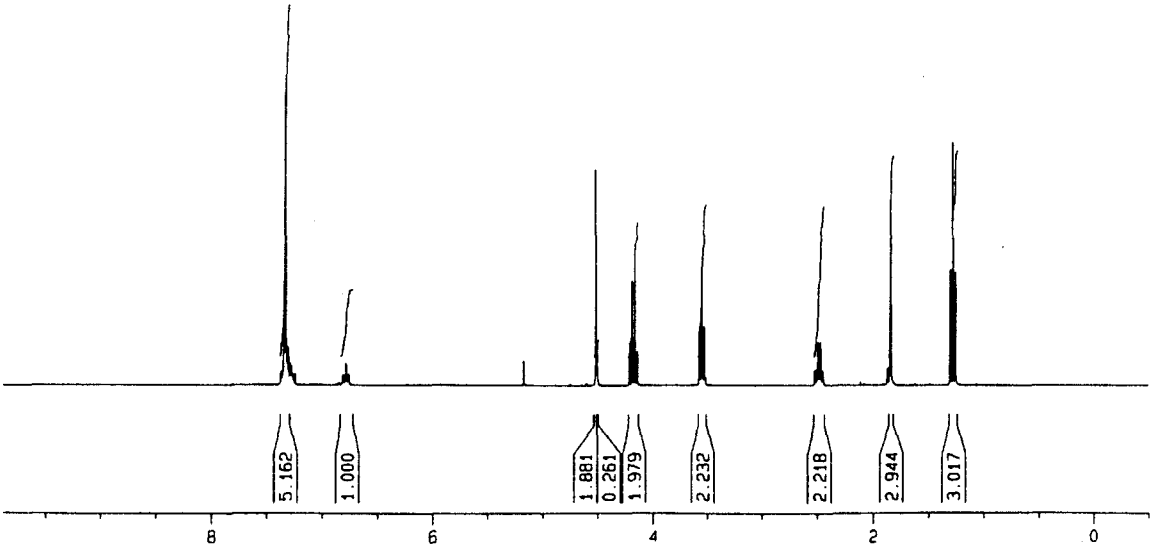
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 167.9 (C_4), 138.2 (CH), 138.1 (C_4), 129.3 (C_4), 128.3 (CH), 127.9 (CH), 127.5 (CH), 72.9 (CH_2), 68.5 (CH_2), 60.4 (CH_2), 29.3 (CH_2), 14.2 (CH_3), 12.5 (CH_3)

FTIR (neat, cm^{-1}) 3031, 2859 (s), 1710 (s), 1454 (s), 1366 (s), 1098 (s)

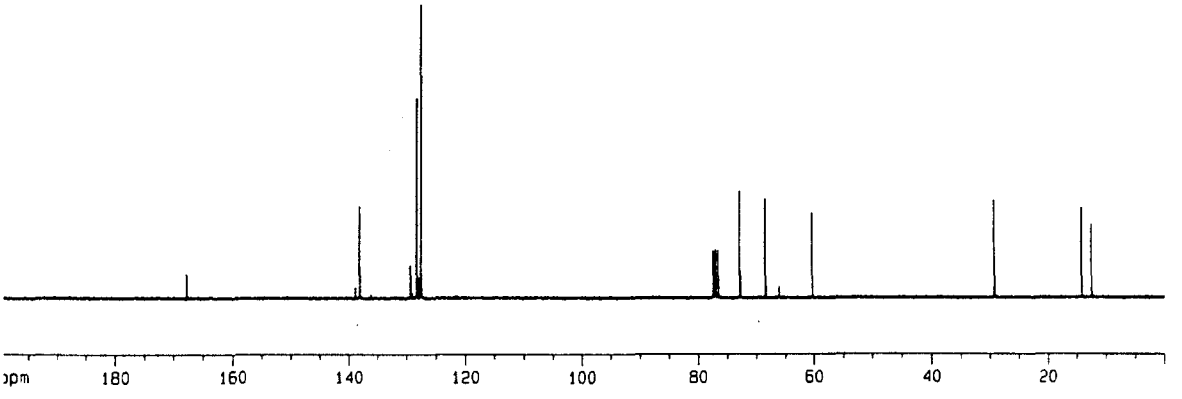
HRMS (EI, m/z) Expected for $C_{12}H_{15}O$ [$(M-C_3H_5O_2)^+$]: 175.1123, found: 175.1123 (17.9%)

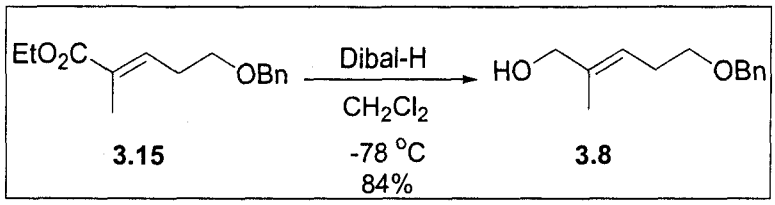


^{1}H NMR (300 MHz, $CDCl_3$)



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





(*E*)-5-(Benzyloxy)2-methyl-pent-2-en-1-ol (3.8). A solution of α,β-unsaturated ester **3.15** (278 mg, 1.19 mmol) in CH_2Cl_2 (5 mL) at -78 °C was treated with a drop-wise addition of Dibal-H (2.49 mL, 1.0 M in CH_2Cl_2, 2.49 mmol). After stirring for 30 min the reaction was quenched with 1N HCl (50 mL). The product was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (1:1 hexanes: EtOAc) provided 205 mg of alcohol **3.8** (84%) as a clear colorless oil.

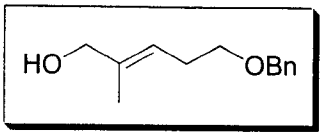
Data for **3.8:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.33 – 7.28 (m, 5H), 5.45 – 5.41 (m, 1H), 4.50 (s, 2H), 3.98 (s, 2H), 3.48 (t, J = 6.9 Hz, 2H), 2.36 (q, J = 6.9 Hz, 2H), 1.66 (s, 3H), 1.56 – 1.55 (m, 1H)

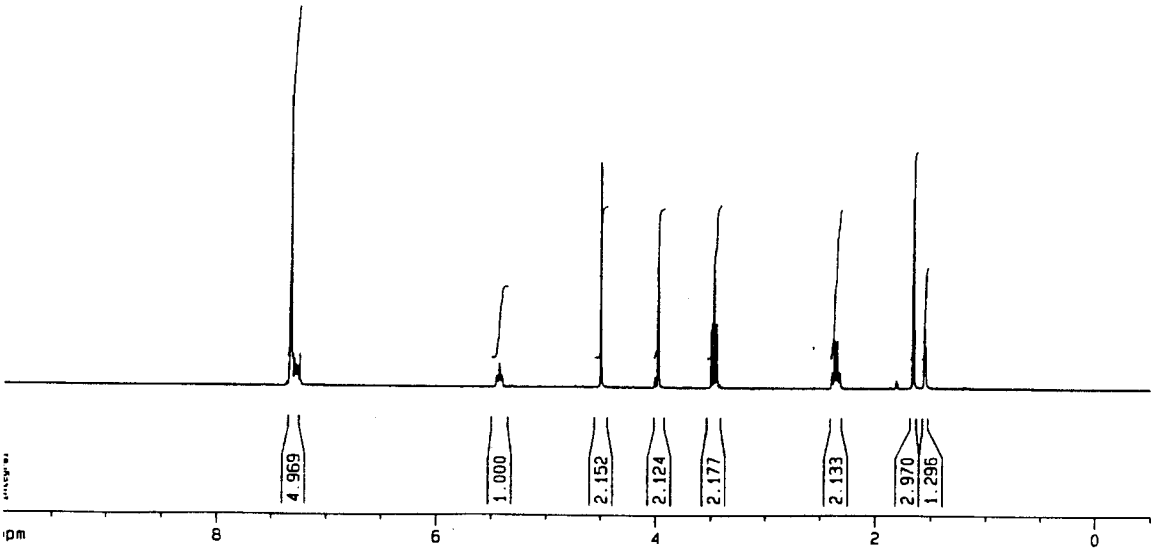
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 138.3 (C_4), 136.7 (C_4), 128.3 (CH), 127.6 (CH), 127.5 (CH), 121.8 (CH), 72.8 (CH_2), 69.6 (CH_2), 68.6 (CH_2), 28.2 (CH_2), 13.7 (CH_3)

FTIR (neat, cm^{-1}) 3404 (brs), 2859 (s), 1454 (s), 1362 (s), 1094 (s)

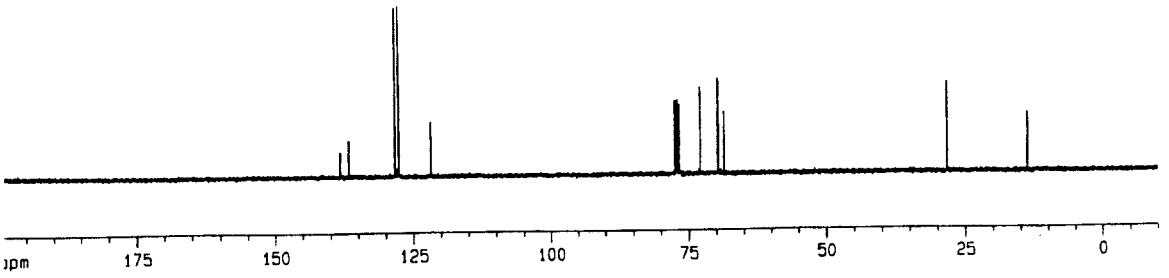
HRMS (EI, m/z) Expected for $C_{13}H_{18}O_2$ [$(M)^+$]: 206.1307, found: 206.1319 (0.46%)

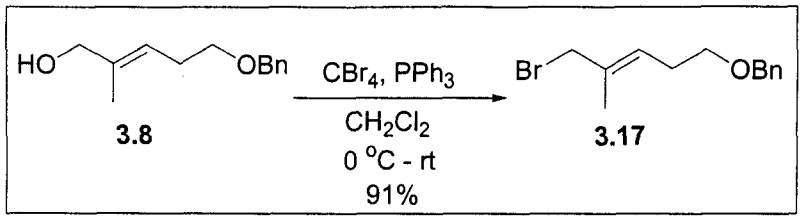


^{1}H NMR (300 MHz, $CDCl_3$)



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





(5-Bromo-4-methyl-pent-3-enyloxymethyl)-benzene (3.17). A solution of alcohol **3.8** (177 mg, 0.858 mmol) and CBr_4 (285 mg, 0.858 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with PPh_3 (236 mg, 0.900 mmol). The solution was warmed to room temperature and stirred for 2 h before being poured into 20 mL of a 9:1 solution of hexanes:Et_2O. Triphenylphosphine oxide readily precipitated out and was filtered through a pad of silica gel. The filtrate was concentrated *in vacuo* to provide a crude yellow oil. Purification by flash chromatography on silica gel (10:1 hexanes: Et_2O) provided 210 mg of **3.17** (91%) as a clear colorless oil.

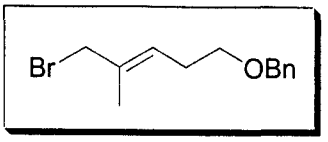
Data for **3.17:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.38 - 7.28 (m, 5H), 5.69 – 5.64 (m, 1H), 4.50 (s, 2H), 3.95 (s, 2H), 3.48 (t, J = 6.8 Hz, 2H), 2.35 (q, J = 6.9 Hz, 2H), 1.76 (s, 3H)

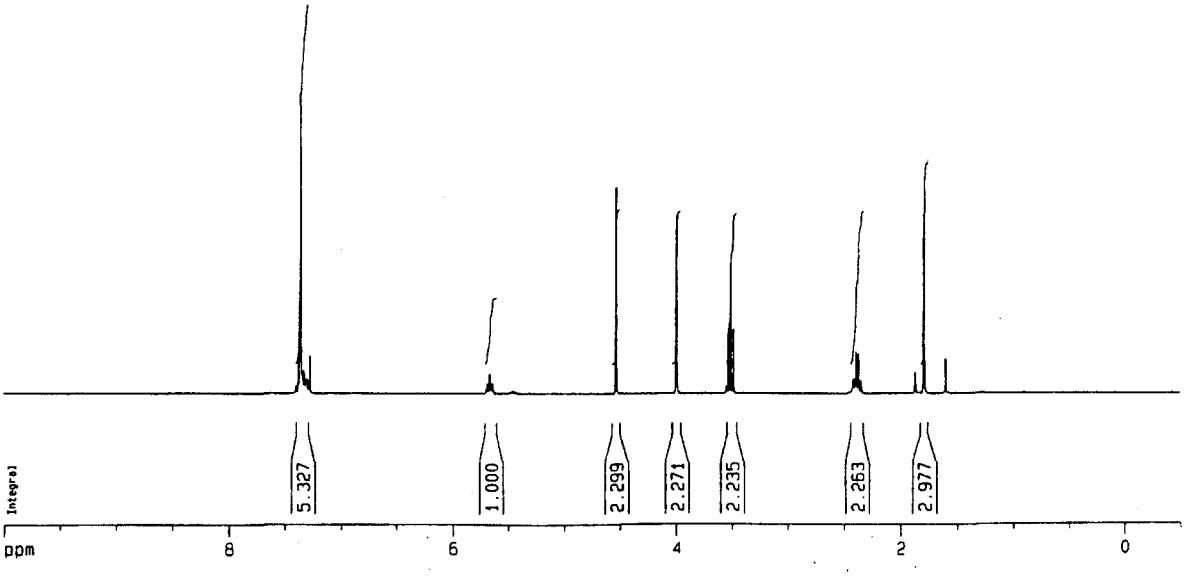
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 138.3 (C_4), 133.8 (C_4), 128.4 (CH), 127.61 (CH), 127.58 (CH), 127.5 (CH), 72.9 (CH_2), 69.1 (CH_2), 41.4 (CH_2), 29.0 (CH_2), 14.8 (CH_3)

FTIR (neat, cm^{-1}) 3033 (m), 2857 (m), 1496 (w), 1454 (m), 1103 (s)

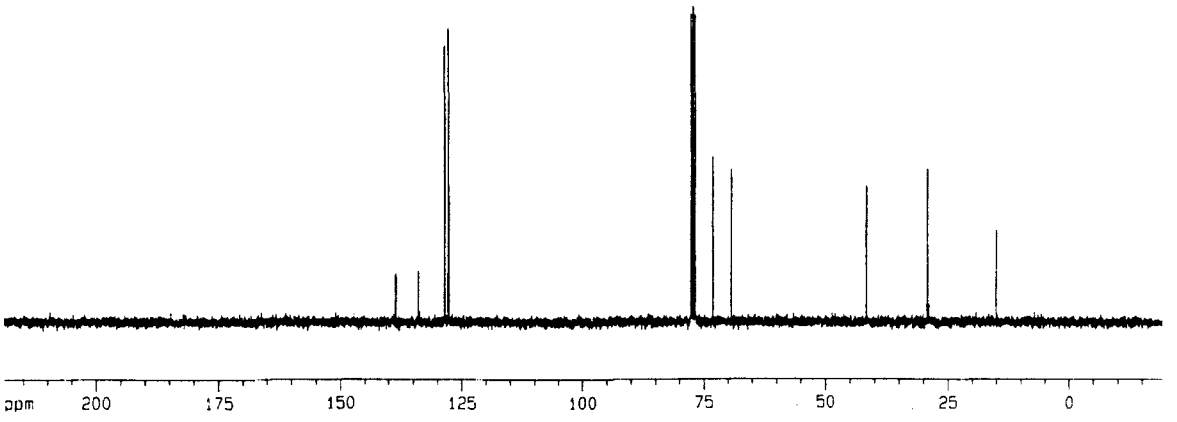
HRMS (EI, m/z) Expected for $C_{13}H_{17}O$ [$(M\text{-}Br)^+$]: 189.1279, found: 189.1266

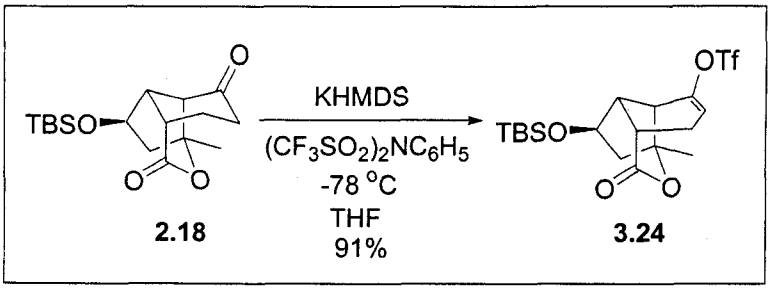


^{1}H NMR (300 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-2-oxo-3-oxatricyclo[5.4.0.0^{4,8}]undec-9-en-9-yl trifluoromethansulfonate (3.24). Ketone **2.18** (25 mg, 0.077 mmol) was added drop-wise to a mixture of KHMDS (31 mg, 0.15 mmol) in THF (0.5 mL) at -78 °C and stirred for 30 min. $PhN(Tf)_2$ (61 mg, 0.17 mmol) was then added and the reaction was stirred for 1 h at -78 °C and then warmed to 0 °C and stirred for an additional 3 h. The solvent was removed *in vacuo* and the product was purified by flash chromatography on silica gel (10:1 hexanes: Et_2O) to provide 32 mg of **3.24** (91%) as a white solid (melting point: 86.7 °C – 87.9 °C).

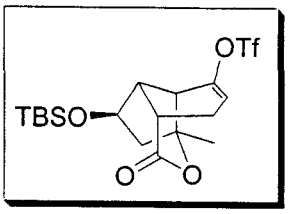
Data for **3.22:**

^{1}H NMR (300 MHz, C_6H_6) δ_{ppm} 5.27 (dd, J = 5.6, 2.1 Hz, 1H), 3.72 (ddd, J = 9.2, 6.7, 2.2 Hz, 1H), 2.90 – 2.89 (m, 1H), 2.17- 2.09 (m, 2H), 1.82 (ddd, J = 7.2, 5.2, 2.6 Hz, 1H), 1.68 – 1.66 (m, 1H), 1.61 – 1.60 (m, 1H), 1.37 – 1.26 (m, 1H), 1.16 (s, 3H), 0.88 (s, 9H), -0.10 (s, 3H), -0.11 (s, 3H)

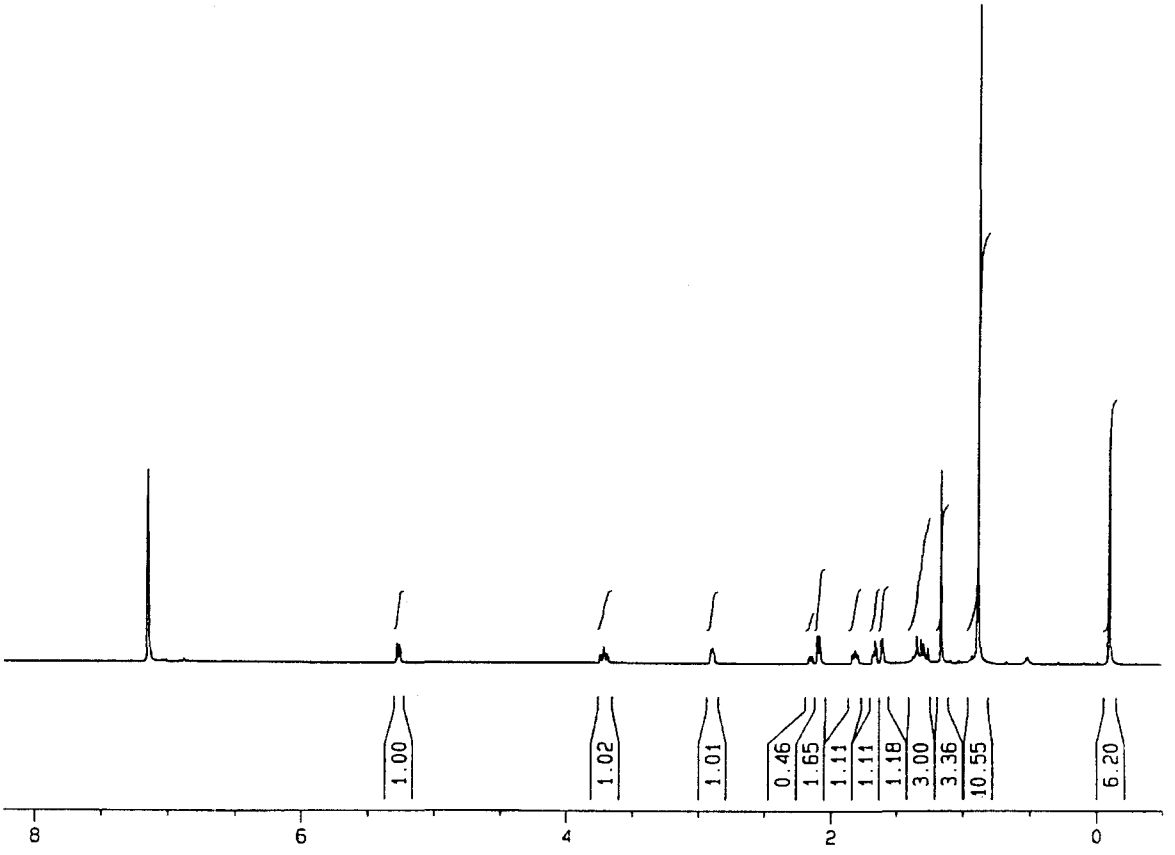
^{13}C NMR (75 MHz, C_6H_6) δ_{ppm} 170.8 (C_4), 145.0 (C_4), 121.2 (CH) 87.3 (C_4), 69.9 (CH), 48.5 (CH_2), 46.7 (CH), 44.1 (CH), 36.1 (CH), 29.2 (CH_2), 25.9 (3xCH_3), 22.2 (CH_3), 18.2 (C_4), -4.8 (CH_3), -5.0 (CH_3)

FTIR (neat, cm^{-1}) 2933 (s), 2856 (m), 1743 (s), 1420 (s), 1212 (s), 1005 (m)

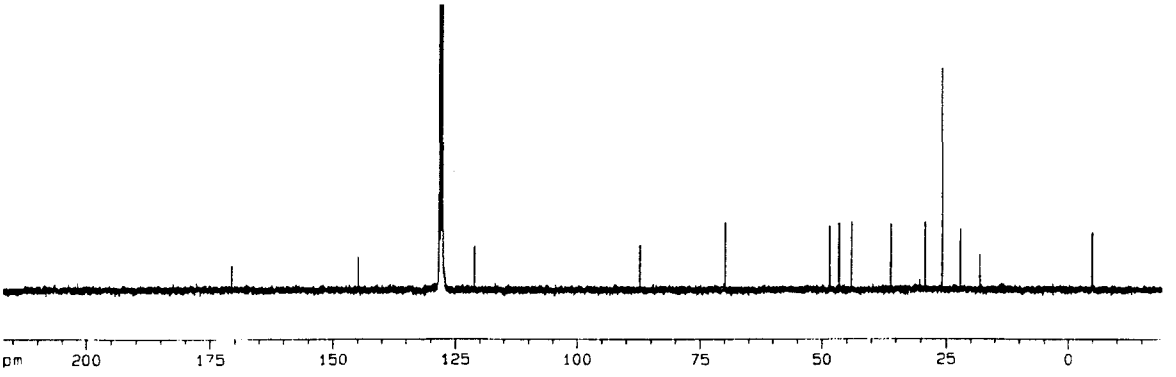
HRMS (EI, m/z) Expected for $C_{18}H_{27}O_6SSiF_3$ [$(M)^+$]: 456.1250, found: 456.1259 (4.40%)

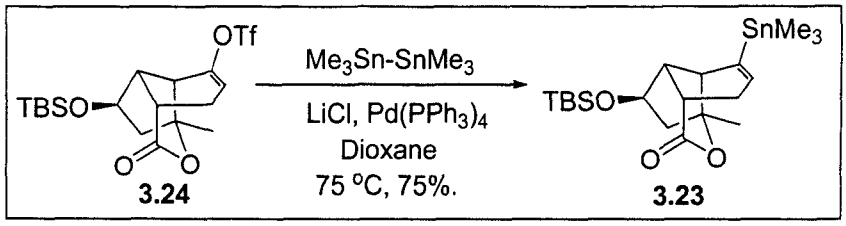


^{1}H NMR (300 MHz, C_6H_6)



^{13}C NMR (75 MHz, C_6H_6)





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-2-oxo-3-oxatricyclo[5.4.0.0^{4,8}]undec-9-en-9-yl trimethylstannane (3.23). Hexamethylditin (118 mg, 0.18 mmol) was added to a mixture of triflate **3.24** (84 mg, 0.18 mmol), LiCl (23 mg, 0.54 mmol), $Pd(PPh_3)_4$ (21 mg, 0.0188 mmol) and dioxane (3.6 mL) at room temperature under an atmosphere of argon. After stirring for 24 h at 75 °C, the reaction was quenched H_2O (5 mL) and the product was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (100% hexanes) provided 65 mg of **3.23** (75%) as a white solid (melting point: 109.7 °C - 112.6 °C).

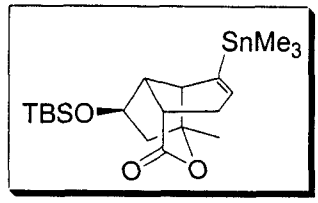
Data for **3.23:**

^{1}H NMR (300 MHz, C_6H_6) δ_{ppm} 5.85 – 5.83 (m, 1H), 3.97 (ddd, J = 9.3, 6.6, 2.6 Hz, 1H), 3.17 (m, 1H), 2.54 (ddd, J = 18.2, 4.5, 2.2 Hz, 1H), 2.12 – 1.99 (m, 2H), 1.93 – 1.89 (m, 1H), 1.83 (dd, J = 14.8, 2.5 Hz, 1H), 1.58 (dd, J = 14.7, 9.6 Hz, 1H), 1.15 (s, 3H), 0.95 (s, 9H), 0.11 (s, 9H), 0.02 (s, 6H)

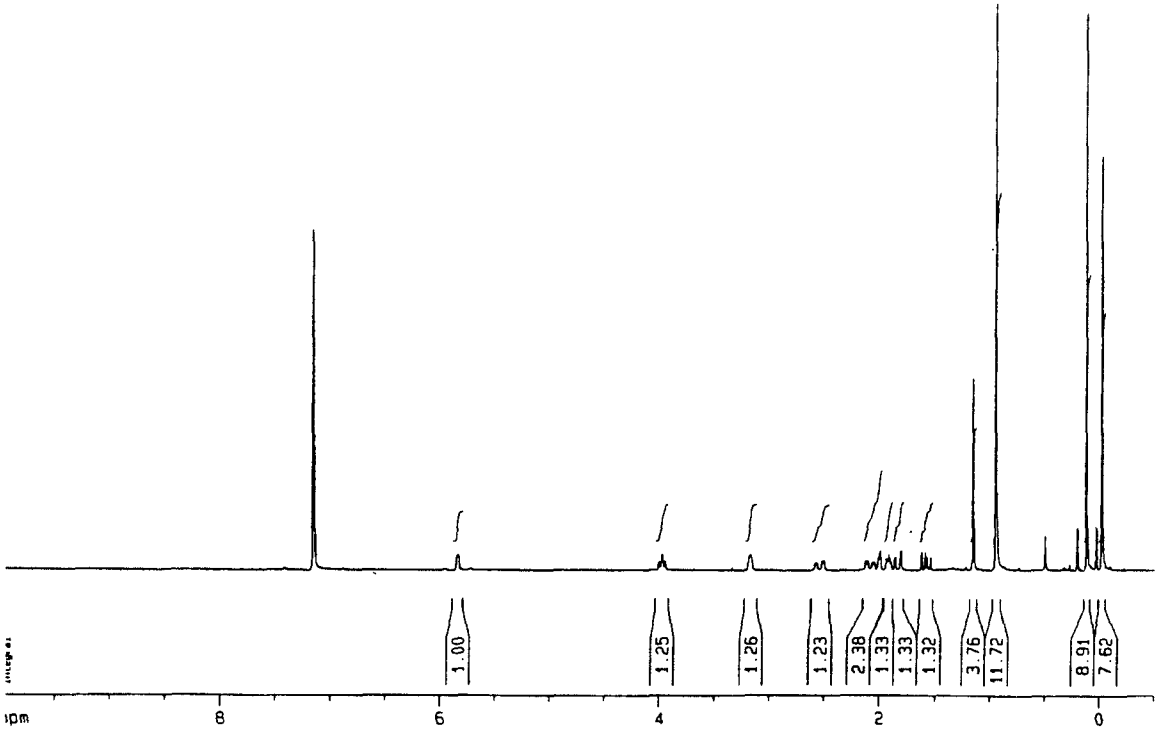
^{13}C NMR (75 MHz, C_6H_6) δ_{ppm} 172.9 (C_4), 142.0 (CH), 137.3 (C_4), 88.0 (C_4), 70.9 (CH), 49.6 (CH_2), 48.4 (CH), 44.5 (CH), 37.1 (CH), 35.0 (CH_2), 26.3 (3xCH_3), 23.2 (CH_3), 18.6 (C_4), -4.3 (CH_3), -4.6 (CH_3), -8.5 (CH_3)

FTIR (neat, cm^{-1}) 2925 (s), 2853 (m), 1726(s), 1251 (s), 1149 (s)

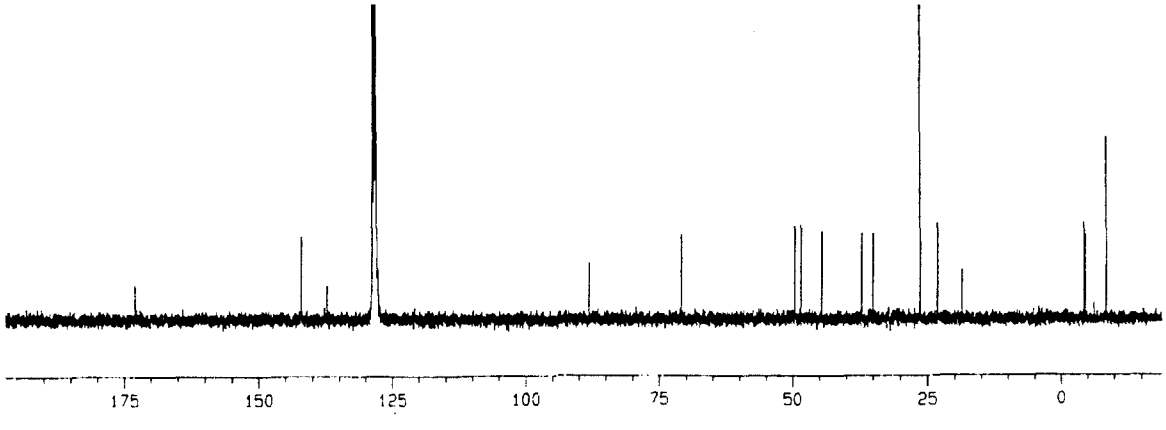
HRMS (EI, m/z) Expected for $C_{19}H_{33}O_3SiSn$ [(M-CH_3)$^+$]: 457.1221, found: 457.1371 (23.73%)

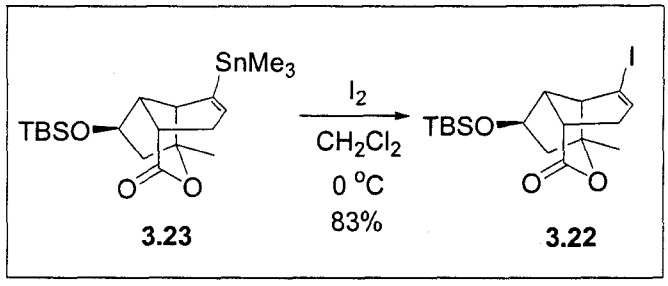


^{1}H NMR (300 MHz, C_6H_6)



^{13}C NMR (75 MHz, C_6H_6)





3.23 3.22

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-butyl-dimethyl-silanyloxy)-9-iodo-4-methyl-3-oxa-tricyclo[5.4.0.0^{4,8}]undec-9-en-2-one (3.22). Iodine (500 mg) was dissolved in CH_2Cl_2 (5 mL) and added drop-wise to a solution of **3.23** (63 mg, 0.133 mmol) in CH_2Cl_2 (2 mL) at 0 °C until a permanent pink color remained. The product was diluted with CH_2Cl_2 (20 mL) and washed with a saturated aqueous $NaHCO_3$ solution. The organic phase was washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (20:1 hexanes: EtOAc) provided 48 mg of **3.22** (83%) as a white solid (melting point: 141.2 °C – 141.8 °C).

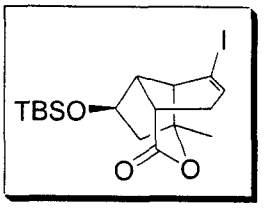
Data for **3.22:**

^{1}H NMR (300 MHz, C_6H_6) δ_{ppm} 6.12 (dd, J = 5.1, 2.5 Hz, 1H), 3.78 (ddd, J = 9.3, 6.7, 2.6 Hz, 1H), 3.06 – 3.04 (m, 1H), 2.20 (ddd, J = 18.3, 5.2, 2.2 Hz, 1H), 2.03 – 2.01 (m, 1H), 1.84 – 1.79 (m, 2H), 1.75 – 1.71 (m, 1H), 1.67 – 1.66 (m, 1H), 1.41 (s, 3H), 0.91 (s, 9H), -0.07 (s, 6H)

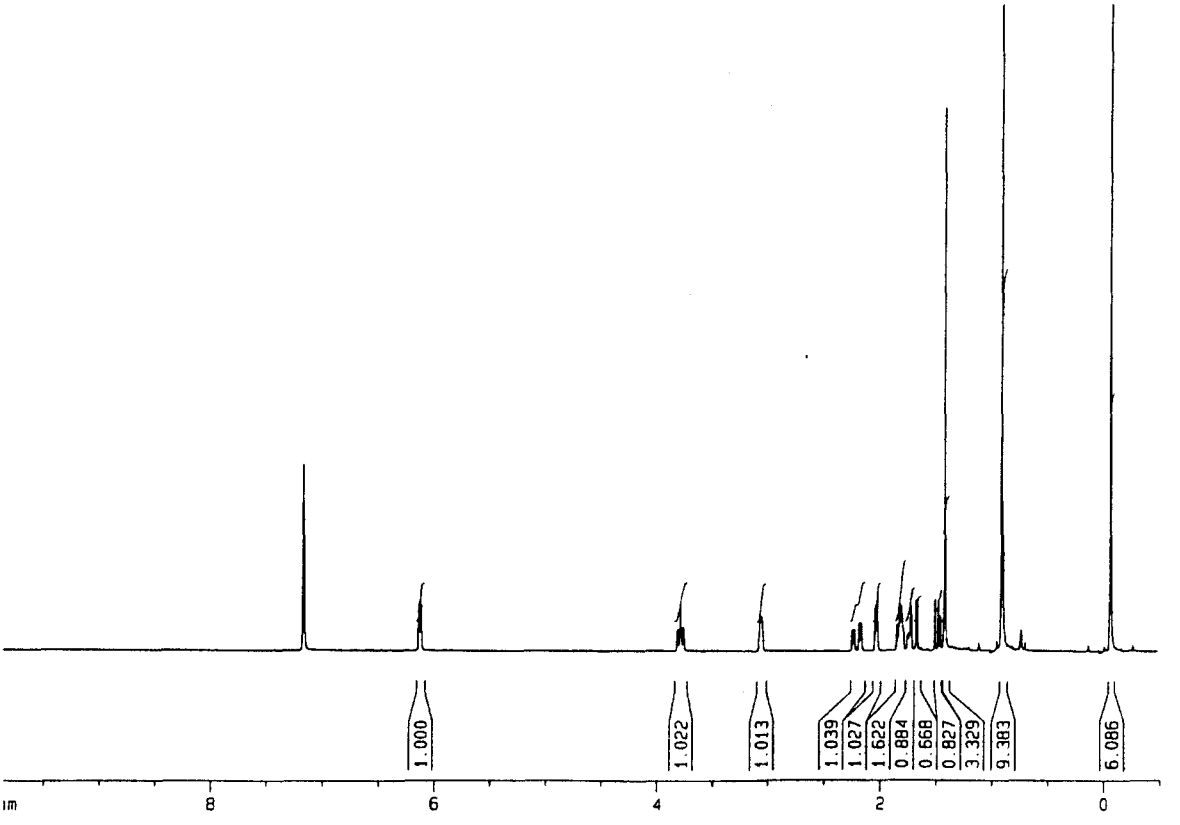
^{13}C NMR (75 MHz, C_6H_6) δ_{ppm} 171.9 (C_4), 140.8 (CH), 89.1 (C_4), 88.4 (C_4), 69.6 (CH), 53.6 (CH), 49.6 (CH_2), 45.9 (CH), 35.8 (CH), 35.5 (CH_2), 26.2 (3xCH_3), 23.5 (CH_3), 18.5 (C_4), -4.4 (CH_3), -4.7 (CH_3)

FTIR (neat, cm^{-1}) 2929 (s), 2856 (m), 1727 (s), 1253 (m), 1092 (m)

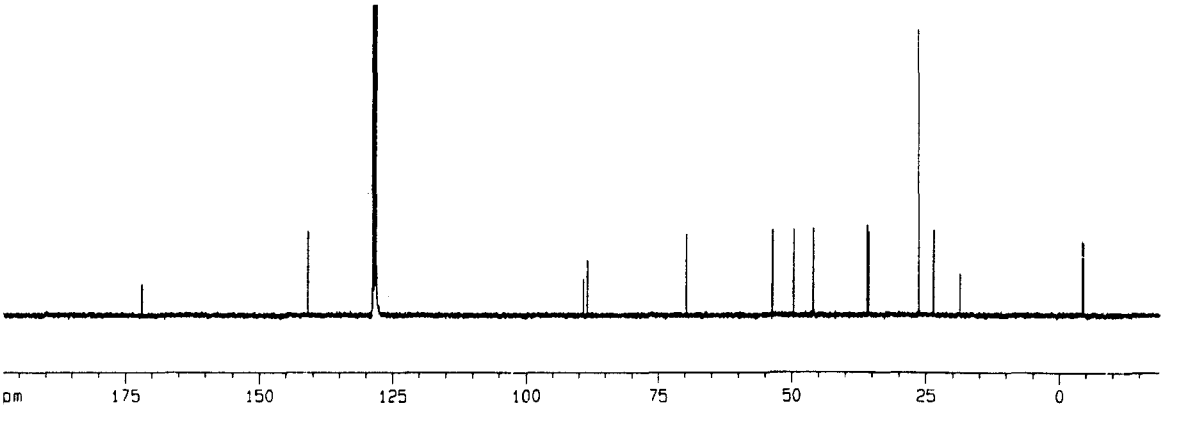
HRMS (EI, m/z) Expected for $C_{17}H_{27}O_3SiI$ [$(M)^+$] 434.0774, found: 434.0759 (2.67%)

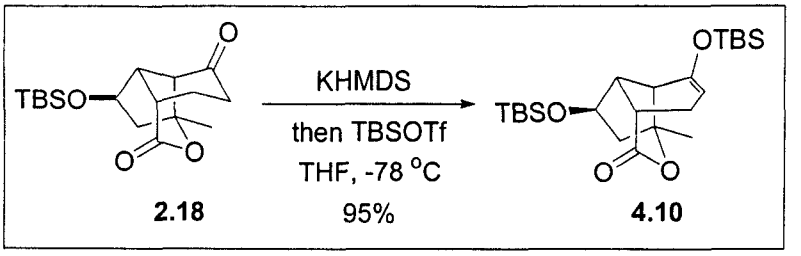


^{1}H NMR (300 MHz, C_6H_6)



^{13}C NMR (75 MHz, C_6H_6)





2.18 **4.10**

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-butyl-dimethyl-silanyloxy)-9-(tert-butyl-dimethyl-silanyloxy)-4-methyl-3-oxa-tricyclo[5.4.0.0^{4,8}]-undec-9-en-2-one (4.10). A solution of ketone **2.18** (30 mg, 0.092 mmol) in THF (1 mL) was slowly added to a mixture of KHMDS (37 mg, 0.18 mmol) in THF (1 mL) at -78 °C and stirred for 30 min. TBSOTf (47 μL, 0.20 mmol) was then added and stirring continued for an additional 30 min. The reaction was quenched with Et_3N at -78 °C and the product was extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (95:5 hexanes: Et_2O) provided 38 mg of **4.10** (95% yield) as a white solid (melting point: 120.4 °C – 120.8 °C).

