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Development of the Tandem Oxy-Cope/Ene Rearrangement and its Application Toward Natural Antibiotic Tetrodecamycin

by

Jeffrey M. Warrington

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirments for the
Philosophiae Doctor (Ph.D.) degree in chemistry

Candidate

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To my parents... For everything

Abstract

This thesis explores the development of the tandem oxy-Cope/ene rearrangement and its application toward the synthesis of natural antibiotic tetrodecamycin. These studies have been carried out to better understand the chemical synthesis of decalin natural products, and provide a springboard from which further studies can be launched.

The first part of the study focueses on the tandem oxy-Cope/ene rearrangement and the unravelling of the intricate aspects governing the selectivity, stereochemistry, and transition state conformers at play. As a result of this study, we have developed a general methodology for rapidly constructing decalins bearing a ring junction alcohol via cascade oxy-Cope/ene rearrangement of 1,2-divinyl cyclohexanols.

The second part of this study involved the application of this methodology to the decalin skeleton present in tetrodecamycin. Described in this section is the development of the synthetic chemistry en route to the core of the natural product, along with the serendipitous discovery of a tandem oxy-Cope/Claisen/ene/Claisen rearrangement.

Finally, the decalin core provided by the tandem rearrangement was fully functionalised to resemble that of the natural product (including all 6 contiguous stereocentres), and the synthetic efforts toward the completion of tetrodecamycin are described.

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4-Benzyloxy-3-(3,4-dihydroxy-1-triethylsilanyloxymethyl-4a-trimethylsilanyloxy-decahydro-naphthalene-1-carbonyl)-5-methylene-5H-furan-2-one (3.107) 230

Toluene-4-sulfonic acid 2-methylene-5-oxo-2,5-dihydro-furan-3-yl ester (3.119) 231

Toluene-4-sulfonic acid 4-[hydroxy-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-yl)-methyl]-2-methylene-5-oxo-2,5-dihydro-furan-3-yl ester (3.120) 231

4-Allyloxy-5-methylene-3-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (3.124) 235

3-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl]-4-hydroxy-5-methylene-5H-furan-2-one (3.103) 238

3-(3,4-Dihydroxy-1-triethylsilanyloxymethyl-4a-trimethylsilanyloxy-decahydro-naphthalene-1-carbonyl)-4-hydroxy-5-methylene-5H-furan-2-one (3.128) 242

8-Allyl-8-methyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (4.1) 244

3-Methyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.5) 248

7a-Hydroxy-3-methyl-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (4.7) 252

3-Methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (4.10) 254

4-Benzyloxy-5-methylene-3-(3-methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (4.11) 256

4-Hydroxy-5-methylene-3-(3-methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (4.12) 258

4-Allyl-4-methyl-2-phenylselanyl-octahydro-naphthalene-1,8a-diol (4.27) 260

6-Allyl-6-methyl-6,6a,7,8,9,10-hexahydro-3aH-naphtho[1,8a-d][1,3]dioxol-2-one (4.34) 262

5-Allyl-5-methyl-1,2,3,4,4a,5-hexahydro-naphthalene (4.36) 264

8-Allyl-5,8-dimethyl-1,3,4,5,8,8a-hexahydro-2H-naphthalen-4a-ol (4.39) 266

8-Allyl-7,8-dimethyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (4.40) 269

3-Allyl-2,3-dimethyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (19) 273

2,3-Dimethyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.42) 275

4-Methyl-2-phenylselanyl-4-propenyl-octahydro-naphthalene-1,8a-diol (4.44) 277

6-Allyl-6-methyl-6,6a,7,8,9,10-hexahydro-3aH-naphtho[1,8a-d][1,3]dioxol-2-one (4.45) 279

2,3-Dimethyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.42) 281

2,3-Dimethyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-yloxy)-trimethyl-silane (TMS-4.42) 282

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carbaldehyde (4.48) .. 284

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carbaldehyde (2a) 286

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] aphthalene-3-carboxylic acid (4.61) . 287

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a]naphthalene-3-carbothioic acid S-p-tolyl ester (4.71) 291

4-Benzyloxy-5-methylene-3-tributylstannanyl-5H-furan-2-one (4.73) 293

4-Benzyloxy-3-(2,3-dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5-methylene-5H-furan-2-one (4.50) 295

3-Methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carboxylic acid (4.74) 297

4-Benzyloxy-5-methylene-3-(3-methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (4.11). 300

3-(2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carbonyl)-4-hydroxy-5-methylene-5H-furan-2-one (4.51) 301

1

Natural Product Synthesis

Introduction

"The goal is always finding something new, hopefully unimagined and, better still, hitherto unimaginable."

K. B. Sharpless

"The unique challenge which chemical synthesis provides for the creative imagination and skilled hands ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, practical, or both"

R. B. Woodward

Why perform total synthesis? Humans have been fascinated with what they can accomplish with their own hands and minds since Man first combined wood and stone to form tools necessary for survival. Nature continually presents the alert scientist with new insights into the delicate machinery of Life itself: Every day, discoveries are made which shape the way we interact with our environment, harvest resources, and carry on with our

daily lives. Since Hippocrates discovered that powders made from willow trees could be used to treat toothaches in 400 B.C., scientists have long been fascinated with the wealth of chemical complexity that Nature presents, and their potential benefit to mankind.

The synthesis of natural compounds has come a long way since Wöhler's 1828 urea synthesis,[1] and every decade of synthetic challenges presents ingenious solutions.[2] The wealth of books and journals on total syntheses published every year are a testament to the synthetic art's scientific value. There is simply no better way to learn something than to teach it; and undeniably there is no better way to understand a chemical compound than to make it. Regardless of the battery of tests, or models built, the secrets of a molecule can not be truly understood until its synthesis is undertaken.[3]

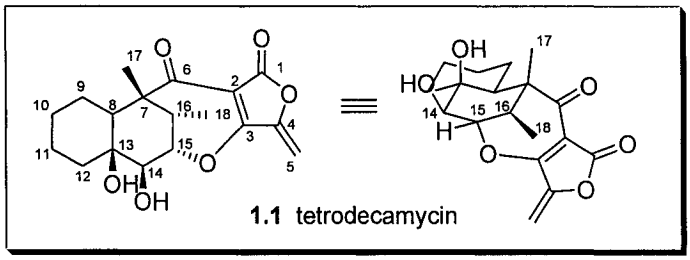
Not only has chemical synthesis enjoyed a pivotal role in the development of modern science; but the creation of natural products has continued to serve as an invaluable training tool for organic chemists all over the world. The breadth of experience that a student is subjected to over the course of a synthetic project provides a solid foundation for the understanding of many aspects of chemistry. It is one thing to observe, but yet quite another to create.

With these thoughts in mind, we now delve into the synthetic studies of natural antibiotic tetrodecamycin, and the development of the oxy-Cope/ene reaction.

Tetrodecamycin

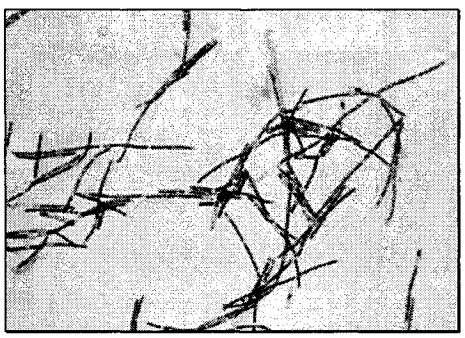
Tetrodecamycin (**1.1**) is a naturally occurring antibiotic isolated in 1997 from methanolic extracts of *Streptomyces nashvillensis* MJ885-mF8.[4] It has shown distinct activity against Gram-positive bacteria including Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and *Bacillus anthracis*.

Figure 1.1 – Natural Antibiotic Tetrodecamycin



Strains of MRSA, methicillin-resistant coagulase negative staphylococci (MRCNS), vancomycin-resistant *Enterococcus faecalis* and *E. faecium* (VRE) were shown to give particular problems to patients suffering from nosocomial ICU-acquired infection.[5]

Figure 1.2 -- Baccillus Anthracis, Gram Stain (CDC)[6]

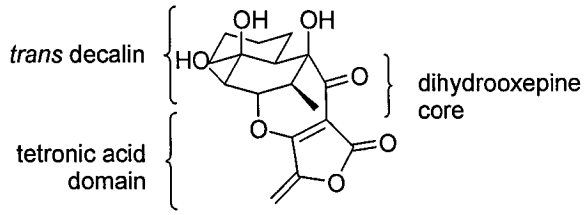


Bacillus anthracis endospores are known to initiate anthrax infections (also known as woolsorters' disease). The organism is soil dwelling, with endospores that do not divide and have no measurable metabolism. They are resistant to drying, heat, ultraviolet light, gamma radiation, and many disinfectants.[7] Human infections are rare, and usually result from exposure to contaminated animals or animal products. Although cutaneous anthrax (the most common form) is usually curable, a small percentage of these infections become systemic. Systemic infection resulting from inhalation has a mortality rate approaching 100 percent.[8]

Structural motifs

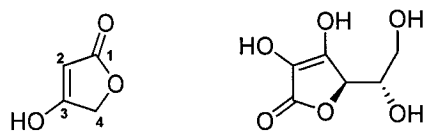
The structure of tetrodecamycin has been fully characterized by spectroscopic means including X-ray crystallography.[9] The molecule appears as a polyketide containing both a tetronic acid moiety, and a *trans*-decalin fragment (Figure 1.3)

Figure 1.3 - Structural Motifs of Tetrodecamycin



Tetronic acid (**1.2**, Figure1.4) is a cyclic four-carbon β-keto lactone; the derived sesquiterpenes are abundant and ubiquitous in nature. This general class of compounds can include ascorbic acid (**1.3**) (Vitamin C) as one of its members, and is found in an abundance of foods, and essential to the human diet.[10] While the C3 oxygen is formally drawn as an alcohol, the proton is strongly acidic in aqueous solution (pKa = 3.76).[11] Solid infrared absorptions at 1690 (C=0) and 1635 (C=C) cm^{-1} are also consistent with an enolic structure.[12] In ethanolic solutions, tetronic acid exists as a mixture of the protonated and deprotonated forms, the proportion depending on pH.[13]

Figure1.4 - Tetronic and Ascorbic Acid



1.2
tetronic acid

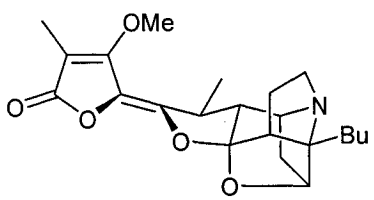
1.3
ascorbic acid

The tetronic acid motif is present in a wide variety of biologically relevant marine extracts, with structural diversity arising from alkylation at C2 or C4, or etherification of the C3 oxygen.

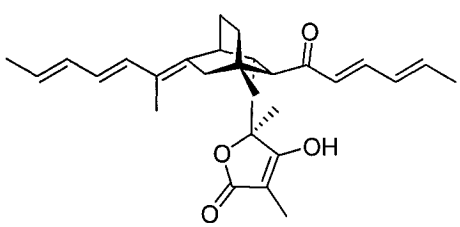
Naturally Occurring Tetronic Acids

In most cases, the acidic C3 oxygen is often found methylated in natural products such as the insecticidal stemofolines (**1.4**),[14] but it is often found in the free-acid form, such as the structurally complicated antifungal bislongiquinolide (**1.5**)[15] (which has been associated with TNF-α inhibition in macrophages and monocytes).[16]

Figure 1.5 – Some Naturally Occurring Tetronic Acids



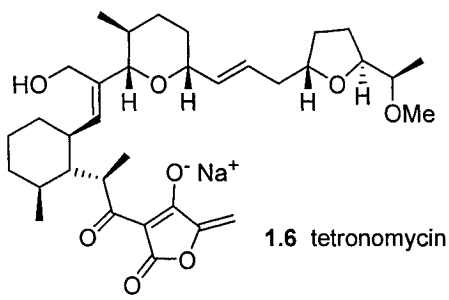
1.4 stemofoline



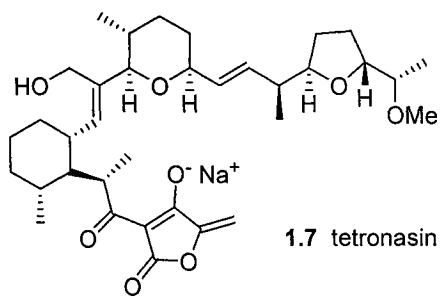
1.5 bislongiquinolide

In some cases, the free acid moiety can serve as a primary metal binding site, such as in ionophore antibiotics tetronomycin (**1.6**)[17] and teronasin (**1.7**).[18] Macrocyclic polyketide antiviral quatromycin (**1.8**)[19] contains four spirotetronic acid residues, and possesses excellent antiviral activity against herpes simplex virus type I, influenza type A, and HIV.

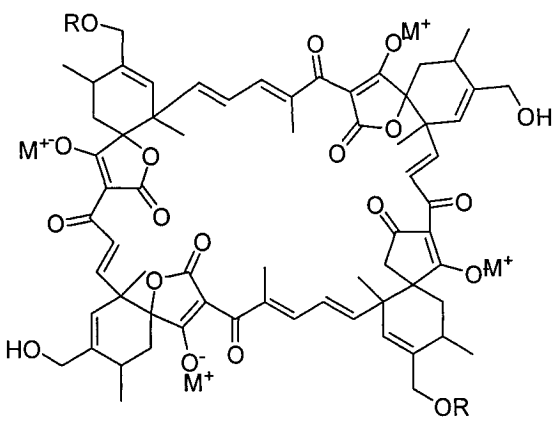
Figure 1.6 – Natural Tetronic Acids as Metal Binding Sites



1.6 tetronomycin



1.7 tetronasin

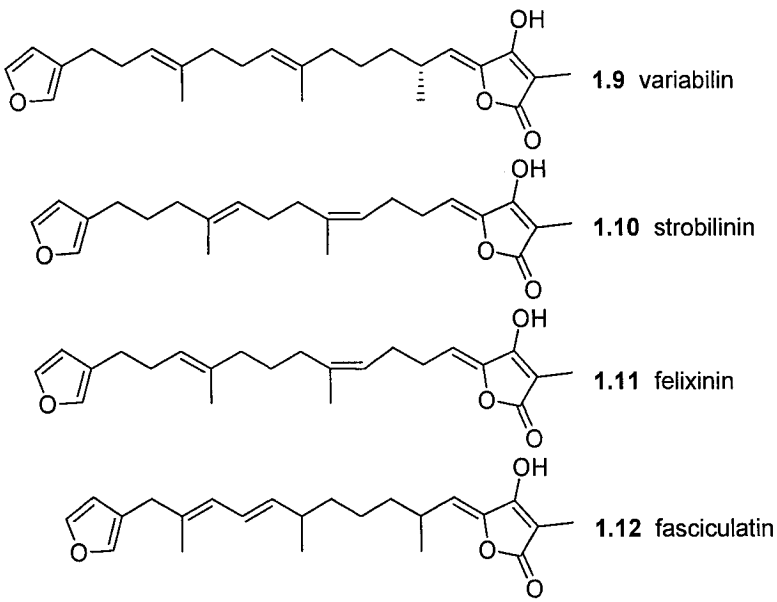


1.8 quatromycin A_3

R = D galactosyl
M = Na^+, K^+, Ca^{++}

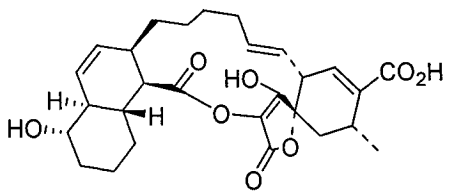
Substitution at C2 is also common; with derivitization via acylation as in tetrodecamycin (**1.1,** Figure 1.1), tetronasin, tetronomycin and quatromycin above, (**1.6 – 1.8,** Figure 1.6), or methylation (as in variabilin (**1.9**), strobilinin(**1.10**),[20] felixinin(**1.11**),[21] and fasciculatin (**1.12**),[22] Figure 1.7) showing a clear predominance.

Figure 1.7 – Marine Tetronic acids



Replacement of one or both of the protons at C5 with an alkyl chain gives even further structural diversity; spirotetronic acids such as chlorothricolide (**1.13**) have been shown to be powerful antibiotics.[23,24]

Figure 1.8 – A Spirotetronic Acid



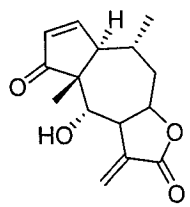
1.13 chlorothricolide

Methylene at C3 in Tetronic Acid Derived Natural Products

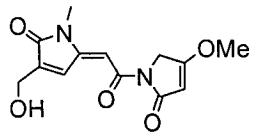
An element of key synthetic and biological interest is the γ-methylene unit present in Tetrodecamycin, where C4 and C5 are the home to an electrophilic double bond. Sesquiterpene lactones, particularly those bearing an α-alkylidene functionality (e.g. anti-

tumor agent helenalin **1.14**[25]) are known to possess significant biological activity,[26] with mode of action being attributed to the exo-methylene's Michael acceptor capability, or the formation of 2 + 2 cycloadducts with DNA base thymine.[27]

Figure 1.9 - Related Exo-Methylenes



1.14 helenalin

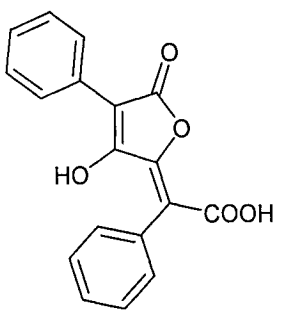


1.15 pukeleimide A

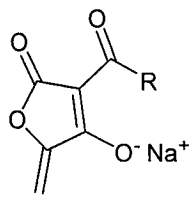
The related 5-alkylidene-2,5-dihydropyrrol-2-ones (tetramic acids) are of considerable pharmacological significance, and occur in an array of natural products (eg. pukeleimide A (**1.15**, Figure 1.9).[28]

Tetronic acid derivatives bearing a γ-methylene unit are somewhat less common. Natural antibiotics tetronomycin (**1.6**),[17] the agglomerins (**1.17**, Figure1.10),[29,30] and the mushroom isolates pulvinic acids (**1.16**)[31] all possess tetronic acid residues with an *exo*-alkylidene functionality.

Figure1.10 – Pulvinic Acid and Agglomerins



1.16 pulvinic acid



1.17 agglomerins

A R =

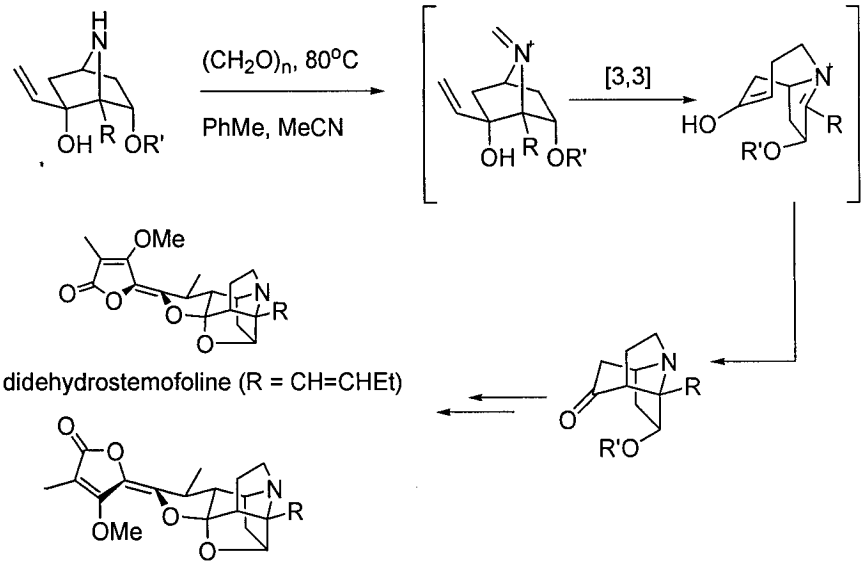
B R =

C R =

D R =

The synthetically challenging stemofoline shows powerful insecticidal activity arising from antagonism of insect nicotinic acetylcholine receptors,[32] the relative configuration of the tetrahydrofuranylidene butenolide plays an important role in bioactivity.[33] The clever 2003 synthesis by Overman *et al.* highlights some challenges present in this class of natural products (Figure 1.11).[34]

Figure 1.11 Synthsis of Stemofolines (L. Overman, 2003)



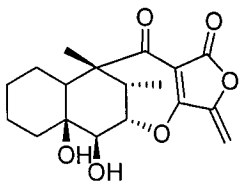
Interestingly, the combination 2-acyl, 4-alkylidene tetronate motif is shared between tetrodecamycin and several of the other tetronic acid-derived antibiotics. Likely this enhancement of the Michael-acceptor ability gives rise to their potent antimicrobial activity.

Exo-methylene in Tetrodecamycin is a Potent Michael Acceptor

In the early investigations of tetrodecamycin, the *exo*-methylene moiety indeed shows electrophilic characteristics: thiols such as *N*-acetylcysteamine and 2-mercaptoethanol add cleanly across the double bond at room temperature - leading to alkylated products (**1.20** → **1.21**, Table 1.1).[35] Unlike dihydrotetrodecamycin (**1.21c**) and dibromodetrodecamycin (**1.21d**) where the olefin has been irreversibly saturated, these alkylated products (**1.21a**,

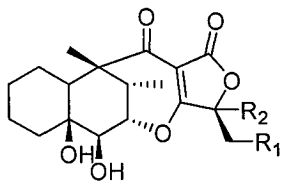
1.21b) still maintained high *in vitro* activity against several bacterial strains. This may be explained by an elimination to re-generate tetrodecamycin in situ (i.e. **1.21** → **1.20**).

Table 1.1 – Michael-Additions to Tetrodecamycin



1.20

R1 - R2



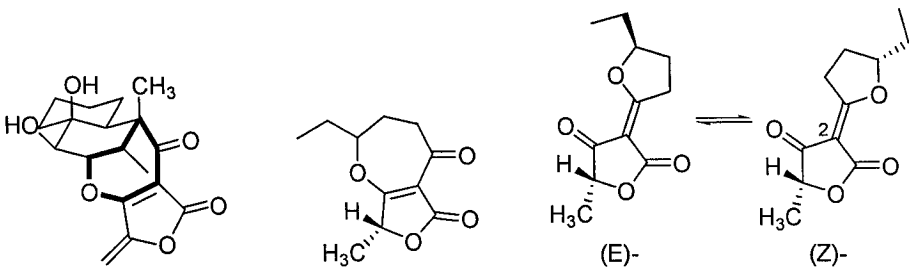
1.21a (R_1 = $S(CH_2)_2NHAc$, R_2 = H)
1.21b (R1 = $S(CH2)_2OH$, R_2 = H)
1.21c (R_1 = R_2 = H)
1.21d (R_1 = R_2 = Br)

	Minimum Inhibitory Concentrations (μg/mL)				
	Tetrodecamycin (**1.20**)	**1.21a**	**1.21b**	**1.21c**	**1.21d**
Staph. aureus FDA209P	6.25	12.5	25	> 100	> 100
Staph. aureus Smith	12.5	25	25	> 100	> 100
Micro. luteus FDA16	12.5	50	100	> 100	> 100
Bacillus anthracis	6.25	12.5	12.5	> 100	> 100
Shigella dysenteriae JSI1910	50	> 100	> 100	> 100	> 100

Acyl Tetronic Acids

The unique tetracyclic ring system contains a seven-member tetronic acid derived dihydro oxepine core; this ring system is identical to that initially proposed for *Penicillium charlesii* isolate carolic acid (Figure 1.12).[36] The natural compound is beleived to exist in the free-acid form, while in solvent it is thought to cyclize to form a seven member ring (**1.22**). It was later determined that this structure was untenable, and the related tetronates isolated from *P. terrestre* and *P. cinerascens* exist primarily in the tetrahydrofuranyl form as a mixture of *E* and *Z* isomers (**1.23**).[37] Moreover, when carolic acid is recrystallized in the dark from ethanol and dissolved in pure acetonitrile-d_3, there is only the E-isomer present. The presence of light can influence this equilibration, suggesting radical formation at C2.

Figure 1.12 – Oxpenine Derived Tetronic Acids



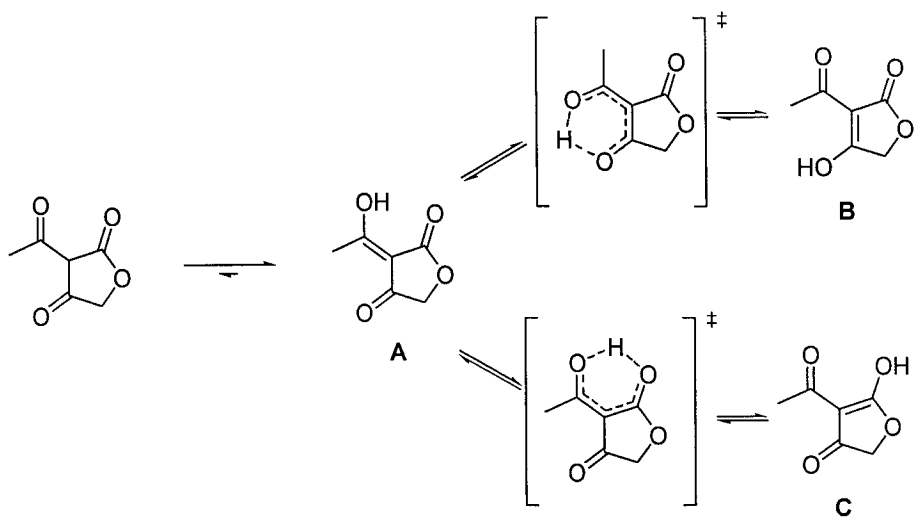
1.20

1.22
carolic acid
(1975)

1.23
carolic acid, revised structure
(1978)

This observation is consistent with the evidence that 2-acyl tetronic acids exist in a mixture of tautomers (Figure 1.13). The most recent evidence suggests that these compounds exist primarily in the **A** and **B** tautomeric forms, with equilibration taking place via *intra*-molecular tautomerization.[38]

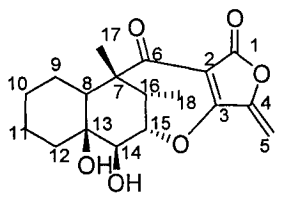
Figure 1.13 – Tautomerism in Acyl Tetronic Acids



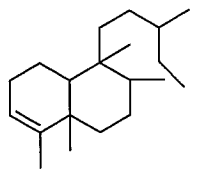
Decalin core

The decalin core of tetrodecamycin bears structural similarity to the clerodane diterpenoids,[39] a family of structurally similar compounds containing thousands of members (**1.24**, Figure 1.14). However, the lack of any functional groups on the C8-C13 ring of tetrodecamycin betrays its bacterial (and polyketidic) origins. Amongst diterpenoids, the *trans-cis*-decalin skeleton posessing an alcohol at ring junction is conspicuously rare; salient members of this class are the decalins ambiol (**1.25**), agelasamine a (**1.26**), aurol (**1.27**), and the furanoditerpenoids chettaphanin I and II, isolated from the plant *Adenochlaena siammensis* Ridl (*Euphorbiaceae*) (**1.29**, **1.30**, Figure 1.15). Both were synthesized in 2003 starting from *ent*-halimic acid (**1.28**).[40]

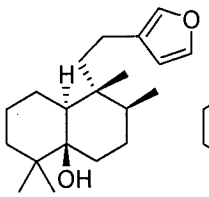
Figure 1.14 – Comparison Between Tetrodecamycin and Other Decalins



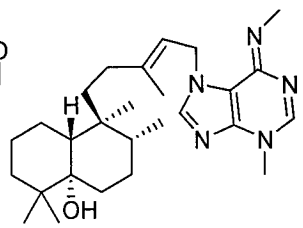
1.1
tetrodecamycin



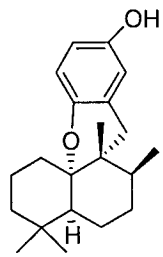
1.24
clerodane skeleton



1.25
ambiol B



1.26
agelasimine A



1.27
aureol

The tertiary alcohol in this case was carried out by an epoxidation/epoxide opening sequence following isomerization of the double bond present in *ent*-halimic acid (**1.28** → **1.29**).

The tertiary ether in (+)-aureol (an extract from marine sponge *Smenospongia aurea*) was constructed from Lewis-acid promoted 1,2-suprafacial methyl and proton migrations of natural product (+)-arenarol (**1.31** → **1.27**, *Figure 1.16*).[41]

Figure 1.15 – Synthesis of Chettaphanins I and II

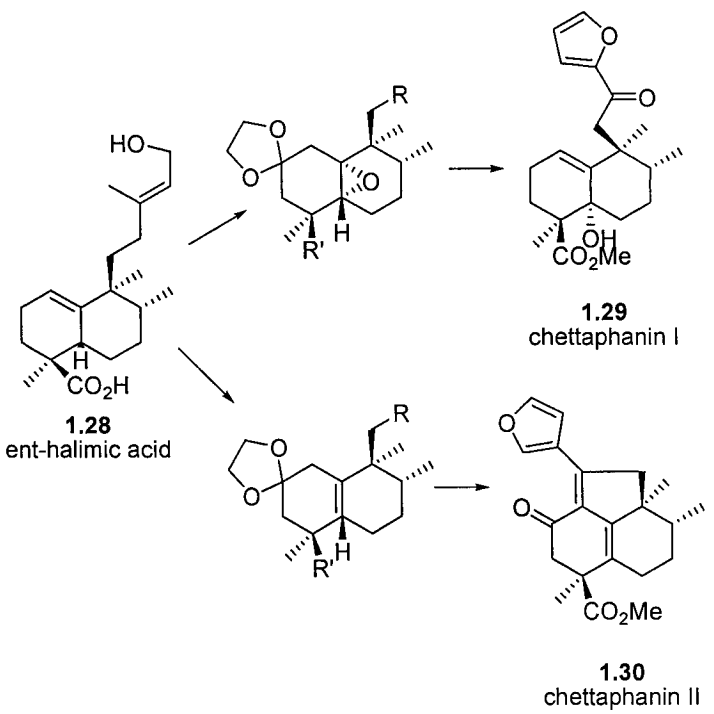
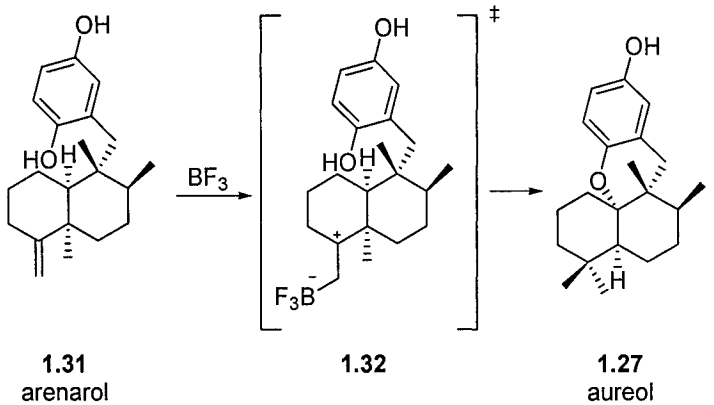
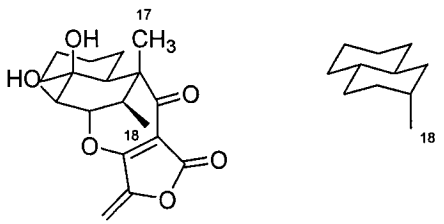


Figure 1.16 – Synthesis of Aureol



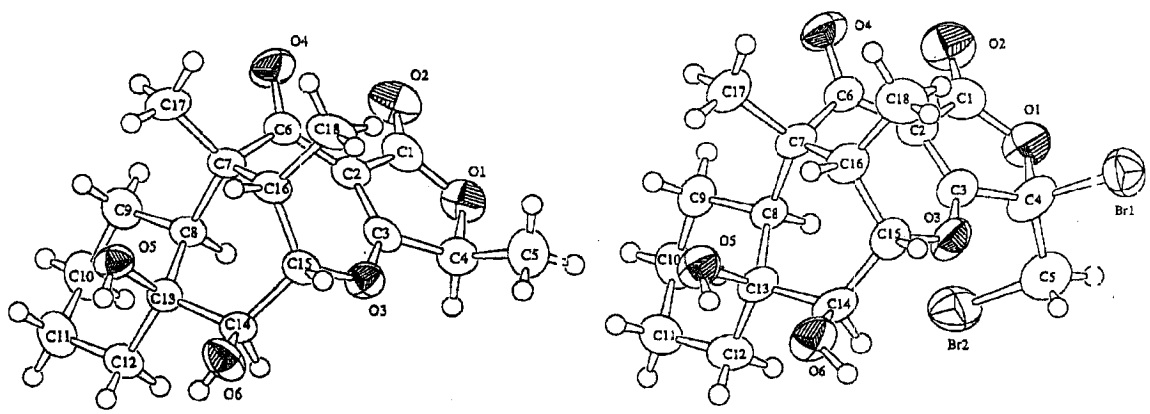
The decalin core embedded in tetrodecamycin bears two methyl groups, C17 and C18. The C18 methyl occupies a pseudoequitorial position in the closed-ring system of tetrodecamycin (imposed by the tetrahydrooxepine core), but would occupy an axial position in a simpler trans-decalin missing this seven member ring. This imposes a unique strain on this portion of the molecule (Figure 1.17).

Figure 1.17 – Conformation of Decalin Core



Confirmation by X-ray analysis of derivatives reveals the functionality-bearing decalin ring in tetrodecamycin to be distinctly boat-like in conformation, which allows the C_{16} methyl group to occupy a pseudoequatorial position. This, in turn, places the alcohols at C_{13} and C_{14} in pseudoaxial positions – making this region of the molecule highly polar (Figure 1.). Tsuchida and co-workers[35] demonstrated that capping the secondary C_{14} alcohol with a naphthoyl ester could produce up to a six-fold increase in activity.

Figure 1.18 –ORTEP Images of Dihydro- (left) and Dibromo- (right) Tetrodecamycin



Decalin Core Structure–Activity Relationship

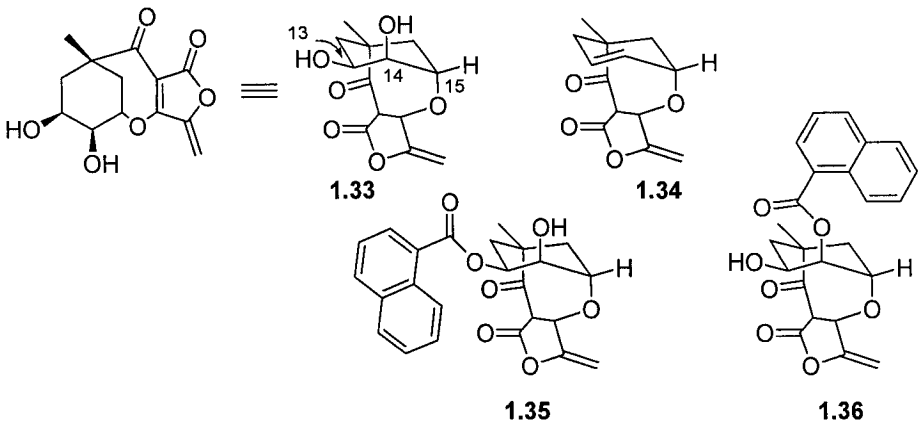
In their studies on simplified tetrodecamycin skeletons, Paintner and his group synthesized and tested a group of products that do not contain the *trans*-decalin ring; but in its place have a simpler cyclohexane rings (**1.33**, Table 1.2).[42] Their studies suggested that the boat-like conformation of the cyclohexyl ring in natural tetrodecamycin is crucial for biological activity. Since their system does not contain the full decalin or the C16 methyl group, the spatial orientation of the C13 and C14 alcohols are dramatically different, and the cyclohexyl ring is distinctly chair-like.

Consequently, this simplified molecule had no biological activity under the conditions tested. However, capping the axial alcohol via naphthoyl ester did produce a weakly active compound (**1.36**), and a further 16-fold enhancement was obtained by capping the neighbouring C13 alcohol instead (**1.35**). The most potent activity was obtained when these alcohols were excised completely (**1.34**), and an olefin left in its place – resulting in minimum inhibitory concentrations (MIC) against *S. aureus* and *E. faecalis* in the 4 μg/mL range, comparable to that of natural tetrodecamycin.

The additional unsaturation in this case not only removes the polarity in this portion of the molecule, but a close inspection of their X-ray structure of a compound similar to **1.34** reveals that the cyclohexyl ring is planarized, and bears a closer resemblance to that found in the natural product (Figure 1.19).[43]

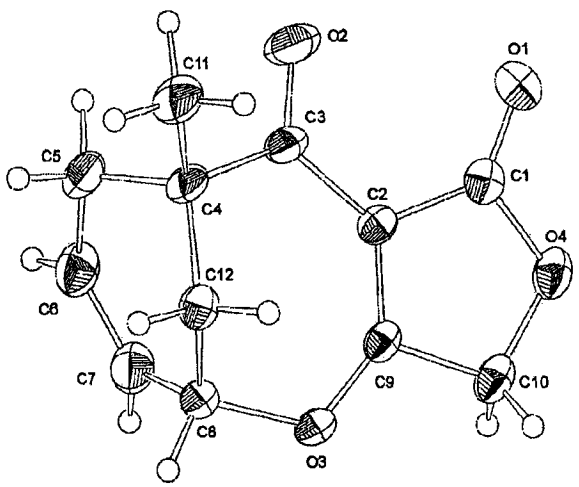
From these studies, it seems clear that the biological activity of tetrodecamycin is linked directly to the orienting effect of the decalin ring, combined with the restraints emplaced by the C18 methyl group. With these considerations in mind, our synthetic strategy would focus upon constructing the decalin core of tetrodecamycin with the stereochemical features seen in the natural product.

Table 1.2 – Biological Activity of Tetrodecamycin Partial Structures[42]



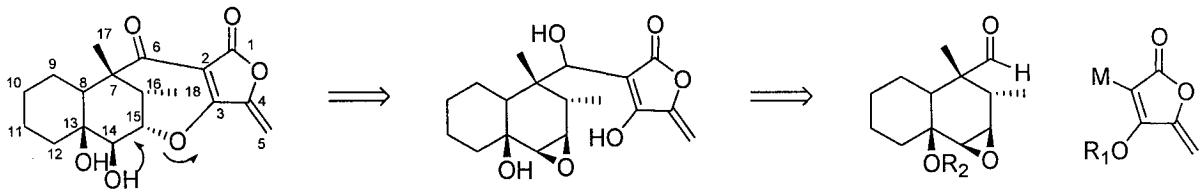
	Minimum Inhibitory Concentrations (μg/mL)			
	1.33	**1.34**	**1.35**	**1.36**
Staph. aureus	>128	4	8	128
MRSA	>128	8	16	>128
E. faecalis	>128	4	4	64

Figure 1.19 –Tetrodecamycin Partial Structure[43]



Retrosynthetic Analysis

Figure 1.20 – Retrosynthetic Analysis



1.1
Tetrodecamycin

1.37

1.38

1.39

At first glance, tetrodecamycin poses a difficult synthetic challenge, but closer inspection reveals a few key disconnection points (Figure 1.20): we envisioned the C15-O bond could arise from an *intra*-molecular attack C3 tetronic acid onto an epoxide between C14 and C15, which may come from free tetronic acid (**1.37**). Subsequent aldol disconnection of the C6-C2 acyl bridge reveals a metallated tetronic acid ester (**1.39**), and a decalin core (**1.38**) containing 6 contiguous sterocenters, including one quaternary carbon. As alluded to earlier, the methods of constructing such functionally dense decalins are rare – and most would not apply in this case.

Since the synthesis of tetronic acids is largely known,[44] the task that now lay before us is the construction of trans-decalin core **1.38**. Our journey into uncharted synthetic waters had begun.

2

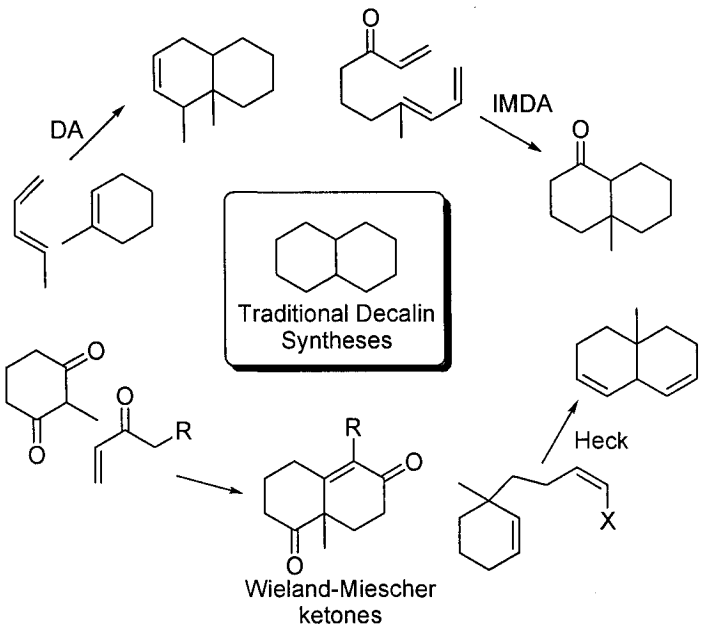
Decalin Core Synthesis: Development of the Oxy-Cope/Ene Rearrangement

Introduction

Some of the more traditional methods of constructing decalin cores include *intra-* and *inter-* molecular Diels Alder reactions, variations of Robinson or aldol annulations (including the Wieland-Miescher ketone synthesis), and other metal catalyzed intramolecular coupling reactions.[45] The rarity of methods available for constructing decalin cores of the unique geometry presented in tetrodecamycin poses a daunting synthetic challenge (Figure 2.1).[46]

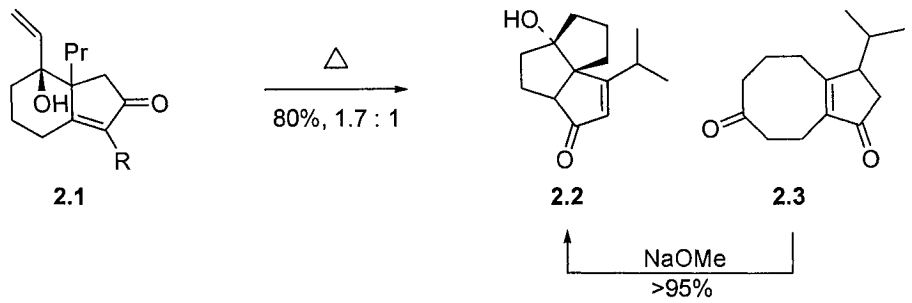
In 1991, Sutherland *et al.* reported low yields of undesired angular triquinanes while attempting anionic oxy-Cope rearrangement for the synthesis of bicyclo-[6.3.0]-cycloundecanes – the result of a subsequent ene rearrangement of the oxy-Cope product (**2.1** → **2.2** + **2.3**, Scheme 2.1).[47] They also reported the complete conversion of the oxy-Cope product **2.3** to the triquinane **2.2** upon exposure to base. Following this work, Rajagopalan

Figure 2.1 – Traditional Decalin Core Syntheses

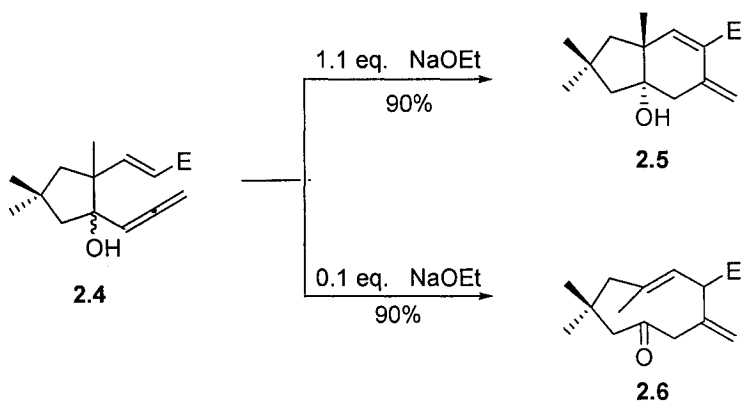


and co-workers described a rapid synthesis of a bicyclo[4.3.0]nonane while attempting oxy-Cope rearrangements of substituted 1,2 divinyl cyclopentanols and cyclohexanols via allene intermediates (Scheme 2.2).[48] These researchers determined that the oxy-Cope product (**2.5**) could be produced efficiently by catalytic amounts of methoxide base, but stoichiometric base produced exclusively the product of a cascade oxy-Cope/ene rearrangement (**2.6**). While this product was decreed the result of an unwanted side reaction, the result is nevertheless a richly functionalized bicyclic system containing an alcohol at the ring junction.

Scheme 2.1 – Oxy-Cope/Ene Rearrangement (Sutherland, 1991)



Scheme 2.2 – Oxy Cope/Ene Rearrangement (Rajagopalan, 1993)



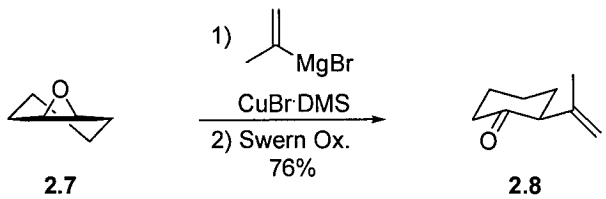
In 1999, Paquette and co-workers noted that the unwanted transannular ene reaction of 1,2 divinyl cyclopentanones could only be averted by trapping the resultant enolate with an electrophile, or quenching at low temperature.[49]

Following these observations, our research focused on whether that this "unwanted" domino oxy-Cope/ene transformation could be (a) made to be the exclusive product (using heat instead of base), and (b) applied to the synthesis of advanced decalin ring structures such as that found in tetrodecamycin.

Oxy-Cope/Ene rearrangement of 1,2-divinyl cyclohexanols

To study the feasibility of this mode of reactivity, a variety of 1,2 – divinylcyclohexanols had to be constructed (Scheme 2.3). Starting from the commercially available cyclohexene oxide (**2.7**), ring opening with isopropenyl magnesium bromide and Copper (I) Bromide dimethyl sulfide,[50] followed by Swern oxidation[51] produced 2-isopropenyl cyclohexanone (**2.8**) in 76% overall yield.

Scheme 2.3 – Preparation of Ketone Template



2.7 **2.8**

This ketone served as a template for further functionalization with other nucleophiles to produce some simple 1,2-divinyl cyclohexanols.

For our initial study, we chose to alkylate ketone (**2.8**) with vinylmagnesium bromide, which furnishes 1,2-divinyl cyclohexanol (**2.9**) as a single diastereomer in 61% yield after purification. Eager to attempt the rearrangement, we attempted thermal rearrangement by placing **2.9** at reflux in toluene; unfortunately this produced no rearrangement even at long reaction times. However, increasing the temperature to 220 °C in a sealed tube furnished a new product whose NMR spectrum was consistent with a decalin bearing an *exo*-methylene. Indeed, further analysis confirmed that the product was the result of a putative oxy-Cope/ene cascade sequence, producing a new bicyclo [4.4.0] decane with alcohol at ring junction (**2.10**) as a single diastereomer. Excited by this promising result, we rapidly constructed an array of other substrates to test the reaction.

Scheme 2.4 – Monocyclic Substrates

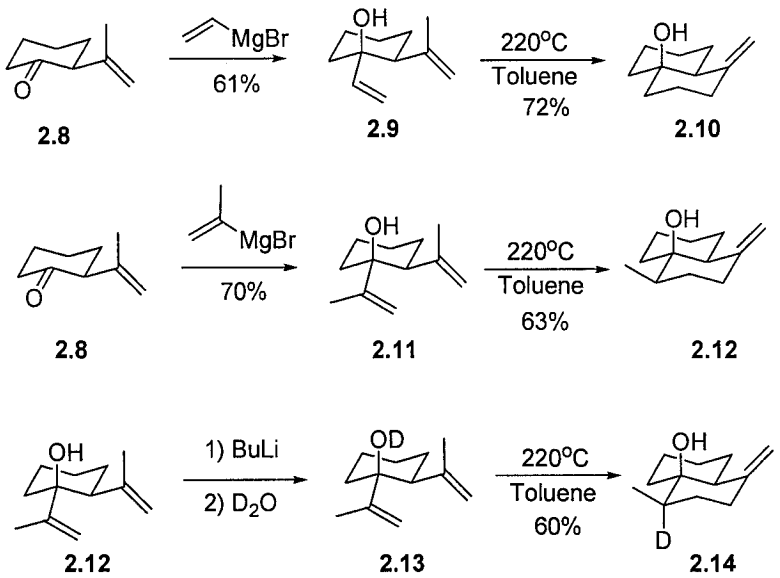
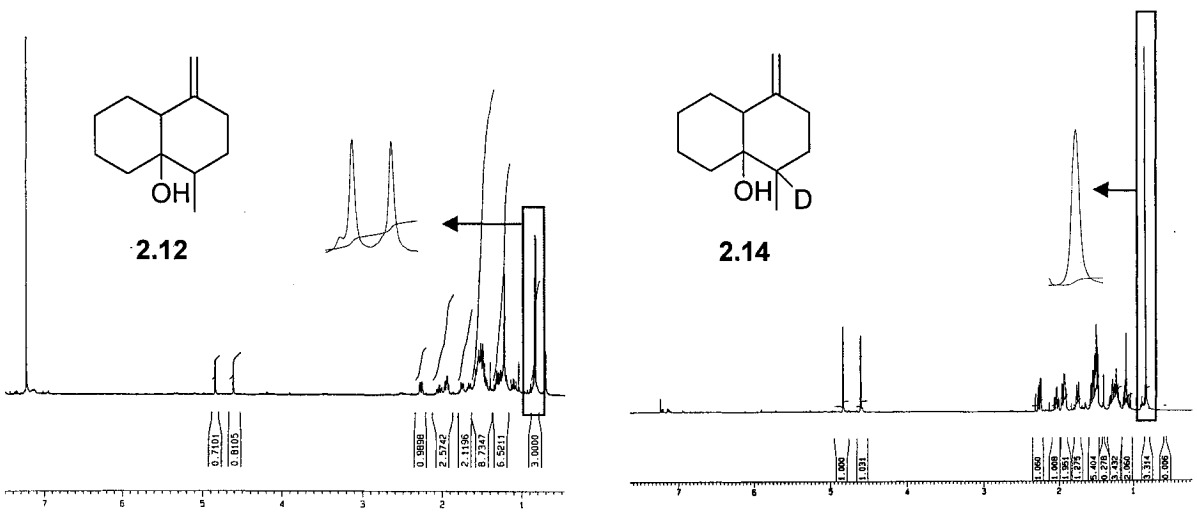


Figure 2.2 – Deuteration Study

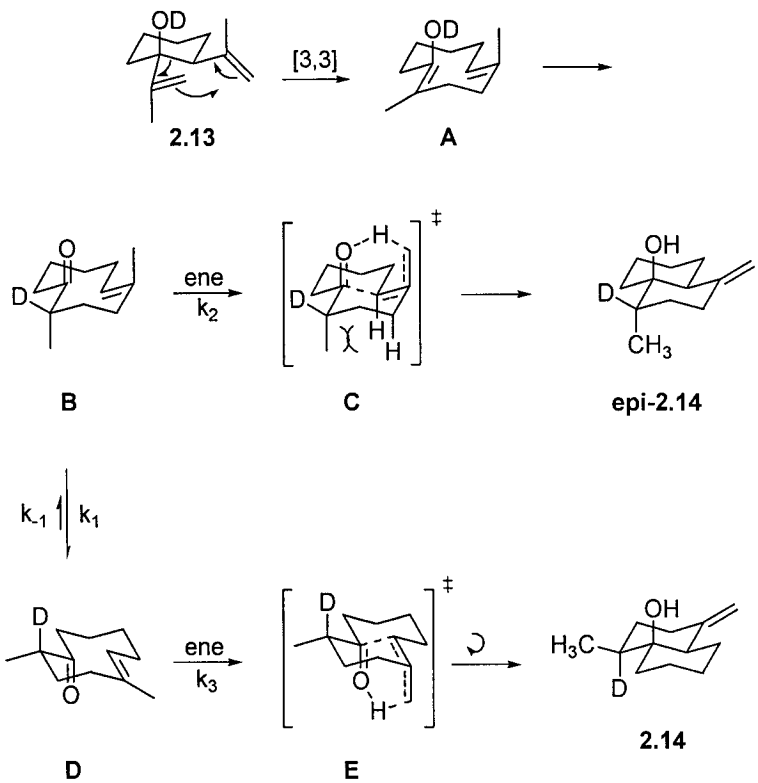


Alkylation of **2.8** with isopropenyl magnesium bromide, followed by heating produced **2.11** as a single diastereomer. Ascertaining the specific stereochemistry was difficult, as NOE experiments were uninformative on this particular molecule. Studies carried out by co-worker D. Gauvreau[52] suggested that the relative configuration of the methyl is *anti* to the ring junction alcohol in simpler systems. Deuteration of the alcohol of

2.12 prior to heating places the deuterium adjacent to the ring junction alcohol (**2.13** → **2.14**), providing support for intramolecular tautomerisation.

Following analysis of these results, we proposed a simplified mechanism for the transformation, below (Figure 2.3). From a thermally-induced oxy-cope rearrangement of substrate **2.12**, the resulting macrocyclic enol **A** undergoes a highly diastereoselective *intra*molecular tautomerization to produce cyclodecanone **B**, with rate of ring inversion k_1 to macrocyclic ketone **D** (and rate constant k_{-1} for reverse reaction). Ene reaction of cyclodecanone **B** via transition state **C** (with rate constant k_2) would result in **epi-2.14**. However, 1,3-allylic interactions likely raise the energy of this transition state, and allows ring inversion to occur in preference. Inversion to **D** then occurs, which undergoes ene reaction via transition state **E** (and rate constant k_3) to produce selectively **2.14**. With the assumption that ring inversion is relatively fast[53] (i.e. k_1 and k_{-1} >> k_2 or k_3), then the reaction pathway is under Curtin-Hammet control.[54] The destabilization of transition state **C** relative to transition state **E** gives rise to the high diastereoselectivity observed.

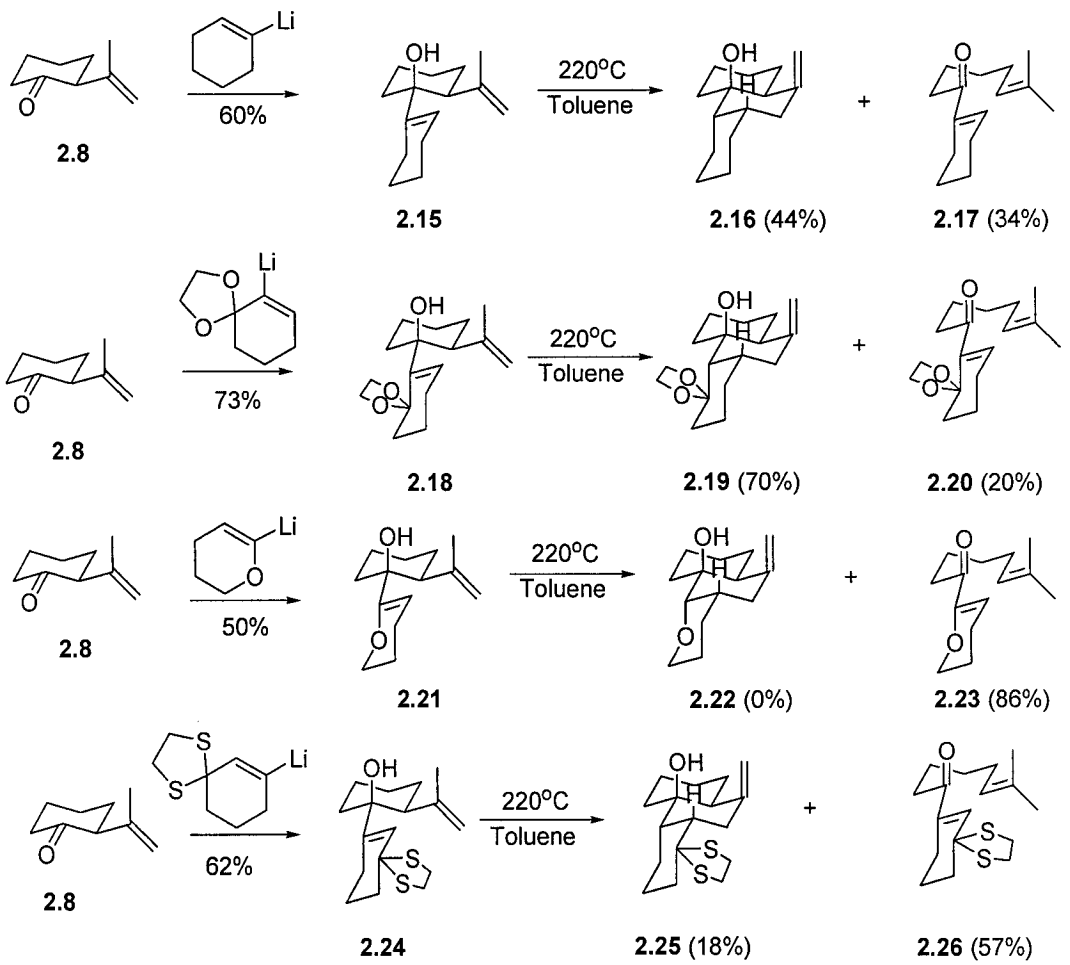
Figure 2.3 – Proposed Mechanism of Oxy-Cope/Ene Rearrangement



Cyclic Allylic Alcohols

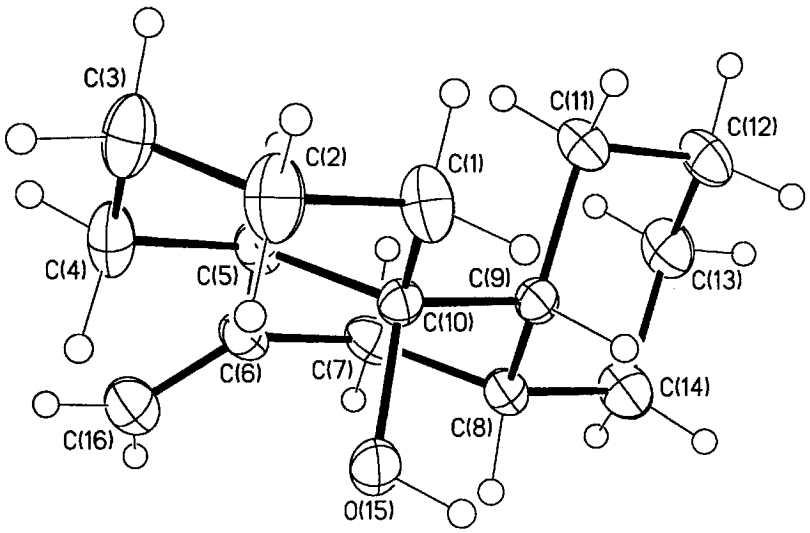
To better explore the possibility of generating other stereocenters, we wanted to produce compounds with both cyclic *ene* donors, and cyclic allylic alcohols. Alkylation of ketone **2.8** with lithiocyclohexene (produced by Shapiro reaction)[55] gave exclusively *cis* divinylcyclohexanol **2.15**. Heating this substrate in Toluene produced tricyclic product **2.16** possessing *trans-syn-cis* stereochemistry as the major product (See Figure 2.4). The minor product was straight-chain ketone **2.17** produced in 34%.

Scheme 2.5 – Cyclic Allylic Alcohols



Similarly, alkylation with a cyclic acetal gave **2.18**[56] and lithiodihydropyran[57] produced divinylcyclohexanol **2.21**. Heating cyclic acetal **2.18** under the rearrangement conditions produced **2.19** in 70% and **2.20** in 20%. No oxy-Cope/ene product was isolated with the dihydropyranyl derivative **2.21**, and an 86% yield of the ketone **2.23** was isolated. The mechanism for the formation of the oxy-Cope/ene products seems identical to those above. However, we now observe the possibility of a retro-ene pathway to form these acyclic products in competition with the oxy-Cope/ene pathway (Figure 2.5).

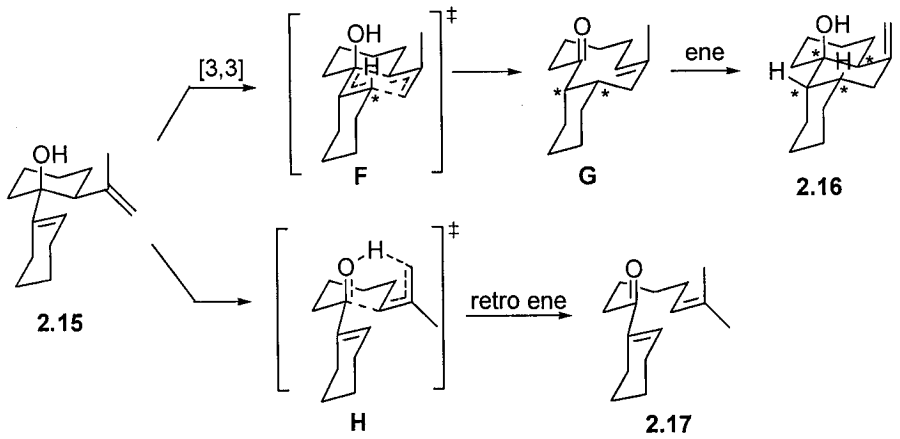
Figure 2.4 – ORTEP plot of 2.16



The high diastereoselectivities with these new cyclic allylic alcohols can be explained as follows: (Figure 2.5) Divinyl cyclohexanols with cyclic allylic alcohols will prefer conformations that minimize gauche interactions between the alkyl rings, or between the olefin-bearing ring and the ring junction alcohol. The most stable conformer is then depicted by **2.15**. As the dominant pathway, the oxy-Cope rearrangement preferentially occurs via chair-like transition state **F**, producing the new stereocentre marked with '*'. The resultant enol is then protonated on the external face of the macrocyclic cage to give ketone **G**, and thus creating to the observed cis external ring junction. Note that ring inversion is not possible in these cases, and proton transfer then must occur via the mode indicated.[58] Ene rearrangement of macrocyclic ketone **G** then furnishes the two remaining stereocentres in a

highly diastereoselective fashion. The new *trans* decalin formed now potentially has five contiguous stereocentres, arising from the initial stereochemistry of the substrate.

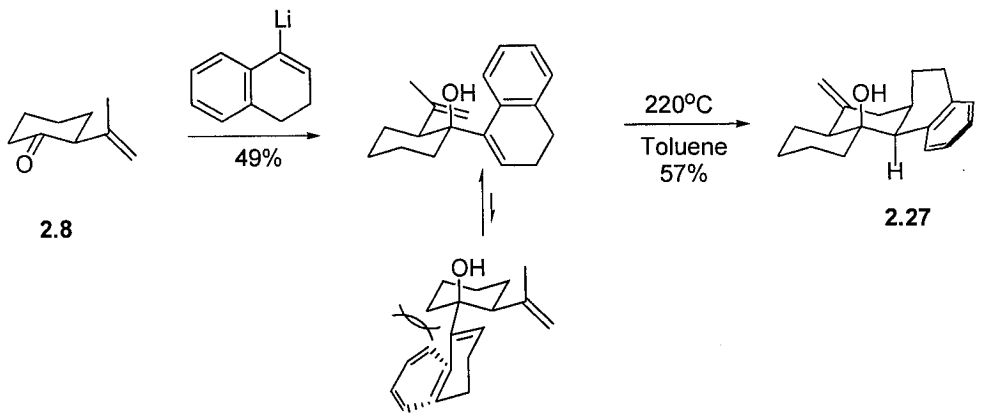
Figure 2.5 – Competition Between oxy-Cope/ene and Retro Ene Pathways



The minor product arising from the rearrangement of **2.15** is the unsaturated ketone **2.17**, a result of a retro-ene reaction (transition state **H**) between the tertiary alcohol and proximal olefin. Interestingly, when a dihydropyranyl unit is used as the allylic alcohol (**2.21**, Scheme 2.5), the retro-ene pathway is the sole mode of reactivity observed.[59] When the cyclic olefin contains an acetal (**2.18**), the oxy-Cope/ene pathway shows a clear dominance. Based on preliminary results in our laboratory and others,[60] it seems that if the allylic alcohol is electron-rich, then the retro-ene pathway dominates. However, introduction of electron-withdrawing groups allows the tandem process to occur in preference. Indeed, the cyclic thioacetal **2.24** shows a clear preference for the retro ene pathway.[61]

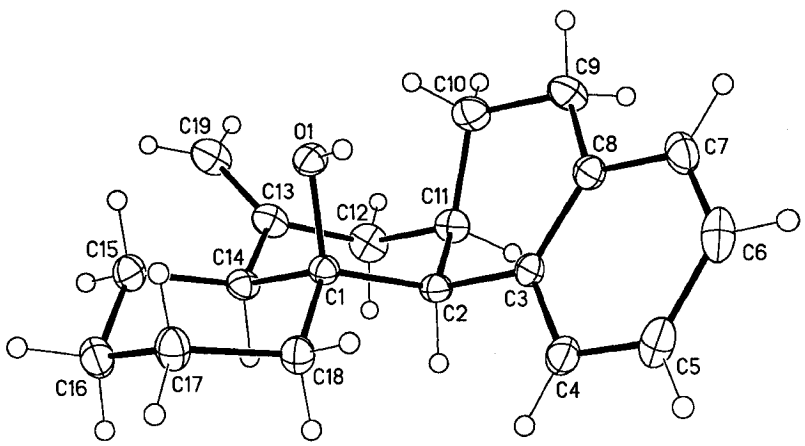
Interestingly, β-tetralone derivative **2.26** cleanly produced tetracyclic structure **2.27**, but of different stereochemistry than observed previously. The *trans-anti-cis* stereochemistry results from a severe interaction between the aromatic ring and the unsaturated cycloalkyl ring, in the conformer depicted for **2.15**. This forces the rearrangement to occur via otherwise unfavourable boat-like transition state. No retro-ene product is observed here, owing to the electron-withdrawing nature of the aromatic ring.

Scheme 2.6 – oxy-Cope/ene Rearrangement of Tetralone Derivative



2.8 **2.27** **2.26**

Figure 2.6 – ORTEP Plot of 2.27

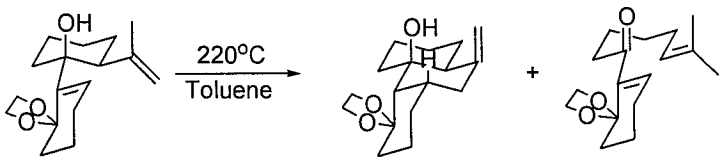


DBU Assisted Oxy-Cope/ene Rearrangements

Following the pioneering work of Evans and co-workers on anionic oxy-Cope rearrangements,[62] our own studies have shown that addition of the powerful amine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) enhances the rate of the oxy-Cope rearrrangement significantly, and an augmentation of product yield corresponding to that pathway is observed.[60a] DBU enhances the ratio of oxy-Cope/ene to retro ene product in cyclic acetals

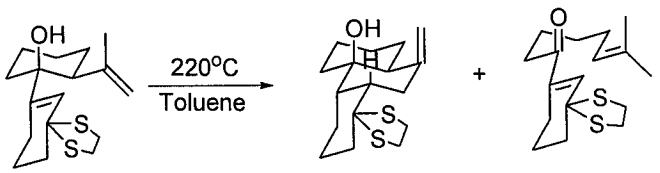
2.18 and **2.24** but the retro ene pathway in the reaction of dihydropyranyl derivative **2.21** proved clearly dominant unless a hundred-fold excess of base was used.

Scheme 2.7 – oxy-Cope/ene Rearrangements in the Presence of DBU[60]



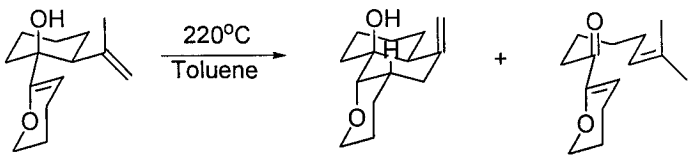
2.18 **2.19** **2.20**

Additive	Product Ratio	Yield
No DBU	3.5 : 1	77%
20 equiv. DBU	20 : 1	75%



2.24 **2.25** **2.26**

Additive	Product Ratio	Yield
No DBU	1 : 3	75%
20 equiv. DBU	1 : 1	56%

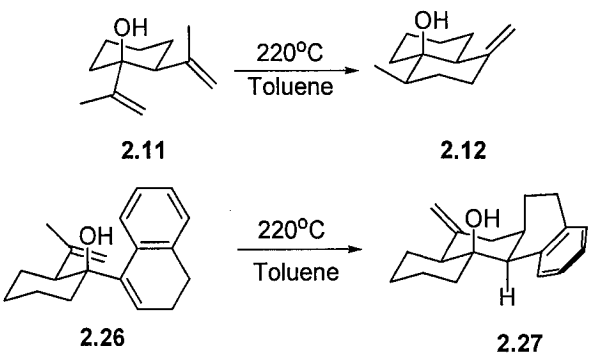


2.21 **2.22** **2.23**

Additive	Product Ratio	Yield
No DBU	0 : 1	86%
20 equiv. DBU	1 : 6.2	77%
20 equiv. DBU	1.4 : 1	46%

While little effect was observed on the outcome of the reaction (in terms of ratio of oxy-Cope/ene to retro ene product), using microwaves as the heat source showed a dramatic increase in reaction rate and a modest increase in yield.[63] For example, allylic alcohol **2.11** is converted into the *trans* decalin **2.12** in 45 minutes with microwave assistance, but takes over 4 hours via conventional heating (Table 2. 1). Similar results were observed with tetralone derivative **2.26**.

Table 2. 1 – Microwave Acceleration



Substrate	Time	DBU (equiv.)	Heat Source	Yield
2.11	4 hr	0	conventional	63%
2.11	45 min	0	microwave	85%
2.26	24 hr	0	conventional	57%
2.26	6 hr	20	conventional	56%
2.26	2 hr	20	microwave	64%

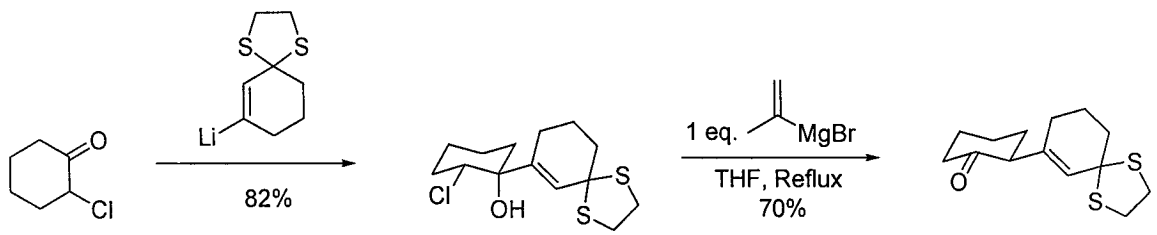
Cyclic Ene Donors

In order to test the rearrangement of cyclic ene donors, cyclic versions of ketone **2.8** had to be constructed. Preparation of these substrates by the *cyclohexene oxide ring opening – oxidation – alkylation* strategy employed earlier failed outright, since the cyclic organometallic species employed failed to open cyclohexene oxide.

Fortunately, these substrates could be prepared via clever rearrangement of chlorohydrin **2.29** produced from 2-chlorocyclohexanone (Scheme 2.8).[64] The desired bicyclohexyl-1'-ene-2-one **2.30** was prepared by refluxing the chlorohydrin in the presence of one equivalent of Grignard, or could be carried directly to the 1,2-divinyl cyclohexanol **2.31** or **2.32** (Scheme 2.9) by using an excess of the Grignard reagent. Better results were obtained when **2.30** was isolated and purified before further alkylation. Bicyclic ketone **2.33** was also prepared in an analogous manner; recently this compound has become commercially available.

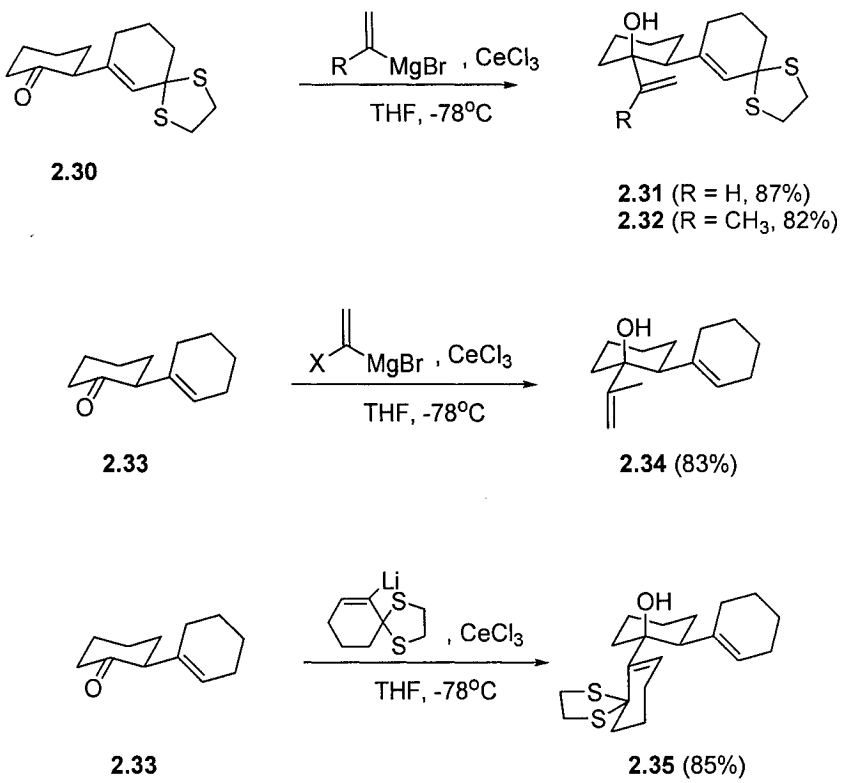
Hindered ketones **2.30** and **2.33** could not be alkylated with Grignard reagents under standard conditions. However, stirring the ketone with $CeCl_3$ for 24 hr prior to low-temperature treatment with Grignard reagent gave good yields of alkylated products **2.31**, **2.32**, **2.34**, and **2.35**.[65]

Scheme 2.8 – Preparation of Bicyclic Ketones



2.28 **2.29** **2.30**

Scheme 2.9 – Preparation of Cyclic Ene Donors

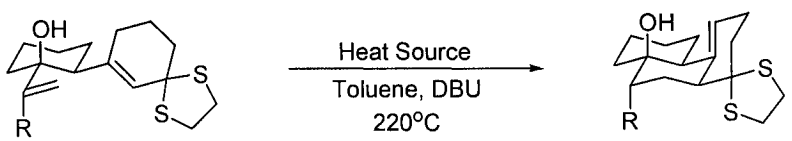


Subjecting the bicyclic substrates **2.31**, **2.32**, and **2.34** to the rearrangement conditions gave exclusively the oxy-Cope/ene products in moderate to good yields (see Table 2.2 and Table 2.3). A significant enhancement in rate was noted by using microwave heat for **2.31** and **2.32**, but the rearrangement of these substrates proved especially sluggish. When the allylic alcohol was less electron rich (X = H, **2.31** → **2.36**), the rearrangement took aver 10 hr to complete in the microwave; with an alkyl substituted olefin (X = CH_3, **2.32** → **2.37**), the rearrangement took only 4.5 hr under the same conditions. Using conventional heat (wax bath, hot plate) slowed the reaction down to a crawl, and took more than 24hr in both cases.

A similar rate enhancement was noted with bicyclic precursor **2.34**, but the rearrangement took under one hour in the microwave. This seems to suggest that the sterically hindered thioacetal moiety present in **2.31** and **2.32** considerably slows down the ene reaction.

The tricyclic precursor **2.35** could not be converted into the tetracyclic oxy-Cope/ene product under a number of conditions tried. The only observed compound was the retro ene product **2.39** isolated in 85% yield (Scheme 2.10).

Table 2.2 – Rearrangement of Cyclic Ene Donors 2.31and 2.32



2.31 (R = H)
2.32 (R = CH_3)

2.36 (R = H)
2.37 (R = CH_3)

Compound	Time	DBU (equiv.)	Heat Source	Yield
2.31	10 hr	10	microwave	90%
2.31	> 48 hr	10	conventional	35%
2.32	4.5 hr	10	microwave	84%
2.32	30 hr	10	conventional	74%

*Figure 1.21 – ORTEP Plot of **2.37***

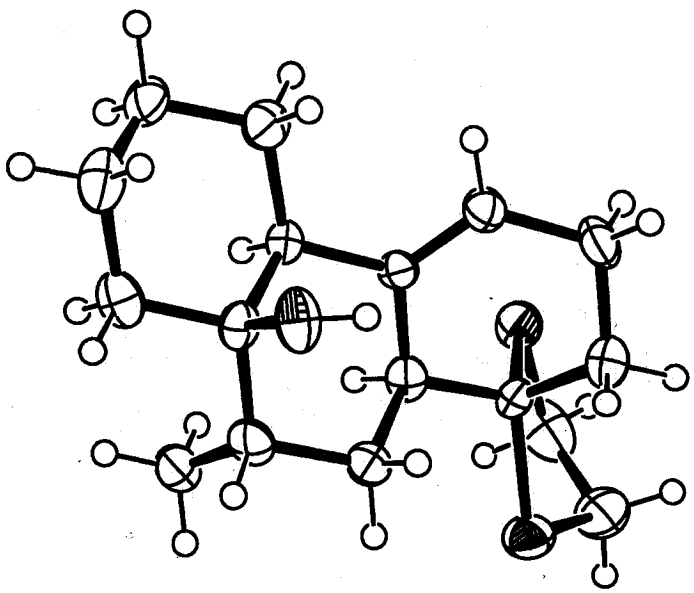
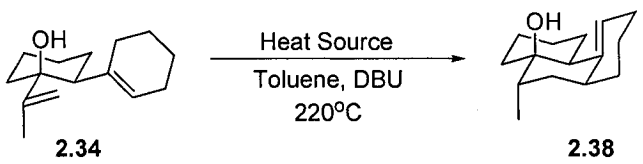


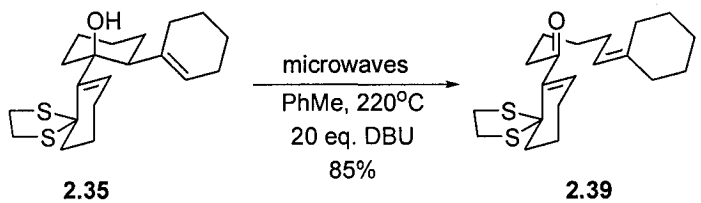
Table 2.3 – Oxy-Cope/Ene Rearrangement of ***2.34***[66]



2.34 **2.38**

Time	DBU (equiv.)	Heat Source	Yield
145 min	0	conventional	82%
60 min	20	conventional	82%
55 min	40	conventional	66%
35 min	10	microwave	78%

Scheme 2.10 – Retro Ene Reaction of Tricyclic Substrate



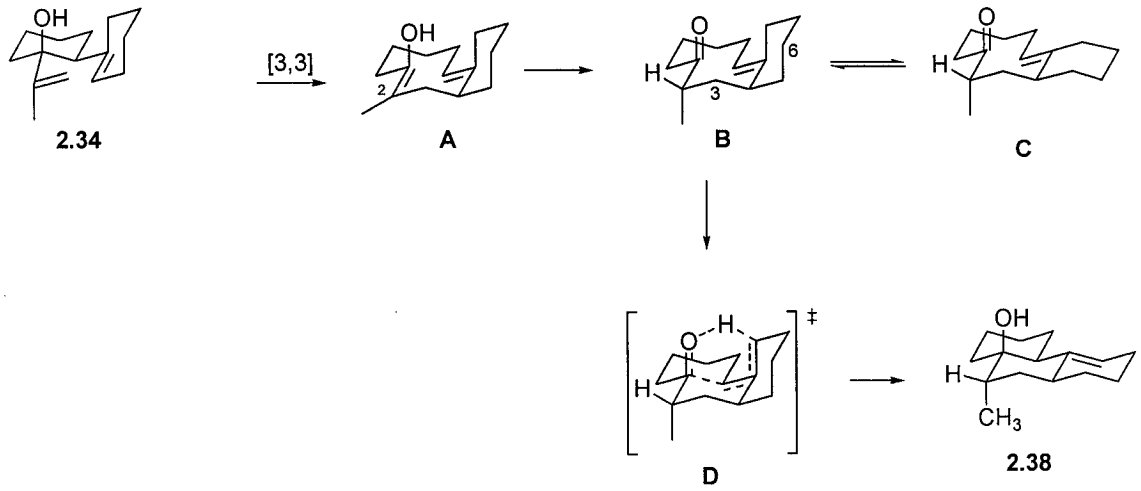
2.35 **2.39**

Mechanism and Stereochemical Outcome

The stereochemistry at C2 in the oxy-Cope/ene rearrangement is opposite to that previously noted in the monocyclic substrates. The transformation can then be rationalized in the following manner: after oxy-Cope rearrangement of substrate **2.34** (Figure 2.7), enol **A** undergoes intramolecular tautomerization to afford macrocyclic ketone **B**. However, in this case, the additional fused ring precludes a ring inversion (e.g. Figure 2.3), and therefore the substituent at C2 must be *anti* to ring junction alcohol. The observed sluggishness of reactions involving cyclic ene donors may be, in part, explained by the higher energetic cost in both achieving oxy-Cope rearrangement with bulkier olefins, or in placing the ene donor ring in its reactive pseudoaxial position prior to the ene rearrangement (eg. the gauche interaction between C3 and C6 in conformer **B** raises its energy relative to **C**).

Intramolecular ene reaction via transition state **D** then gives the product **2.38** in a highly stereocontrolled fashion.

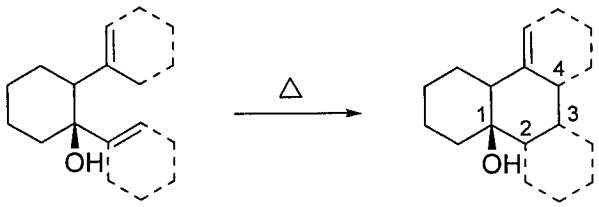
Figure 2.7 – Cyclic Ene Donor Mechanism



Conclusions

Through a comprehensive study of the oxy-Cope/ene rearrangement, we have demonstrated its utility in generating complex decalin cores with varying functionalitities, with largely predictable stereochemical outcome. Specifically, we were successful in generating the *trans* decalin core present in a number of natural products, posessing the crucial tertiary ring junction alcohol. A few general observations can be made: (a) in relatively simple decalin precursors, where ring inversion is rapid, the alkyl unit at C2 generally appears *syn* to ring junction alcohol. (b) in cylic allylic alcohols and systems where ring inversion is impossible, the alkyl substituent at C2 appears *anti* to ring junction alcohol, and (c) substrates with cyclic ene donors generally place the ring junction at C4 *syn* relative to alcohol at C1.

Figure 2.8 – Overview of Oxy-Cope/Ene Rearrangement



Microwaves were noted to cause significant rate enhancements of the rearrangement, often taking a fraction of the time required by conventional heating methods. The powerful amine base DBU was also observed to have beneficial rate enhancements on the oxy-Cope/ene rearrangement. The remaining task for our research program was now to apply this interesting rearrangement to biologically significant tetrodecamycin.

3

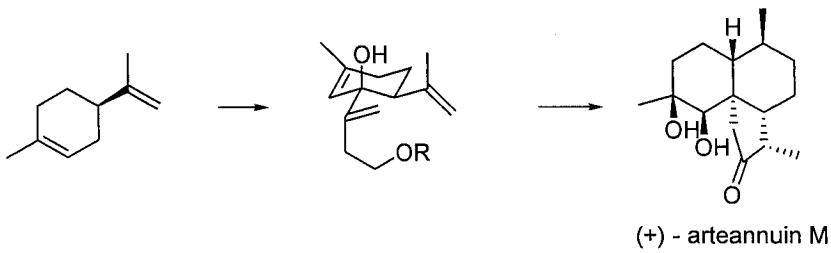
Synthetic Studies Toward Tetrodecamycin

Part I: Analogue Synthesis

Adaptation of oxy-Cope/ene Rearrangement to Tetrodecamycin

As a result of the oxy-Cope/ene rearrangemt, we have sucessfully in produced a decalin core bearing an alcohol at ring junction, an olefin at C_7 for further elaboration, and possible functionalities at C_{14} and C_{15}. This strategy was carried forward to the synthesis of (+)-arteanniun M by Barriault and Deon in 2001 (Figure 3.1).[67]

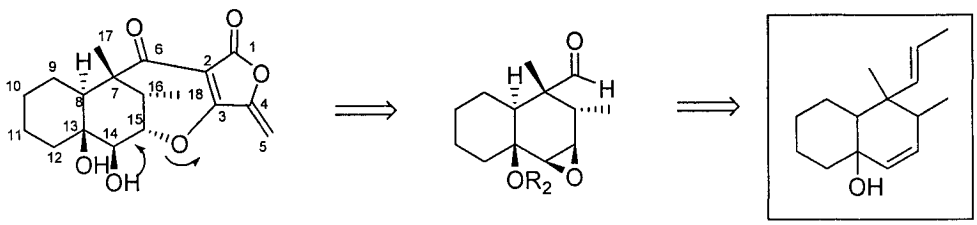
Figure 3.1 Synthesis of (+)-arteannuin M (Barriault, 2001)



(+) - arteannuin M

Several key adjustments must be made to the current methodology, however, before it could be applied to the synthesis of tetrodecamycin. At this point in the study, there were no examples with functionality pre-installed at C16, and preparing the quaternary centre at C7 in a stereoselective fashion from a simple olefin may be a challenge in and of itself (Figure 3.2, Figure 3.3).[68] A review of methods available for installation of quaternary centres[69] suggests a Claisen rearrangement of an allyl ether (**3.2**, Figure 3.3) derived from oxy-Cope/ene product (**2.10**) to produce the desired quaternary centre at C7 (**3.3**).

Figure 3.2 – Proposed Route to Tetrodecamycin Decalin Core

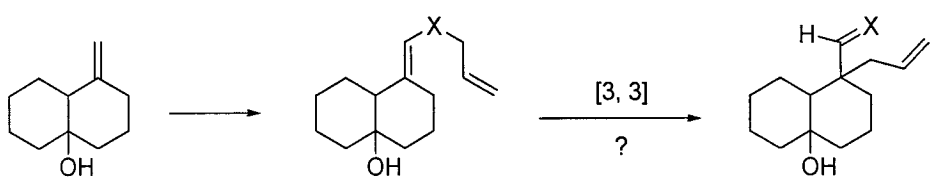


1.1
tetrodecamycin

1.36

3.1

Figure 3.3 – Claisen Rearrangement to Prepare C7



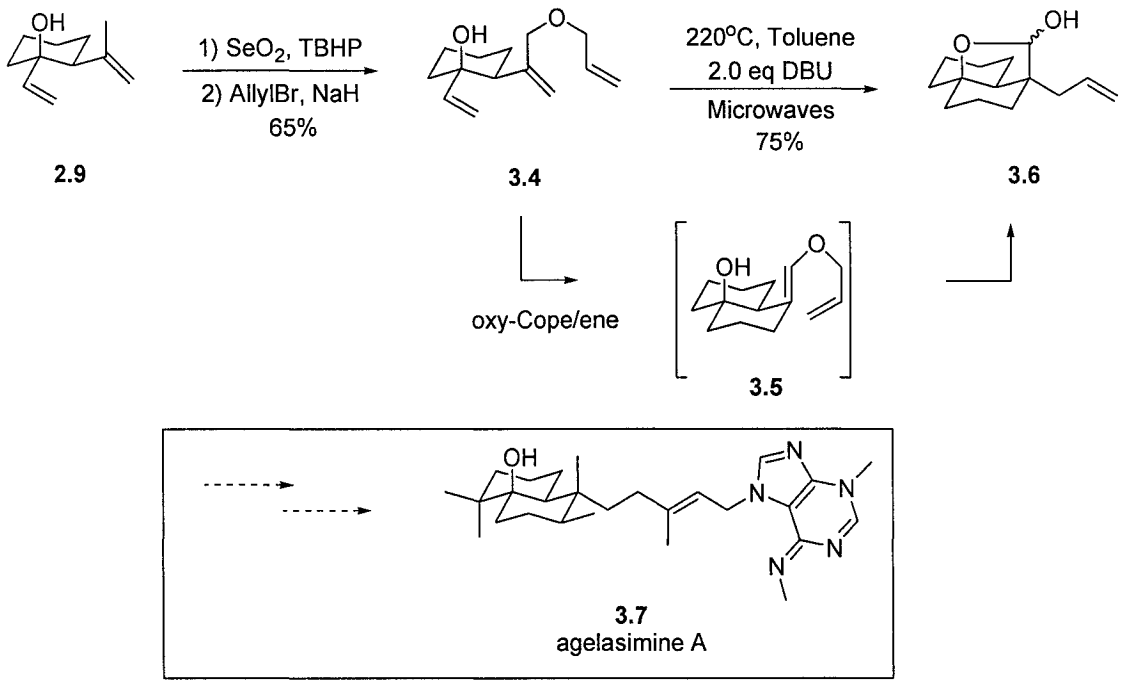
2.10
oxy-Cope/ene
product

3.2

3.3

Fortunately, in her studies toward agelasamine A, co-worker I. Denissova had discovered that indeed introducing an allyl ether tether (**2.9** → **3.4,** Figure 3.4) at this centre could induce a concomitant Claisen rearrangement of the resulting alkene produced by oxy-Cope/ene sequence (**3.4** → **3.5** → **3.6**), stereoselectively furnishing functionality at C7.[70]

Figure 3.4 – Synthetic Studies Toward Agelasamine A (Barriault & Denissova, 2002)



In a parallel study, pre-installation of the C16 methyl group (**4.6,** Figure 3.5) and rearrangement of trisubstituted olefins gave low yields of near-intractable mixture of products.[46] While the solution to this problem was not immediately evident, we continued to explore the synthesis of a simpler structure containing no C18 methyl group. Envisioning a retro-epoxide opening between tetronate ether at C15 and C14 reveals an oxirane adjacent to the ring junction alcohol (**1.38**), which could be a product of a facially-selective tethered epoxidation (from **3.15**).[71] This epoxide could also serve as a handle to install C18 at a later time.

Figure 3.5 – Oxy-Cope/Ene Rearrangement of Trisubstituted Olefins (Denissova & Barriault, 2003)

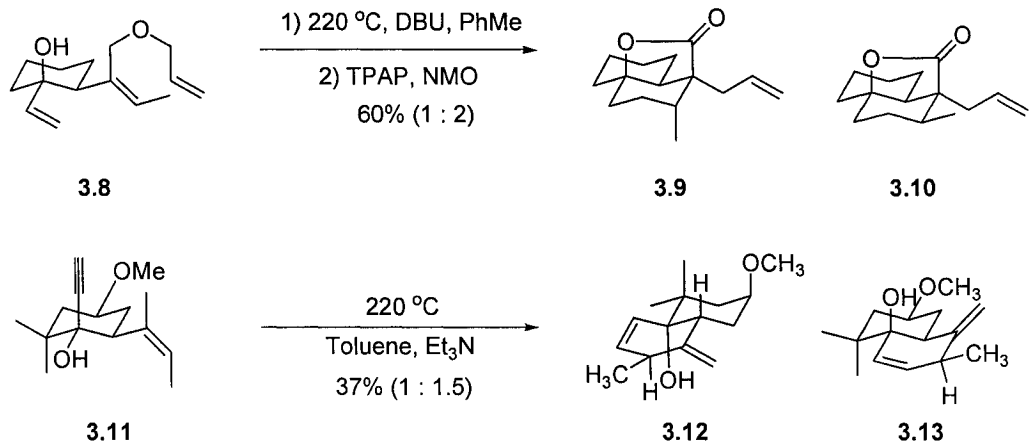
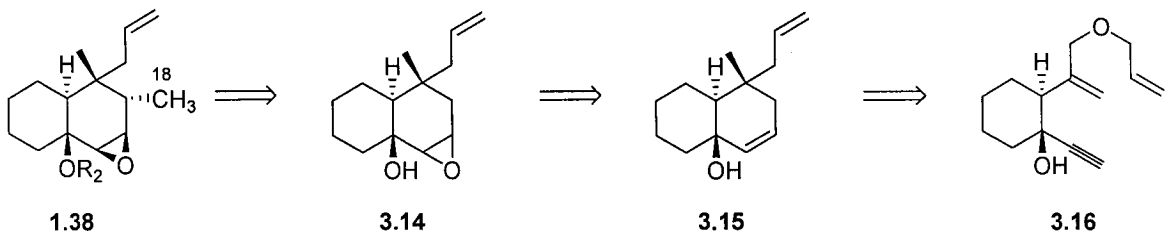


Figure 3.6 – Simplified Decalin Retrosynthesis



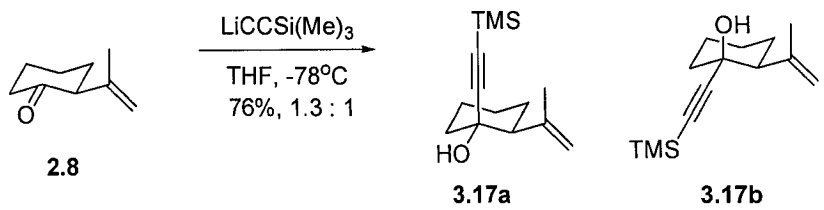
Given these factors, a decalin bearing epoxide **3.14** could be made via epoxidation of allylic alcohol **3.15**, which in turn could arise from acetylene-bearing divinylcyclohexanol of the form **3.16**.

Synthetic Studies on Tetrodecamycin

Synthesis of Oxy-Cope/Ene/Claisen Rearrangement Substrate

Beginning with known ketone **2.8**, installation of the requisite acetylene was fairly straightforward. Deprotonation of trimethylsilylacetylene followed by alkylation produced **3.17a** and **3.17b** in an 1.3:1 diastereomeric ratio, with the undesired *cis* ring junction alcohol (**3.17a**) as the major product (Scheme 3.1).

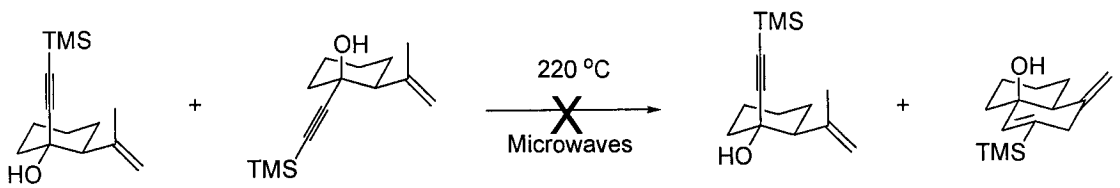
Scheme 3.1 – Installation of Acetylene Unit



2.8 **3.17a** **3.17b**

Chromatographic separation at this point was difficult owing to the similarity in polarity of both diastereomers. Determination of which of the isomers isolated had the desired *trans* ring junction stereochemistry was difficult (owing to ambiguity of NOE experiments). We sought to perform a "chemical identification" by subjecting both isomers to the oxy-Cope/ene rearrangement; with the reasoning that *cis* ring junction alcohol **3.17a** would not react. Unfortunately, neither isomer reacted (Scheme 3.2).

Scheme 3.2 – Attempted Chemical Differentiation of Stereoisomers



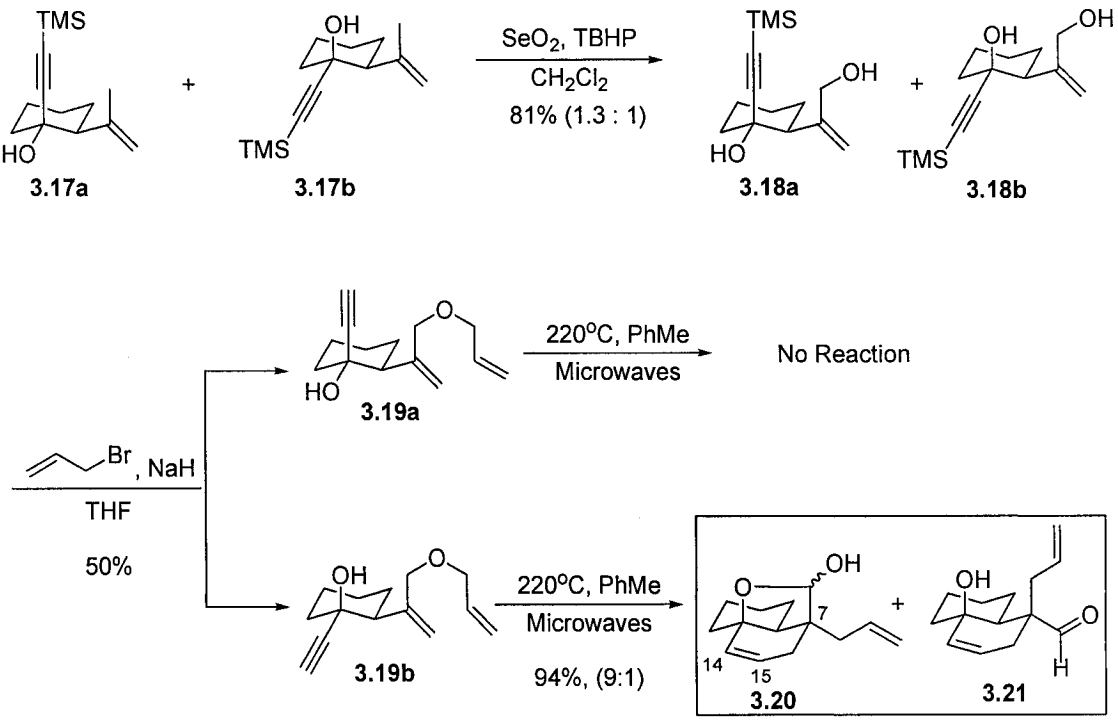
3.17a **3.17b** **3.18a** **3.18b** (not observed)

Despite this ambiguity, synthesis continued with selenium catalyzed allylic oxidation of the isopropene unit to give allylic alcohols **3.18a** and **3.18b** (Scheme 3.3).[72,73] Allylation of these alcohols resulted in a mixture of products containing TMS-deprotected acetylenes. Re-submitting the mixture of products to the allylation conditions gave allyl ethers **3.19a** and **3.19b**, respectively. We still had no information on which isomer was which – only that we had two products that had very similar spectroscopic properties.

However, upon heating the mixture of allyl ethers in the microwave, isomer **3.19b** reacted cleanly to give decalin lactol **3.20** in 85% yield and an isomeric aldehyde **3.21** in 9% yield. Isomer **3.19a** gave only starting material. The decalin lactol **3.20** formed was the result

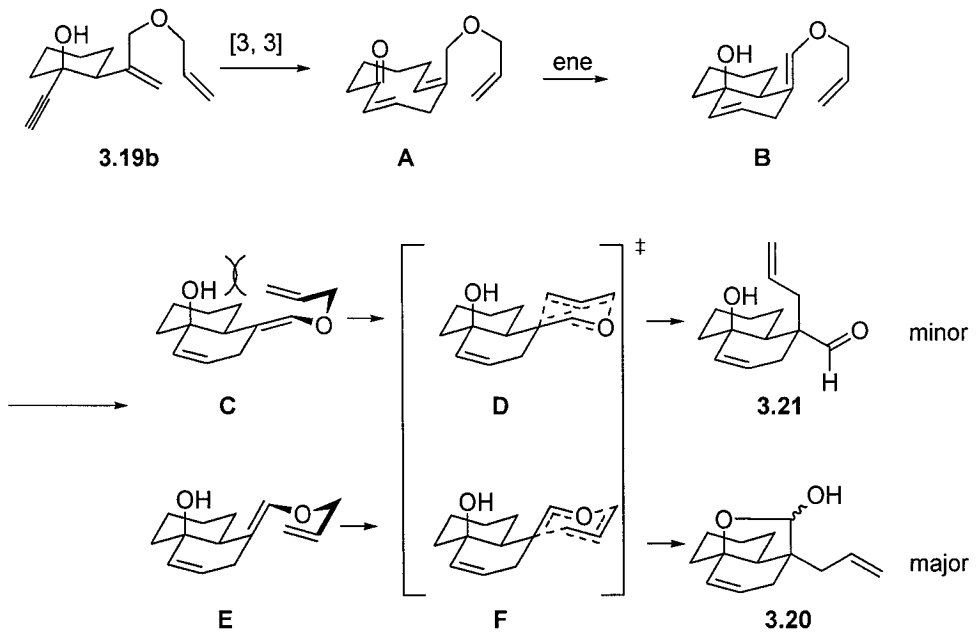
of a putative oxy-Cope/ene/Claisen sequence - cleanly producing a new *trans* decalin possessing an allyl functionality at C7, and a double bond between C14 and C15 for further elaboration.

Scheme 3.3 – Oxy-Cope/Ene/Claisen Rearrangement Containing Acetylene Unit



Interestingly, a minor compound **3.21** was also formed. It is believed that this compound arised from a *top* face Claisen rearrangement of the allyl enol ether tether following the oxy-Cope/ene rearrangement. Though this type of product had not been observed by Barriault and Denissova in 2002,[70] the systems they had studied did not contain a triple bond.

Figure 3.7 – Mechanism of Oxy-Cope/Ene/Claisen Rearrangement



Following the oxy-Cope rearrangement of allyl ether **3.19b** (Figure 3.7), the macrocyclic ketone formed (**A**) then abstracts a proton from the transannular allyl ether to give enol ether **B**. This enol ether can then undergo Claisen rearrangement from the top face (**C** → **D** → **3.21**) or the bottom face (**E** → **F** → **3.20**) of the decalin ring system. Transannular steric interactions between the allyl chain and tertiary alcohol disfavours Claisen rearrangement from the top face (via transition state **D**), and the bottom face rearrangement (via transition state **F**) is preferred – giving rise to the major product. In the studies by Denissova and Barriault,[70] their systems contained no unsaturation in the active cyclohexyl ring. In this system, however, it is likely that the planarization imposed by the additional unsaturation allows the *top* face rearrangement to occur – giving rise to small amounts of the undesired stereoisomer.

Nonetheless, the rearrangement itself was an efficient method of constructing the desired decalin, but the yields of the transformations leading to this substrate were unsuitable for further investigations, and some optimization of these steps was required before the synthesis could continue.

Optimization of Subsrate Synthesis

Deprotection of the TMS-acetylene gave low yields of diol **3.27** under standard conditions (Scheme 3.4). Usage of lithium acetylide (prepared by bubbling acetylene into BuLi at -78°C) to prepare **3.28** was difficult at best, and the reaction was quite slow. The formation of dilithium acetylide is also a complicating factor. The commercially available ethynyl magnesium bromide was a much easier reagent to handle. The alkylation is quite sluggish with this Grignard, as compared with lithium TMS-acetylene (three to four hours at room temperature, in place of minutes at dry ice temperature), but this source of acetylene is far more cost effective. Unfortunately, the small size of the nucleophile allows for formation of large amounts of the undesired stereoisomer (which is discarded). Fortunately **3.27** was a crystalline compound which allowed unambiguous determination of its relative stereochemistry.[74]

Scheme 3.4 – Optimization and Characterization of Diol

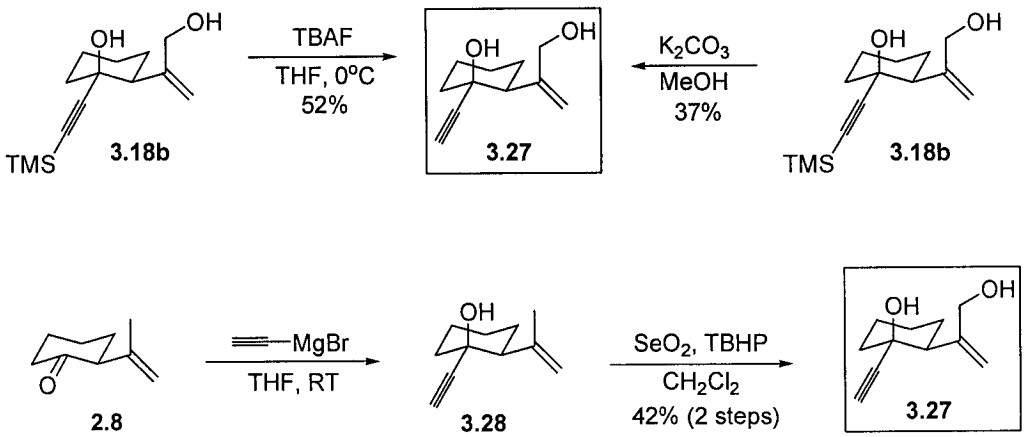
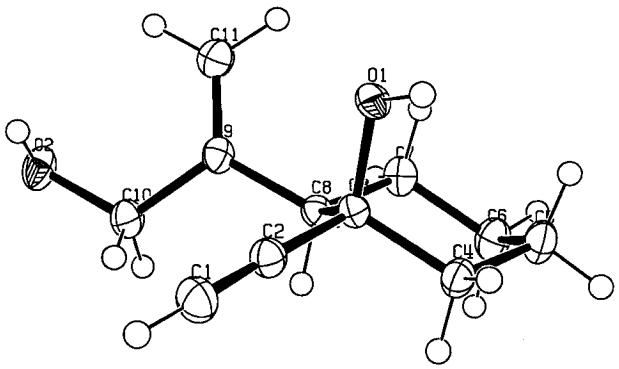


Figure 3. 8 – ORTEP Plot of 3.27



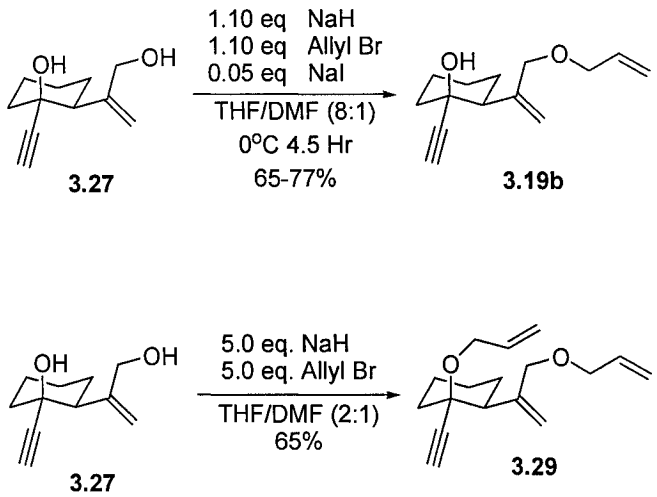
We had initially contemplated performing the allylic oxidation of **2.8** prior to alkylation with acetylides to induce a chelation effect between the ketone and a magnesium alkoxide tether (and presumably enhance selectivity). However, research done by Irina Denissova had shown that allylic oxidation of ketone **2.8** was complicated by the formation of a variety of products, with a preference for oxidation α to the carbonyl.[75]

Fine-tuning of the allylation step to produce allyl ether **3.19b** proved to be more challenging (Scheme 3.5). Heating the mixture of allyl bromide, diol **3.27**, and sodium hydride led to a plethora of decomposition products. ^{1}H NMR reveals a missing acetylene unit, possibly from (a) a retro addition of acetylene to re-produce a ketone at C13, (b) a premature anionic oxy-Cope rearrangement, or (c) allylation followed by any of the above.

Attempts to purify these products for characterization were unsuccessful. Similary, attempts to re-alkylate this material with ethynyl magnesium bromide also failed.

Using excesses allyl bromide or hydride bases in the allylation reaction gave similar results. Changing the hydride base to potassium hydride gave no improvement of yield, and no product was obtained when using *n*-butyllithium as the anion source.

Scheme 3.5 – Optimization of Allylation Conditions and Unexpected Result



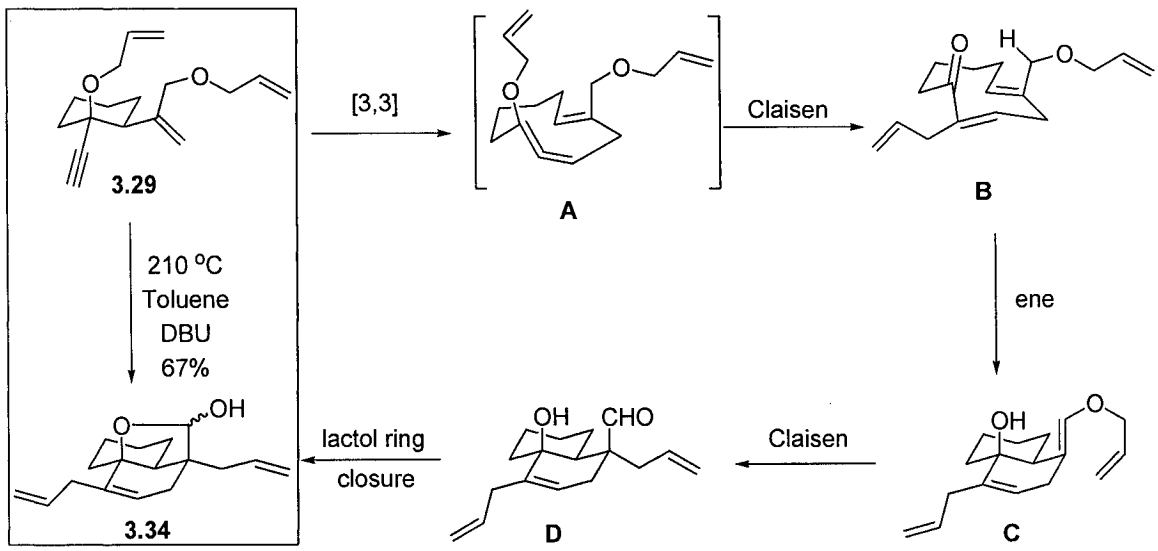
Use of a less polar (benzene) or more polar (*N,N*-dimethylformamide) solvent had only detrimental influences in yield. However, utilizing a mixture of DMF and THF with excesses of base and electrophile produced a new product whose ^{1}H NMR spectrum showed a striking similarity to monoallylated compound **3.19b**, but closer inspection reveals double integration for allyl ether signals; revealing di-allyl adduct **3.29**.

Cascade Oxy-Cope/Claisen/Ene/Claisen Rearrangement

Studies performed on similar substrates in our laboratory had indicated that allylation of tertiary alcohol present in **3.27** was impossible owing to the steric crowding around this site.[52] However, these newly developed conditions now mysteriously provided tertiary allylated product **3.29** in good yield. Being adventuresome, we chose to attempt rearrangement on this substrate as well; heating this compound in the microwave under standard rearrangement conditions gave a product whose spectroscopic properties indicated a poly-allylated decalin similar to that furnished before. However, this new product was consistent with the result from a putative tandem oxy-Cope/Claisen/ene/Claisen rearrangement sequence (**3.34**); further analysis demonstrated that this indeed was the case. Not only does this method provide a unique decalin core of defined stereochemistry, it provides a method to rapidly access further functionalization at C14 (Figure 3.6). The mechanism is rationalised as follows: sigmatropic [3,3] rearrangement of allyl ether gives

allene-containing cyclodecane **A**. Sigmatropic rearrangement of the enol ether gives macrocyclic ketone **B**, which undergoes a transannular ene reaction to give another enol ether **C**. A final Claisen rearrangement of this enol ether then furnishes decalin **D**, and lactol ring closure gives the observed product **3.34** in 67% yield.

Scheme 3.6 – Oxy-Cope/Claisen/Ene/Claisen Rearrangement



Co-worker D. Gauvreau carried further studies on this reaction pathway and determined it to be of some use in producing complicated decalins bearing allene functionalities. Unfortunately, the rearrangement suffered from lower yields, thereby mitigating its synthetic utility (Scheme 3.7).