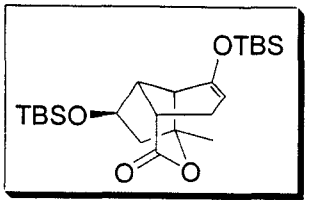
Data for **4.10:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 4.81 (dd, J = 5.4, 2.1 Hz, 1H), 3.98 (ddd, J = 9.3, 6.7, 2.4 Hz, 1H), 3.17 – 3.16 (m, 1H), 2.48 (ddd, J = 17.0, 5.4, 2.5 Hz, 1H), 2.08 – 2.00 (m, 2H), 1.84 (dd, J = 14.7, 2.4 Hz, 1H), 1.79 (d, J = 14.7, 2.4 Hz, 1H), 1.57 (dd, J = 14.6, 9.6 Hz, 1H), 1.35 (s, 3H), 0.96 (s, 9H), 0.95 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H)

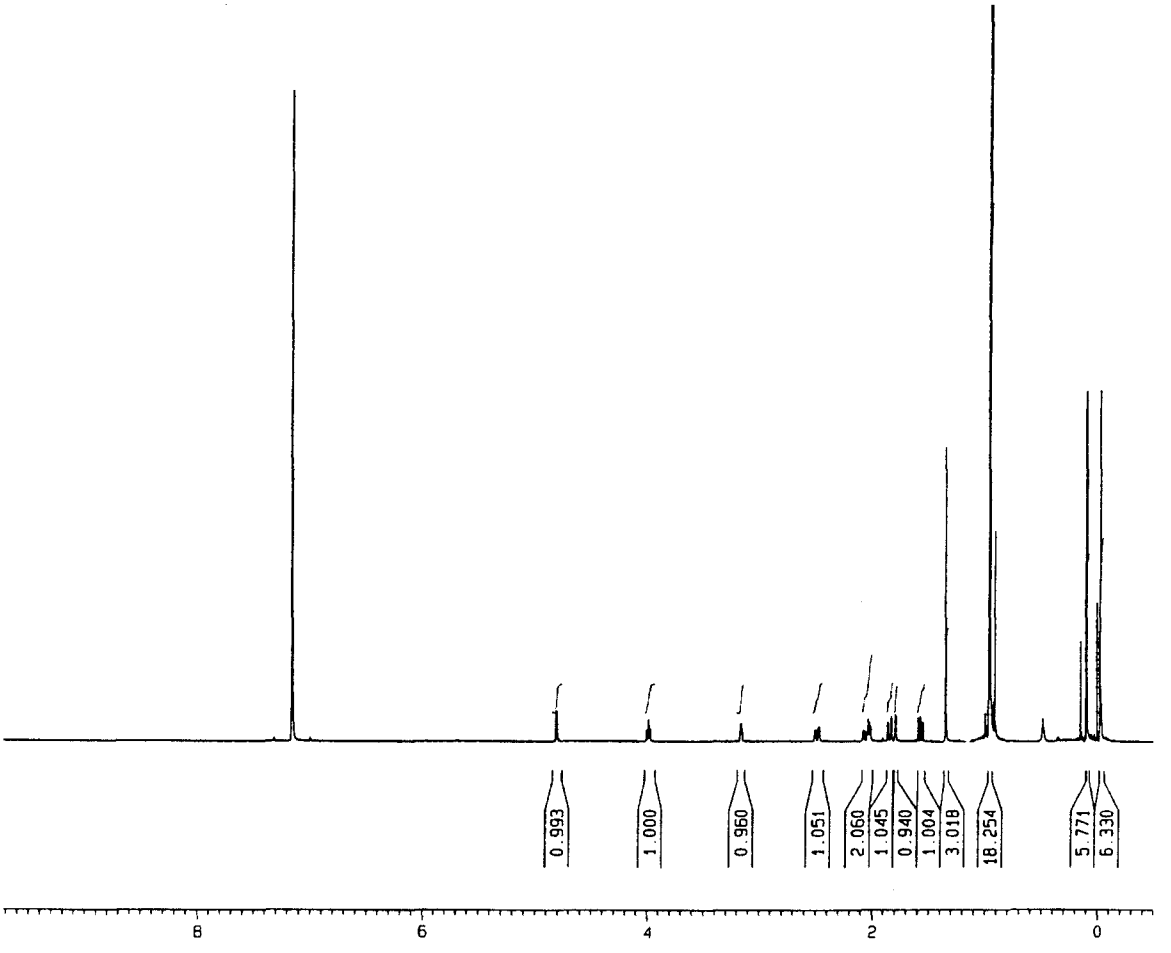
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} δ 172.6 (C_4), 148.3 (C_4), 103.7 (CH), 87.8 (C_4), 71.0 (CH), 49.5 (CH_2), 48.9 (CH), 44.9 (CH), 37.5 (CH), 30.0 (CH_2), 26.3 (3xCH_3), 26.2 (3xCH_3), 23.6 (CH), 18.6 (C_4), 18.4 (C_4), -4.1 (CH_3), -4.2 (CH_3), -4.4 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2955 (s), 2930 (s), 2895 (s), 2857 (s), 1739 (s), 1661 (m), 1472 (m), 1254 (s), 1150 (m)

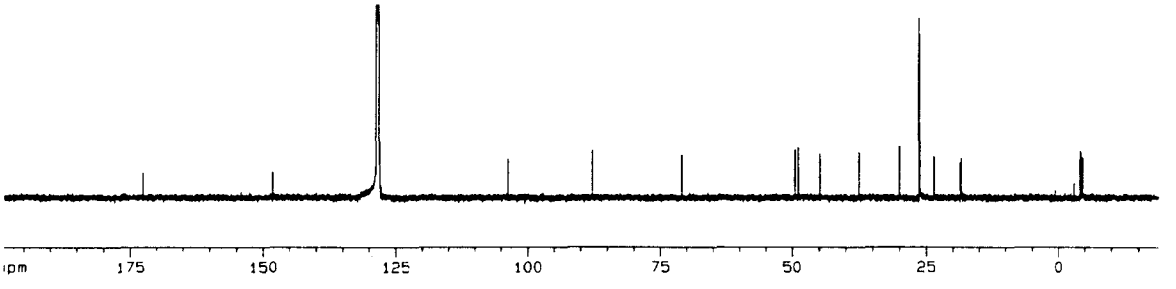
HRMS (EI, m/z) Expected for $C_{19}H_{33}O_4Si_2$ [(M- $C_4H_9)^+$]: 381.1917, found: 381.6339 (50.6%)

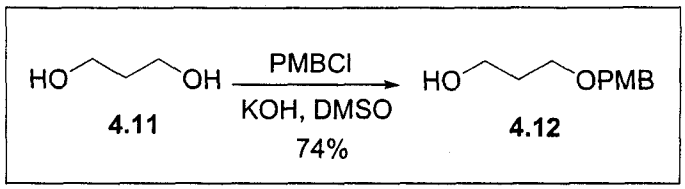


^{1}H NMR (500 MHz, C_6D_6)



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





3-(4-Methoxybenzyloxy)propan-1-ol (4.12). A flame-dried round bottom flask was charged with 1,3-propanediol (1.0 g, 13.1 mmol), DMSO (2.6 mL) and finely ground KOH (773 mg, 13.7 mmol) and cooled to 0 °C. PMBCl (890 μL, 6.6 mmol) was then added and stirring continued for 2 h at 0 °C. The reaction was then quenched with a saturated aqueous solution of NH_4Cl and the product was extracted with Et_2O (3x50 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (1:4 EtOAc:hexanes) provided 1.90 g of **4.12** (74%) as a clear colorless oil.

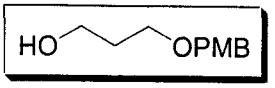
Data for **4.12:**

^{1}H NMR (300 MHz, Acetone d_6) δ_{ppm} 7.28 – 7.25 (m, 2H), 6.92 – 6.88 (m, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.67 – 3.61 (m, 2H), 3.57 – 3.53 (m, 3H), 1.78 (quint, J = 6.3 Hz, 2H)

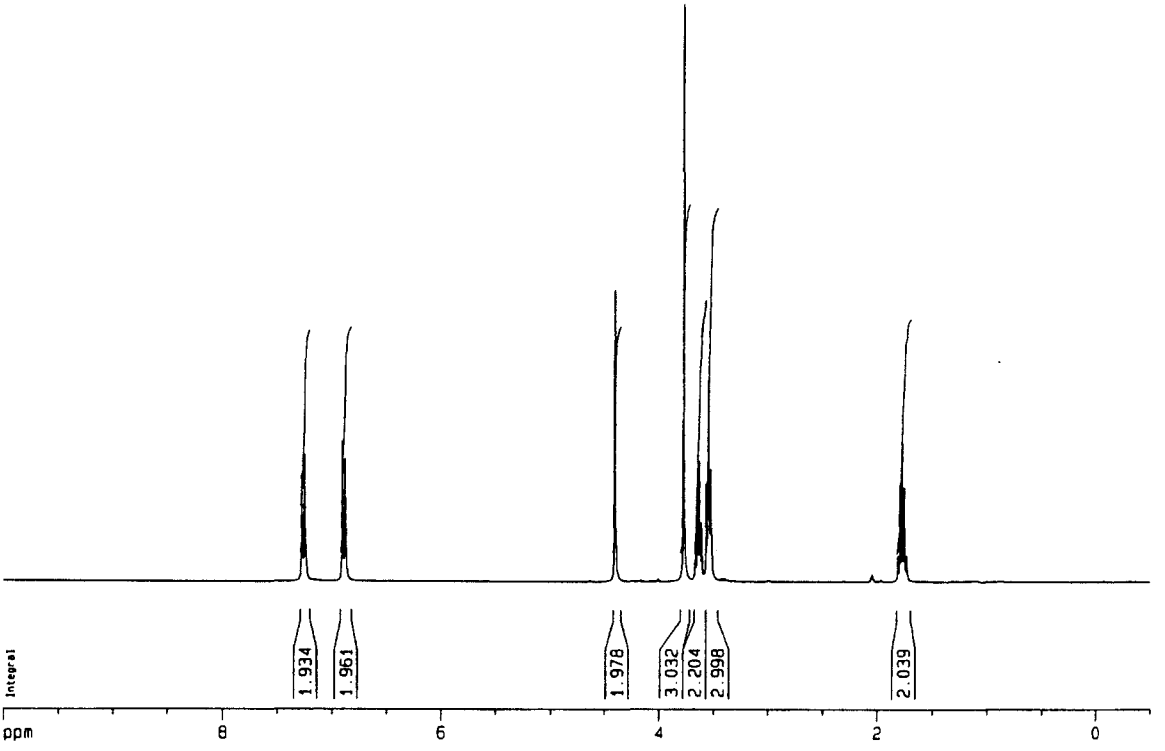
^{13}C NMR (75 MHz, Acetone d_6) δ_{ppm} 160.1 (C_4), 131.9 (C_4), 129.9 (CH), 114.4 (CH), 73.0 (CH_2), 68.1 (CH_2), 60.0 (CH_2), 55.5 (CH_3), 33.9 (CH_2)

FTIR (neat, cm^{-1}) 3420 (brs), 2936 (m), 2865 (m), 1613, 1513

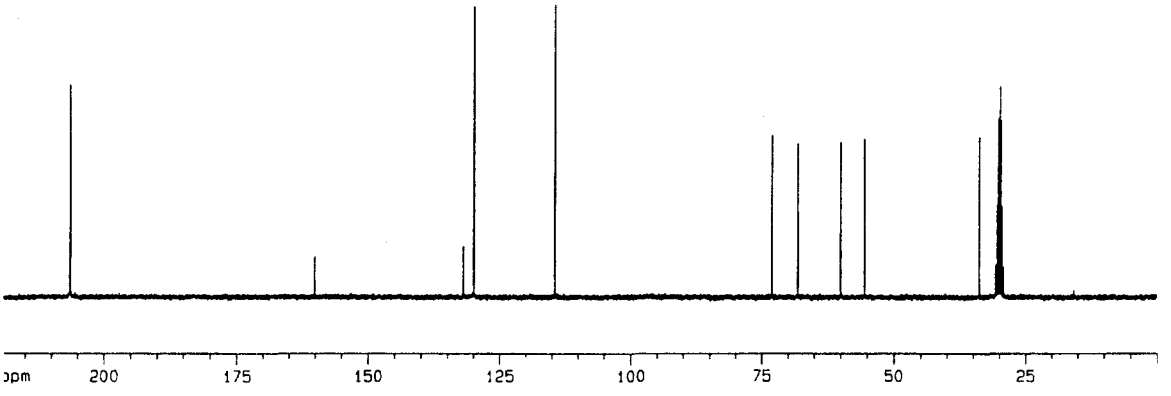
HRMS (EI, m/z) Expected for $C_{11}H_{16}O_3$ [$(M)^+$]: 196.1099, found: 196.1085 (12.8%)

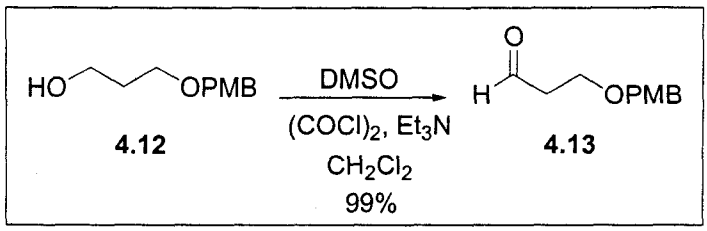


^{1}H NMR (300 MHz, Acetone d_6)



^{13}C NMR (75 MHz, Acetone d_6)





3-(4-Methoxybenzyloxy)propanal (4.13). Dimethylsulfoxide (433 μL, 6.11 mmol) was added drop-wise to a solution of oxalyl chloride (565 μL, 3.06 mmol) in CH_2Cl_2 (20 mL) at -78 °C and stirred for 20 min. A solution of alcohol **4.12** (500 mg, 2.54 mmol) in CH_2Cl_2 (5 mL) was then cannulated into the flask and stirring continued for 1.5 h at -78 °C. Et_3N (1.78 mL, 12.7 mmol) was then added and the reaction was warmed to room temperature and stirred for an additional 20 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the product was extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (5:1 hexanes:Et_2O) provided 490 mg of aldehyde **4.13** (99%) as a clear colorless oil.

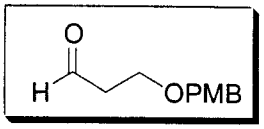
Data for **4.13:**

^{1}H NMR (300 MHz, Acetone d_6) δ_{ppm} 9.71 (t, J = 2.0 Hz, 1H), 7.29 – 7.25 (m, 2H), 6.93 – 6.88 (m, 2H), 4.44 (s, 2H), 3.80 – 3.76 (m, 5H), 2.65 – 2.60 (m, 2H)

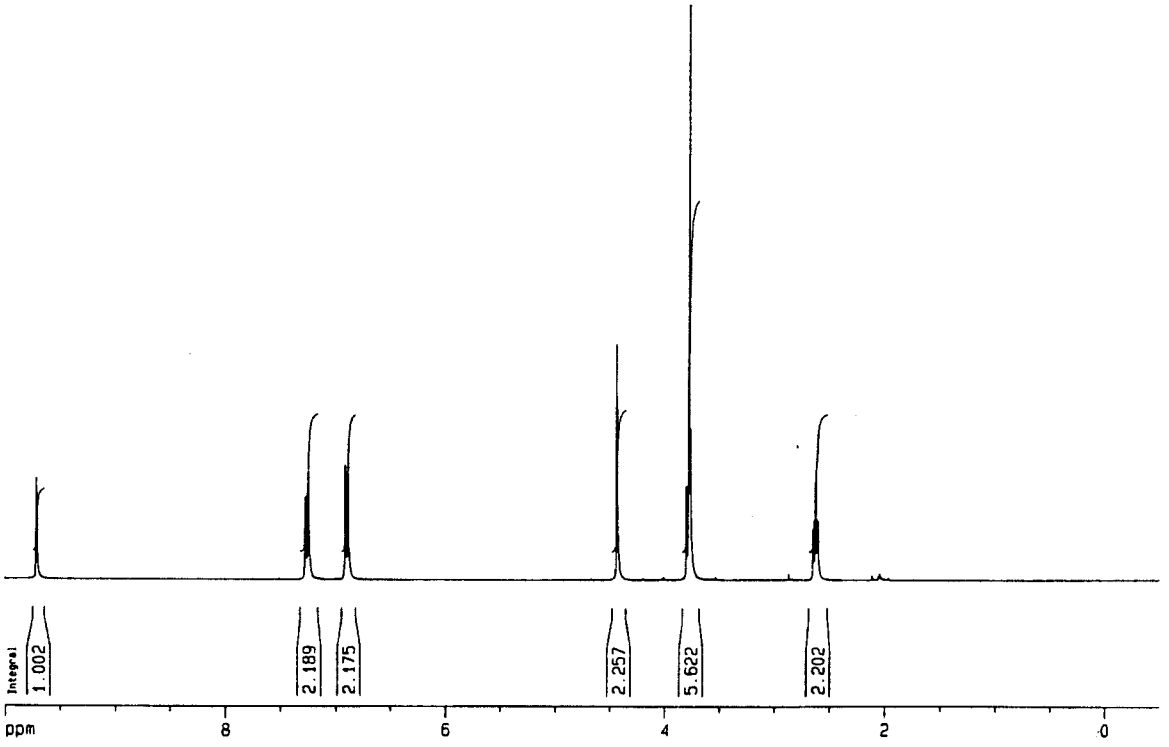
^{13}C NMR (75 MHz, Acetone d_6) δ_{ppm} 201.9 (C_4), 160.2 (C_4), 131.4 (C_4), 130.1 (CH), 114.5 (CH), 73.1 (CH_2), 64.5 (CH_2), 55.5 (CH_3), 44.5 (CH_2)

FTIR (neat, cm^{-1}) 3002 (m), 2861 (m), 2838 (m), 2733 (m), 1724 (s), 1513 (s), 1248(s), 1092 (s)

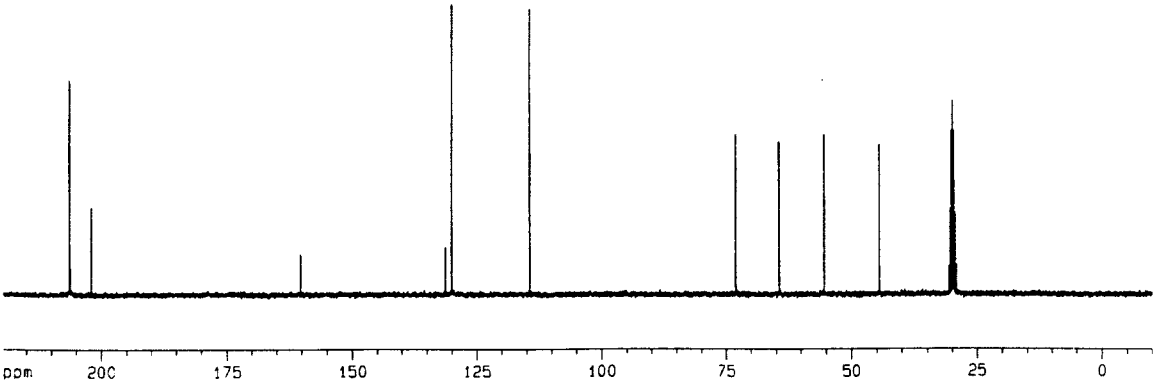
HRMS (EI, m/z) Expected for $C_{11}H_{14}O_3$ [$(M)^+$]: 194.0943, found: 194.0928 (10.6%)

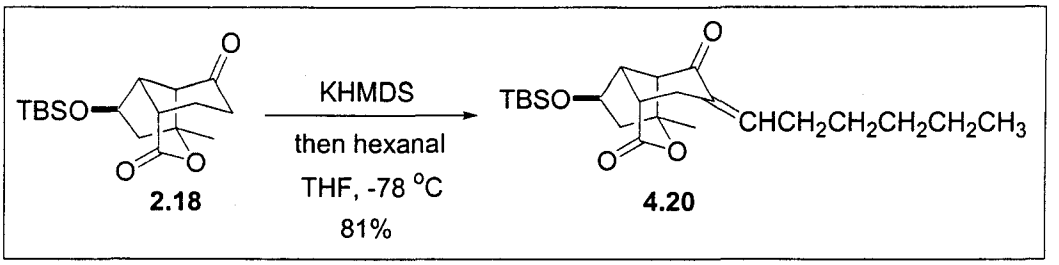


^{1}H NMR (300 MHz, Acetone d_6)



^{13}C NMR (75 MHz, Acetone d_6)





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-hexylidene-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undecane-2,9-dione (4.20). A solution of ketone **2.18** (20 mg, 0.062 mmol) in THF (2 mL) was slowly added to a mixture of KHMDS (21 mg, 0.12 mmol) in THF (1 mL) at -78 °C and stirred for 30 min. Hexanal (75 μL, 0.62 mmol) was added and stirring was continued for an additional 30 min at -78 °C. The reaction was then quenched with 0.5 N HCl (at -78 °C) and the flask was warmed to room temperature. The product was extracted with CH_2Cl_2 (3x30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (20:1 hexanes:Et_2O) provided 21 mg of **4.20** (81%) as a clear colorless oil.

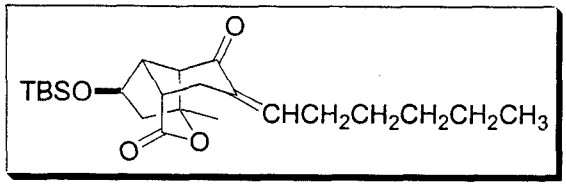
Data for **4.20:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 7.11 – 7.08 (m, 1H), 3.85 (ddd, J = 9.0, 5.8, 2.8 Hz, 1H), 3.29 – 3.28 (m, 1H), 3.05 – 3.01 (m, 1H), 2.09 – 2.05 (m, 2H), 2.04 – 1.99 (m, 1H), 1.79 – 1.70 (m, 3H), 1.46 (dd, J = 9.6, 5.2 Hz, 1H), 1.33 (s, 3H), 1.17 – 1.11 (m, 4H), 1.09 – 1.03 (m, 2H), 0.96 (s, 9H), 0.83 – 0.80 (m, 3H), -0.02 (s, 3H), -0.05 (s, 3H)

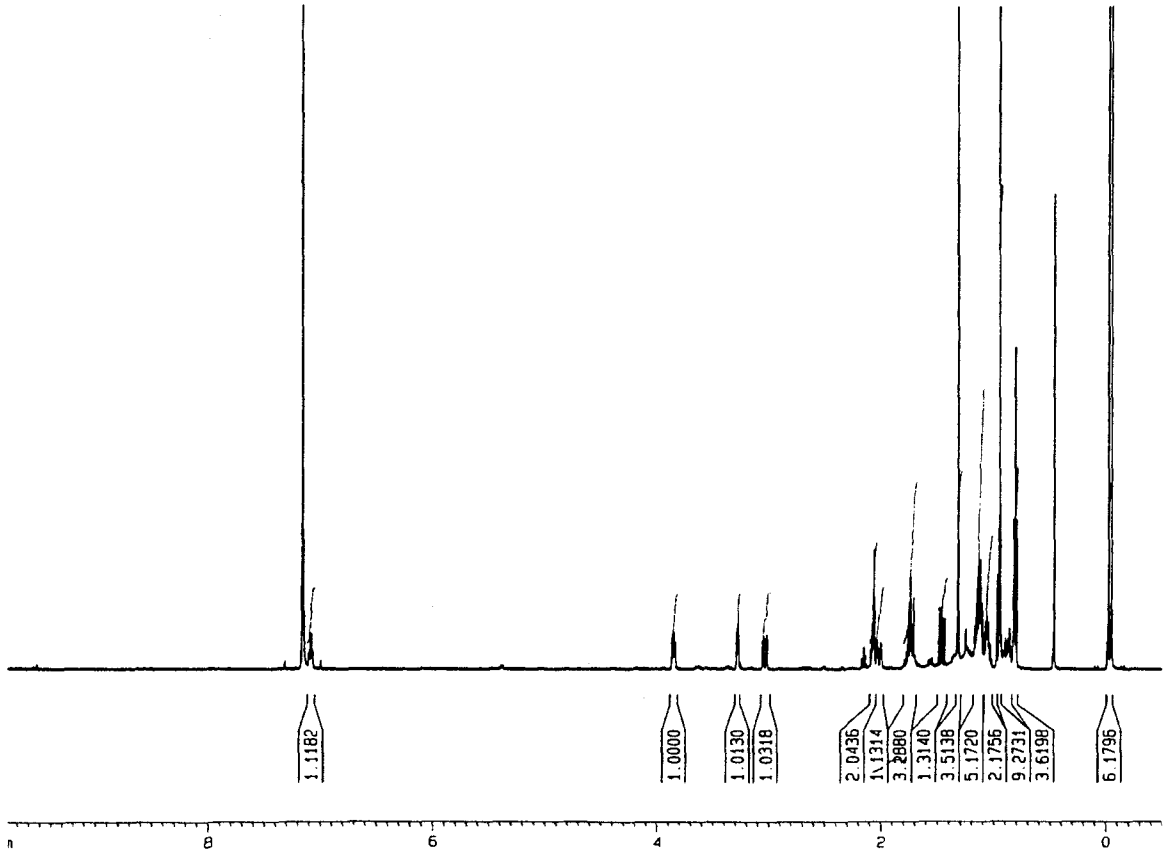
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 195.1 (C_4), 171.5 (C_4), 144.1 (CH), 132.7 (C_4), 88.9 (C_4), 71.5 (CH), 55.6 (CH), 49.2 (CH_2), 45.8 (CH), 38.2 (CH), 32.1 (CH_2), 31.7 (CH_2), 28.55 (CH_2), 28.49 (CH_2), 26.3 (3xCH_3), 23.1 (CH_2), 22.7 (CH_3), 18.6 (C_4), 14.5 (CH_3), -4.4 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2955 (s), 2930 (s), 2858 (s), 1744 (s), 1686 (m), 1611 (m), 1464 (m) 1147 (m)

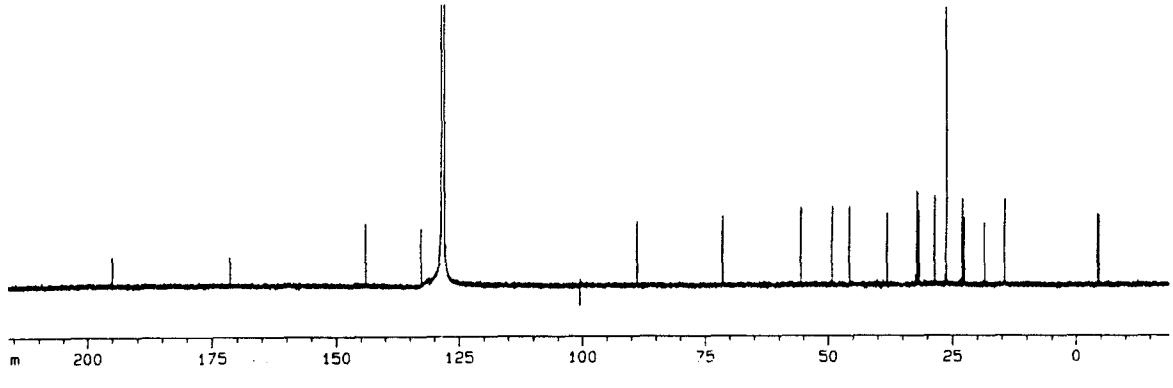
HRMS (EI, m/z) Expected for $C_{19}H_{29}O_4Si$ $[(M-C_4H_9)^+]$: 349.1835, found: 349.1802 (13.2%)

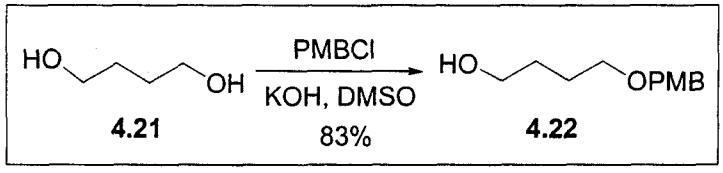


^{1}H NMR (500 MHz, C_6D_6)



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





4.21 4.22

4-(4-Methoxybenzyloxy)butan-1-ol (4.22). A flame-dried round bottom flask was charged with 1,4-butanediol (2.0 g, 22 mmol), DMSO (8.9 mL) and finely ground KOH (1.30 g, 23.3 mmol) and cooled to 0 °C. PMBCl (1.50 mL, 6.21 mmol) was added and the contents of the flask were stirred for 2 h at 0 °C. The reaction was then quenched with an aqueous solution of NH_4Cl and the product was extracted with Et_2O (3x50 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography on silica gel (1:4 EtOAc:hexanes) provided 3.87 g of **4.22** (83%) as a clear colorless oil.

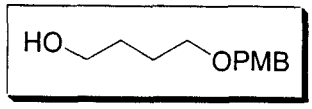
Data for **4.22:**

^{1}H NMR (300 MHz, Acetone d_6) δ_{ppm} 7.28 – 7.25 (m, 2H), 6.90 – 6.88 (m, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.57 – 3.55 (m, 3H), 3.45 (t, J = 5.9 Hz, 2H), 1.69 – 1.58 (m, 4H)

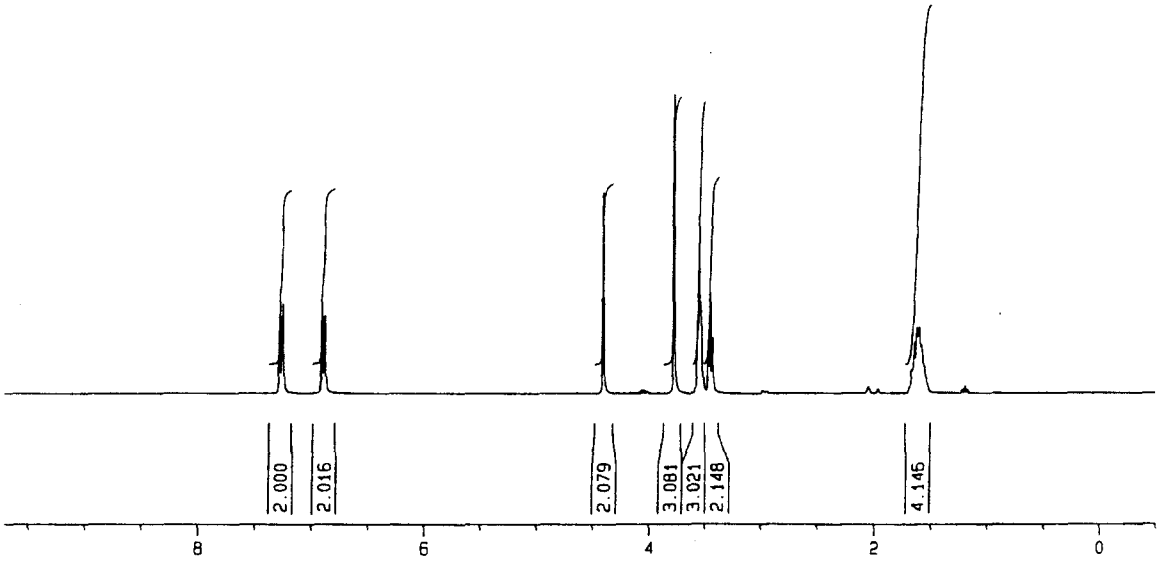
^{13}C NMR (75 MHz, Acetone d_6) δ_{ppm} 160.1 (C_4), 131.9 (C_4), 129.9 (CH), 114.0 (CH), 72.9 (CH_2), 70.6 (CH_2), 62.3 (CH_2), 55.5 (CH_3), 30.7 (CH_2), 27.2 (CH_2)

FTIR (neat, cm^{-1}) 3393 (brs), 2938 (s), 2863 (s), 1513 (m), 1464 (m), 1247 (s), 1096 (s)

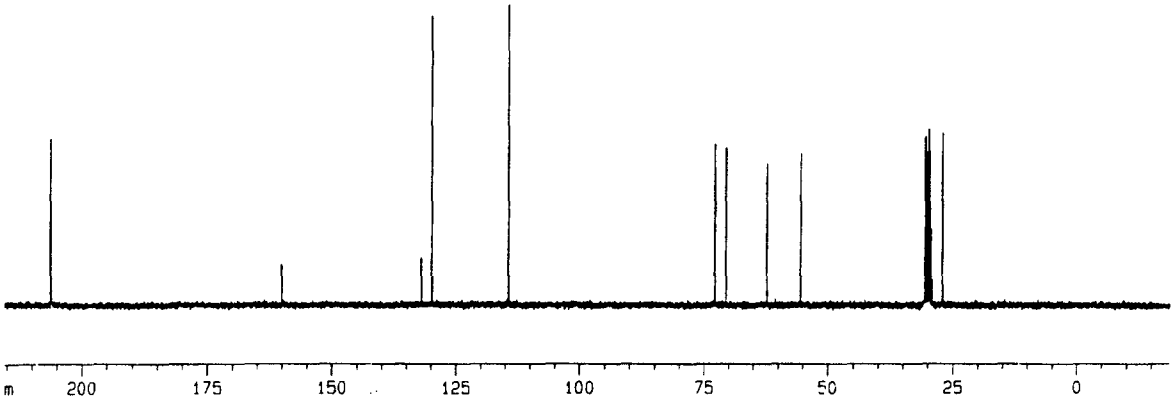
HRMS (EI, m/z) Expected for $C_{12}H_{18}O_3$ [$(M)^+$]: 210.1256, found: 210.1276 (5.2%)

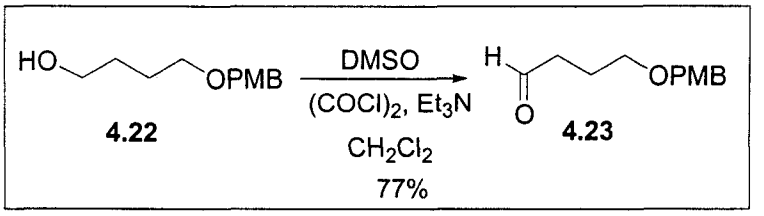


^{1}H NMR (300 MHz, Acetone d_6)



^{13}C NMR (75 MHz, Acetone d_6)





4-(4-Methoxybenzyloxy)butanal (4.23). Dimethylsulfoxide (405 μL, 5.71 mmol) was added drop-wise to a solution of oxalyl chloride (249 μL, 2.85 mmol) in CH_2Cl_2 (18 mL) at -78 °C and stirred for 20 min. A solution of alcohol **4.22** (500 mg, 2.38 mmol) in CH_2Cl_2 (6 mL) was then cannulated into the flask and stirring continued for 1.5 h at -78 °C. Et_3N (1.66 mL, 11.9 mmol) was added and the reaction was warmed to room temperature and stirred for an additional 20 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the product was extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (5:1 hexanes: Et_2O) provided 382 mg of aldehyde **4.23** (77%) as a clear colorless oil.

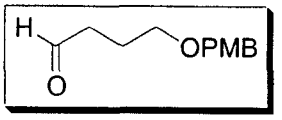
Data for **4.23:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 9.74 (t, J = 1.6 Hz, 1H), 7.27 – 7.21 (m, 2H), 6.89 – 6.85 (m, 2H), 4.41 (s, 2H), 3.78 (s, 3H), 3.46 (t, J = 6.1 Hz, 2H), 2.51 (dt, J = 7.1, 1.6 Hz, 2H), 1.95 – 1.87 (m, 2H)

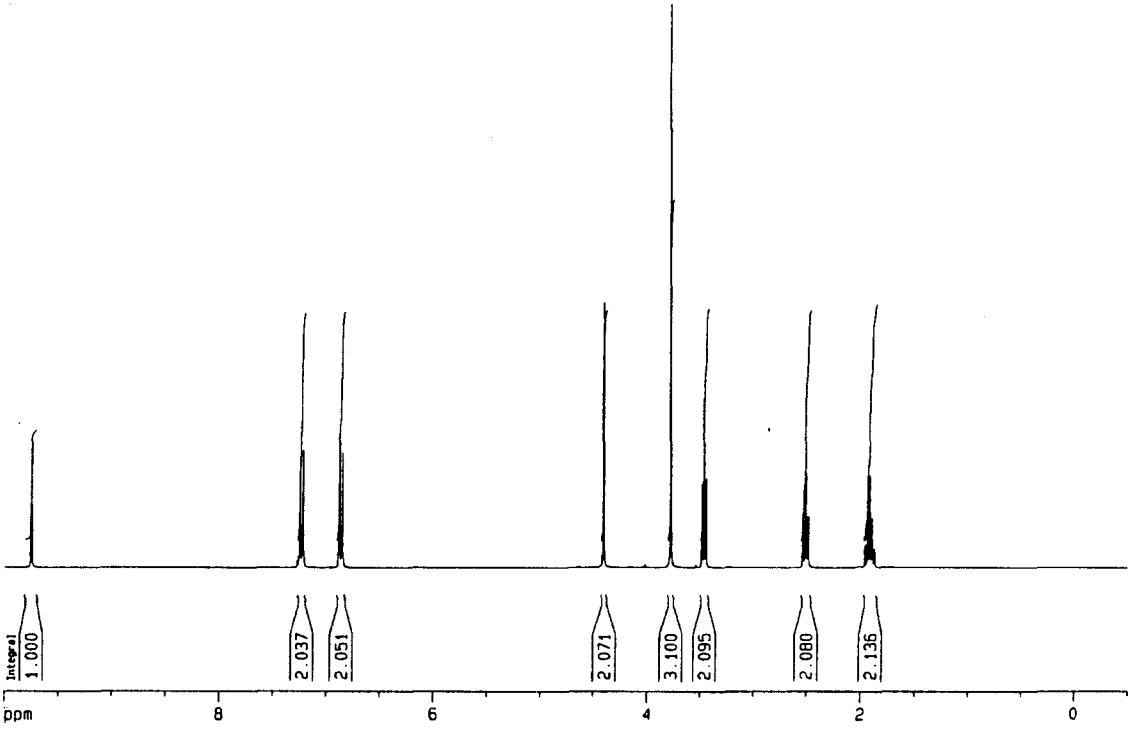
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 202.4 (CH), 159.2 (C_4), 130.4 (C_4), 129.3 (CH), 113.8 (CH), 72.6 (CH_2), 68.9 (CH_2), 55.3 (CH_3), 41.0 (CH_2), 22.6 (CH_2)

FTIR (neat, cm^{-1}) 2951 (s), 2858 (s), 2837 (m), 2726 (m), 1722 (s), 1513 (s), 1247 (s)

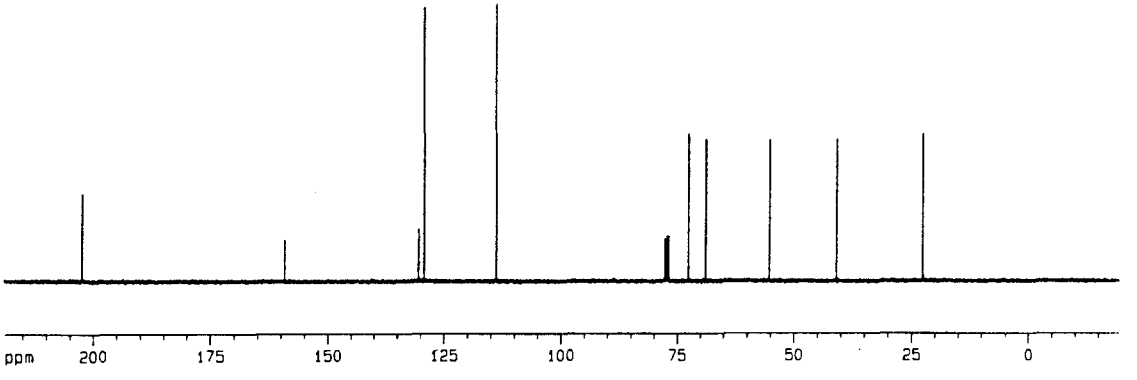
HRMS (EI, m/z) Expected for $C_{12}H_{16}O_3$ [$(M)^+$]: 208.1099, found: 208.1113 (5.7%)

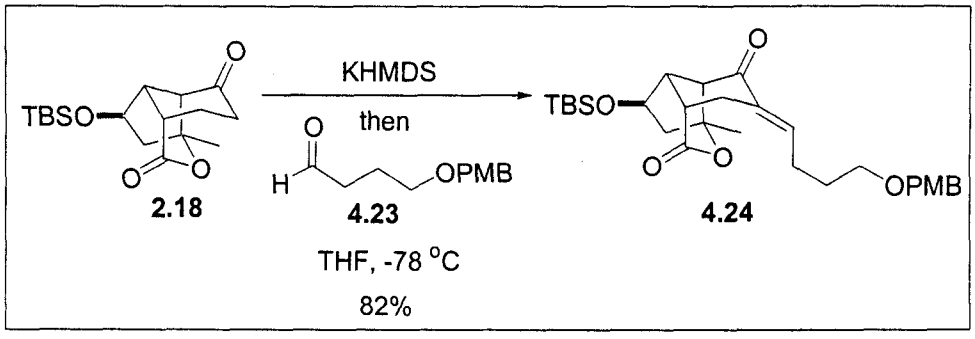


^{1}H NMR (300 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,10*E*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-(4-(4-methoxybenzyloxy)butylidene)-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undecane-2,9-dione (4.24). A solution of ketone **2.18** (50 mg, 0.15 mmol) in THF (1 mL) was slowly added to a mixture of KHMDS (54 mg, 0.32 mmol) in THF (1 mL) at – 78 °C and stirred for 30 min. A solution of aldehyde **4.23** (67 mg, 0.32 mmol) in THF (1 mL) was cannulated into the flask and the contents were stirred for an additional 30 min. The reaction was then quenched with 0.5 N HCl (at -78 °C) and the flask was warmed to room temperature. The product was extracted with CH_2Cl_2 (3x30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) provided 53 mg of **4.24** (82%) as a clear colorless oil.