With the knowledge that these tertiary alcohol allylations were possible, co-worker E. Sauer carried forward research on the oxy-Cope/Claisen/ene rearrangement, and explored the highly efficient transfer of chirality available from these transformations (**3.40** → **3.41**).[76] The methodology was also applied to the synthesis of the proposed structure for Wiedemannic acid analogue **3.42** (Figure 3.9).[77]

Scheme 3.7 – Oxy-Cope/Claisen/EneClaisen Rearrangement with Various Ethers

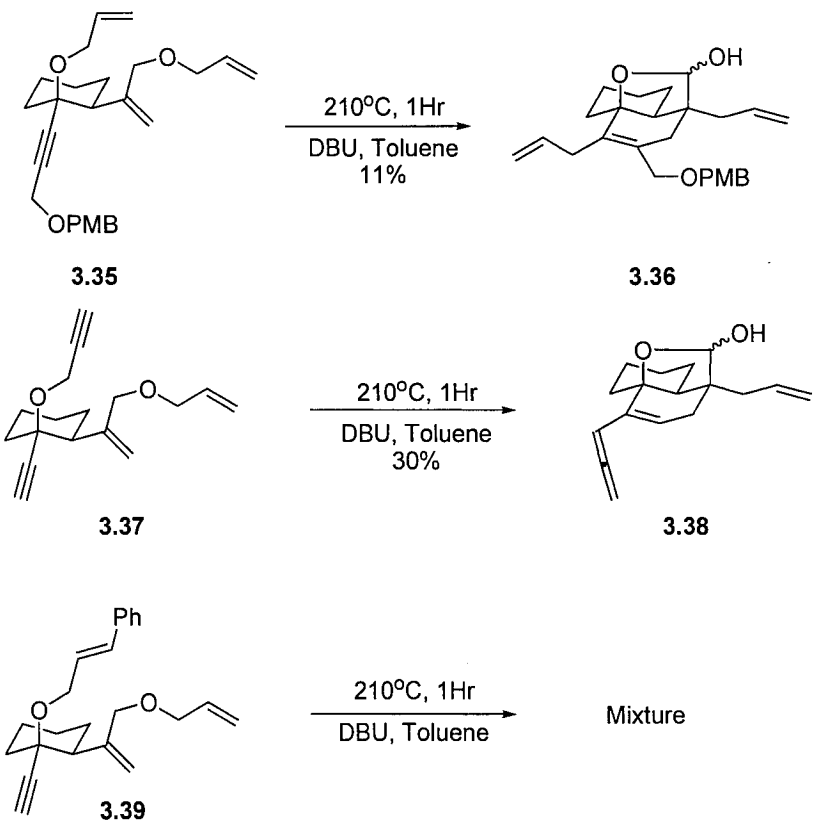
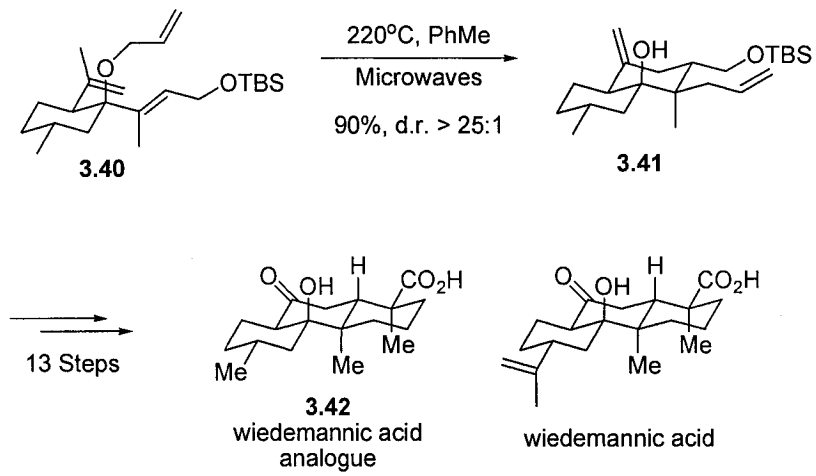


Figure 3.9 – Application of Oxy-Cope/Claisen/Ene to the Wiedemannic Acid Core

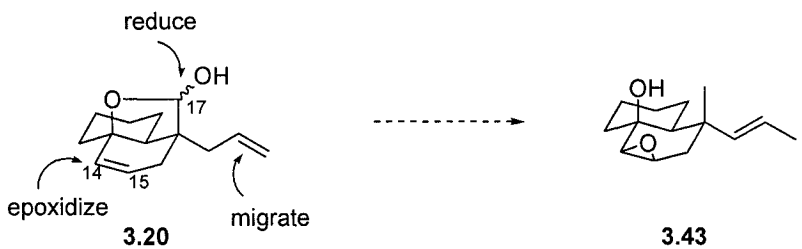


Modification of the Decalin Core

Returning to the synthetic work at hand, further refinement of the etherification conditions showed that a 9:1 ratio of THF to DMF was preferable, and addition of catalytic amounts of NaI maximized the yield. Using two equivalents of base to deprotonate both alcohols is unnecessary, and only a small excess of allyl bromide should be used. Timing is critical – maximal yield of product takes 3 to 4 hours, but prolonged exposure (6 hours or more) to the reaction conditions results in extrusion of the acetylene functionality and decomposition.

With lactol **3.20** in hand, the next three separate synthetic tasks had to be accomplished in the following order: (1) de-oxygenate C17, (2) perform an epoxidation on the C14 – C15 olefin, and (3) internalize the terminal bond for ozonolysis to give **3.43** (Figure 3.10).

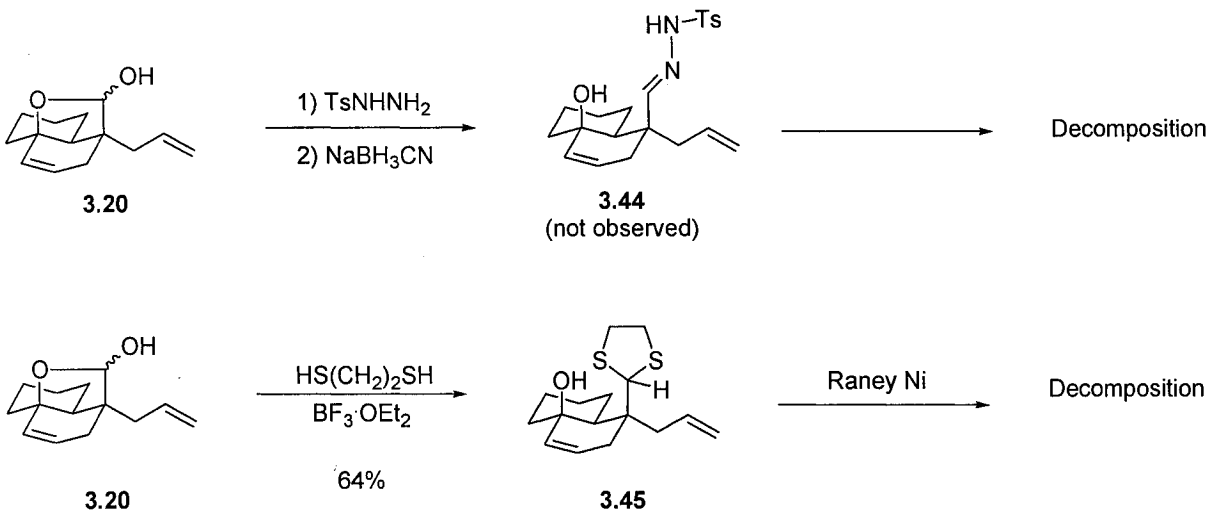
Figure 3.10 – Task Outline



Deoxygenation Attempts at C17

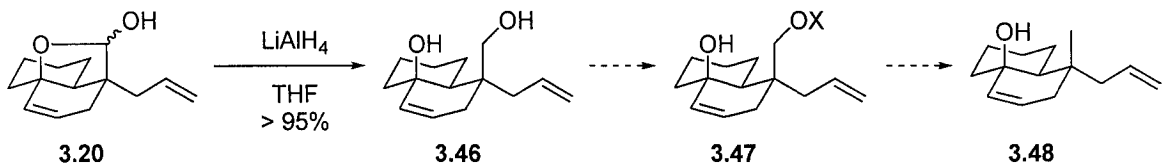
While there are a variety of methods of deoxygenating lactols to the cyclic ethers,[78] reduction directly to alkane and alcohol is somewhat less common. The reaction is further complicated in this case by the proximity of the reduction site (C17) and ring junction alcohol. Deoxygenation of the lactol directly via reduction of the tosylhydrazone[79] was unsucessful. No tosylhydrazone (**3.44**) was formed under a number of conditions attempted. Though the thioacetal **3.45** was formed quite readily, nickel desulfurization attempts only resulted in decomposition (Scheme 3.8).

Scheme 3.8 – Direct Lactol Deoxygenation Attempts



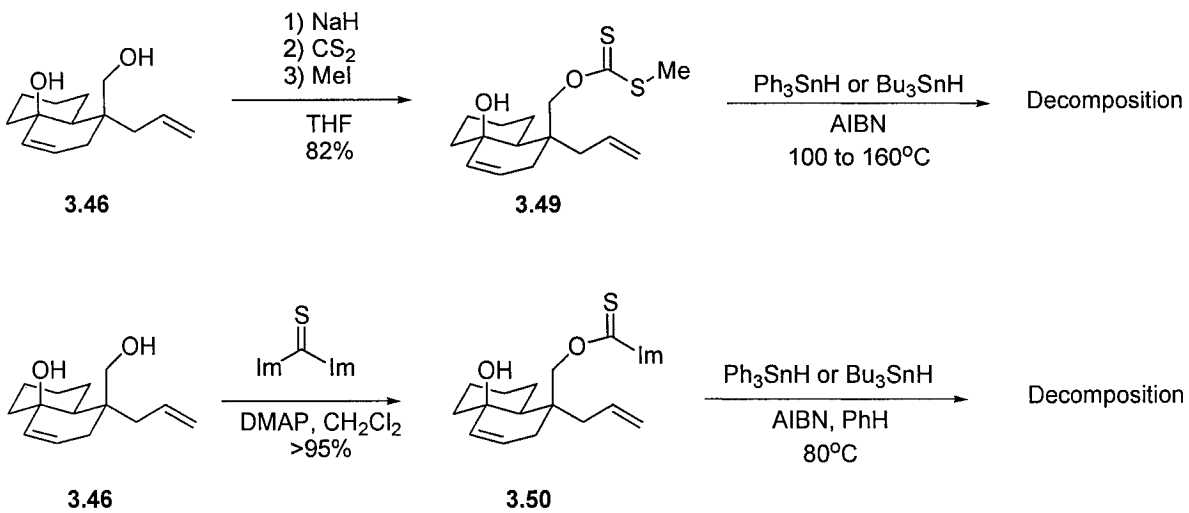
Reduction of lactol **3.20** to diol **3.46** was effected using $LiAlH_4$ as reducing agent. The cleanliness and high yield of this reaction prompted investigations toward deoxygenation of **3.46** and direct deoxygenation of lactol **3.20** was abandoned for the time being (Scheme 3.10).

Scheme 3.9 – Reduction via Diol



Deoxygenation of alcohols has been well covered in the literature, and there are a variety of methods available.[80] Starting with the most common Barton-M^{c}Combie deoxygenation,[81] primary alcohol **3.46** was transformed into xanthate ester **3.49** by reaction with sodium hydride and by carbon disulfide, followed by trapping of the resultant thiolate with iodomethane.

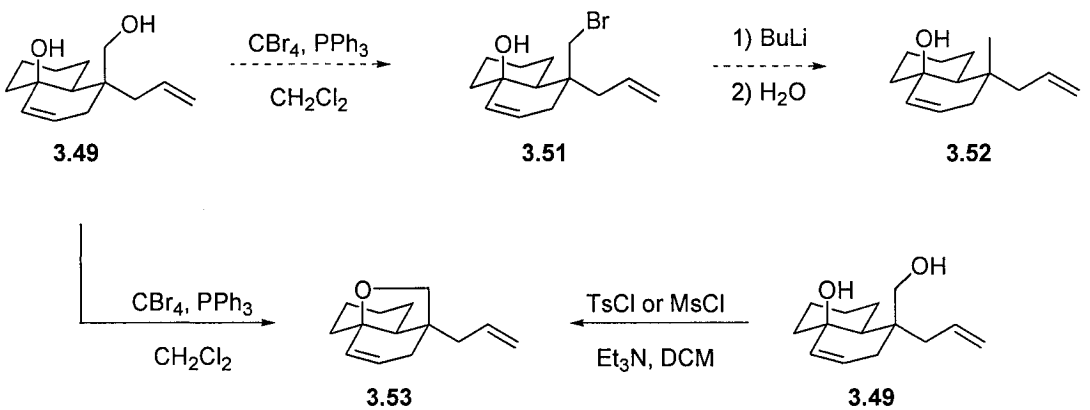
Scheme 3.10 – Barton-McCombe Deoxygenation Attempts



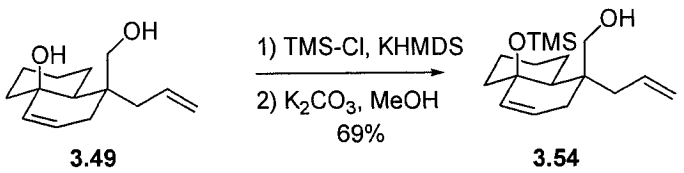
A number of tin hydride reductions of this xanthate ester were tried with no success. Similarly, the imidazolium xanthate **3.50** was formed readily, but subsequent reduction with triphenyl or tributyltin hydrides failed (Scheme 3.10).[82]

Conversion of the primary alcohol to a primary halide failed, and resulted in formation of an ether ring between C17 and bridgehead alcohol instead (**3.53**, Scheme 3.11). Not surprisingly, attempts to produce the tosyl or mesyl esters also led to formation of the cyclic ethers.

Scheme 3.11 – Cyclic Ether Formation

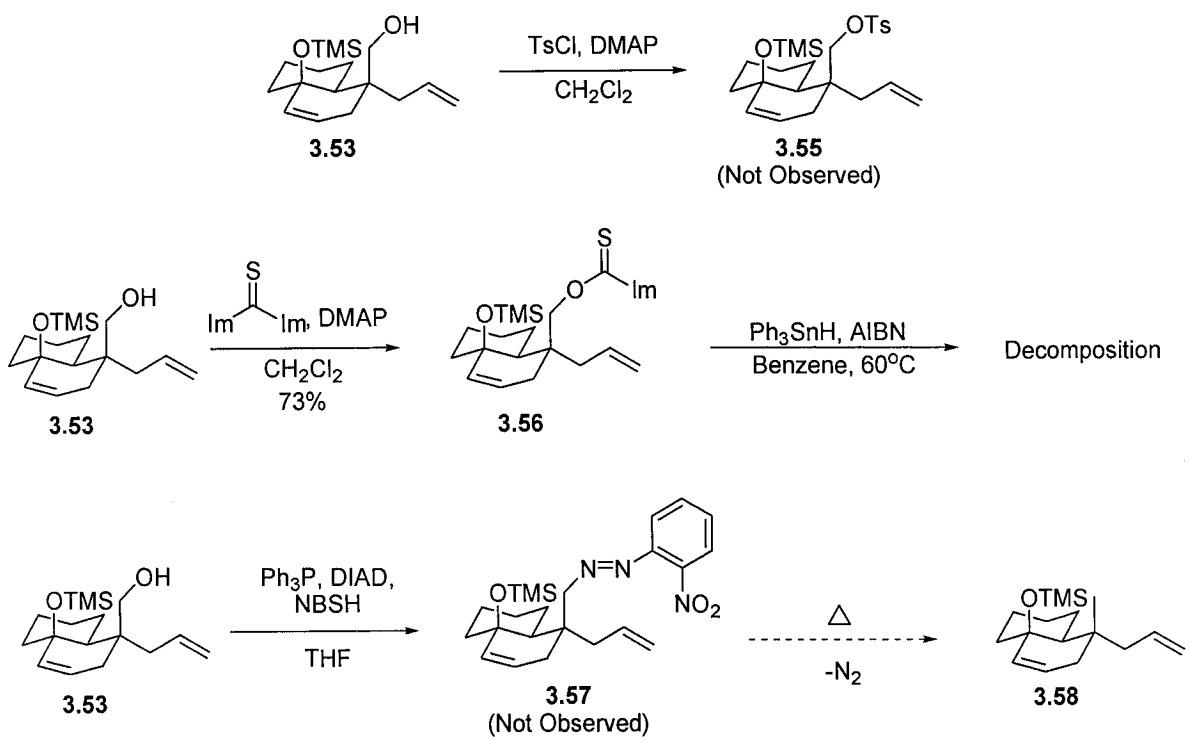


Scheme 3.12 – Preparation of Monosilylated Alcohol



3.49 **3.54**

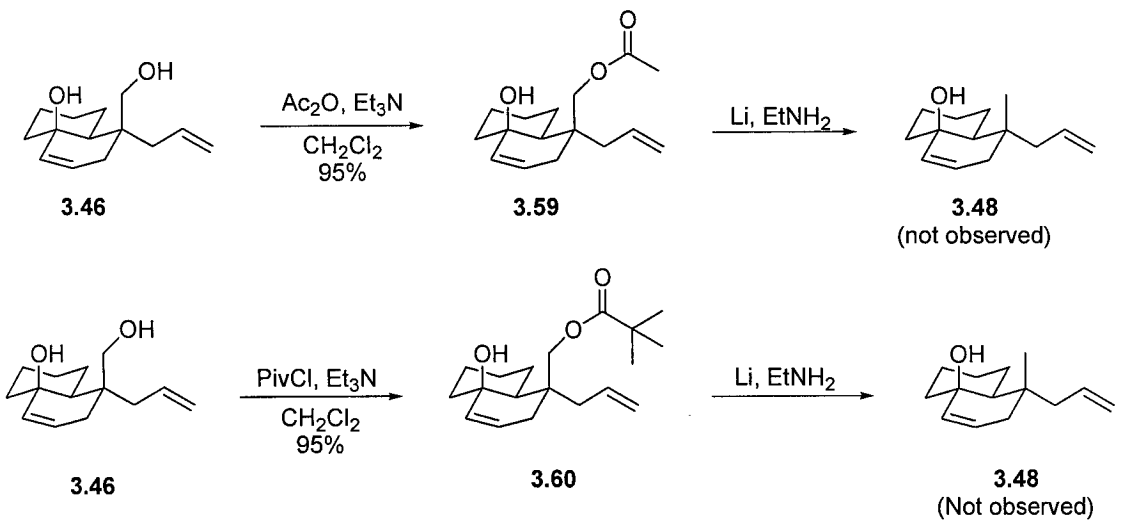
Scheme 3.13 Alkoxide Deoxygenation Attempts



A protection/deprotection sequence afforded the monosilylated free alcohol **3.54** in 69% yield (Scheme 3.12). A few attempts were made here as well with no success: Tosylation or mesylation of the primary alcohol failed, giving only starting material (**3.55**). Although the xanthate ester with thiocarbonyl diimidazole was formed quite readily (**3.56**), radical fragmentation attempts only resulted in decomposition. An attempt was also made to perform a Mitsonobu displacement[83] of the primary alcohol with o-nitrobenzene sulfonylhydrazine[84] (NBSH) for heating and radical decomposition,[85] but this too led only to recovery of starting material (**3.57**).

Stymied by these unpromising results, we turned to dissolving metal Bouveault-Blanc[86] reduction of the acetate. Treating primary alcohol **3.46** with either acetic anhydride or pivaoyl chloride and triethylamine in dichloromethane gave the primary acetates **3.59** and **3.60** in quantitative yield. After multiple attempts at dissolving metal reduction, partial hydrolysis back to the diol was the only product observed (Scheme 3.14).

Scheme 3.14 – Deoxygenation Attempts with Bouveault-Blanc Reduction

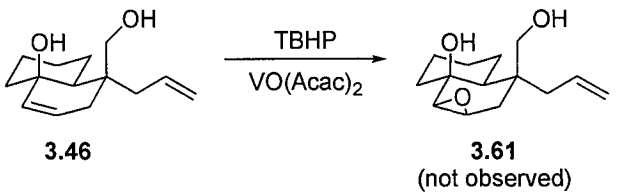


Having spent considerable time and effort on this deoxygenation, with acetates **3.59** and **3.60** in hand we decided to proceed with these derivatives, and worry about the deoxygenation of C17 at a later time.

Continued Synthesis of Derivatives With Acetate at C13

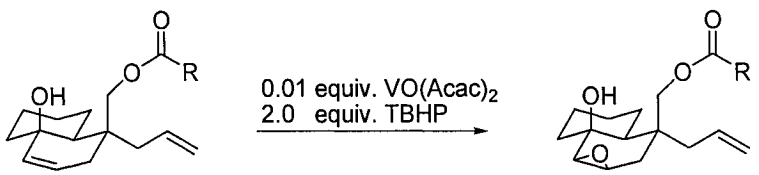
Direct Sharpless epoxidation[87] of the diol failed (**3.47** → **3.61,** Scheme 3.15), but after a brief struggle with conditions it could be performed on either acetate quite readily. Interestingly, the reaction is much quicker in the substrate containing the more hindered pivaloate ester, taking only two hours (Table 3.1).

Scheme 3.15 – Attempted Sharpless Epoxidation of Diol 3.46



3.46 **3.61** (not observed)

Table 3.1 – Sharpless Epoxidation of Acetate



3.58 (R = CH_3)
3.60 (R = $C(CH_3)_3$)

3.62 (R = CH_3)
3.63 (R = $C(CH_3)_3$)

Entry	R	Solvent	Time	Temperature	Yield
1	CH_3	Dichloromethane	1 Hr	Room Temp.	0 %
2	CH_3	Dichloromethane	1 Hr	40 °C	0 %
3	CH_3	Benzene	1 Hr	90 °C	37%
4	CH_3	Toluene	18 Hr	120 °C	98%
5	$C(CH_3)_3$	Toluene	2 Hr	120 °C	85%

Epoxides **3.62** and **3.63** were now prepared, but several tasks lay ahead: internalization of the double bond for ozonolysis; and aldol condensation with the tetronate unit. The acetate was subjected to conditions employed by Roy *et al.*[88] for deprotection of allyl ethers. After some experimentation (Figure 3.11), the reaction was successful in producing the more thermodynamically stable internal olefins **3.64** and **3.65** in 77% and 75% yields, respectively (Scheme 3.16).

Scheme 3.16 Analogue Decalin Core Completion

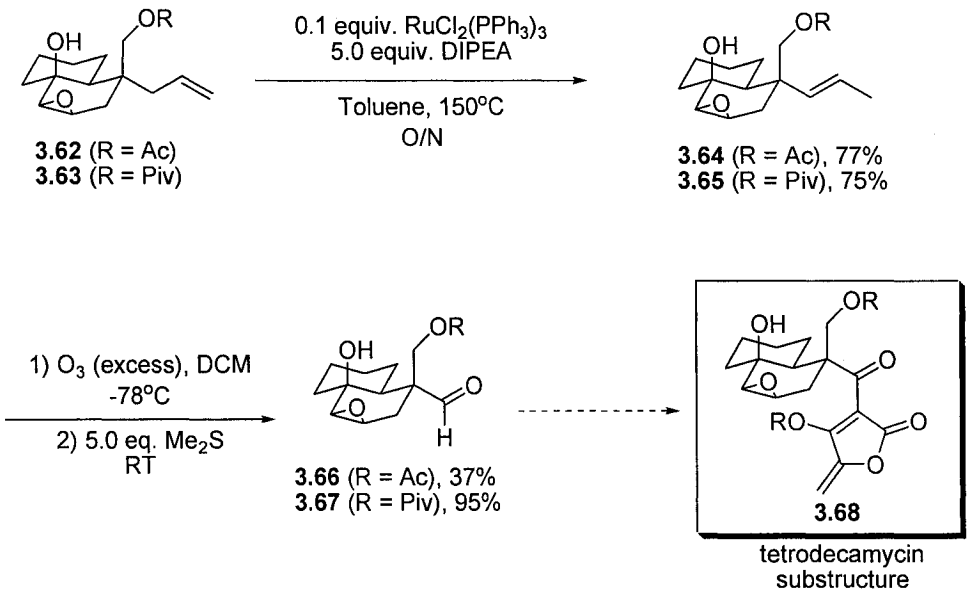
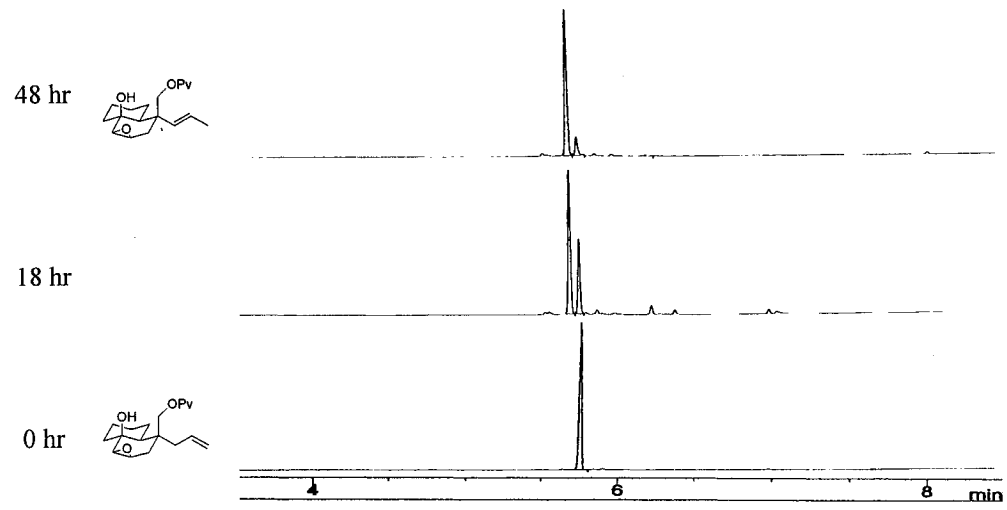


Figure 3.11 – GC tracking of Ru-catalyzed Isomerization



Ozonolysis of the resultant disubstituted olefin gave the aldehydes **3.66** and **3.67** in modest yield. No improvement was noted by utilizing Lemieux-Johnson oxidation conditions.[89] Reaction osmium tetroxide dihydroxylation followed by periodate cleavage gave the aldehyde **3.66** in 28% yield, and the yield was slightly better with the more

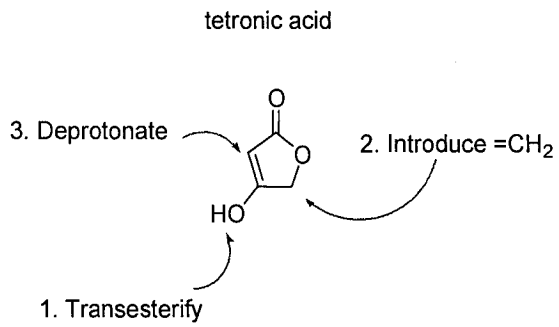
hindered neopentyl ester. With aldehydes **3.66** and **3.67** in hand, we sought to couple the tetronate to the free aldehyde, to produce tetrodecamycin substructure **3.68**.

Tetronate Synthesis

Fortuitously, the syntheses of tetronic acids and derivatives have been comprehensively investigated over the past few decades. The first synthesis of tetronic acid was reported in 1896, and is now a commercial product. Traditional syntheses of acyl tetronic acids typically involve Dieckmann condensation of the required β-ketoester.[90] However, application of this method to the synthesis of a tetronate with a 4-*exo*-methylene unit would be more challenging.

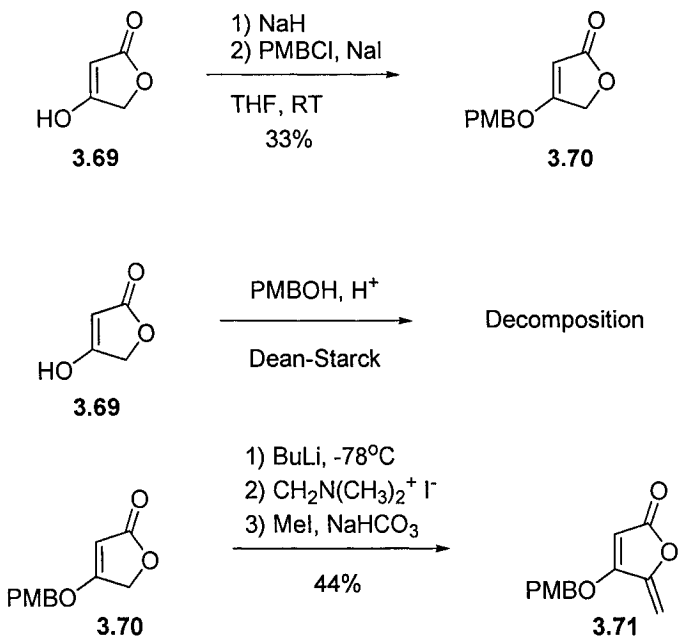
We chose to begin instead with commercially available tetronic acid, onto which three operations had to be carried out: 1) Protection of the acid, 2) Introduction of the *exo* methylene via deprotonation with LDA and trapping with Eschenmoser's Salt, and 3) Deprotonation α to the carbonyl to give the tetronate nucleophile required to continue the synthesis (Scheme 3.17).

Scheme 3.17 – Tetronic Acid Modification Strategy



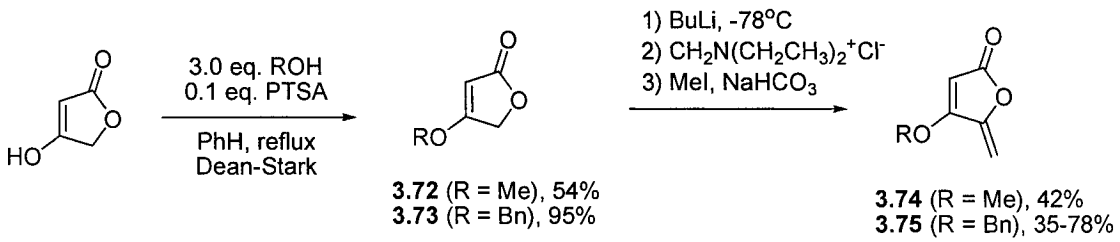
For initial studies, we chose *para*-methoxybenzyl (PMB) as a protecting group, for its reported ease of removal. However, low yields of the isolated PMB ether discouraged the use of this protecting group for further studies. Nevertheless, the small amount available was fitted with an exo methylene via the sequence described above.

Scheme 3.18 – Preparation of PMB tetronates



These PMB tetronates proved to be difficult to handle (low yields and rapid thermal decomposition), and other tetronic acid esters were tested. The methyl or benzyl ethers of tetronic acid (**3.72** and **3.73**, Scheme 3.19), can be constructed using known methods,[91] and were formed in good yields. The tetronic ethers can then be deprotonated selectively at the C4-position using LDA. The same metallation can be accomplished by canulating a solution of the tetronic ester into a flask charged with solvent and BuLi precooled to -78°C. Addition of a Mannich's salt[92] (as a solid, in a single portion) followed by warming, and allowing stirring with MeI and $NaHCO_3$ gives the tetronate derivatives **3.74** and **3.75**. The yields of isolated product for these transformations were extremely erratic in these cases as well, and it was noted that if one was not careful in maintaining low rotovap temperature during the workup of this sequence, polymers formed quite readily. The usage of the diethyl (methylene)ammonium salt prepared from diethylamine[93] is far more cost effective than the commercial Eschenmoser's salt (dimethyl (methylene)ammonium iodide), and gave similar yields.

Scheme 3.19 – Preparation of benzyl and methyl tetronates



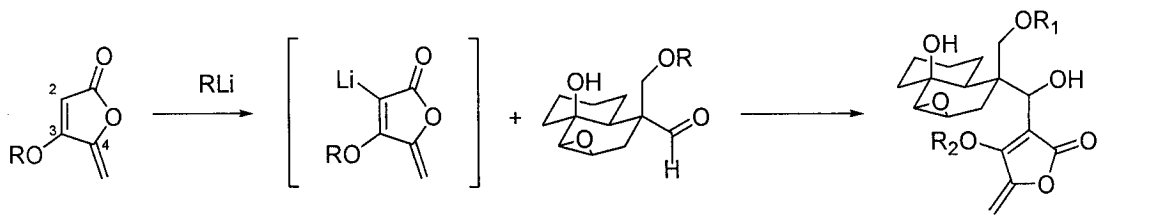
3.72 (R = Me), 54%
3.73 (R = Bn), 95%

3.74 (R = Me), 42%
3.75 (R = Bn), 35-78%

Tetronate and Decalin Condensation

Having tetronates **3.74** and **3.75** in one hand, and aldehydes **3.66** and **3.67** in the other, we were in a good position to attempt the anionic coupling (Scheme 3.20).

Scheme 3.20 – Anionic Coupling Between Tetronate and Aldehyde



3.74 (R = Me)
3.75 (R = Bn)

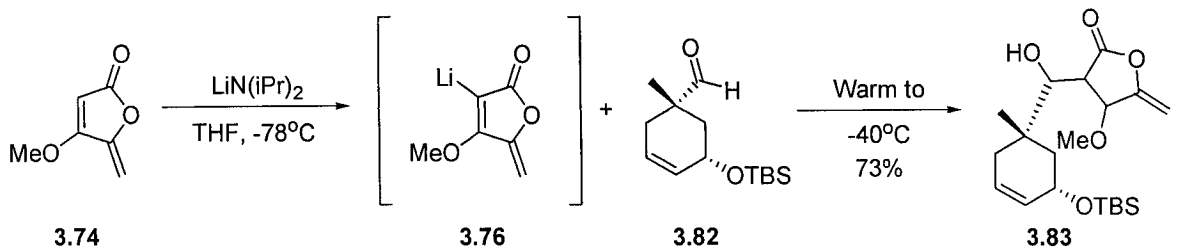
3.76 (R = Me)
3.77 (R = Bn

3.66 (R = Ac)
3.67 (R = Piv)

3.78 (R_1 = Ac, R_2 = Me))
3.79 (R_1 = Ac, R_2 = Bn)
3.80 (R_1 = Piv, R_2 = Me)
3.81 (R_1 = Piv, R_2 = Bn)

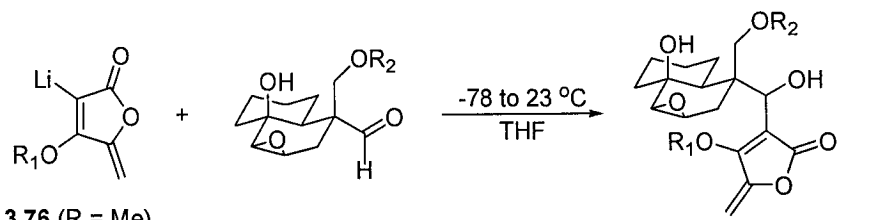
The α-lithiation of 4-disubstituted tetronates (**3.76, 3.77**) is known, but the experimental procedures published are bereft of detail. In their synthetic studies on tetrodecamycin substructures, Paintner and co-workers used LDA to effect lithiation of a methyl tetronate, but noted that the temperature had to be increased from -78°C to -40°C to perform the alkylation.[94]

Figure 3.12 – Anionic Coupling Example (Paintner et al., 2000)



In our hands, the alkylation proved to be somewhat more difficult. Adding a freshly titrated solution of LDA to a solution of tetronate at -90 °C, one immediately notices that the solution immediately turns dark red-orange. Addition of aldehydes **3.66** or **3.67** at -78 °C results in a dark red-black sludge that is difficult to stir. Only the starting aldehyde was recovered after gradually warming to room temperature – the anion of both benzyl and methyl tetronates **3.76** and **3.77** decomposed quite readily above -30°C (indicated by baseline product(s) on TLC plate). Only sporadic coupling reactions were successful, and a small amount of **3.79** was isolated for partial characterization (Table 3.2).

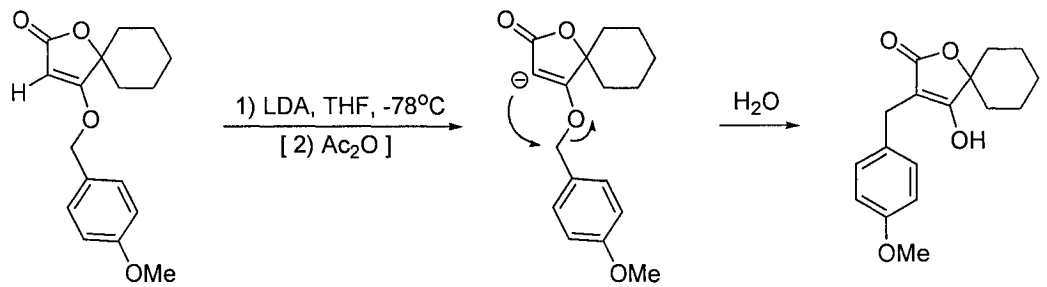
Table 3.2 – Anionic coupling of acetate derivatives



Entry	Product	R_1	R_2	Yield
1	**3.78**	Me	Ac	0%
2	**3.79**	Bn	Ac	21%
3	**3.80**	Me	Pv	0%
4	**3.81**	Bn	Pv	0%

It was noted in 2001 by Schobert and co-workers[95] that methoxybenzyl tetronate anions undergo anionic [1,3] rearrangements instantaneously at low temperature. None of these products were observed in our case, but provides a possible pathway for quenching of the tetronate anion as the temperature is elevated.

Figure 3.13 – Anionic Decomposition of PMB Tetronates (Schobert, 2001)



3.84 **3.85** **3.86**

A small amount of alkylated product may have been observed with the benzyl tetronate (entry 1, Table 3.2), but the trace amount of product co-eluted perfectly with leftover tetronate, and the reaction was not clean by any means. We did not spend much time experimenting with alkylation conditions here, since the acetate and pivaoyl protecting groups were likely not the best choice in the first place. However, with the synthetic route pre-navigated, changing to the more robust *tert*-butyl dimethylsilyl or triethylsilyl ethers was unproblematic (**3.46** → **3.87, 3.88**; Scheme 3.21). The aldehdydes **3.93** and **3.94** were generated in four synthetic steps from diol **3.46** in 41% and 33% overall yields, respectively (Scheme 3.21).

Alkylation of these aldhehydes with the tetronate residues met with similar failure. TLC observations suggested that the lithiated tetronate was decomposing before the alkylation process could occur. To eliminate the possibility that the solution of aldehyde or tetronate were warming in the canula, an insulated, pre-cooled canula was used. Modest yields of the desired product were noted when this technique was used (entry 5, Table 3.3).

Unfortunately, the alkylation was highly irreproducible, and direct mesityllithium alkylation of the aldehyde was often observed (mesityllithium was generated by the reaction of mesityl bromide and *tert*-butyllithium).

Scheme 3.21 – Synthesis of silyl derivatives

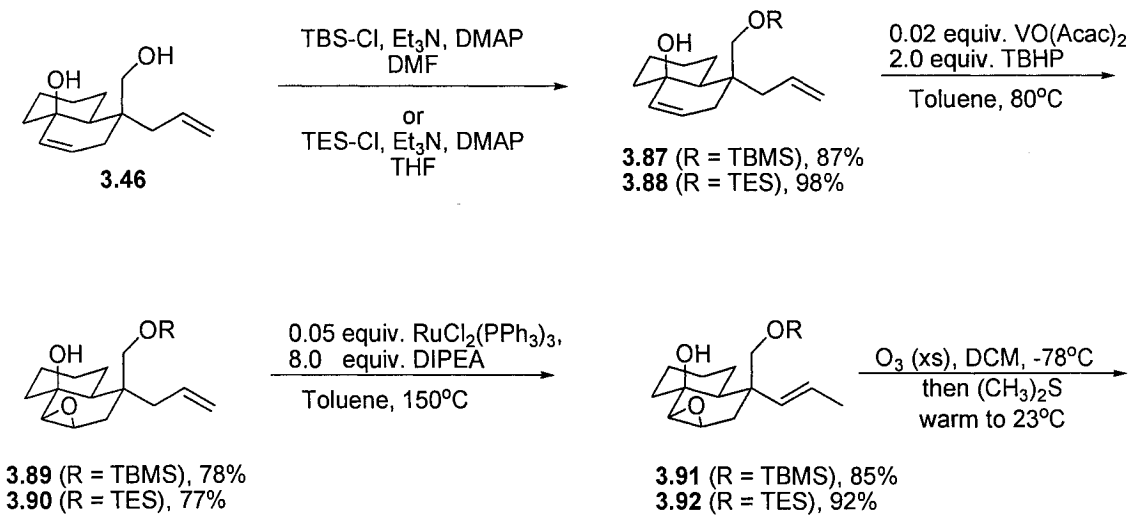
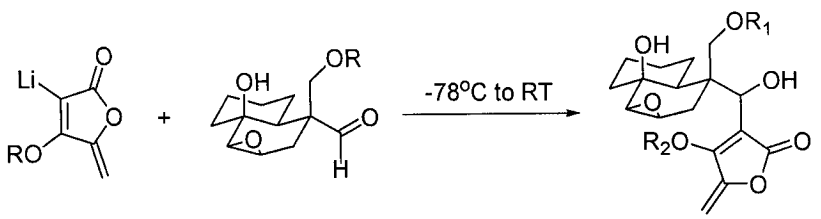


Table 3.3 – Coupling Attempts on Monosilylated Derivatives



3.76 (R = Me)
3.77 (R = Bn)

3.93 (R = TBMS)
3.94 (R = TES)

3.95 (R_1 = TBMS, R_2 = Me)
3.96 (R_1 = TBMS, R_2 = Bn)
3.97 (R_1 = TES, R_2 = Me)
3.98 (R_1 = TES, R_2 = Bn)

Entry	Product	R_1	R_2	Solvent, Additive	Base	Addition Method	Yield
1	**3.95**	Me	TBS	THF	BuLi	Sequential	0%
2	**3.95**	Me	TBS	THF, LiBr	Mes-Li	Sequential	0%
3	**3.95**	Me	TBS	THF	LDA	Combined	36 to 42%
4	**3.95**	Me	TBS	Ether	LDA	Combined	0%
5	**3.95**	Me	TBS	Toluene	LDA	Combined	0%
6	**3.95**	Me	TBS	Hexanes	LDA (in ether)	Combined	0%
7	**3.96**	Bn	TBS	THF	LDA	Sequential	0%
8	**3.96**	Bn	TBS	THF	BuLi	Sequential	0%
9	**3.96**	Bn	TBS	THF, LiBr	Mes-Li	Sequential	0 to 52%
10	**3.98**	Bn	TES	THF	LDA	Combined	24%
11	**3.98**	Bn	TES	THF, HMPA	LDA	Combined	0%

To conclusively eliminate the possibility of local hotspots during the addition, the reagent addition order was modified slightly. Instead of adding the base to the tetronate followed by the addition of the aldehyde (sequential, entries 1-5), the base was generated at low temperature, and a pre-cooled mixture of the aldehyde and tetronate was then added (combined, entry 3).

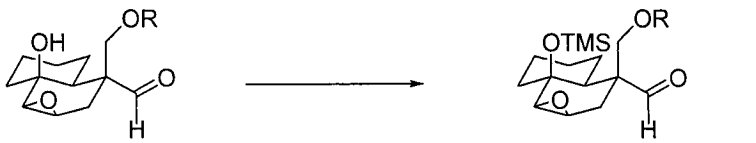
This improved procedure furnished the desired alkylated product **3.95** in low yields. The reaction was somewhat more reproducible than the attempts with sequential addition, and was much cleaner. Attempts to perform the alkylation in other solvents (including nonpolar toluene and hexanes) failed (entries 4-7), and no alkylated product was observed. Fearing deprotonation of the TBS group, we explored the alkylation with TES protecting the primary alcohol. A number of attempts were made with aldehydes bearing this protecting group were tried, with no success. In each case, the excess of lithiated tetronate (3 to 5 equiv.) decomposed before any alkylation could be observed.

Reasoning that the alkoxides formed from the tertiary alcohol may be generating unfavourable aggregates (a noticeable thickening and darkening of the solution is noted as the solution is warmed past -60°C), we attempted to disrupt these by the addition of HMPA, DMPU, or crown ether. Unfortunately, we determined that these additives only hastened the decomposition of the tetronate (the solution turns black rapidly, even at -100° C), without assisting in the alkylation.

To completely eliminate the possibility of the formation of these unfavourable aggregates, we decided to further silylate decalin core **3.94** and **3.95**. Protection with trimethylsilyl chloride fails, and no protected product is observed after prolonged elevated temperatures. The powerful silylating agent trimethylsilyl triflate also fails, possibly through reaction with the epoxide (indicated by loss of corresponding oxirane peaks in crude NMR). After a brief struggle, the best set of conditions was revealed as trimethylsilyl chloride with potassium hexamethydisilazide as base (**3.94,3.95** → **3.99, 3.100**, Table 3.4).

Thankfully, alkylation of these di-protected silyl ethers was much improved over the previous series. In addition, it was noted that the alkylation proceeded quite smoothly by holding the reaction temperature at -78°C for 1.5 hr, and no warming was needed (**3.99** or **3.99** + **3.75** → **3.101**, **3.102**, Scheme 3.22).

Table 3.4 – Protection of Tertiary Alcohol

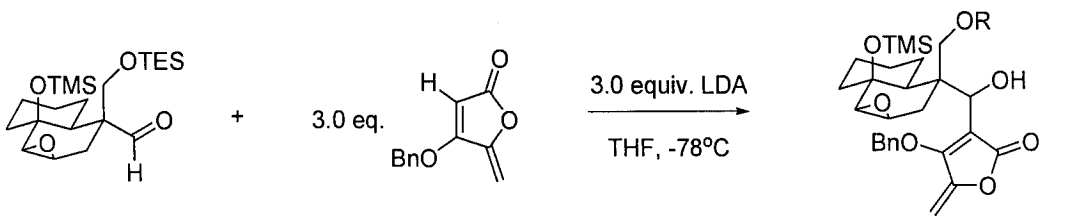


3.94 (R = TBMS)
3.95 (R = TES)

3.99 (R = TBMS)
3.100 (R = TES)

Entry	R	Conditions	Result
1	TBMS	TMS-Cl, Et_3N, DMAP, DCM, 40°C	SM
2	TBMS	TMS-OTf, DCM, -78°C to RT	Decomp.
3	TBMS	TMS-Cl, KHMDS THF, 0 °C	**3.99** (89%)
4	TES	TMS-Cl, KHMDS THF, 0°C	**3.100** (95%)

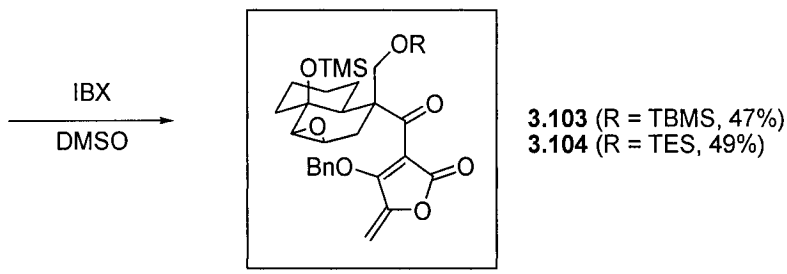
Scheme 3.22 – Alkylation of Disilylated Decalin Core



3.99 (R = TBMS)
3.100 (R = TES)

3.75

3.101 (R = TBMS, 38%)
3.102 (R = TES, 50%)



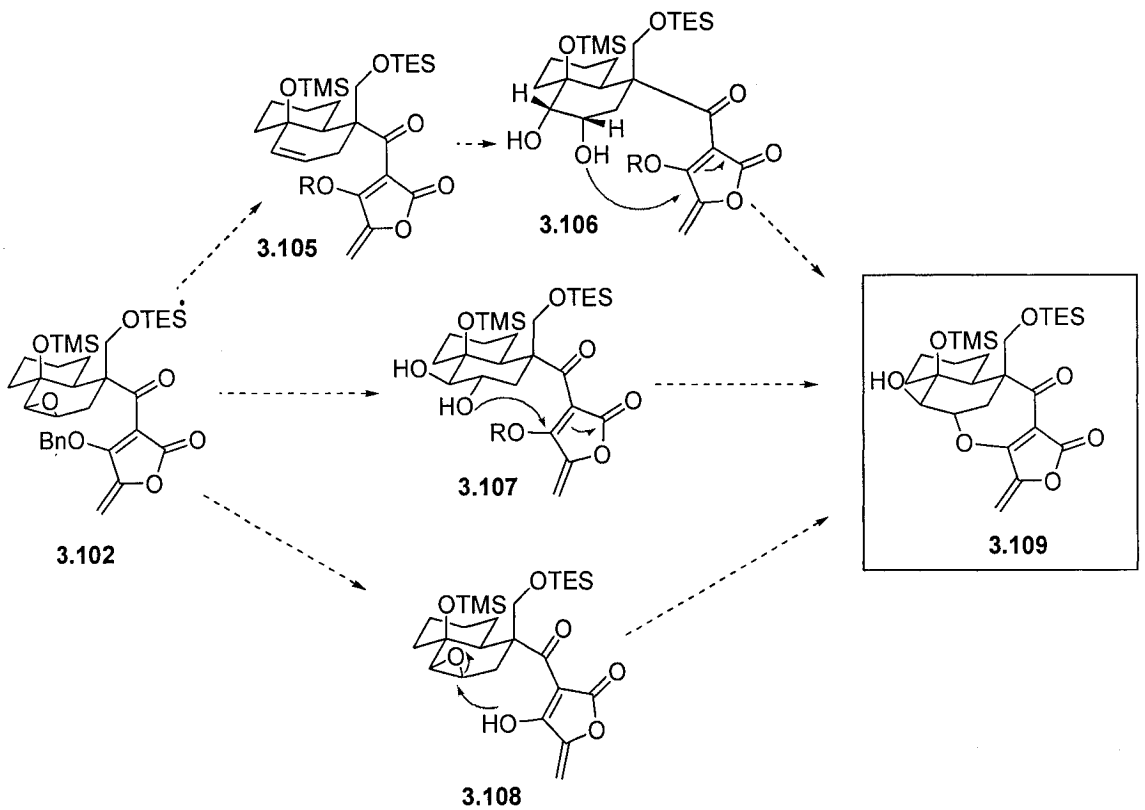
3.103 (R = TBMS, 47%)
3.104 (R = TES, 49%)

Oxidation of the secondary alcohols **3.103** and **3.104** was accomplished by iodoxybenzoic acid (IBX) in dimethyl sulfoxide at room temperature, in 45 to 50% yield.

Epoxide Cyclisation Attempts

With tetrodecamycin substructures **3.103** and **3.104** in hand, we envisioned several different approaches to finishing the molecule: (1) reductive removal of the epoxide with WCl_6/BuLi followed by dihydroxylation and ether ring closure by addition-elimination to the tetronate, (2) epoxide hydrolysis (in a hopefully stereoselective manner), followed by ether ring closure, or (3) removal of the tetronate protecting group, followed by nucleophilic attack onto the epoxide (Figure 3.14).

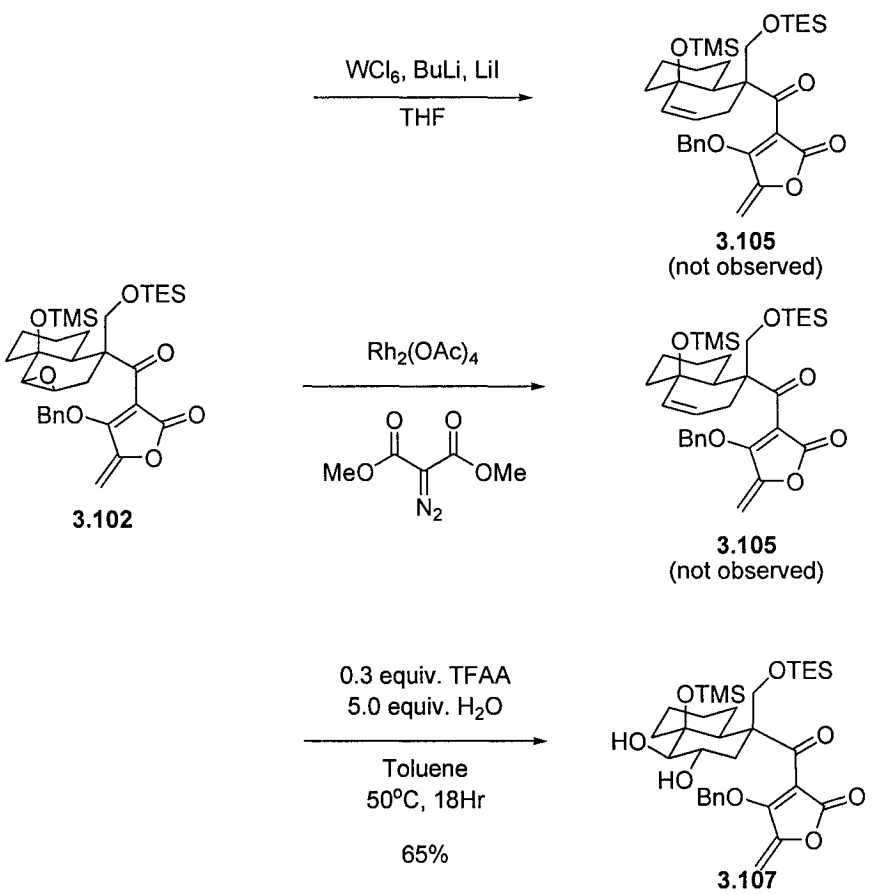
Figure 3.14 – Epoxide Cyclisation Strategies



The first route involved the addition of many steps to the synthetic sequence (in addition to a requisite epimerization of the C14 alcohol – not shown), and only merits a brief mention. Deoxygenation of the C14-C15 epoxide by the Sharpless protocol[96] with tungsten

hexachloride, n-butyllithium and lithium iodide led only to recovery of some starting material, and product decomposition. The dimethyl diazomalonate / dirhodium tetraacetate system developed by Ganem *et al* [97] failed to 7 deoxygenated product.

Scheme 3.23 – Attempted Epoxide Removals

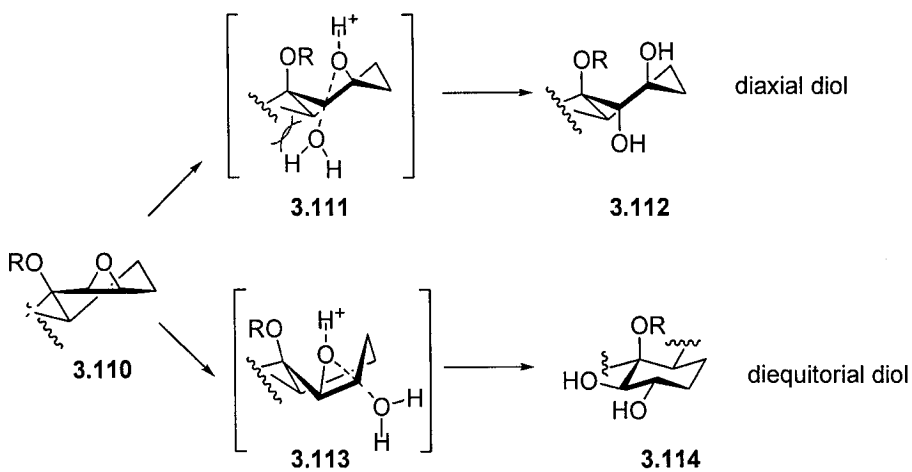


Serendipitously, treating this epoxide with trifluoroacetic anhydride and sodium iodide in toluene gave a 30% yield of a product whose spectra are consistent with bis-equitorial diol **3.107**. None of the anticipated iodohydrin was observed.[98] To verify this result, the experiment was repeated with water in place of sodium iodide to give a 65% yield of the same diol **3.107**. Albeit not the mode of reactivity we were aiming for, this result merits some discussion in its own right. The catalyst responsible for the transformation is likely trifluoroacetic acid formed by reaction of the anhydride with water (present in trace amounts from the solvent or sodium iodide in the first case). Stereoelectronic effects would predict that such an acid-catalyzed epoxide hydrolysis should occur via chair-like transition

state (**3.11**, Figure 3.15). This allows the incipient nucleophile (water) to enter 180° relative to the leaving epoxide oxygen. Such a transition state would lead to the unobserved diaxial diol (**3.112**).

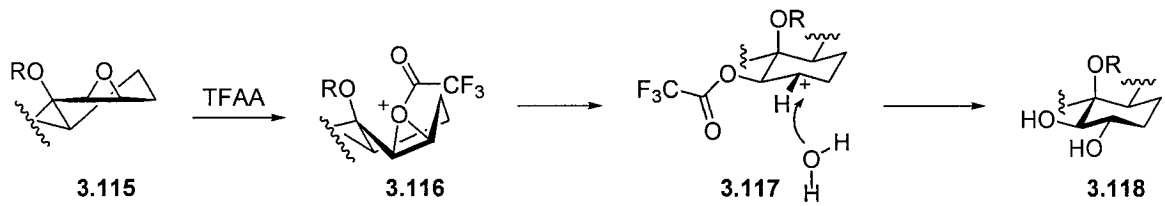
It is likely that steric interactions between the incoming water molecule and the second cyclohexyl ring disfavour the top pathway entirely, and allow the transformation to occur via the bottom pathway (**3.113** → **3.114**).

Figure 3.15 – Epoxide Opening Pathways



Interestingly, the transformation is not nearly as effective when trifluoroacetic acid and water are used directly; only trace amounts of the hydrolysis product are observed. We can therefore not rule out a mechanism involving formation of an oxo-trifluoroacetate intermediate, with the possible formation of a true 2° cation (eg. **3.117**, Figure 3.16). Opening of the epoxide in the manner shown allows formation of the more thermodynamically stable equitorial acetate. The incipient oxygen would prefer to enter *anti* relative to the trifluoroacetate formed.

Figure 3.16 – Speculated Trifluoroacetate Induced Epoxide Opening

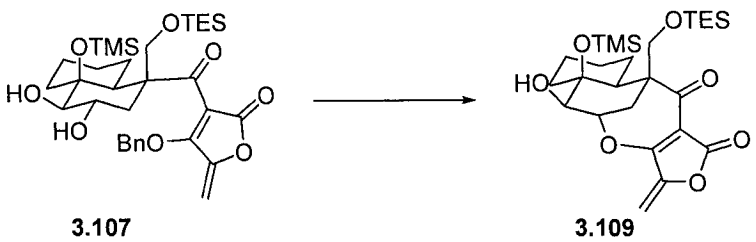


Inverse Cyclisation Attempts

Since diol **3.107** posessed the correct stereochemistry of the natural product, we attempted to form the elusive seven-member dihydrooxepine by addition-elimination onto the tetronate ether (Table 3.5). Numerous Lewis acids were tried with no success. The polyoxygenated nature of this substrate makes selectivity an issue for any oxophilic Lewis acid. In addition, the presumably chair-like conformation of the diol-bearing cyclohexyl ring makes this process highly energetically demanding. For the addition to occur, the diol must adopt the thermally unfavourable boat like conformation, to place both alcohols in pseudoaxial positions.

Notably, neither Lewis (Ti^{2+} or Ti^{4+}) or Brönsted acids performed the desired cyclization (entries 1-3, and 10-12 respectively). Employing the dehydrating conditions used to form the benzyl tetronate in the first place failed as well, leading only to the decomposition. To place a better leaving group on the tetronate, tosyl tetronate **3.114** was synthesized. However, it should be noted that this species was extremely intolerant to handling, and would polymerize readily even after storing at low temperature under inert atmosphere for longer than a few days.

Table 3.5 – Alcohol Additions to Tetronate

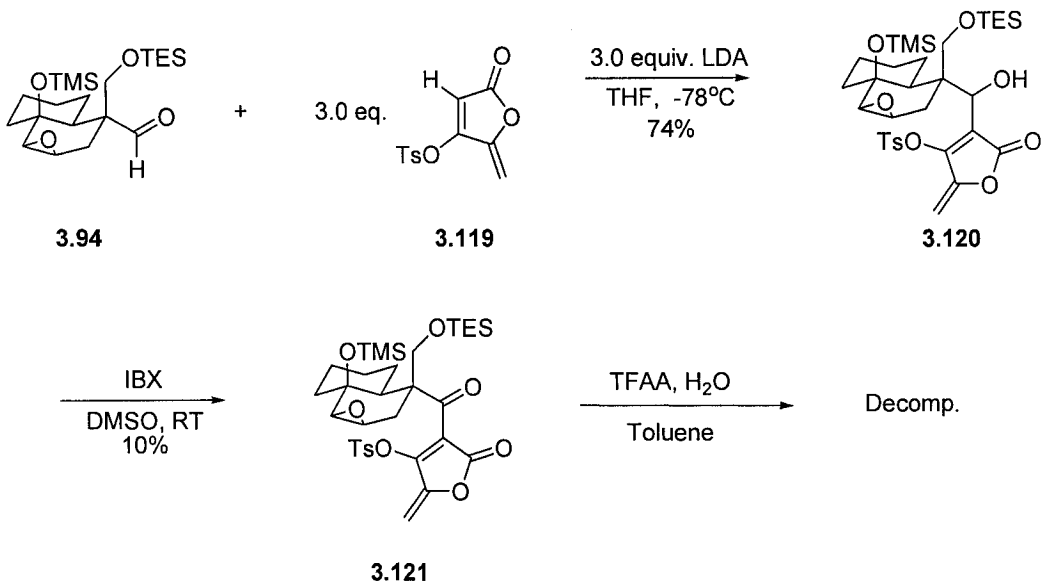


3.107 **3.109**

Entry	Acid or Base	Solvent	Temperature	Result
1	$TiCl_4$ (5 equiv.)	THF	RT	SM
2	$TiCl_4$ (5 equiv.) then DIPEA (5 equiv.)	CH_2Cl_2	RT	SM
3	Cp_2TiCl_2 (5 equiv.) then DIPEA (5 equiv.)	CH_2Cl_2	RT	SM
4	none	DMF	110°C, 20 min	decomp.
5	none	DMF	60°C, O/N	SM
6	none	Toluene	120°C, 3 Hr	SM
7	DMAP	Toluene	180°C, O/N	SM
8	Pyridine	Toluene	170°C, 30 min	decomp.
9	DBU	Toluene	RT, 2 hr	SM
10	TfOH	CH_2Cl_2	RT	SM
11	H_2SO_4	Acetone, DCM, MeOH, THF or MeCN	0°C to reflux	SM + decomp.
12	PTSA	Benzene	RT to reflux	decomp.

The alkylation of tosyl tetronate **3.119** and aldehyde **3.94** proceeded efficiently, to give alcohol **3.120** in 74% yield. Oxidation of the secondary alcohol failed using a number of conditions. A 10% yield of the oxidized product was formed when using IBX as the oxidant, but this material decomposed upon exposure to the hydrolysis conditions employed before.

Scheme 3.24 – Attempted Tosyl Tetronate Strategy



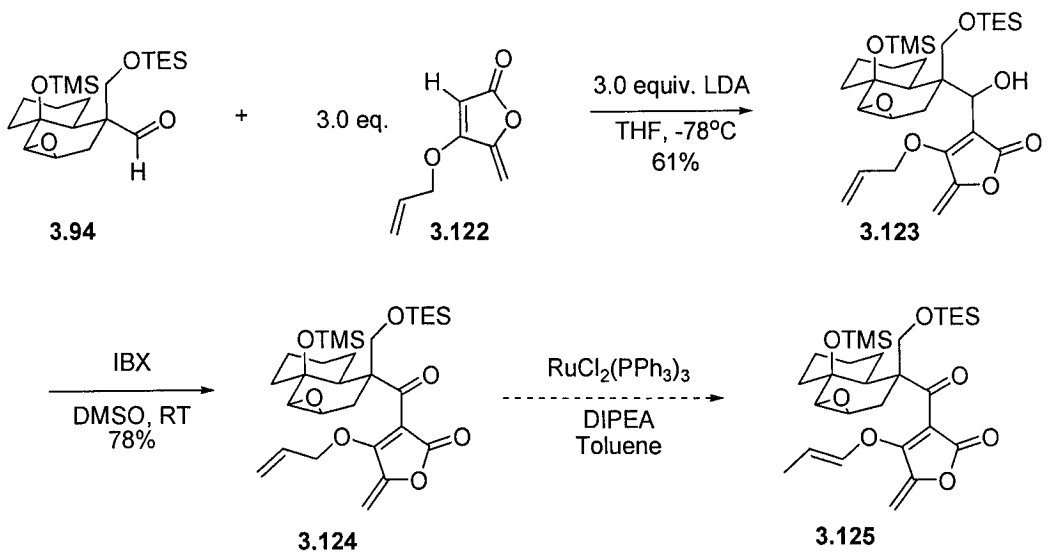
3.94 **3.119** **3.120**

3.121

Nucleophilic Epoxide Opening Cyclisation Attempts

With the first two strategies a failure, the strategy involving nucleophilic opening of the epoxide by tetronate residue was the only remaning path to be explored. In seeking a protecting group that could be removed under mild conditions, we attempted synthesis of allyl derivative **3.124** (Scheme 3.25). Anionic coupling of tetronate **3.122** and aldehyde **3.122** gave the secondary alcohol **3.123** in 61% yield, and oxidation with IBX proceeded smoothly to give **3.124** in 78% yield. A number of attempts were made to isomerize the allyl , with both Ru^{2+} and Rh^{1+}; but none were successful.

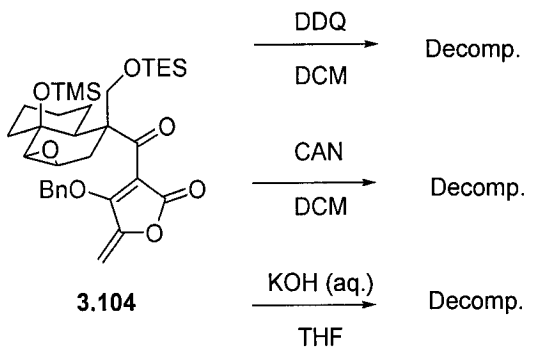
Scheme 3.25 – Attempted Allyl Tetronate Strategy



Benzyl Ether Cleavage

Oxidative cleavage of the benzyl protecting group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and ceric ammonium nitrate (CAN)[99] failed. Basic cleavage with aqueous potassium hydroxide (KOH) or sodium hydroxide (NaOH) in THF also failed, giving no isolable products.

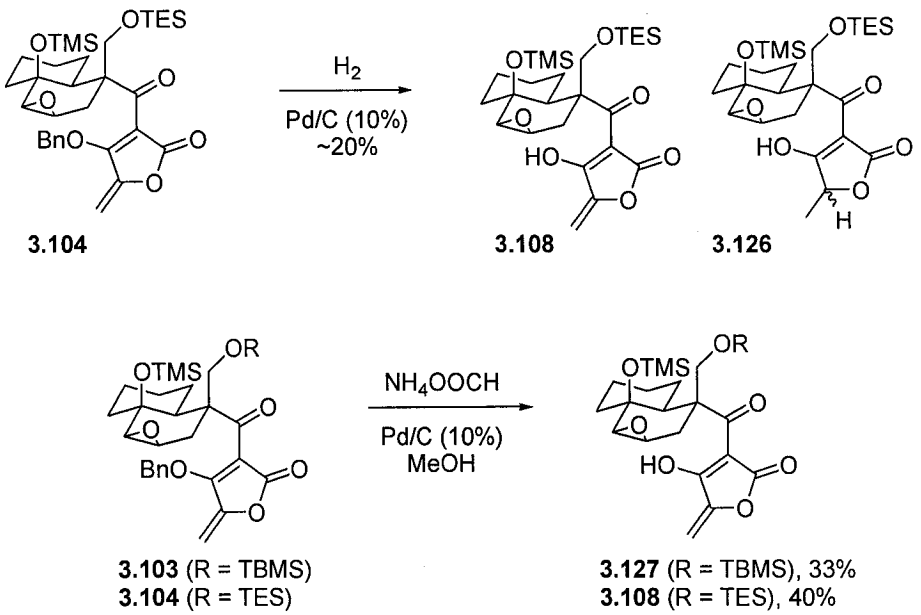
Scheme 3.26 – Failed Benzyl Ether Cleavages



Hydrogenative de-benzylation of the benzyl ether gave low yield of a mixture of de-benzylated and overhydrogenated products in which the C4-C5 olefin had been reduced (**3.126**, Scheme 3.27). Usage of ammonium formate as the hydrogen source[100] curbed this

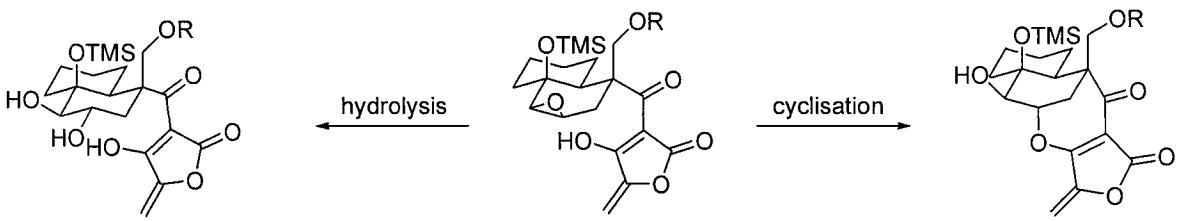
problem, and the free acids **3.108** and **3.127** could be formed cleanly in modest 33% and 40% yields.

Scheme 3.27 – Benzyl Ether Hydrogenations



With acids **3.108** and **3.127** in hand, we attempted to effect a 7-*exo*-tet ring opening of the epoxide. Numerous attempts were tried (a few are highlighted below), and the only products that were isolated were consistent with triols **3.128** or **3.129**; a result of simple epoxide hydrolysis.

Table 3.6 – Lewis Acid Cyclisation Attempts



3.128 (R = TES)
3.129 (R = TBS)

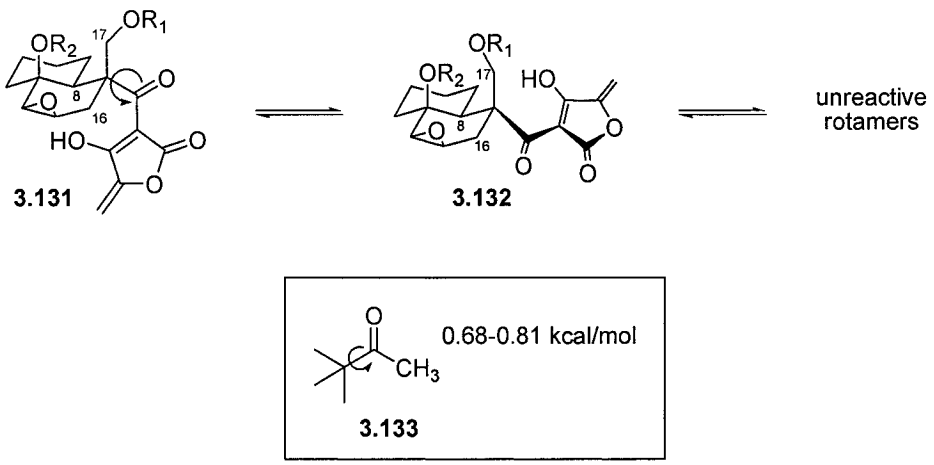
3.108 (R = TES)
3.127 (R = TBS)

3.109 (R = TES)
3.130 (R = TBS)

Entry	R	Conditions	Result
1	TES	TFAA Toluene	**3.128** (37%)
2	TES	TFA CH_2Cl_2	removal of TES
3	TES	TFA Toluene, MS4Å	SM
4	TES	PPTS Toluene, DCM, or THF	decomp.
5	TES	AcOH CH_2Cl_2 or THF	SM
6	TES	Al_2O_3 Et_2O	SM
7	TBS	$BiCl_3$ MeCN, Et_2O, THF, NMM, Dioxane, Acetone, or DMSO	SM
8	TBS	$BiCl_3$ Benzene or Hexanes	**3.129** (trace)
9	TBS	2.0 equiv. $Cu(BF_4)_2$ (x H_2O) DCM	**3.129** (38%)

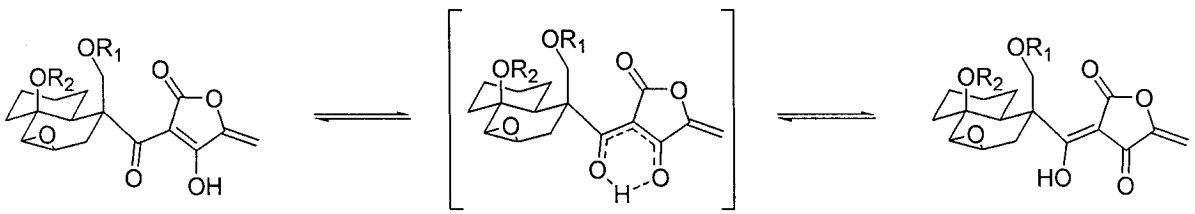
Several factors complicate this cyclization (Figure 3.17), and we have postulated a few explanations to clarify the results observed. With the assumption that this molecule behaves as most carbonyl compounds, the C6 carbonyl prefers to be in an eclipsed conformation with either C7, C16 or C8. The comparable pinacolone (**3.133**) is reported to have energy barriers of 0.81 (Durig *et al.*, IR)[101] 0.72 and 0.68 kcal/mol (Langley *et al.*, calculation).[102] The tetronic acid residue in our case may prefer an unreactive rotamer (eg. **3.132**), with the relative population of the potentially reactive species (**3.131**) being low.

Figure 3.17 – Rotation of the acyl tetronate



Our situation is further complicated that acyl tetronic acids are known to exist in a number of different tautomers (Figure 3.18),[38] with tautomerization between the acyl substituent and the tetronic acid ketone **3.134** having a clear dominance. It is suggested that the tautomerization occurs intramolecularly through sigmatropic hydrogen shift (**3.135**). It was difficult to determine whether this tautomerism was occuring in our case by NMR spectroscopy, but if this is the case, it surely puts a damper on the nucleophilic capacity of the tetronic acid residue.

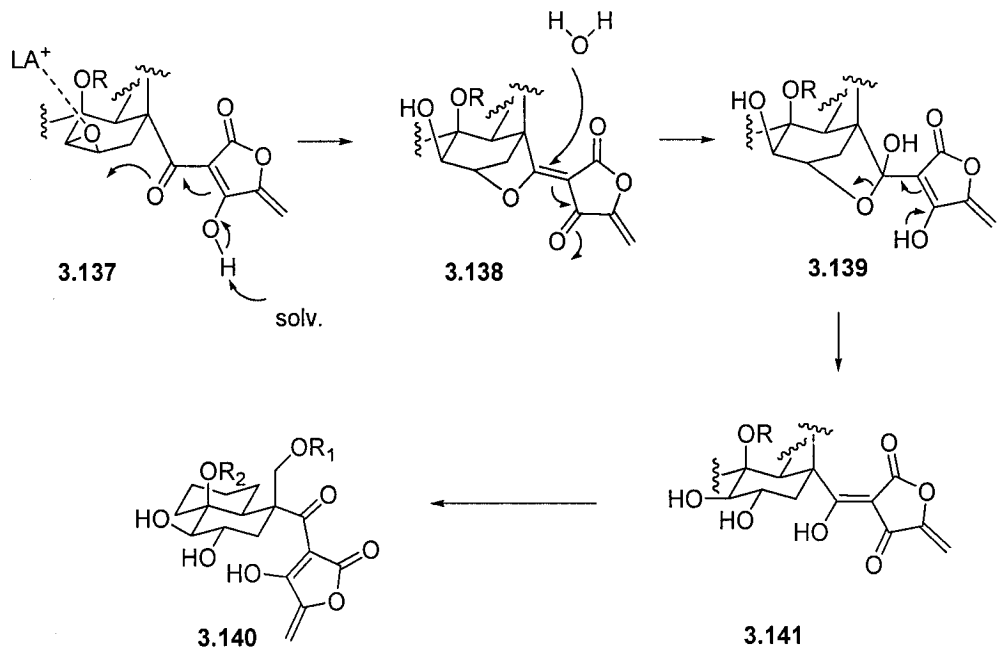
Figure 3.18 – Tautomerism in Acyl Tetronic Acid



3.134 **3.135** **3.136**

In concordance to this postulation, we also theorize that the neopentyl ketone itself may be responsible for the epoxide opening to produce diols **3.140** (Figure 3.19). Initial attack of the ketone on epoxide would produce tetrahydrofuranylidene **3.138** followed by hydrolysis and acetal cleavage to produce **3.140**. This pathway has yet to be conclusively ruled out or proven.

Figure 3.19 – Possible Epoxide Opening Mechanism

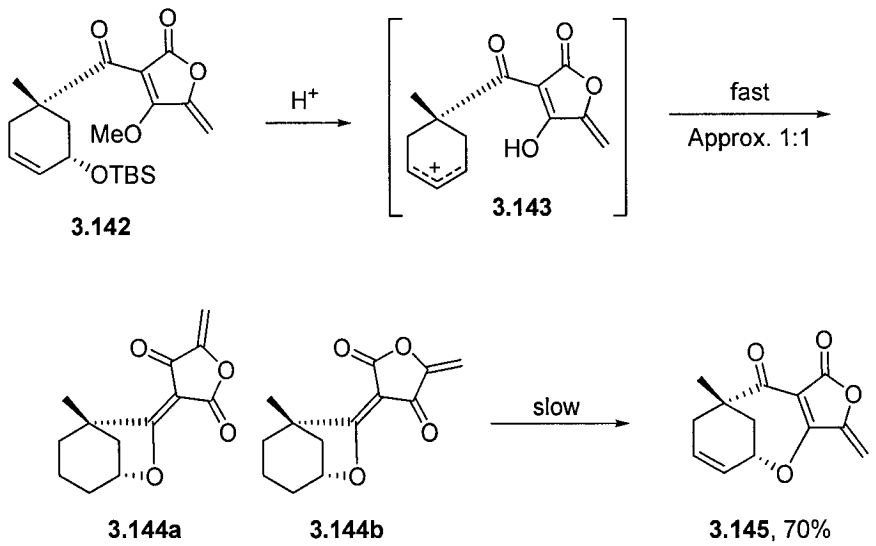


3.137 **3.138** **3.139** **3.140** **3.141**

In their studies on simpler systems, Paintner and co-workers noted that indeed the cationic cyclisation of 2-acyltetronic acids tested (eg. **3.142**) preferred kinetic formation of

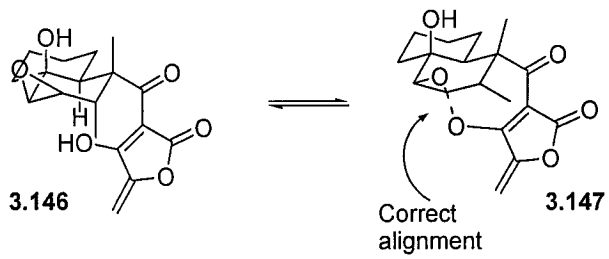
the 5 membered furanolides (as a mixture of E and Z isomers, **3.144a** and **3.144b**), but slowly equilibrate to the 7 member oxepine **3.145** (Figure 3.20).[94]

Figure 3.20 – Cyclisation of Tetrodecamycin Substructure (Paintner et al., 2000)[94]



These observations suggest that the correct oxygen must be directed to the electrophilic site. If indeed nature constructs the molecule in a similar fashion to that which we have proposed, the C18 methyl group may play a role in directing the tetronic acid residue toward the electrophilic site in the correct alignment, and would therefore be necessary for the success of this cyclisation strategy (Figure 3.21).

Figure 3.21 – C18 Methyl May Be Necessary for Cyclisation



Conclusions

This chapter has highlighted some of the challenges present in the tetrodecamycin core. We have successfully completed the synthesis of tetrodecamycin structures lacking the C18 methyl group. A few setbacks were experienced with the deoxygenation of C7, and generation of the oxygen-containing oxepine ring present in tetrodecamycin proved problematic. The failure for free tetronic acids to undergo cyclisation may, in part, be attributed to the conformational restraints imposed by this missing methyl group in the natural product. With the majority of the synthetic pathway laid out, we now set upon installation of this remaining carbon, and push forward to the synthesis of the natural molecule.

4

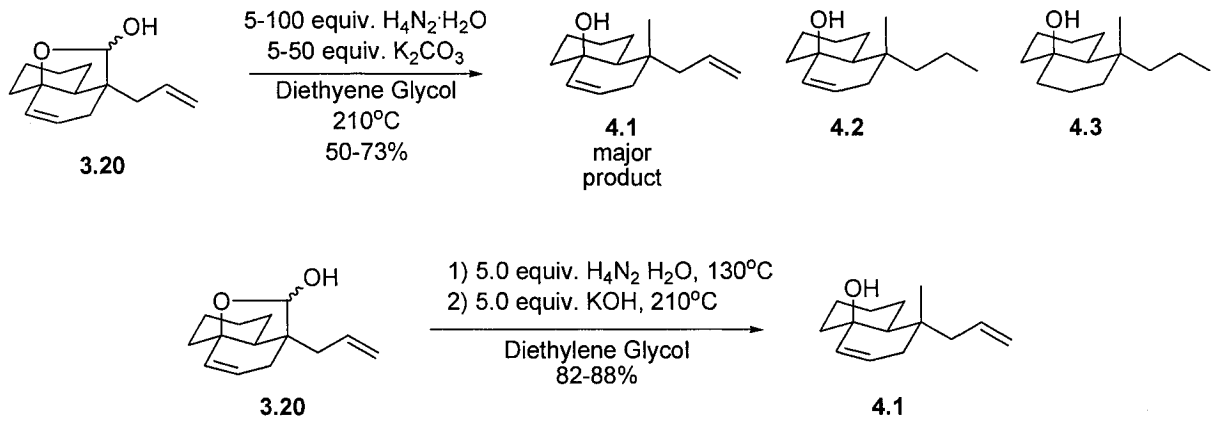
Synthetic Studies Toward Tetrodecamycin

Part II: Natural Core

Approach to Natural Tetrodecamycin decalin core

Among our early deoxygenation attempts of C17, the simple Wolff-Kishner[103] reduction of the masked aldehyde using hydrazine and base is only made conspicuous by its absence. To our surprise, the first attempt using conditions developed by Paquette and co-workers was successful.[104] Heating of lactol **3.20** in the presence of a large excess (up to 100 equivalents) of hydrazine hydrate and potassium carbonate gave the allylic alcohol **4.1** in 50-73% yield. Despite sparging with copious amounts of argon, these reduction conditions also afforded varying amounts of the diazine-reduced products, presumably from the air-induced decomposition of hydrazine.[105] It was not until much later in our research program that we discovered that diazine reduction could be halted by a) degassing the solution under high vacuum (0.1 mmHg) for 1 hr, and b) performing the reduction in two consecutive heating steps. This also led to an increase in yield of the desired free alcohol **4.1** (88%).

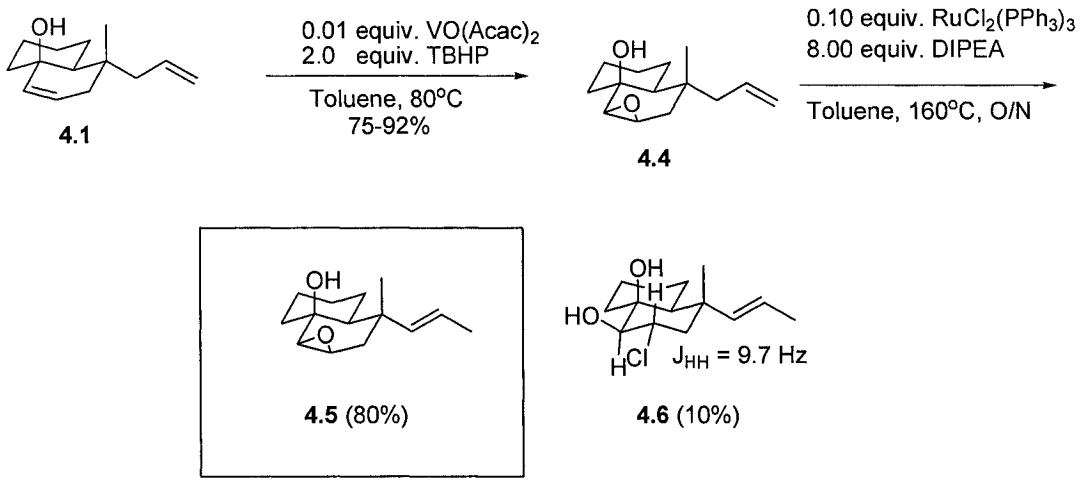
Scheme 4.1 – Deoxygenation of C17



Now having deoxygenated allyl alcohol **4.1**, we continued toward the synthesis of tetrodecamycin analogues without an alkoxy substiuent at the C17 position. The synthetic tasks were identical to that of the previous series: epoxidation of the ring double bond, and internalization of the terminal olefin for ozonolysis.

Sharpless directed epoxidation proceeded as before, in 75-92% yield to give epoxide **4.4** as a single diastereomer. The conditions that had performed the olefin internalisation (0.1 equiv. $RuCl_2(PPh_3)$, 5.0 equiv. DIPEA, 130°C) failed here, but increasing to 8 equivalents of base and raising the pot temperature to 150-160°C gave an 80% yield of the internal olefin **4.5**. Interestingly, a small amount (10%) of ruthenium mediated chlorination (**4.6**) of the epoxide was observed when the reaction was carried out on large scale (Scheme 4.2). The large (9.7 Hz) coupling between the two adjacent protons is coincident with opening of the epoxide at C15. In the absence of a tetronic acid residue on this molecule, it suggests that nucleophiles prefer attack at this carbon simply for steric reasons, but this does not discount the tetronic acid-assisted mechanism for the hydrolysis of epoxide proposed earlier.

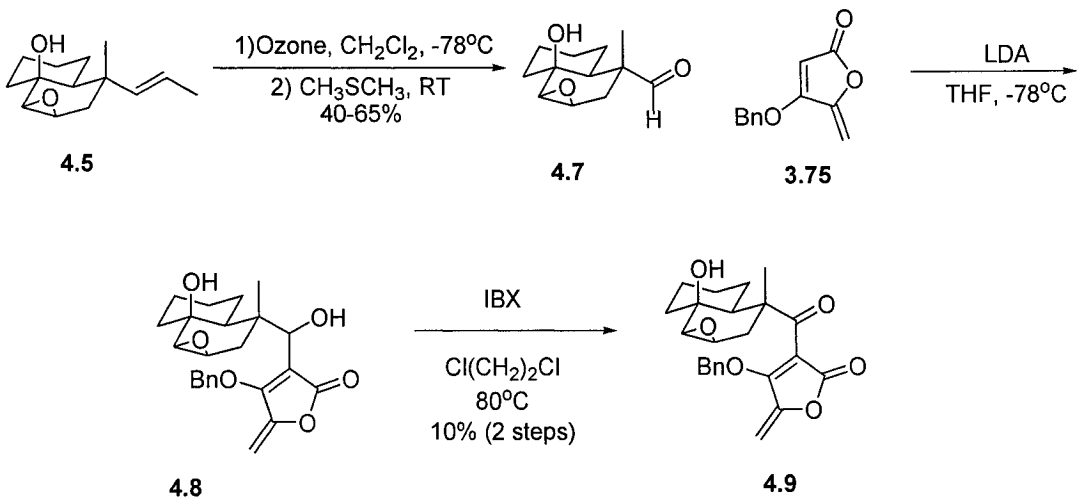
Scheme 4.2 – Epoxidation and Isomerization of Deoxygenated Core



Ozonolysis of the disubstituted olefin gave aldehyde **4.7** in 40-65% yield. Subjecting this aldehyde to the alkylation conditions with benzyl tetronate **3.75** gave the secondary alcohol **4.8**, that was oxidized without purification to give the diketone **4.9** in 10% overall yield. Insufficient amounts of material were available for further studies (Scheme 4.3).

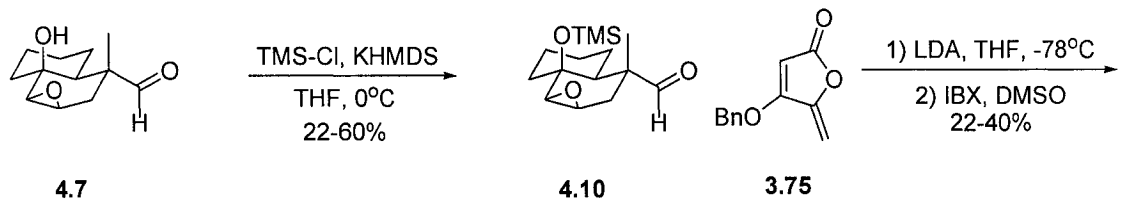
We surmised that, as before, the tertiary alcohol must be protected to ensure the success of the alkylation. The protection conditions for the tertiary alcohol on **4.7** that had worked better in the past now gave a 22-60% yield of the desired trimethylsilyl ether **4.10** (Scheme 4.4). Alkylation and oxidation of the alcohol gave the diketone **4.11** in up to 40% yield. Standard hydrogenolysis of the benzyl protecting group was not possible owing to the sensitive exocyclic double bond, but ammonium formate deprotection of the benzyl ether gave acid **4.12** in up to 80% yield. Once again, this yield proved to be highly erratic, with occaisional complete decomposition as a result. Precise monitoring of temperature was a critical factor to the success of this transformation.

Scheme 4.3 – Alkylation Attempts

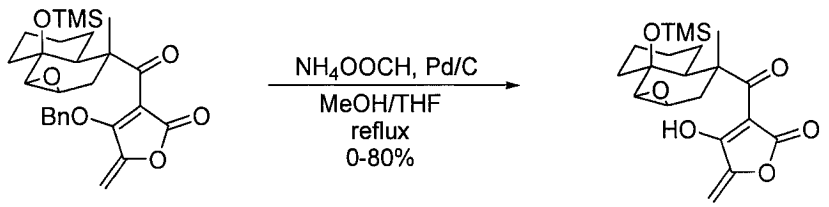


A number of Lewis acids were attmpted on the available tetronic acid **4.12** with no success (Scheme 4.5). Both of these alkylation protocols suffered from poor reproducibility, possibly due to the decomposition of the tetronate unit during the oxidation. Determination of the yield of alkylation was difficult, owing to chromatographic overlap between the excess tetronate, starting aldehyde, and product. Ths sparse availability of material in the last few steps prompted investigations to avoid the difficult oxidation of the severely crowded secondary alcohol, or improve the alkylation step.

Scheme 4.4 – Alkylation with Silyl Ether

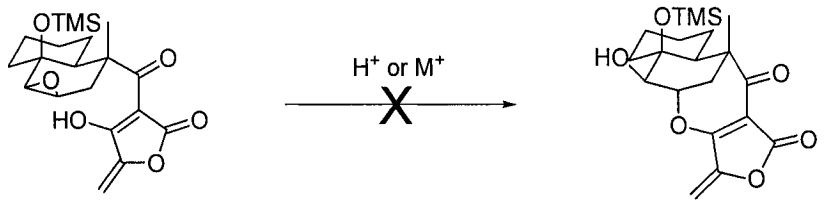


4.7 **4.10** **3.75**



4.11 **4.12**

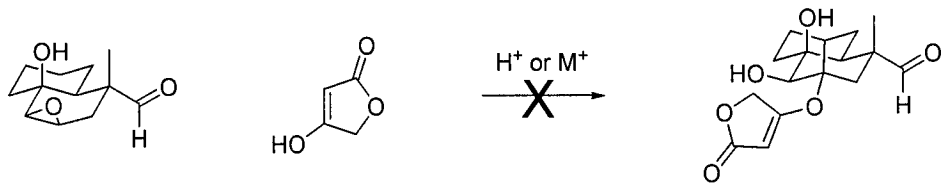
Scheme 4.5 – Attempted Cyclisations



4.12 **4.13**
(not observed)

Some effort was made to perform the cyclisation in a 'backwards' manner, by intermolecular reaction between epoxide and tetronic acid (Scheme 4.6). However, none of the desired epoxide opening product **4.14** was observeable under the conditions attempted.

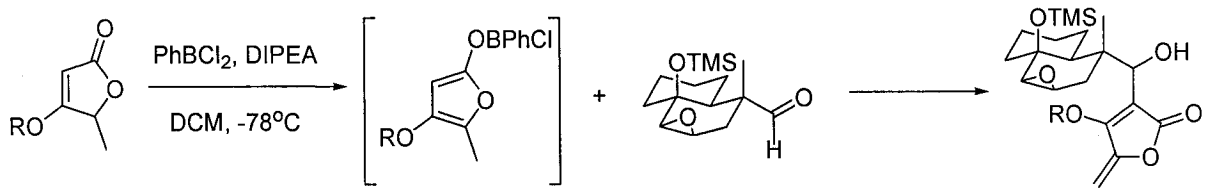
Scheme 4.6 – Sequence Order Reversal Attempt



4.7 **1.2**
tetronic acid
4.14
(not observed)

Atttempts at generating boron alkoxy furanolates[106] (**4.17**) also failed, leading only to recovery of the starting aldehyde (Scheme 4.7).

Scheme 4.7 – Boron Furanolate Coupling Attempt



4.15 (R = CH_3)
4.16 (R = Bn)

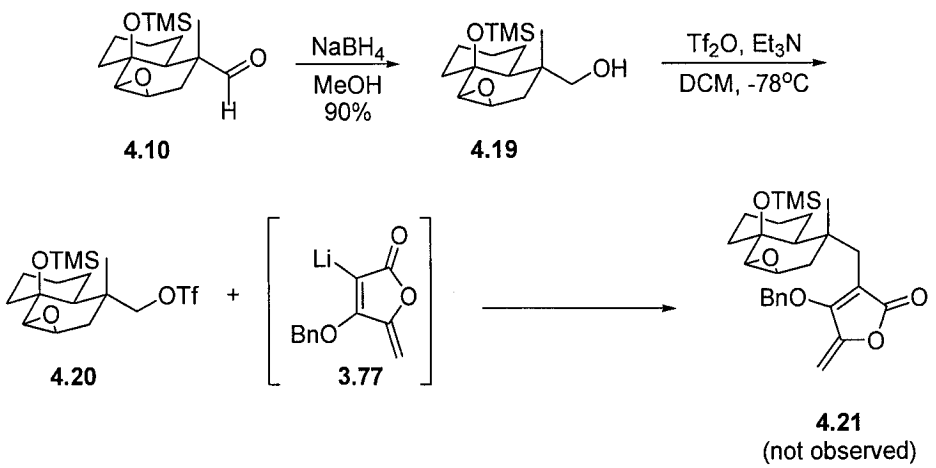
4.17

4.10

4.18
(not observed)

Excision of the ketone entirely via reduction followed by triflate displacement[107] of the resulting alcohol **4.19** led to no isolable product (Scheme 4.8). Mitsonobu displacement[83] of the primary alcohol with iodine failed, and the primary tosylate could not be synthesized via conventional means.

Scheme 4.8 – Triflate Mediated C-C Bond Forming Attempt



4.10

4.19

4.20

3.77

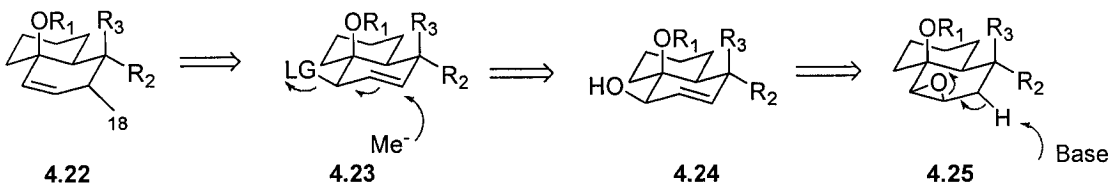
4.21
(not observed)

Progress of the analogues was halted for the time being, and research focused on accessing the tetrodecamycin C18 methyl group.

Installation of C18 Methyl

Our synthetic plan for the installation of C18 revolved around an S_N2' addition to olefin **4.23**, which could, in turn, arise from alcohol **4.24**. This allylic alchol could then be a direct result of either base[108] or acid[109] induced rearrangement of the oxirane **4.25**.

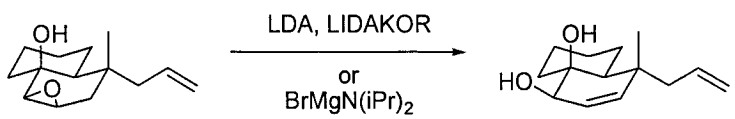
Figure 4.1 – Retrosynthetic Analysis for Installation of C18



4.22 **4.23** **4.24** **4.25**

The rearrangement of epoxides under basic conditions has been extensively covered in the literature. The transformation usually requires the presence of strong dialkylamides,[110] and can have problems with competing pathways. Recently, it has been shown that mixed metal bases such as LIDAKOR (a mixture of LDA and KOt-Bu)[111] and magnesium bromide diisopropyl amide can effect the transformation of alkyl oxiranes at lower temperatures. A number of different mixed metal bases and Lewis acids were attempted with epoxide **4.4** unsuccessfully (Scheme 4.9).[112]

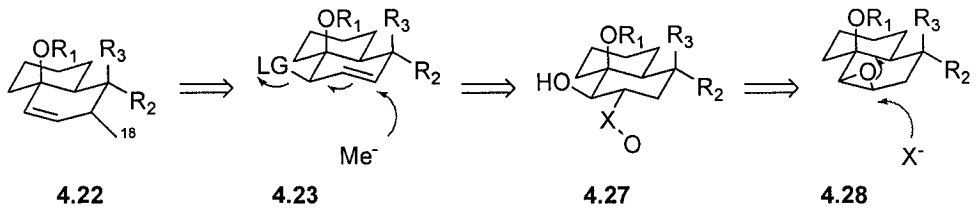
Scheme 4.9 – Attempted Base-Mediated Epoxide Isomerization



4.4 **4.26** (not observed)

Armed with the knowledge that epoxides between C14 and C15 open exclusively at C15 (with H_2O see Scheme 3.23, with Cl see Scheme 4.2), then a sulfur or selenium nucleophile should also open the epoxide at this carbon to provide **4.27** (Figure 4.2).

Figure 4.2 – Alternative Strategy for C18

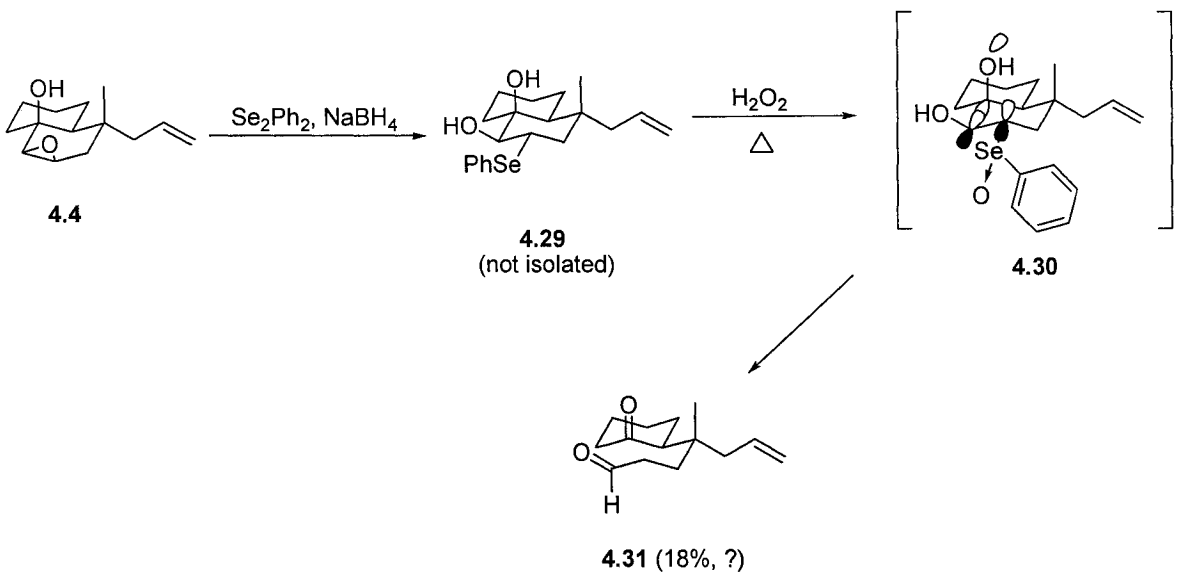


4.22 **4.23** **4.27** **4.28**

Oxidative elimination would then serve to install a double bond between C15 and C16. The resultant alcohol **4.23** could be transformed into a leaving group, ready for addition via methyl cuprate. Providing that this addition proceeds in an S_N2'-anti manner, it should provide decalin **4.22** with methyl at C18 of the correct stereochemistry.

The conversion of epoxides to allylic alcohols with selenium was examined by Sharpless and Lauer in 1973.[113] The selenium anion can be prepared readily by reduction of diphenyldiselenide and sodium borohydride, or displacement by *n*-BuLi. Reaction of epoxide **4.4** with sodium borohydride in ethanol gave a new product by TLC (whose structure was confirmed later). The crude was heated in the presence of hydrogen peroxide to give a compound whose structure is tentaviley assigned as **4.31**. The alignment of lone pairs on the free oxygen are perfectly antiperiplanar to the leaving selenoxide, making elimination quite facile.

Scheme 4.10 – Oxidative Selenide Elimination



4.4

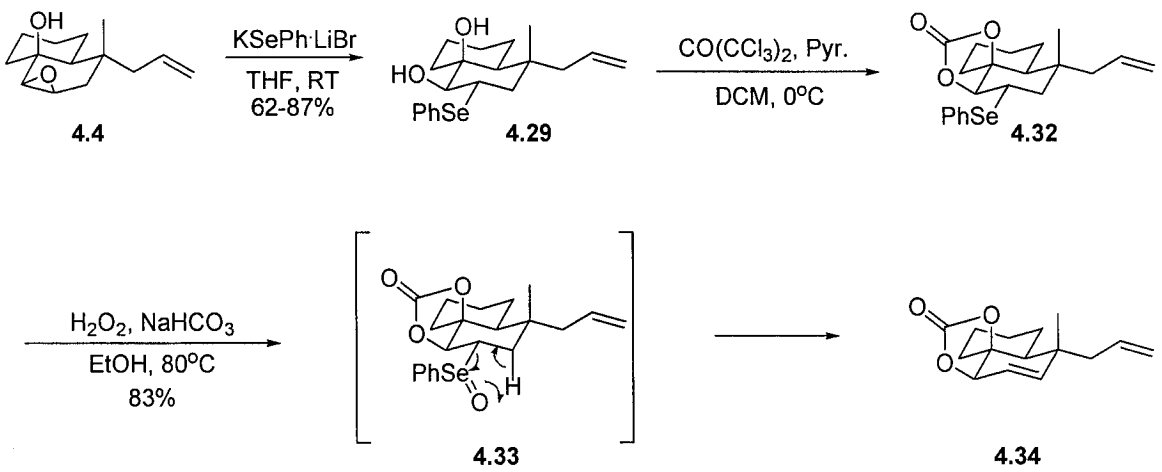
4.29
(not isolated)

4.30

4.31 (18%, ?)

To maximize the yield of the resulting phenyl selenide alcohol **4.29**, a one step epoxide opening was carried out with lithium phenylselenide and potassium bromide additive to give **4.29** in 62-87% yield. To prevent oxidative ring opening of the diol, it was necessary to devise a protection strategy. Derivatization via the carbonate not only protects the tertiary alcohol, it simultaneously converted the C14 alcohol into a good leaving group. Diol **4.29** was treated with triphosgene and pyridine at low temperature, and carbonate **4.32** was formed in good yield (Scheme 4.11). Treatment of this selenide with hydrogen peroxide gives selenoxide **4.33** and elimination then occurs quite readily, giving phenyl selenol and the allylic carbonate **4.34** in 83% yield over two steps.

Scheme 4.11 – Carbonate Selenide Elimination



4.4 **4.29** **4.32** **4.33** **4.34**

Additions to allylic carbonates and carbonyls has been extensively studied in the literature, with specific attention to palladium catalysed allylic substitutions.[114] Often these substitutions suffer from poor selectivity in non-symmetrical substrates, owing to indescrimintate π-allyl palladium intermediates. Cuprate additions have also been actively researched[115] and do not generally suffer from these selectivity issues. Cuprate additions generally proceed in an S_N2'-anti manner, and offer predictable regiochemical and stereochemical outcome.[116] Our system is somewhat complicated by the presence of a quaternary carbon adjacent to the desired addition site (C16), which makes nucleophilic attack at this position somewhat difficult.

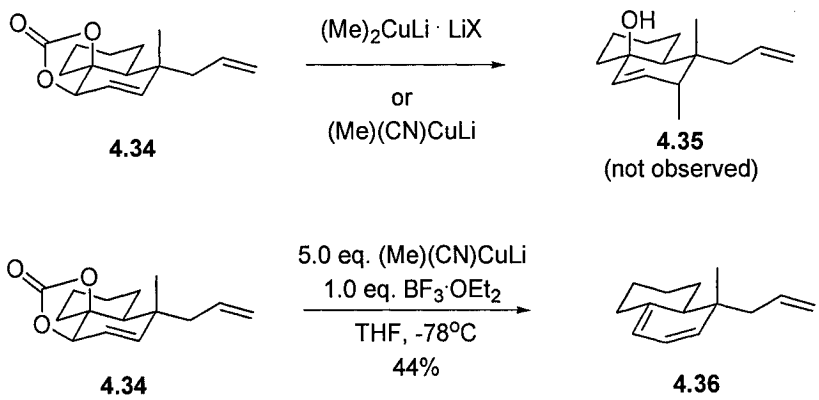
Cuprate Conjugate Addition to Allylic Carbonate

Despite much experimental and theoretical research, some elements of cuprate conjugate additions remain under debate.[117] Recent studies suggest that the rate limiting step of the reaction is reductive elimination of the putative Cu(III) species following initial coordination of the Cu(I) centre to the olefin.[118] Lewis acids such as BF_3 or TMS-Cl have been shown to dramatically improve reactivity of cuprates in some cases. Analysis of BF_3-complexed cuprates fails to account the ehanced reactivities of these reagents[119] but calculations show that coordination of the Lewis acid to the trialkyl Cu(III) complex is responsible for their enhanced reactivity.[120]

Attempts with dimethyl cuprates generated from methyllithium and copper (I) iodide gave only starting material. Altering the copper source to copper (I) bromide or copper (I)

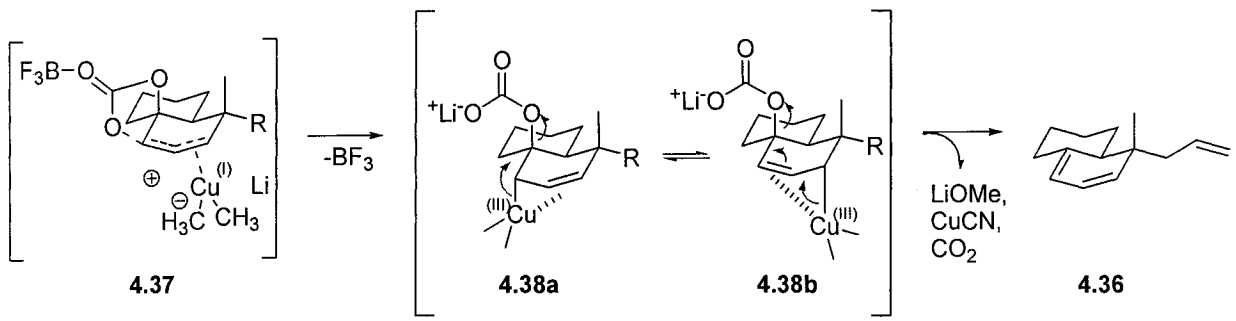
cyanide failed with both one and two equivalents of alkyllithium; addition of lithium iodide did not help. Curiously, addition of BF_3 activator[121] gave exclusive formation of the 1,3-diene **4.36** in 44% yield. This mode of reactivity has been reported as a footnote in an early paper by Kang and co-workers[121] in their work on cuprate additions to allylic cyclic carbonates, but was more prevalent in subsequent investigations surrounding dienyl cyclic carbonates.[122]

Scheme 4.12 – Cuprate Additions to Allylic Carbonate



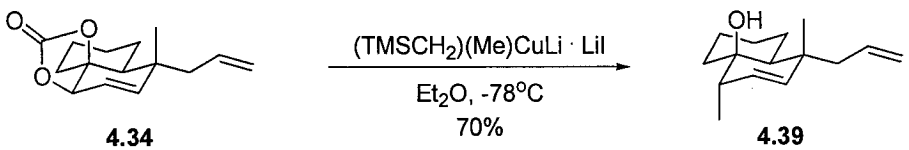
Based on recent theoretical investigations by Nakamura and co-workers,[123] we propose a mechanism as follows: Initial attack at C14 or C16 by MeCuCNLi upon **4.37** generates π-allyl Cu(III) complex **4.38**. In one of its two enyl[σ + π] representations (**4.38a** and **4.38b**), it appears as an organometallic with β-X substituent (where X is CO_3Li) which can readily undergo elimination to produce the diene (direct γ elimination may also occur) and formally $(CO_3Li)(Me)CuCN$, which is likely highly unstable and presumably decomposes to CuCN, MeOLi and CO_2.[124]

Figure 4.3 – Proposed Mechanism for Formation of 4.36



Organocuprates formed from one equivalent of copper and two equivalents of organometallic are often referred to as "Gillman reagents," after the scientist who first noticed their unique reactivity.[125] With few exceptions, the doubly alkylated Copper center generally only transfers one of the alkyl groups to the electrophilic target.[126] Recent work by Bertz and co-works has shown that mixed cuprates of the form $(R)((Me)_3Si\text{-}CH_2)CuX$ are especially reactive and thermally stable.[127] In our hands, we were initially quite pleased when the cuprate formed from one equivalent of trimethylsilylmethyllithium, one equivalent of methyllithium and one equivalent of copper (I) iodide reacted smoothly with carbonate **4.34** at -78°C to give a new product whose ^1H NMR showed a new methyl doublet, and olefinic peaks corresponding to a putative addition to the allylic carbonate. Unfortunately HMBC experiments later showed this compound to have the connectivity shown in scheme **4.39** – a result of an S_N2 displacement of carbonate, opposed to the desired S_N2' reaction.

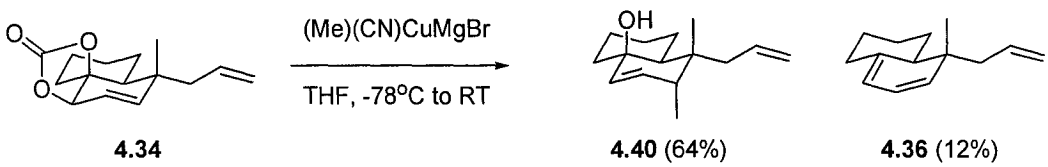
Scheme 4. 13 – Gillman Cuprate Addition Proceeds in S_N2 Manner



4.34 **4.39**

This was a minor setback in our synthetic efforts, but did demonstrate that cuprates could add to our system in some manner, even if not the way desired. After many further attempts it was suggested[128] that true Grignard reagents may offer better nucleophilic reactivity. Small amounts of a new product were formed when carbonate **4.34** was exposed to the cuprate generated from equimolar (10 equiv. total) amounts of methyl magnesium bromide and copper (I) bromide-dimethyl sulfide complex in DMS and Et_2O at -78°C. Further optimizations revealed that the best yields of **4.40** were formed using copper (I) cyanide and methyl magnesium bromide in THF at low temperature with gradual warming. Varying amounts of diene **4.36** were also formed, and could not be averted regardless of the conditions attempted.

Scheme 4.14 – Monoalkyl Cuprate Delivers Correct Stereochemistry



4.34 **4.40** (64%) **4.36** (12%)

The striking similarity between the spectra of **4.39** and **4.40** are deconvoluted nicely by 2D NMR experiments. Figure 4.4 and Figure 4.5 illustrate some of the subtle difference in connectivity patterns elucidated by HMBC and NOE.[129]

Figure 4.4 – HMBC and NOE Correlations

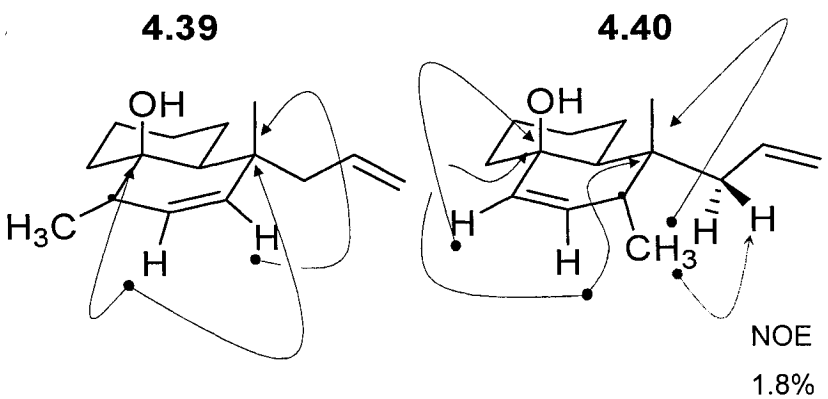
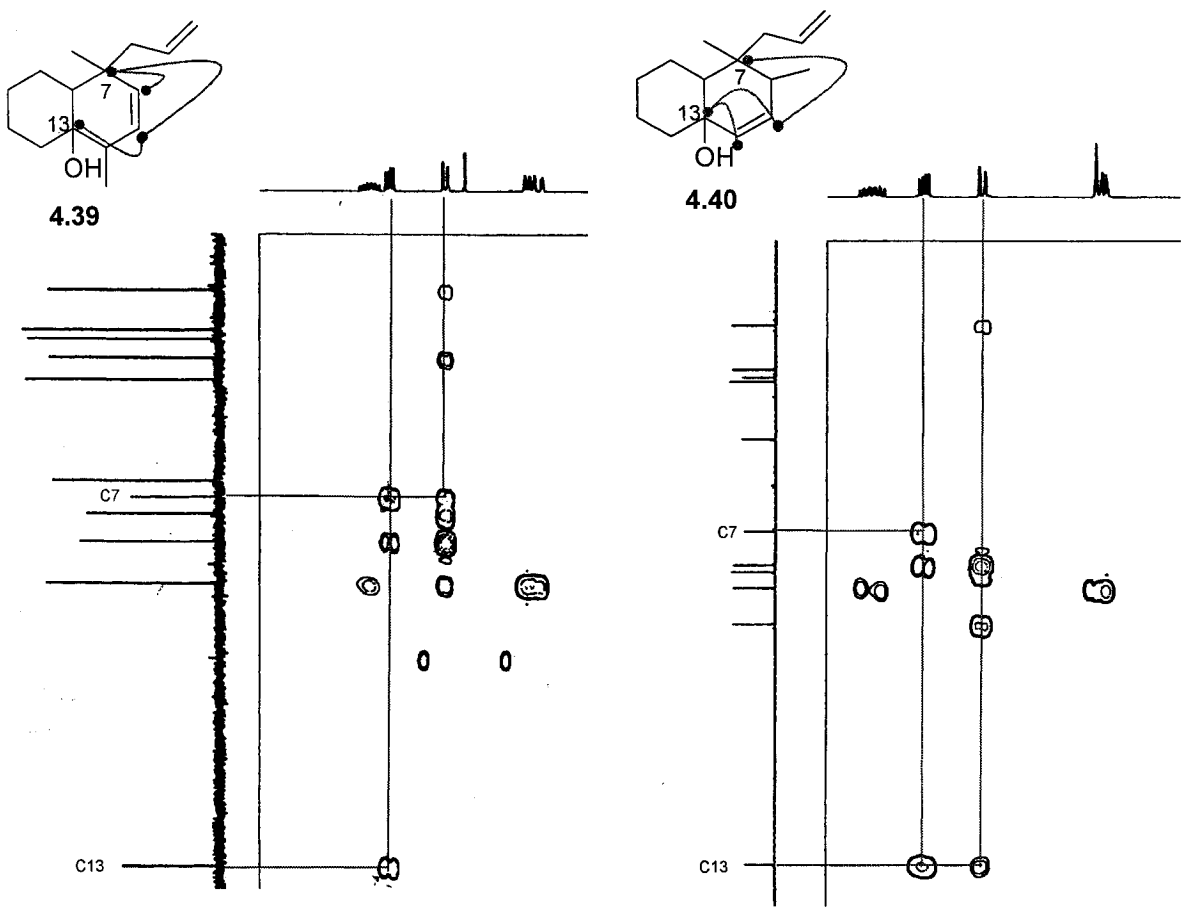


Figure 4.5 –Distinguishing HMBC Correllations for 4.39 and 4.40

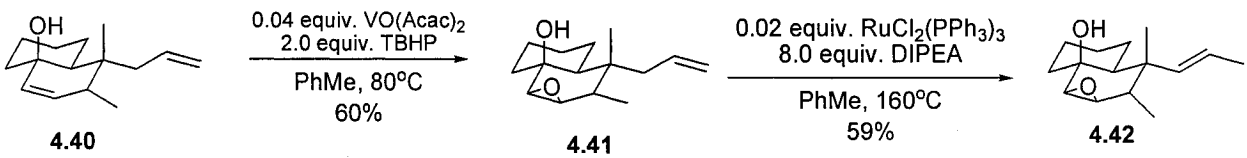


Alkylation With True Tetrodecamycin Core

With olefin **4.40** in hand, synthesis resumed it's previously plotted course: (a) epoxidation of the allylic alcohol, (b) migration of the double bond, (c) ozonolysis and (d) alkylation of the tetronate moiety. The first two steps in this sequence were unproblematic. Epoxidation (**4.40** → **4.41**) proceeded smoothly, and was complete in only 45 minutes (compared with the 3 hr required when there was no methyl at C16, compound **4.1**). Heating terminal olefin **4.41** at 160°C overnight in the presence of $RuCl_2(PPh_3)_3$ and DIPEA gave the bond-migrated product **4.42** in 59% yield. Olefin migration suffered from lower yields; possibly owing to the greater steric crowding near the migration site (with this additional methyl group now in place). Compound **4.42** could also be accessed in a slightly more efficient manner if the isomerization is performed first (**4.8** → **4.44** → **4.45** → **4.42,** Scheme 4.16).