Data for **4.24:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 7.28 – 7.26 (m, 2H), 7.09 – 7.06 (m, 1H), 6.85 – 6.81 (m, 2H), 4.35 (d, J = 11.5 Hz, 1H), 4.28 (d, J = 11.6 Hz, 1H), 3.87 – 3.83 (m, 1H), 3.32 (s, 3H), 3.25 – 3.24 (m, 1H), 3.20 – 3.11 (m, 2H), 3.07 – 3.04 (m, 1H), 2.07 – 2.04 (m, 2H), 2.00 – 1.89 (m, 3H), 1.73 (dd, J = 14.9, 2.8 Hz, 1H), 1.55 – 1.39 (m, 3H), 1.32 (s, 3H), 0.95 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H)

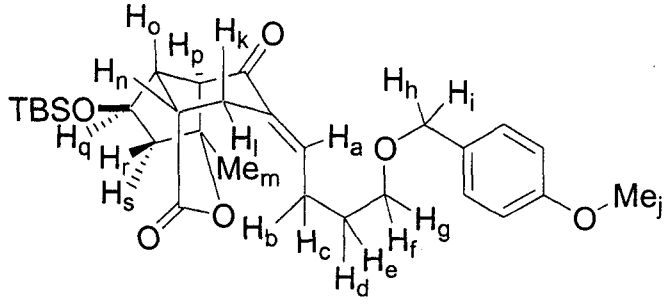
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 195.1 (C_4), 171.7 (C_4), 160.1 (C_4), 143.6 (CH), 133.1 (C_4), 131.7 (C_4), 129.9 (CH), 114.4 (CH), 88.9 (C_4), 73.0 (CH_2), 71.5 (CH), 69.2 (CH_2), 55.6

(CH), 55.1 (CH_3), 49.2 (CH_2), 45.7 (CH), 38.1 (CH), 31.6 (CH_2), 29.0 (CH_2), 26.3 (3xCH_3), 25.4 (CH_2), 22.7 (CH_3), 18.6 (C_4), -4.4 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2932 (s), 2857 (s), 1744 (s), 1684 (s), 1512 (m), 1458 (m), 1247 (s)

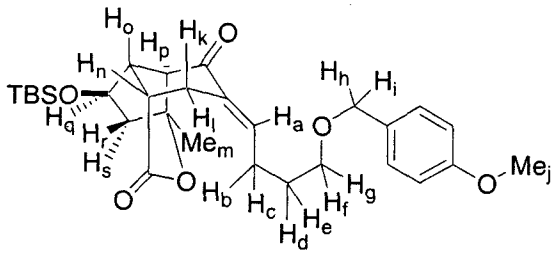
HRMS (EI, m/z) Expected for $C_{29}H_{42}O_6Si$ [$(M)^+$]: 514.2751, found: 514.2742 (5.6%)

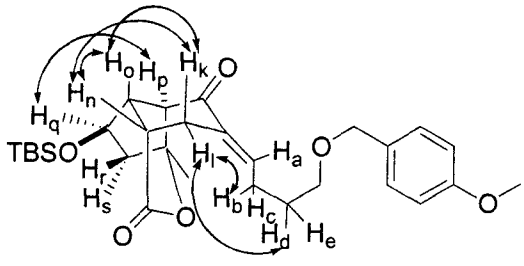
Table 7.1: *COSY data for* ***4.24***



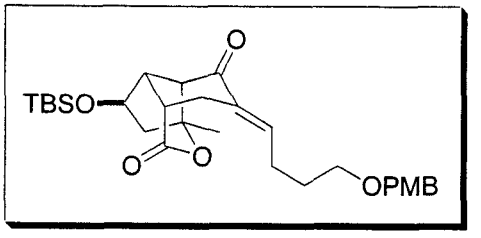
COSY data			
Proton (δ)	**Correlation**	**Proton (δ)**	**Correlation**
H_a (7.08)	$H_{(b,c,k)}$	Aromatic (6.84)	Aromatic (7.27)
$H_{(b,c,k)}$ (1.95)	H_a, $H_{(d,e,s)}$, H_l, H_n	H_l (3.05)	$H_{(b,c,k)}$, H_n
$H_{(d,e,s)}$ (1.46)	$H_{(b,c,k)}$, $H_{(f,g)}$, H_q, H_r	Me_m (1.32)	-
$H_{(f,g)}$ (3.16)	$H_{(d,e,s)}$	H_n (3.25)	$H_{(b,c,k)}$, H_l, $H_{(o,p)}$
$H_{(h\ or\ i)}$ (4.35)	$H_{(h\ or\ i\ at\ 4.28)}$	$H_{(o,p)}$ (2.05)	H_n, H_q
$H_{(h\ or\ i)}$ (4.28)	$H_{(h\ or\ i\ at\ 4.35)}$	H_q (3.78)	$H_{(o,p)}$, H_r, $H_{(d,e,s)}$
Me_j (3.32)	-	H_r (1.73)	$H_{(d,e,s)}$, H_q
Aromatic (7.27)	Aromatic (6.84)		

Table 7.2: NOESY data for ***4.24***

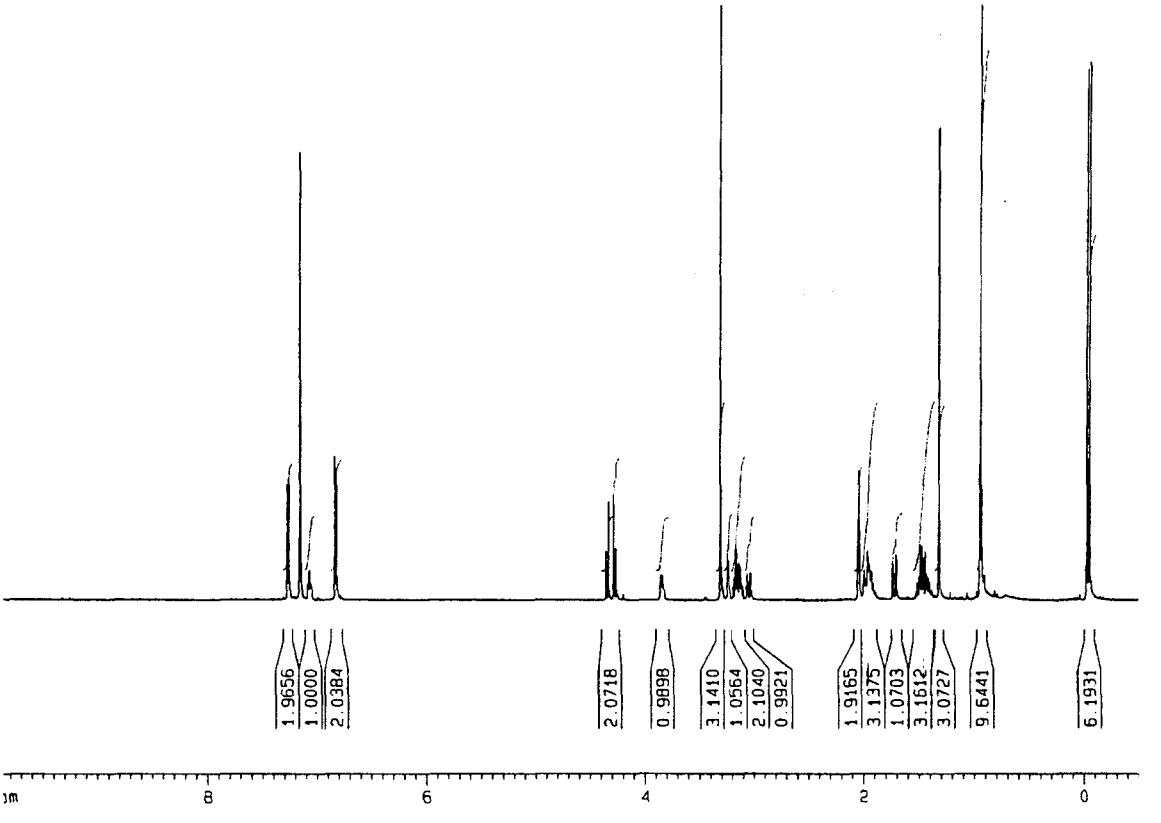




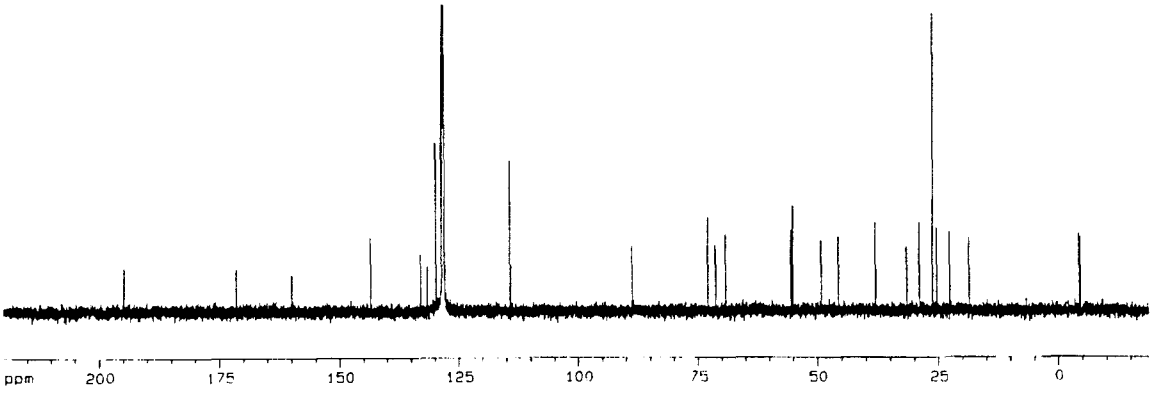
NOESY data			
Proton (δ)	**nOe with proton**	**Proton (δ)**	**nOe with proton**
H_a (7.08)	$H_{(b,c,k)}$, $H_{(d,e,s)}$, $H_{(f,g)}$	Aromatic (6.84)	Aromatic (7.27), Me_j
$H_{(b,c,k)}$ (1.95)	H_a, $H_{(d,e,s)}$, $H_{(f,g)}$, H_l, H_n, $H_{(o,p)}$	H_l (3.05)	$H_{(b,c,k)}$, $H_{(d,e,s)}$, H_n
$H_{(d,e,s)}$ (1.46)	H_a, $H_{(b,c,k)}$, $H_{(f,g)}$, H_l, H_n, $H_{(o,p)}$, H_q, H_r, Me_m	Me_m (1.32)	$H_{(o,p)}$, H_r, H_s
$H_{(f,g)}$ (3.16)	H_a, $H_{(b,c,k)}$, $H_{(d,e,s)}$, $H_{(h \text{ or } i \text{ at } 4.28)}$, $H_{(h \text{ or } i \text{ at } 4.35)}$, Aromatic (7.27)	H_n (3.25)	$H_{(b,c,k)}$, $H_{(d,e,s)}$, H_l, $H_{(o,p)}$, H_q
$H_{(h \text{ or } i)}$ (4.35)	Aromatic (7.27), $H_{(f,g)}$, $H_{(h \text{ or } i \text{ at } 4.28)}$	$H_{(o,p)}$ (2.05)	$H_{(b,c,k)}$, $H_{(d,e,s)}$, Me_m, H_n, H_q,
$H_{(h \text{ or } i)}$ (4.28)	Aromatic (7.27), $H_{(f,g)}$, $H_{(h \text{ or } i \text{ at } 4.35)}$	H_q (3.78)	$H_{(d,e,s)}$, H_n, $H_{(o,p)}$, H_r
Me_j (3.32)	Aromatic (6.84)	H_r (1.73)	$H_{(d,e,s)}$, Me_m, H_q
Aromatic (7.27)	$H_{(h \text{ or } i \text{ at } 4.28)}$, $H_{(h \text{ or } i \text{ at } 4.35)}$, $H_{(f,g)}$, Aromatic (6.84)		

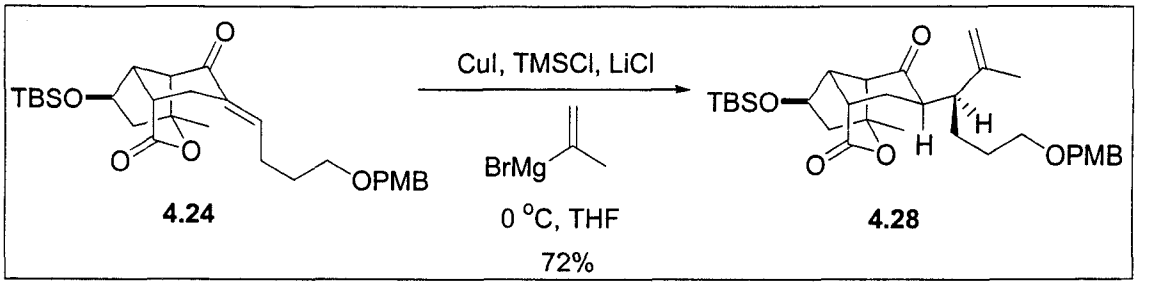


^{1}H NMR (500 MHz, C_6D_6)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,10*R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(3*S*)-6-(4-methoxybenzyloxy)-2-methylhex-1-en-3-yl]-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undecane-2,9-dione (4.28). Lithium chloride (6 mg, 0.1 mmol) was flame dried under vacuum in a round bottom flask. After cooling to room temperature, the flask was filled with argon and CuI (13 mg, 0.07 mmol) was added followed by THF (1 mL). The suspension was then cooled to 0 °C. Ketone **4.24** (15 mg, 0.035 mmol) was cannulated into the mixture followed by the drop-wise addition of freshly distilled TMSCl (180 μL, 1.4 mmol). After stirring at 0 °C for 10 min, isopropenylmagnesium bromide (706 μL, 0.353 mmol) was added. The reaction was stirred for 4 h at 0 °C and then quenched with Et_3N (2 mL) and poured into water. The product was extracted with Et_2O (3x30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (20:1 hexanes: EtOAc) provided 13 mg of **4.28** (72%) as a clear colorless oil.

Data for **4.28:**

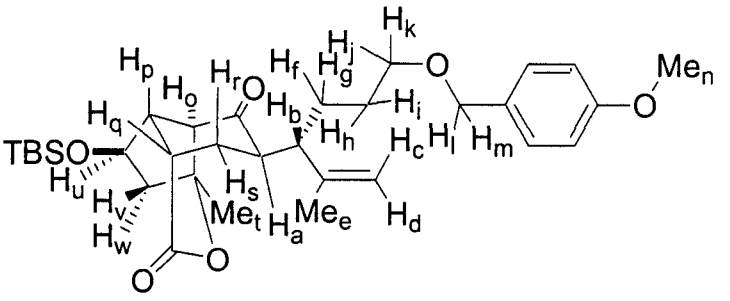
^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 7.29 – 7.27 (m, 2H), 6.84 – 6.81 (m, 2H), 4.80 – 4.79 (m, 1H), 4.73 – 4.72 (m, 1H), 4.36 (s, 2H), 3.77 (ddd, J = 9.0, 6.2, 2.5 Hz, 1H), 3.41 – 3.35 (m, 2H), 3.31 (s, 3H), 3.07 – 3.04 (m, 1H), 2.74 (ddd, J = 11.0, 7.4, 4.2 Hz, 1H), 2.36 (dt, J = 14.0, 6.4 Hz, 1H), 2.17 (ddd, J = 13.5, 6.4, 4.3 Hz, 1H), 2.07 – 2.02 (m, 2H), 1.95 – 1.88 (m, 1H), 1.73 – 1.58 (m, 3H), 1.47 (s, 3H), 1.40 – 1.35 (m, 1H), 1.31 (dd, J = 14.5, 9.5 Hz, 1H), 1.24 (ddd, J = 13.5, 13.5, 2.9 Hz, 1H), 1.12 (s, 3H), 0.95 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H)

^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 207.8 (C_4), 171.1 (C_4), 160.0 (C_4), 145.4 (C_4), 132.0 (C_4), 129.7 (CH), 114.9 (CH_2), 114.4 (CH), 87.5 (C_4), 73.1 (CH_2), 71.3 (CH), 70.6 (CH_2), 59.4 (CH), 55.1 (CH_3), 50.5 (CH), 49.3 (CH_2), 48.9 (CH), 46.7 (CH), 39.4 (CH), 33.6 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 26.2 (3xCH_3), 22.4 (CH_3), 20.2 (CH_3), 18.5 (C_4), -4.5 (CH_3), -4.7 (CH_3)

FTIR (neat, cm^{-1}) 2952 (s), 2931 (s), 2856 (m), 1750(s), 1702 (s), 1643 (m), 1513 (m), 1248 (s), 1100 (s)

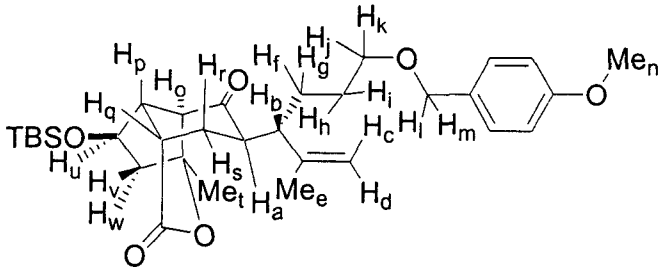
HRMS (EI, m/z) Expected for $C_{32}H_{48}O_6Si$ [$(M)^+$]: 556.3220, found: 556.3229 (5.8%)

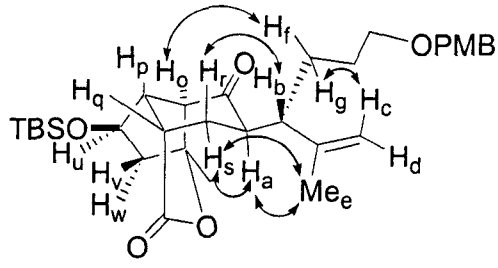
Table 7.3: *COSY data of* ***4.28***



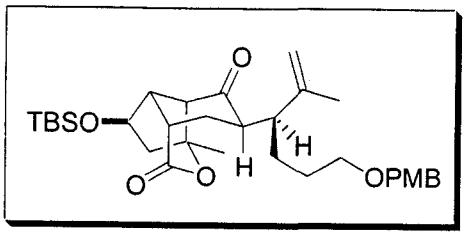
COSY data			
Proton (δ)	**Correlation**	**Proton (δ)**	**Correlation**
H_a (2.36)	H_b, H_s, H_r	$H_{(l,m)}$ (4.36)	-
H_b (2.74)	H_a, H_f, H_g	Me_n	-
H_c (4.73)	H_d	$H_{(o,p)}$ (2.05)	H_q, H_u
H_d (4.80)	H_c	H_q (3.06)	$H_{(o,p)}$, H_r, H_s
Me_e (1.47)	-	H_r (1.24)	H_a, H_q, H_s
H_f (1.92)	H_b, $H_{(h,i,w)}$, H_g	H_s (2.17)	H_a, H_r, H_q
H_g (1.37)	H_b, $H_{(h,i,w)}$, H_f	Me_t (1.12)	-
$H_{(h,i,w)}$ (1.66)	H_f, H_g, $H_{(j,k)}$, H_u, H_v	H_u (3.77)	$H_{(o,p)}$, $H_{(h,i,w)}$, H_v
$H_{(j,k)}$ (3.37)	$H_{(h,i,w)}$	H_v (1.31)	H_u, $H_{(h,i,w)}$
Aromatic (7.28)	Aromatic (6.83)	Aromatic (6.83)	Aromatic (7.28)

Table 7.4: NOESY data of ***4.28***

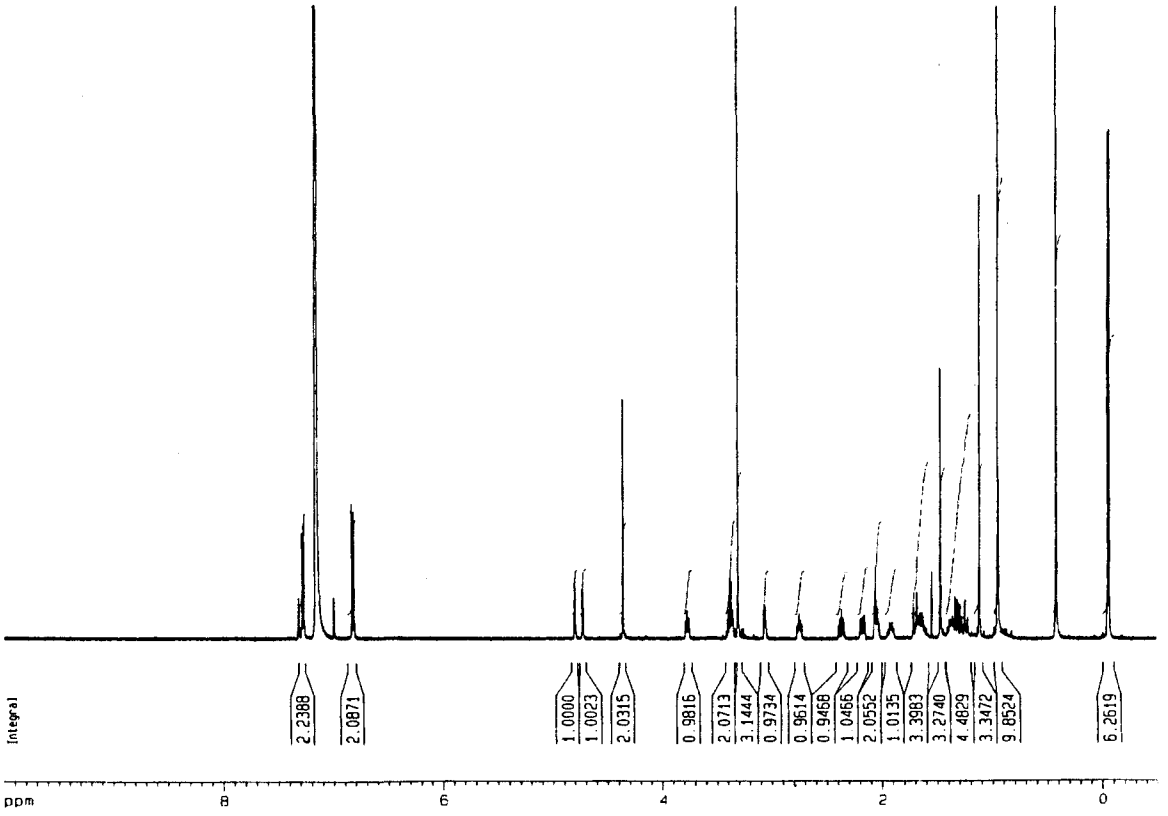




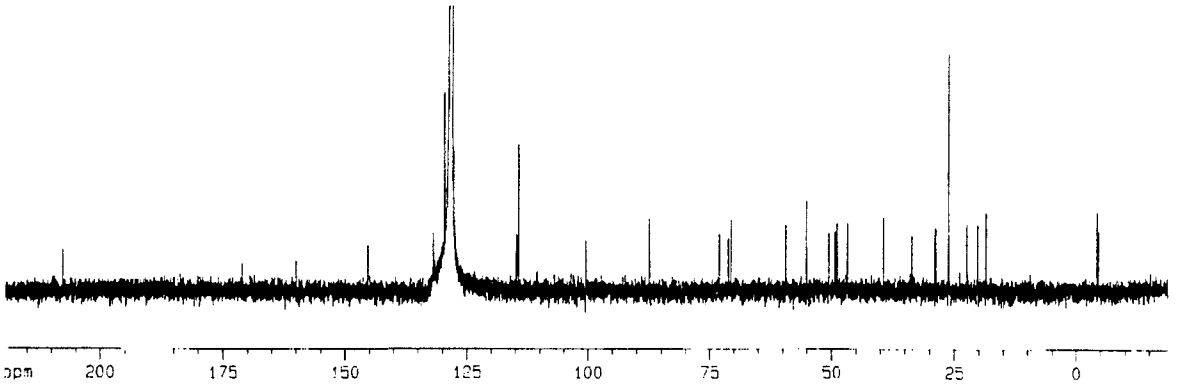
NOESY data			
Proton (δ)	**nOe with proton**	**Proton (δ)**	**nOe with proton**
H_a (2.36)	H_b, H_f, H_s, Me_e, Me_t	$H_{(l,m)}$ (4.36)	$H_{(j,k)}$, Aromatic (6.83)
H_b (2.74)	H_a, H_c, H_f, $H_{(h,i,w)}$, H_r, Me_e	Me_n (3.31)	Aromatic (6.83)
H_c (4.73)	H_b, H_d, H_g	$H_{(o,p)}$ (2.05)	H_f, $H_{(h,i,w)}$, H_q, H_r, H_u, Me_t
H_d (4.80)	H_c, Me_e	H_q (3.06)	$H_{(o,p)}$, H_r, H_s
Me_e (1.47)	H_a, H_b, H_d, $H_{(h,i,w)}$, H_r, H_s	H_s (2.17)	H_a, H_q, H_r, Me_e
H_f (1.92)	H_a, H_b, H_g, $H_{(h,i,w)}$, $H_{(j,k)}$	H_r (1.24)	H_b, $H_{(o,p)}$, H_q, H_s, Me_e
H_g (1.37)	H_c, H_f, $H_{(h,i,w)}$, $H_{(j,k)}$	Me_t (1.12)	H_a, $H_{(h,i,w)}$, $H_{(o,p)}$, H_v
$H_{(h,i,w)}$ (1.66)	H_b, H_f, H_g, $H_{(j,k)}$, H_u, H_v, Me_e, Me_t,	H_u (3.77)	$H_{(h,i,w)}$, $H_{(o,p)}$, H_v
$H_{(j,k)}$ (3.37)	H_f, H_g, $H_{(h,i,w)}$, $H_{(l,m)}$	H_v (1.31)	H_u, $H_{(h,i,w)}$, Me_t
Aromatic (6.83)	Aromatic 7.28, $H_{(l,m)}$, Me_n	Aromatic (7.28)	Aromatic 6.38

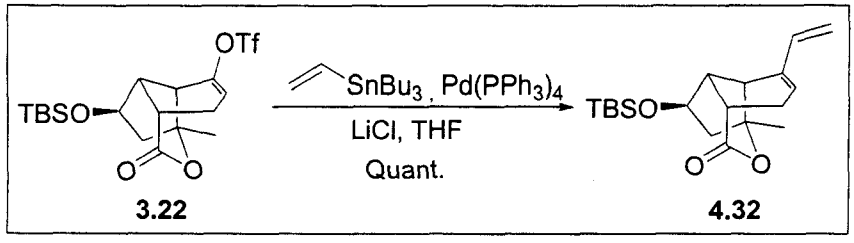


^{1}H NMR (500 MHz, C_6D_6)



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





3.22 4.32

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-9-vinyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-9-en-2-one (4.32). Lithium chloride (139 mg, 3.29 mmol) was place into a Schlenk tube and flame dried under vacuum. After cooling to room temperature, the vessel was filled with argon and a solution of $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) and vinyl triflate **3.22** (500 mg, 1.10 mmol) in THF (6 mL) was added, followed by tributyl(vinyl)tin (320 μL, 1.10 mmol). The yellow mixture was placed into a 55 °C oil bath for 12 h. The reaction was then quenched with H_2O, extracted with EtOAc (3x20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes: EtOAc) furnished 364 mg of **4.32** (quantitative yield) as a white solid. (melting point: 114.3 °C – 116.7 °C).

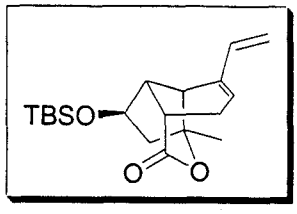
Data for **4.32:**

^{1}H NMR (300 MHz, C_6H_6) δ_{ppm} 6.23 (dd, J = 17.7 Hz, 11.0 Hz, 1H), 5.55 – 5.52 (m, 1H), 5.00 – 4.88 (m, 2H), 4.01 (ddd, J = 9.4, 6.6, 2.7 Hz, 1H), 3.15 – 3.14 (m, 1H), 2.50 (ddd, J = 19.2, 4.9, 1.9 Hz, 1H), 2.11 – 2.10 (m, 1H), 2.05 – 1.97 (m, 1H), 1.87 – 1.80 (m, 2H), 1.63 (dd, J = 14.8, 9.6 Hz, 1H), 1.16 (s, 3H), 0.95 (s, 9H), -0.01 (m, 6H)

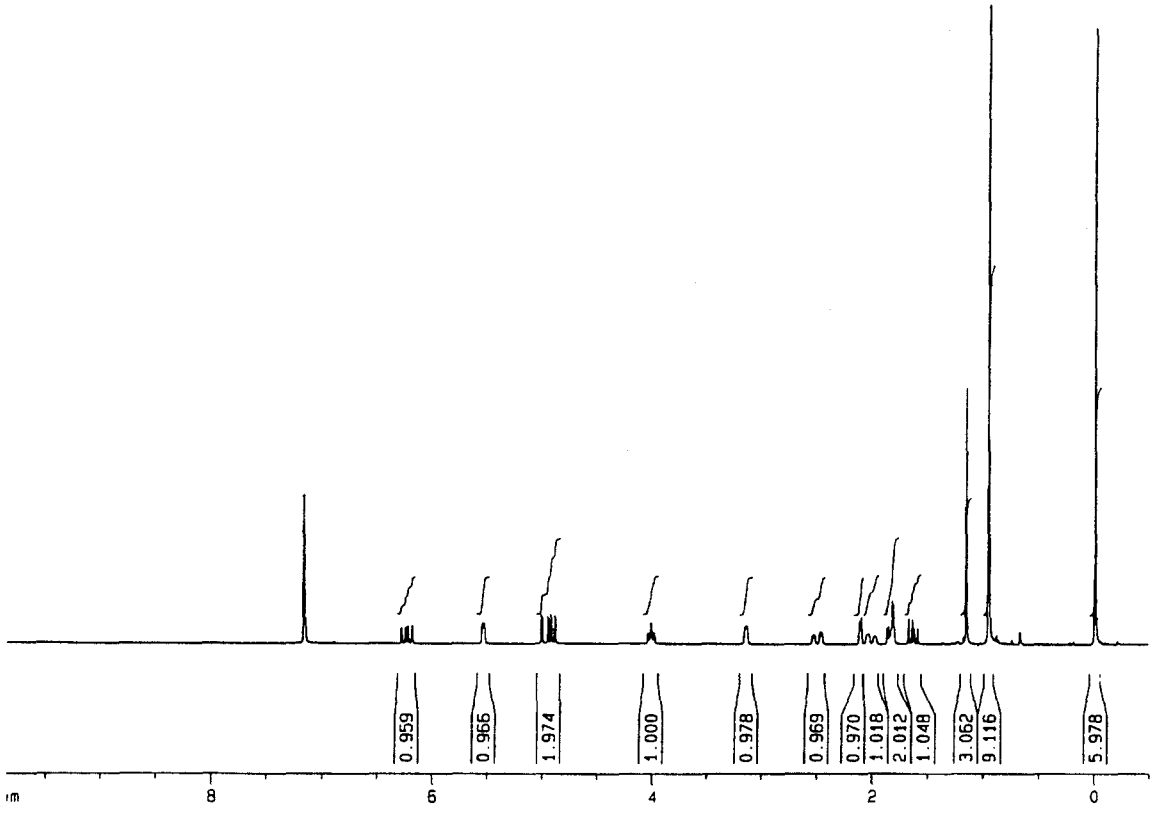
^{13}C NMR (75 MHz, C_6H_6) δ_{ppm} 172.7 (C_4), 139.8 (CH), 133.6 (C_4), 131.7 (CH), 112.0 (CH_2), 88.6 (C_4), 71.1 (CH), 49.8 (CH_2), 44.3 (CH), 41.9 (CH), 37.3 (CH), 32.6 (CH_2), 26.3 (3xCH_3), 24.3 (CH_3), 18.6 (C_4), -4.3 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2930 (s), 2857 (s), 1735 (s), 1255 (m), 1097(s), 836 (s)

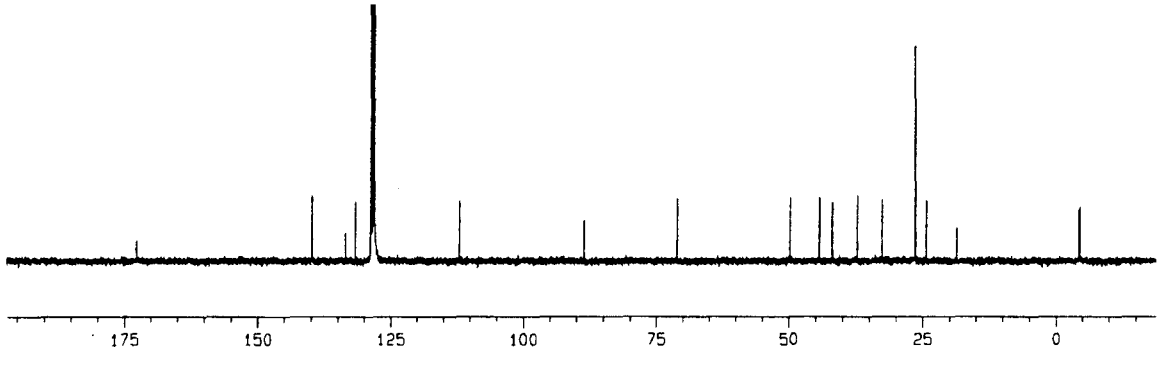
HRMS (EI, m/z) Expected for $C_{19}H_{30}O_3Si$ [$(M)^+$] 334.1964, found: 334.1961 (1.17%)

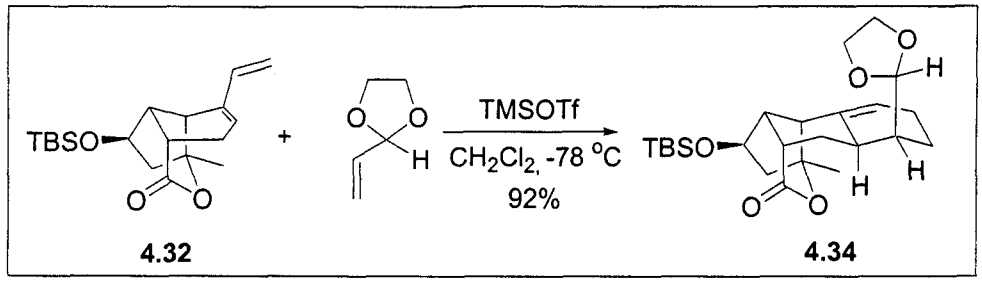


^{1}H NMR (300 MHz, C_6H_6)



^{13}C NMR (75 MHz, C_6H_6)





4.32 4.34

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,13*R*,14*R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-13-(1,3-dioxolane)-3-oxatetracyclo[8,3,2,$0^{7,8}0^{9,14}$]pentadeca-9-en-2-one (4.34). Trimethylsilyl triflate (10 μL, 0.060 mmol) was added to a solution of diene **4.32** (20 mg, 0.060 mmol) and 2-vinyl-1,3-dioxolane (12 μL, 0.12 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C. After stirring for 30 min, the reaction treated with Et_3N (1 mL) (at -78 °C). The solution was poured in water (50 mL) and the product was extracted with CH_2Cl_2 (3x30 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (9:1 hexanes: EtOAc) provided 24 mg of **4.34** (92% yield) as a white foam.

Data for **4.34:**

^{1}H NMR (300 MHz, C_6H_6) δ_{ppm} 5.41 – 5.40 (m, 1H), 4.82 (d, J = 6.8 Hz, 1H), 4.02 (ddd, J = 9.2, 6.7, 2.5 Hz, 1H), 3.47 – 3.44 (m, 2H), 3.32 - 3.29 (m, 2H), 3.29 – 3.27 (m, 1H), 2.72 – 2.68 (m, 1H), 2.42 (ddd, J = 13.6, 4.6, 4.6 Hz, 1H), 2.24 – 2.19 (m, 1H), 2.07 – 2.06 (m, 1H), 2.00 – 1.93 (m, 2H), 1.89 – 1.87 (m, 1H), 1.84 – 1.83 (m, 1H), 1.80 – 1.77 (m, 1H), 1.72 (d, J = 4.6 Hz, 1H), 1.57 – 1.52 (m, 2H), 1.14 (s, 3H), 1.00 (s, 9H), 0.02 (s, 6H)

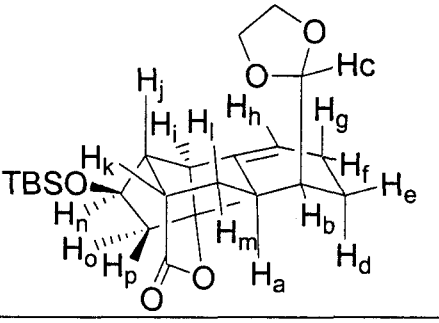
^{13}C NMR (75 MHz, C_6H_6) δ_{ppm} 172.5 (C_4), 135.2 (C_4), 126.9 (CH), 104.7 (CH), 88.4 (C_4), 71.4 (CH), 65.1 (CH_2), 64.6 (CH_2), 52.9 (CH), 49.7 (CH_2), 48.1 (CH), 40.9 (CH), 40.1 (CH),

35.8 (CH), 34.1 (CH_2), 26.3 (3xCH_3), 24.2 (CH_2), 23.6 (CH_2), 22.2 (CH_3), 18.6 (C_4), -4.4 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2929 (m), 2857 (m), 1735 (s), 1558 (m), 1457 (m)

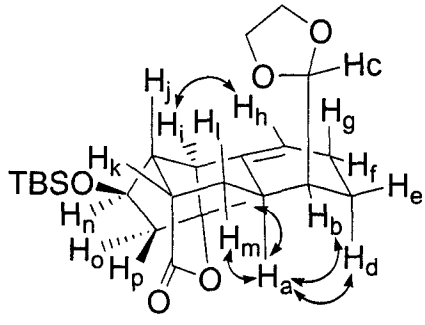
HRMS (EI, m/z) Expected for $C_{24}H_{38}O_5Si$ [$(M)^+$] 434.2489, found: 434.2485 (5.68 %)

Table 7.5: *COSY data for compound* ***4.34***

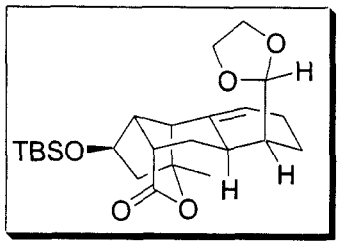


COSY data			
Proton (δ)	**Correlation**	**Proton (δ)**	**Correlation**
H_a (2.70)	H_b, H_h, H_l, H_m	H_i (1.72)	H_h, H_j, H_k
H_b (1.88)	H_a, H_c, H_d, H_e	H_j (2.06)	H_i, H_k, H_n
H_c (4.82)	H_b	H_k (3.25)	H_i, H_j, H_l, H_m
$H_{(d,o)}$ (1.55)	H_b, H_e, H_f, H_g, H_n, H_p	H_l (1.79)	H_a, H_k, H_m
$H_{(e,f)}$ (1.96)	H_b, H_d, H_g, H_h,	H_m (2.42)	H_a, H_k, H_l
H_g (2.21)	H_d, H_e, H_f, H_h	H_n (4.02)	H_j, H_o, H_p
H_h (5.40)	H_a, H_f, H_g, H_i	H_p (1.85)	H_n, H_o
Acetal CH_2 (3.46)	Acetal CH_2 (3.32-3.27)	Acetal CH_2 (3.32-3.27)	Acetal CH_2 (3.46)

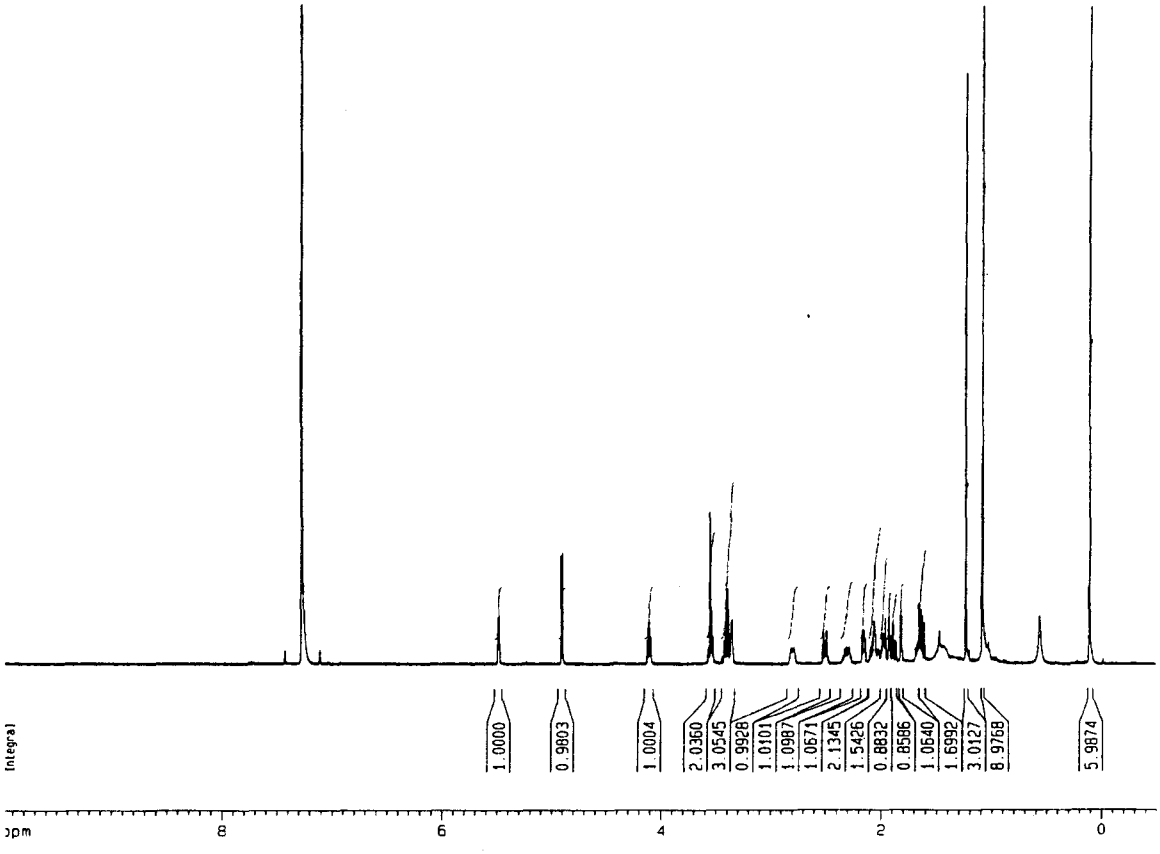
Table 7.6: *nOe data for compound* ***4.34***



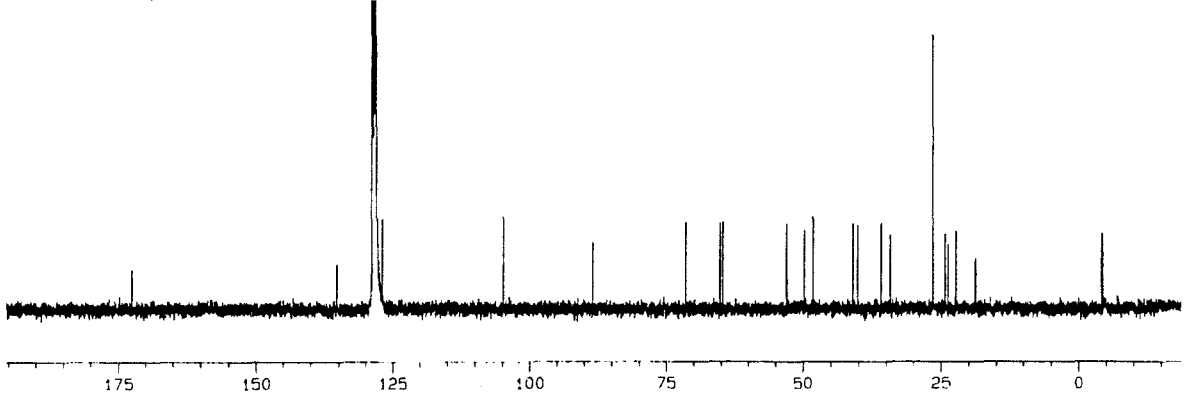
nOe data	
Irradiated proton (δ)	**Correlation (%)**
H_a (2.70 ppm)	Me (1.28), H_b (10.3), H_c (4.90), $H_{(d,o)}$ (4.35), H_m (4.28)
H_c (4.82 ppm)	H_a (0.31), H_b (5.07), H_e (2.07), H_g (1.78), H_m (0.31)
H_h (5.40 ppm)	Me (1.28), $H_{(e,f)}$ (3.14), H_g (2.87), H_i (8.46)
H_i (1.72 ppm)	Me (3.64), H_h (11.25), H_j (3.95), H_n (2.81), $H_{(d,o)}$ (2.38)
H_j (2.06 ppm)	H_i (2.82), H_k (3.08), H_l (4.17), H_n (5.98)
H_m (2.42 ppm)	H_a (3.35), H_c (2.57), H_k (5.69), H_b (22.29)

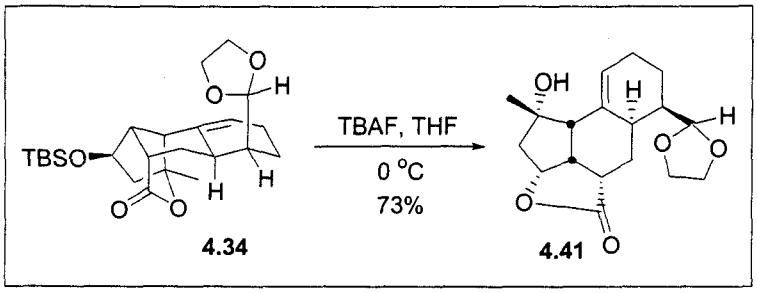


^{1}H NMR (300 MHz, C_6H_6)



^{13}C NMR (75 MHz, C_6H_6)





(+/-)-(1*R*,2*S*,5*R*,7*S*,8*S*,13*R*,14*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-7-methyl-13-(1,3-dioxolane)-4-oxa-tetracyclo[10,2,1,$0^{1,8}0^{9,14}$]pentadeca-9-en-3-one (4.41).

Tetrabutylammonium fluoride (69 μL, 1.0 M solution in THF, 0.069 mmol) was added to a solution of **4.34** (15 mg, 0.035 mmol) in THF (1.5 mL) at 0 °C and stirred for 1 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (5 mL) and the product was extracted with EtOAc (3 x 20 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes:EtOAc) provided 8 mg of **4.41** (73%) as a clear colorless oil.