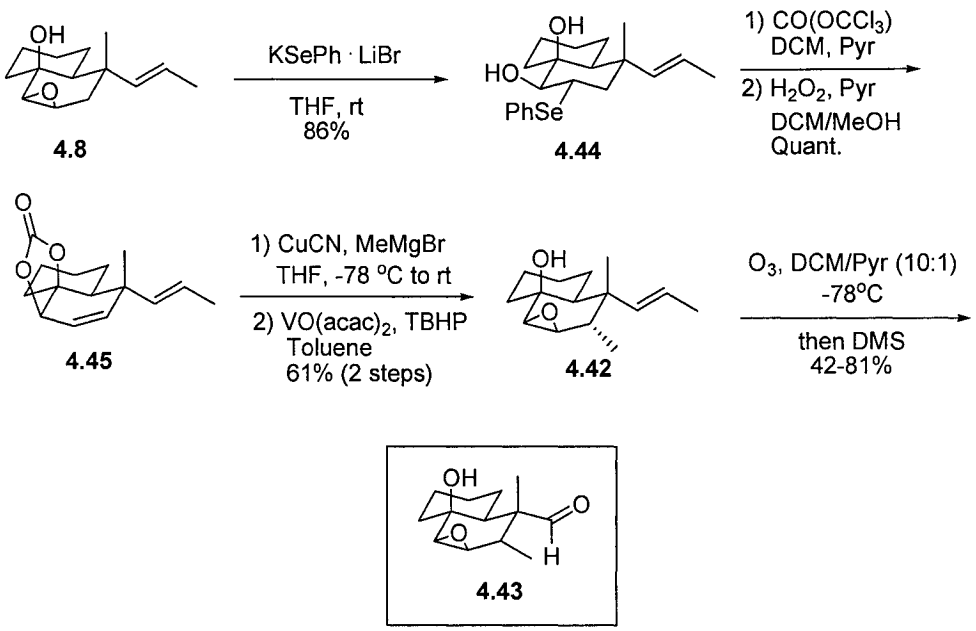
Ozonolysis of the resultant disubstituted olefin **4.42** gave the aldehyde **4.43** in varying yields. Disappointingly, the ozonolysis suffered from unpredictable reproducibility even at -100°C.[130] Lemieux-Johnson oxidation gave none of the desired aldehyde. It was noted in 1958 by Slomp and co-workers that the addition of small amounts of pyridine (1% v/v) can dramatically influence the selectivity of ozonolysis reactions.[131] Undeniably, treating alkene **4.42** with ozone in dichloromethane containing 10% pyridine (by volume) gave cleaner cleavage of the alkene with less formation of side products, but yields still varied (42 to 81%). Alkylation attempts were continued with the available aldehyde.

Scheme 4.15 – Continuation of Natural Product Core



4.40 **4.41** **4.42**

Scheme 4.16 – Isomerization First

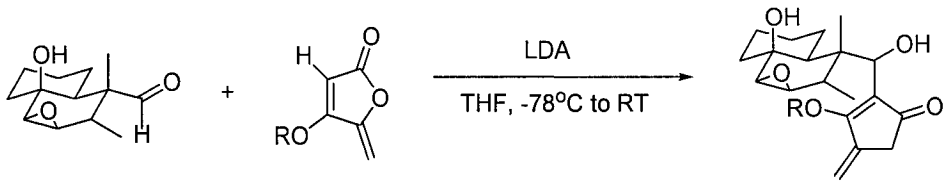


4.8 **4.44** **4.45** **4.42**

4.43

Not surprisingly, direct alkylation attempts of aldehyde **4.43** gave only trace amounts of the desired adduct **4.46**/**4.47** after numerous attempts. From our previous work, it was known that the free alcohol present must be protected for the success of the alkylation.

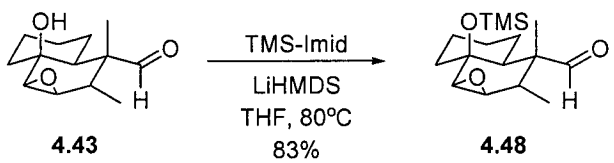
Scheme 4.17 – Attempted Coupling with C18 Present



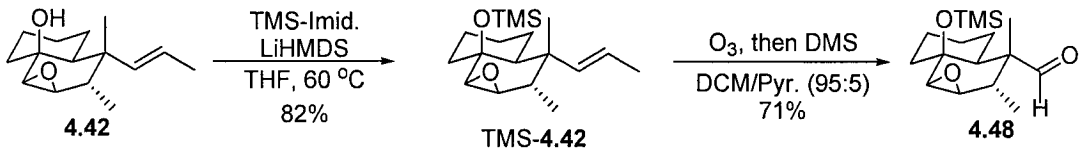
4.43 | **3.74** (R = Me), **3.75** (R = Bn) | **4.46** (R = Me), **4.47** (R = Bn) (neither is observed)

Treating tertiary alcohol with KHMDS and TMSCl at elevated temperatures afforded none of the protected product. Similar results were observed with TMSOTf and *N,O*-bis-(Trimethylsilyl) trifluoroacetamide at elevated temperatures. Numerous other silylation conditions were attempted, but none of the desired silyl ether could be formed. Thankfully, TMS-Imidazole and LiHMDS at reflux provided protected tertiary alcohol **4.48** in 83% yield.[132] A slight improvement in overall yield was noted when this protection was carried out prior to ozonolysis (**4.42** → **4.43**, Scheme 4.18).

Scheme 4.18 – Protection Prior to Ozonlysis



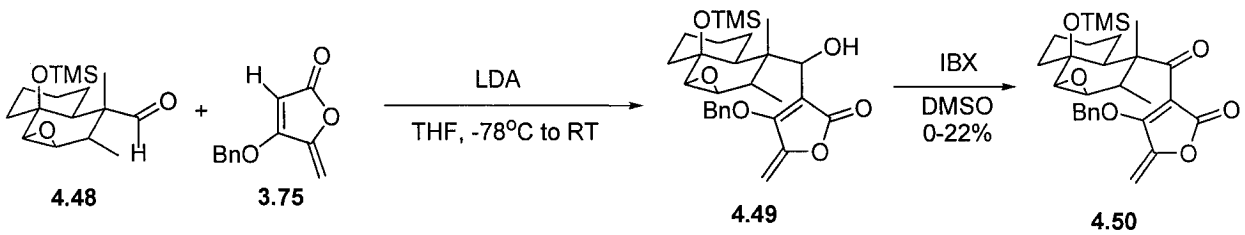
4.43 | **4.48**



4.42 | TMS-**4.42** | **4.48**

Alkylation of this aldehyde with the conditions developed previously gave a low yield of coupled alcohol **4.49**. Tracking of this reaction was rendered extremely difficult owing to the chromatographic similarity between tetronate and coupled alcohol. A crude mixture of alcohol **4.49** was then subjected to IBX oxidation to give benzyl ether **4.50** in 22% maximum yield over 2 steps.

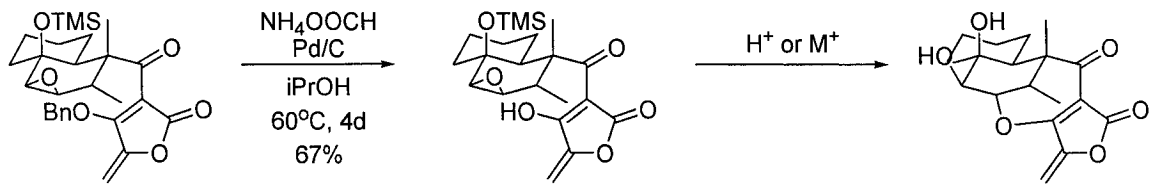
Scheme 4.19 – Attempted Coupling with Silyl Ether



The ammonium formate deprotection strategy for these benzyl ethers now failed, giving only trace amounts of the unprotected free tetronic acid **4.51**. Conditions were somewhat optimized and usage of isopropanol solvent, and lower temperature (40°C instead of 80°C) over a longer period of time (4 days, instead of 12 hr) gave free acid **4.51** in 67% yield.

A sample of natural tetrodecamycin was obtained through collaboration with T. Tsuchida, and this enabled small scale (<1mg) ring closure attempts.[133] General acid catalysis for the ether ring closure failed (to generate **1.1**, potentially). A range of mild (amberlyst-15) to strong (H_2SO_4) acids was tried in both apolar (DCM) and polar (MeOH) solvents with no success. Some Lewis acids ($Cu(BF_4)_2$, $BF_3{\cdot}OEt2$, $BiCl_3$,) were also attempted, but to no avail (Scheme 4.20 – Attempted Cyclisation).

Scheme 4.20 – Attempted Cyclisation



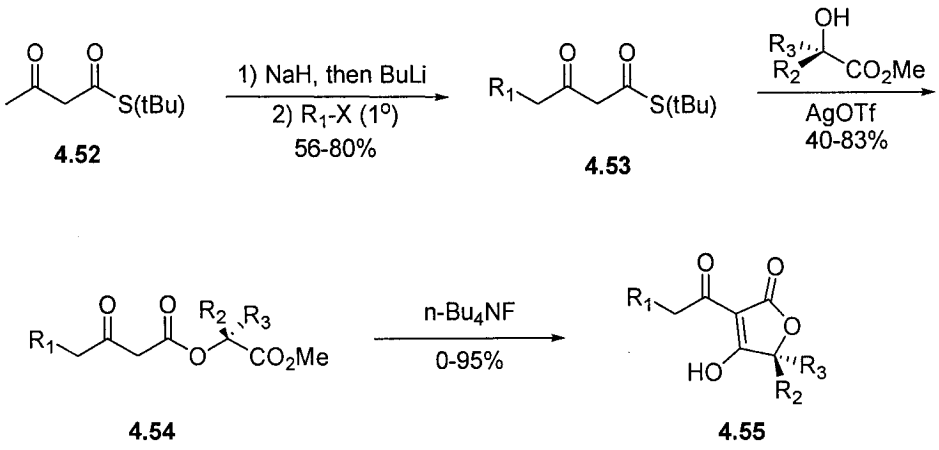
4.50 **4.51** **1.1** (not observed)

The difficulty in procuring free acid **4.51** (owing to low yields) prompted investigations into alternative methods of introducing the tetronic acid residue onto the decalin core **4.48**.

Alternative Coupling Strategies

In 1987 Ley and co-workers reported a novel three-step entry into γ-substituted (C4) acyltetronic acids.[134] The procedure involved alkylation of S-tert-butyl acetothioacetate **4.52** with primary alkyl halide followed by transesterification with an α-hydroxyester (**4.53**) and Dieckmann cyclisation to give actyltetronic acids **4.55** in good yields.

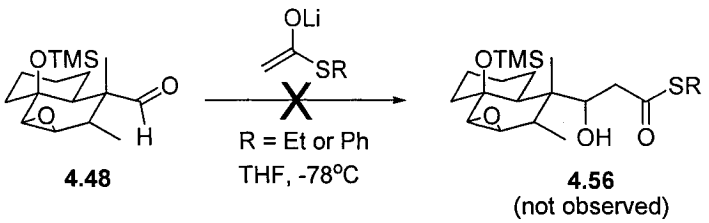
Figure 4.6 - Approach to Acyl Tetronic Acids (Ley, 1987)



4.52 **4.53** **4.54** **4.55**

This specific order of events is obviously inapplicable in our case, and we attempted alkylation of the aldehyde with phenyl thioacetate (**4.48** → **4.56**, Scheme 4.21) and butylthioacetate with no success.

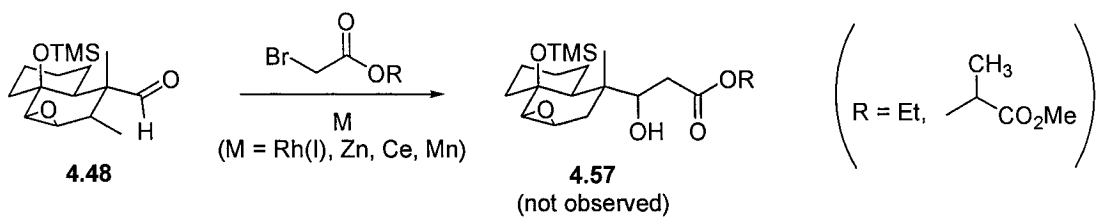
Scheme 4.21 – Attempted Thiolate Alkylation



4.48 **4.56** (not observed)

Reformatsky reaction was also attempted a number of times on bromoacetates using Zn, Mn, Rh(I), or Ce but gave none of the desired hydroxyesters (**4.48** → **4.57**, Scheme 4. 22).[135]

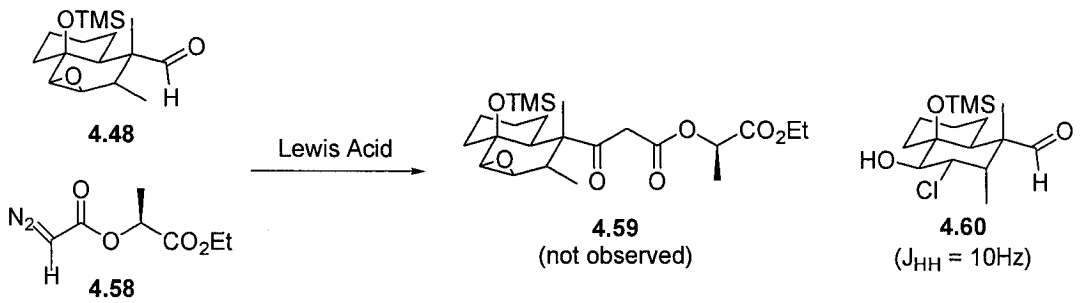
Scheme 4. 22 – Attempted Reformatsky Alkylation



4.48 **4.57** (not observed)

Roskamp and co-workers reported the use of Lewis acid catalysed C-H insertion into aldehydes for the synthesis of β-keto esters.[136] This strategy was modified in 1994 by Nomura and co-workers specifically for the synthesis of acyl tetronic acids.[137] They found that insertion of methyl (diazoacetoxy)acetates into even hindered pivaoyl aldehydes could be accomplished by catalytic Zr(IV) salts. C-H insertion reaction of diazolactate ester **4.58** was attempted under a number of conditions, but with no success. Interestingly, chlorination of the epoxide was noted when $ZrCl_4$ or $TiCl_4$ was used (**4.60**). The large coupling constant (10 Hz) indicates attack of chloride at C15.

Scheme 4. 23 – Attempted C-H insertion



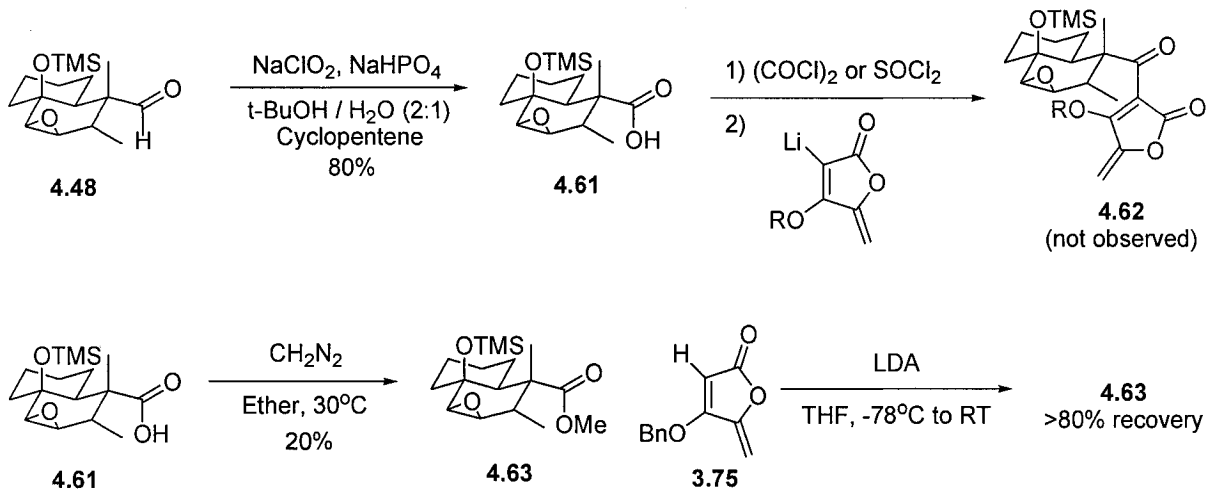
Ley and Wadsworth introduced a palladium catalysed acylation of protected tributylstannyl tetronates in the course of their synthesis of tetronasin (Figure 1.6).[138] The researchers noted that acyl chlorides readily underwent coupling in the presence of *trans*-(Bn)(Cl)Pd(PPh_3)$_2$, giving the corresponding 2-acyltetronates in good yields. Oxidation of the aldehyde **4.48** to the acid was accomplished by $NaClO_2$ to give acid **4.61** in 80% yield.

Acyl chlorides prepared in the same manner as before were canulated into a solution of lithiotetronate. No formation of alkylated products **4.62** was observed. NMR analysis of the "acyl chloride" showed only unidentifiable products missing the C14-C15 epoxide.

Surprisingly, treating hindered acid **4.61** with diazomethane at 0°C gave none of the anticipated methyl ester. Allowing the solution to warm slightly (30°C) gave low yields of methyl ester **4.63**. This methyl ester was totally unreactive towards alkylation, and could be recovered in >80% yield (Scheme 4.24).

The methylaluminum bis(2,6-diphenylphenoxide) system reported by Yamamoto *et al*[139] for alkylation of hindered aldehydes was not effective in performing this transformation, resulting in recovery of starting material and/or decomposition.

Scheme 4.24 – Attempted Acyl Halide and Ester Alkylations

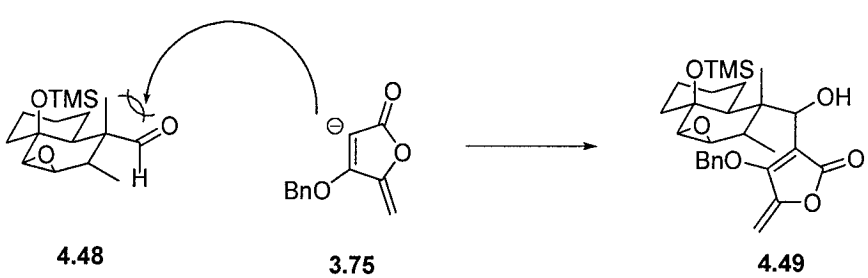


Aldol Condensation With Various Bases

Stymied by the failure of these synthetic attempts, we returned to alkylation of aldehyde **4.48** with tetronate **3.75**. We that envisioned that the either the electrophilic capacity of the aldehyde had to be improved in some way, the nucleophile had to be made more powerful, or a mixture of both.

The aldehyde **4.48**, now with an additional β-substituent, was proving particularly stubborn toward alkylation. With most of the Bürgi-Dunitz trajectories[140] to the aldehyde blocked regardless of conformation, alkylation would require an extremely powerful nucleophile. We envisioned that alkyl magnesium halides might be more suited to the task than alkyllithiums

Scheme 4.25 – Hindered Alkylation

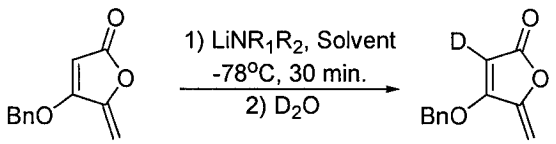


Reaction of the tetronate with isopropyl or methyl magnesium bromide gave no deuterated tetronate after quenching with deuterium oxide. The alkyl magnesium halides were then attempted by deprotonation of tetronate **3.75** followed by transmetallation with $MgBr{\cdot}OEt_2$. This alkylation protocol was not improved over the system that used only LDA. Only small (<20%) amounts of the desired alkylated product were formed after a number of attempts. From the hindered nature of the aldehyde, we reasoned that alkylation would have to occurr at a much higher termperature, to give greater populations of reactive aldehyde conformers. Unfortunately, it was noted that both methyl and benzyl anionic tetronates decomposed quickly above -40°C (*Table 4.1*).

A survey of dialkyl amide base (of the form $(R_1)(R_2)N^-M^+$) literature[141] reveals that the pKa of these bases changes subtly as R_1 and R_2 are modified from one alkyl group to the next. Counterions and steric factors also influence reactivity, and longevity of the resultant enolates. Deuteration studies (*Table 4.1*) revealed that $LiN(iPr)_2$, $LiN(Et)_2$, $LiN(Cy)_2$, LTMP, and LiN(Cy)(iPr) all demonstrated an ability to deprotonate at C2 (observed by quenching with deuterium oxide). However, LiHMDS and KHMDS gave no deprotonation, even after warming to room temperature. The thermal stability of the anions generated by the different amide bases was difficult to track. GC analyses of quenched aliquots were uninformative, but TLC analysis suggested that the cleanest results were obtained with LiN(Cy)(iPr).

A similar study was carried out on aldehyde **4.48**. Treatment of the aldehyde with various bases at low temperature followed by warming led to the following conclusions: $LiN(Et)_2$ and $LiN(Cy)_2$ gave some decomposition at above -20°C, and the aldehyde was completely destroyed at room temperature; LDA and LiN(iPr)(Cy) gave very minimal decomposition (>90% recovery) of the aldehyde even after prolonged exposure (1 hr) at ambient temperature.

Table 4.1 – Tetronate Deuteration Study

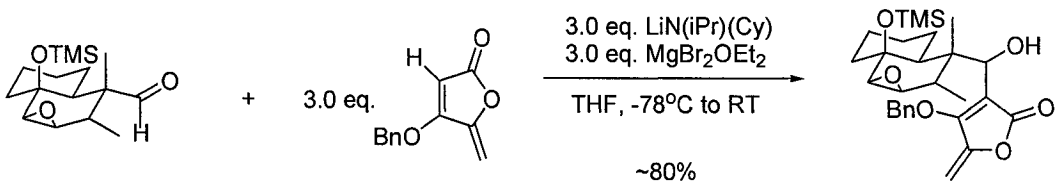


3.75 **4.64**

R1	Solvent	Deuteration (by NMR)	Decomposition upon warming to -40°C
$LiN(Cy)_2$	THF	Yes	Yes
	Et_2O	Yes	Yes
	MTBE	No	Yes
LiN(iPr)(Cy)	THF	Yes	No
	Et_2O	Yes	No
	MTBE	No	Yes
LiHMDS	THF	No	No
KHMDS	THF	No	Yes
$LiN(Et)_2$	THF	No	Yes
LDA	THF	Yes	No

When these factors are taken together, the best chance of success lies with using LiN(iPr)(Cy) as base. We next looked at additives for the alkylation process. $BF_3{\cdot}OEt_2$, $CeCl_3$, and TMS-Cl gave no improvement on the alkylation, with only recovery of the starting aldehyde. However, when 3 equiv. of $MgBr_2{\cdot}OEt_2$ was added (equimolar with tetronate), a noticeable improvement in yield was noted. For example, a flask charged with 10 equiv. of LiN(iPr)(Cy) was cooled to -78°C and a solution of tetronate **3.75** (3 equiv.), the aldehdye **4.48** (1 equiv.), and $MgBr{\cdot}OEt_2$ (3 equiv.) was added. The solution is then gradually allowed to warm to room temperature over 2 hr. Empricially, one immediately notices a difference. With LDA or the other amide bases, such solutions of tetronate turned dark-red or black within 30 minutes. Solutions of tetronate anion produced by this amide/$MgBr_2$ mixture stayed a pale yellow even after warming to near 0°C for several hours. After workup and purification, the alkylated product **4.49** is obtained in > 80% yield (yield estimated by ^{1}H NMR – **3.75** is inseparable from **4.49** chromatographically).

Scheme 4.26 – Optimized Alkylation Conditions



4.48 **3.75** **4.49**

Surprisingly, oxidation of this material with a new batch of IBX (prepared in a manner identical to the previous one)[142] gave only a retro-aldol reaction to produce the aldehyde **4.48** (in 80% recovery) and starting tetronate (Scheme 4.27). To our dismay, several different batches of IBX were tried with the same result. It would appear that a contaminant present (possibly iodosobenzoic acid) in the first batch was carrying out a low-yield oxidation of alkylated products. Other oxidation methods were attempted: Swern/$(COCl)_2$, Swern/TFAA, MnO_2, TPAP(stoichiometric), TPAP/NMO, TEMPO, SO_3·Pyr., PCC, PDC, Jones, $RuCl_3/H_2O$, DDQ, and Ceric Ammonium Nitrate. All oxidation methods failed, leading either to recovery of the aldehyde (retro-aldol) or decomposition. Heating the alcohol in dichloroethane in the presence of IBX generates ketone **4.68** in 32% yield.

This product (**4.68**) was not the cyclisation product we had wanted, but several things could be gleaned by examination of its X-ray structure (Figure 4.7). Most importantly, the crystal structure unambiguously confirms the stereochemistry of C18 methyl group, and it is of the orientation desired. Second, the benzyl ether oxygen is correctly situated directly beneath C15, and shows promise for our cyclisation strategy. Third, is the conformation of the C7-C16 ring – it is distinctly boat-like, which places the alkyl chain possessing the tetronic acid residue in a pseudoaxial position. Lastly, it is worthy to note that the tertiary C13 alcohol has been deprotected. We are unsure of when this silyl ether was cleaved, but it is possible that the deprotection of this alcohol is necessary for the cyclisation to occur.

Scheme 4.27 – Problematic Oxidation

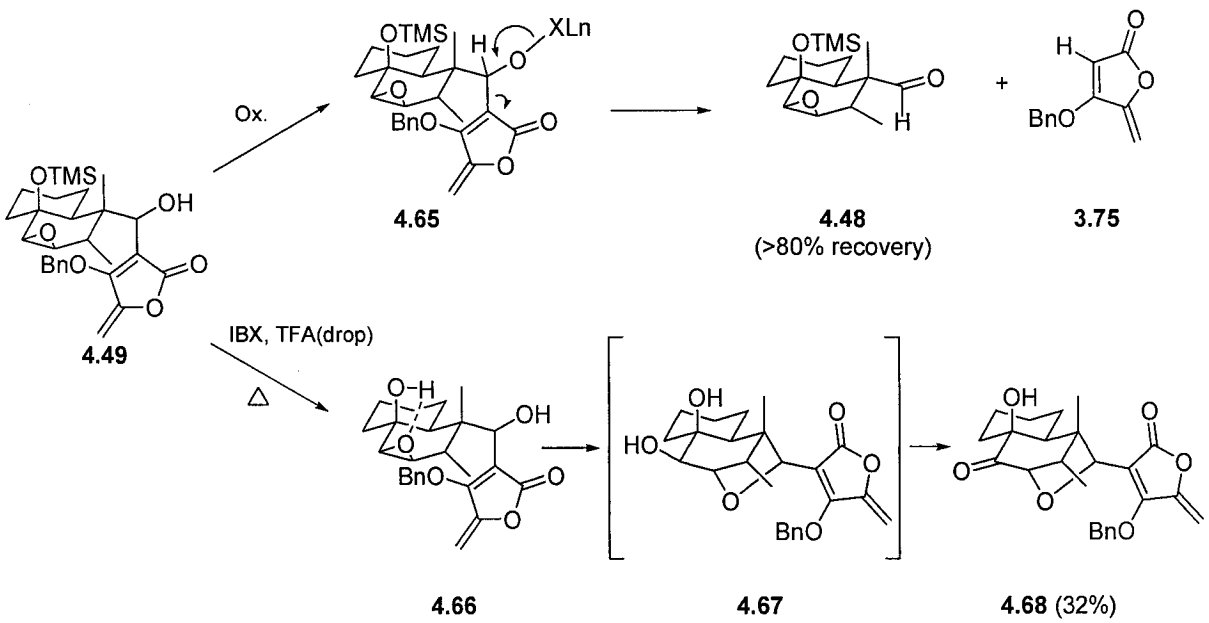
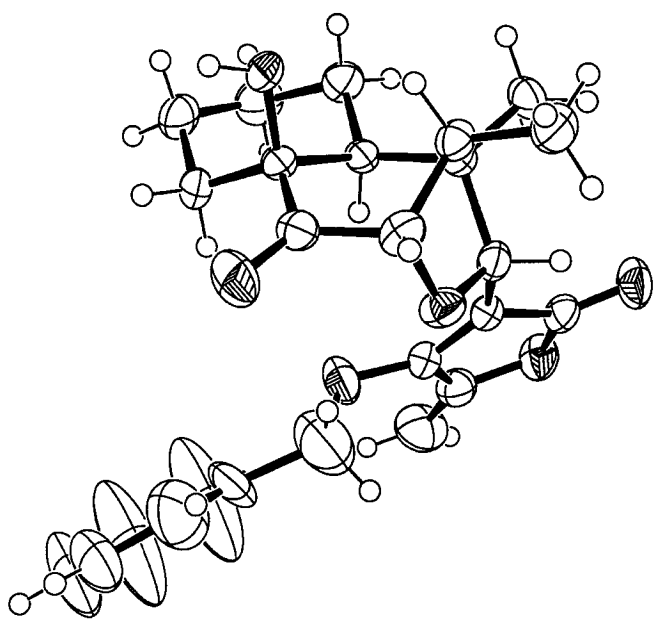


Figure 4.7– ORTEP Plot of 4.68

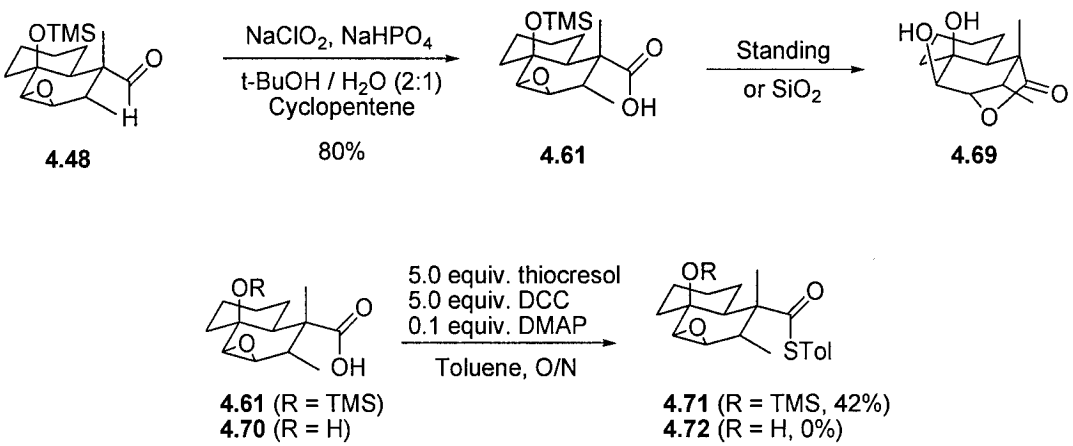


Oxidation Avoidance

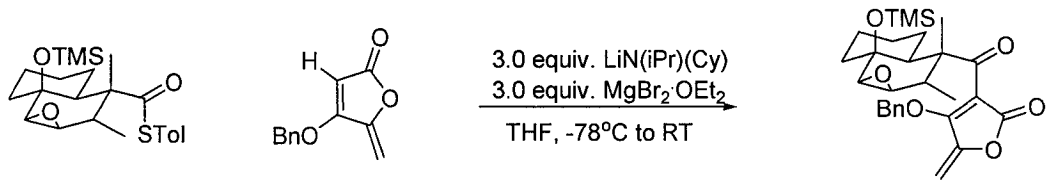
Given new hope, research was continued in vigor. Earlier attempts at alkylating methyl ester **4.63** (Scheme 4.24) had failed, and were tried again with the optimized conditions with no success. Thioester **4.61** was prepared by DCC-coupling free acid **4.61** to thiocresol in 48% yield. No product was obtained with ethanethiol. Lithium alkylation of thioester **4.71** gave similar results to the methyl ester: recovery of starting material. This is surprising, since thioesters are reported to be some 2000-fold more reactive towards nucleophiles than their oxoester cousins.[143] It is worthy to note that unprotected free acid **4.70** does not transesterify with thiocresol, even after prolonged heating at high temperature.

Allowing acid **4.61** to sit for prolonged periods in solution gave 5-exo-tet cyclisation side product **4.69**. Interestingly this side product was not noted in the acid bearing a free alcohol (**4.70**). This result showed promise for our epoxide-opening strategy for the formation of tetrodecamycin's oxepine ring.

Scheme 4.28 – Thioester Synthesis



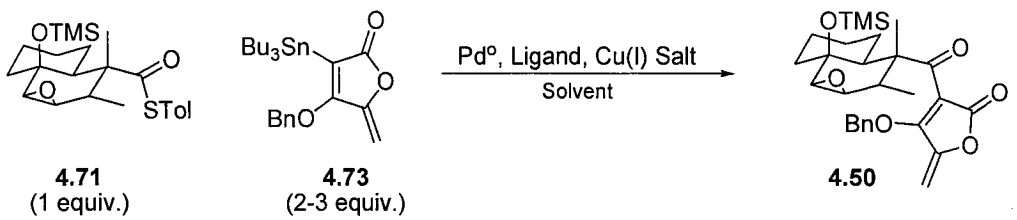
Scheme 3. 28 – Attempted Thioester Alkylation



4.71 **3.75** **4.50** (not observed)

It was noted in 2003 by Liebeskind and co-workers that thioesters and organostannes could be Pd(0) cross-coupled in the presence of Cu(I) carboxylate salts.[144] Numerous attempts were made to cross-couple tetronate **4.73** with thioester **4.71** using the conditions cited in this paper, with no success (Table 4.2). Altering the Pd-source to $Pd(Ph_3)_4$, $PdCl_2(PPh_3)_2$, or *trans*-(Bn)(Cl)$Pd(PPh_3)_2$ (which had been used to cross-couple acyl chlorides and stannyl tetronates by Ley *et al.*) gave none of the desired products.[145] A large percentage of the tetronate was protodestannylated or homodimierized. When $Pd(PhCN)_2(PPh_3)_2$ was used in combination with $AsPh_3$, a small yield (10%) of the coupled ketone **4.50** was observed. Switching the ligand to P(tifluorotolyl)$_3$ gave a 37%, usage of a biaryl ligand[146] gave **4.50** in 33% yield. The best yields of ~50% was obtained using P(furyl)$_3$ on a 10 mg scale. Attempts to scale this reaction were unsuccessful, and gave only 5mg of desired product when numerous attempts were made with 44 mg of thioester **4.71** (which requires 300 mg of stannane **4.73** for 3 equivalents). It should be noted that stoichiometric Pd does not help, and the absense of either Pd or the Cu(I)diphenyl phosphinate prevents the coupling from occurring.

Table 4.2 – Pd(0) Liebeskind Coupling



4.71 (1 equiv.) **4.73** (2-3 equiv.) **4.50**

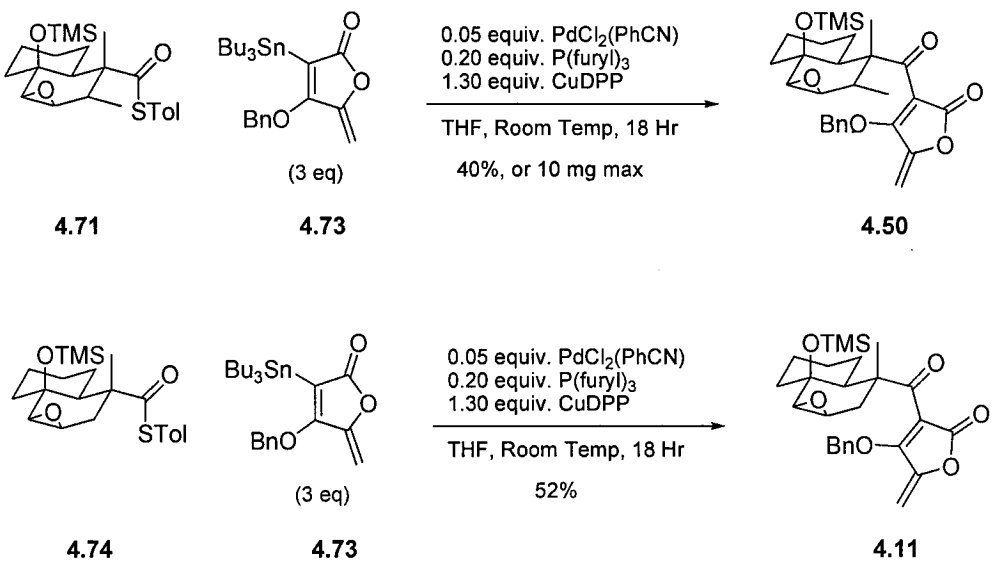
Entry	Scale	Ligand	Pd source	Cu(I)salt	Yield
1	10 mg	None	(1.0 equiv.) $(Bn)(Cl)Pd(PPh_3)_2$	None	0 %
2	5.0 mg	None	(1.0 equiv.) $(Bn)(Cl)Pd(PPh_3)_2$	(2.0 equiv.) CuDPP	0 %
3	5.0 mg	None	None	(2.0 equiv.) CuDPP	0 %
4	5.0 mg	(2.4 equiv.) TFP	(0.3 equiv.) $Pd_2(dba)_3$	(2.0 equiv.) CuTC	0 %
5	5.0 mg	(2.4 equiv.) TFP	(0.3 equiv.) $Pd_2(dba)_3$	(2.0 equiv.) CuDPP	0 %
6	5.0 mg	(2.4 equiv.) $AsPh_3$	(0.3 equiv.) $Pd_2(dba)_3$	(2.0 equiv.) CuDPP	0 %
7	7.0 mg	(1.6 equiv.) $AsPH_3$	(0.4 equiv.) $PdCl_2(PhCN)_2$	(2.0 equiv.) CuDPP	22 %
8	7.0 mg	(0.4 equiv.) $P(PhCF_3)_3$	(0.1 equiv.) $PdCl_2(PhCN)_2$	(1.3 equiv.) CuDPP	37 %
8	7.0 mg	(0.4 equiv.) $P(PhCF_3)(PhPh)$	(0.1 equiv.) $PdCl_2(PhCN)_2$	(1.3 equiv.) CuDPP	33 %
9	11 mg	(0.4 equiv.) TFP	(0.1 equiv.) $PdCl_2(PhCN)_2$	(1.3 equiv.) CuDPP	40 %
10	44 mg	(0.4 equiv.) TFP	(0.1 equiv.) $PdCl_2(PhCN)_2$	(1.3 equiv.) CuDPP	13 %

Knowing the difficulty we had been having in oxidizing alcohol **4.49** to the ketone, we had some concern whether we had formed ketone **4.50** at all in the past. Our fears were abated when the spectroscopic data taken from the ketone generated via this Pd cross

coupling is perfectly coincident with that of the ketone generated by the alkylation-oxidation sequence employed earlier in our synthetic studies.

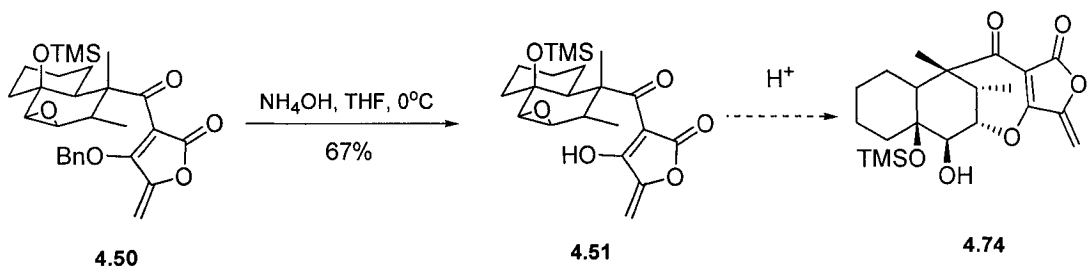
Under the optimized conditions above, the Liebeskind coupling protocol can also be applied to a thioester with no C18 substituent, but the yield is only moderate (52%) here as well. Unlike **4.71**, the less sterically congested **4.74** was less sensitive to scale, and the coupling reaction was successfully performed on a 100 mg scale.

Scheme 4.29 – Liebeskind Coupling



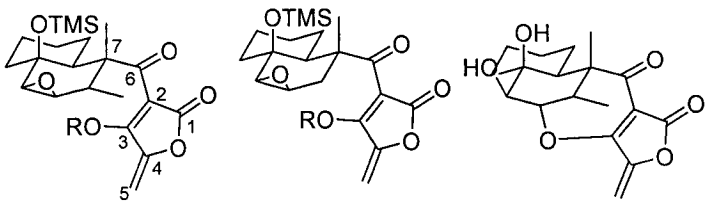
Serendipitously, while attempting to remove the copper salts from the workup of these Pd-catalyzed couplings, treatment of a THF solution containing **4.50** with NH_4OH resulted in hydrolysis of the benzyl ether to give free acid **4.51** in 62% yield. Numerous Lewis acids were attempted here as well, but with no success. (For example, $GaCl_3$, $Cu(OTf)_2$, $Bi(OTf)_3$). Only starting material or decomposition products were noted.

Scheme 4.30 – Hydrolysis and Attempted Cyclisation



4.50 **4.51** **4.74**

Table 4.3 – Comparative ^{13}C NMR Shifts



4.50 (R = Bn)
4.51 (R = H)

4.11 (R = Bn)
4.12 (R = H)

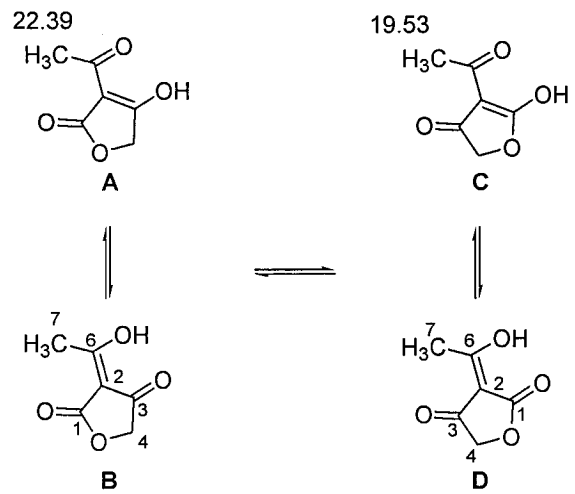
1.1
Tetrodecamycin

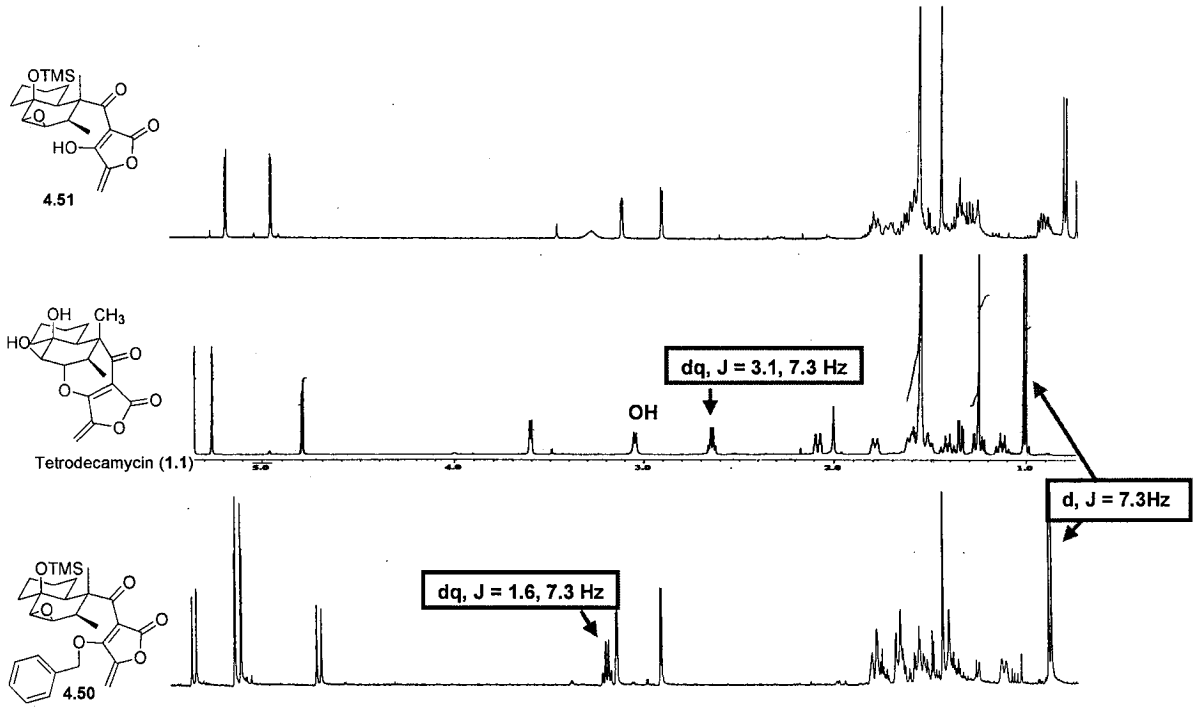
Compound	^{13}C NMR Shifts (δ_{ppm})						
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**
4.50	166.25	108.75	165.07	149.19	94.67	204.55	53.82
4.11	166.24	108.76	165.05	149.19	94.65	204.53	53.81
4.51	165.25	97.77	163.09	148.39	92.09	203.56	51.71
4.12	165.97	95.79	163.95	148.17	92.58	204.18	49.17
1.1	164.64	100.79	164.64	148.39	96.40	194.53	53.10

Upon comparison of ^{13}C NMR spectra of **4.50** (C18 present) and **4.11** (no C18) and their free acids **4.51** and **4.12**, respectively, a few observations can be made. First, the signals in the tetronate portion of the molecule are nearly identical for benzyl ethers **4.50** and **4.11**,

but differ somewhat in the free acids **4.51** and **4.12**. Of key interest is the quaternary carbon at C7. It is well recorded in the literature that alkyl groups adjacent to an enolizable ketone have higher chemical shifts in the keto form.[147] In their study on tetronic acid tautomers, Gelin and Pollet (ref. 38) report that higher shifts correspond to **A** ↔ **B** tautomeric pair (that is primarily in the **A** form), while lower shifts correspond to the **C** ↔ **D** tautomeric pair (primarily in the **D** form) (Figure 4.8). Similar results were reported by Wessels and Steyn in 1978.[148] The two benzyl ethers **4.50** and **4.11** and in tetrodecamycin **(1.1)** itself, the chemical shift of this carbon is nearly identical (δ = ~53ppm). In these compounds, where the tautomeric state is 'locked', C7 resonates at a higher field. The chemical shift for compound **4.12** (δ = 49.17 ppm) is somewhat lower than chemical shift for C18-containing compound **4.51** (δ = 51.71 ppm). While the precise nature of this difference is difficult to ascertain concretely, it can be rationalized that the C18 methyl group may also assist in perturbing the equilibrium further to the thermodynamically favoured **A** ↔ **B** side of the equilibrium (and the form necessary for cyclisation). If indeed, the orientation of the acid residue is as depicted in Figure 4.8 (where the acyl substituent and tetronic acid enol are on the same side), then this may pose a problem for our proposed cyclisation strategy. On the other side of the coin, the higher chemical shift in **4.51** may show a higher proportion of the desired tetronic acid tautomer (eg. **A**) present in solution, regardless of rotamer, and could show promise for our strategy.

Figure 4.8 – ^{13}C NMR shifts of tetronic acid tautomers





The ^{1}H NMR tells a different story, however. Examining the spectra of tetrodecamycin (**1.1**) and benzyl ether **4.50** we see that the doublet of quartet signal from the proton adjacent to C18 methyl group shifts significantly downfield at ~3 ppm. This is likely caused by the anisotropy[149,150] from the orientation of the π-electron[151,152] system present in **1.1**, or from any of those prsent in **4.50**. The analogous proton in **4.51** resonates significantly upfield (<2 ppm), suggesting a lack of nearyby π systems to cause anisotropy, and therefore an unfavourable orientation of the tetronic acid sidechain. Of course, these observations must be regarded with all due skepticism.

Conclusions

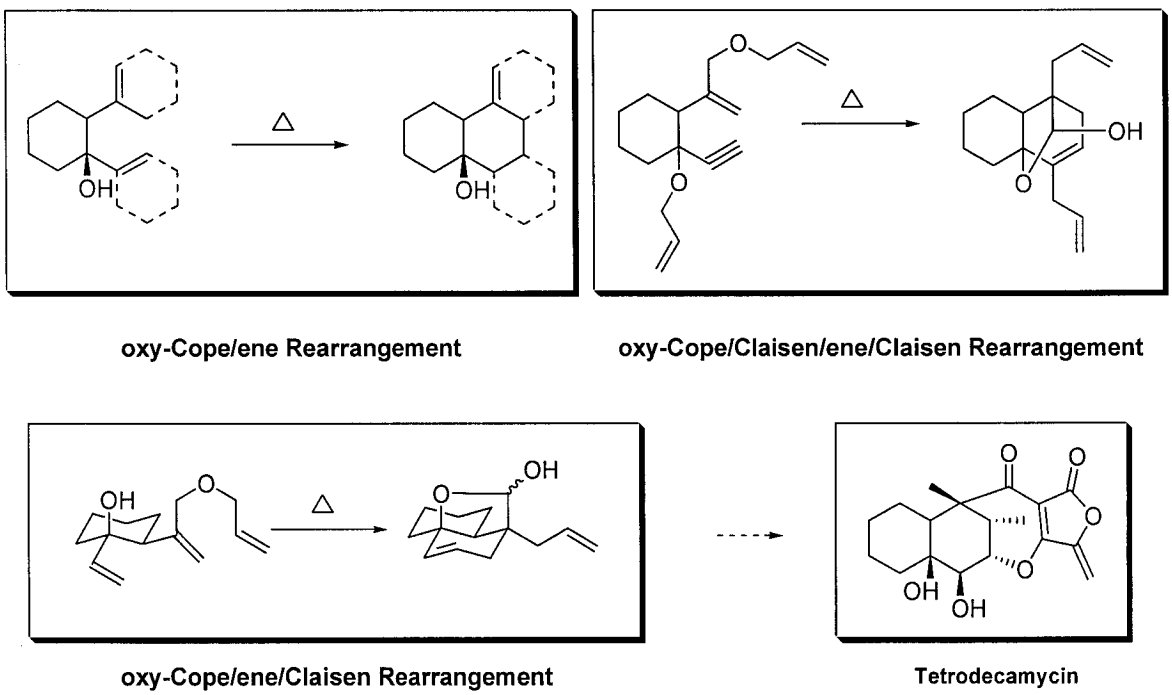
In this last chapter, the decalin core provided by the oxy-Cope/ene/Claisen rearrangement was further modified to produce the core of tetrodecamycin in a highly efficient manner. The conjugate addition chemistry to a hindered allylic carbonate was investigated, and applied to our goals. While aldol condensation between the decalin core and tetronic acid residue met with mixed success, the most predictable outcome was had using Pd(0) catalyzed addition of stannane to thioester. Hydrolysis of the tetronic acid ether furnished a TMS-protected isomer of tetrodecamycin.

5

Summary and Outlook

Summary and Outlook

Figure 5.1 – Novel Rearrangements and Tetrodecamycin



oxy-Cope/ene Rearrangement

oxy-Cope/Claisen/ene/Claisen Rearrangement

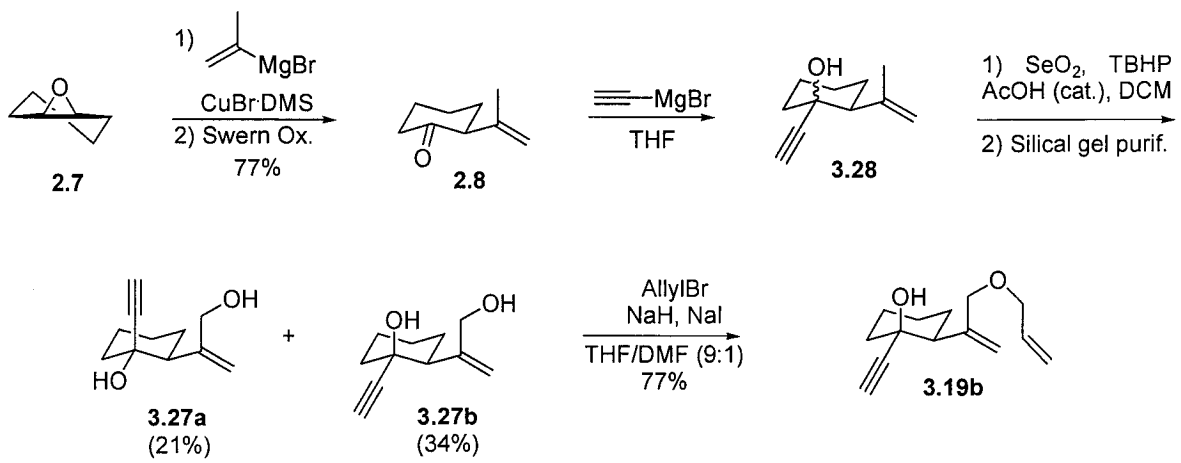
oxy-Cope/ene/Claisen Rearrangement

Tetrodecamycin

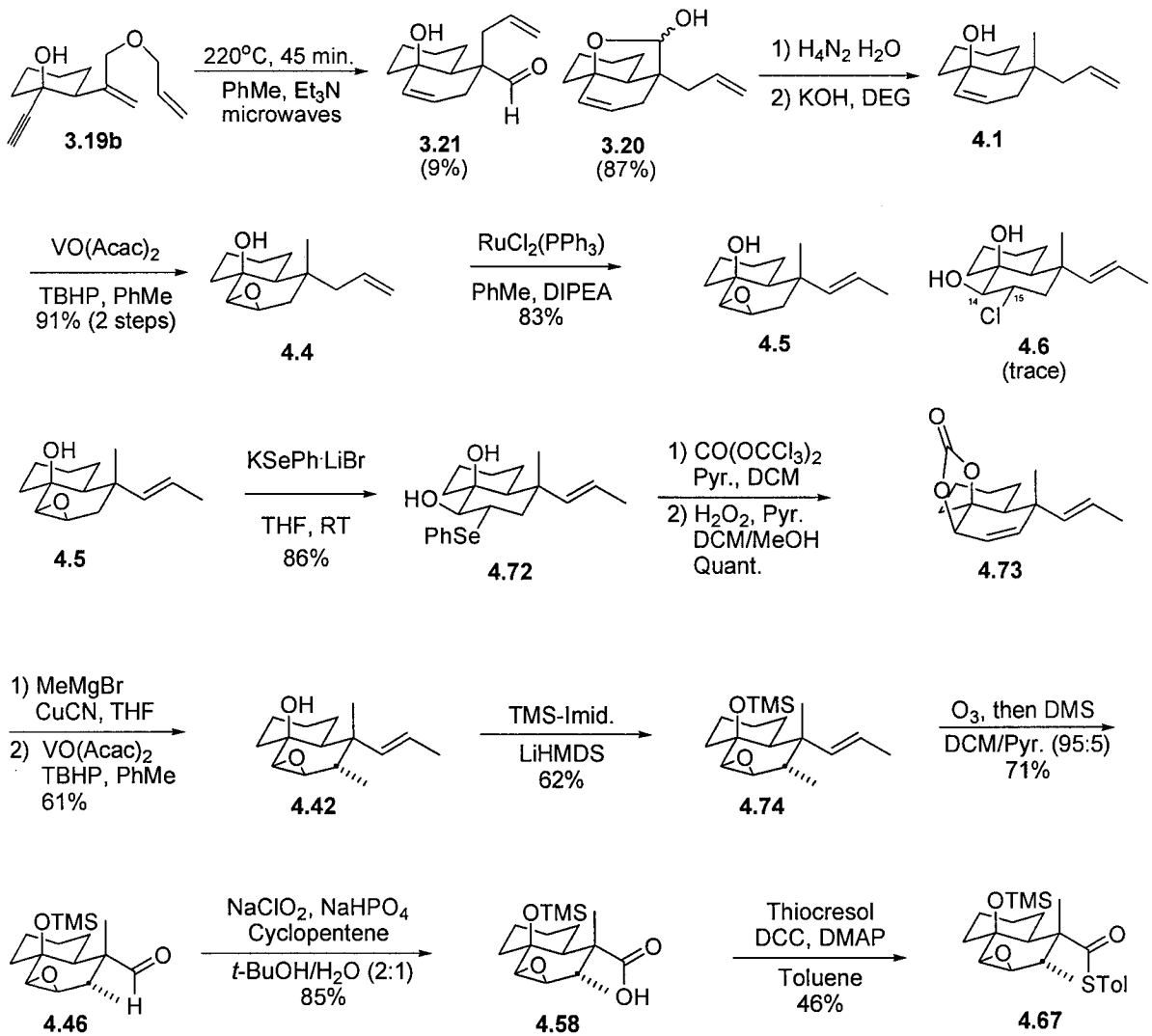
Summary

The studies in our laboratory have resulted in a number of novel rearrangements, including the oxy-Cope/ene, oxy-Cope/ene/Claisen, and oxy-Cope/Claisen/ene/Claisen rearrangements (Figure 5.1) and have opened the door for solutions to a number of otherwise challenging synthetic problems. Specifically, the oxy-Cope/ene has been proven as a powerful tool, providing general access to a number of polycyclic decalins, with tertiary alcohol at ring junction – it has also seen use in our laboratory for the synthesis of natural product arteannuin M.[67] The original rearrangement has been expanded to include a concomitant Claisen rearrangement(s) of enol ethers,[53,70] and was applied to natural product wiedemannic acid.[77] We have demonstrated the development of an efficient synthetic route to a TMS-isomer of natural antibiotic tetrodecamycin, in 20 steps from commecially available cyclohexene oxide. The summarized synthesis (including a few minor step-order changes) is highlighted in (Scheme 5.1 to 5.3). Many lessons have been learned along the way that could have been gleaned in a manner no other than through the exercise of its synthesis.

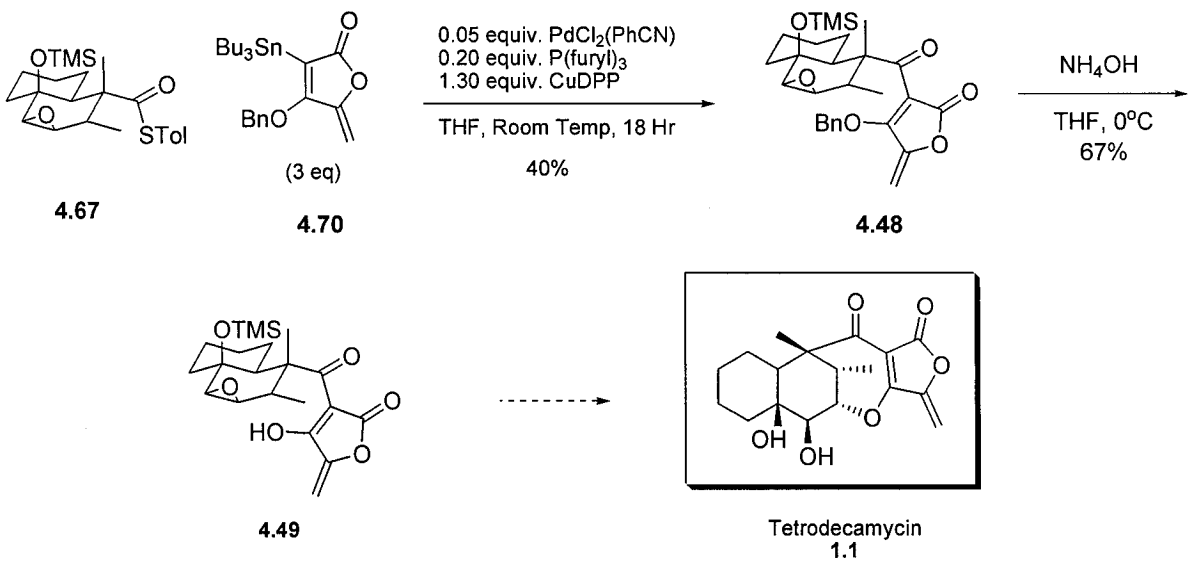
Scheme 5.1 – Summarized Synthetic Route for Tetrodecamycin (I)



Scheme 5.2 – Summarized Synthetic Route for Tetrodecamycin (II)



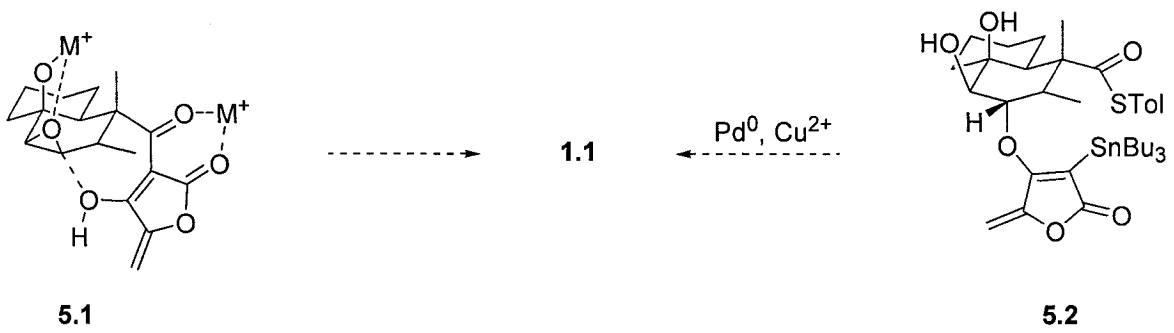
Scheme 5.3 - Summarized Synthetic Route for Tetrodecamycin (III)



Outlook

While it is heartbreaking to leave the synthesis in its current state, we continue to strive toward the completion of this natural product. Amongst several others, a couple plans for the completion are highlighted in Figure 4.9. We envision it may be necessary to tether the diketone present in our tetrodecamycin via some means, and to activate the epoxide simultaneously. To this end, the silyl group must be removed (**5.1**). (Several attempts have been made to remove this hindered silyl ether, but yielded no result.) Alternatively, the Liebeskind coupling could be attempted in reverse (**5.2**), by performing the epoxide opening step first. While this approach was unsuccessful in the past, more work must be done to rule it out entirely.

Figure 4.9 – Proposed Completion of Tetrodecamycin



5.1 **5.2**

For future studies on tetrodecamycin, we hope to investigate a number of key points:

1. Further investigations of what role the *exo*-methylene moiety of tetrodecamycin plays in its biological activity.
2. Whether other structure modifications of either the decalin core or the tetronic acid moiety will induce activity changes.
3. If it is possible to install the exo-methylene unit at a later time in the synthetic route.

Further studies on the newly discovered oxy-Cope/Claisen/ene/Claisen rearrangement are also being carried out in our laboratory:

1. To determine whether this rearrangement be coupled to others in cascade (e.g. Diels-Alder) to give even further structural diversity in a single option.
2. The application of this methodology to other natural products, and the development of other structurally diverse natural product skeletons

Final Comments

The work presented in this thesis has been focused around gaining insight into the nature of tandem reactions, and their usefulness in organic synthesis. Studies were carried out on the rearrangements of 1,2-divinyl cyclohexanols to better understand the complex mechanisms underlying these transformations.

We have thoroughly explored the synthetic chemistry *en route* to tetrodecamycin, and have gained some insight into the complex structure-reactivity relationship present in this class of natural products. We have succesfully elaborated the decalin core provide by the oxy-Cope/ene/Claisen rearrangement to install the 6 contiguous natural centres present in tetrodecamycin; in an entirely stereoselective manner. To this end, our synthetic route also employs Cu conjugate additions, and Pd-catalyzed couplings on extremely hindered systems, and illustrates some of the strengths and limitations of these methodologies. Our study has completed with the synthesis of an isomer of the natural product, and we have every reason to hope for its completion in the near future.

Claims to Original Research

1. Developed the thermal oxy-Cope/ene rearrangement on a variety of substrates, and provided a facile entry to bi- tri- and tetra- cyclic decalin skeletons with alcohol at ring junction.
2. Discovery of a thermal oxy-Cope/Claisen/ene/Claisen rearrangement, and provided rapid access to poly-allylated decalin cores.
3. Extended the oxy-Cope/ene/Claisen rearrangement to encompass formation of decalin cores with unsaturation between C14 and C15
4. Succesfully elaborated the decalin core provided by oxy-Cope/ene/Claisen rearrangement to the trans-decalin framework of tetrodecamycin, including stereospecific synthesis of all 6 contiguous stereocentres in the natural product.
5. Established protocols for coupling tetronic acid resiudes to hindered aldehydes and thioesters using novel synthetic methodologies.
6. Succeeded in constructing a trimethylsilyl-bearing isomer of tetrodecamycin, whose total synthesis completion is well within reach.

Publications From This Work

Warrington, J.; Barriault, L. "Synthesis of the C7-C15 *trans* Decalin Portion of the Natural Antibiotic Tetrodecamycin." *Organic Letters*, **2005**, *7*, 4589

Warrington, J.; Barriault, L.; Yap, G. P. A. "Tandem Oxy-Cope/Transannular Ene Reaction of 1,2-Divinylcyclohexanols." *Organic Letters*, **2000**, *2*, 663

6

Experimental

General Experimental

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

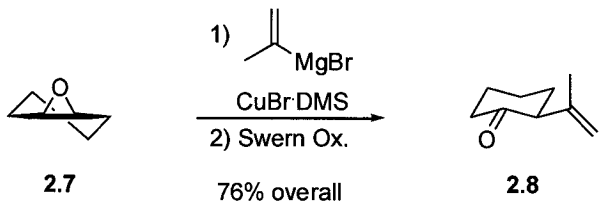
Microwave reactions were preformed using a CEM Model ESP-1500 Plus microwave oven equipped with a pressure monitoring device and an EST-300 Plus fiber optic temperature probe. The reaction vessel was a quartz tube, and in each case was added a carboflon^{TM} to aid in the absorption of microwave radiation.

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

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz, Bruker Avance 500 MHz or Varian INOVA 500 MHz spectrometers in the specified deuterated solvent. IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer. HRMS spectra were obtained using a Kratos Analytical Concept spectrometer, and melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus.

General Microwave Procedure

A clean, dry microwave cell (quartz tube) fitted with two carboflons (a glass coated polymer based microwave absorbant) was charged with a solution of the substrate in appropriate solvent and additives. The solution was degassed by bubbling with argon for 15 minutes. The tube was sealed, fitted with temperature and pressure probes, and placed in the microwave. The temperature was ramped gradually to the final set temperature, and was held there for the time indicated. After cooling, the solution was concentrated and subjected to flash chromatography.

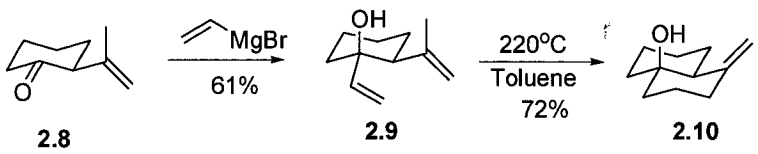


2.7 76% overall **2.8**

2-Isopropenyl-cyclohexanone (2.8). A clean, dry 1L roundbottom flask fitted with a large magnetic stirring bar was flame-dried under vacuum and allowed to cool. The flask was backfilled with Argon, charged with Cu(I)Br dimethyl sulfide (2.6g, 0.013 mol), and dry THF (200 mL). After fitting with a septum and balloon, the slurry was stirred for a few minutes prior to immersion in an isopropanol dry ice bath at -50°C. Once cool, isopropenyl magnesium bromide (0.5 M in THF, 0.250 mol) was added over 20-30 minutes to give the reaction mixture an orange colour. The reaction was allowed to warm to -30°C and cyclohexene oxide (30.4 mL, 0.250 mol) was added dropwise. The mixture was allowed to warm to room temperature over 3 hours at which point it had taken on a dark brown rhum colour. The reaction was quenched with $NH_4Cl_{(sat)}$ (100 mL) at 0°C. Ether (100 mL) was added, and the reaction was stirred rapidly overnight under air to allow oxidation of

remaining copper salts (the initial black emulsion gradually becomes a yellow organic layer over a blue aqueous phase). Extraction of the organic phase (4 x 50 mL Et_2O), drying over $MgSO_4$ and removal of the volatiles gave a yellow oil which was used for the next without further purification.

A clean dry flask under argon fitted with a magnetic stirrer was charged with bulk grade dichloromethane (500 mL) followed by oxalyl chloride (38.3 mL, 0.375 mol). The mixture was cooled to -78°C and DMSO (62 mL, 0.75 mol) was added very slowly. (CAUTION: copious amounts of gas are produced and extra venting must be provided). After 30 minutes, a solution of the crude alcohol (0.250 mol maximum) in dichloromethane (100 mL) was added and allowed to stir. After 2 hr, a white-yellow precipitate had formed, and Et_3N (0.75 mol) was added to give a thick sludge. The slurry was allowed to warm to room temperature, and stirred manually periodically over 1 hr. Water (100 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic (bottom) layers were dried over $MgSO_4$ and concentrated. The crude was redissolved in diethyl ether (150 mL) and filtered to remove the dissolved ammonium salts. After removal of the volatiles, the orange residue was dry packed on silica subjected to flash chromatography. (0 to 15% EtOAc in 3 steps) to give **2.8** as a pale yellow oil. (32.0g, 76%). Spectral data available from Barriault, L.; Warrington, J.; Yap, G. P. *Org. Lett.* **2000**, *2*, 663.



2.8 **2.9** **2.10**

1-Methylene-octahydro-naphthalen-4a-ol (2.10). A solution of the ketone (126 mg, 912 μmol) in THF (9.0 mL, 0.1M) was stirred at 0°C under N_2, and the gringard (1.0M in THF, 2.7 mL, 3 equiv.) was added. After 30 min. stirring, the reaction was quenched with $NH_4Cl_{(aq)}$ (3 mL), extracted with diethyl ether (3 x 5 mL), dried over $MgSO_4$ and concentrated. The crude was subjected to flash chromatography (10% EtOAc in Hexanes) to give **2.9** as a colourless oil. (92 mg, 61%). The oil was redissolved in dry toluene, and subjected to the general microwave procedure. Flash chromatography (10% EtOAc in Hexanes) gave **2.10** as a light yellow oil. (66 mg, 72%).

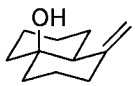
Data for **2.10**

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 4.85 (s, 1H), 4.61 (s, 1H), 2.33-2.27 (m, 1H), 2.10-1.87 (m, 2H), 1.82-1.73 (m, 1H), 1.69-1.50 (m, 6H), 1.52-1.35 (m, 6H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 150.1 (C_4), 108.3 (CH_2), 71.8 (C_4), 49.3 (CH), 39.7 (CH_2), 38.5 (CH_2), 36.5 (CH_2), 25.9 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 21.3 (CH_2).

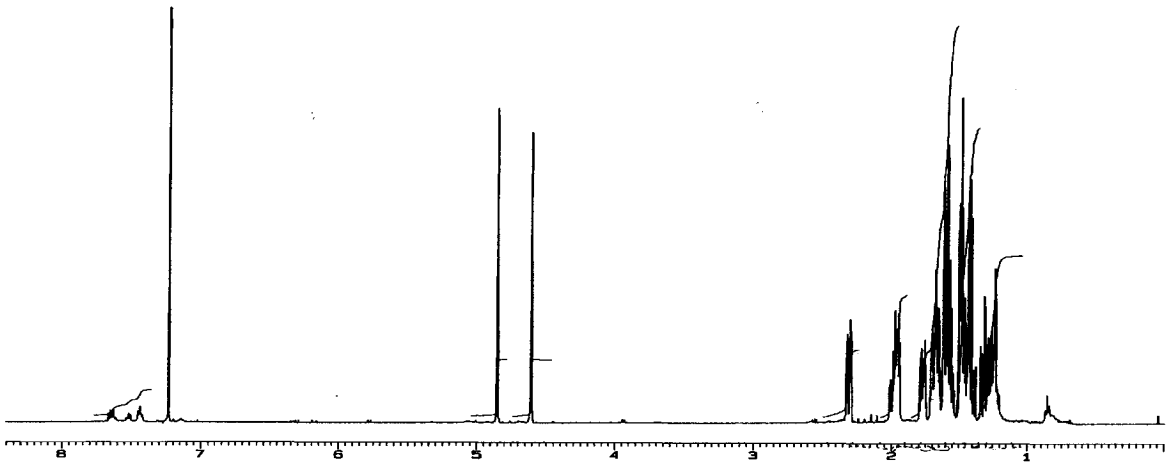
FTIR (neat, cm^{-1}) υ = 3550 (s), 3078 (s), 1447, 1375, 896.

HRMS (EI, m/z) Expected for $C_{11}H_{18}O$ [$(M)^+$]: 166.13576, found: 166.13623 (2.3%)

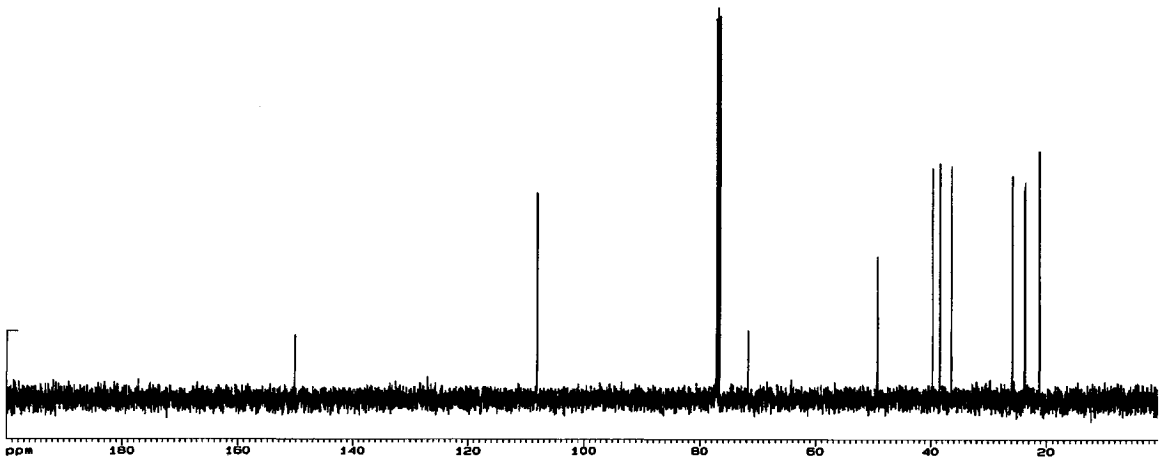


2.10

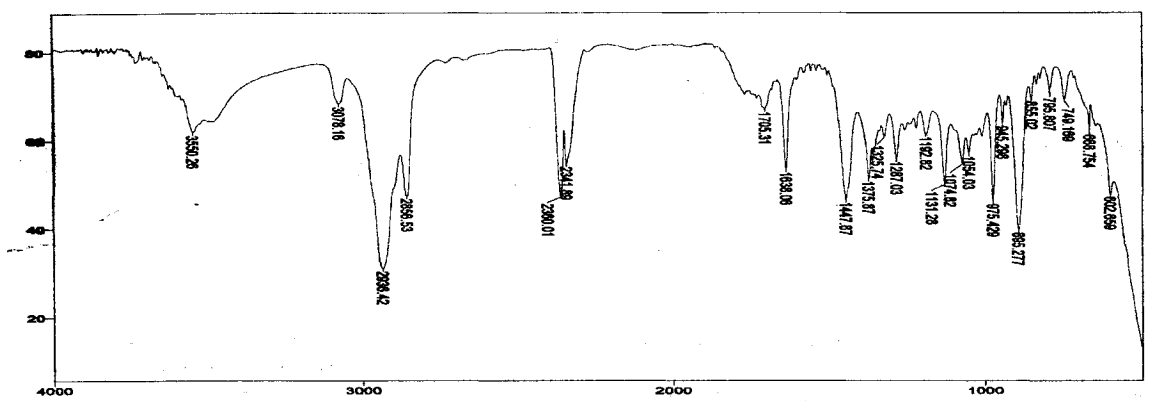
^{1}H NMR ($CDCl_3$, 500 MHz)

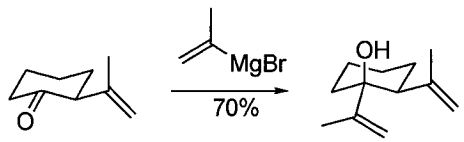


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





2.8 **2.11**

1,2-Diisopropenyl-cyclohexanol (2.11). A solution of the ketone (177 mg, 1.28 mmol) in THF (13 mL, 0.1 M) was stirred at 0°C under Argon. The Grignard (0.5M in THF, 5.10 mL, 2 equiv.) was added, and the reaction was allowed to stir for 45 minutes. The reaction was quenched with $NH_4Cl_{(aq.)}$ (5 mL), and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The oily residue was subjected to flash chromatography (10% EtOAc in Hexanes) to afford **2.11** as a light yellow oil. (144 mg, 70%)

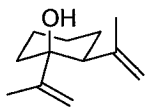
Data for **2.11**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 4.97 (dd, J = 0.8, 1.7 Hz, 1H), 4.82 (ddd, J = 3.1, 1.5, 1.7 Hz, 1H), 4.76 (ddd, J = 3.1, 1.3, 1.5, Hz, 1H), 4.72 (dd, J = 0.9, 0.9 Hz, 1H), 2.28 (dd, J = 3.5, 12.6 Hz, 1H), 1.82-1.76 (m, 1H), 1.77 (dd, J =, 0.6, 1.3 Hz, 3H), 1.76-1.70 (m, 2H), 1.69 (dd, J = 0.8, 1.5 Hz, 3H), 1.68-1.60 (m, 2H), 1.52-1.41 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 150.9 (C_4), 148.3 (C_4), 111.5 (CH_2), 109.3 (CH_2), 75.0 (C_4), 49.5 (CH), 36.5 (CH_2), 27.5 (CH_2), 26.0 (CH_2), 24.2 (CH_3), 21.1 (CH_2), 19.9 (CH_3)

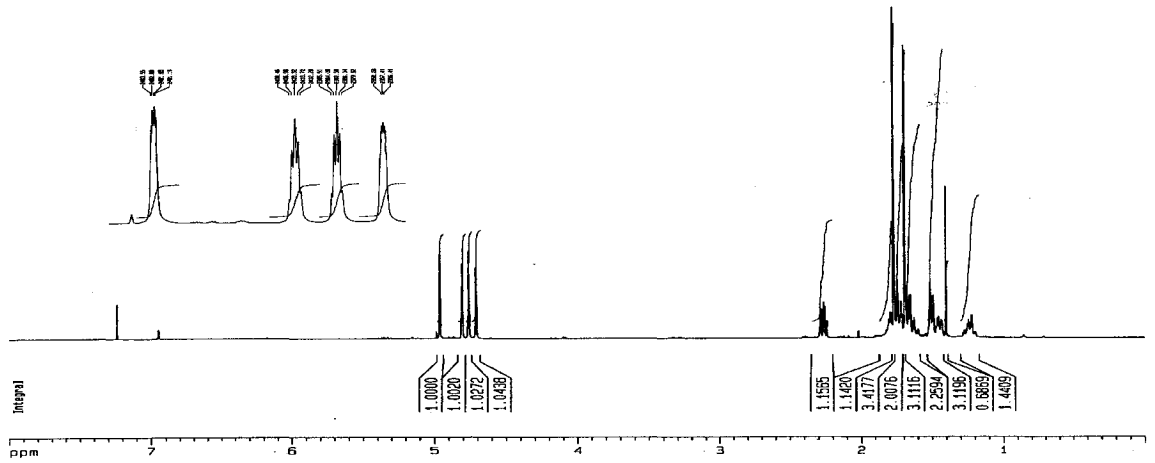
FTIR (neat, cm^{-1}) υ = 3540 (s), 2935 (s), 2855, 1638, 1447, 975, 893

HRMS (EI, m/z) Expected for $C_{12}H_{20}O$ [$(M)^+$]: 180.15141, found: 180.15091 (14.2%)

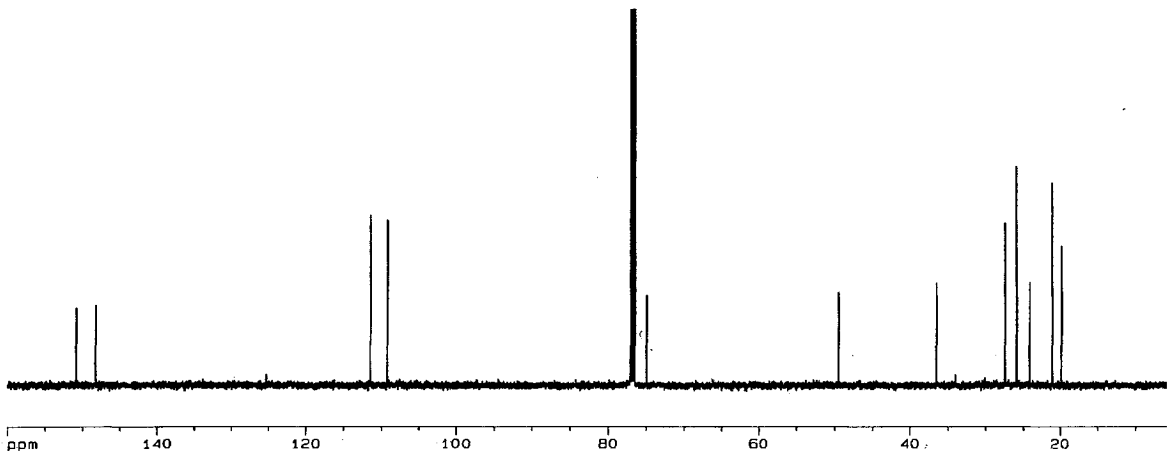


2.11

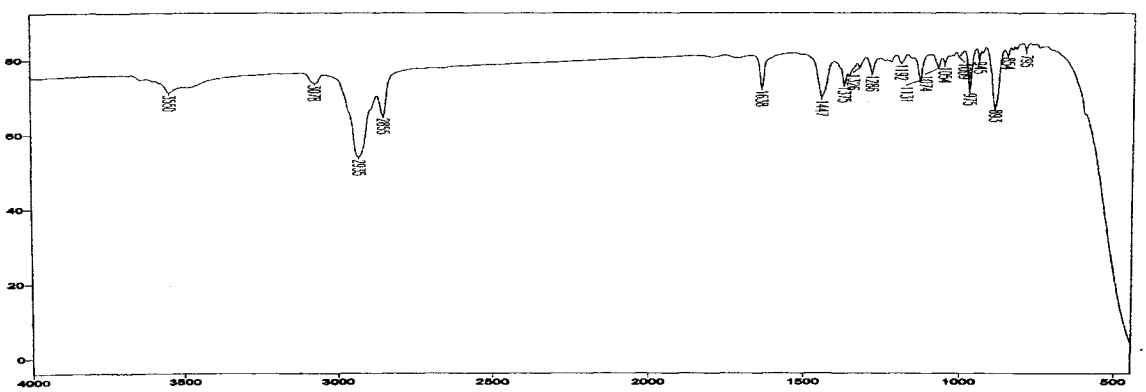
^{1}H NMR ($CDCl_3$, 500 MHz)

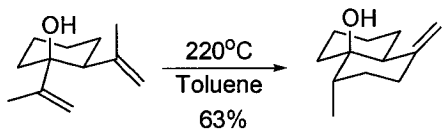


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





2.11 **2.12**

4-Methyl-1-methylene-octahydro-naphthalen-4a-ol (2.12). A solution of the olefin **2.11** (42 mg, 233 μmol) in toluene (17 mL) was heated in the microwave under the standard procedure. Ramp time: 15 minutes. Final temp: 220°C. Hold time: 45 min. Flash chromatography (15% EtOAc/Hexanes) gave **2.12** as a colourless oil (36mg, 85%).

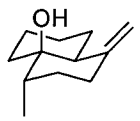
Data for **2.12**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 4.85 (dd, J = 3.2, 1.5 Hz, 1H), 4.62 (br d, J = 1.1 Hz), 2.28 (ddd, J = 12.8, 4.3, 2.3 Hz, 1H), 2.25-1.9 (m, 2H), 1.85-1.21 (m, 13H + grease), 0.85 (d, J = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 150.1 (C_4), 108.3 (CH_2), 73.1 (C_4), 49.6 (CH), 41.5 (CH), 36.2 (CH_2), 35.0 (CH_2), 32.7 (CH_2), 25.6 (CH_2), 24.0 (CH_2), 21.4 (CH_2), 14.3 (CH_3).

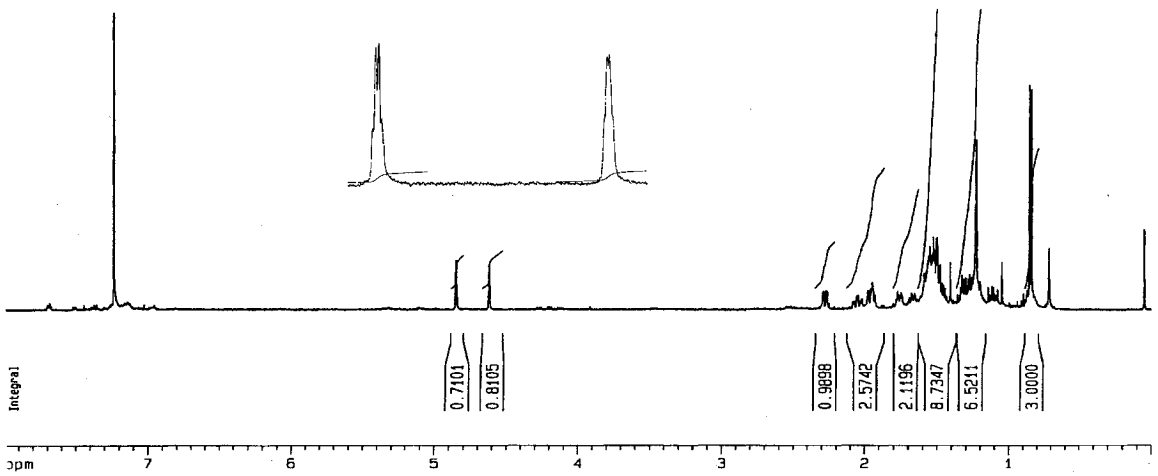
FTIR (neat, cm^{-1}) υ = 3564 (br), 2926 (s), 2853 (s), 1460 (m), 955, 945

HRMS (EI, m/z) Expected for $C_{12}H_{20}O$ [$(M)^+$]: 180.1514, found: 180.1512 (28.6%)

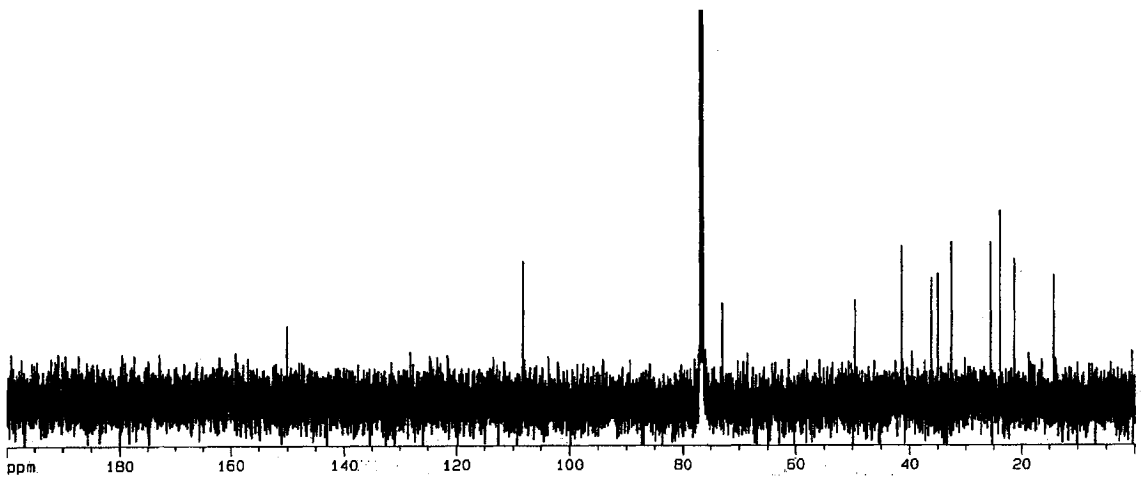


2.12

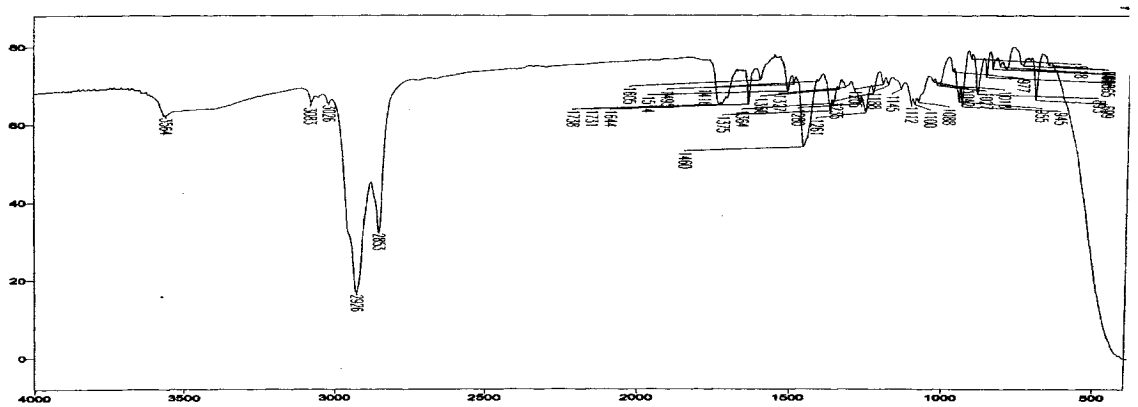
^{1}H NMR ($CDCl_3$, 500 MHz)

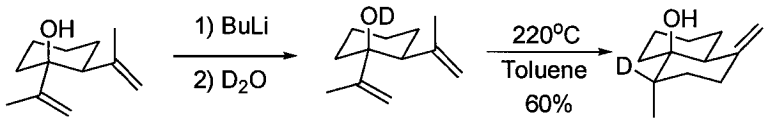


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





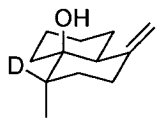
2.12 **2.13** **2.14**

4-Deuterio-4-methyl-1-methylene-octahydro-naphthalen-4a-ol (2.14). A solution of alcohol **2.12** (36 mg, 200 μmol) in THF (3 mL) was stirred at -78°C, and BuLi (2.7M in Pentane, 148 μL, 2 equiv.) was added via syringe. The mixture was stirred for 5 min, and quenched with D_2O (1 mL). The organic layer was extracted with ether (2 x 2 mL), dried over $MgSO_4$ and concentrated. The crude was redissolved in toluene (4 mL) and placed in a sealed tube. The solution was heated to 220°C (wax bath) for 4 hr. After cooling, the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (15% EtOAc in Hexanes) to give **2.14** as a colourless oil (21 mg, 60%)

Data for **2.14**:

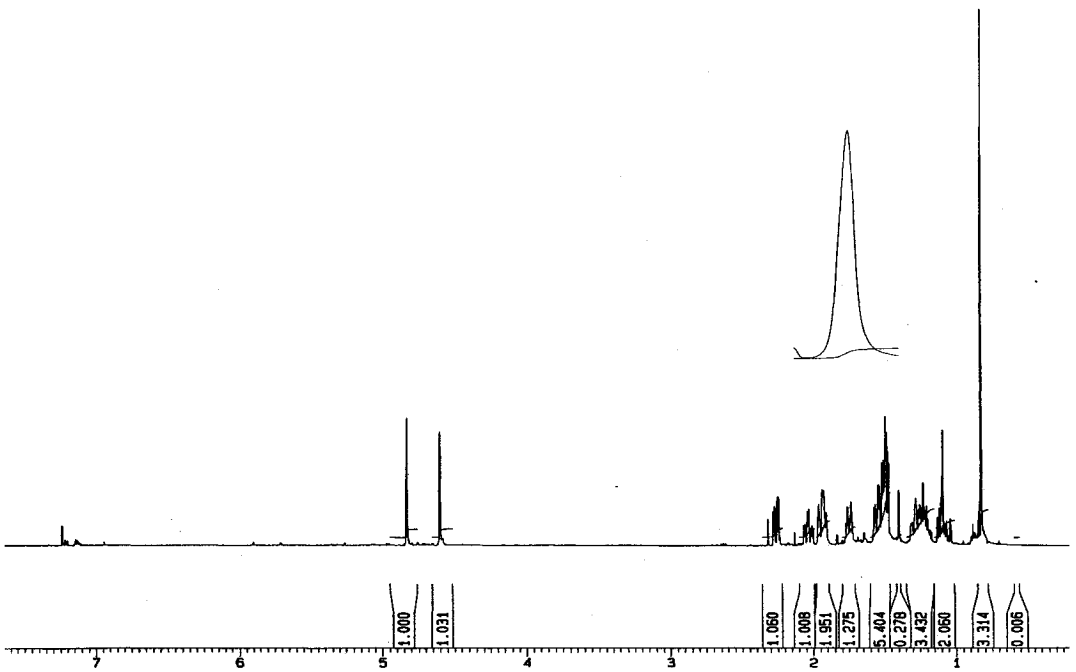
^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 4.82 (s, 1H), 4.62 (s, 1H), 2.28-2.22 (m, 1H), 2.25-2.20 (m, 1H), 1.85-1.83 (m, 2H), 1.80-1.72 (m, 1H), 1.69-1.42 (m, 5H), 1.32-1.13 (m, 6H), 0.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 150.2 (C_4), 108.3 (CH_2), 73.1 (C_4), 49.7 (CH), 36.3 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 32.8 (CH_2), 25.8 (CH_2), 24.0 (CH_2), 21.5 (CH_2), 14.3 (CH_3)

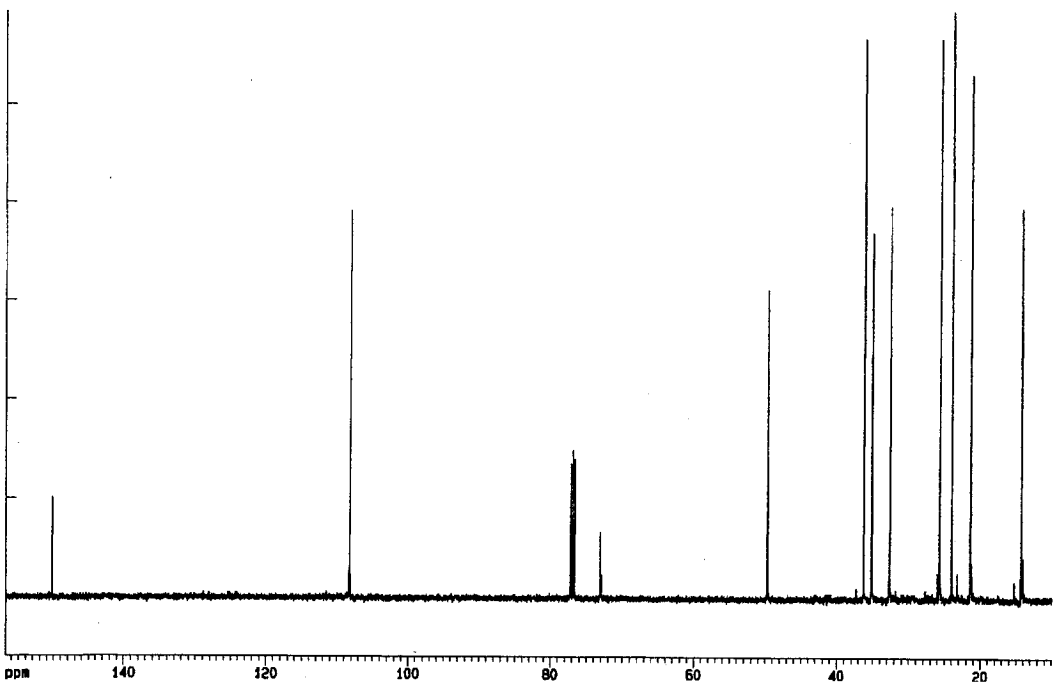


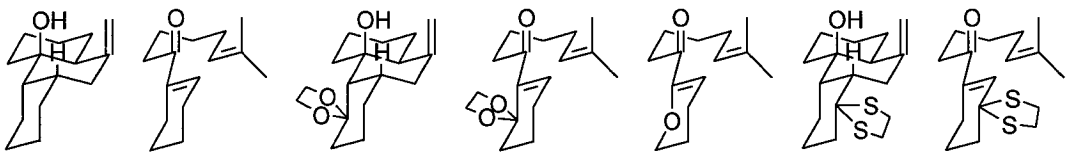
2.14

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



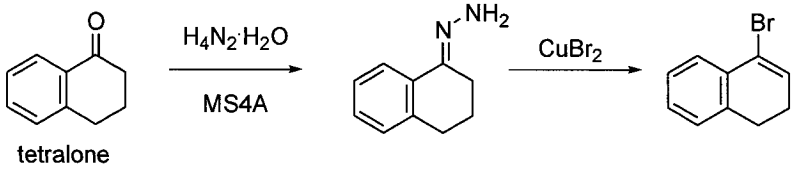
^{13}C NMR ($CDCl_3$, 125 MHz)





2.16 **2.17** **2.19** **2.20** **2.23** **2.25** **2.26**

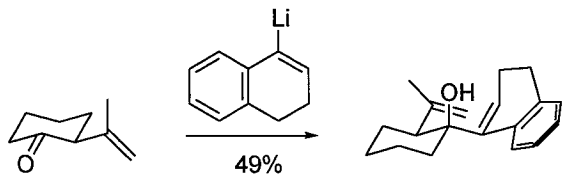
For compounds **2.16** to **2.26**, please refer to: (a) Deon, D., M. Sc. Thesis, University of Ottawa, **2001**, Ottawa, ON. (b) Barriault, L.; Warrington, J. Yap, G. P. *Org. Lett.* **2000**, *2*, 663.



tetralone

Preparation of 4-Bromo-1,2-dihydro-naphthalene. A clean 250 mL roundbottom flask was charged with MS4Å (14g) and flame-dried under high vacuum. After flushing with nitrogen, MeOH (100 mL) was added, followed by hydrazine hydrate (13.2 mL, 20 equiv.). After stirring for 5 min, a MeOH solution of α-Tetralone (1.27 mL, 1 equiv. in 5 mL MeOH) was introduced dropwise and the mixture was stirred for 2 hr. Molecular sieves were filtered off and washed with ether. The filtrate was concentrated under reduced pressure and the excess hydrazine was further removed from the residue under vacuum (7-8 Torr) with gentle heating (30 °C) and stirring over 20 min to give the crude hydrazide.

A mixture of THF (100 mL) and *t*-BuOH (4.0 mL, 3 equiv.) was stirred at 0°C under argon. n-BuLi (2.9 M in Hexanes, 14.1 mL) was added dropwise, and the mixture was stirred for 5 min. Copper (II) bromide (18g, 6 equiv.) was added to the mixture as a single portion. The cooling bath was removed and stirring was continued for 20 min. to give a dark brown mixture. A THF (10 mL) solution of crude hydrazide (14 mmol max) was added dropwise. Gentle evolution of nitrogen was observed during the addition. After stirring for 3 hr, the reaction was quenched with $NH_4Cl/NH_4OH_{(aq)}$ (8:1, 20 mL). The organic materials were extracted with DCM (4 x 50 mL), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (100% hexanes) to give 4-Bromo-1,2-dihydro-naphthalene (1.76g, 62%). Original reference: Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron.* **1997**, *53*, 557.



2.8 **2.26**

1-(3,4-Dihydro-naphthalen-1-yl)-2-isopropenyl-cyclohexanol (2.26). A flame-dried 50 mL roundbottom flask fitted with a magnetic stirbar was charged with a solution of 4-bromo-1,2-dihydro-naphthalene (301mg, 1.44 mmol, 1.3 equiv.) in THF (10 mL) and cooled to -78°C. *t*-BuLi (1.7M, 1.70 mL, 2.6 equiv.) was added dropwise, and the reaction was allowed to stir for 10 minutes. A pre-cooled solution of **2.8** (154 mg, 1.11 mmol, 1 equiv.) in THF (2 mL) was canulated, and the reaction was allowed to stir for 30 min. The cold bath was removed, and the reaction was allowed to further warm for another 5 minutes. The reaction was quenched by addition of $NH_4Cl_{(sat.)}$ and extracted with ether. The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (0 to 10% EtOAc in Hexanes) to give **2.26** as a light yellow powder (147 mg, 49%).

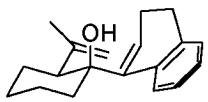
Data for **2.26**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.68 (d, J = 7.9 Hz, 1H), 7.21-7.05 (m, 3H), 6.39 (t, J = 4.9 Hz, 1H), 4.85 (m, 1H), 4.73 (br s, 1H), 2.97 (dd, J = 3.5, 12.4 Hz, 1H), 2.70-2.53 (m, 2H), 2.26-2.20 (m, 1H), 2.19-2.13 (m, 2H), 2.05 (s, 1H), 1.85-1.70 (m, 4H), 1.60-1.47 (m, 2H), 1.40 (br s, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 148.6 (C_4), 143.1 (C_4), 138.2 (C_4), 134.1 (C_4), 128.0 (CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 124.9 (CH), 112.1 (CH_2), 73.8 (C_4), 49.4 (CH), 37.5 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 24.9 (CH_3), 23.1 (CH_2), 21.8 (CH_2)

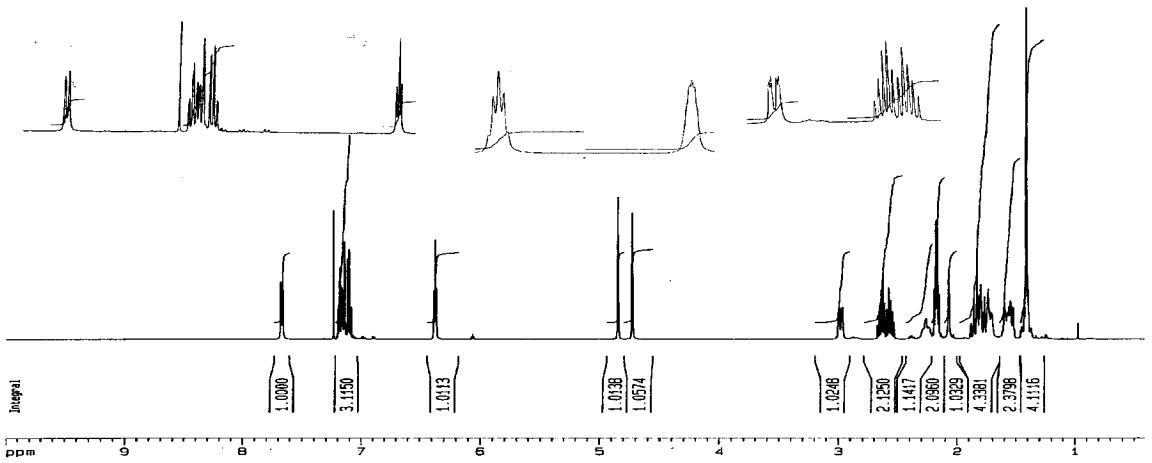
FTIR (neat, cm^{-1}) υ = 3536 (br), 2931 (s), 2856 (m), 2830 (m), 1633 (m), 1481 (s), 1447 (s), 981 (m), 763 (m), 739 (m).

HRMS (EI, m/z) Expected for $C_{19}H_{24}O$ [$(M)^+$]: 268.18272, found: 268.18405 (23.9%)

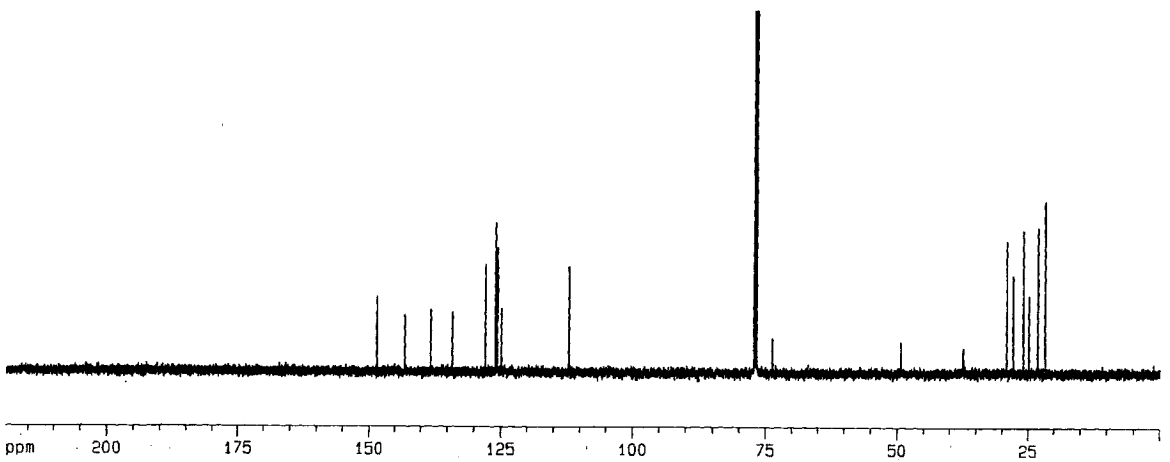


2.26

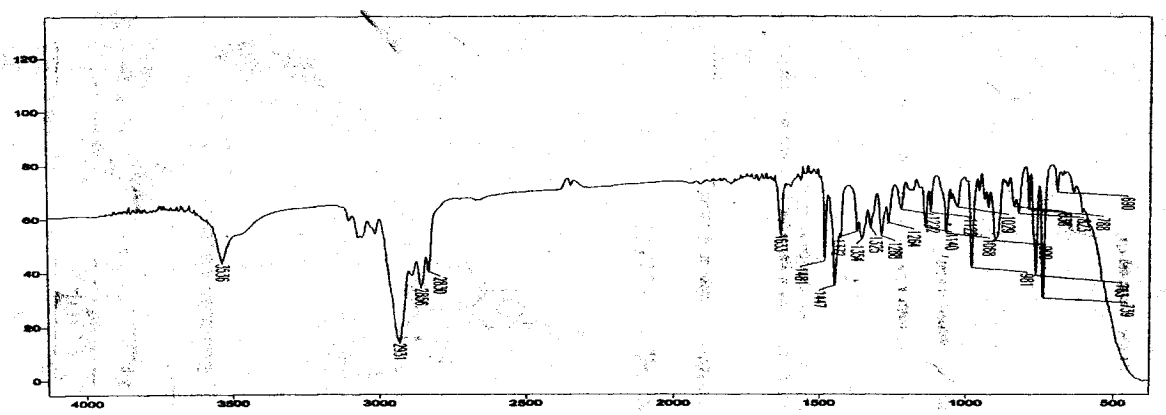
^{1}H NMR ($CDCl_3$, 500 MHz)

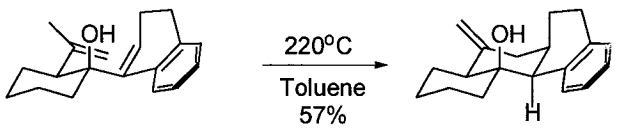


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





2.26 **2.27**

8-Methylene-5,6a,7,8,8a,9,10,11,12,12b-decahydro-6H-benzo[c]phenanthren-12a-ol (2.27). A solution of **2.26** (50.0 mg, 187 umol) in toluene (17 mL) and DBU (500 µL, 20 equiv.) was subjected to the general microwave procedure. Final temp: 220°C, ramp time: 15 min., hold time: 120 min. Flash chromatography (0 to 25% EtOAc/Hexanes) gave **2.27** as a white solid (32.0mg, 64%).

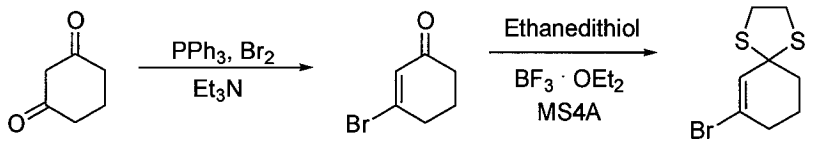
Data for **2.27**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = (mixture with phthalates) 7.10-7.05 (m, 4H), 4.90 (m, 1H), 4.77 (br s, 1H) 2.98 (m, 1H), 2.32-2.25 (m, 1H), 2.23 (dd, J = 2.1, 12.9 Hz, 1H), 2.18-2.08 (m, 2H), 1.82-1.72 (m, 2H), 1.70-1.43 (m, 8H)

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

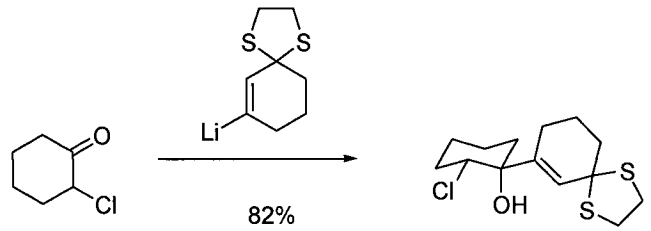
FTIR (neat, cm^{-1}) υ = 3494, 3066, 3025, 2933, 1607, 1454, 1326, 1293, 757

HRMS (EI, m/z) Expected for $C_{19}H_{24}O$ [$(M)^+$]: 268.18272, found: 268.1811 (2.2 %)



Preparation of 7-Bromo-1,4-dithia-spiro[4.5]dec-6-ene. A clean 500 mL roundbottom flask was charged with a solution of triphenyl phosphine (37.0g, 1.6 equiv.) in benzene (240 mL) and was cooled 0°C under argon. A solution of bromine (7.40 mL, 1.6 equiv.) in benzene (30 mL) was added via dropping funnel over 1.5 hr. After the addition was complete, a solution of 1,3-cyclohexanedione (10.0g, 90 mmol, 1.0 equiv.) in dichloromethane (40 mL) (insoluble in benzene) was added over 1 hr. The reaction was allowed to stir overnight while warming to room temperature. In the morning, the entire reaction mixture was filtered through a pad of celite, washed with H_2O (2 x 30 mL), Brine (2 x 50 mL), dried over $MgSO_4$ and concentrated carefully (CAUTION: Product is volatile! Do not use excessive heat on the rotovap.) The residue was subjected to flash chromatography (50% Et_2O in Pet. Ether), with careful concentration to give 3-bromo-cyclohex-2-ene-1-one (9.2g, 62%). Original reference: Arain, M. F.; Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *Aus. J. Chem.* **1988**, *41*, 505.

A solution of bromoketone (2.67g, 15.3 mmol) in dichloromethane (100 mL) was stirred at room temperature, and MS4Å (4.5 g) was added, followed by ethanedithiol (1.411 mL, 1.1 equiv.) and BF_3OEt_2 (970 uL, 0.3 equiv.). The reaction was allowed to stir for 3 hr, prior to filtration and washing with aqueous $NaHCO_{3(sat.)}$ (3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude was subjected to flash chromatography (5 % Et_2O in Pet. Ether) gave 7-Bromo-1,4-dithia-spiro[4.5]dec-6-ene (3.25g, 85%) as a stinky yellow liquid which solified upon standing in the freezer. Original reference: Swenton, J. S.; Shih, C. *J. Org. Chem.* **1982**, *47*, 2825.



2.28 **2.29**

2-Chloro-1-(1,4-dithia-spiro[4.5]dec-6-en-7-yl)-cyclohexanol (2.29). A solution of 7-Bromo-1,4-dithia-spiro[4.5]dec-6-ene (704 mg, 2.82 mmol, 1.1 equiv.) in dry THF (30 mL) under argon was cooled to -78°C and t-BuLi (1.20M, 4.70mL, 2.2 equiv.) was added. After stirring for 10 minutes the solution had assumed a green-brown colour, and 2-chloro-cyclohexanone (340 mg, 1.0 equiv.) was added as a pre-cooled THF solution (3 mL). After stirring for 10 minutes, the reaction was quenched with aqueous $NH_4Cl_{(sat.)}$ (5 mL) and extracted with ether (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude was subjected to flash chromatography (20% EtOAc in Hexanes) to give **2.29** (640 mg, 82%) as a clear colourless oil that solidified upon standing in the freezer.