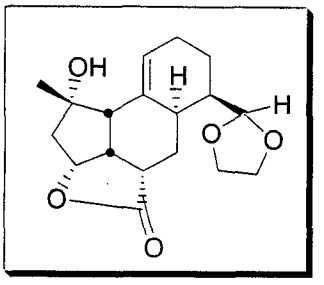
Data for **4.41:**

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 5.54 – 5.52 (m, 1H), 4.94 (dd, J = 6.3, 4.8 Hz, 1H), 4.86 (d, J = 4.7 Hz, 1H), 3.94 – 3.92 (m, 2H), 3.86 – 3.84 (m, 2H), 3.09 (ddd, J = 10.5, 10.5, 6.4 Hz, 1H), 2.91 (ddd, J = 16.4, 6.0, 1.9 Hz, 1H), 2.77 – 2.74 (m, 1H), 2.38 – 2.34 (m, 2H), 2.28 (d, J = 15.1 Hz, 1H), 2.08 – 2.06 (m, 2H), 2.02 – 1.99 (m, 1H), 1.82 (dd, J = 15.0, 4.7 Hz, 1H), 1.68 – 1.56 (m, 2H), 1.41 – 1.36 (m, 2H), 1.27 (s, 3H)

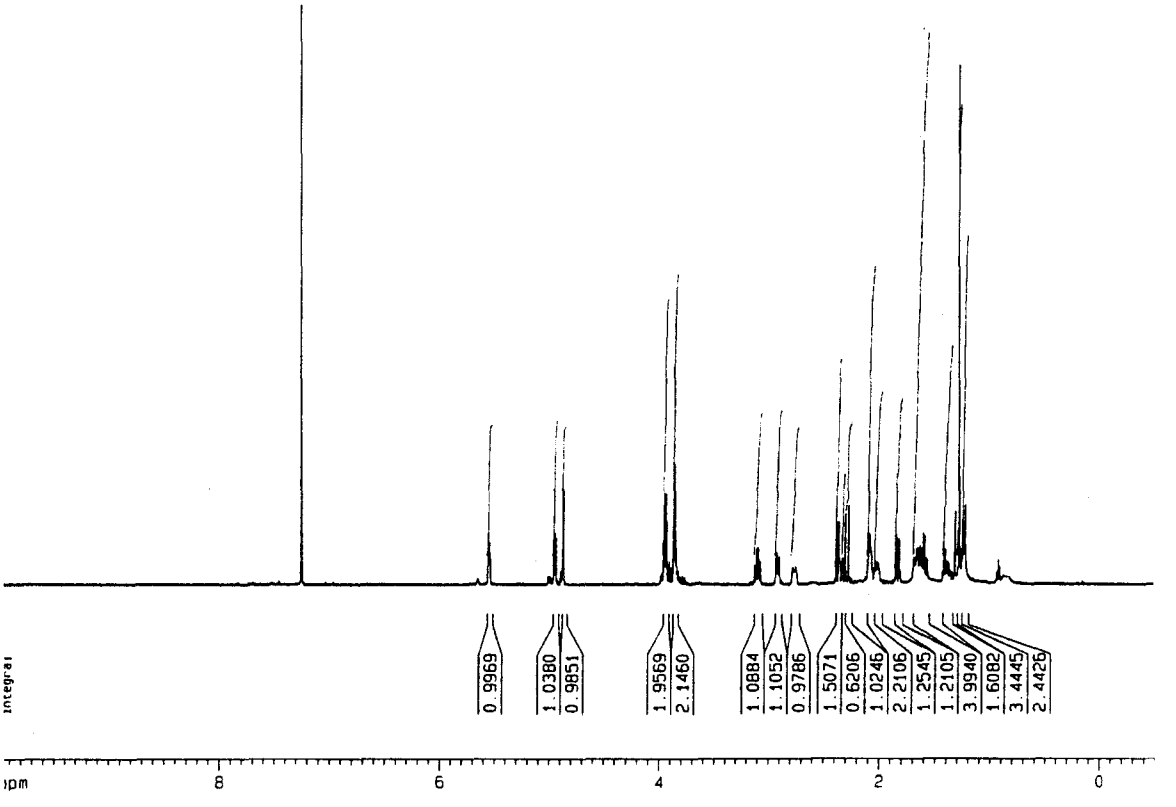
^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 178.7 (C_4), 136.5 (C_4), 126.1 (CH), 105.6 (CH), 82.6 (CH), 81.4 (C_4), 65.1 (CH_2), 64.7 (CH_2), 55.1 (CH), 46.9 (CH_2), 42.7 (CH), 41.2 (CH) 39.5 (CH), 32.6 (CH_3), 26.6 (CH_2), 26.6 (CH), 25.5 (CH_2), 18.2 (CH_2)

FTIR (neat, cm^{-1}) 3484 (bs), 2957 (m), 2925 (m), 1760 (s), 1455 (m), 1372 (m), 1170 (m)

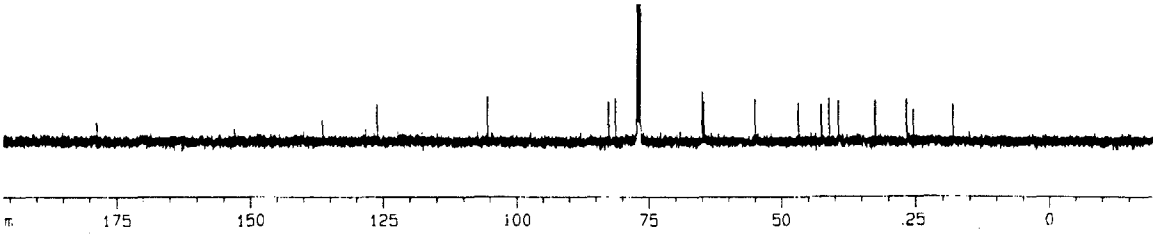
HRMS (EI, m/z) Expected for $C_{18}H_{24}O_5$ [$(M)^+$] 320.1624, found: 320.1613 (20.85%)

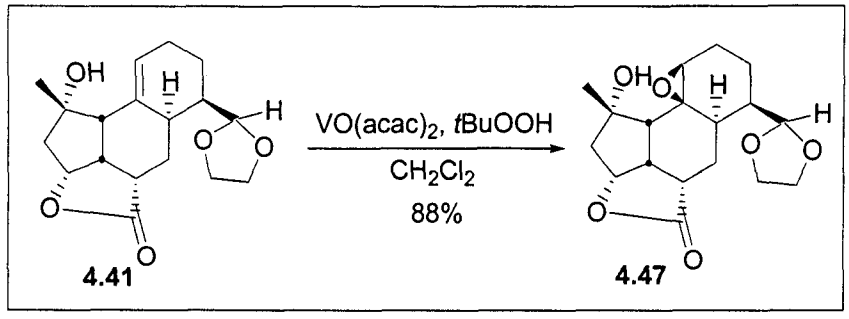


^{1}H NMR (500 MHz, $CDCl_3$)



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





(+/-)-(1*R*,2*S*,5*R*,7*S*,8*S*,9*R*,10*S*,13*R*,14*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-9,10-epoxy-7-methyl-13-(1,3-dioxolane)-4-oxa-tetracyclo[10,2,1,$0^{1,8}0^{9,14}$]pentadeca-3-one (4.47).

Vanadyl acetylacetonate (5 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (500 μL) and cannulated into a solution of alkene **4.41** (13 mg, 0.041 mmol) in CH_2Cl_2 (500 μL). *tert*-Butyl hydroperoxide (10 μL, 5 M solution in decane, 0.049 mmol) was then added and the dark red solution was stirred for 1 h at room temperature. Upon completion, the solution turned yellow. The reaction was quenched with an aqueous solution of Na_2SO_3 and extracted with CH_2Cl_2 (3x20 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (95:5 hexanes:EtOAc) provided 12 mg of epoxide **4.47** (88% yield) as a clear colorless oil.

Data for **4.47:**

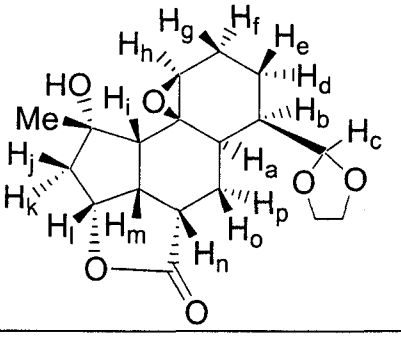
^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 4.71 (d, J = 4.3 Hz, 1H), 4.23 – 4.21 (m, 1H), 3.53 – 3.45 (m, 2H), 3.33 – 3.24 (m, 2H), 3.19 (ddd, J = 13.2, 3.9, 3.9 Hz, 1H), 2.70 – 2.66 (m, 1H), 2.47 (dddd, J = 11.4, 3.8, 3.8, 3.8 Hz, 1H), 2.31 (d, J = 4.4 Hz, 1H), 2.30 – 2.20 (m, 2H), 1.85 – 1.78 (m, 1H), 1.73 (d, J = 14.8 Hz, 1H), 1.67 – 1.60 (m, 1H), 1.50 – 1.42 (m, 2H), 1.37 – 1.28 (m, 2H), 1.18 (s, 3H), 0.98 (dd, J = 14.8, 5.0 Hz, 1H), 0.89 (d, J = 10.0 Hz, 1H)

^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 177.2 (C_4), 106.7 (CH), 82.6 (C_4), 81.8 (CH), 65.4 (CH_2), 64.9 (CH_2), 63.0 (C_4), 58.9 (CH), 52.2 (CH), 48.0 (CH_2), 42.6 (CH), 38.8 (CH), 36.9 (CH), 31.4 (CH), 29.2 (CH_3), 23.7 (CH_2), 23.4 (CH_2), 14.9 (CH_2)

FTIR (neat, cm^{-1}) 3489 (bs), 2953 (m), 2926 (m), 1760 (s), 1166 (s), 1121 (s), 1088 (m)

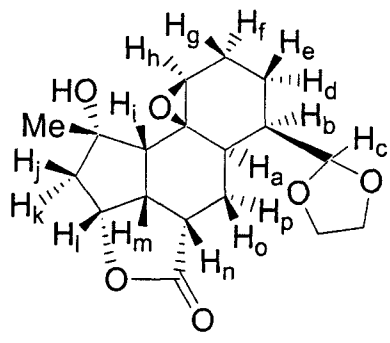
HRMS (EI, m/z) Expected for $C_{18}H_{24}O_6$ [$(M)^+$] 336.1573, found: 336.1569 (1.22%)

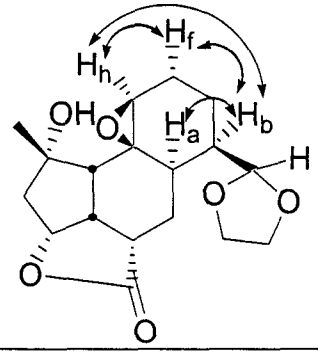
Table 7.7: *COSY data for compound* ***4.47***



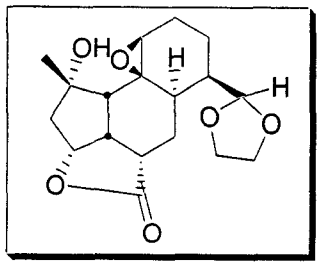
COSY data			
Proton (δ)	**Correlation**	**Proton (δ)**	**Correlation**
H_a (3.19)	H_b, H_o, H_p	H_i (0.891)	H_m
H_b (2.47)	H_a, H_c, H_d, H_e	H_j (0.976)	H_k, H_l
H_c (4.71)	H_b	H_k (1.73)	H_j
$H_{(d,o)}$ (1.46)	H_a, H_b, H_e, H_f, H_g, H_n, H_p	H_l (4.22)	H_j, H_m
H_e (1.32)	H_b, H_d, H_f, H_g	$H_{(m,n)}$ (2.25)	H_i, H_l, H_o, H_p
H_f (1.81)	H_d, H_e, H_g, H_h	H_p (2.67)	H_a, H_n, H_o
H_g (1.63)	H_d, H_e, H_f, H_h	Acetal CH_2 (3.49)	Acetal CH_2 (3.28)
H_h (2.31)	H_f, H_g	Acetal CH_2 (3.28)	Acetal CH_2 (3.49)

Table 7.8: *NOESY data for compound* ***4.47***

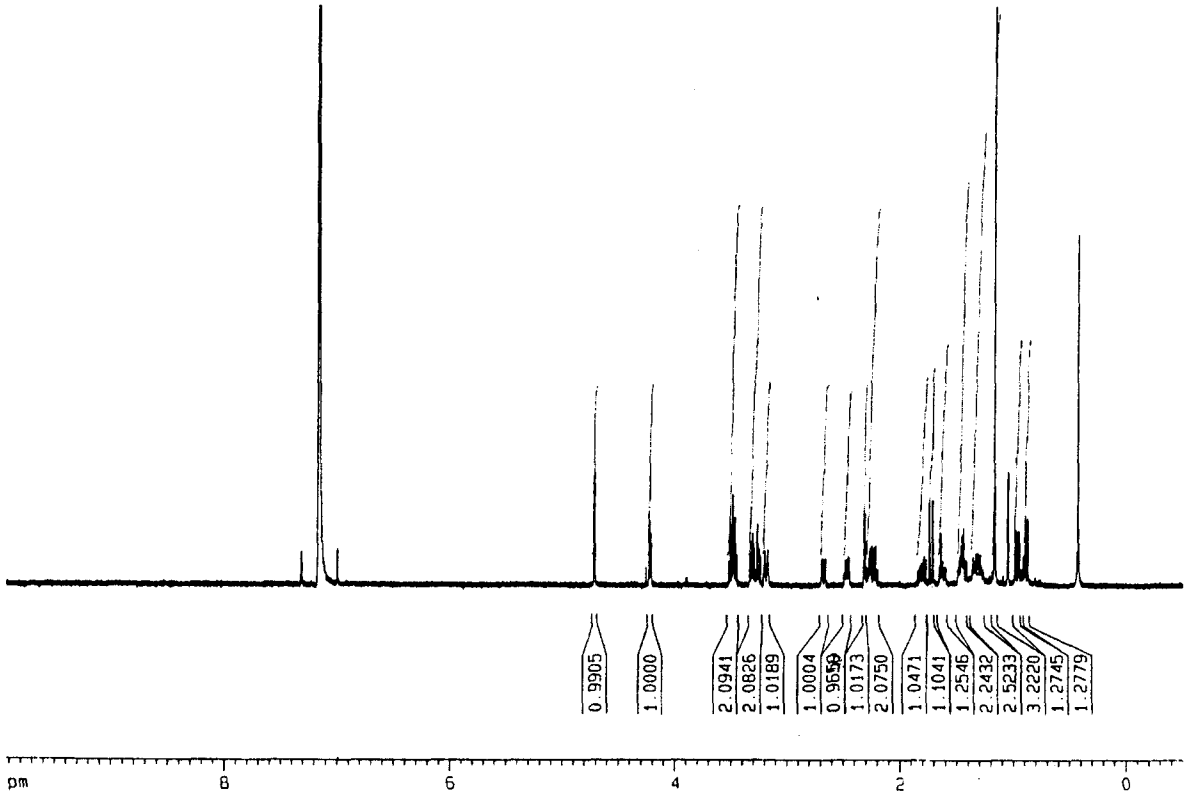




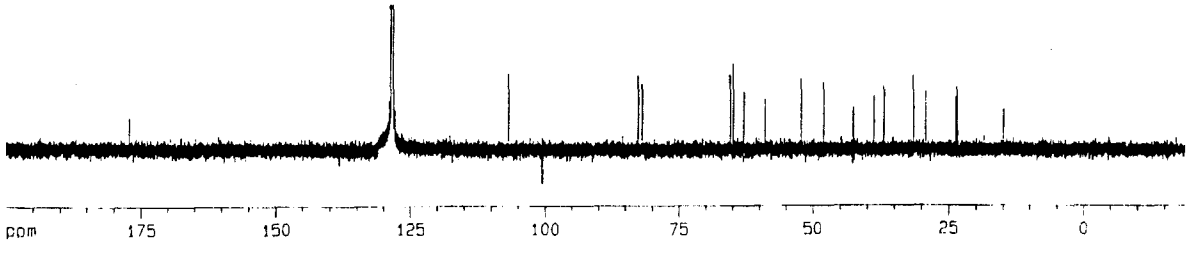
NOESY data			
Proton (δ)	**nOe with proton**	**Proton (δ)**	**nOe with proton**
H_a (3.19)	H_b, H_c, $H_{(d,o)}$ (weak), H_p	H_i (0.891)	$H_{(m,n)}$, Methyl
H_b (2.47)	H_a, H_c, $H_{(d,o)}$, H_e, H_f, H_h,	H_j (0.976)	H_k, H_l, $H_{(m,n)}$, Methyl
H_c (4.71)	H_a, H_b, $H_{(d,o)}$, H_e	H_k (1.73)	H_j, H_l, H_p (weak)
$H_{(d,o)}$ (1.46)	H_a, H_b, H_c, H_e, H_f, H_g, $H_{(m,n)}$, H_p	H_l (4.22)	H_j, H_k, $H_{(m,n)}$
H_e (1.32)	H_b, H_c, $H_{(d,o)}$, H_g	$H_{(m,n)}$ (2.25)	H_i, H_j, H_l, $H_{(d,o)}$, H_p
H_f (1.81)	H_b, $H_{(d,o)}$, H_g, H_h	H_p (2.67)	H_a, H_k (weak), $H_{(m,n)}$, $H_{(d,o)}$
H_g (1.63)	$H_{(d,o)}$, H_e, H_f	Acetal CH_2 (3.49)	Acetal CH_2 (3.28)
H_h (2.31)	H_b, H_f	Acetal CH_2 (3.28)	Acetal CH_2 (3.49)

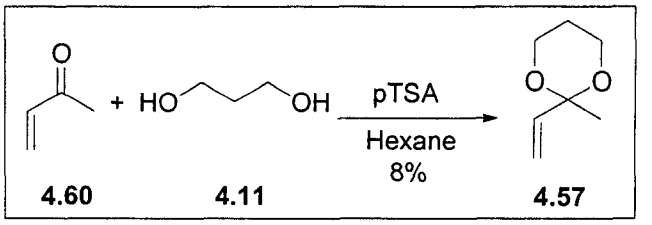


^{1}H NMR (500 MHz, C_6D_6)



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





2-Methyl-2-vinyl-1,3-dioxane (4.57). Pyridinium *p*-toluenesulfonate (99 mg, 0.40 mmol) was added to a solution of methyl vinyl ketone (10 mL, 113 mmol) and 1,3-propanediol (8.58 g, 113 mmol) in hexanes (225 mL, 2 mL/mmol) in a flame-dried round bottom flask equipped with a Dean-stark apparatus. After refluxing for 4 h, the solution was cooled to rt and $NaHCO_3$ (200 mL) was added. The product was extracted with Et_2O (3x30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated (note: the compound is very volatile!) Purification by flash chromatography on silica gel (95:5, petroleum ether: Et_2O) provided 1.2 g of **4.57** (8%) as a clear colorless oil.

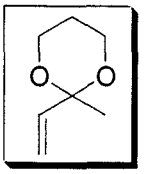
Data for **4.57:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 5.80 (dd, J = 17.8, 10.9 Hz, 1H), 5.41 – 5.34 (m, 2H), 3.99 – 3.77 (m, 4H), 2.08 – 1.92 (m, 1H), 1.38 – 1.31 (m, 4H)

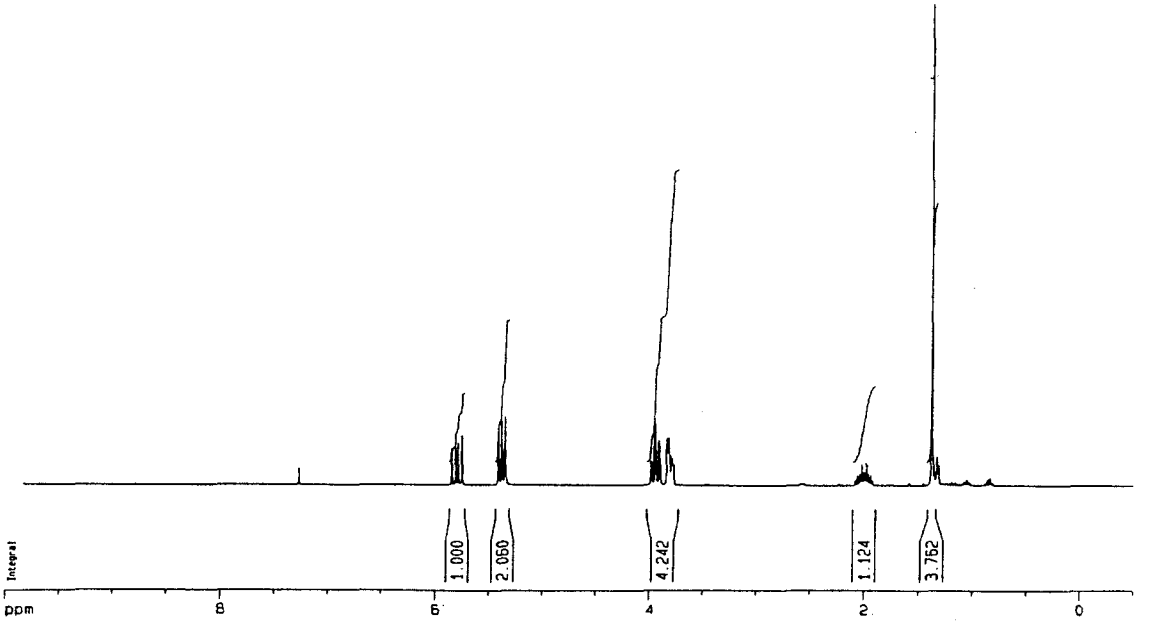
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 138.9 (CH), 118.3 (CH_2), 99.2 (C_4), 61.3 (2xCH_2), 29.2 (CH_3), 25.9 (CH_2)

FTIR (neat, cm^{-1}) 2962 (m), 2861 (m), 1404 (m), 1369 (m), 1191 (s), 1145 (s), 1087 (s)

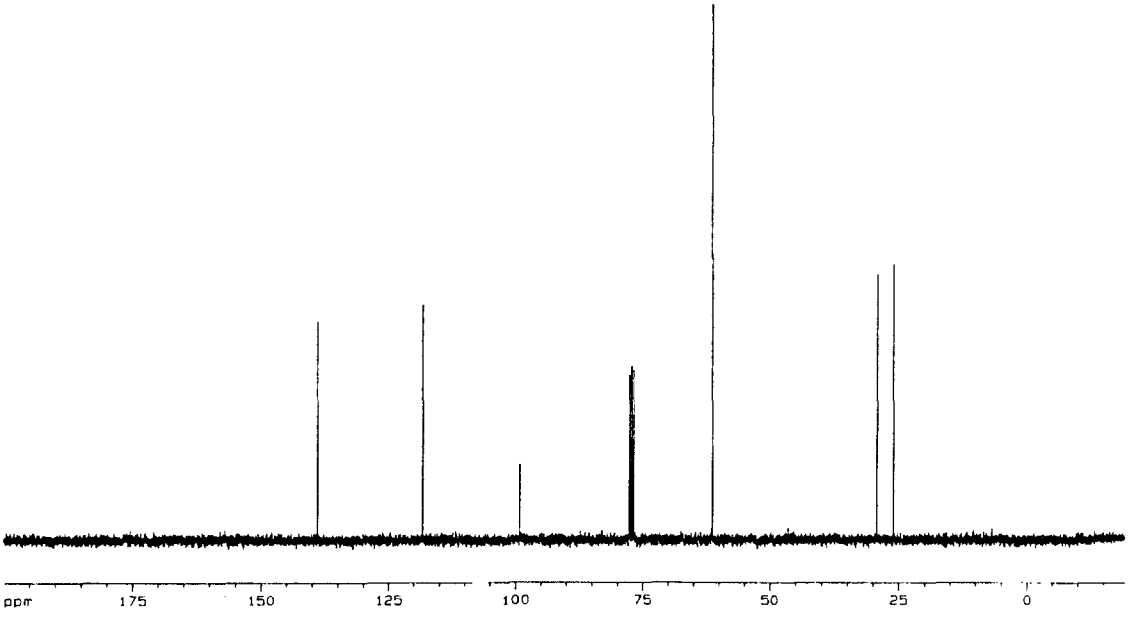
HRMS (EI, m/z) Expected for $C_5H_9O_2$ [$(M-C_2H_3)^+$] 101.0603, found: 101.0619 (95.03%)

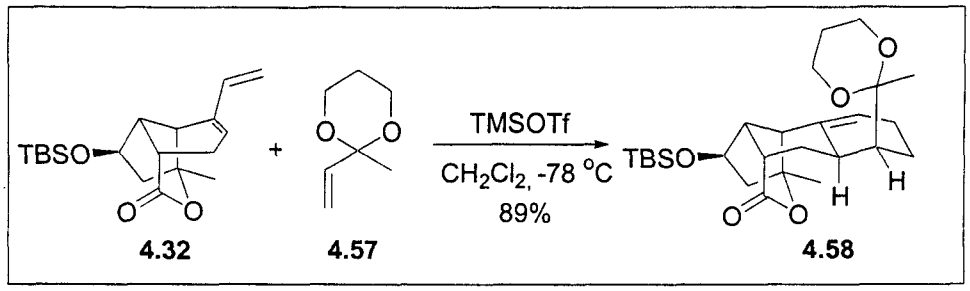


^{1}H NMR (300 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,13*R*,14*R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-13-(2-methyl-1,3-dioxane)-3-oxatetracyclo[8,3,2,$0^{7,8}0^{9,14}$]pentadeca-9-en-2-one (4.58).

Trimethylsilyl triflate (67 μL, 0.389 mmol) was added to a solution of diene **4.32** (65 mg, 0.19 mmol) and dienophile **4.57** (50 mg, 0.39 mmol) in CH_2Cl_2 (1.5 mL) at -78 °C. After stirring for 30 min, Et_3N (3 mL) was added (at -78 °C). The solution was poured in water (50 mL) and the product was extracted with CH_2Cl_2 (3x30 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (9:1 hexanes: EtOAc) provided 80 mg of **4.58** (89% yield) as a clear colorless oil.

Data for **4.58:**

^{1}H NMR (500 MHz, C_6H_6) δ_{ppm} 5.45 (m, 1H), 4.01 (ddd, J = 9.0, 6.6, 2.4 Hz, 1H), 3.60 – 3.49 (m, 4H), 3.21 – 3.20 (m, 1H), 3.00 – 2.98 (m, 1H), 2.69 (ddd, J = 12.5, 4.2, 4.2 Hz, 1H), 2.12 – 2.04 (m, 5H), 1.84 – 1.79 (m, 2H), 1.72 – 1.66 (m, 1H), 1.62 – 1.61 (m, 1H), 1.59 – 1.55 (m, 1H), 1.50 (dd, J = 14.3, 9.2 Hz, 1H), 1.34 (s, 3H), 1.17 (s, 3H), 0.98 (s, 9H), 0.71 (m, 1H), -0.01 (s, 6H)

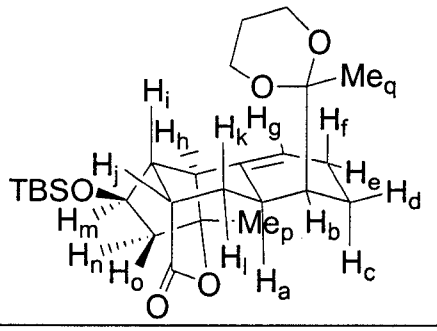
^{13}C NMR (125 MHz, C_6H_6) δ_{ppm} 172.8 (C_4), 139.0 (C_4), 125.6 (CH), 100.5 (C_4), 88.0 (C_4), 71.2 (CH), 59.8 (CH_2), 59.6 (CH_2), 53.9 (CH), 50.3 (CH_2), 49.6 (CH), 48.4 (CH), 40.9 (CH),

34.9 (CH), 34.2 (CH_2), 27.6 (CH_2), 26.3 (3xCH_3), 26.1 (CH_2), 22.3 (CH_3), 19.8 (C_4), 18.6 (CH_2), 17.4 (CH_3), -4.4 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2954 (s), 2930 (s), 1742 (s), 1382 (m), 1147 (s), 964 (m)

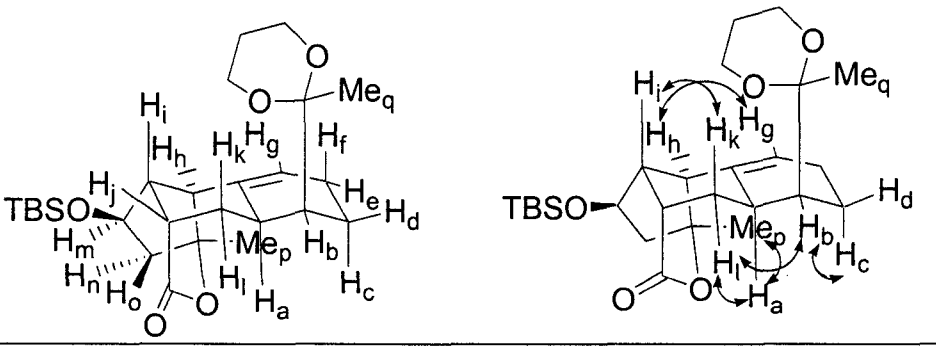
HRMS (EI, m/z) Expected for $C_{26}H_{42}O_5Si$ [$(M)^+$] 462.2802, found: 462.2781 (1.59%)

Table 7.9**: COSY data for **4.58

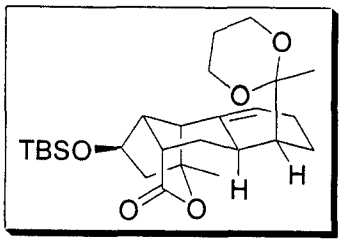


COSY data			
Proton (δ)	**Correlation**	**Proton (δ)**	**Correlation**
H_a (2.99)	H_b, $H_{(c,d,e,f,i)}$, H_k, H_l	H_j (3.21)	$H_{(c,d,e,f,i)}$, H_k, H_l
H_b (1.62)	H_a, $H_{(c,d,e,f,i)}$, H_k	H_k (1.57)	H_a, H_b, $H_{(c,d,e,f,i)}$, H_j, H_l
$H_{(c,d,e,f,i)}$ (2.08)	H_a, H_b, H_g, $H_{(h,o)}$, H_j, H_k, H_m	H_l (2.69)	H_a, H_j, H_k
H_g (5.45)	$H_{(c,d,e,f,i)}$, $H_{(h,o)}$	H_m (4.01)	$H_{(c,d,e,f,i)}$, H_n, $H_{(h,o)}$
$H_{(h,o)}$ (1.80)	$H_{(c,d,e,f,i)}$, H_m, H_n	H_n (1.50)	H_m, $H_{(h,o)}$

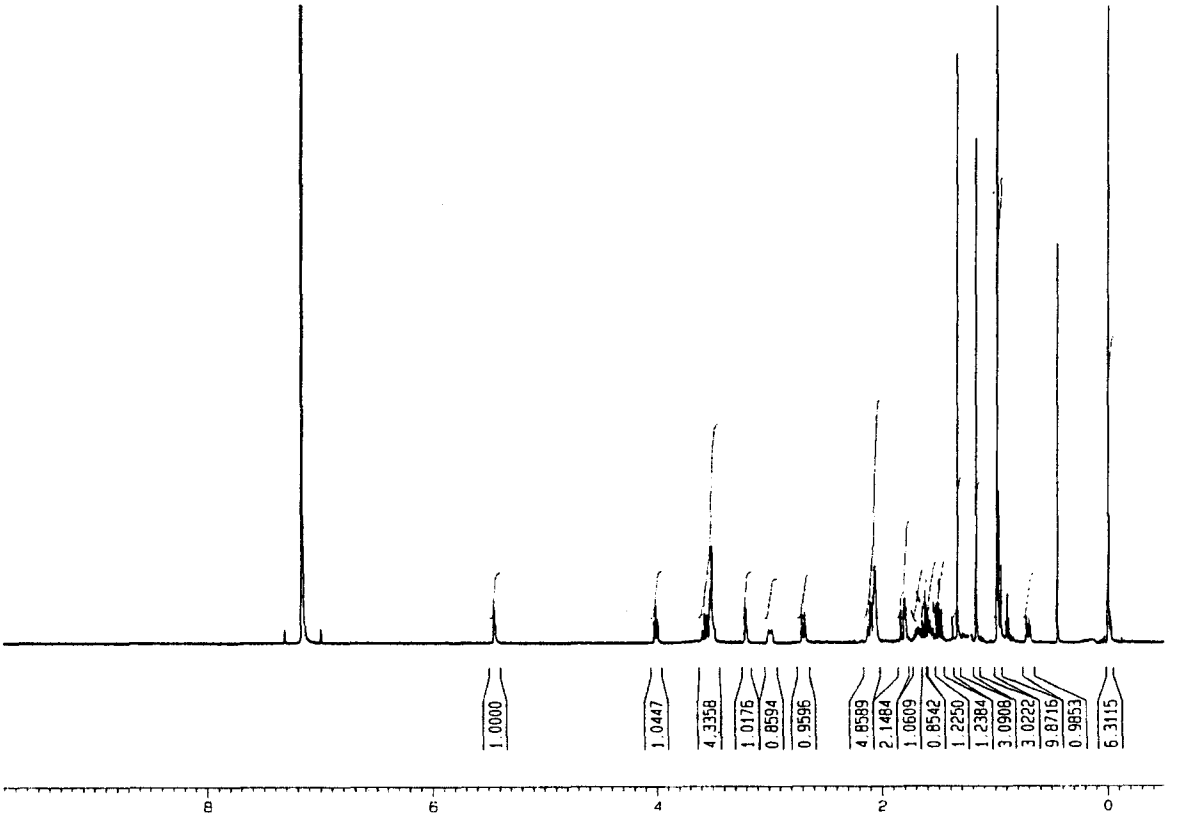
Table 7.10: NOESY data for ***4.58***



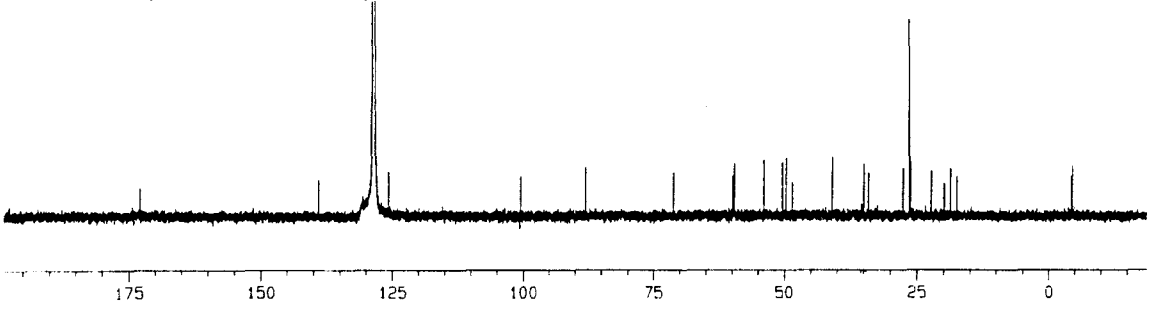
NOESY data			
Proton (δ)	**nOe with proton**	**Proton (δ)**	**nOe with proton**
H_a (2.99)	$H_{(c,d,e,f,i)}$, H_l, Me_p, Me_q	H_j (3.21)	H_k, H_l, $H_{(c,d,e,f,i)}$
H_b (1.62)	$H_{(c,d,e,f,i)}$, H_l	H_k (1.57)	$H_{(c,d,e,f,i)}$, H_j
$H_{(c,d,e,f,i)}$ (2.08)	H_a, H_b, H_g, H_j, H_k, H_m, $H_{(h,o)}$, Me_q	H_l (2.69)	H_a, H_b, H_j, Me_q
H_g (5.45)	$H_{(c,d,e,f,i)}$, $H_{(h,o)}$	H_m (4.01)	$H_{(c,d,e,f,i)}$, $H_{(h,o)}$, H_n
$H_{(h,o)}$ (1.80)	$H_{(c,d,e,f,i)}$, H_g, H_m, H_n, Me_p	H_n (1.50)	H_m, $H_{(h,o)}$, Me_p
Me_p (1.14)	H_a, $H_{(h,o)}$, H_n	Me_q (1.34)	H_a, $H_{(c,d,e,f,i)}$, H_l

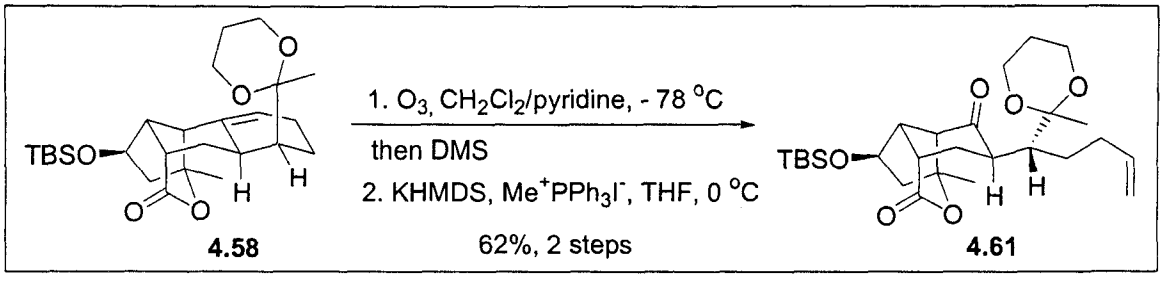


^{1}H NMR (500 MHz, C_6H_6)



^{13}C NMR (125 MHz, C_6H_6)





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,10*R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-(2-methyl-2-[(1*R*)-1-pent-4-en-1-yl]-1,3-dioxane)-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undecane-2,9-dione (4.61). A solution of alkene **4.58** (30 mg, 0.065 mmol) in CH_2Cl_2 (5 mL) containing 5% pyridine was cooled to -78 °C and bubbled with oxygen for 5 min, followed by ozone for 15 min (solution turned blue). Oxygen was again bubbled for 5 min and then methylsulfide (480 μL, 6.50 mmol) was added. The solution was slowly warmed to room temperature and then poured into water. The product was extracted with CH_2Cl_2 (3x20 mL) and the combined extracts were dried with $MgSO_4$, filtered and concentrated. The product was filtered through a pipette containing silica gel, eluted with Et_2O and concentrated to yield the crude aldehyde. In a separate flask, KHMDS (65 mg, 0.33 mmol) was added to a mixture of methyltriphenylphosphonium iodide (130 mg, 0.325 mmol) in THF (0.5 mL) at 0 °C and stirred for 30 min. A solution of the crude aldehyde in THF (0.5 mL) was slowly cannulated into the yellow mixture and then stirred for 30 min at 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (9:1 hexanes: Et_2O) provided 20 mg of **4.61** (62% yield beginning from **4.58**) as a clear colorless oil.

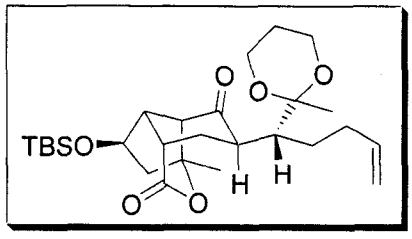
Data for **4.61:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 5.94 (ddt, J = 17.1, 10.3, 6.6 Hz, 1H), 5.15 – 5.11 (m, 1H), 5.04 – 5.02 (m, 1H), 3.80 (ddd, J = 9.0, 6.4, 2.3 Hz, 1H), 3.53 – 3.46 (m, 3H), 3.44 – 3.36 (m, 2H), 3.25 (m, 1H), 3.23 – 3.20 (m, 1H), 2.89 (ddd, J = 13.4, 6.8, 4.4 Hz, 1H), 2.24 – 2.18 (m, 2H), 2.09 – 2.08 (m, 1H), 2.07 – 2.05 (m, 1H), 1.88 – 1.81 (m, 1H), 1.74 – 1.63 (m, 3H), 1.52 – 1.44 (m, 1H), 1.36 (dd, J = 14.6, 9.5 Hz, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 0.96 (s, 9H), 0.72 (dt, J = 13.2, 2.6 Hz, 1H), -0.03 (s, 3H), -0.06 (s, 3H)

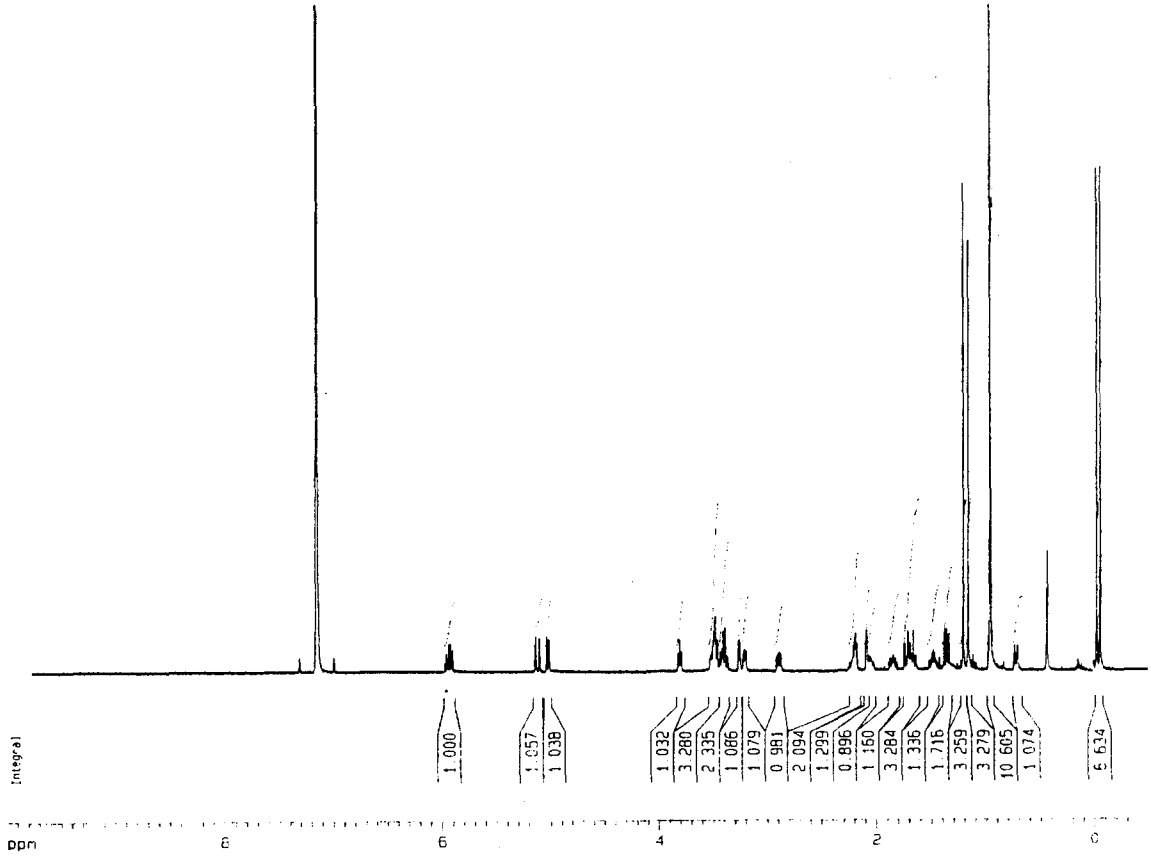
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 208.0 (C_4), 171.7 (C_4), 139.6 (CH), 115.0 (CH_2), 100.9 (C_4), 87.9 (C_4), 71.3 (CH), 60.01 (CH_2), 59.96 (CH_2), 58.3 (CH), 49.2 (CH_2), 47.8 (CH), 47.3 (CH), 44.6 (CH), 39.2 (CH), 34.5 (CH_2), 30.9 (CH_2), 26.5 (CH_2), 26.23 (CH_2), 26.19 (3xCH_3), 22.4 (CH_3), 18.5 (C_4), 18.2 (CH_3), -4.4 (CH_3), -4.7 (CH_3)

FTIR (neat, cm^{-1}) 2928 (s), 2857 (s), 1749 (s), 1699 (s), 1250 (s), 1145 (s)

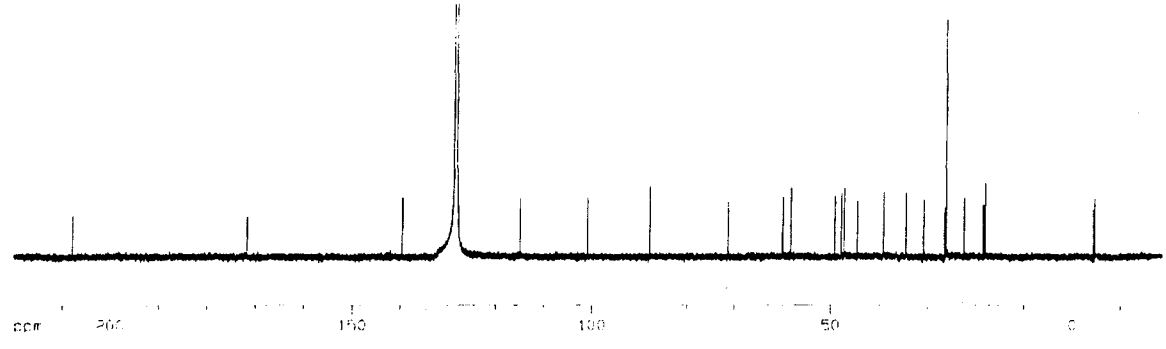
HRMS (EI, m/z) Expected for $C_{26}H_{41}O_6Si$ [$(M\text{-}CH_3)^+$] 477.2672, found: 477.2670 (15.51%)

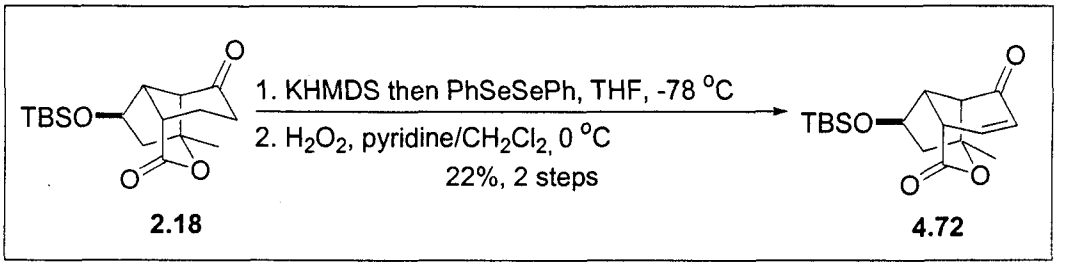


^{1}H NMR (500 MHz, C_6D_6)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (4.72). A solution of ketone **2.18** (20 mg, 0.062 mmol) in THF (1 mL) was slowly added to a mixture of KHMDS (13.5 mg, 0.068 mmol) in THF (0.5 mL) at -78 °C and stirred for 30 min. A solution of PhSeSePh (42 mg, 0.14 mmol) in THF (0.5 mL) was then cannulated into the flask and the reaction was stirred for 2 h at -78 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (3x10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was then filtered through a pipette containing silica gel, eluted with Et_2O and concentrated once again. After dissolving the oil in a solution of CH_2Cl_2/pyridine (1:1) (2 mL), H_2O_2 (1 mL, 30% wt in water) was added and the solution was stirred at 0 °C for 3 h. The reaction was quenched with 0.5 N HCl and the product was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (10:1 hexanes:Et_2O), provided 4 mg of **4.72** (22%) as a clear colorless oil.