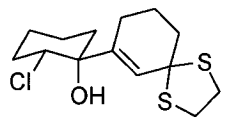
Data for **2.29**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 6.01 (s, 1H), 4.09 (dd, J = 5.9, 11.1 Hz, 1H), 3.47-3.22 (m, 4H), 2.23-1.35 (m, 15H + grease)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 142.6 (C_4), 126.6 (CH), 75.6 (C_4), 65.4 (CH), 65.3 (C_4), 40.8 (CH_2), 40.0 (CH_2), 39.8 (CH_2), 36.1 (CH_2), 32.0 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 22.9 (CH_2), 20.3 (CH_2)

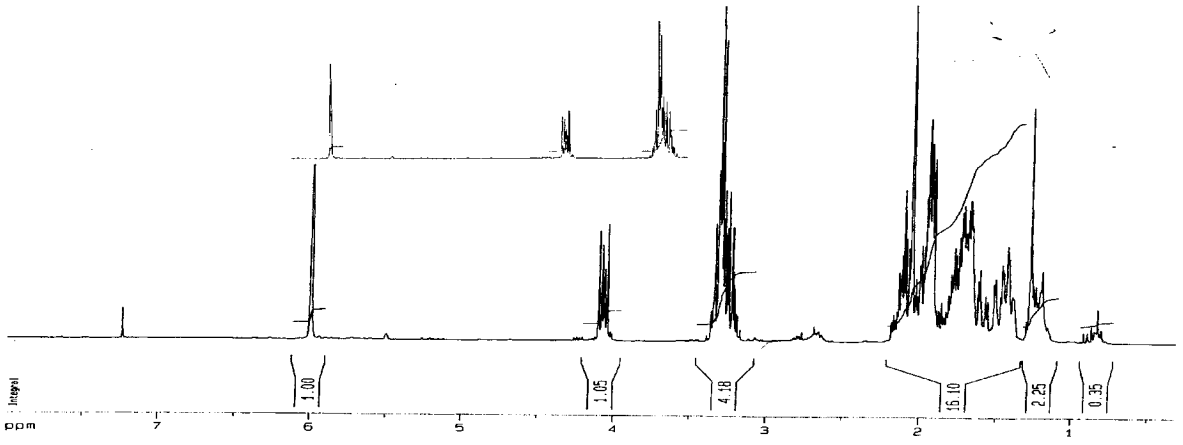
FTIR (neat, cm^{-1}) υ = 3467 (br s), 2935 (s), 2858 (s), 1445 (s), 1276 (s), 999, 985, 749.

HRMS (EI, m/z) Expected for $C_{14}H_{21}S_2ClO$ [$(M)^+$]: 304.07223, found: 304.07237 (18.9 %), 305.07473 (3.6%)

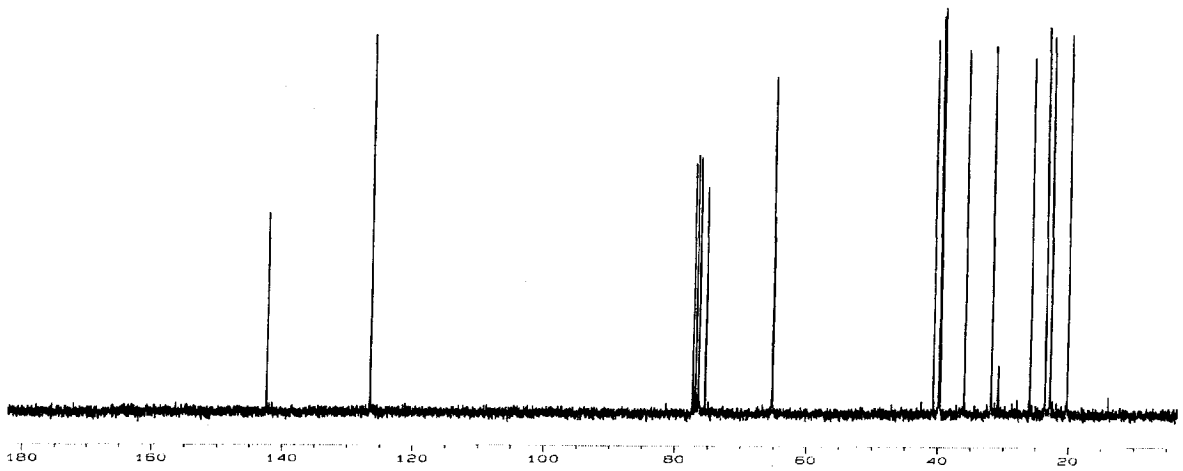


2.29

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



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



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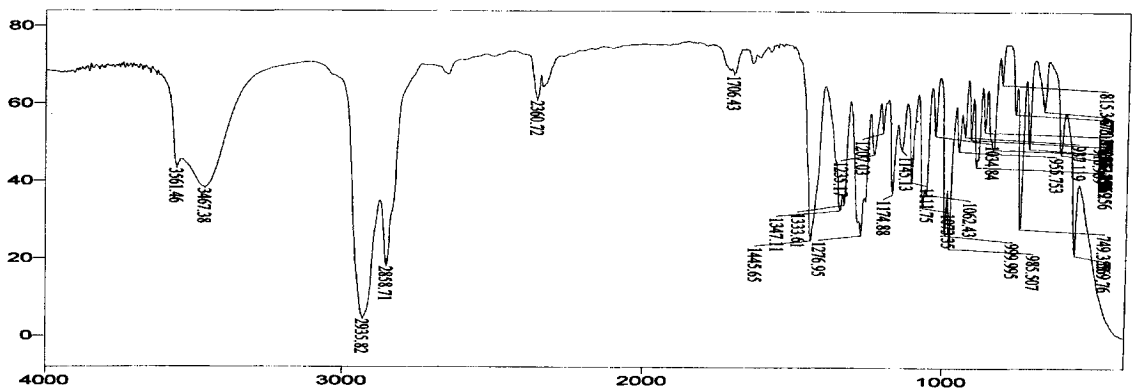
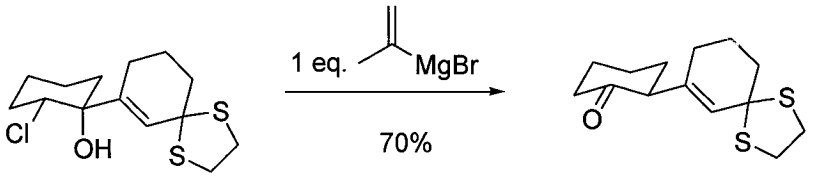




2.29 **2.30**

2-(1,4-Dithia-spiro[4.5]dec-6-en-7-yl)-cyclohexanone (2.30). A solution of chlorohydrin **2.29** (612 mg, 2.01 mmol) in THF (30 mL) was stirred at room temperature, and isopropenyl magnesium bromie (0.5M, 1.05 equiv.) was added, dropwise. The solution was heated to reflux for 2 hr, and allowed to cool. The reaction was quenched with aqueous $NH_4Cl_{(sat.)}$ (5 mL), extracted with ether (3 x 10 mL), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (0 to 10% EtOAc in Hexanes) to give **2.30** as a light yellow oil (377 mg, 70%).

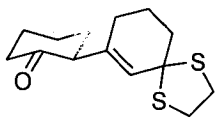
Data for **2.30**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.51 (s, 1H), 3.42-3.25 (m, 4H), 2.85 (dd, J = 5.0, 11.4 Hz, 1H), 2.42-1.51 (m, 14H + grease).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 210.1 (C_4), 131.3 (C_4), 128.3 (CH), 65.4 (C_4), 58.0 (CH), 42.0 (CH_2), 41.2 (CH_2), 39.8 (CH_2), 39.7 (CH_2), 31.6 (CH_2), 27.4 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 24.6 (CH_2), 22.6 (CH_2).

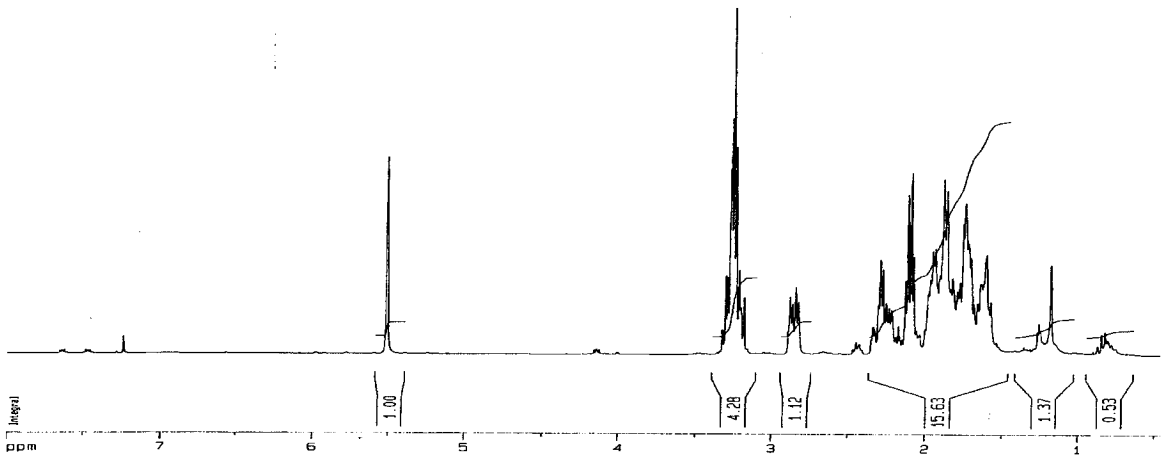
FTIR (neat, cm^{-1}) υ = 2931 (s), 2859 (s), 1709 (s), 1448 (s), 1123 (s), 886 (s)

HRMS (EI, m/z) Expected for $C_{14}H_{20}S_2O$ [$(M)^+$]: 268.0956, found: 268.09512 (100%)

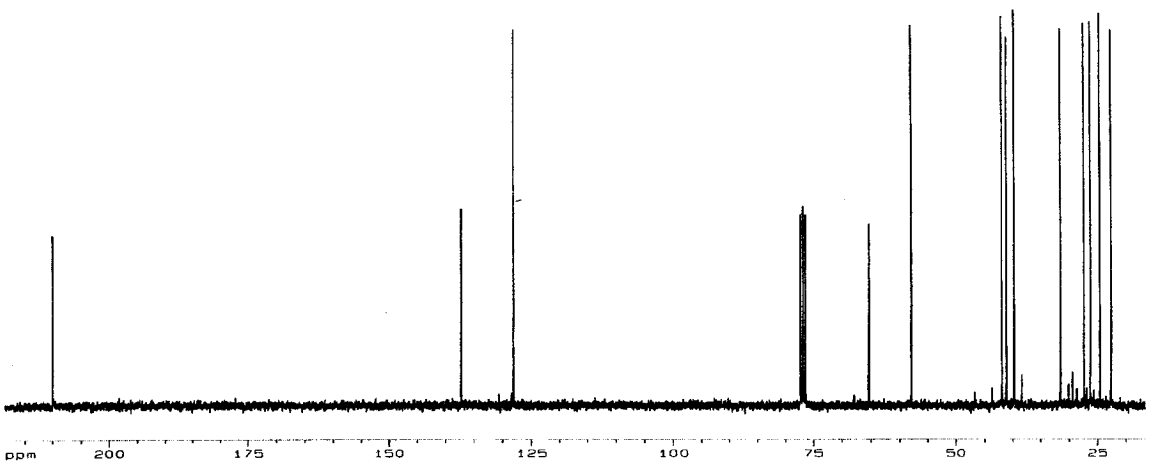


2.30

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



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



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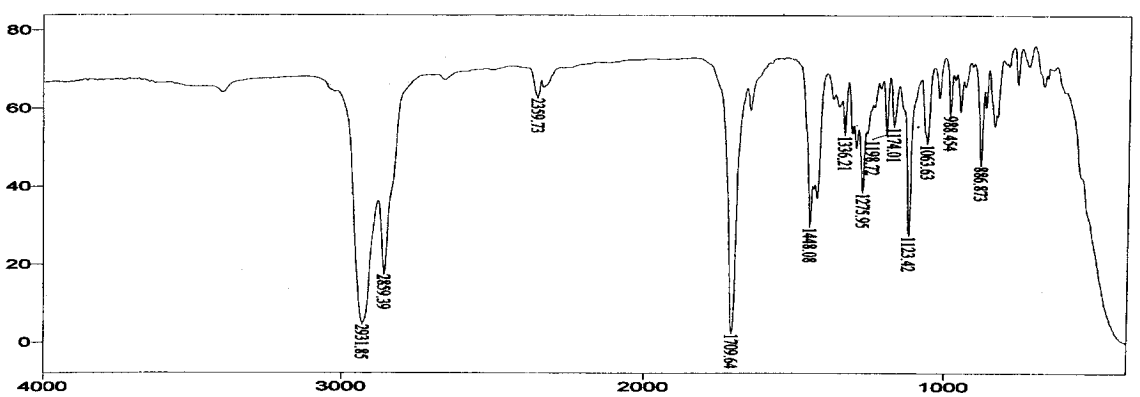
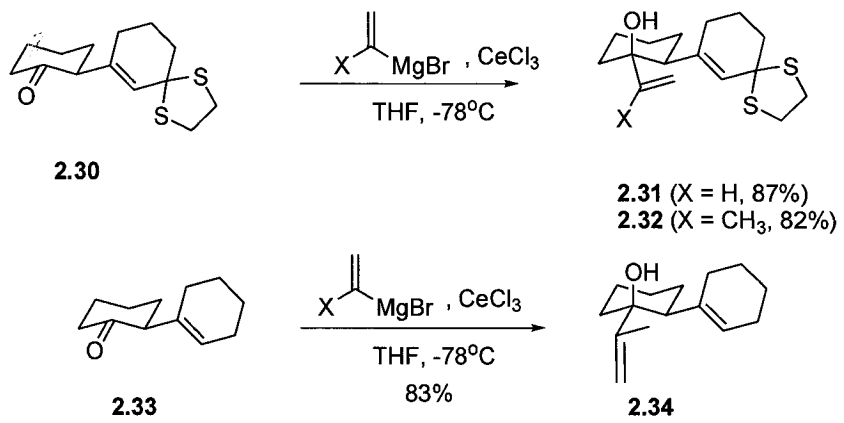




2-(1,4-Dithia-spiro[4.5]dec-6-en-7-yl)-1-vinyl-cyclohexanol (2.31), 2-(1,4-Dithia-spiro[4.5]dec-6-en-7-yl)-1-isopropenyl-cyclohexanol (2.32) and **2-Isopropenyl-bicyclohexyl-1'-en-2-ol (2.34)**. Representative procedure: A clean, dry, flame-dried flask fitted with a septum under argon was charged with $CeCl_3$ (275 mg, 3.0 equiv.). The flask was placed in an ice bath (0°C). THF (10 mL) was slowly added down the sides of the flask. Stirring was initiated, and the slurry was allowed to stir 30 min. A solution of **2.30** (100 mg, 373 umol, 1.0 equiv.) was added, and the mixture was allowed to stir overnight at room temperature. The following day, the reaction was cooled to -78°C and vinyl magnesium bromide (3.0 equiv.) was added. The reaction was allowed to stir for 20 minutes, quenched with aqueous $NH_4Cl_{(sat.)}$, extracted with ether (3x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (0 to 10% Et_2O in Hexanes) to give **2.31** (97 mg, 87%) as a colourless oil that solidified upon sitting in the freezer.

Data for **2.31**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.80 (dd, J = 10.6, 17.2 Hz, 1H), 5.63 (s, 1H), 5.11 (d, J = 17.2 Hz, 1H), 4.94 (d, J = 10.6 Hz, 1H), 3.35-3.21 (m, 4H), 2.13-1.23 (m, 16H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 145.8 (CH), 141.1 (C_4), 128.5 (CH), 110.6 (CH_2), 76.6 (C_4), 73.3 (C_4), 65.6 (C_4), 52.1 (CH), 41.2 (CH_2), 40.1 (CH_2), 40.0 (CH_2), 38.1 (CH_2), 29.9 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 21.1 (CH_2).

FTIR (neat, cm^{-1}) υ = 3480 (br), 2929 (s), 2856 (s), 1437, 970, 915

HRMS (EI, m/z) Expected for $C_{16}H_{24}S_2O$ [$(M)^+$]: 296.12685, found: 296.12576 (100%)

Data for **2.32**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.61 (s, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 3.32-3.15 (m, 4H), 2.15-1.80 (m, 7H), 1.74 (s, 3H), 1.72-1.35 (m, 9H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 150.6 (C_4), 141.5 (C_4), 128.0 (CH), 109.5 (CH_2), 75.8 (C_4), 65.7 (C_4), 49.8 (CH), 41.2 (CH_2), 40.0 (CH_2), 39.9 (CH_2), 36.7 (CH_2), 28.6 (CH_2), 26.8 (CH_2), 26.0 (CH_2), 22.9 (CH_2), 21.2 (CH_2), 20.1 (CH_3).

FTIR (neat, cm^{-1}) υ = 3545 (br), 2929 (s), 2856 (m), 1446 (m), 976 (m), 894 (m)

HRMS (EI, m/z) Expected for $C_{17}H_{26}S_2O$ [$(M)^+$]: 310.14240, found: 310.14189 (100%)

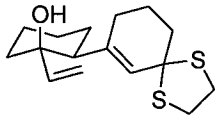
Data for **2.34**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.42 (m, 1H), 4.91 (d, J = 1.1 Hz, 1H), 4.73 (dd, J = 1.5, 1.5 Hz, 1H), 2.10 (dd, J = 3.4, 12.4 Hz, 1H), 2.01-1.77 (m, 6H), 1.75 (s, 3H), 1.72-1.43 (m, 11H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 151.3 (C_4), 140.5 (C_4), 122.4 (CH), 109.2 (CH_2), 75.2 (C_4), 49.9 (CH), 36.4 (CH_2), 30.4 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 25.4 (CH_2), 23.1 (CH_2), 22.4 (CH_2), 21.3 (CH_2), 20.2 (CH_3)

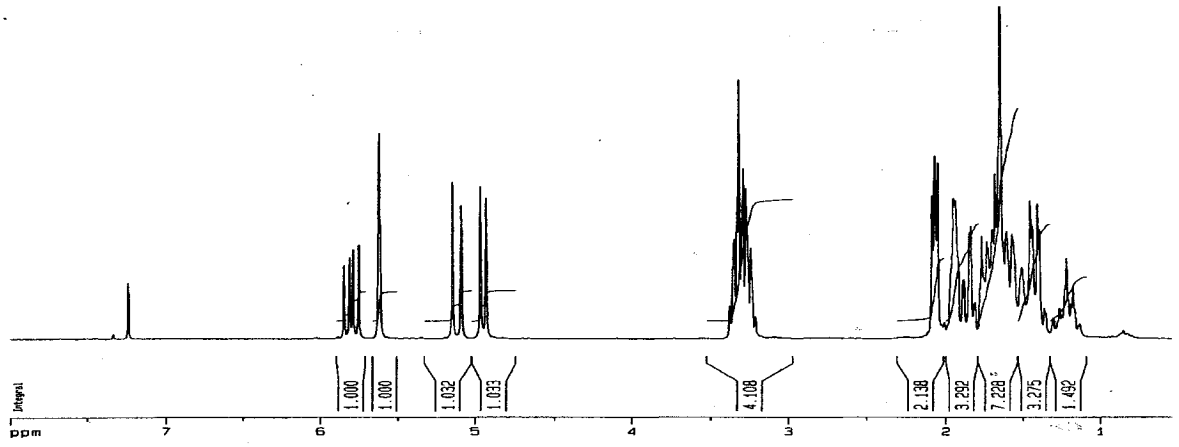
FTIR (neat, cm^{-1}) υ = 3546 (br), 2930 (s), 2855 (s), 1447 (s), 1133 (s), 975 (m), 890 (m)

HRMS (EI, m/z) Expected for $C_{15}H_{24}O$ [$(M)^+$]: 220.18272, found: 220.18239 (47.1%)

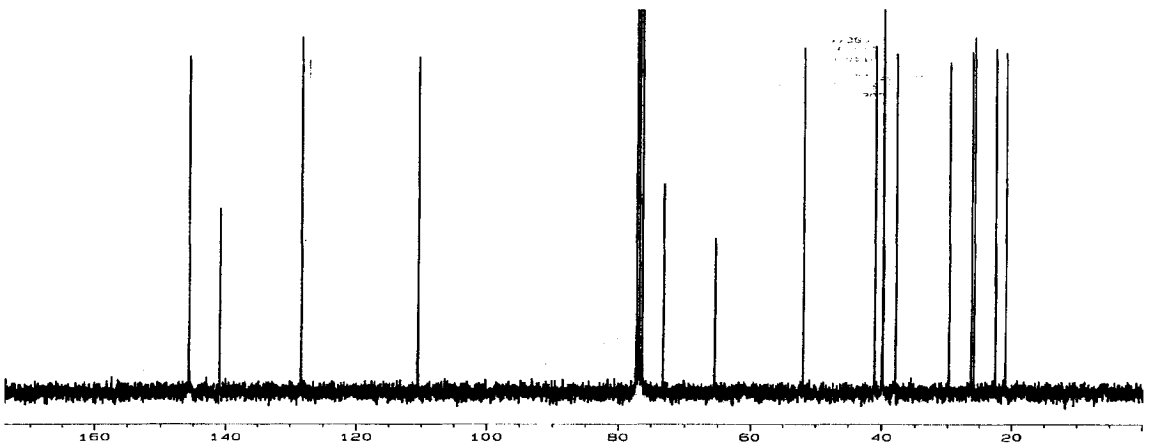


2.31

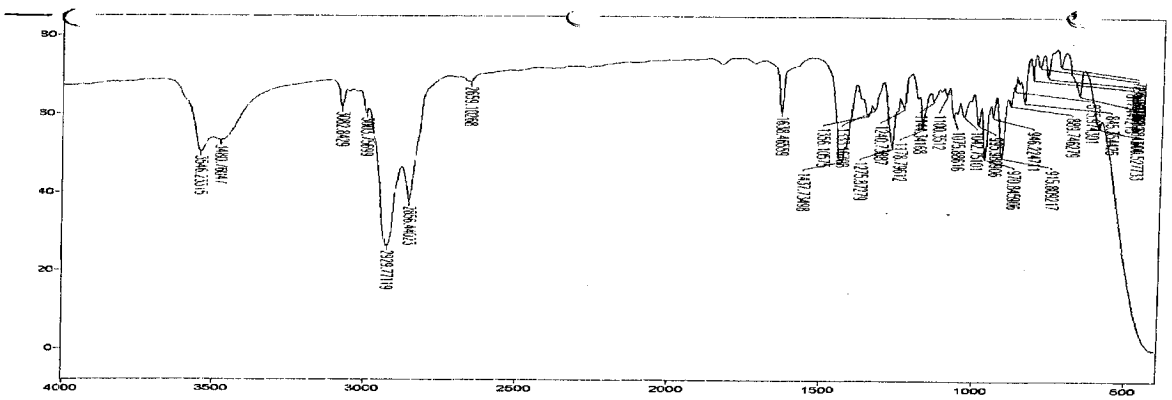
^{1}H NMR ($CDCl_3$, 300 MHz)

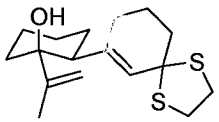


^{13}C NMR ($CDCl_3$, 75 MHz)



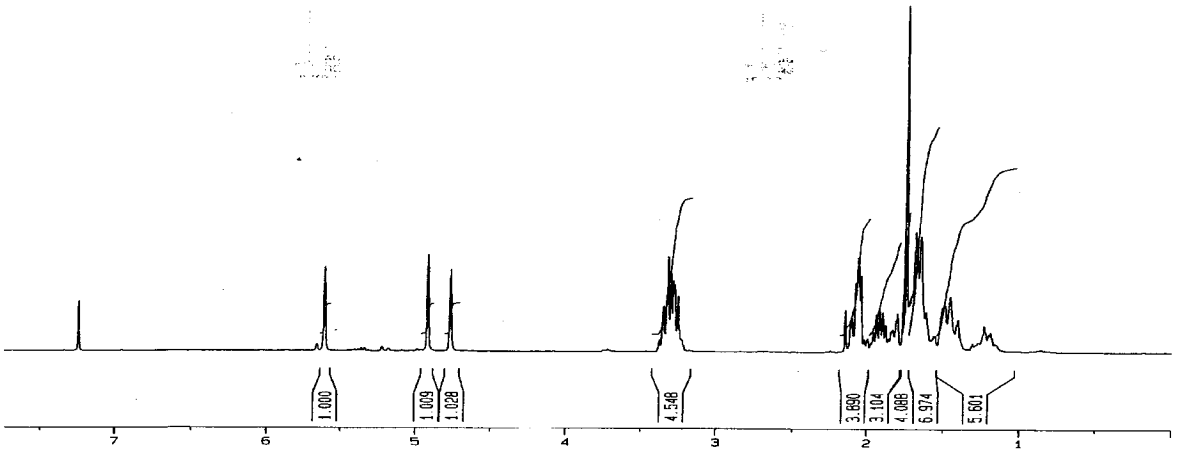
FTIR (neat)



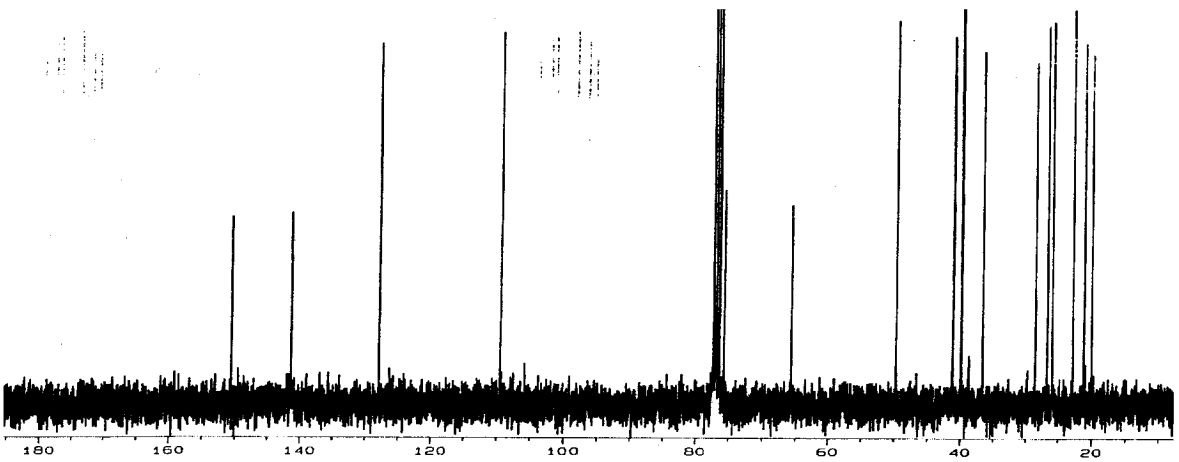


2.32

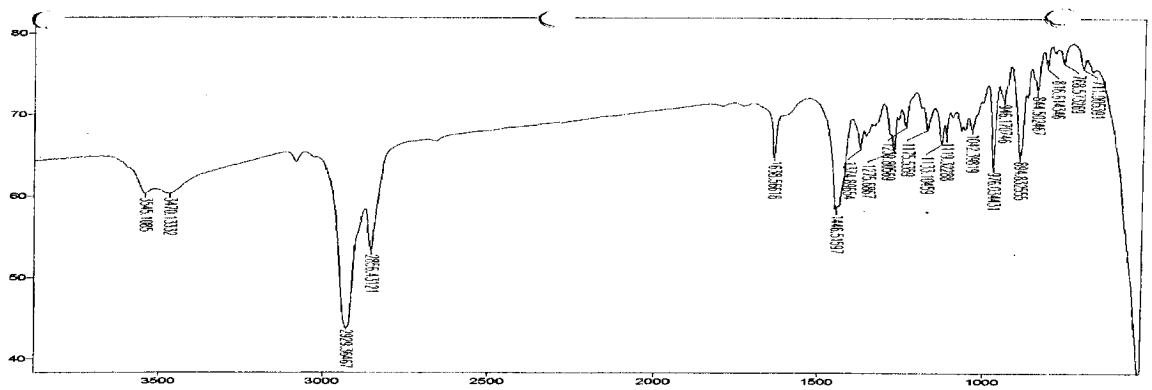
^{1}H NMR ($CDCl_3$, 300 MHz)

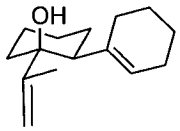


^{13}C NMR ($CDCl_3$, 75 MHz)



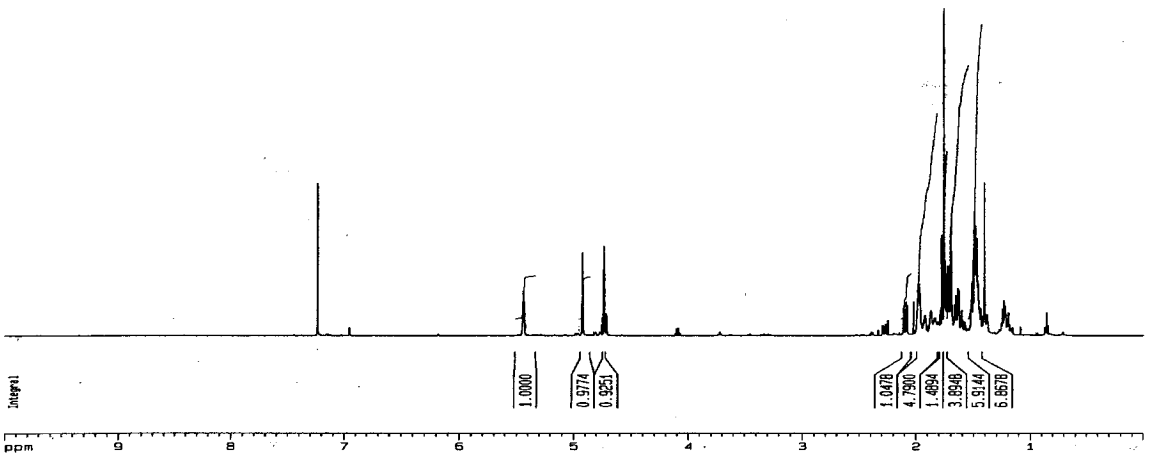
FTIR (neat)



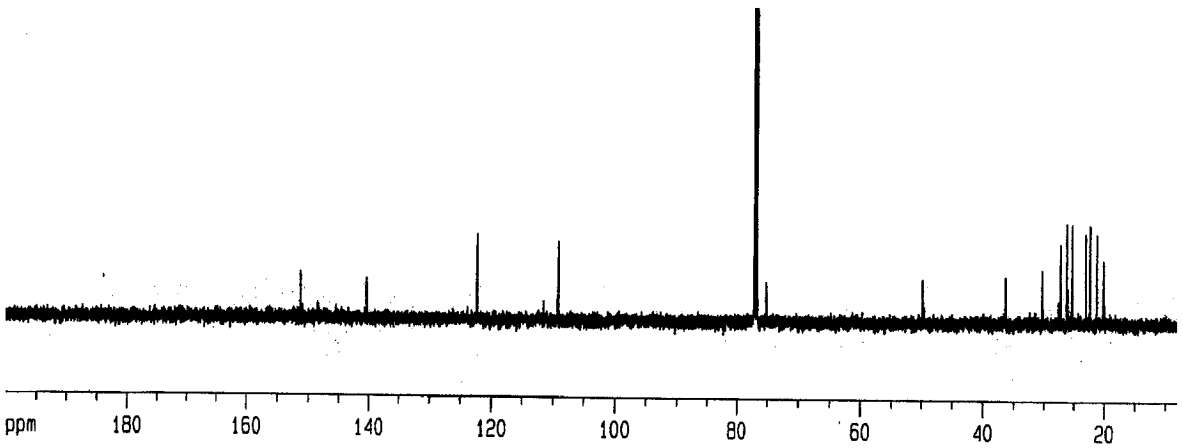


2.34

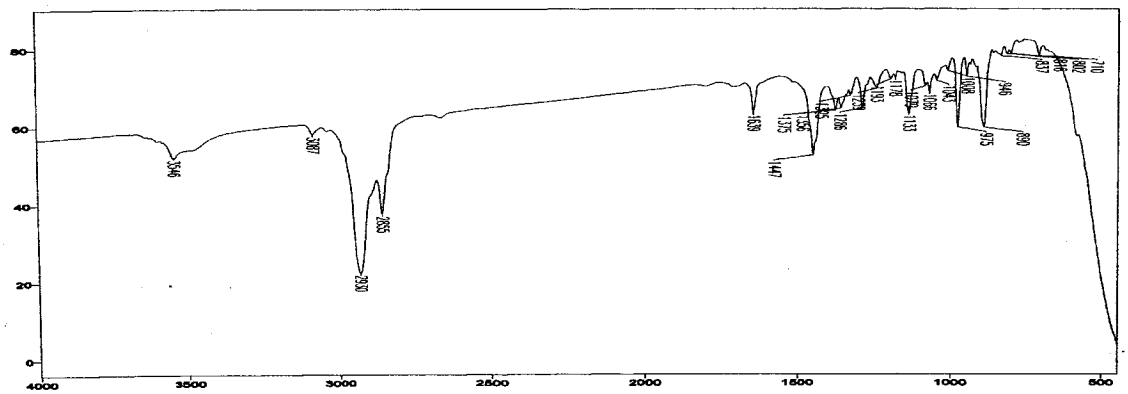
^{1}H NMR ($CDCl_3$, 300 MHz)

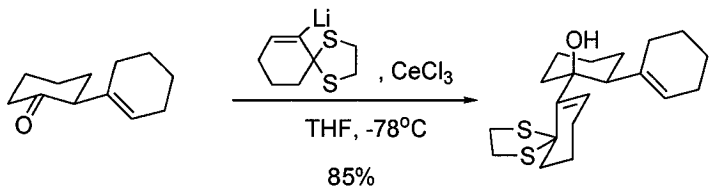


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





2.33 **2.35**

2-(1,4-Dithia-spiro[4.5]dec-6-en-6-yl)-bicyclohexyl-1'-en-2-ol (2.35).A flame-dried 50 mL roundbottom flask was charged with anhydrous cerium trichloride[65] (414 mg, 3.0 eq.), and cooled to 0°C. THF (10 mL) was added gradually down the sides of the flask, and the slurry was stirred at 0°C for 45 min. A solution of the ketone (100 mg, 560 umol, 1 eq.) was added, and the mixture was allowed to stir overnight while warming to room temperature. The following day, a separate flame-dried flask under argon was charged with 7-Bromo-1,4-dithia-spiro[4.5]dec-6-ene (420 mg, 3.0 eq.) and THF (10 mL). Both flasks were cooled to -78°C, and t-BuLi (3.20 mL, 6.0 eq.) was added slowly to the flask containing the thioacetal. After 10 minutes, the contents of the thioacetal flask was quickly canulated into the flask containing the ketone via a dry-ice cooled canula. The combined mixture was stirred for 10 minutes, quenched with aqueous $NH_4Cl_{(sat.)}$ (5 mL), extracted with ether (4x), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (0 to 20% EtOAc in Hexanes) to give **2.35** as a clear foam (167mg, 85%).

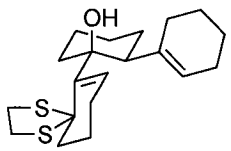
Data for **2.32**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.81 (br s, 1H), 5.41 (br s, 1H), 3.40-3.16 (m, 4H), 2.21-1.15 (m, 24H + grease)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 145.2 (C_4), 140.0 (C_4), 124.2 (CH), 122.9 (CH), 75.0 (C_4), 66.0 (C_4), 50.6 (C_4), 41.5 (CH), 40.0 (CH_2), 39.6 (CH_2), 36.3 (CH_2), 29.8 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 25.5 (CH_2), 24.9 (CH_2), 23.1 (CH_2), 22.7 (CH_2), 22.4 (CH_2), 21.2 (CH_2)

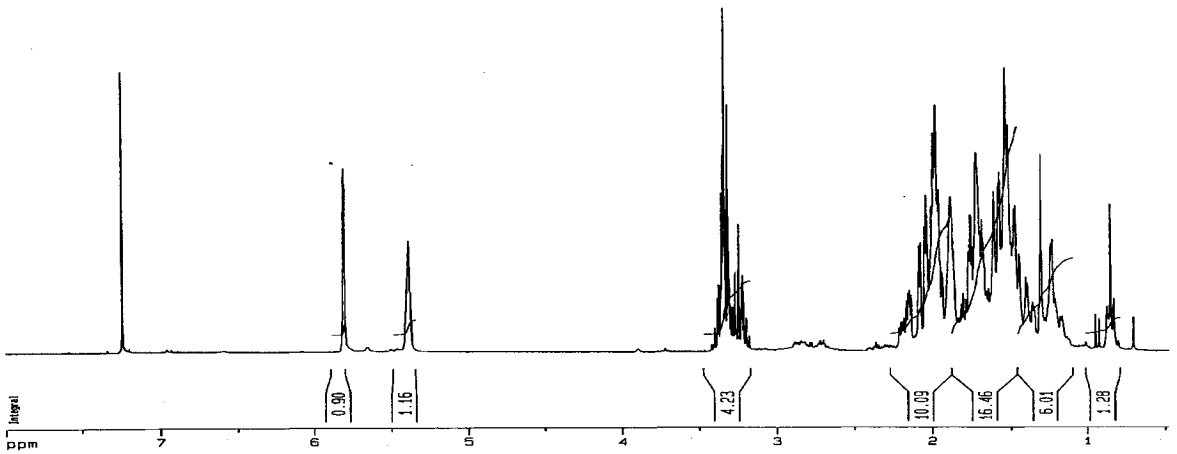
FTIR (neat, cm^{-1}) υ = 3503 (br), 2927 (s), 2855 (s), 1446 (m), 1437 (m), 984 (m), 733 (m)

HRMS (EI, m/z) Expected for $C_{20}H_{30}S_2O$ [$(M)^+$]: 350.17381, found: 350.17483 (23.8%)

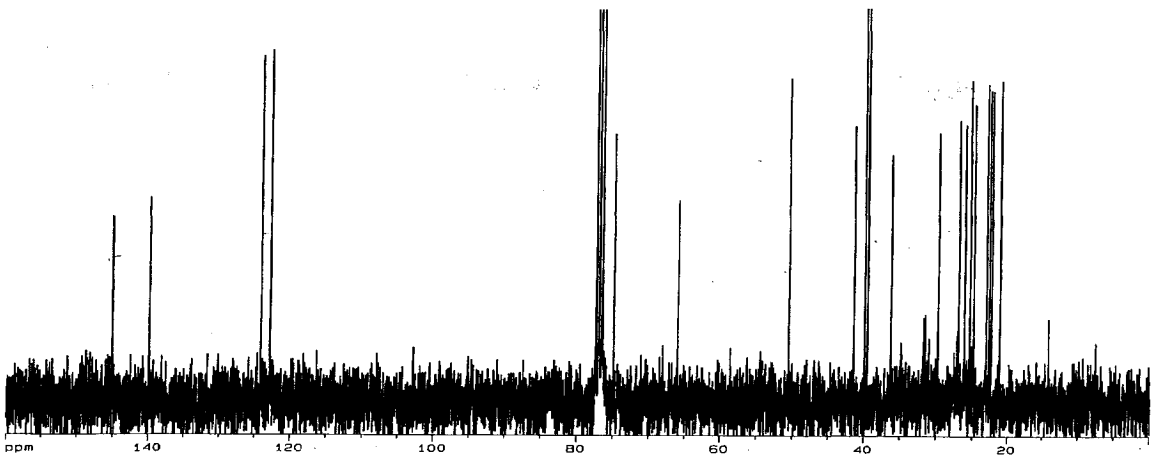


2.35

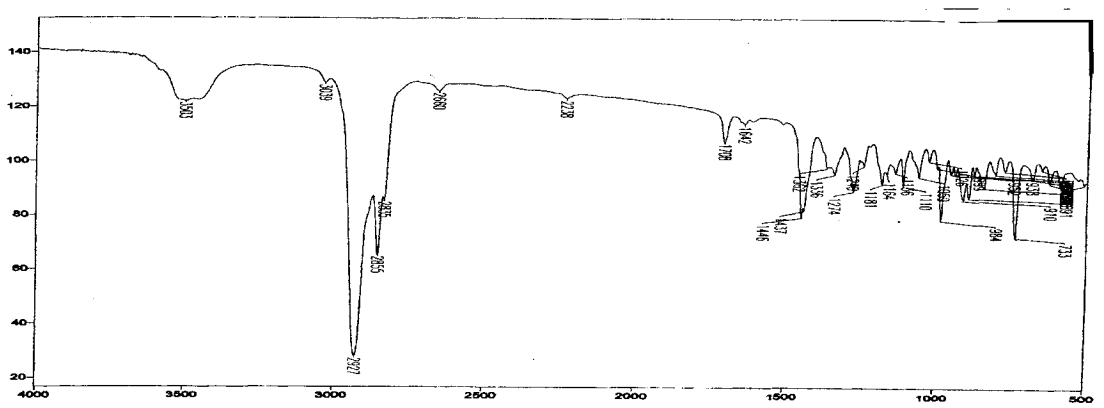
^{1}H NMR ($CDCl_3$, 500 MHz)

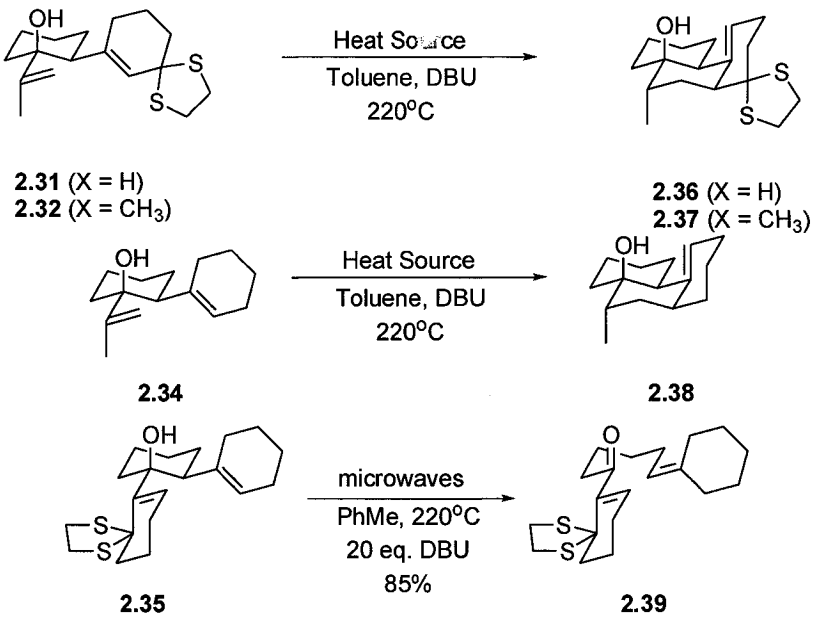


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





1-dithioacetyl-1,3,4b,5,6,7,8,9,10,10a-decahydro-2H-phenanthren-8a-ol (2.36), 1-dithioacetyl-9-methyl-1,3,4b,5,6,7,8,9,10,10a-decahydro-2H-phenanthren-8a-ol (2.37), 9-Methyl-1,3,4b,5,6,7,8,9,10,10a-decahydro-2H-phenanthren-8a-ol (2.38), and **6-Cyclohexylidene-1-(1,4-dithia-spiro[4.5]dec-6-en-6-yl)-hexan-1-one (2.39)**. All compounds were heated in the microwave or via wax bath according to the general procedure, with yields and reaction times as reported in Tables 2.2 and 2.3, and Scheme 2.10.

Data for **2.36**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.34 (br s, 1H), 3.35-3.18 (m, 4H), 2.42-2.32 (m, 2H), 2.23-2.14 (m, 1H), 2.14-2.02 (m, 2H), 1.92-1.85 (m, 2H), 1.79-1.65 (m, 3H), 1.62-1.42 (m, 8H), 1.30-1.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 141.3 (C_4), 118.9 (CH), 71.4 (C_4), 70.9 (C_4), 52.1 (CH), 50.3 (CH), 40.0 (CH_2), 38.4 (CH_2), 38.3 (CH_2), 38.1 (CH_2), 35.4 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 21.2 (CH_2).

FTIR (neat, cm^{-1}) υ = 3538 (br), 2927 (s), 2855 (s), 1443 (s), 1245 (m), 954 (s)

HRMS (EI, m/z) Expected for $C_{16}H_{24}S_2O$ [$(M)^+$]: 296.12685, found: 296.12507 (4.7%)

Data for **2.37**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.35 (br s, 1H), 3.32-3.16 (m, 4H), 2.53-2.48 (m, 1H), 2.39-2.31 (m, 1H), 2.25-2.06 (m, 3H), 1.97-1.90 (m, 2H), 1.85-1.70 (m, 3H), 1.65-1.45 (m, 8H), 1.07 (d, 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 141.7 (C_4), 119.1 (CH), 74.5 (C_4), 71.0 (C_4), 46.0 (CH), 44.1 (CH), 40.3 (CH), 38.4 (CH_2), 38.3 (CH_2), 34.9 (CH_2), 25.7 (2 x CH_2), 25.1 (2 x CH_2), 23.5 (CH_2), 21.3 (CH_2), 16.3 (CH_3)

FTIR (neat, cm^{-1}) υ = 3492 (br), 2924 (s), 2858 (s), 1443 (s), 1250 (m), 967 (s)

HRMS (EI, m/z) Expected for $C_{17}H_{26}S_2O$ [$(M)^+$]: 310.14250, found: 310.14090 (1.3%)

Data for **2.38**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.45 (br s, 1H), 2.25-2.04 (m, 4H), 1.82-1.37 (m, 15H), 1.23-1.14 (m, 1H + grease) 1.09 (d, J = 7.4 Hz, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 141.4 (C_4), 121.1 (CH), 74.6 (C_4), 42.7 (CH), 39.9 (CH), 38.3 (CH_2), 35.2 (CH_2), 31.8 (CH), 30.8 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 23.9 (CH_2), 21.4 (CH_2), 20.8 (CH_2), 16.2 (CH_3).

FTIR (neat, cm^{-1}) υ = 3470 (br), 2925 (s), 2857 (s), 1447 (s), 1244 (m), 961 (s), 947 (m)

HRMS (EI, m/z) Expected for $C_{15}H_{24}O$ [$(M)^+$]: 220.18272, found: 220.18118 (100%)

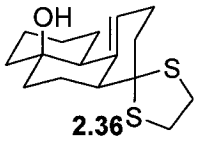
Data for **2.39**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 6.79 (s, 1H), 5.07 (dd, J = 7.2, 7.2 Hz, 1H), 3.47-3.29 (m, 4H), 2.67 (t, J = 7.3 Hz, 2H), 2.23-1.97 (m, 10H), 1.84-1.73 (m, 2H), 1.64-1.42 (m, 10H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 201.6 (C=O), 141.2 (CH), 139.9 (C_4), 136.7 (C_4), 120.9 (CH), 64.4 (C_4), 40.3 (CH_2), 40.2 (CH_2), 37.2 (CH_2), 37.1 (2 x CH_2), 29.8 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 24.1 (CH_2), 22.3 (CH_2), 22.2 (CH_2).

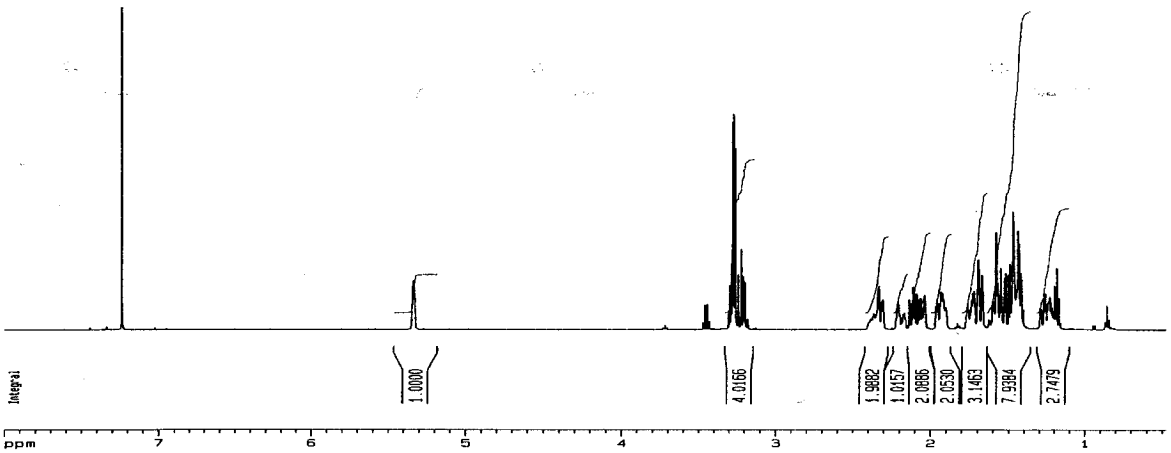
FTIR (neat, cm^{-1}) υ = 3411 (br), 2924 (s), 2852 (s), 1670 (s), 1623 (m), 1446 (s), 1275 (m), 1236 (m), 1182 (s), 850 (m)

HRMS (EI, m/z) Expected for $C_{20}H_{30}S_2O$ [$(M)^+$]: 350.17381, found: 350.17436 (92.5%)

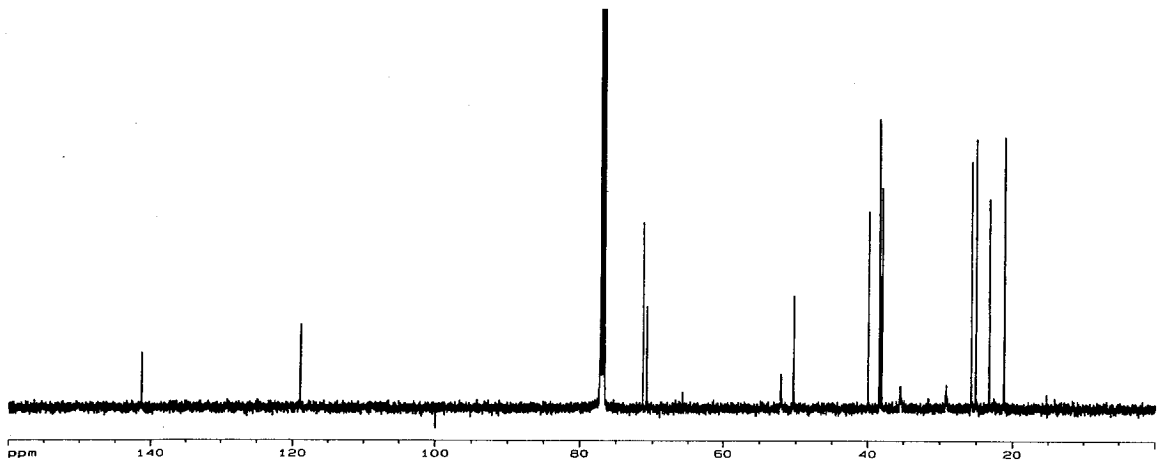


2.36

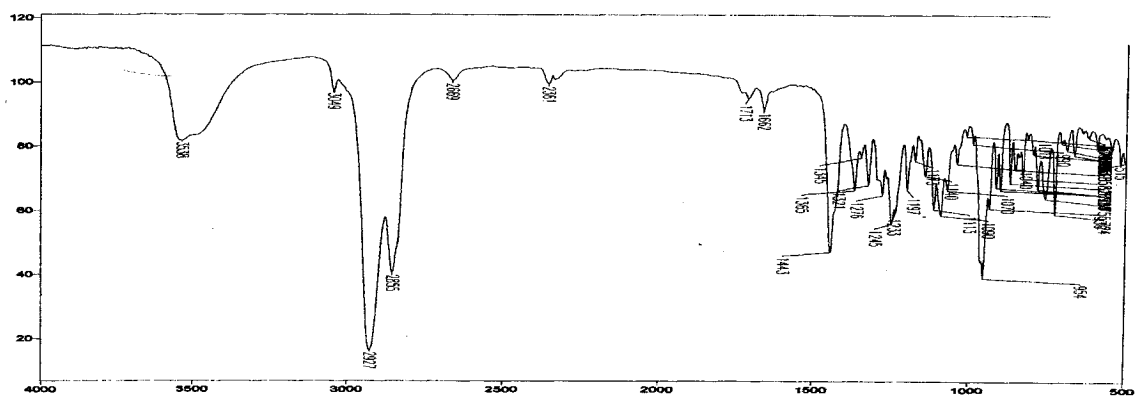
^{1}H NMR ($CDCl_3$, 500 MHz)

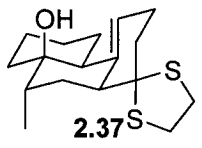


^{13}C NMR ($CDCl_3$, 125 MHz)

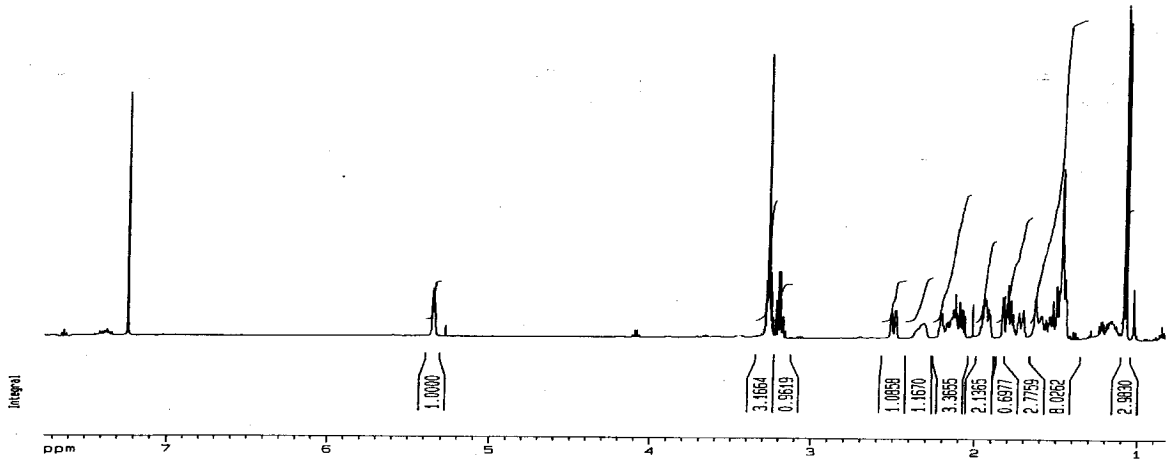


FTIR (neat)

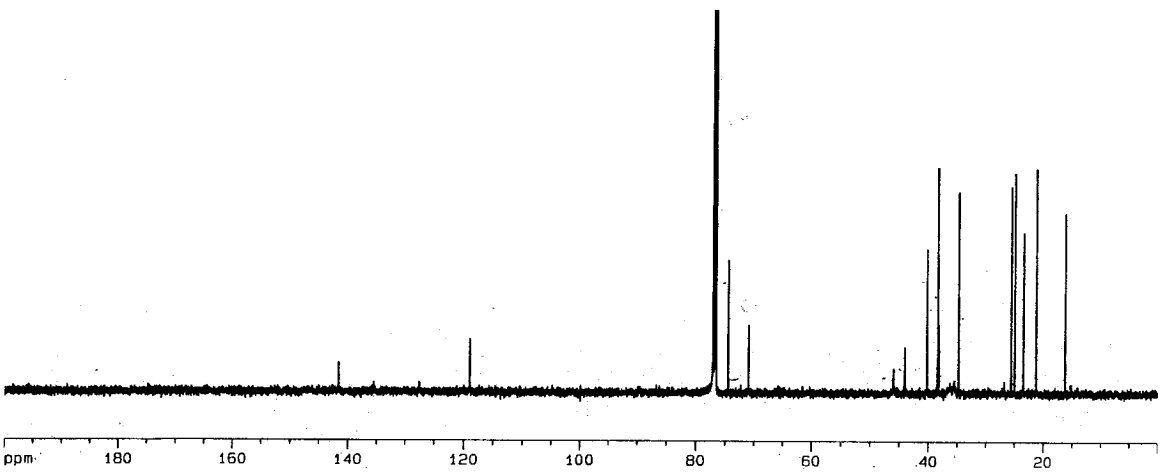




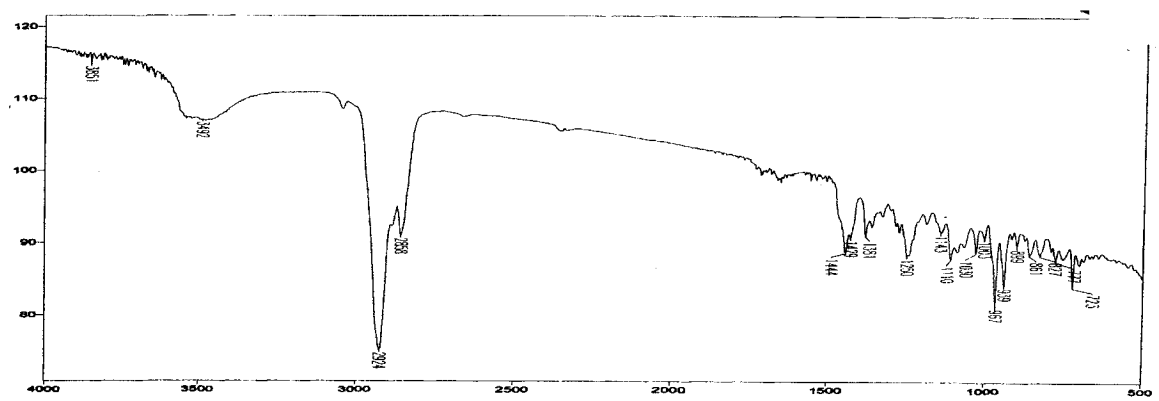
^{1}H NMR ($CDCl_3$, 500 MHz)