Data for **4.72:**

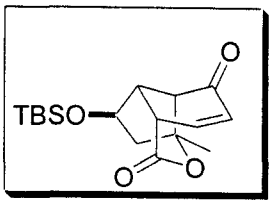
^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 6.51 (dd, J = 9.5, 7.7 Hz, 1H), 5.87 (d, J = 9.5 Hz, 1H), 3.71 (ddd, J = 9.1, 6.4, 2.3 Hz, 1H), 3.37 (ddd, J = 7.6, 3.6, 1.4 Hz, 1H), 2.33 – 2.30 (m, 1H), 1.84

(d, J = 5.0 Hz, 1H), 1.71 (dd, J = 15.1, 2.4 Hz, 1H), 1.36 (dd, J = 15.0, 9.6 Hz, 1H), 1.24 (s, 3H), 0.95 (s, 9H), -0.07 (s, 3H), -0.09 (s, 3H)

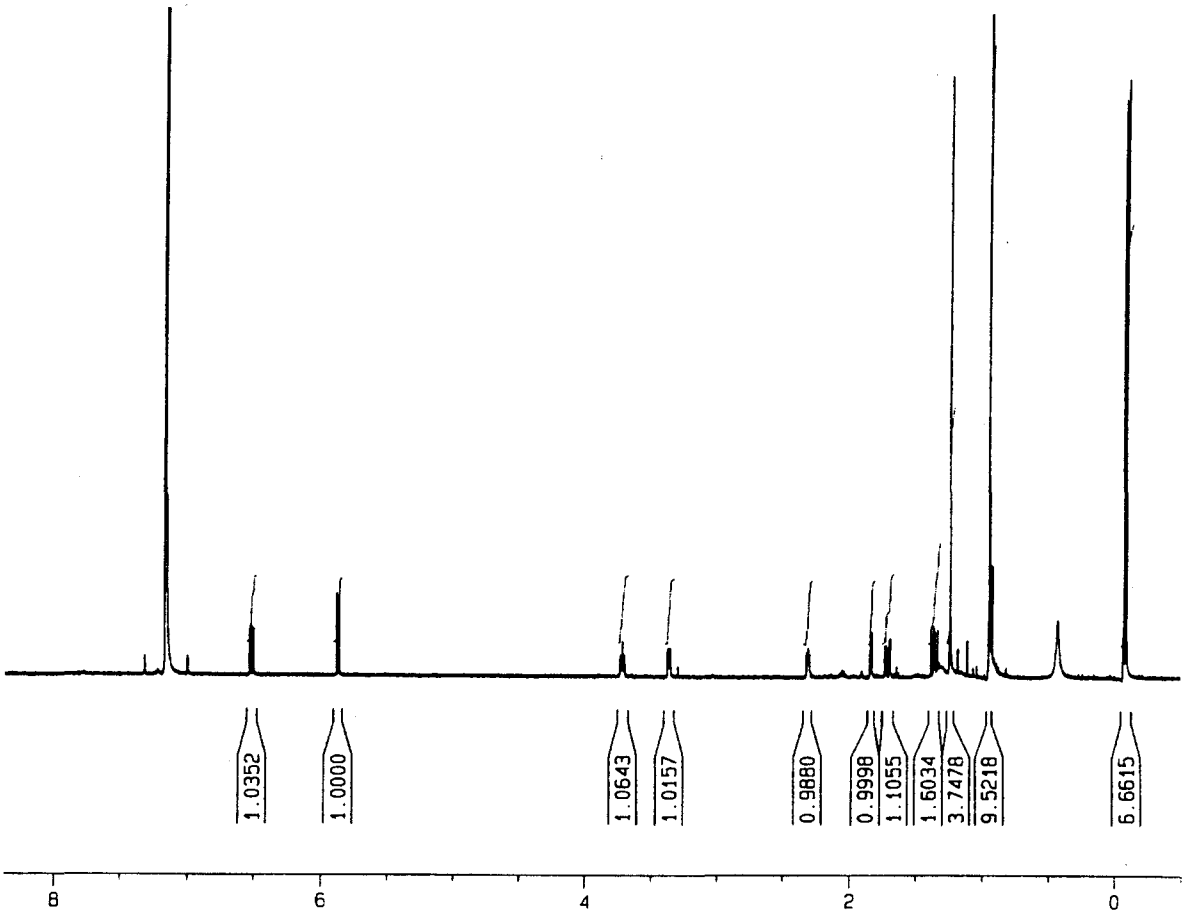
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 194.4 (C_4), 167.3 (C_4), 147.8 (CH), 132.4 (CH), 88.0 (C_4), 70.5 (CH), 54.2 (CH), 49.6 (CH_2), 48.1 (CH), 41.0 (CH), 26.2 (3xCH_3), 22.4 (CH_3), 18.5 (C_4), -4.5 (CH_3), -4.8 (CH_3)

FTIR (neat, cm^{-1}) 2930 (s), 2857 (s), 1746 (s), 1677 (s), 1472 (m), 1261 (m), 1152 (m),

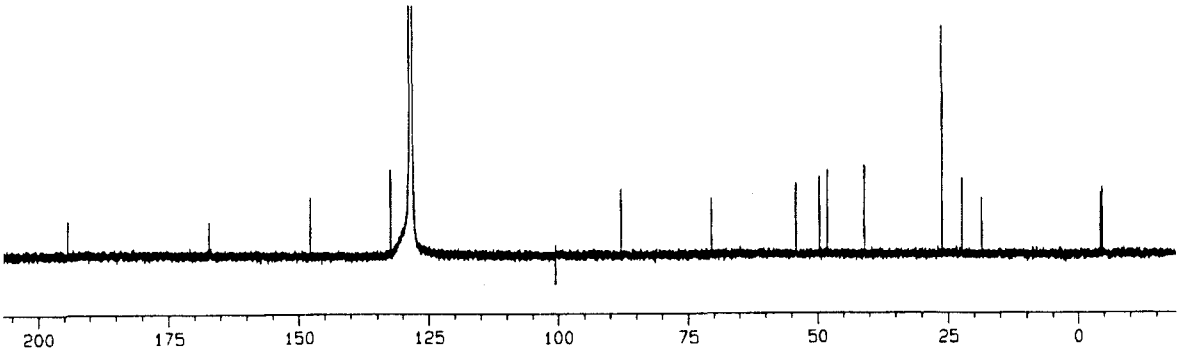
HRMS (EI, m/z) Expected for $C_{13}H_{17}O_4Si$ [$(M-C_4H_9)^+$] 265.0897, found: 265.0995. (9.6%)

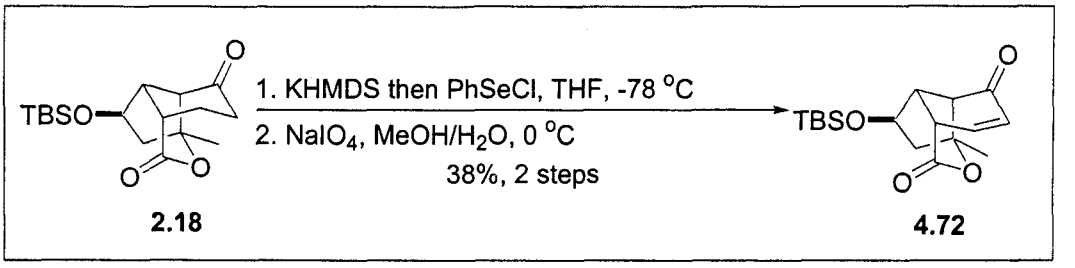


^{1}H NMR (500 MHz, C_6D_6)



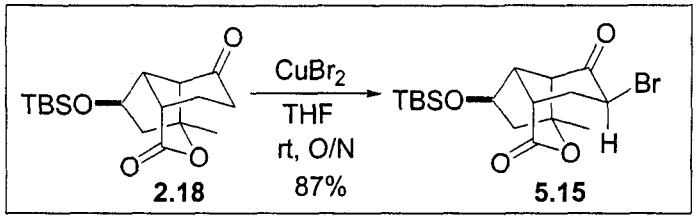
^{13}C NMR (125 MHz, C_6D_6)





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (4.72). A solution of ketone **2.18** (40 mg, 0.12 mmol) in THF (1 mL) was slowly added to a mixture of KHMDS (27 mg, 0.14 mmol) in THF (1 mL) at -78 °C and stirred for 30 min. A solution of PhSeCl (52 mg, 0.27 mmol) in THF (0.5 mL) was then cannulated into the flask and the reaction was stirred for 1 h at -78 °C. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and the product was extracted with EtOAc (3x20 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was then filtered through a pipette containing silica gel to remove the excess PhSeCl and concentrated once again to provide an oil. After dissolving the oil in a solution of MeOH/H_2O (3:1, 3 mL), the flask was cooled to 0 °C and $NaIO_4$ (53 mg, 0.25 mmol) was added. After stirring for 30 min, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_4$ (5 mL) and the product was extracted with Et_2O (3x30 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (10:1 hexanes:Et_2O), provided 15 mg of **4.72** (38%) as a clear colorless oil.

Data for **4.72:** See above for characterization data.



(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,10*S*)-10-Bromo-6-(*tert*-butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undecane-2,9-dione (5.15). Copper bromide (28 mg, 0.12 mmol) was added to a solution of ketone **2.18** (20 mg, 0.062 mmol) in THF (1.0 mL) and stirred O/N at room temperature. H_2O (5 mL) was added and the product was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O), provided 19 mg of **5.15** (87%) as a white solid (melting point: 151.8 °C – 152.9 °C)

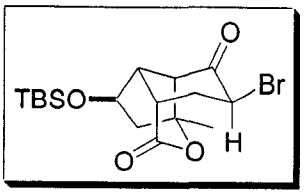
Data for **5.15:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 4.34 (dd, J = 13.0, 7.1 Hz, 1H), 3.63 (ddd, J = 9.5, 6.5, 2.2 Hz, 1H), 2.88 – 2.87 (m, 1H), 2.63 (ddd, J = 13.2, 7.2, 4.0 Hz, 1H), 2.04 – 2.03 (m, 1H), 1.81 – 1.72 (m, 2H), 1.57 (dd, J = 14.9, 2.4 Hz, 1H), 1.20 (dd, J = 14.8, 9.6 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 9H), -0.11 (s, 3H), -0.12 (s, 3H)

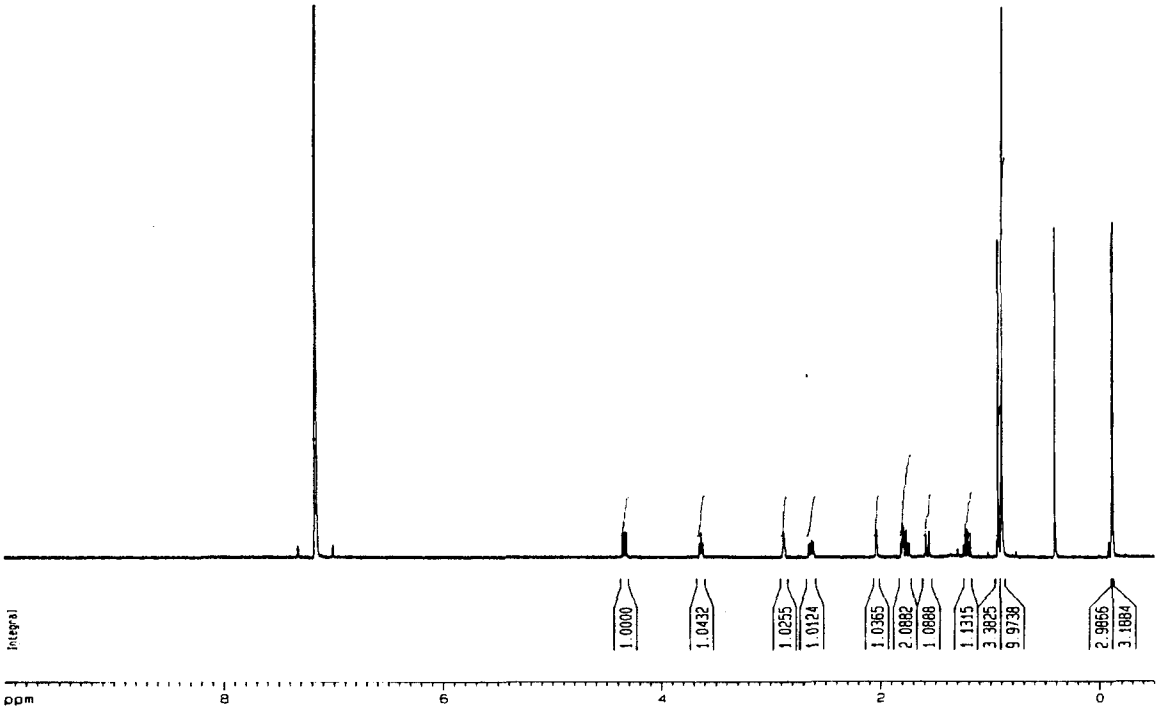
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 198.0 (C_4), 169.7 (C_4), 87.9 (C_4), 71.0 (CH), 58.5 (CH), 51.1 (CH), 48.9 (CH_2), 47.8 (CH), 40.7 (CH), 40.1 (CH_2), 26.1 (3xCH_3), 22.1 (CH_3), 18.5 (C_4), -4.5 (CH_3), -4.8 (CH_3)

FTIR (neat, cm^{-1}) 2930 (s), 2857 (s), 1749 (s), 1721 (s), 1257 (m), 835 (s)

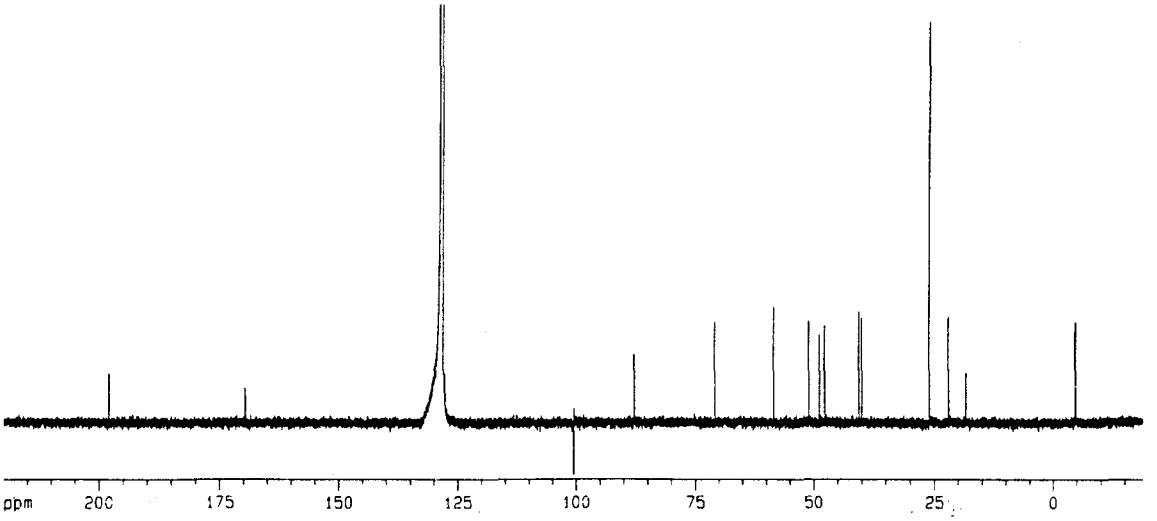
HRMS (EI, m/z) Expected for $C_{13}H_{18}O_4BrSi$ [$(M-C_4H_9)^+$] 345.0158, found: 345.0203. (67.9%)

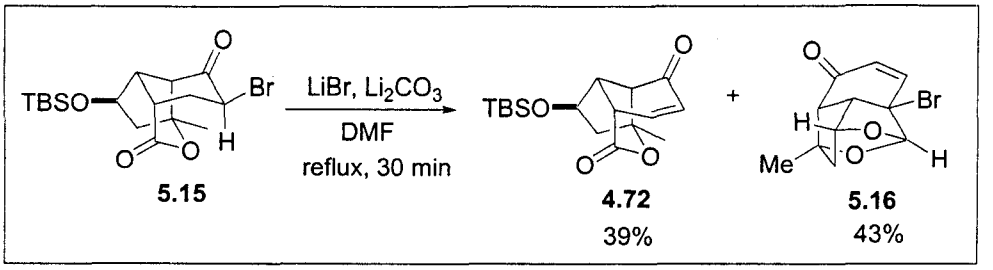


^{1}H NMR (500 MHz, C_6D_6)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo-[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (4.72) and **5.16.** Lithium bromide (97 mg, 1.1 mmol) and Li_2CO_3 (83 mg, 1.1 mmol) were flame-dried under high vacuum. After cooling to room temperature, the flask was filled with argon. Ketone **5.15** (90 mg, 0.22 mmol) was cannulated into the flask as a solution in DMF (5 mL) and the contents were refluxed for 30 min. After cooling to room temperature, a saturated aqueous solution of NH_4Cl (5 mL) was added and the organic product was extracted with Et_2O (3x20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) provided 26 mg of **5.16** (43%) as a white solid (melting point: 129.8 °C – 131.8 °C) and 28 mg of **4.72** (39%) as a clear colorless oil.

Data for **4.72:** See above for characterization data.

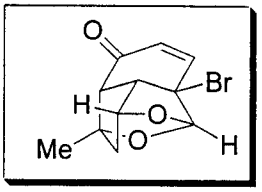
Data for **5.16:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 6.45 (d, J = 10.1 Hz, 1H), 5.77 (dd, J = 10.1, 0.8 Hz, 1H), 5.04 (s, 1H), 4.34 (dd, J = 4.1, 4.1 Hz, 1H), 3.07 (ddd, J = 6.4, 4.8, 1.3 Hz, 1H), 1.84 – 1.80 (m, 2H), 1.00 (s, 3H), 0.75 – 0.72 (m, 1H)

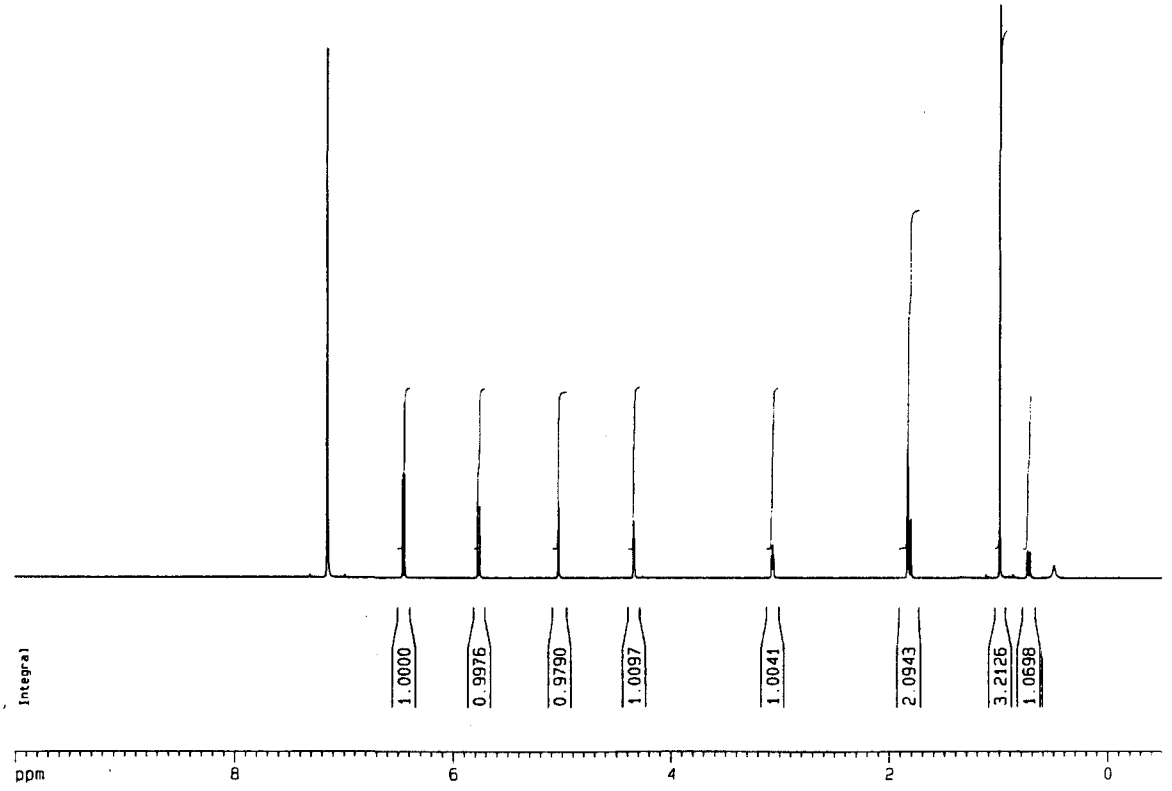
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 193.9 (C_4), 147.8 (CH), 130.1 (CH), 102.1 (CH), 83.1 (C_4), 79.3 (CH), 65.7 (C_4), 60.9 (CH), 55.6 (CH), 45.6 (CH_2), 20.4 (CH_3)

FTIR (neat, cm^{-1}) 2981 (m), 2935 (m), 1676 (s), 1386 (s), 1264 (s), 1072 (s)

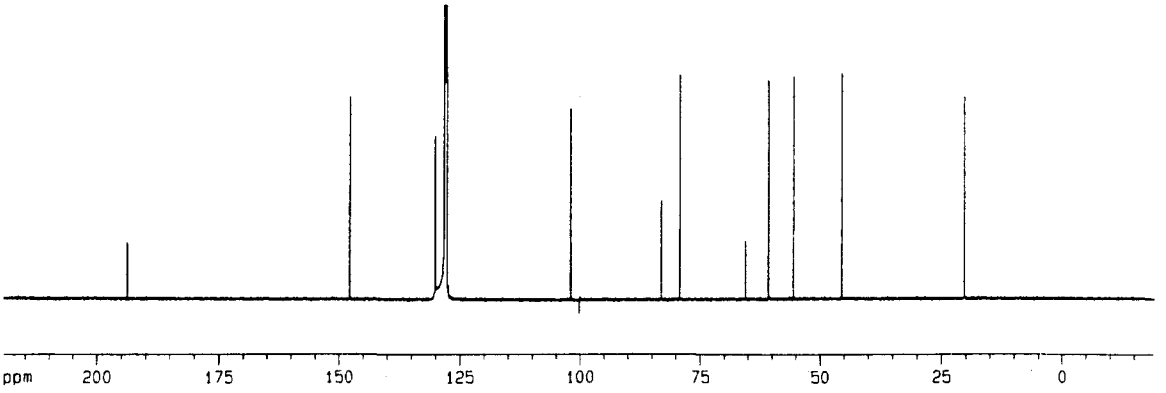
HRMS (EI, m/z) Expected for $C_{10}H_{10}O_2Br$ [(M-CHO)$^+$] 240.9680, found: 240.9875. (0.8%)

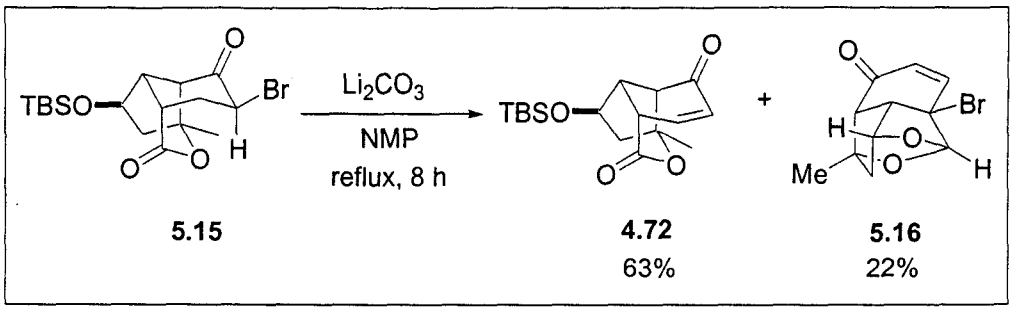


^{1}H NMR (500 MHz, C_6D_6)



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



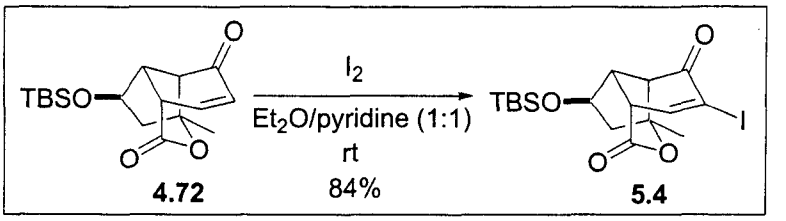


5.15 **4.72** 63% **5.16** 22%

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (4.72) and **5.16**. A mixture of lithium carbonate (18 mg, 0.25 mmol) and ketone **5.15** (20 mg, 0.050 mmol) were refluxed in NMP (2 mL) for 8 h. After cooling to room temperature, a saturated aqueous solution of NH_4Cl (5 mL) was added and the organic product was extracted with Et_2O (3x20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) provided 10 mg of **4.72** (63%) as a clear colorless oil and 3 mg of **5.16** (22%) as a white solid.

Data for **4.72:** See above for characterization data.

Data for **5.16:** See above for characterization data.



(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-iodo-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (5.4). Enone **4.72** (119 mg, 0.369 mmol) was dissolved in a 1:1 solution of Et_2O/pyridine (5 mL) at room temperature. Iodine (73.0 mg, 0.369 mmol) was then added and the dark red solution was stirred for 1 h. The contents of the flask were then poured into a 1N solution of HCl (5 mL) and the product was extracted with Et_2O (3x20 mL). The combined organic phases were washed with a saturated aqueous solution of Na_2SO_3, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (20:1 hexanes:Et_2O) provided 105 mg of **5.5** (84%) as a white solid (melting point: 179.1 °C – 179.5 °C).

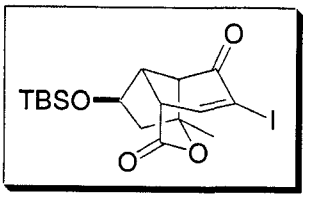
Data for **5.4:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 7.25 (d, J = 8.0 Hz, 1H), 3.62 (ddd, J = 9.1, 6.4, 2.3 Hz, 1H), 3.18 (ddd, J = 8.0, 3.4, 1.7 Hz, 1H), 2.17 – 2.14 (m, 1H), 1.92 – 1.91 (m, 1H), 1.61 (dd, J = 15.1, 1.8 Hz, 1H), 1.27 (dd, J = 14.8, 9.6 Hz, 1H), 1.84 (s, 3H), 0.93 (s, 9H), -0.14 (s, 3H), -0.11 (s, 3H)

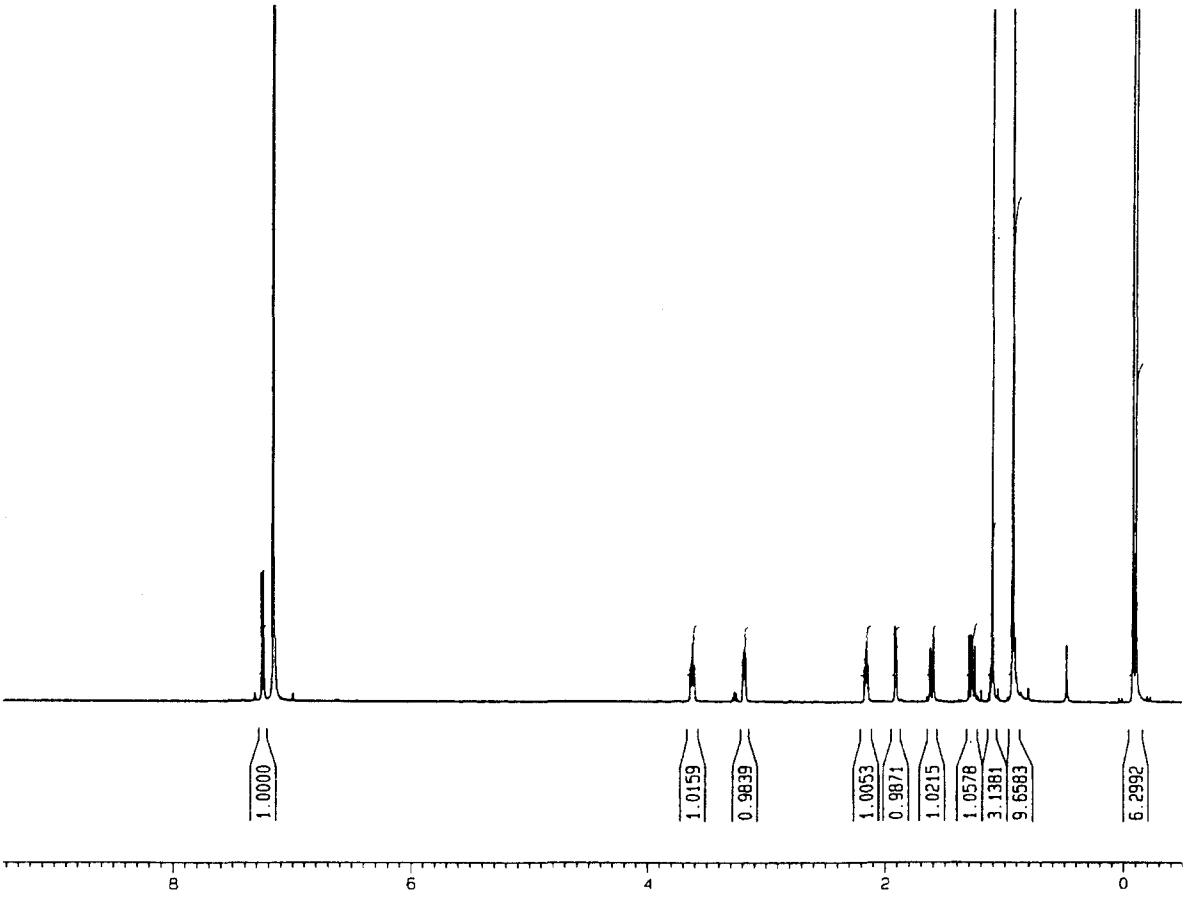
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 188.2 (C_4), 165.8 (C_4), 155.7 (CH), 106.8 (C_4), 88.1 (C_4), 70.0 (CH), 53.1 (CH), 49.3 (CH_2), 48.0 (CH), 44.7 (CH), 26.1 (3xCH_3), 22.2 (CH_3), 18.5 (C_4), -4.5 (CH_3), -4.8 (CH_3)

FTIR (neat, cm^{-1}) 2950 (s), 2929 (s), 2866 (s), 2856 (s), 1732 (s), 1580 (s), 1256 (s), 1149 (s), 1097 (s)

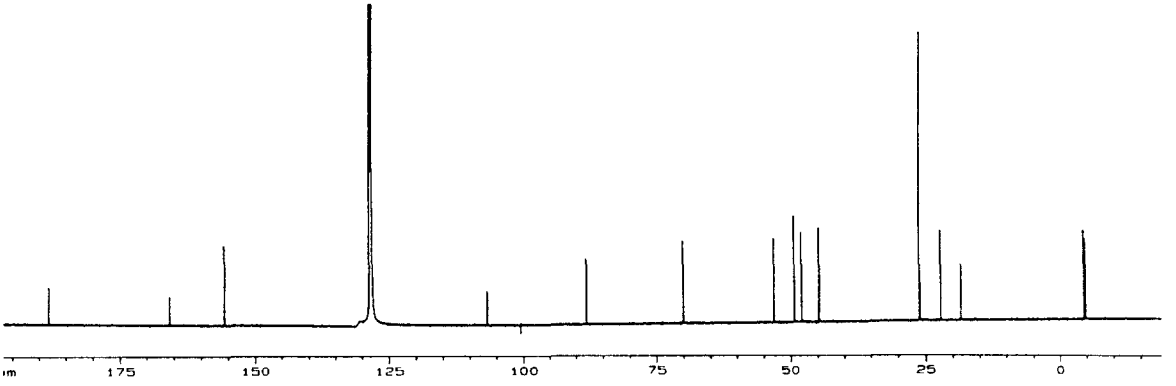
HRMS (EI, m/z) Expected for $C_{13}H_{16}O_4Si$ [(M-C_4H_9I)$^+$] 264.0818, found: 264.0779. (1.1%)

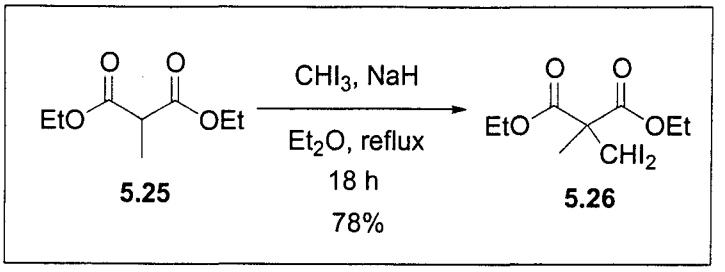


^{1}H NMR (500 MHz, C_6D_6)



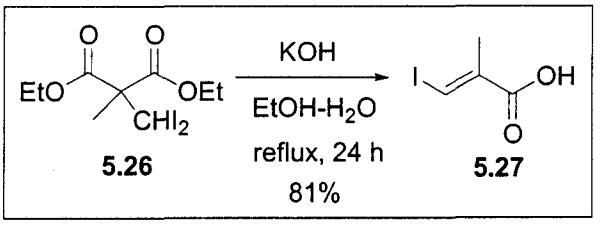
^{13}C NMR (125 MHz, C_6D_6)





Diethyl di-iodomethylmethylmalonate (5.26). Diethyl methylmalonate (30.0 g, 0.172 mol) was added drop-wise over a period of 1 h to a mixture of NaH (6.89 g, 60% dispersion in mineral oil, 0.176 mol) in Et_2O (210 mL). The viscous mixture was refluxed for 2.5 h. Iodoform (67.8 g, 0.172 mmol) was then added and refluxing continued for an additional 20 h. After cooling to 0 °C, a 10% aqueous solution of HCl (100 mL) was added and the mixture was stirred for 10 min. The organic phase was then decanted, dried over anhydrous $MgSO_4$, filtered and concentrated. The remaining residue was diluted with petroleum ether and the precipitated iodoform was filtered and discarded. The solvent was removed once again and the remaining oil was distilled (130 °C at 4 mmHg) to provide 59 g of **5.26** (78%) as a pale pink oil.

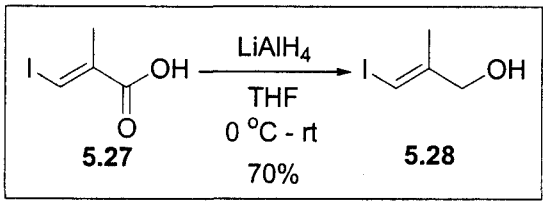
Spectral data of **5.26** is in accordance with the literature data: Baker, D.; Castro, J. L. *J. Chem. Soc. Perkin Trans 1.* **1990**, *1*, 47.



***(E)*-3-Iodo-2-methylpropen-2-oic acid (5.27).** A solution of **5.26** (57.7 g, 0.108 mol) and KOH (18.6 g, 0.331 mol) in a mixture of water-EtOH (1:3, 145 mL) was refluxed for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in a 10% aqueous solution of K_2CO_3 (100 mL) and washed with

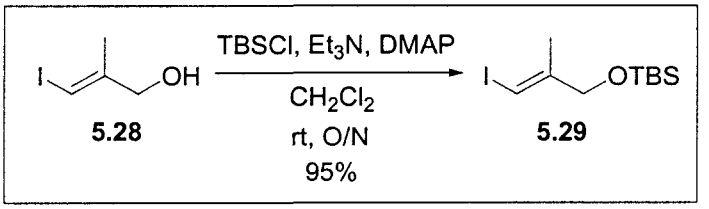
CH_2Cl_2 (2x50 mL). The basic solution was acidified with 12N HCl and the product was extracted with CH_2Cl_2 (3x50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide 23.0 g of **5.27** (81%) which was used directly in the next step without purification.

Spectral data of **5.27** is in accordance with the literature data: Baker, D.; Castro, J. L. *J. Chem. Soc. Perkin Trans 1.* **1990**, *1*, 47.



***(E)*-3-Iodo-2-methylprop-2-enol (5.28).** Lithium aluminum hydride (2.15 g, 56.6 mmol) was added in small portions over a period of 30 min to a 0 °C solution of *(E)*-3-iodo-2-methylpropen-2-oic acid (12.0 g, 56.6 mmol) in THF (95 mL). After stirring for 3 h, a saturated aqueous solution of Na_2SO_4 was added drop-wise to quench the excess hydride. 1N HCl (50 mL) was then added and the product was extracted with Et_2O (3x50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide 7.85 g of **5.28** (70%) which was used directly in the next step without purification.

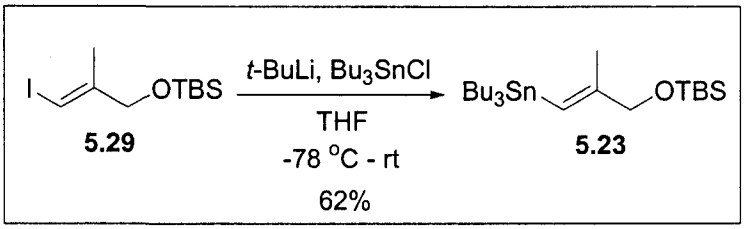
Spectral data of **5.28** is in accordance with the literature data: Baker, D.; Castro, J. L. *J. Chem. Soc. Perkin Trans 1.* **1990**, *1*, 47.



***(E)*-1-(*tert*-Butyldimethylsiloxy)-3-iodo-2-methyl-2-propene (5.29).** *tert*-Butyl dimethylsilyl chloride (9.38 g, 62.2 mmol) was added to a solution of **5.28** (11.2 g, 56.6

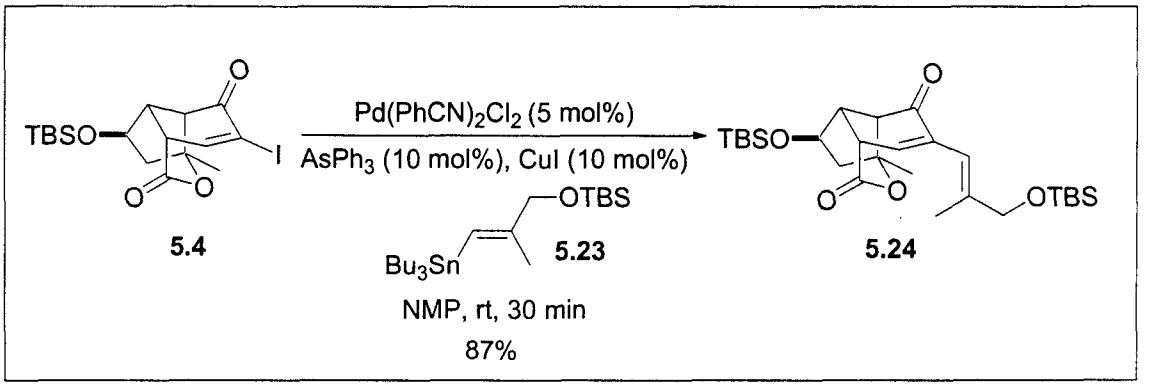
mmol), Et_3N (15.8 mL, 0.113 mol) and DMAP (138 mg, 1.13 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The solution was warmed to room temperature and stirred O/N. The contents of the flask were poured into water (100 mL) and the product was extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with 1N HCl then brine and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel provided 15.2 g of **5.29** (95%) as a clear colorless oil.

Spectral data of **5.29** is in accordance with the literature data: Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139.



***(E)*-1-(*tert*-Butyldimethylsiloxy)-2-methyl-3-(tributylstannyl)-2-propene (5.23).** *tert*-butyllithium (13.1 mL, 1.7 M in pentane, 22.3 mmol) was added over a period of 30 min to a -78 °C solution of vinyl iodide **5.29** (3.0 g, 0.011 mol) in THF (70 mL). The mixture was stirred for 30 min at 78 °C before tributyltin chloride (3.15 mL, 11.7 mmol) was added drop-wise. Following an additional 30 min (at -78 °C), the mixture was warmed to room temperature and stirred for 15 min. The product was concentrated under reduced pressure, suspended in hexanes (50 mL) and washed with H_2O (2x30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash chromatography on silica gel basified with Et_3N (100% hexanes) provided 3.1 g of **5.23** (62%) as a clear colorless oil.

Spectral data of **5.18** is in accordance with the literature data: Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139.



(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-(*tert*-butyl-dimethyl-silanyloxy)-2-methylprop-1-en-1-yl]-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (5.24). Triphenylarsine (5 mg, 10 mol%, 0.01 mmol), $Pd(PhCN)_2Cl_2$ (3 mg, 5 mol%, 0.007 mmol) and CuI (3 mg, 10 mol%, 0.01 mmol) were weighed in the glove-box and placed into a flame-dried round bottom flask. After equipping the flask with a balloon of argon, a solution of iodoenone **5.4** (50 mg, 0.15 mmol) in NMP (1.5 mL) was added. Vinyl stannane **5.23** (70 mg, 0.15 mmol) was then cannulated into the mixture using 1 mL of NMP and the reaction was stirred for 30 min. The contents of the flask were then poured into H_2O (5 mL) and the product was extracted with EtOAc (3x20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes: EtOAc) provided 65 mg of **5.24** (87%) as a clear colorless oil.

Data for **5.24:**

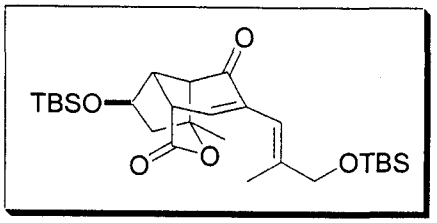
^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 6.81 (d, J = 7.9 Hz, 1H), 6.65 (m, 1H), 3.97 (s, 2H), 3.77 (ddd, J = 9.1, 6.3, 2.5 Hz, 1H), 3.61 (ddd, J = 7.6, 3.5, 1.7 Hz, 1H), 2.47 – 2.42 (m, 1H), 1.96

(d, J = 5.2 Hz, 1H), 1.76 (dd, J = 14.2, 2.1 Hz, 1H), 1.51 (s, 3H), 1.40 (dd, J = 14.9, 9.6 Hz, 1H), 1.26 (s, 3H), 1.01 (s, 9H), 0.97 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), -0.03 (s, 3H), -0.06 (s, 3H)

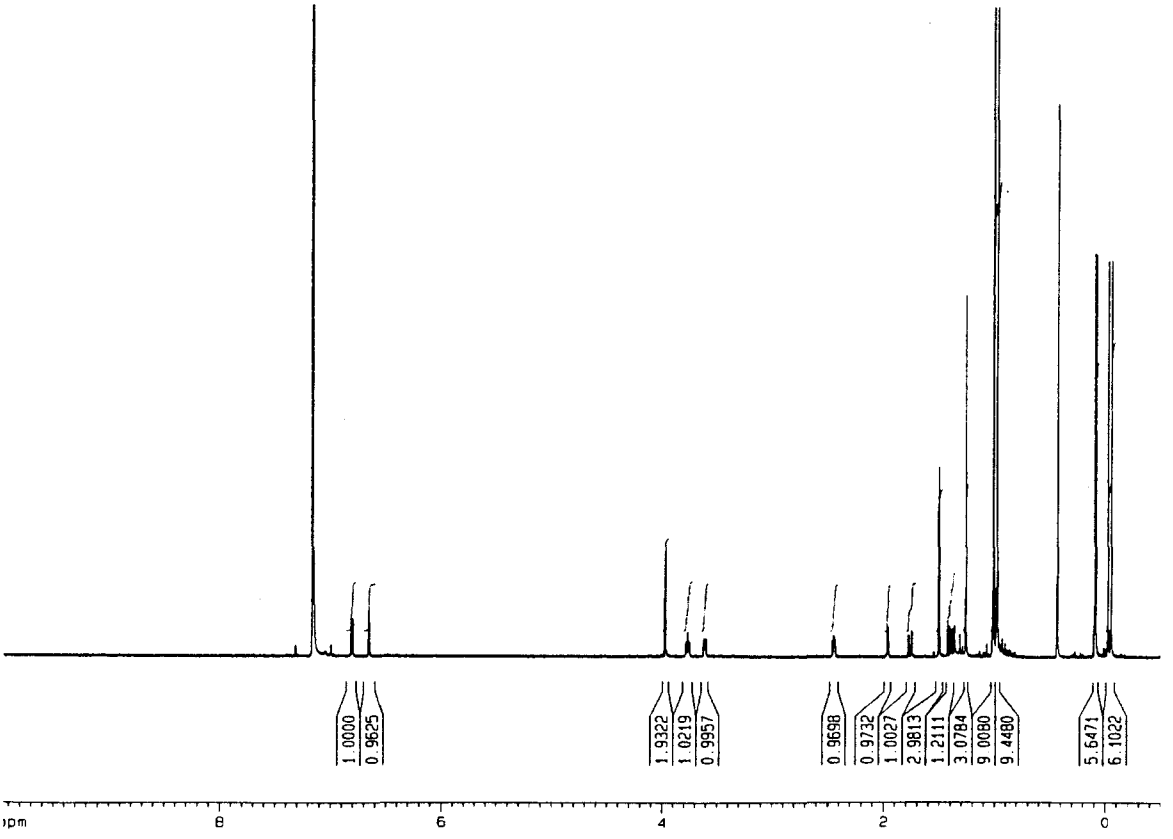
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 194.4 (C_4), 168.2 (C_4), 143.8 (CH), 142.0 (C_4), 139.8 (C_4), 117.3 (CH), 88.2 (C_4), 70.9 (CH), 69.0 (CH_2), 54.7 (CH), 50.0 (CH_2), 48.2 (CH), 41.6 (CH), 26.8 (3xCH_3), 26.6 (3xCH_3), 22.8 (CH_3), 19.2 (C_4), 18.9 (C_4), 16.0 (CH_3), -4.1 (CH_3), -4.4 (CH_3), -4.5 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2954 (m), 2929 (s), 2856 (s), 1744 (s), 1678 (s), 1251 (s), 1084 (s), 837 (s)

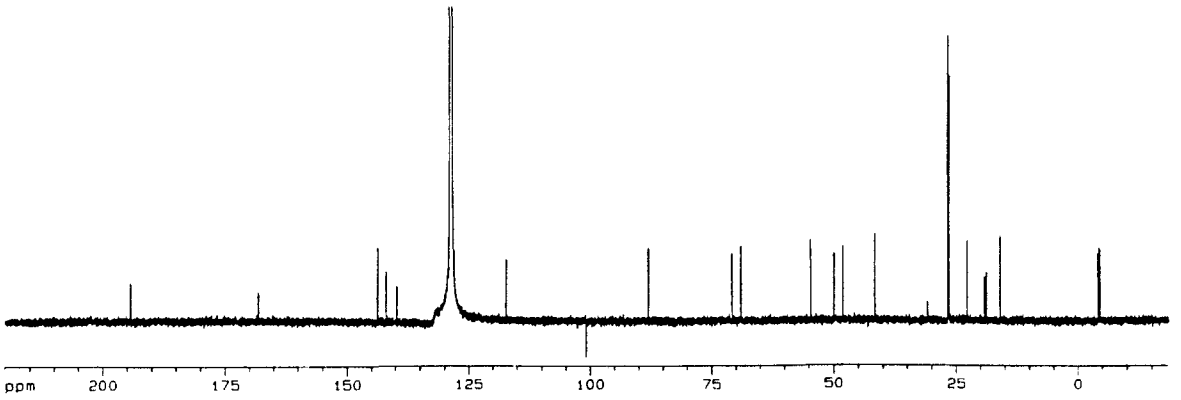
HRMS (EI, m/z) Expected for $C_{27}H_{46}O_5Si_2$ [$(M)^+$] 506.2884, found: 506.2864. (8.75%)

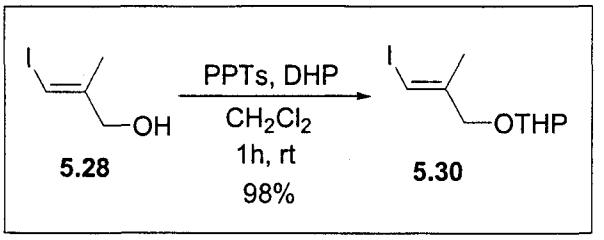


^{1}H NMR (500 MHz, C_6D_6)



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





2-((*E*)-3-Iodo-2-methylallyloxy)-tetrahydro-2*H*-pyran (5.30). (*E*)-3-Iodo-2-methylprop-2-en-1-ol (1.0 g, 5.1 mmol) was dissolved in CH_2Cl_2 (10 mL). Dihydropyran (0.69 mL, 7.6 mmol) was added followed by pyridinium *p*-toluenesulfonate (127 mg, 0.505 mmol). The reaction was stirred for 1 h at room temperature and then poured into brine (50 mL). The product was extracted with CH_2Cl_2 (3x50 mL) dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel provided 1.40 g of **5.30** (98%) as a clear colorless oil.

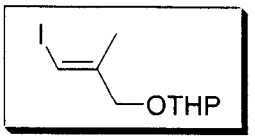
Data for **5.30:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 6.24 – 6.23 (m, 1H), 4.59 – 4.57 (m, 1H), 4.15 (d, J = 12.9 Hz, 1H), 3.95 (d, J = 12.9 Hz, 1H), 3.84 – 3.77 (m, 1H), 3.51 – 3.45 (m, 1H), 1.81 (s, 3H), 1.76 – 1.48 (m, 6H)

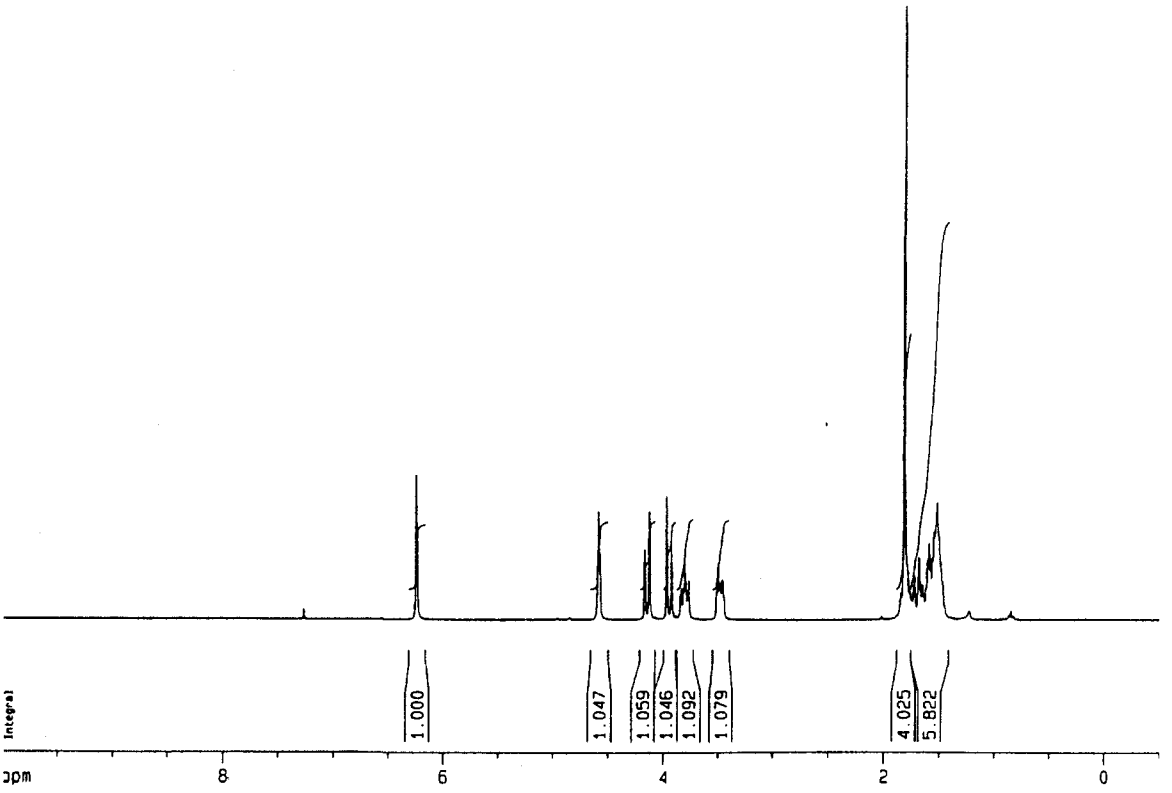
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 144.4 (C_4), 97.4 (CH), 78.1 (CH), 70.4 (CH_2), 61.9 (CH_2), 30.3 (CH_2), 25.6 (CH_2), 21.6 (CH_3), 19.1 (CH_2)

FTIR (neat, cm^{-1}) 2940 (s), 2870 (s), 2849 (s), 1621 (w), 1453 (m), 1347 (m), 1287 (s)

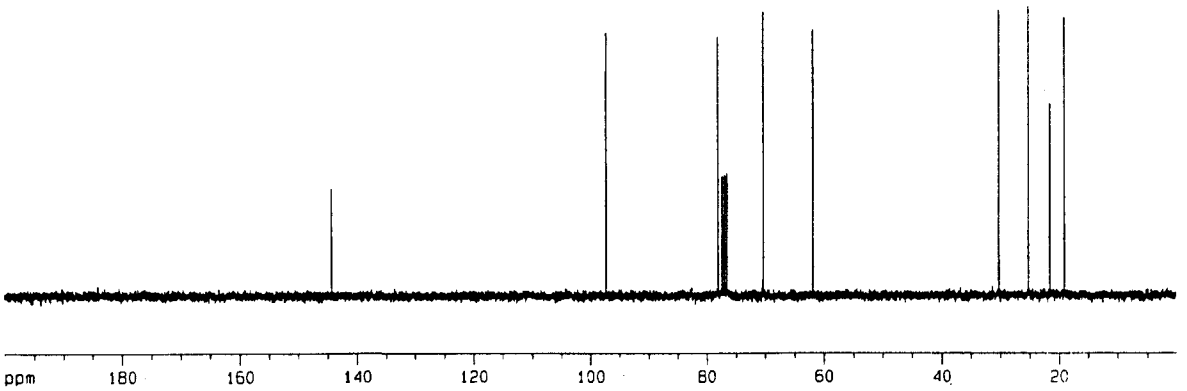
HRMS (EI, m/z) Expected for $C_9H_{15}O_2$ [$(M-I)^+$] 155.1072, found: 155.1090. (5.2%)

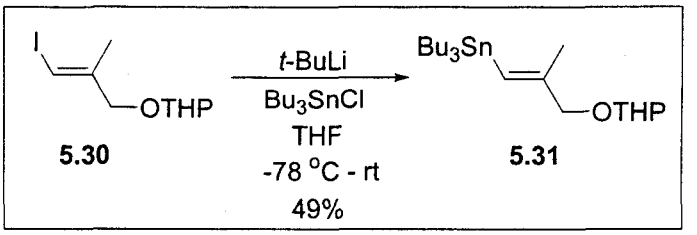


^{1}H NMR (300 MHz, $CDCl_3$)



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





Tributyl((*E*)-2-methyl-3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-enyl)stannane (5.31). *tert*-Butyllithium (2.6 mL, 4.1 mmol) was added drop-wise over a period of 20 min to vinyl iodide **5.30** (555 mg, 1.98 mmol) in THF (12 mL) at – 78 °C. After stirring for 30 min, Bu_3SnCl (0.58 mL, 2.2 mmol) was slowly added. Following an additional 30 min of stirring at – 78 °C, the flask was warmed to room temperature and stirred for 15 min. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel to provide 430 mg of **5.31** (49%) as a clear colorless oil.

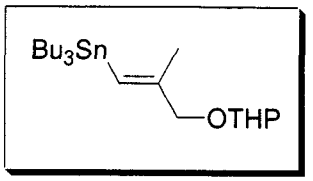
Data for **5.31:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 5.81 (s, 1H), 4.63 – 4.61 (m, 1H), 4.18 (d, J = 13.3 Hz, 1H), 3.98 – 3.80 (m, 2H), 3.54 – 3.47 (m, 1H), 1.77 (s, 3H), 1.59 – 1.41 (m, 6H), 1.38 – 1.24 (m, 9H), 0.82 (m, 18H)

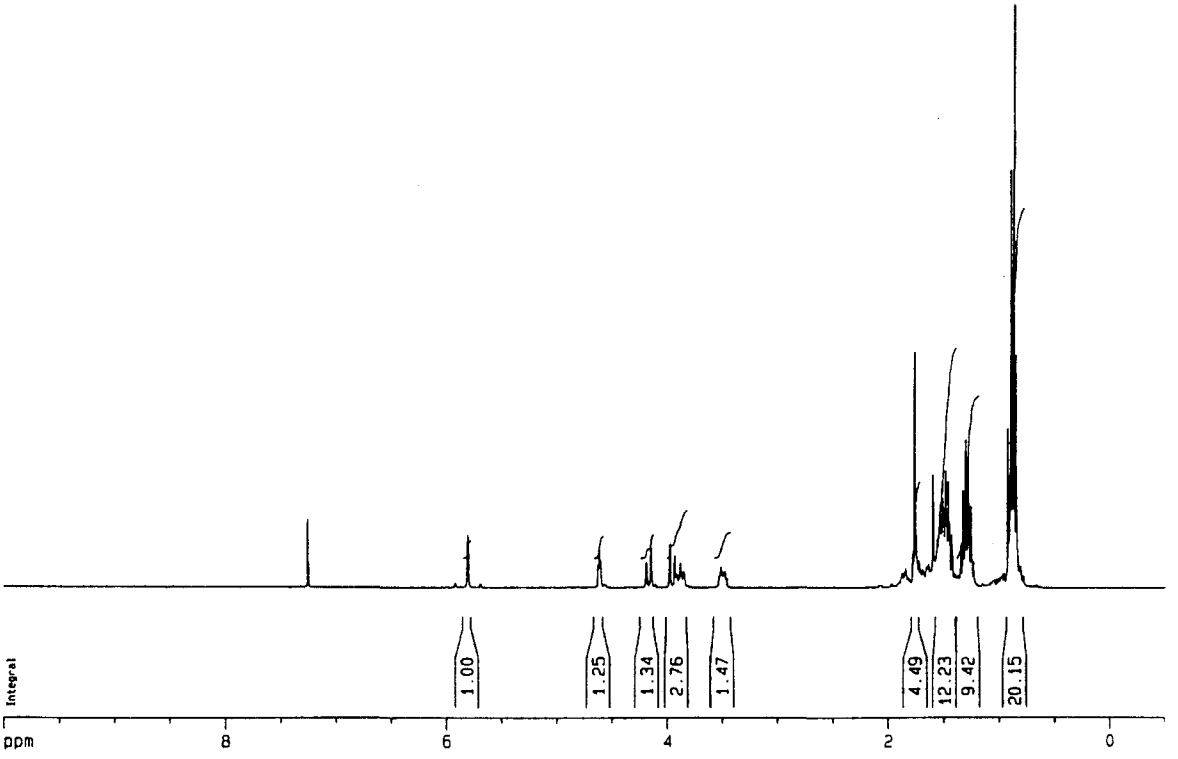
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} 150.3 (C_4), 123.9 (CH), 97.4 (CH), 73.1 (CH_2), 62.2 (CH_2), 30.7 (CH_2), 29.2 (CH_2), 27.3 (CH_2), 25.5 (CH_2), 21.7 (CH_3), 19.5 (CH_2), 13.7 (CH_3), 10.0 (CH_2)

FTIR (neat, cm^{-1}) 2955 (s), 2925 (s), 2852 (s), 1674 (w), 1463 (m), 1021 (s)

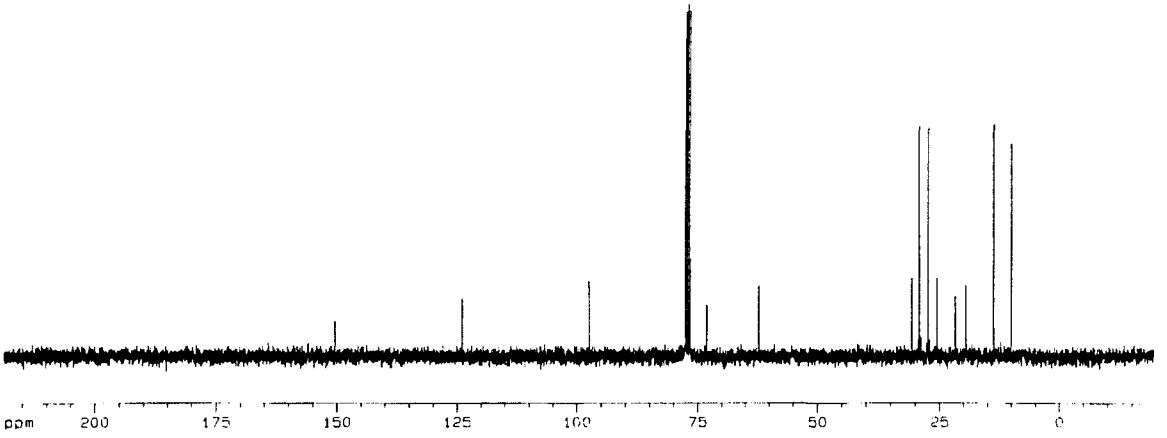
HRMS (EI, m/z) Expected for $C_{17}H_{33}O_2Sn$ [$(M-C_4H_9)^+$] 389.1503, found: 389.1484. (44.7%)

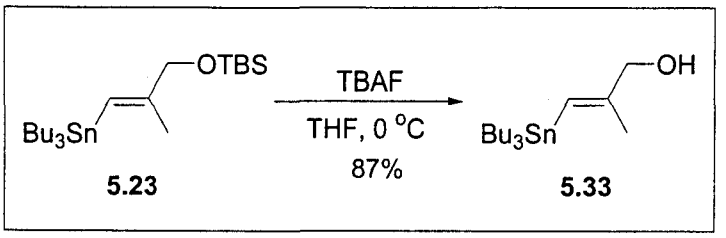


^{1}H NMR (300 MHz, $CDCl_3$)



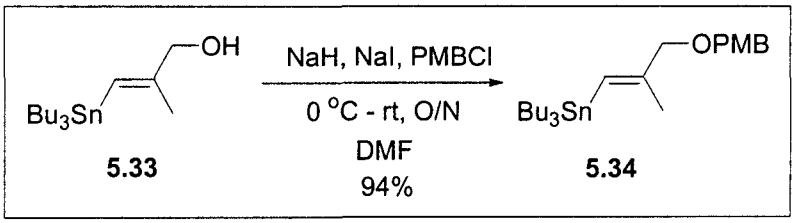
^{13}C NMR (75 MHz, $CDCl_3$)





***(E)*-3-(Tributylstannyl)-2-methylpropen-1-ol (5.33).** Tetrabutylammonium fluoride (4.2 mL, 1.0 M in THF, 4.2 mmol) was added to a solution of **5.23** (2.0 g, 4.2 mmol) in THF (50 mL) at 0 °C. The contents were warmed to room temperature and stirred for 1 h before being quenched with a saturated aqueous solution of NH_4Cl (~2 mL). The mixture was concentrated under reduced pressure and then dissolved in Et_2O (30 mL). The organic phase was washed with H_2O, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (5:1 hexanes:EtOAc) provided 1.32 g of **5.33** (87%) as a clear colorless oil.

Spectral data of **5.33** is in accordance with the literature data: Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139.



((*E*)-3-(4-Methoxybenzyloxy)-2-methylprop-1-enyl)tributylstannane (5.34). Sodium iodide (1 mg, 0.007 mmol) was flame-dried under vacuum in a round bottom flask. After cooling to room temperature, the flask was fitted with a balloon of argon and DMF (1 mL) was added followed by NaH (28 mg, 0.69 mmol). The mixture was cooled to 0 °C and then **5.33** (50 mg, 0.14 mmol) was cannulated into the flask as a solution in DMF (0.5 mL). After

stirring for 5 min, PMBCl (87 mg, 0.55 mmol) was added. The contents of the flask were warmed to room temperature and stirred O/N. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (3x30 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) provided 63 mg of **5.34** (94%) as a clear colorless oil.

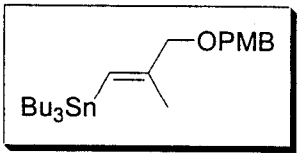
Data for **5.34:**

^{1}H NMR (300 MHz, C_6D_6) δ_{ppm} 7.30 – 7.27 (m, 2H), 6.82 – 6.79 (m, 2H), 6.12 (m, 1H), 4.41 (s, 2H), 3.96 (s, 2H), 3.29 (s, 3H), 1.89 – 1.85 (m, 3H), 1.68 – 1.55 (m, 6H), 1.44 – 1.33 (m, 6H), 1.06 – 1.01 (m, 5H), 0.96 – 0.91 (m, 10H)

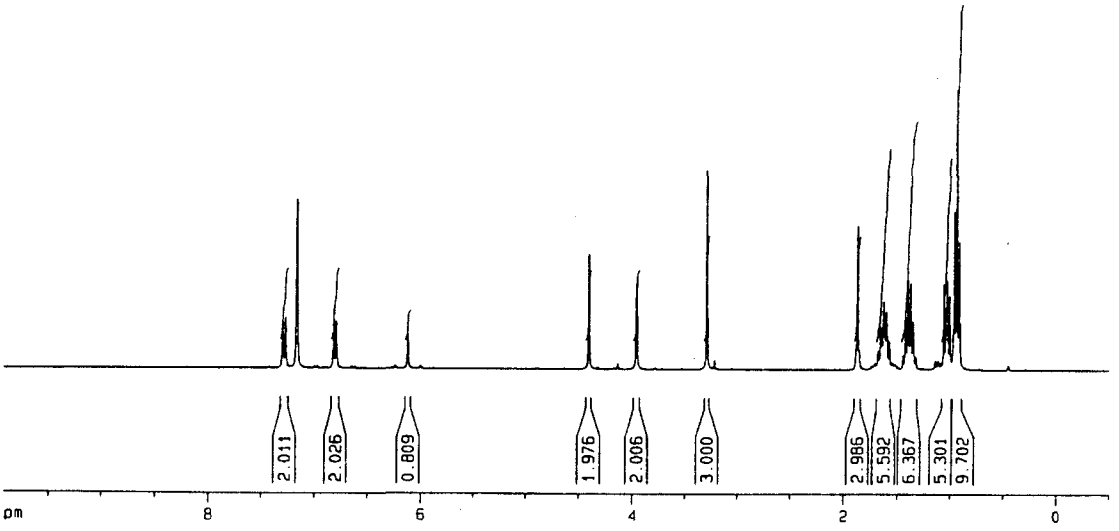
^{13}C NMR (75 MHz, C_6D_6) δ_{ppm} 160.5 (C_4), 152.0 (C_4), 131.6 (C_4), 129.8 (CH), 124.3 (CH), 114.4 (CH), 77.0 (CH_2), 72.1 (CH_2), 55.1 (CH_3), 30.1 (CH_2), 28.1 (CH_2), 22.3 (CH_3), 14.3 (CH_3), 10.8 (CH_2)

FTIR (neat, cm^{-1}) 2955 (s), 2925 (s), 2851 (s), 1613 (m), 1513 (m), 1463 (m), 1248 (s)

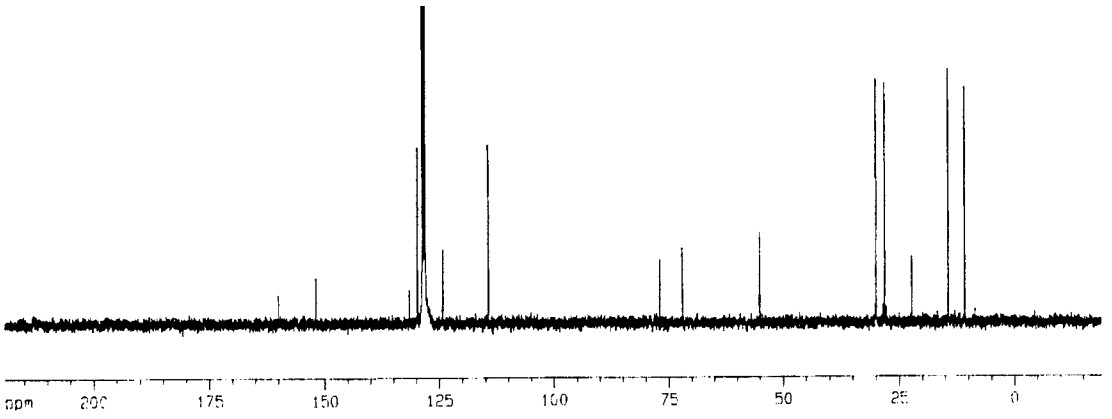
HRMS (EI, m/z) Expected for $C_{20}H_{33}O_2Sn$ $[(M-C_4H_9)^+]$ 425.1503, found: 425.1512. (60.7%)

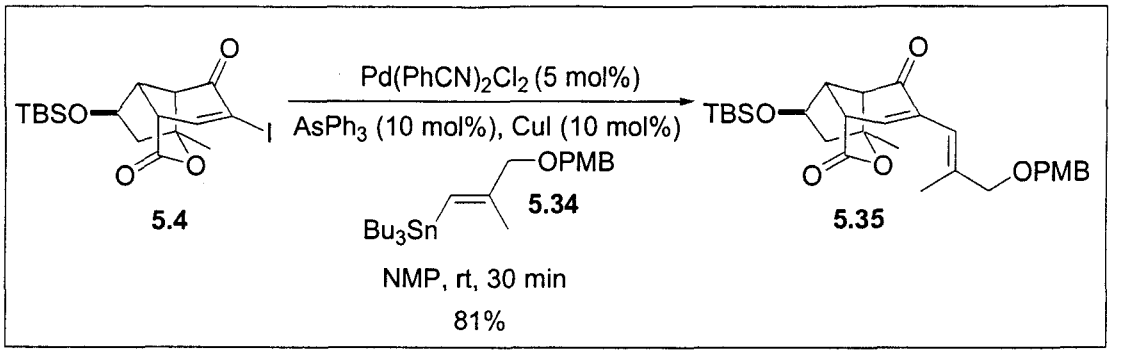


^{1}H NMR (300 MHz, C_6D_6)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-(4-methoxybenzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (5.35). Triphenylarsine (9 mg, 10 mol%, 0.03 mmol), $Pd(PhCN)_2Cl_2$ (5 mg, 5 mol%, 0.01 mmol), and CuI (5 mg, 10 mol%, 0.03 mmol) were weighed in the glove-box and placed into a flame-dried round bottom flask. After equipping the flask with a balloon of argon, a solution of enone **5.4** (96 mg, 0.28 mmol) in NMP (1.5 mL) was added. Vinyl stannane **5.34** (136 mg, 0.140 mmol) was then cannulated into the mixture using 1 mL of NMP and the reaction was stirred for 30 min. The contents of the flask were then poured into H_2O (5 mL) and the product was extracted with EtOAc (3x10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 hexanes: EtOAc) provided 117 mg of **5.35** (81%) as a white solid (melting point: 60.8 °C – 61.9 °C).

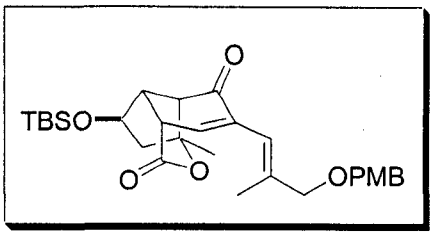
Data for **5.35:**

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 7.30 – 7.28 (m, 2H), 7.12 (dd, J = 8.0 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.26 (m, 1H), 4.51 (ddd, J = 8.9, 6.6, 2.5 Hz, 1H), 4.43 (s, 2H), 3.98 (s, 2H), 3.82 (s, 3H), 3.65 (ddd, J = 7.8, 3.3, 1.7 Hz, 1H), 3.18 (ddd, J = 6.0, 5.1, 3.5 Hz, 1H), 2.56 (d, J = 5.1 Hz, 1H), 2.24 (dd, J = 15.0, 9.4 Hz, 1H), 2.12 (dd, J = 15.5, 2.1 Hz, 1H), 1.77 (d, J = 1.3 Hz, 3H), 1.47 (s, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

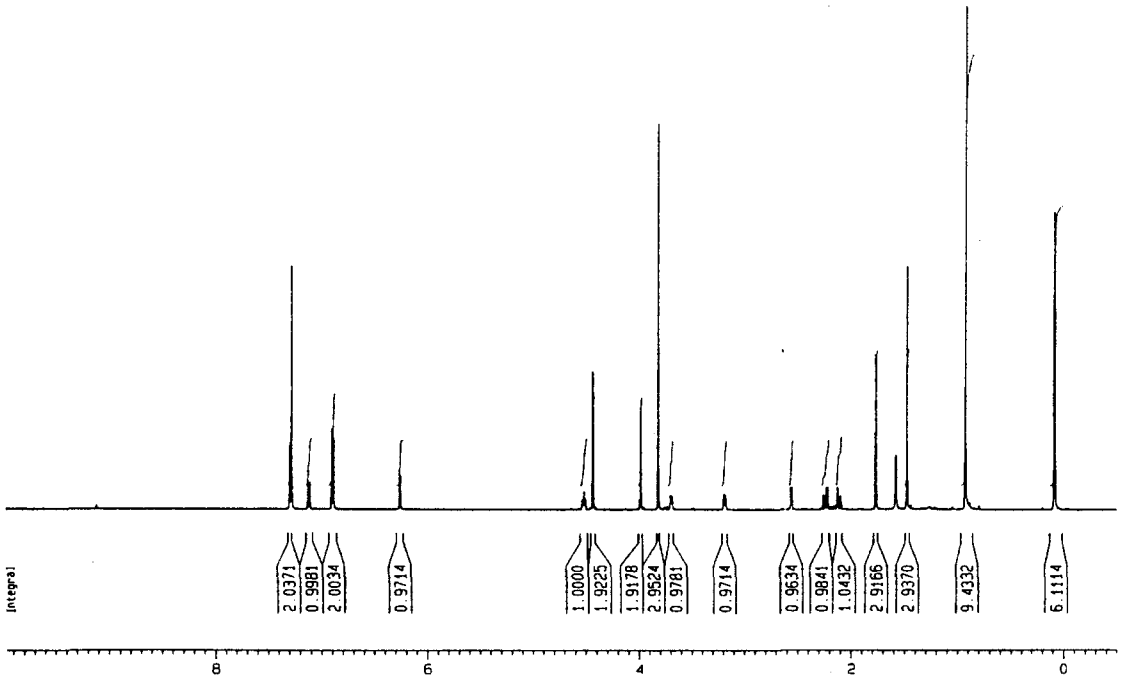
^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 194.3 (C_4), 168.8 (C_4), 159.4 (C_4), 143.9 (CH), 139.7 (C_4), 139.0 (C_4), 130.5 (C_4), 129.7 (CH), 118.9 (CH), 114.0 (CH), 88.5 (C_4), 75.6 (CH_2), 71.8 (CH_2), 70.0 (CH), 55.5 (CH_3), 54.2 (CH), 49.8 (CH_2), 47.6 (CH), 40.6 (CH), 25.9 (3xCH_3), 22.1 (CH_3), 18.2 (C_4), 16.2 (CH_3), -4.6 (CH_3), -4.9 (CH_3)

FTIR (neat, cm^{-1}) 2925 (s), 2854 (s), 1746 (s), 1698 (s), 1613 (m), 1513 (m), 1247 (s), 1081 (m)

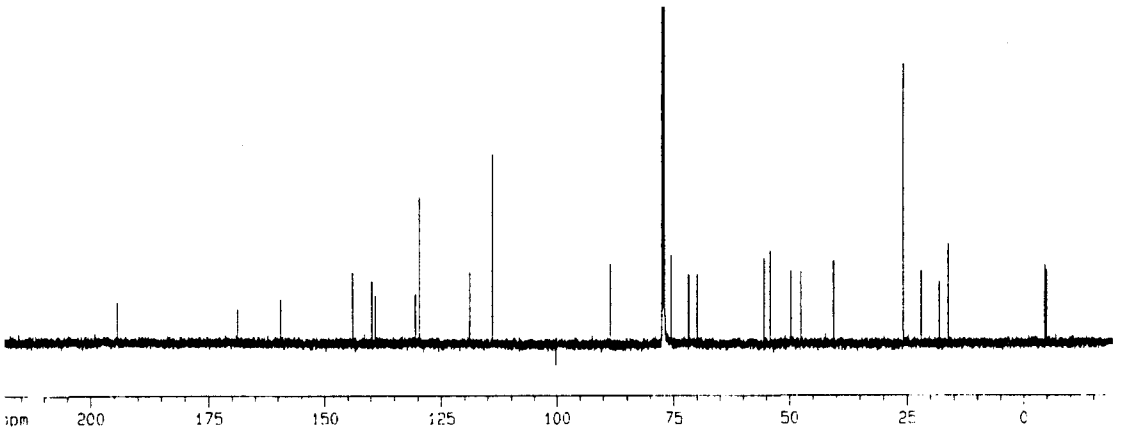
HRMS (EI, m/z) Expected for $C_{29}H_{40}O_6Si$ [$(M)^+$] 512.2594, found: 512.2568. (8.5%)

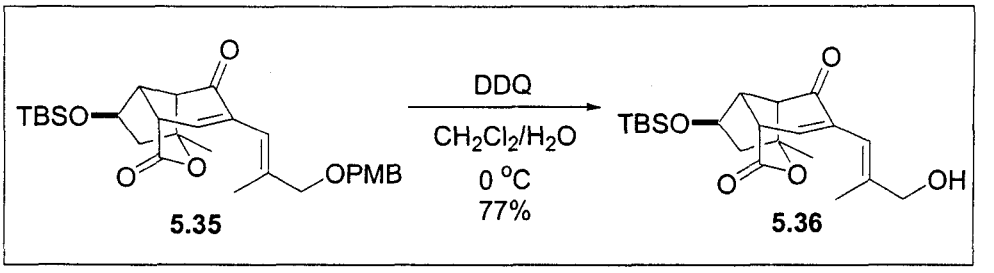


^{1}H NMR (500 MHz, $CDCl_3$)



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





5.35 **5.36**

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-hydroxy-2-methylprop-1-en-1-yl]-4-methyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-ene-2,9-dione (5.36). Ketone **5.35** (20 mg, 0.039 mmol) was dissolved in a biphasic mixture of CH_2Cl_2 (0.9 mL) and H_2O (0.1 mL) and cooled to 0 °C. DDQ (9 mg, 0.04 mmol) was then added. The reaction was stirred for 1 h at 0 °C before being quenched with an aqueous saturated solution of $Na_2S_2O_3$ (5 mL). The product was extracted with CH_2Cl_2 (3x10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (1:5 EtOAc:hexanes) provided 11 mg of **5.36** (77%) as a clear colorless oil.

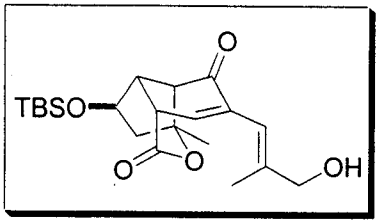
Data for **5.36:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.11 (d, J = 7.7 Hz, 1H), 6.24 (m, 1H), 4.52 (ddd, J = 9.0, 7.2, 2.8 Hz, 1H), 4.14 (s, 2H), 3.72 – 3.68 (m, 1H), 3.20 (ddd, J = 6.1, 5.2, 3.5 Hz, 1H), 2.56 (d, J = 9.1 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.11 (dd, J = 14.9, 2.2 Hz, 1H), 1.76 – 1.75 (m, 3H), 1.61 (brs, 1H) 1.47 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H)

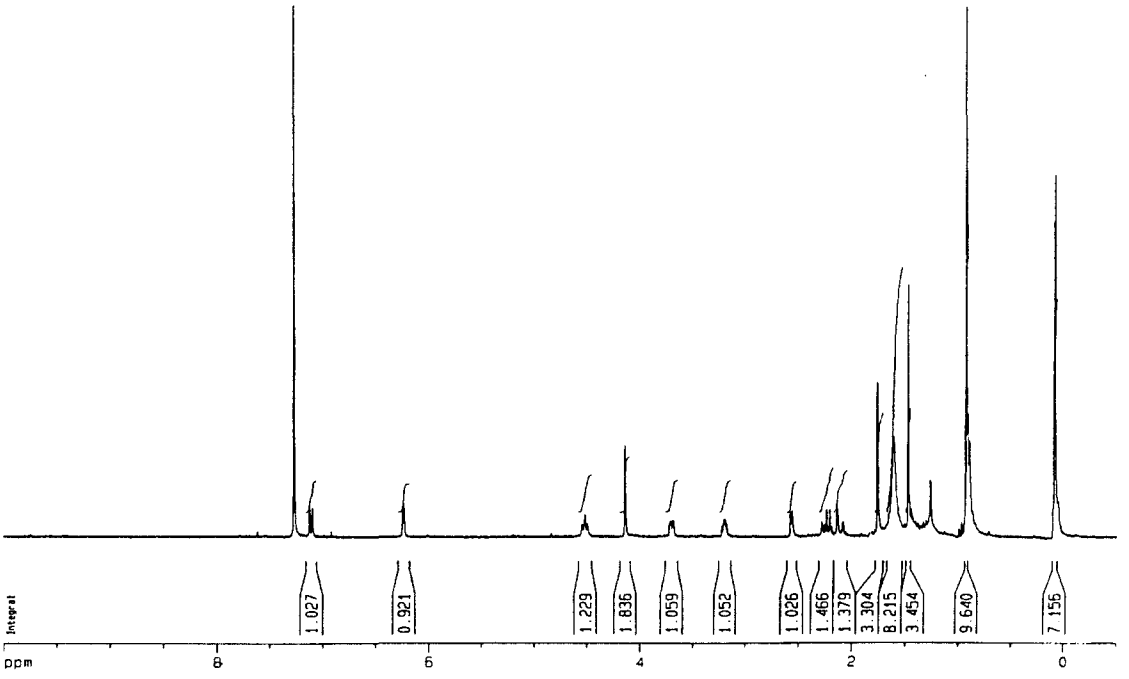
^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 194.5 (C_4), 168.8 (C_4), 144.1 (CH), 142.3 (C_4), 139.0 (C_4), 116.8 (CH), 88.5 (C_4), 70.0 (CH), 68.5 (CH_2), 54.2 (CH), 49.8 (CH_2), 47.6 (CH), 40.6 (CH), 25.9 (3xCH_3), 22.1 (CH_3), 18.2 (C_4), 15.9 (CH_3), -4.6 (CH_3), -4.9 (CH_3)

FTIR (neat, cm^{-1}) 3461 (brs), 2956 (m) 2929 (s), 2858 (s), 1735 (s), 1676 (s), 1246 (m)

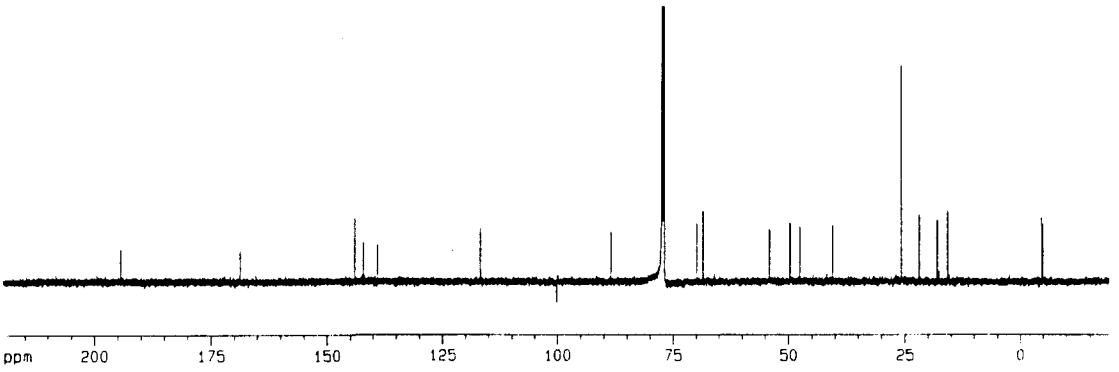
HRMS (EI, m/z) Expected for $C_{17}H_{23}O_5Si$ [(M-C_4H_9)$^+$] 335.1315, found: 335.1320. (69.7%)

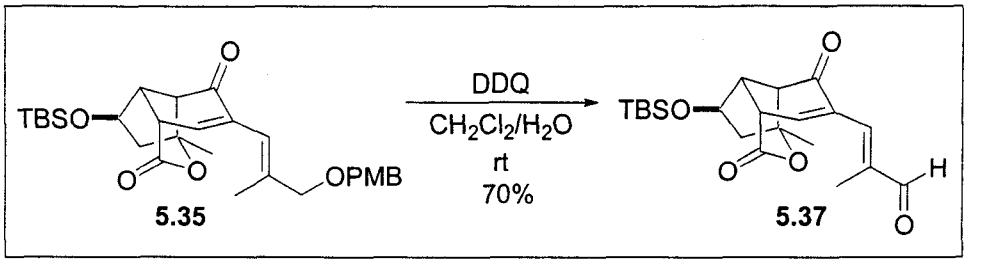


^{1}H NMR (300 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*)-3(*E*)-[6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-2,9-dioxo-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-10-yl]-2-methylacrylaldehyde (5.37). Ketone **5.35** (13 mg, 0.025 mmol) was dissolved in a biphasic mixture of CH_2Cl_2 (0.9 mL) and H_2O (0.1 mL) at 0 °C. DDQ (7 mg, 0.03 mmol) was subsequently added and the flask was warmed to room temperature. After stirring for 1 h, the reaction was quenched with an aqueous saturated solution of $Na_2S_2O_3$ (5 mL). The product was extracted with CH_2Cl_2 (3x10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10:1 Hexanes: Et_2O) provided 7 mg of **5.37** (70%) as a clear colorless oil.