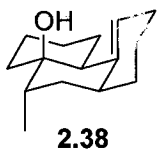


^{13}C NMR ($CDCl_3$, 125 MHz)



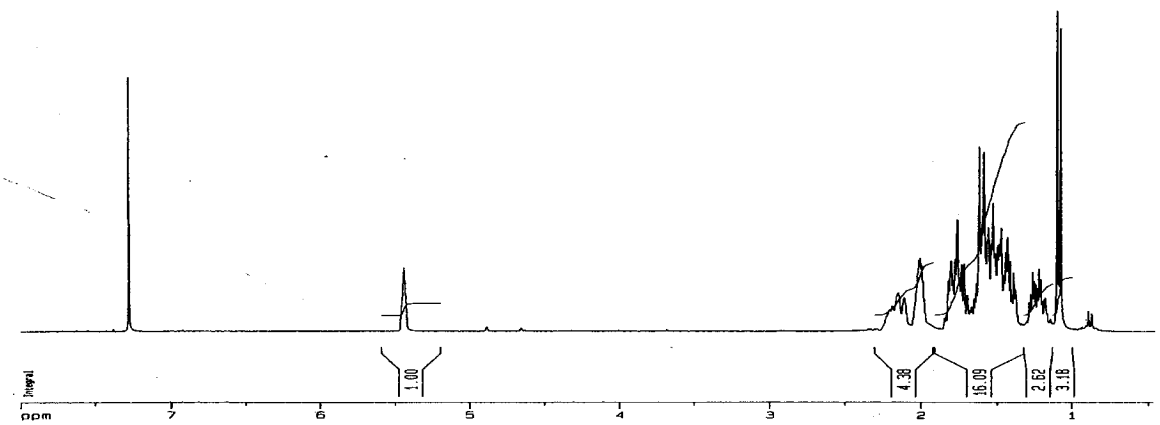
FTIR (neat)



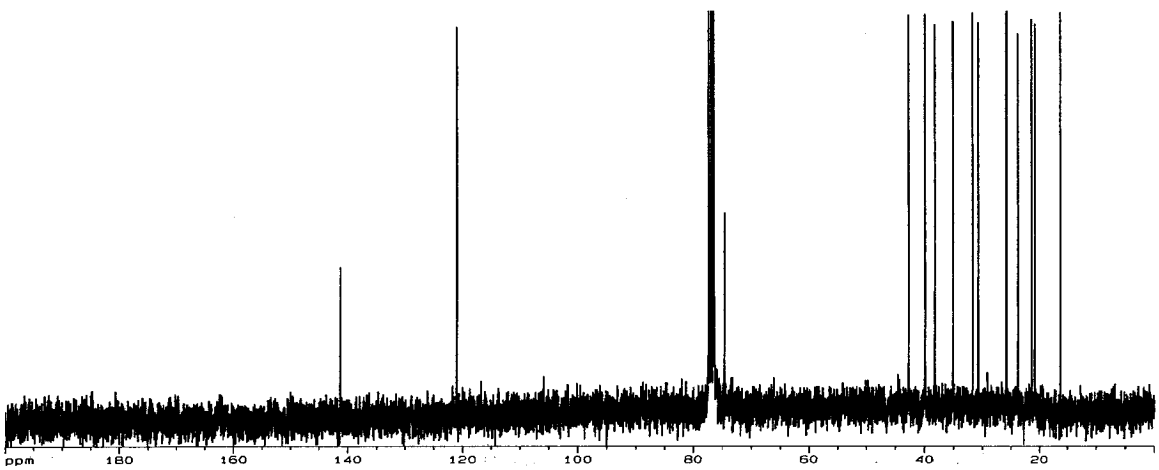


2.38

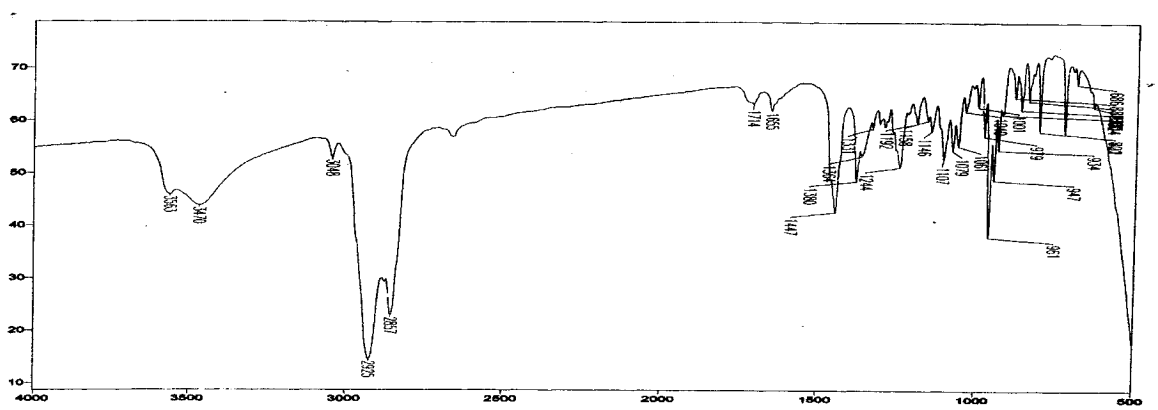
^{1}H NMR ($CDCl_3$, 500 MHz)

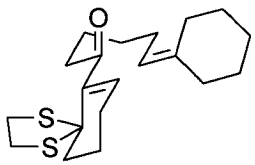


^{13}C NMR ($CDCl_3$, 125 MHz)



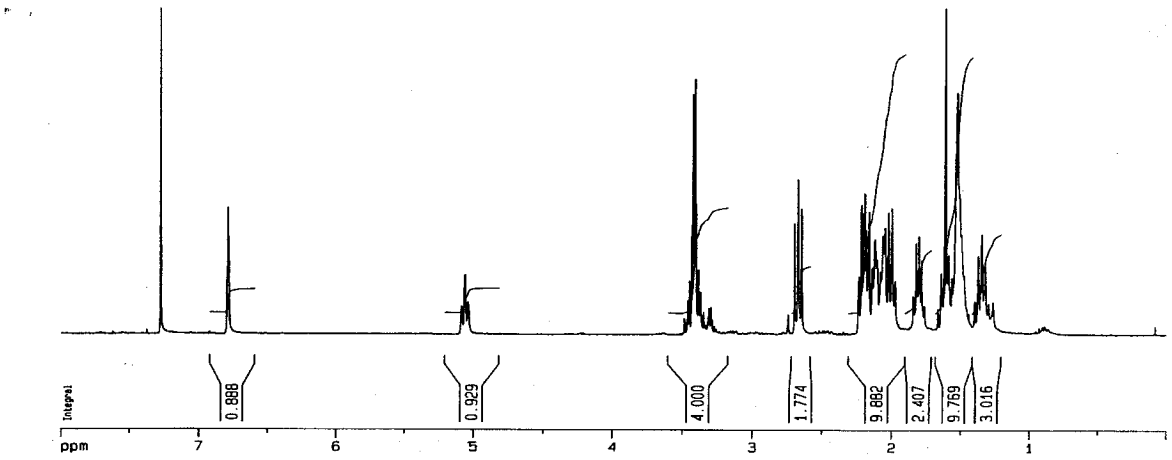
FTIR (neat)



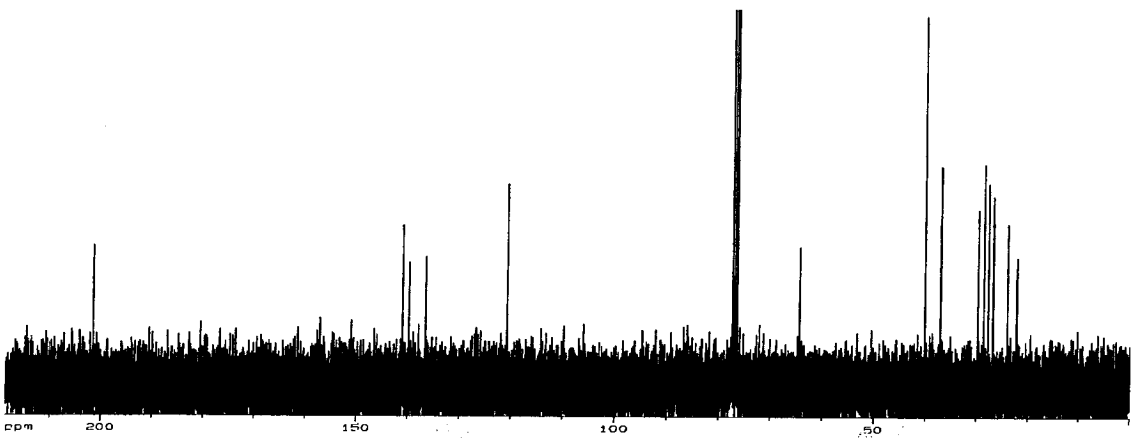


2.39

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



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



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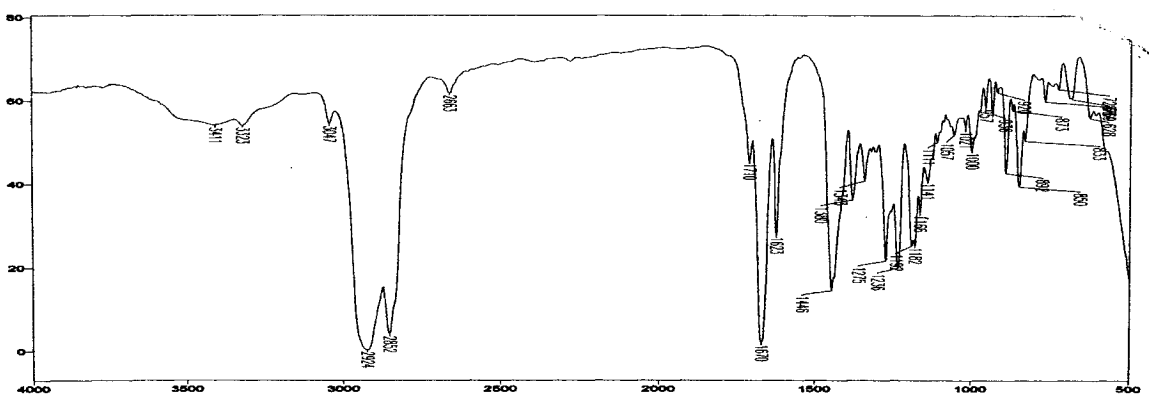
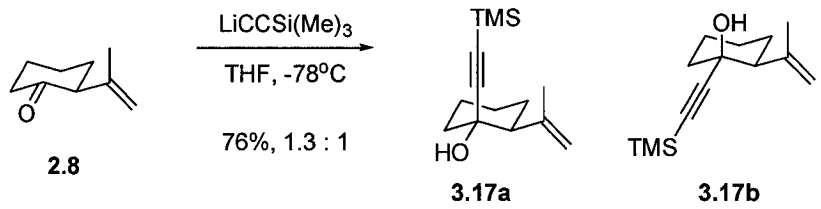




2.8 **3.17a** **3.17b**

2-Isopropenyl-1-trimethylsilanylethynyl-cyclohexanols (3.17a and 3.17b). A solution of TMS Acetylene (2.45 mL, 1.2 eq.) in dry THF (30 mL) under Argon was cooled to -78°C and BuLi (2.44M, 6.5 mL, 1.1 equiv.) was added. After 10 minutes stirring, ketone **2.8** (2.0g, 14.4 mmol) was canulated with THF (10 mL). This was allowed to warm to 0°C over 20 minutes. The reaction was quenched by addition of $NH_4Cl_{(aq)}$, extracted with ether (3 x 10 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (0 to 20% EtOAc in Hexanes) gave **3.17a** (1.46 g, 43%) and **3.17b** (1.12 g, 33%) as a yellow oils.

Data for **3.17a**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 4.98 (br s, 1H), 4.79 (br s, 1H), 2.25-2.13 (m, 3H), 1.96 (s, 3H), 1.78-1.40 (m, 6H), 1.25-1.14 (m, 1H), 0.11 (s, 9H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 148.7 (C_4), 112.5 (CH_2), 111.1 (C_4), 87.4 (C_4), 67.4 (C_4), 52.7 (CH_3), 39.8 (CH_2), 27.1 (CH_2), 26.5 (CH), 26.1 (CH_2), 20.9 (CH_2), 0.2 (3 x CH_3)

FTIR (neat, cm^{-1}) υ = 3457 (br), 2937 (s), 2851 (s), 2162 (w), 1634 (w), 1447 (m), 1250 (m), 863 (s), 842 (s)

HRMS (EI) Expected for $C_{14}H_{24}OSi$ [$(M)^+$]: 236.15964, found: 136.15766 (2.13%)

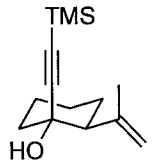
Data for **3.17b**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 4.96 (br s, 1H), 4.88 (br s, 1H), 2.68 (s, 1H), 2.17-1.98 (m, 2H), 1.85 (s, 3H), 1.82-1.20 (m, 7H), 0.13 (s, 9H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 145.8 (C_4), 115.4 (CH_2), 108.2 (C_4), 91.2 (C_4) 70.3 (C_4), 56.7 (CH_3), 40.7 (CH_2), 28.8 (CH_2) 26.0 (CH_2), 24.3 (CH_2), 21.0 (CH), 0.2 (3 x CH_3)

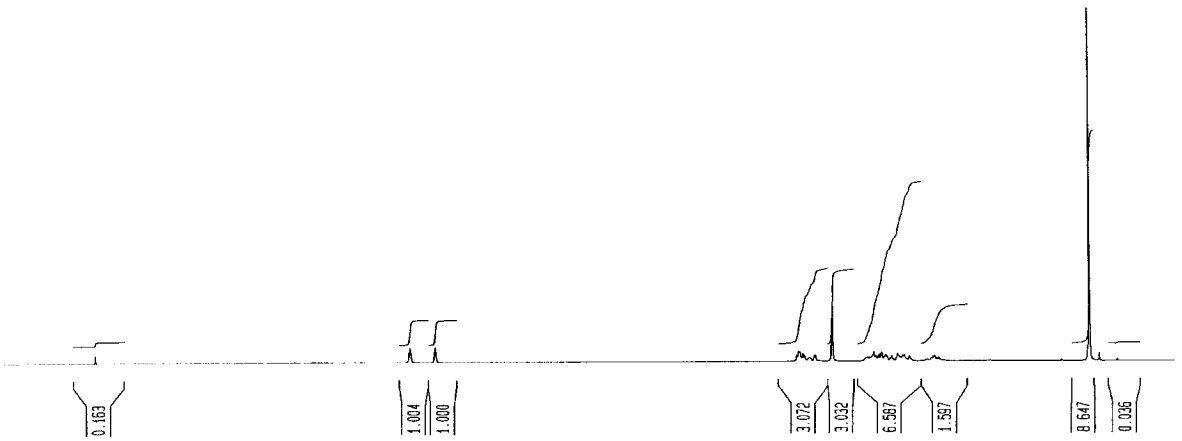
FTIR (neat, cm^{-1}) υ = 3449 (br), 2934 (s), 2859 (s), 2164 (w), 1636 (w), 1447 (m), 1250 (s), 862 (s), 845 (s)

HRMS (EI) Expected for $C_{14}H_{24}OSi$ [$(M)^+$]: 236.15964, found: 236.15726 (1.40%)

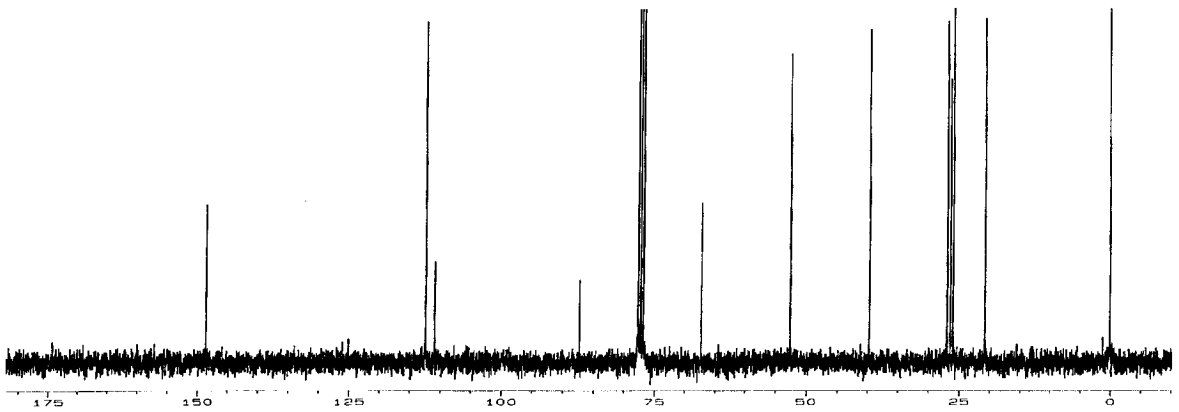


3.17a

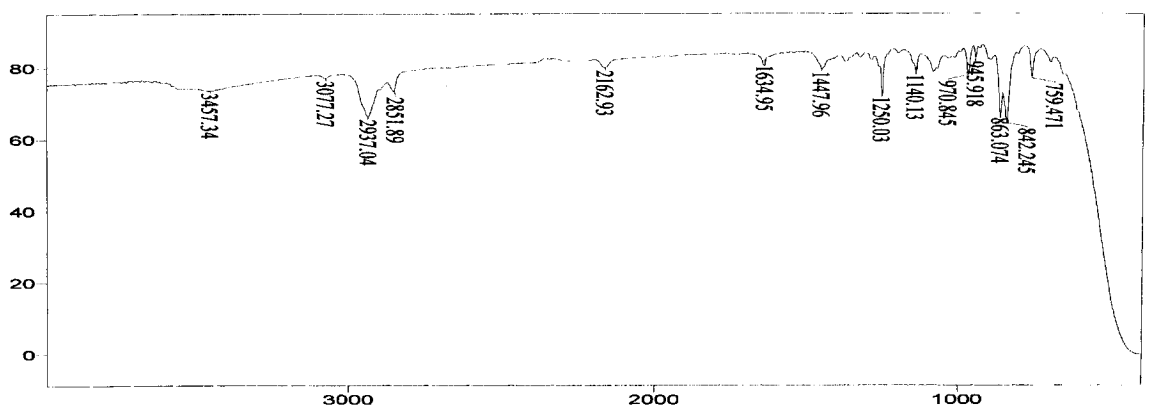
^{1}H NMR ($CDCl_3$, 500 MHz)

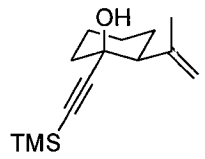


^{13}C NMR ($CDCl_3$, 125 MHz)



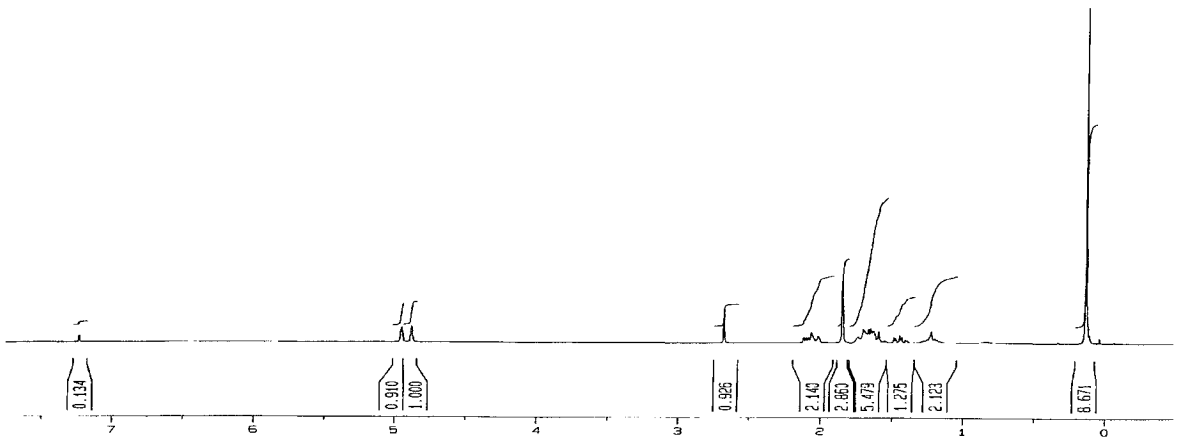
FTIR (neat)



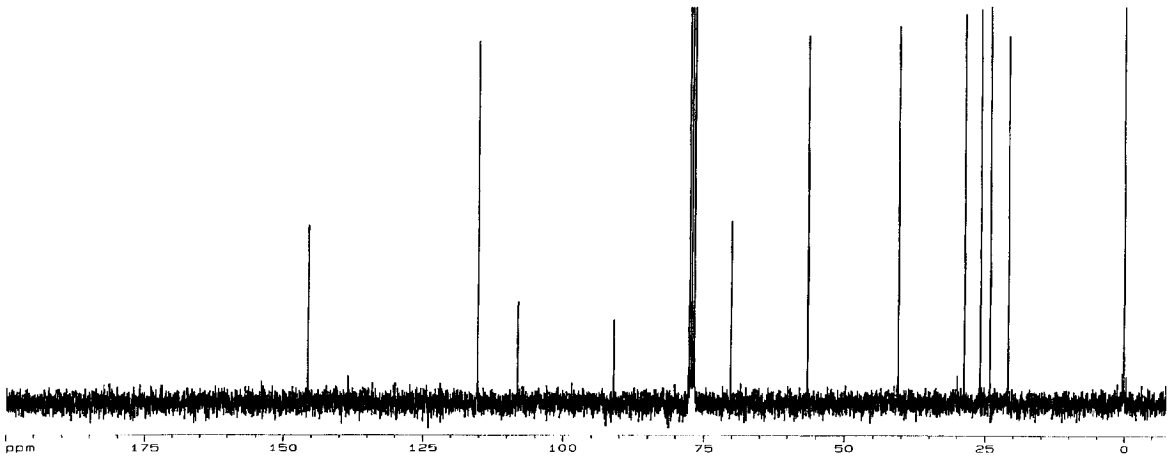


3.17b

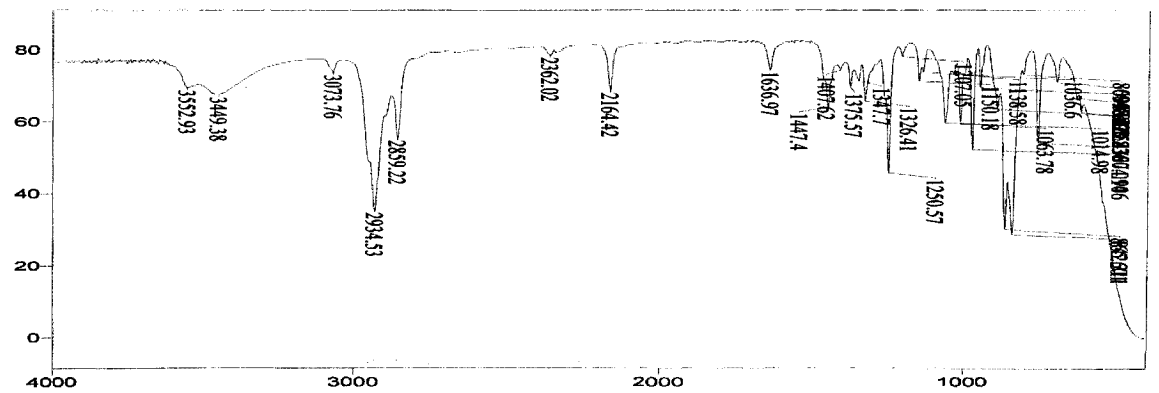
^{1}H NMR ($CDCl_3$, 300 MHz)

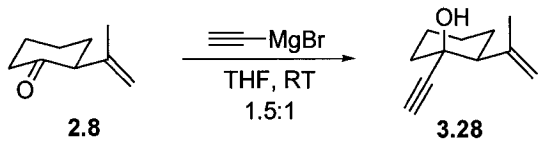


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





2.8 **3.28**

1-Ethynyl-2-isopropenyl-cyclohexanol (3.28). A clean, dry 1L flask fitted with a magnetic stirrer was flame dried and placed under argon. The flask was charged with ether (200 mL) and ketone **2.8** (32.0g, 0.232 mol) and cooled to 0°C. Ethynyl magnesium bromide (0.5 M solution in THF, 600 mL) was added and the reaction was allowed to warm to room temperature over 4 hours. The mixture was recooled to 0°C and quenched by slow addition of saturated $NH_4Cl_{(aq)}$ (100 mL). The organic layers were extracted with ether (4 x 75 mL) dried over $MgSO_4$ and concentrated. The mixture was passed through a short path of silica (20% Ether in Hexanes) to give a yellow oil (34.9g, > 0.250 mol) as a 1.5:1 mixture of diastereomers (GC-MS). (rF in 30% Et_2O in Hexanes: *trans* ring junction: 0.6, *cis* ring junction: 0.55). A small amount of the desired *trans* ring junction was repurified for characterization to give **3.28** as a colorless oil.

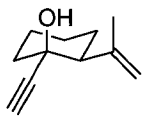
Data for **3.28**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.20 (br s, 1H), 5.03 (br s, 1H), 2.39 (s, 1H), 2.25-2.09 (m, 3H), 1.95 (s, 3H), 1.75-1.42 (m, 6H), 1.35-1.07 (m, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 148.5 (C_4), 112.7 (CH_2), 89.0 (C_4), 71.6 (CH), 67.3 (C_4), 52.8 (CH), 40.0 (CH_2), 27.0 (CH_2), 26.2 (CH_3), 26.0 (CH_2), 20.8 (CH_2)

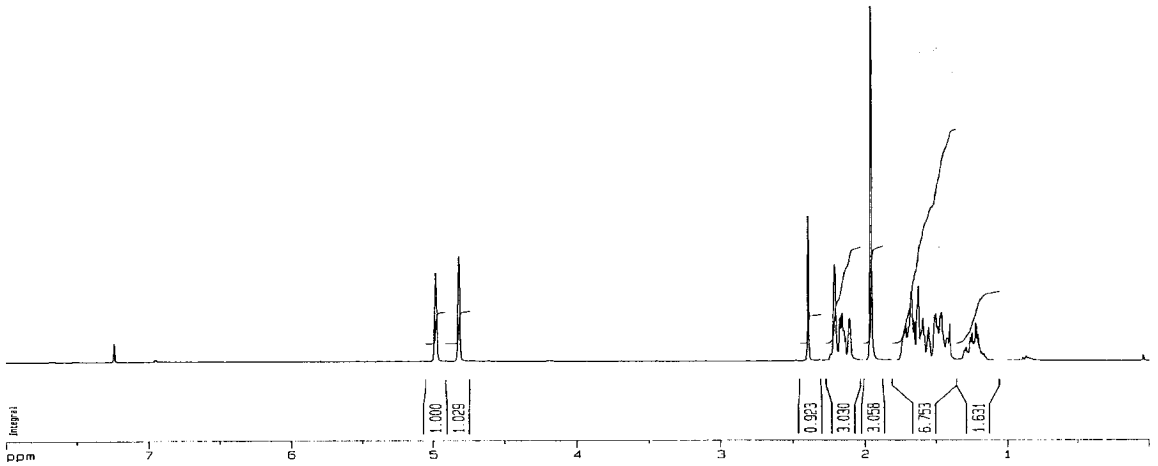
FTIR (neat, cm^{-1}) υ = 3734 (s), 2924 (s), 1558, 1540, 1507

HRMS (EI) Expected for $C_{11}H_{16}O_1$ [$(M)^+$]: 164.12012, found: 164.11865 (2.11%)

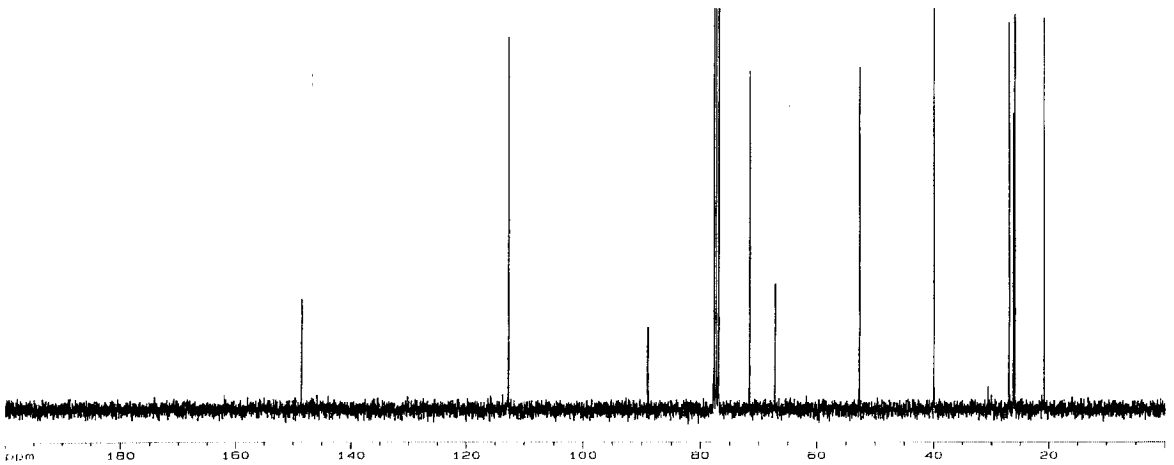


3.28

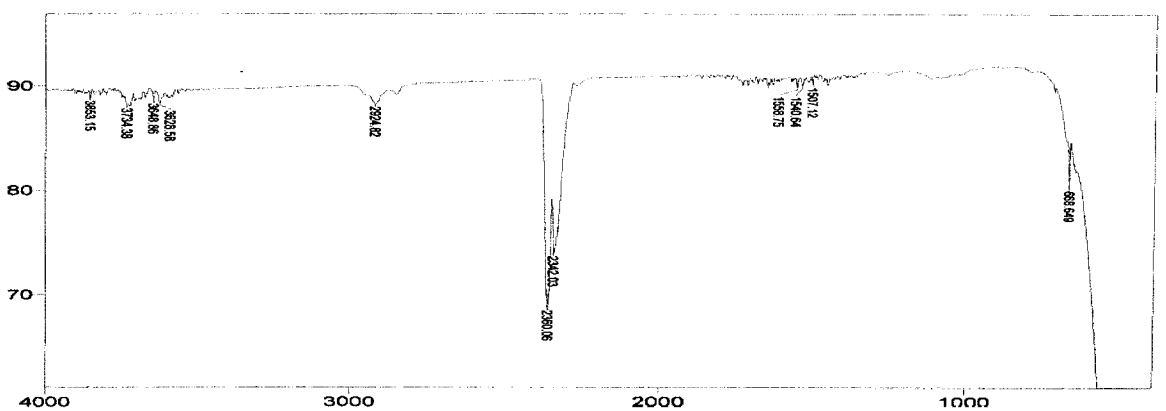
^{1}H NMR ($CDCl_3$, 300 MHz)

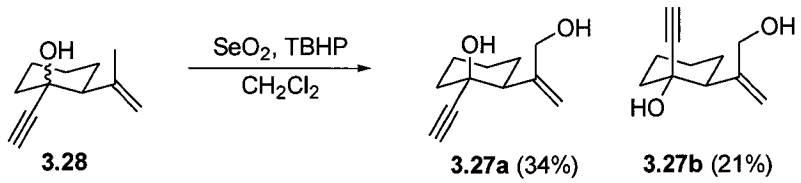


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.28 **3.27a** (34%) **3.27b** (21%)

1-Ethynyl-2-(1-hydroxymethyl-vinyl)-cyclohexanol (3.27). A dry 1L roundbottom flask fitted with a magnetic stirrer was charged with dichloromethane (300 mL) under argon. SeO_2 (11.7g, 0.125 mol) was added, with stirring, followed by *tert*-butyl hydroperoxide (70% in water, 60 mL, 0.500 mol, 2.0 equiv.). The mixture was cooled to 0°C and AcOH (0.025 mol) was added. After most of the Selenium oxide had dissolved (approx. 30 min), a solution of the divinylcyclohexanol **3.28** (34.9g, 0.250 mol) in DCM (50 mL) was added. The reaction was allowed to stir for 2 days at room temperature until most of the starting material had been consumed. The reaction mixture was diluted with benzene (100 mL) and the dichloromethane was removed *in vacuo*. The residue was diluted again with Ethyl Acetate (200 mL), washed with 10% KOH solution (10% w/w in H_2O, 3 x 50 mL), Brine (2 x 50 mL), and dried over $MgSO_4$ and filtered. Silica (~50g) was added prior to removal of the volatiles. The dry powder was subjected to flash chromatography (0 to 30% EtOAc in 3 steps) to give the desired *trans* ring junction diol **3.27a** as a light yellow oil. (15.3 g, 34% over 2 steps). The minor diastereomer **3.27b** was recovered by increasing the polarity to 40% EtOAc in Hexanes (9.25g, 21%). [153]

Data for **3.27a**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.17 (s, 1H), 5.06 (s, 1H), 4.41 (br s, 1H), 4.13 (m, 2H), 2.87 (br s, 1H), 2.41 (s, 1H), 2.34 (dd, J = 3.4, 12.9 Hz, 1H) 2.14-2.06 (m, 1H), 1.87-1.24 (m, 3H), 1.50-1.17 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 148.5 (C_4), 117.4 (CH_2), 88.5 (C_4), 71.8 (C_4), 67.6 (CH), 64.8 (CH_2), 52.4 (CH) 39.5 (CH_2) 26.0 (CH_2), 25.6 (CH_2), 20.4 (CH_2); HRMS (EI) [$(M-H_2O)^+$]: m/z calc'd for $C_{11}H_{14}O$: 162.1045, found: 162.1050.

FTIR (FTIR, cm^{-1}) υ = 3200 (br), 2927 (m), 2847 (w), 1654 (w)

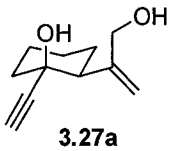
Data for **3.27b**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.25 (s, 1H), 5.19 (s, 1H), 4.36 (s, 1H), 4.18 (d, J=12.4 Hz, 1H), 4.02 (d, J=12.4 Hz, 1H), 3.18 (s, 1H), 2.49 (s, 1H) 2.18-2.05 (m, 2H), 1.77-1.47 (m, 6H) 1.32-1.13 (m, 1H);.

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 148.2 (C_4), 116.0 (CH_2), 85.2 (C4), 74.7 (CH), 72.0 (C_4), 67.4 (CH_2), 51.7 (CH), 41.3 (CH_2), 30.0 (CH_2), 25.7 (CH_2) 23.7 (CH_2);

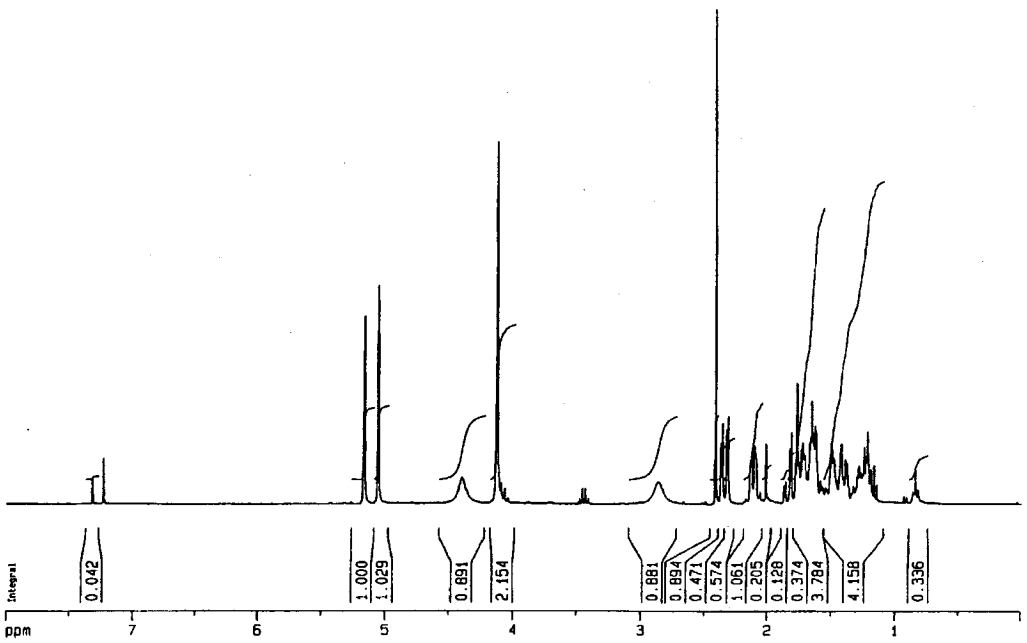
FTIR (neat, cm^{-1}) υ = 3300 (br, m), 2934 (s), 2859 (m), 1651 (w), 1445 (w), 1124 (w), 1064 (m), 1004 (w), 906 (w) cm^{-1}.

HRMS (EI) Expected for $C_{11}H_{16}O_2$ [$(M)^+$]: 180.11503, found: 180.11467

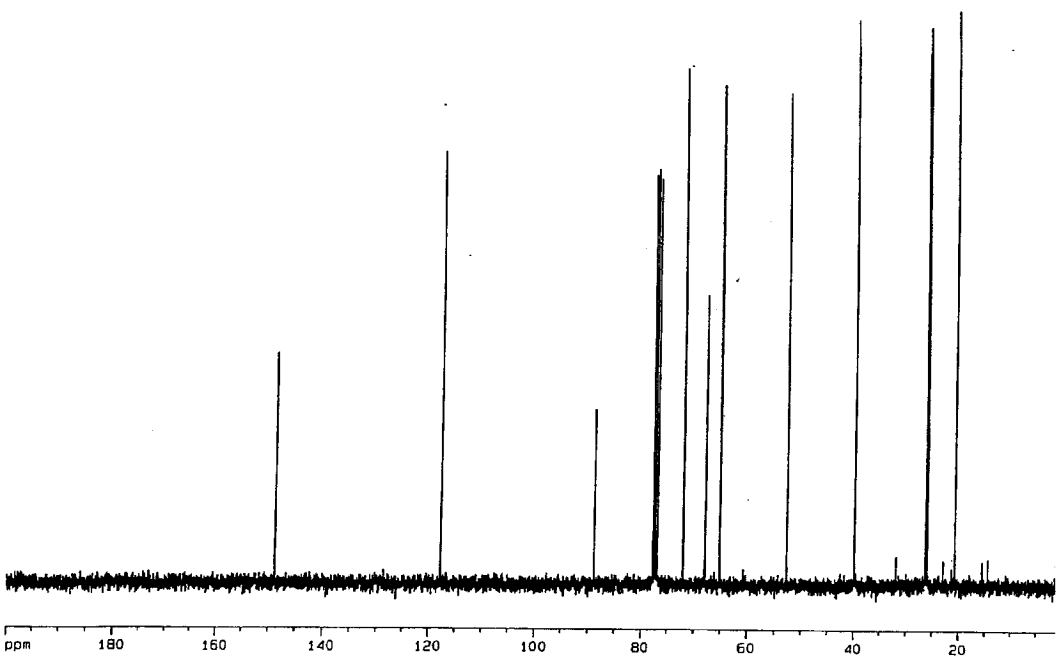


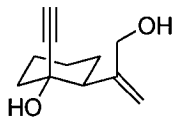
3.27a

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



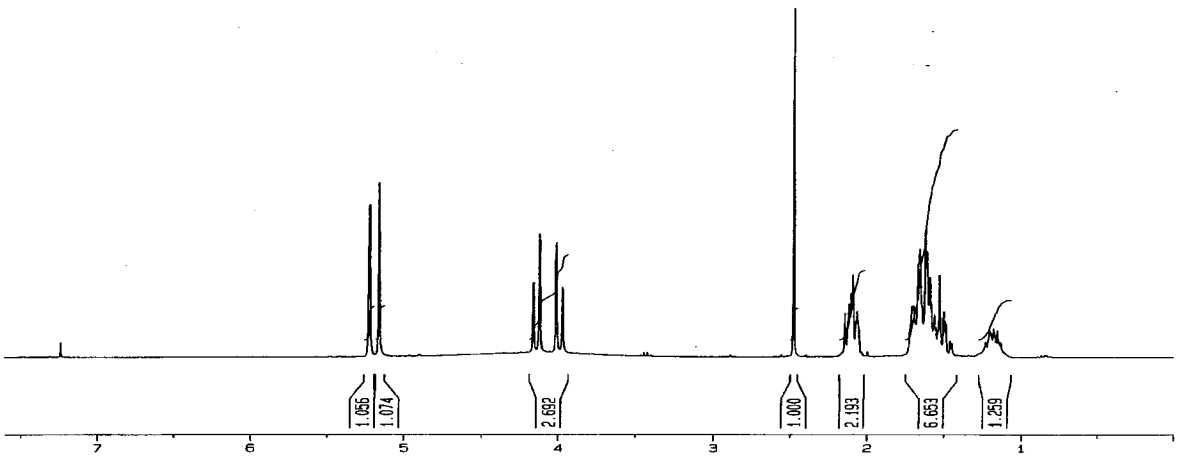
^{13}C NMR ($CDCl_3$, 75 MHz)



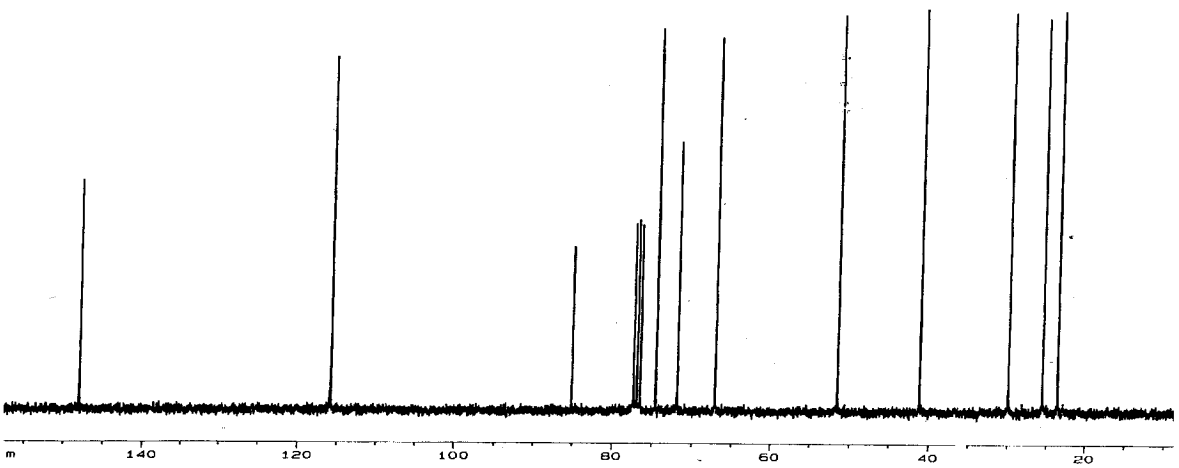


3.27b

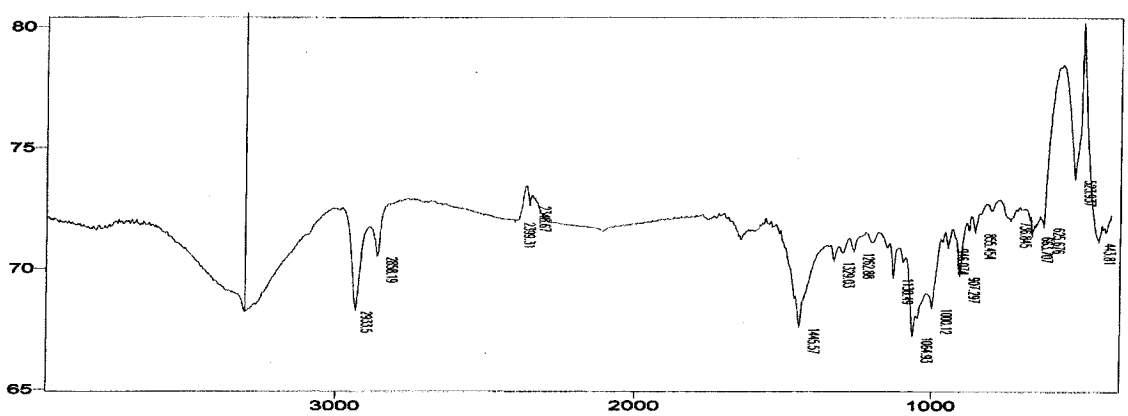
^{1}H NMR ($CDCl_3$, 300 MHz)

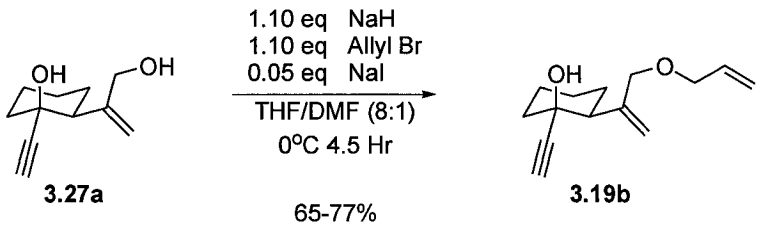


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





2-(1-Allyloxymethyl-vinyl)-1-ethynyl-cyclohexanol (3.19b). A solution of the diol **3.27a** (15.3g, 84.7 mmol, 1.0 equiv.) in a mixture of dry THF (200 mL) and DMF (20 mL) was cooled to 0°C, NaI (1.20g, 8.5 mmol, 0.05 equiv.) and freshly distilled allyl bromide (9.18 mL, 101 mmol, 1.10 equiv.) was added. The mixture was allowed to stir at 0°C for 50 min. NaH (60% w/w, 101 mmol, 1.10 equiv.) was added in small portions, with copious release of H_2 gas. The orange mixture was stirred for 3 hours at 0°C, and quenched by SLOW addition of $NH_4Cl_{(aq)}$ (40 mL), extracted with diethyl ether (4 x), dried over $MgSO_4$ and concentrated. The crude was subjected to flash chromatography (0 to 10% Et_2O in Hexanes) to give the allyl ether **3.19b** as a pale yellow oil (14.2g, 76%)

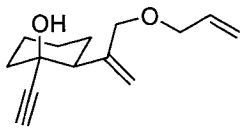
Data for **3.19b**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.92-5.79 (m, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.17-5.13 (m, 3H), 4.48 (s, 1H), 4.11-4.06 (m, 2H), 3.91-3.78 (m, 2H), 2.35-2.27 (m, 2H), 2.10-2.04 (m, 1H), 1.83-1.50 (m, 4H), 1.48-1.13 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 114.8 (C_4) 133.6 (CH), 119.6 (CH_2), 117.7 (CH_2), 88.5 (C_4), 71.5 (CH_2), 71.2 (C_4), 70.4 (CH_2), 67.3 (CH), 52.9 (CH), 39.4 (CH_2), 25.7 (2 x CH_2), 20.3 (CH_2).

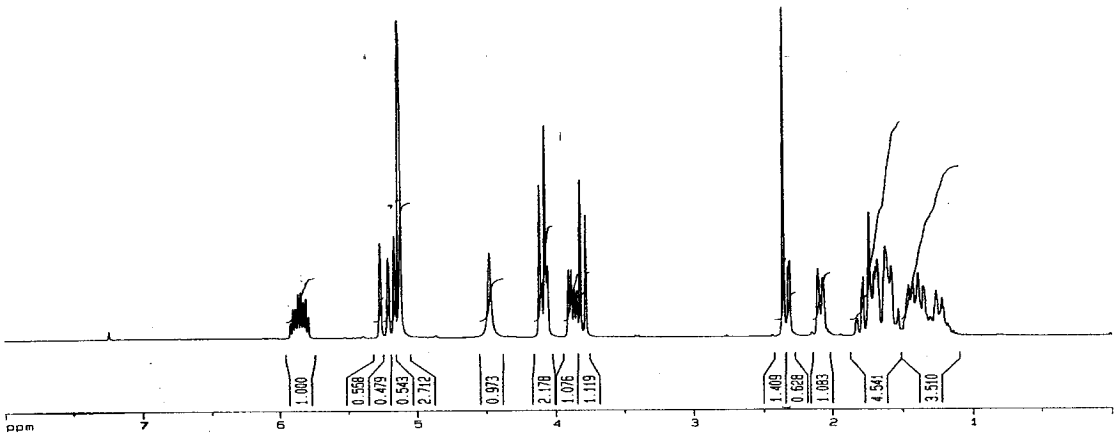
FTIR (neat, cm^{-1}) υ = 3306 (s), 3300 (m), 3079 (m), 2936 (s), 2857 (s), 1644 (m), 1446 (m), 1351 (m), 1144 (m), 1070 (s), 977 (s), 922 (s), 648 (m)

HRMS (EI) Expected for $C_{11}H_{14}O$ [$(M-C_3H_6O)^+$]: 162.1045, found 162.1061.

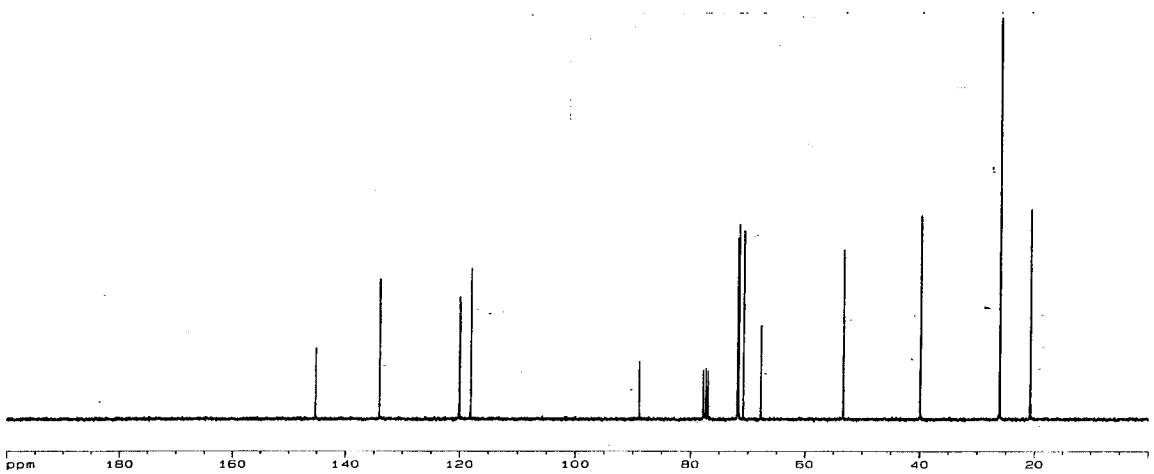


3.19b

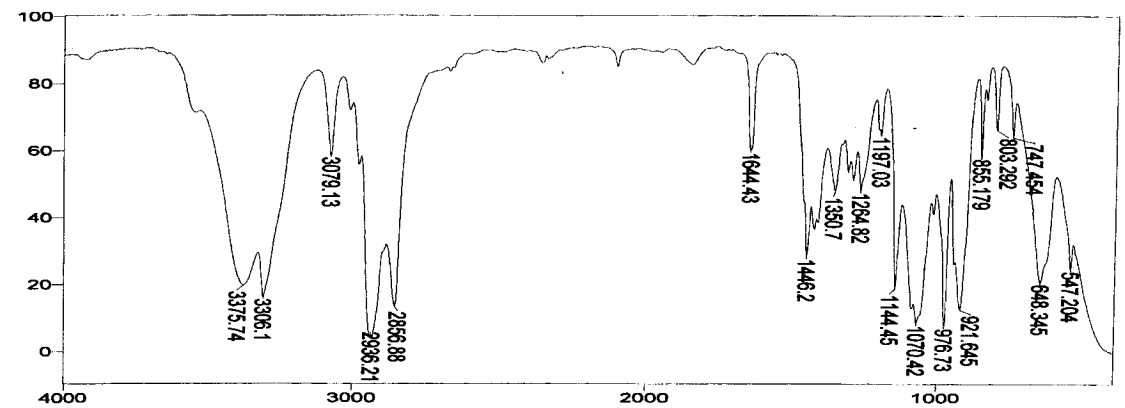
^{1}H NMR ($CDCl_3$, 300 MHz)

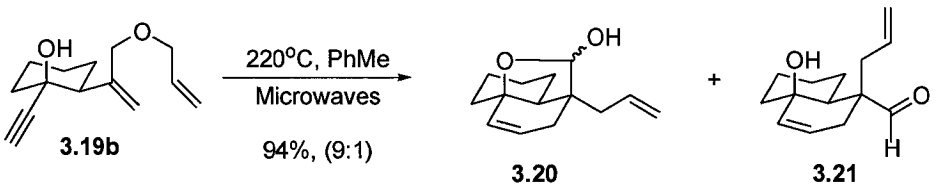


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





7-Allyl-11-oxa-tricyclo[5.3.2.01,6]dodec-9-en-12-ol (3.20) and **1-Allyl-4a-hydroxy-1,2,4a,5,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde (3.21).** A dry microwave cell fitted with two Carboflons™ (a polymer based microwave absorbant) was charged with a solution of the allyl ether **3.19b** (2.00g) and Et_3N (1 mL) in Toluene (17 mL). The mixture was sealed in the microwave apparatus and heated at 220°C for 45 minutes. After cooling, the volatiles were removed, and the residue subjected to flash chromatography. (0 to 30% EtOAc in Hexanes) to give the lactol **3.20** as a mixture of inseparable diastereomers at the anomeric position (total 1.71g, 85%) as a pale yellow solid and the aldehyde **3.21** (173 mg, 9%) as an amorphous yellow solid.

Data for **3.20**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.83-5.51 (m, 3H) 5.24 (d, J = 6.9 Hz, 0.55H), 5.07-4.96 (m, 2.45H) 4.97 (d, J=4.3 Hz, 0.45H) 4.07 (d, J = 4.3 Hz, 0.55H) 2.40-2.11 (m, 3H) 1.98-1.85 (m, 2H) 1.73-1.23 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 137.2, 136.6, 135.4, 134.7, 128.1, 126.5, 117.4, 117.3, 105.1, 103.8, 78.5, 49.3, 49.1, 48.8, 45.9, 38.7, 37.3, 35.3, 33.3, 32.6, 32.4, 29.6, 25.0, 24.7, 23.3, 23.2, 21.0, 20.9.

FTIR (neat, cm^{-1}) υ = 3379 (br, s), 3074, 3025, 2930, 2855, 1822, 1727, 1640, 1143, 1100

HRMS (EI) Expected for $C_4H_{18}O$ $[(M-H_2O)^+]$: 202.1358, found 202.1354.

MP: 55-57°C

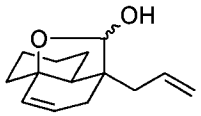
Data for **3.21**:

^{1}H NMR (500 MHz, C_6D_6) δ_{ppm} = 9.28 (s, 1H) 5.82-5.73 (m, 1H), 5.43-5.37 (m, 2H), 5.03-4.95 (m, 2H) 2.77 (dd, J = 8.6, 14 Hz, 1H) 2.65 (ddd, J = 6.1, 14, 1.3 Hz, 1H) 2.12 (d, J = 17 Hz, 1H) 1.86 (dd, J = 17, 2.8 Hz, 1H) 1.80-1.45 (m, 4H), 1.40-0.56 (m, 6H)

^{13}C NMR (125 MHz, C_6D_6) δ_{ppm} = 205.5 (CH), 136.5 (CH), 133.6 (CH), 124.9 (CH), 117.9 (CH_2), 67.3 (C_4), 50.5 (C_4) 46.3 (CH), 40.6 (CH_2), 33.1 (CH_2), 29.6 (CH_2), 26.9 (CH_2), 22.4 (CH_2), 21.3 (CH_2);