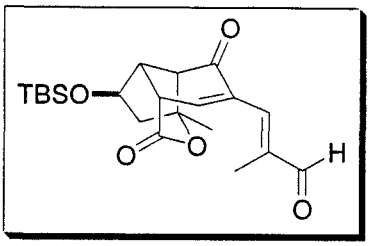
Data for **5.37:**

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 9.56 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.20 – 7.19 (m, 1H), 4.65 (ddd, J = 8.9, 6.5, 2.4 Hz, 1H), 3.83 (ddd, J = 7.8, 3.4, 1.6 Hz, 1H), 3.25 (ddd, J = 6.2, 5.1, 3.5 Hz, 1H), 2.65 – 2.64 (m, 1H), 2.27 (dd, J = 15.0, 9.4 Hz, 1H), 2.16 – 2.12 (m, 1H), 1.91 – 1.90 (m, 3H), 1.50 (s, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H)

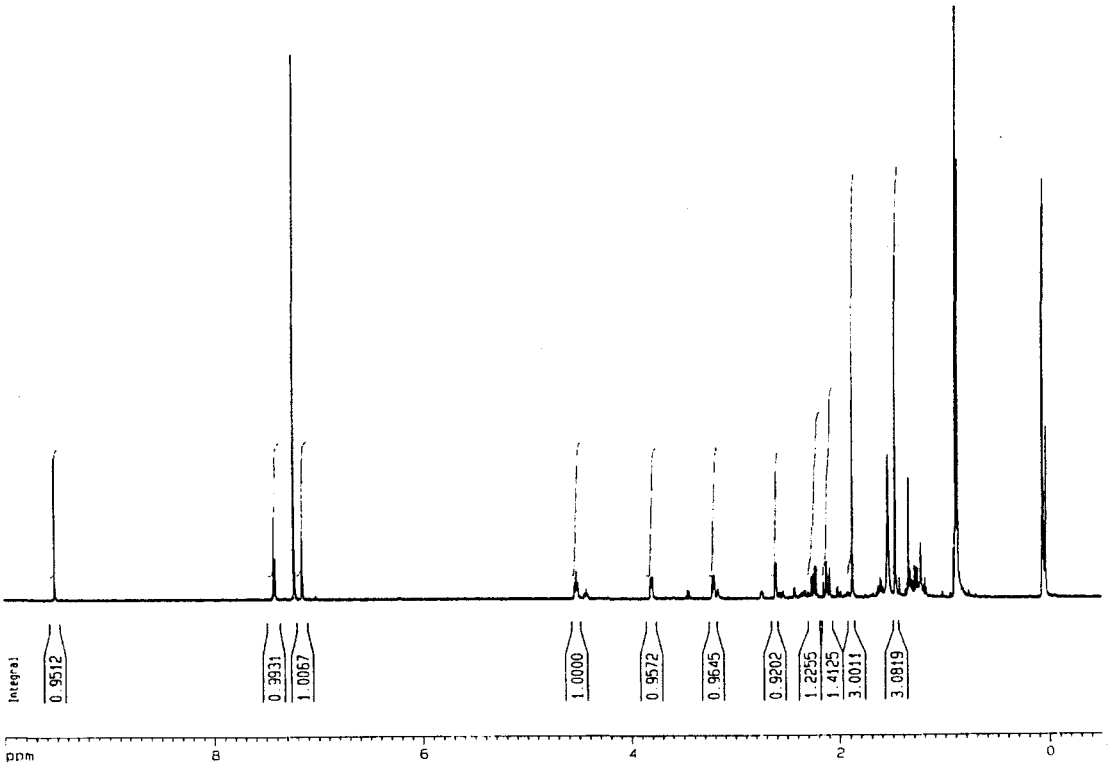
^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 195.2 (CH), 193.4 (C_4), 167.9 (C_4), 147.8 (CH), 141.8 (C_4), 140.0 (CH), 137.8 (C_4), 89.2 (C_4), 70.2 (CH), 54.2 (CH), 49.4 (CH), 47.4 (CH_2), 41.3 (CH), 26.1 (3xCH_3), 22.3 (CH_3), 18.0 (C_4), 11.8 (CH_3), -4.3 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2954 (s), 2930 (s), 2856 (s), 1746 (s), 1682 (s), 1250 (m)

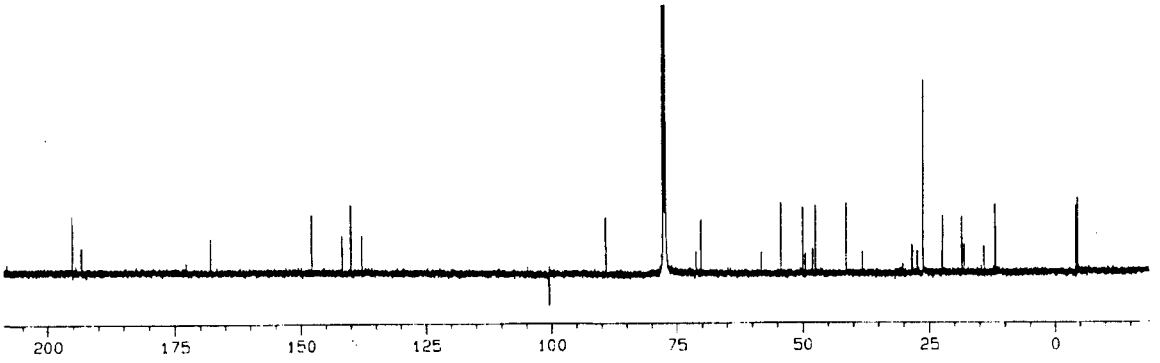
HRMS (EI, m/z) Expected for $C_{17}H_{21}O_5Si$ [(M-C_4H_9)$^+$] 333.1158, found: 333.1144. (2.32%)

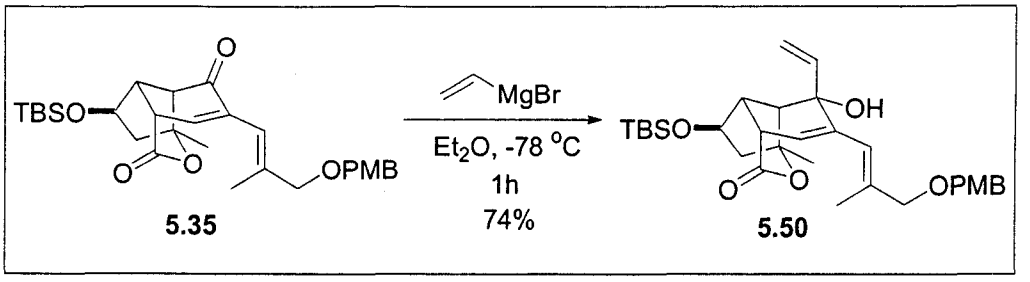


^{1}H NMR (500 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-9-hydroxy-10-[(1*E*)-3-(4-methoxybenzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-9-vinyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.50). Vinylmagnesium bromide (130 μL, 0.86 M, 0.111 mmol) was added to a solution of **5.35** (19 mg, 0.037 mmol) in Et_2O (0.5 mL) at -78 °C and stirred for 1 h. The reaction was quenched with an aqueous solution of NH_4Cl and the product was extracted with Et_2O (3x30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (5:2 hexanes:Et_2O) provided 15 mg of **5.50** (74%) as a clear colorless oil.

Data for **5.50:**

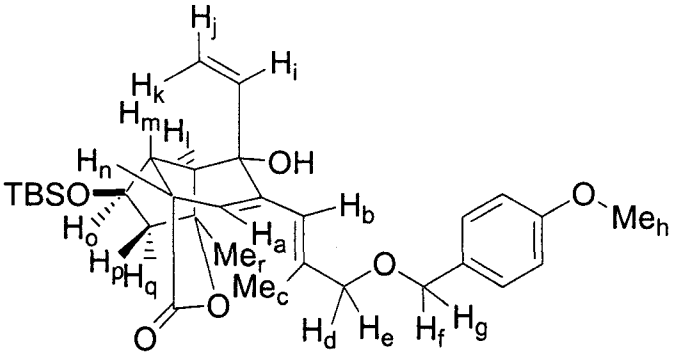
^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 7.26 – 7.25 (m, 2H), 6.90 – 6.88 (m, 2H), 6.04 (d, J = 7.2 Hz, 1H), 5.95 (dd, J_{BX} = 17.1, J_{AX} = 10.5 Hz, 1H), 5.88 – 5.87 (m, 1H), 5.26 (dd, J_{BX} = 17.2, J_{AB} = 0.76 Hz, 1H), 5.15 (dd, J_{AX} = 10.5, J_{AB} = 0.92 Hz, 1H), 4.40 (s, 2H), 4.37 (ddd, J = 9.5, 6.1, 2.9 Hz, 1H), 3.92 (s, 2H), 3.82 (s, 3H), 3.42 – 3.40 (m, 1H), 2.70 (ddd, J = 6.5, 3.9, 3.9 Hz, 1H), 2.19 (dd, J = 15.1, 9.8, 1H), 1.95 – 1.92 (m, 2H), 1.77 – 1.76 (m, 3H), 1.63 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 171.6 (C_4), 159.4 (C_4), 143.9 (CH), 141.4 (C_4), 140.7 (C_4), 130.5 (C_4), 129.6 (CH), 127.2 (CH), 121.7 (CH), 114.0 (CH), 113.2 (CH_2), 89.1 (C_4), 76.3 (C_4), 75.4 (CH_2), 71.9 (CH_2), 69.6 (CH), 55.5 (CH_3), 51.0 (CH_2), 50.2 (CH), 45.2 (CH), 39.7 (CH), 25.9 (3xCH_3), 24.6 (CH_3), 18.2 (C_4), 16.1 (CH_3), -4.6 (CH_3), -4.8 (CH_3)

FTIR (neat, cm^{-1}) 3441 (brs), 2926 (s), 2853 (s), 1738 (s), 1513 (s), 1249 (s), 1084 (m)

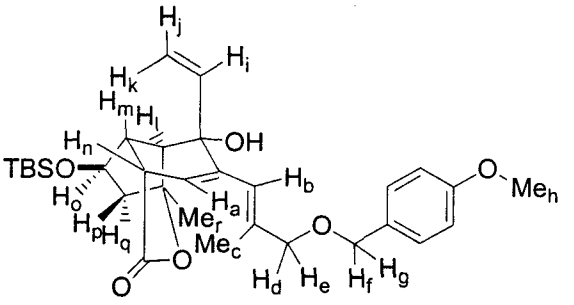
HRMS (EI, m/z) Expected for $C_{31}H_{44}O_6Si$ $[(M)^+]$ 540.2907, found: 540.3082 (31.8%)

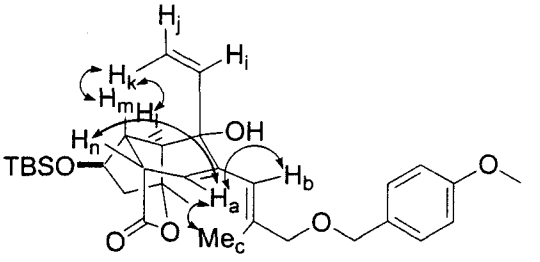
Table 7.11: *COSY data for* ***5.50***



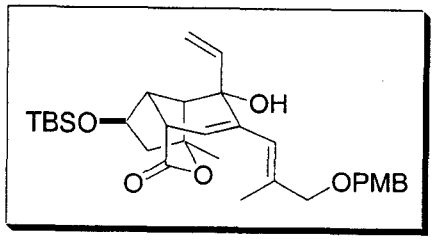
COSY data			
Proton (δ)	**Correlation**	**Proton (δ)**	**Correlation**
H_a (6.04)	H_n	$H_{(l,p)}$ (1.94)	H_m, H_n, H_o, H_q
H_b (5.88)	Me_c, $H_{(d,e)}$	H_m (2.70)	$H_{(l,p)}$, H_n, H_o
Me_c (1.77)	H_b, $H_{(d,e)}$	H_n (3.40)	H_a, $H_{(l,p)}$, H_m
$H_{(d,e)}$ (3.92)	H_b, Me_c	H_o (4.37)	$H_{(l,p)}$, H_m, H_q
$H_{(f,g)}$ (4.40)	Aromatic (7.25)	H_q (2.19)	$H_{(l,p)}$, H_o
Me_h (3.82)	-	Me_r (1.63)	-
H_i (5.95)	H_k, H_j	Aromatic (7.25)	Aromatic (6.89), $H_{(f,g)}$
H_j (5.15)	H_i, H_k	Aromatic (6.89)	Aromatic (7.25)
H_k (5.26)	H_i, H_j		

Table 7.12: NOESY data for ***5.50***

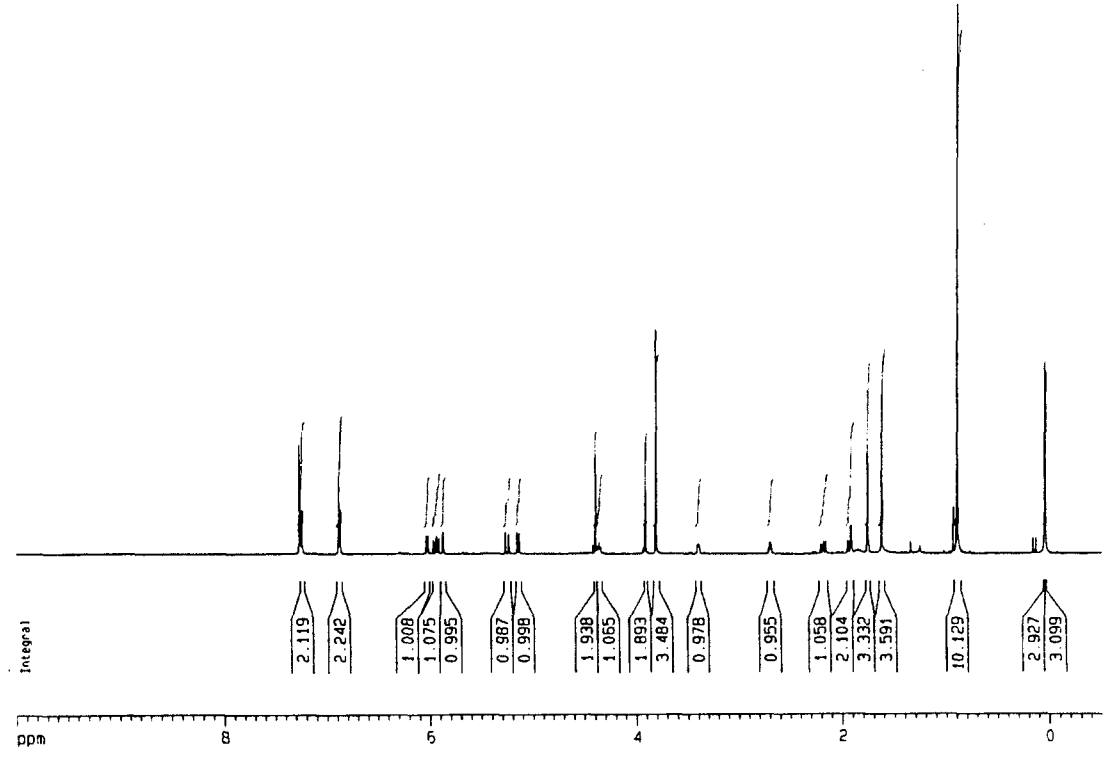




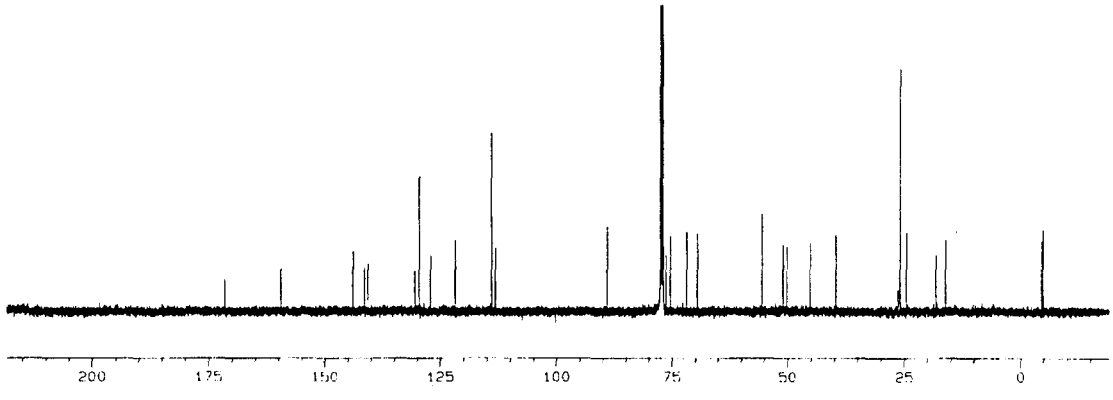
NOESY data			
Proton (δ)	**nOe with proton**	**Proton (δ)**	**nOe with proton**
H_a (6.04)	H_b, Me_c, H_n	$H_{(l,p)}$ (1.94)	H_i, H_k, H_m, H_n, H_o, H_q, Me_r
H_b (5.88)	H_a, Me_c, $H_{(d,e)}$, $H_{(f,g)}$, Me_r	H_m (2.70)	H_i, H_j, H_k, $H_{(l,p)}$, H_n, H_o
Me_c (1.77)	H_a, H_b, $H_{(d,e)}$, $H_{(f,g)}$	H_n (3.40)	H_a, $H_{(l,p)}$, H_m
$H_{(d,e)}$ (3.92)	H_b, $H_{(f,g)}$, Me_c	H_o (4.37)	$H_{(l,p)}$, H_m, H_q
$H_{(f,g)}$ (4.40)	H_b, $H_{(d,e)}$, Aromatic (7.25), Me_c	H_q (2.19)	$H_{(l,p)}$, H_o
Me_h (3.82)	Aromatic (6.89)	Me_r (1.63)	H_b, $H_{(l,p)}$
H_i (5.95)	H_j, H_k, $H_{(l,p)}$, H_m	Aromatic (7.25)	Aromatic (6.89), $H_{(f,g)}$
H_j (5.15)	H_i, H_k, H_m	Aromatic (6.89)	Aromatic (7.25), Me_h
H_k (5.26)	H_i, H_j, $H_{(l,p)}$, H_m		

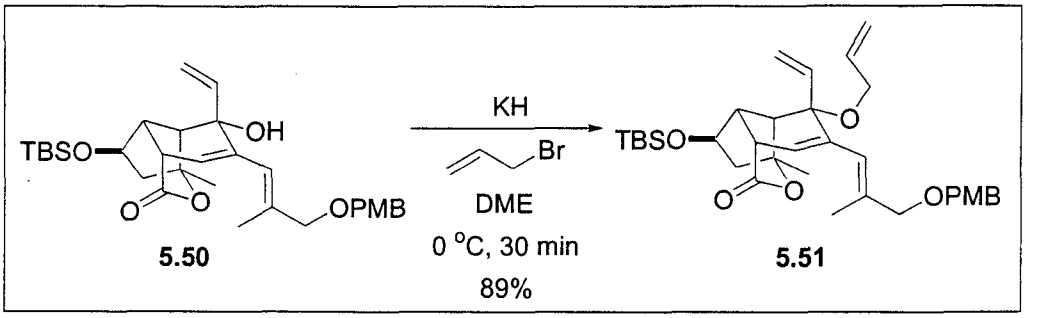


^{1}H NMR (500 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-9-(Allyloxy)-6-(*tert*-butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-(4-methoxy-benzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-9-vinyl-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.51). A flame-dried round bottom flask was charged with KH (211 mg, 35% in mineral oil, 1.85 mmol) and washed with hexanes (3x2 mL). Freshly distilled DME (2 mL) was then added and the flask was cooled to 0 °C. Alcohol **5.50** (40 mg, 0.074 mmol) was cannulated into the flask and the contents were stirred for 20 min before freshly distilled allyl bromide (224 μL, 1.85 mmol) was added. The mixture was stirred at 0 °C for 30 min before being quenched with an aqueous solution of NH_4Cl (5 mL). The product was extracted with Et_2O (3x20 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O) provided 38 mg of **5.51** (89%) as a clear colorless oil.

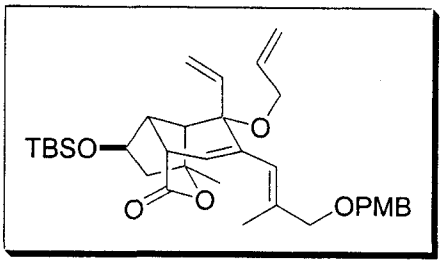
Data for **5.51:**

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 7.26 – 7.23 (m, 2H), 6.89 – 6.86 (m, 2H), 6.10 (d, J = 7.4 Hz, 1H), 6.11 – 6.10 (m, 1H), 5.95 (dd, J = 17.4, 10.8 Hz, 1H), 5.84 (dddd, J = 17.2, 9.7, 4.8, 4.8, 1H), 5.27 – 5.20 (m, 3H), 5.09 (dq, J = 10.6, 1.6 Hz, 1H), 4.38 (s, 2H), 4.33 (ddd, J = 9.1, 6.2, 2.5 Hz, 1H), 4.11 (dddd, J = 13.2, 4.9, 1.6, 1.6 Hz, 1H), 4.03 (dddd, J = 13.3, 4.6, 1.8, 1.8 Hz, 1H), 3.91 (m, 2H), 3.81 (s, 3H), 3.41 – 3.38 (m, 1H), 2.62 (ddd, J = 6.4, 3.8, 3.8 Hz, 1H), 2.19 (dd, J = 14.8, 9.6 Hz, 1H), 1.98 – 1.94 (m, 2H), 1.80 – 1.79 (m, 3H), 1.60 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

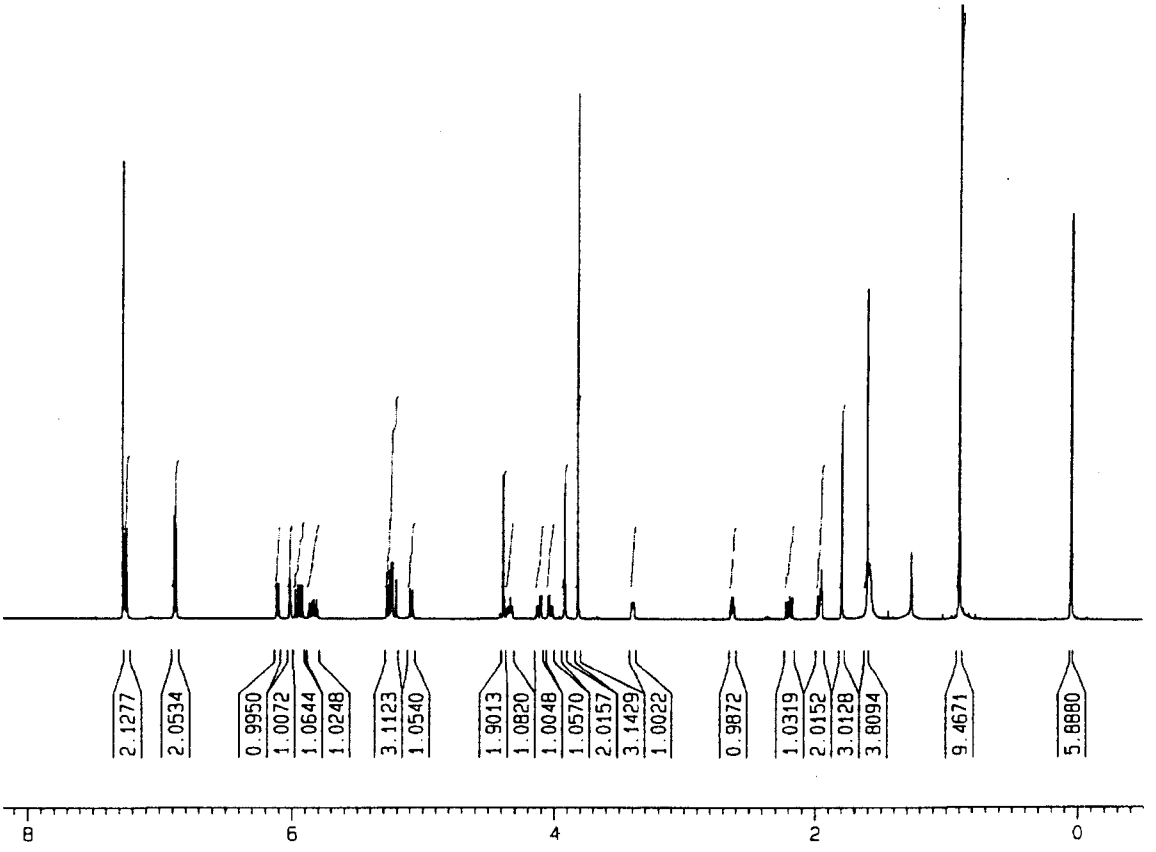
^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 171.2 (C_4), 159.4 (C_4), 142.1 (CH), 140.1 (C_4), 137.2 (C_4), 135.7 (CH), 130.6 (C_4), 129.5 (CH), 129.1 (CH), 124.9 (CH), 115.6 (CH_2), 115.5 (CH_2), 114.0 (CH), 88.6 (C_4), 81.6 (C_4), 75.8 (CH_2) 71.6 (CH_2), 69.3 (CH), 66.4 (CH_2), 55.5 (CH_3), 51.7 (CH_2), 49.8 (CH_3), 45.6 (CH), 39.7 (CH), 25.9 (3xCH_3), 24.1 (CH), 18.2 (C_4), 16.2 (CH_3), -4.6 (CH_3), -4.8 (CH_3)

FTIR (neat, cm^{-1}) 2954 (m), 2931 (s), 2855 (s), 1739 (s), 1513 (m), 1248 (s), 1086 (m)

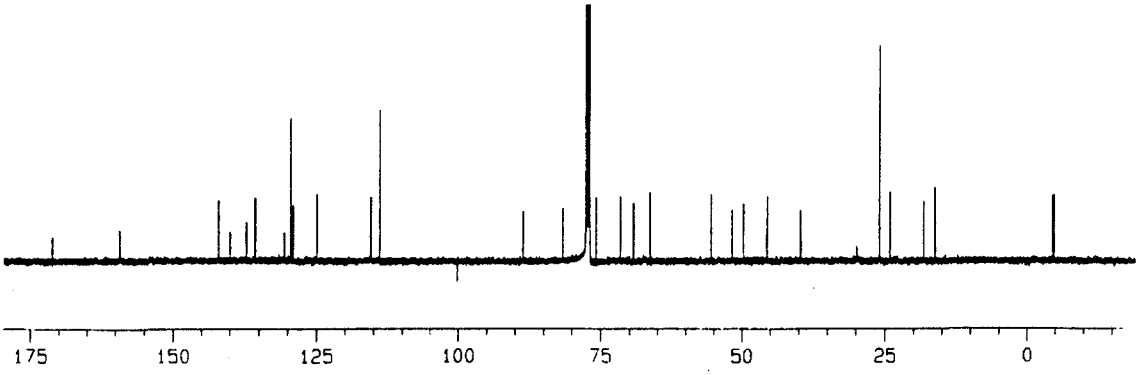
HRMS (EI, m/z) Expected for $C_{30}H_{39}O_6Si$ [$(M-C_4H_9)^+$] 523.2516, found: 523.2540 (1.28%)

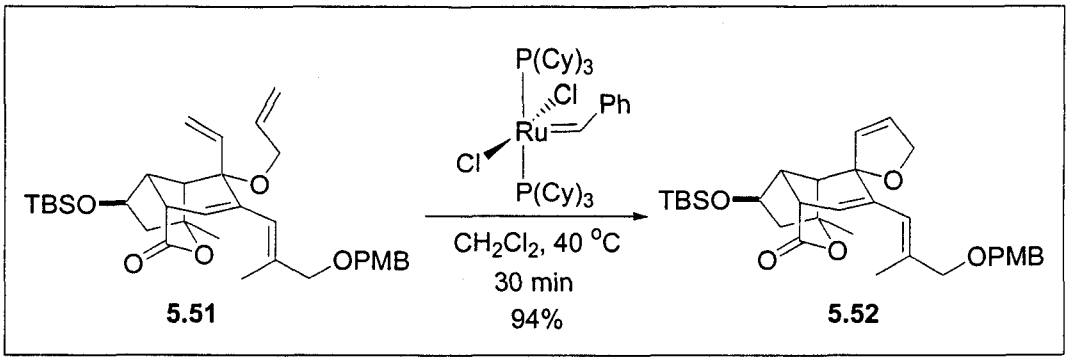


^{1}H NMR (500 MHz, $CDCl_3$)



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





5.51 **5.52**

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-(4-methoxy-benzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.52). Alkene **5.51** (55 mg, 0.095 mmol) was dissolved in CH_2Cl_2 (1.9 mL, 0.05 M) and degassed under a steady stream of argon for 20 min. Meanwhile, Grubbs' 1st generation catalyst (8 mg, 0.009 mmol) was placed in a Schlenk tube, evacuated and filled with argon. Once the degassing was complete, the alkene was cannulated in the Schlenk tube and the contents were placed into a 40 °C oil bath for 30 min. After cooling to room temperature, the solution was concentrated and the crude product was purified by flash chromatography on silica gel (10:1 hexanes:Et_2O) to provide 47 mg of **5.52** (94%) as a clear colorless oil.

Data for **5.52:**

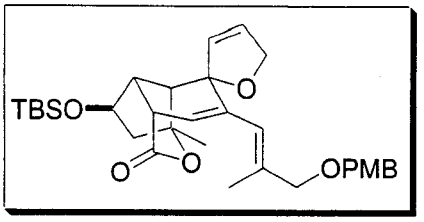
^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} 7.25 – 7.24 (m, 2H), 6.89 – 6.87 (m, 2H), 5.97 – 5.94 (m, 2H), 5.85 (m, 1H), 5.72 (ddd, J = 5.3, 2.3, 2.3 Hz, 1H), 4.70 (m, 2H), 4.39 – 4.35 (m, 3H), 3.91 – 3.90 (m, 2H), 3.81 (s, 3H), 3.39 – 3.37 (m, 1H), 2.73 (ddd, J = 6.1, 4.1, 4.1 Hz, 1H), 2.13 (dd, J = 14.9, 9.5 Hz, 1H), 1.94 (dd, J = 15.1, 2.5 Hz, 1H), 1.87 (d, J = 4.3 Hz, 1H), 1.76 – 1.75 (m, 3H), 1.61 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} 171.4 (C_4), 159.3 (C_4), 141.5 (C_4), 137.6 (C_4), 134.0 (CH), 130.8 (C_4), 129.5 (CH), 126.34 (CH), 126.28 (CH), 123.0 (CH), 114.0 (CH), 91.4

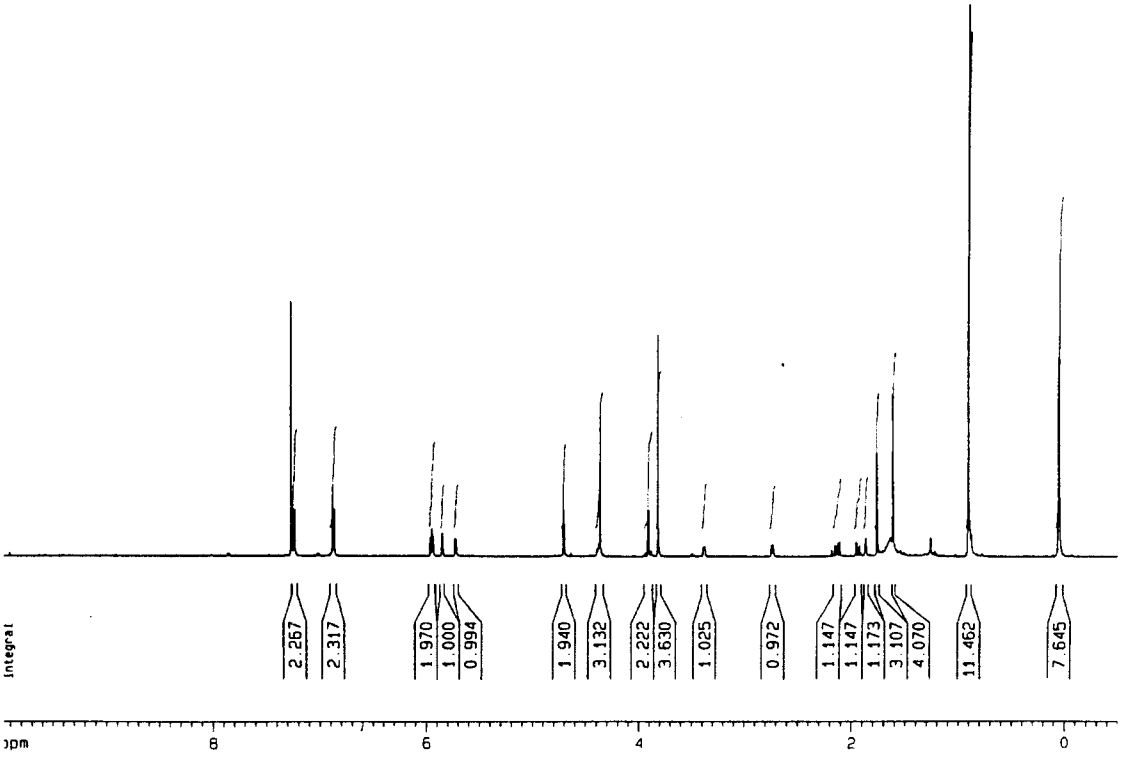
(C_4), 88.8 (C_4), 76.2 (CH_2), 75.9 (CH_2), 71.3 (CH_2), 70.0 (CH), 55.5 (CH_3), 51.0 (CH), 50.7 (CH_2), 46.6 (CH), 39.4 (CH), 25.9 (3xCH_3), 23.8 (CH_3), 18.2 (C_4), 16.1 (CH_3), -4.6 (CH_3), -4.8 (CH_3)

FTIR (neat, cm^{-1}) 2937 (s), 2857 (s), 1738 (s), 1512 (m), 1245 (s), 1086 (s)

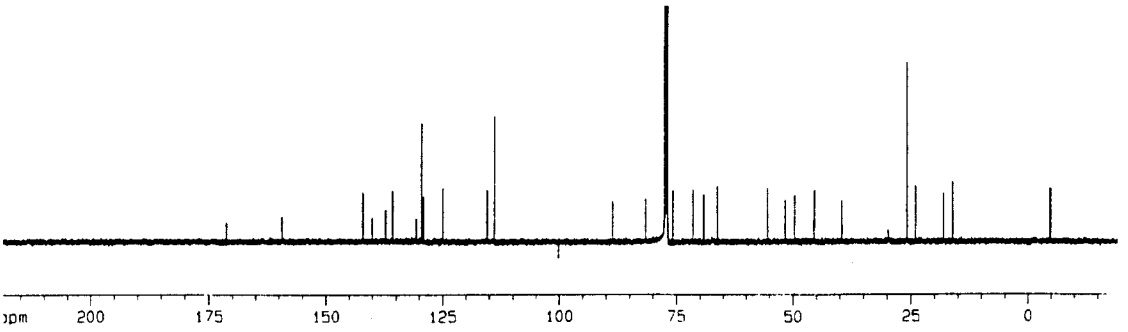
HRMS (EI, m/z) Expected for $C_{28}H_{35}O_6Si$ [$(M-C_4H_9)^+$] 495.2203, found: 495.2202 (1.8%)

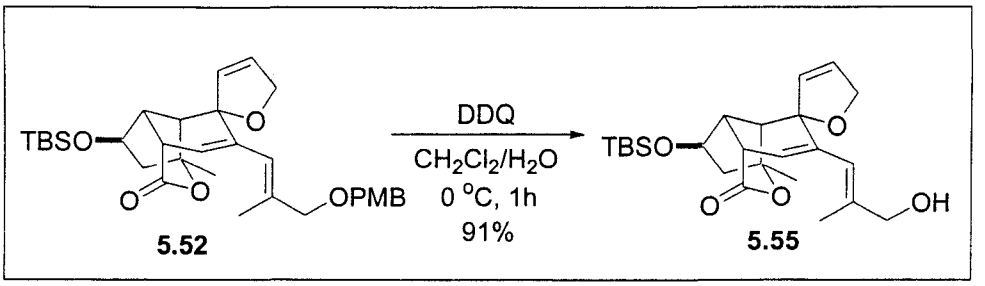


^{1}H NMR (500 MHz, $CDCl_3$)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-hydroxy-2-methylprop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.55). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (10 mg, 0.045 mmol) was added a biphasic solution of **5.52** (25 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) and H_2O (200 μL) at 0 °C. The reaction was stirred for 1 h at 0 °C before being quenched with a saturated aqueous solution of Na_2SO_3 (3 mL). The product was extracted with CH_2Cl_2 (3x10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (5:1 hexanes:Et_2O) provided 17.5 mg of **5.55** (91%) as a clear colorless oil.

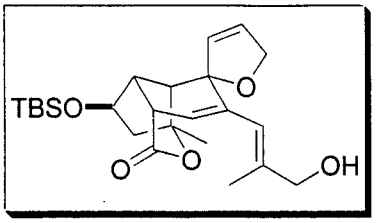
Data for **5.55:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 5.95 – 5.93 (m, 2H), 5.43 – 5.42 (m, 1H), 5.38 – 5.36 (m, 1H), 4.52 – 4.49 (m, 1H), 4.39 – 4.36 (m, 1H), 3.89 (ddd, J = 12.1, 6.2, 2.7 Hz, 1H), 3.72 – 3.71 (m, 2H), 3.53 – 3.51 (m, 1H), 2.39 – 2.37 (m, 1H), 1.83 (dd, J = 14.8, 2.6 Hz, 1H), 1.61 – 1.55 (m, 4H), 1.55 (s, 3H), 1.41 – 1.40 (m, 1H), 1.02 (s, 9H), 0.79 - 0.77 (m, 1H), 0.03 (s, 3H), 0.00 (s, 3H)

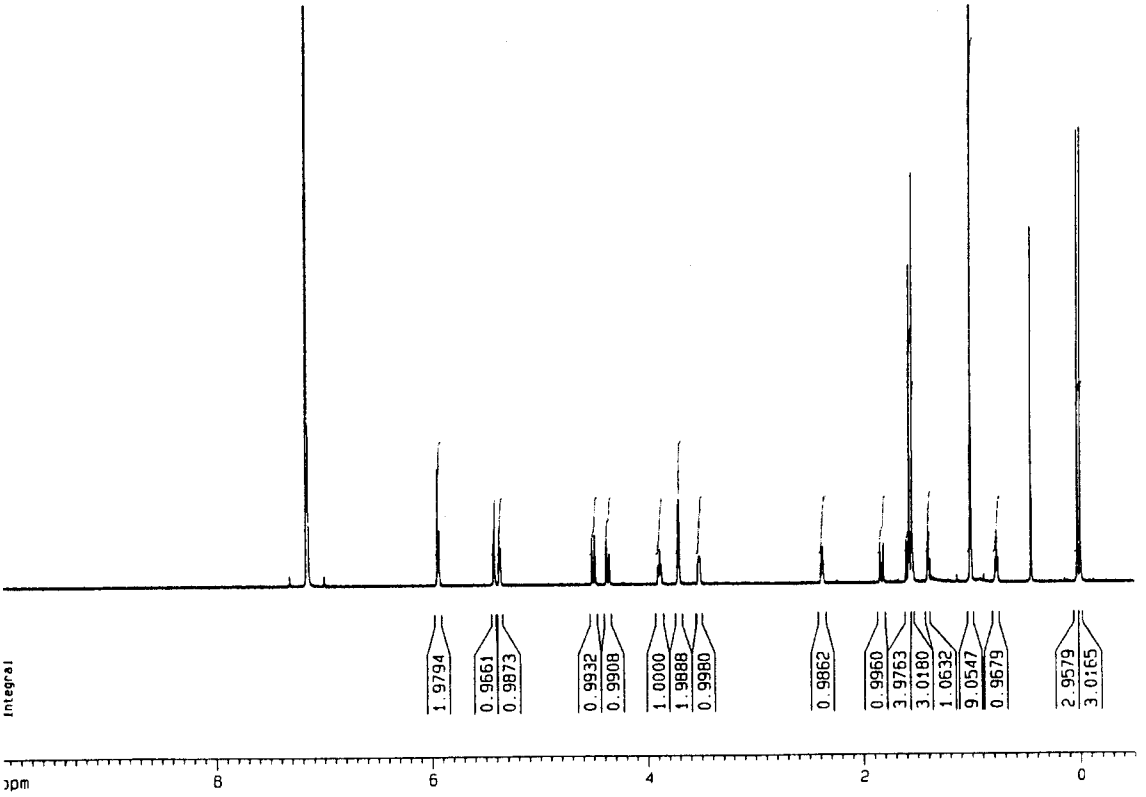
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 170.2 (C_4), 142.2 (C_4), 140.7 (C_4), 134.3 (CH), 126.6 (CH), 126.5 (CH), 120.7 (CH), 92.0 (C_4), 88.2 (C_4), 76.4 (CH_2), 70.7 (CH), 68.5 (CH_2), 51.1 (CH), 51.0 (CH_2), 46.9 (CH), 40.4 (CH), 26.3 (3xCH_3), 24.3 (CH_3), 18.6 (C_4), 15.9 (CH_3), -4.3 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 3422 (brs), 2929 (s), 2985 (s), 1737 (s), 1716 (m), 1083 (m)

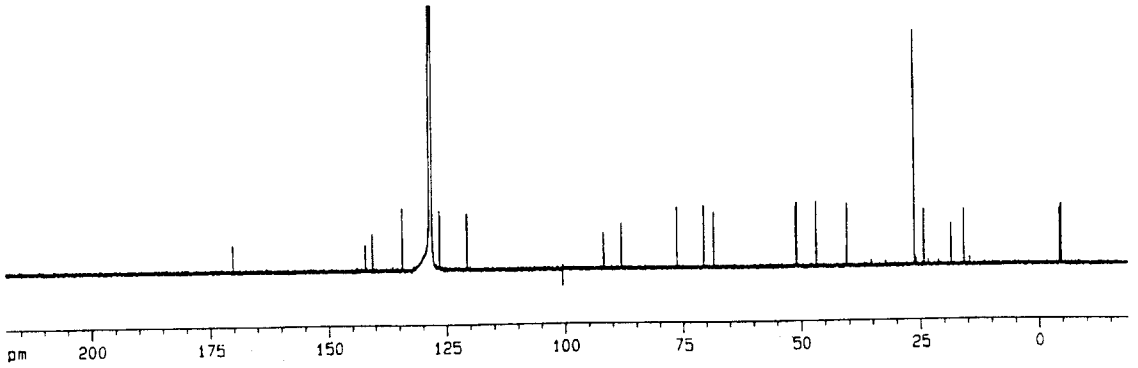
HRMS (EI, m/z) Expected for $C_{20}H_{27}O_5Si$ $[(M-C_4H_9)^+]$ 375.1628, found: 375.1607. (28.4%)

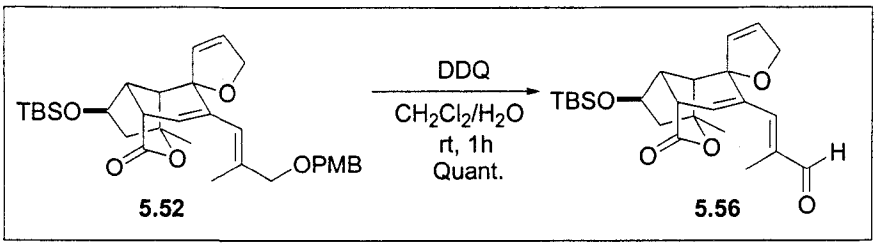


^{1}H NMR (500 MHz, C_6D_6)



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





5.52 5.56

(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-3(*E*)-[6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-2-oxo-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-10-yl]-2-methylacrylaldehyde (5.56). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (10 mg, 0.045 mmol) was added to a biphasic solution of **5.52** (25 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) and H_2O (200 μL). The reaction was stirred for 1 h at room temperature before being quenched with a saturated aqueous solution of Na_2SO_3 (3 mL). The product was extracted with CH_2Cl_2 (3x10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes:Et_2O), provided 19 mg of **5.56** (quant.) as a clear colorless oil.

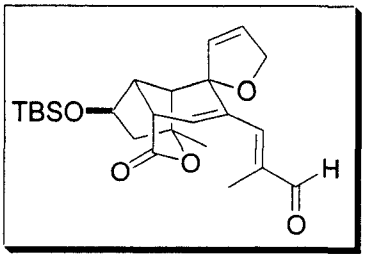
Data for **5.56:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 9.33 (s, 1H), 6.41 (m, 1H), 5.91 (d, J = 7.1 Hz, 1H), 5.32 (dt, J = 14.7, 5.9 Hz, 1H), 5.18 (dt, J = 5.8, 2.5 Hz, 1H), 4.29 – 4.28 (m, 2H), 3.85 (ddd, J = 9.3, 6.2, 2.6 Hz, 1H), 3.50 – 3.48 (m, 1H), 2.25 (ddd, J = 6.2, 4.0, 4.0 Hz, 1H), 1.79 (dd, J = 14.8, 2.5 Hz, 1H), 1.73 (s, 3H), 1.54 (dd, J = 14.9, 9.6 Hz, 1H), 1.49 (s, 3H), 1.32 -1.31 (m, 1H), 1.02 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H)

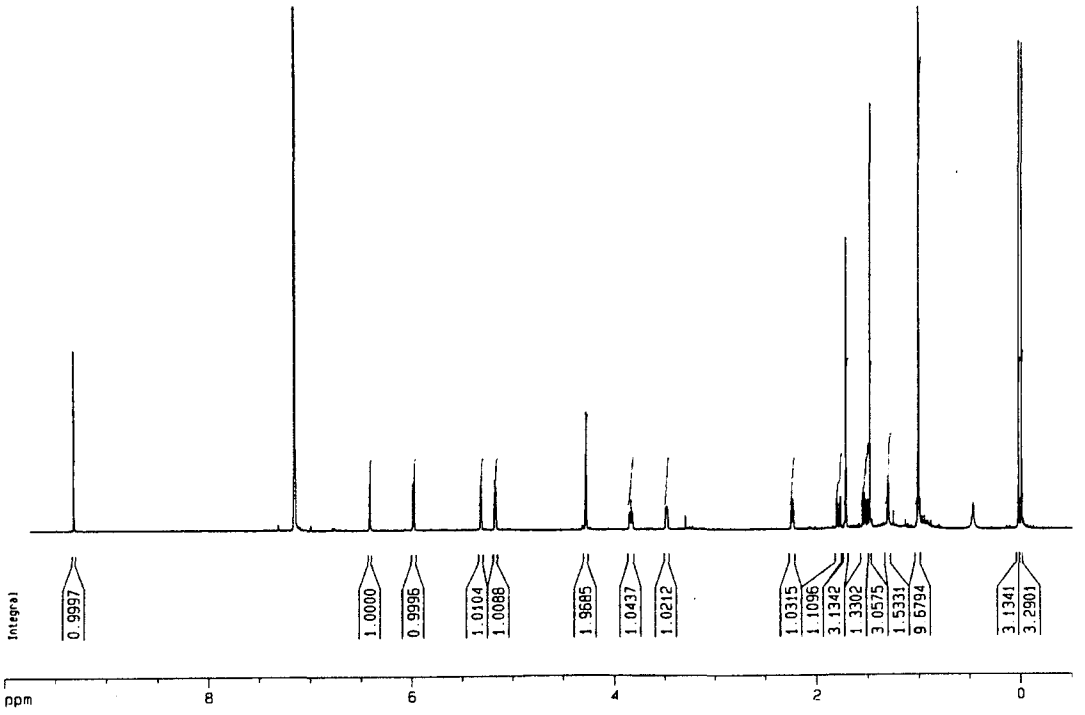
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 194.4 (CH), 169.0 (C_4), 145.0 (CH), 141.4 (C_4), 140.4 (C_4), 133.9 (CH), 130.8 (CH), 126.9 (CH), 91.4 (C_4), 88.3 (C_4), 76.4 (CH_2), 70.5 (CH), 50.8 (CH_2), 50.6 (CH), 46.4 (CH), 40.5 (CH), 26.3 (3xCH_3), 24.1 (CH_3), 18.6 (C_4), 11.6 (CH_3), -4.3 (CH_3), -4.9 (CH_3)

FTIR (neat, cm^{-1}) 2930 (s), 2935 (s), 1739 (s), 1683 (s), 1084 (m)

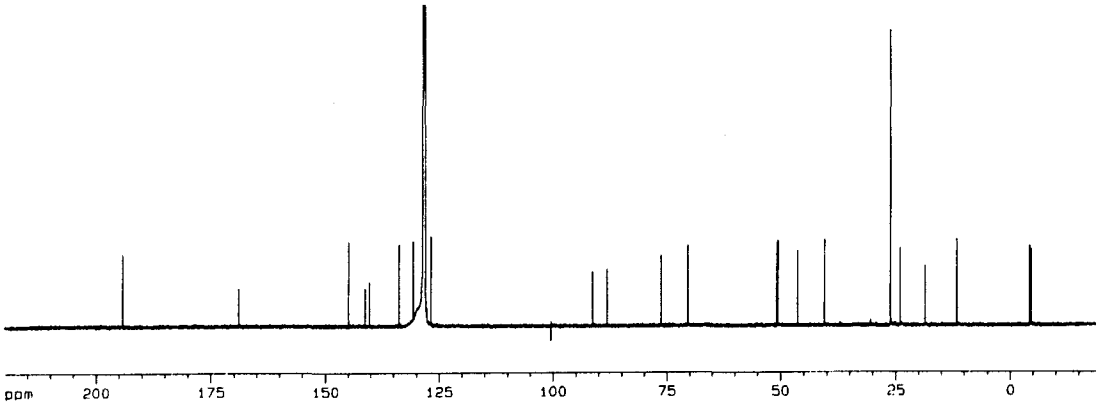
HRMS (EI, m/z) Expected for $C_{24}H_{34}O_5Si$ [(M)$^+$] 430.2176, found: 430.2179. (3.9%)

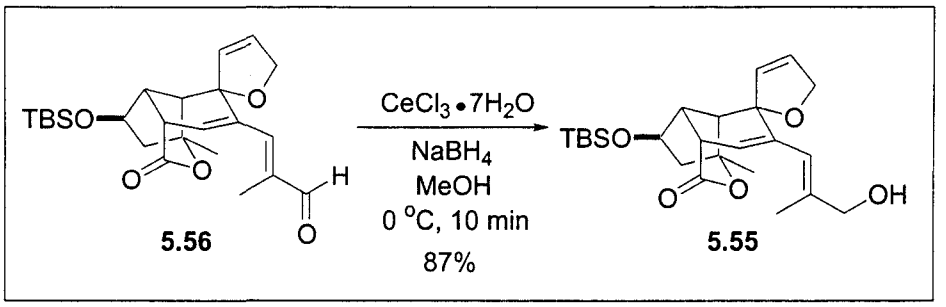


^{1}H NMR (500 MHz, C_6D_6)



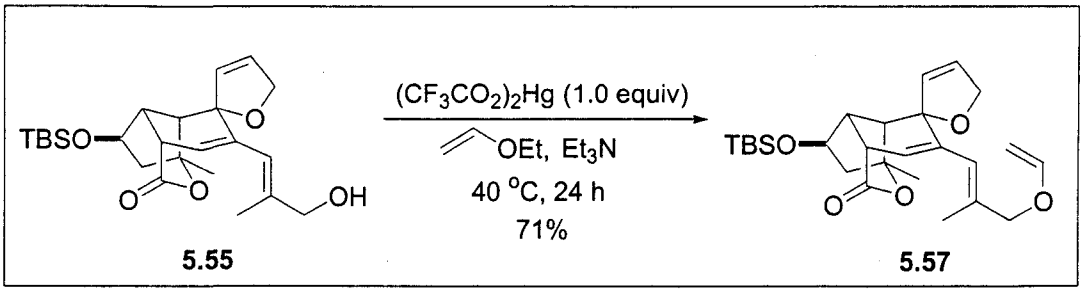
^{13}C NMR (125 MHz, C_6D_6)





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-3-hydroxy-2-methylprop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.55). Aldehyde **5.56** (25 mg, 0.058 mmol) was dissolved in MeOH (2 mL), cooled to 0 °C and treated with $CeCl_3 \cdot 7H_2O$ (108 mg, 0.291 mmol). After stirring for 10 min, $NaBH_4$ (2 mg, 0.06 mmol) was added. Stirring was continued for an additional 10 min before the reaction was quenched with saturated aqueous solution of NH_4Cl (5 mL). The product was extracted with Et_2O (3x10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (5:1 hexanes:Et_2O) provided 21 mg of **5.55** (87%) as a clear colorless oil.

Data for **5.55:** See above.



(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10-[(1*E*)-2-methyl-3-(vinyloxy)prop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.57). Mercury trifluoroacetate (2 mg, 0.07 mmol) was added to a solution of **5.55** (30 mg, 0.069 mmol), Et_3N (5 drops) and freshly distilled ethyl vinyl ether (3 mL) in a Schlenk tube. The contents were placed in a 40 °C oil bath and stirred for 24 h. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and the product was extracted with Et_2O (3x10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (20:1 hexanes:Et_2O) provided 23 mg of **5.57** (71%) as a clear colorless oil.

Data for **5.57:**

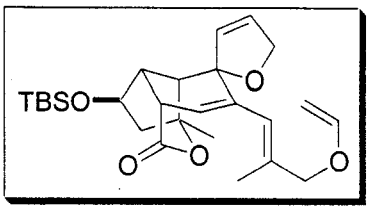
^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 6.37 (dd, J_{BX} = 14.2, J_{AX} = 6.7, 1H), 5.96 (m, 1H), 5.91 (d, J = 7.0 Hz, 1H), 5.42 – 5.41 (m, 1H), 5.33 (dt, J = 4.9, 2.3 Hz, 1H), 4.49 (dt, J = 13.2, 1.8 Hz, 1H), 4.36 (dt, J = 13.2, 1.9 Hz, 1H), 4.22 (dd, J_{BX} = 14.3, J_{AB} = 1.8 Hz, 1H), 3.96 (dd, J_{AX} = 6.7, J_{AB} = 1.8 Hz, 1H), 3.89 (s, 3H), 3.50 – 3.48 (m, 1H), 2.35 (ddd, J = 6.2, 3,9, 3,9 Hz, 1H), 1.82 (dd, J = 14.8, 2.6 Hz, 1H), 1.62 – 1.61 (m, 3H), 1.57 (dd, J = 14.7, 9.7 Hz, 1H), 1.54 (s, 3H), 1.39 (d, J = 4.0 Hz, 1H), 1.01 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H)

^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 170.0 (C_4), 152.3 (CH), 141.8 (C_4), 136.6 (C_4), 134.2 (CH), 127.0 (CH), 126.5 (CH), 123.5 (CH), 91.9 (C_4), 88.1 (C_4), 87.5 (CH_2), 76.3 (CH_2), 74.0

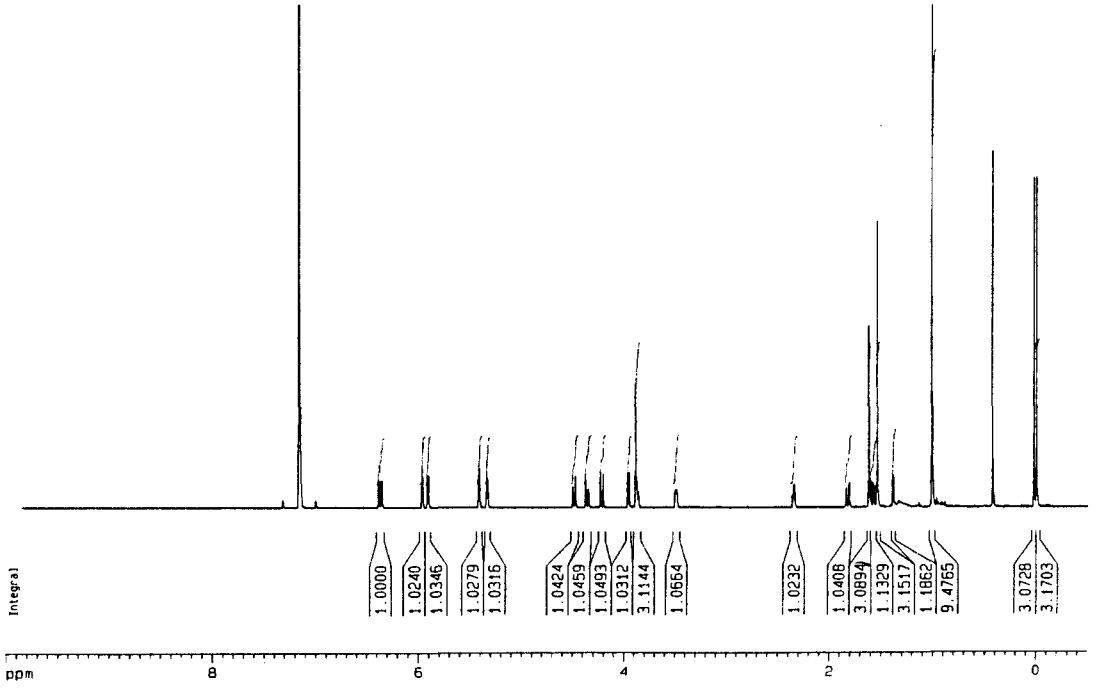
(CH_2), 70.6 (CH), 51.1 (CH), 51.0 (CH_2), 46.9 (CH), 40.4 (CH), 26.3 (3xCH_3), 24.3 (CH_3), 18.6 (C_4), 15.9 (CH_3), -4.3 (CH_3), -4.6 (CH_3)

FTIR (neat, cm^{-1}) 2960 (s), 2929 (s), 2854 (s), 1739 (s), 1633 (m), 1087 (s), 835 (s)

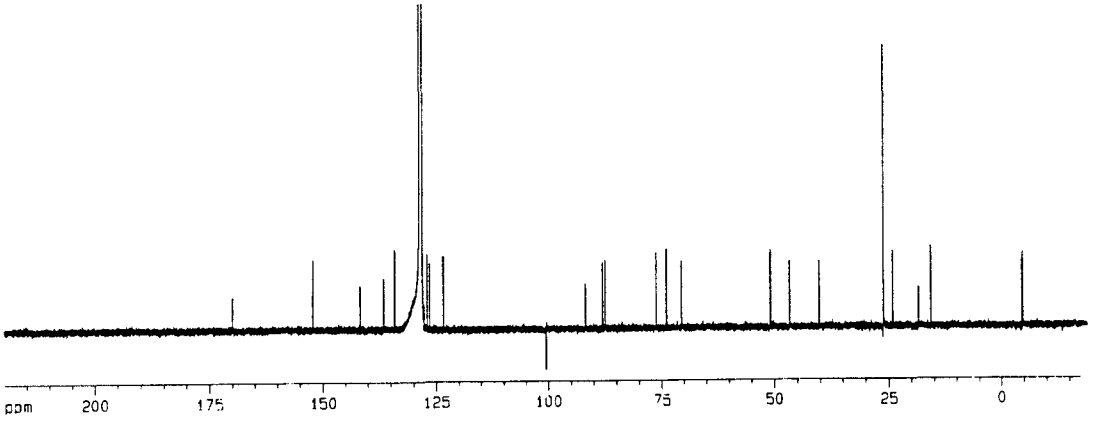
HRMS (EI, m/z) Expected for $C_{24}H_{35}O_4Si$ [$(M-C_2H_3O)^+$] 415.2305, found: 415.2305. (37.1%)

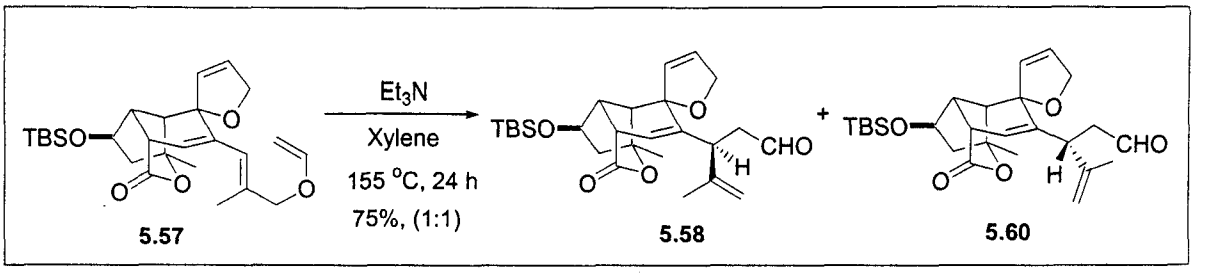


^{1}H NMR (500 MHz, C_6D_6)



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





(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10[(1*S*)-2-methyl-1-(2-oxoethyl)prop-2-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.45) *and* **(+/-)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-10[(1*R*)-2-methyl-1-(2-oxoethyl)prop-2-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{4,8}]-undec-10-en-2-one (5.46).** Triethylamine (1 drop) was added to a solution of **5.57** (5 mg, 0.01 mmol) in xylene (0.5 mL). The contents of the Schlenk tube were degassed under a steady flow of argon for 20 min and then placed in a 155 °C wax bath for 24 h. The crude product was purified directly by flash chromatography on silica gel (100% hexanes then 10:1 hexanes:Et_2O) provided 3.7 mg of **5.58** and **5.60** (75%, dr = 1:1) as a clear colorless oil.

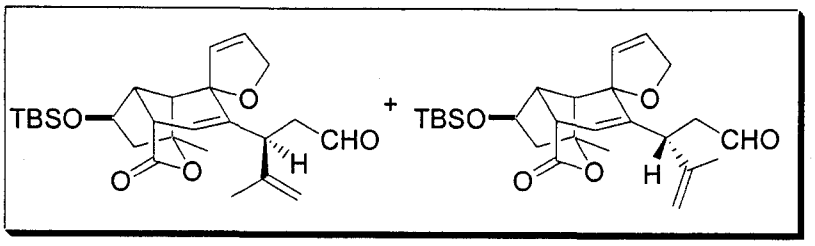
Data for **5.58** and **5.60:**

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} 9.41 - 9.40 and 9.29 – 9.28 (m, 1H), 5.87 and 6.57 (d, J = 6.9 and J = 6.9, 1H), 5.41 – 5.40 and 5.37 – 5.36 (m, 1H), 5.32 – 5.31 and 5.22 – 5.20 (m, 1H), 4.80 and 4.71 (m, 1H), 4.66 and 4.50 (m, 1H), 4.43 – 4.42 and 4.41 – 4.40 (m, 1H), 4.31 - 4.25 (m, 2H), 3.85 - 3.80 (m, 2H), 3.41 – 3.36 (m, 2H), 3.13 - 3.07 (m, 2H), 2.53 (dd, J = 17.4, 3.9 Hz, 1H), 2.34 (ddd, J = 17.3, 10.2, 2.1 Hz, 1H), 2.27 – 2.24 (m, 2H), 2.18 – 2.16 (m, 2H), 1.80 – 1.75 (m, 2H), 1.65 and 1.52 (s, 3H), 1.55 - 1.49 (m, 2H), 1.48 and 1.46 (s, 3H), 1.29 – 1.28 (m, 2H), 1.00 (s, 18H), 0.01 and 0.00 (s, 3H), -0.01 and -0.02 (s, 3H)

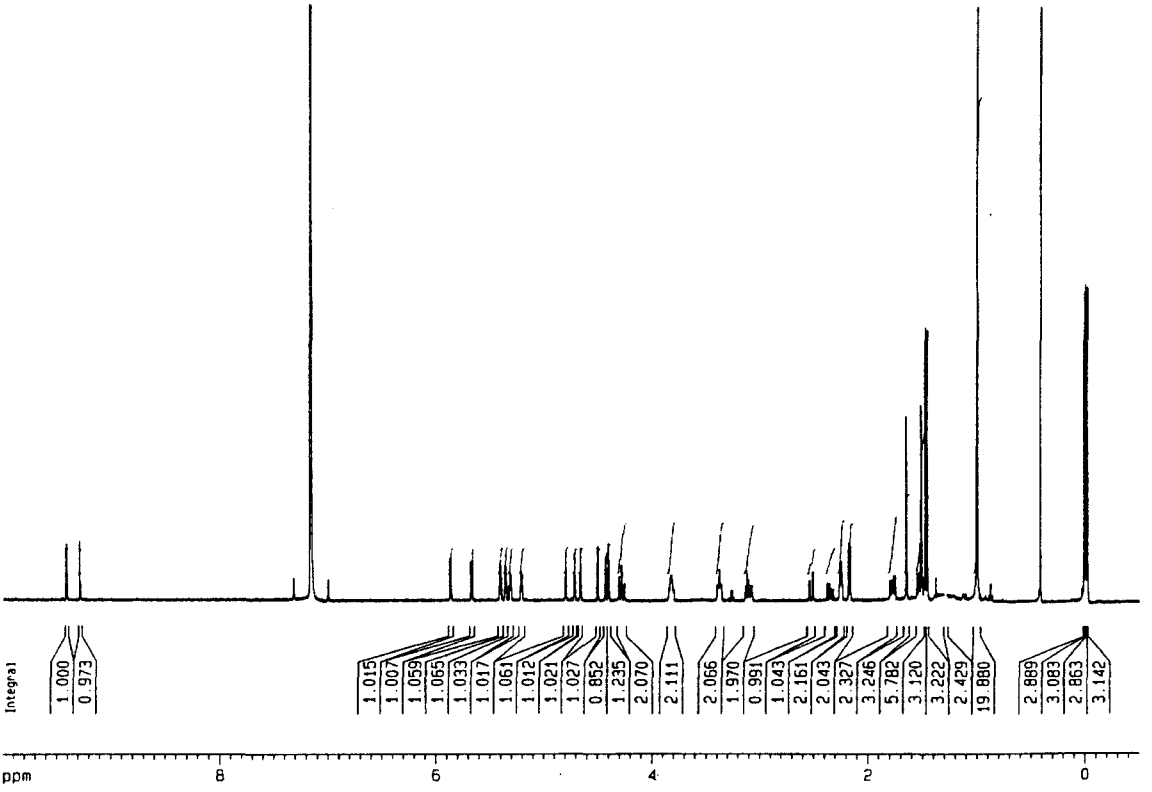
^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} 200.5 and 200.2 (CH), 169.9 and 169.5 (C_4), 148.2 and 145.8 (C_4), 145.52 and 145.46 (C_4), 134.3 and 134.0 (CH), 127.0 and 126.9 (CH), 125.2 and 125.0 (CH), 111.9 and 110.8 (CH_2), 92.9 and 92.4 (C_4), 88.0 (2xC_4), 76.4 and 76.2 (CH_2), 70.5 and 70.5 (CH), 51.2 and 51.0 (CH_3), 50.86 and 50.87 (CH_2), 49.1 and 48.1 (CH_2), 46.7 and 46.5 (CH), 41.1 and 40.7 (CH), 40.4 and 40.2 (CH), 26.26 and 26.25 (3xCH_3), 24.2 and 24.1 (CH), 23.4 and 21.7 (CH_3), 18.6 (2xC_4), -4.3 (2xCH_3), -4.6 (2xCH_3)

FTIR (neat, cm^{-1}) 2956 (s), 2929 (s), 2855 (s), 1739 (s), 1462 (m), 1379 (m), 1174 (m)

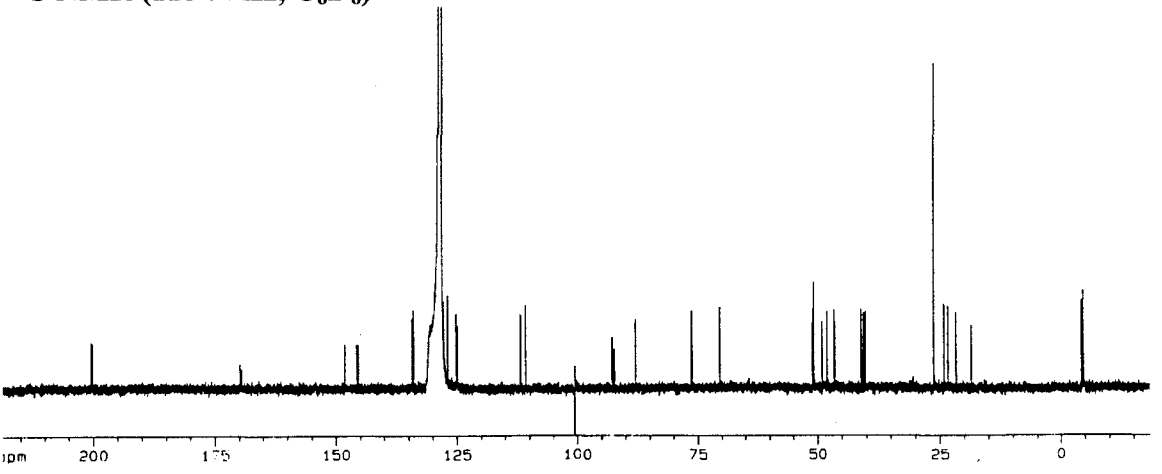
HRMS (EI, m/z) Expected for $C_{22}H_{29}O_5Si$ [$(M-C_4H_9)^+$] 401.1784, found: 401.1783. (28.7%)

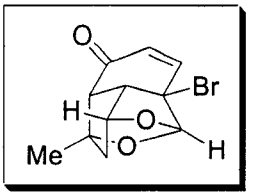


^{1}H NMR (500 MHz, C_6D_6)



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




O
Br
H
O
Me
O
H

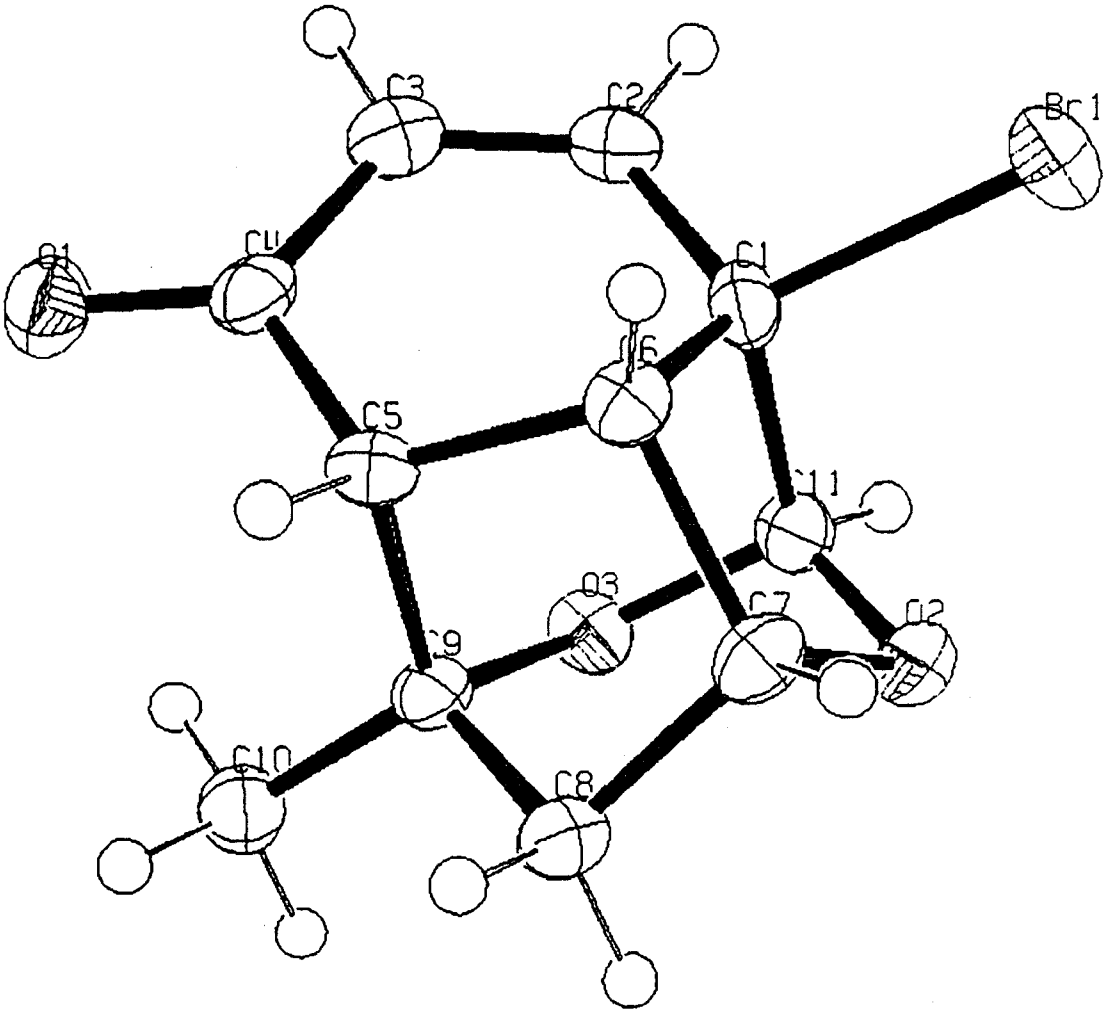

C3
C2
Br1
O1
C4
C1
C6
C5
C11
O3
C7
O2
C9
C10
C8

Table 1. Crystal data and structure refinement for lb31.

Identification code	lb31
Empirical formula	C11 H11 Br O3
Formula weight	271.11
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.680(3) A alpha = 90 deg. b = 8.405(5) A beta = 90 deg. c = 21.474(12) A gamma = 90 deg.
Volume	1025.1(10) A^3
Z, Calculated density	4, 1.757 Mg/m^3
Absorption coefficient	3.992 mm^-1
F(000)	544
Crystal size	0.35 x 0.20 x 0.20 mm
Theta range for data collection	1.90 to 24.78 deg.
Limiting indices	-6<=h<=6, -9<=k<=9, -25<=l<=25
Reflections collected / unique	7461 / 1723 [R(int) = 0.0318]
Completeness to theta = 24.78	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5023 and 0.3355
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1723 / 0 / 137
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0281, wR2 = 0.0808
R indices (all data)	R1 = 0.0287, wR2 = 0.0813
Absolute structure parameter	0.503(14)
Largest diff. peak and hole	0.564 and -0.268 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for lb31.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	1772(1)	10725(1)	5204(1)	33(1)
O(1)	16(5)	10569(4)	2491(1)	34(1)
O(2)	5104(5)	8564(3)	4509(1)	29(1)
O(3)	5358(5)	9848(3)	3548(1)	26(1)
C(1)	2315(7)	10485(5)	4294(2)	25(1)
C(2)	1518(7)	11977(5)	3988(2)	26(1)
C(3)	654(8)	11995(5)	3414(2)	29(1)
C(4)	546(6)	10549(5)	3042(2)	26(1)
C(5)	1300(6)	8998(4)	3344(2)	22(1)
C(6)	1238(6)	8929(4)	4067(2)	23(1)
C(7)	3183(8)	7658(4)	4243(2)	26(1)
C(8)	4101(7)	7070(5)	3617(2)	27(1)
C(9)	3943(7)	8621(5)	3236(2)	24(1)
C(10)	4782(7)	8520(5)	2578(2)	29(1)
C(11)	4929(7)	10029(5)	4203(2)	25(1)

Table 3. Bond lengths [A] and angles [deg] for 1b31.

Br(1)-C(1)	1.990(4)
O(1)-C(4)	1.220(5)
O(2)-C(11)	1.399(5)
O(2)-C(7)	1.448(5)
O(3)-C(11)	1.436(5)
O(3)-C(9)	1.469(5)
C(1)-C(2)	1.486(6)
C(1)-C(6)	1.524(6)
C(1)-C(11)	1.545(5)
C(2)-C(3)	1.327(6)
C(3)-C(4)	1.456(6)
C(4)-C(5)	1.517(5)
C(5)-C(9)	1.552(5)
C(5)-C(6)	1.555(6)
C(6)-C(7)	1.582(5)
C(7)-C(8)	1.523(6)
C(8)-C(9)	1.541(6)
C(9)-C(10)	1.494(6)
C(11)-O(2)-C(7)	103.0(3)
C(11)-O(3)-C(9)	115.3(3)
C(2)-C(1)-C(6)	117.5(3)
C(2)-C(1)-C(11)	116.5(4)
C(6)-C(1)-C(11)	97.6(3)
C(2)-C(1)-Br(1)	107.5(3)
C(6)-C(1)-Br(1)	109.8(3)
C(11)-C(1)-Br(1)	107.3(3)
C(3)-C(2)-C(1)	122.2(4)
C(2)-C(3)-C(4)	121.1(4)
O(1)-C(4)-C(3)	122.1(4)
O(1)-C(4)-C(5)	119.7(4)
C(3)-C(4)-C(5)	118.1(4)
C(4)-C(5)-C(9)	112.7(3)
C(4)-C(5)-C(6)	116.9(3)
C(9)-C(5)-C(6)	99.3(3)
C(1)-C(6)-C(5)	106.1(3)
C(1)-C(6)-C(7)	102.9(3)
C(5)-C(6)-C(7)	104.3(3)
O(2)-C(7)-C(8)	105.1(3)
O(2)-C(7)-C(6)	105.4(3)
C(8)-C(7)-C(6)	104.4(3)
C(7)-C(8)-C(9)	100.0(3)
O(3)-C(9)-C(10)	107.3(3)
O(3)-C(9)-C(8)	108.7(3)
C(10)-C(9)-C(8)	115.8(3)
O(3)-C(9)-C(5)	108.5(3)
C(10)-C(9)-C(5)	117.4(3)
C(8)-C(9)-C(5)	98.7(3)
O(2)-C(11)-O(3)	110.7(3)
O(2)-C(11)-C(1)	103.2(3)
O(3)-C(11)-C(1)	108.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for lb31. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br(1)	40(1)	35(1)	24(1)	-5(1)	4(1)	-1(1)
O(1)	35(2)	37(2)	30(2)	3(1)	-7(1)	2(1)
O(2)	25(1)	35(2)	28(2)	-2(1)	-7(1)	6(1)
O(3)	21(1)	29(1)	28(2)	-3(1)	3(1)	-5(1)
C(1)	24(2)	34(2)	16(2)	-2(2)	-1(1)	-2(2)
C(2)	21(2)	22(2)	34(2)	-4(2)	5(2)	-1(2)
C(3)	26(2)	27(2)	34(2)	4(2)	3(2)	2(2)
C(4)	19(2)	33(2)	27(2)	4(2)	1(1)	4(2)
C(5)	21(2)	18(2)	27(2)	-1(1)	4(2)	0(1)
C(6)	17(2)	25(2)	26(2)	2(2)	1(1)	-4(1)
C(7)	29(2)	23(2)	28(2)	7(2)	-3(2)	1(2)
C(8)	25(2)	24(2)	30(2)	0(2)	-2(2)	5(2)
C(9)	19(2)	26(2)	27(2)	-4(2)	-3(2)	2(2)
C(10)	24(2)	34(2)	28(2)	-1(2)	2(2)	1(2)
C(11)	19(2)	30(2)	25(2)	-6(2)	-3(2)	-1(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for lb31.

	x	y	z	U(eq)
H(2A)	1630	12940	4209	31
H(3A)	103	12958	3245	35
H(5A)	335	8119	3173	26
H(6A)	-337	8699	4243	27
H(7A)	2601	6797	4517	32
H(8A)	3098	6233	3443	32
H(8B)	5725	6683	3648	32
H(10A)	6453	8284	2574	43
H(10B)	4503	9527	2371	43
H(10C)	3933	7683	2363	43
H(11A)	5991	10831	4390	30

Table 6. Torsion angles [deg] for lb31.

C(6)-C(1)-C(2)-C(3)	-25.0(6)
C(11)-C(1)-C(2)-C(3)	90.3(5)
Br(1)-C(1)-C(2)-C(3)	-149.3(4)
C(1)-C(2)-C(3)-C(4)	-2.9(6)
C(2)-C(3)-C(4)-O(1)	-171.4(4)
C(2)-C(3)-C(4)-C(5)	4.0(6)
O(1)-C(4)-C(5)-C(9)	83.3(4)
C(3)-C(4)-C(5)-C(9)	-92.1(4)
O(1)-C(4)-C(5)-C(6)	-162.5(3)
C(3)-C(4)-C(5)-C(6)	22.0(5)
C(2)-C(1)-C(6)-C(5)	45.8(4)
C(11)-C(1)-C(6)-C(5)	-79.4(3)
Br(1)-C(1)-C(6)-C(5)	169.0(2)
C(2)-C(1)-C(6)-C(7)	155.1(3)
C(11)-C(1)-C(6)-C(7)	29.9(4)
Br(1)-C(1)-C(6)-C(7)	-81.7(3)
C(4)-C(5)-C(6)-C(1)	-44.3(4)
C(9)-C(5)-C(6)-C(1)	77.2(3)
C(4)-C(5)-C(6)-C(7)	-152.5(3)
C(9)-C(5)-C(6)-C(7)	-31.1(3)
C(11)-O(2)-C(7)-C(8)	80.1(3)
C(11)-O(2)-C(7)-C(6)	-29.8(4)
C(1)-C(6)-C(7)-O(2)	-2.4(4)
C(5)-C(6)-C(7)-O(2)	108.2(3)
C(1)-C(6)-C(7)-C(8)	-112.9(3)
C(5)-C(6)-C(7)-C(8)	-2.3(4)
O(2)-C(7)-C(8)-C(9)	-75.6(3)
C(6)-C(7)-C(8)-C(9)	35.1(4)
C(11)-O(3)-C(9)-C(10)	-175.3(3)
C(11)-O(3)-C(9)-C(8)	-49.4(4)
C(11)-O(3)-C(9)-C(5)	56.9(4)
C(7)-C(8)-C(9)-O(3)	57.7(4)
C(7)-C(8)-C(9)-C(10)	178.5(3)
C(7)-C(8)-C(9)-C(5)	-55.3(3)
C(4)-C(5)-C(9)-O(3)	64.5(4)
C(6)-C(5)-C(9)-O(3)	-60.0(4)
C(4)-C(5)-C(9)-C(10)	-57.3(5)
C(6)-C(5)-C(9)-C(10)	178.3(3)
C(4)-C(5)-C(9)-C(8)	177.6(3)
C(6)-C(5)-C(9)-C(8)	53.1(3)
C(7)-O(2)-C(11)-O(3)	-64.4(4)
C(7)-O(2)-C(11)-C(1)	51.2(4)
C(9)-O(3)-C(11)-O(2)	52.3(4)
C(9)-O(3)-C(11)-C(1)	-60.1(4)
C(2)-C(1)-C(11)-O(2)	-176.9(3)
C(6)-C(1)-C(11)-O(2)	-51.0(3)
Br(1)-C(1)-C(11)-O(2)	62.6(3)
C(2)-C(1)-C(11)-O(3)	-59.5(4)
C(6)-C(1)-C(11)-O(3)	66.4(4)
Br(1)-C(1)-C(11)-O(3)	179.9(3)

Symmetry transformations used to generate equivalent atoms: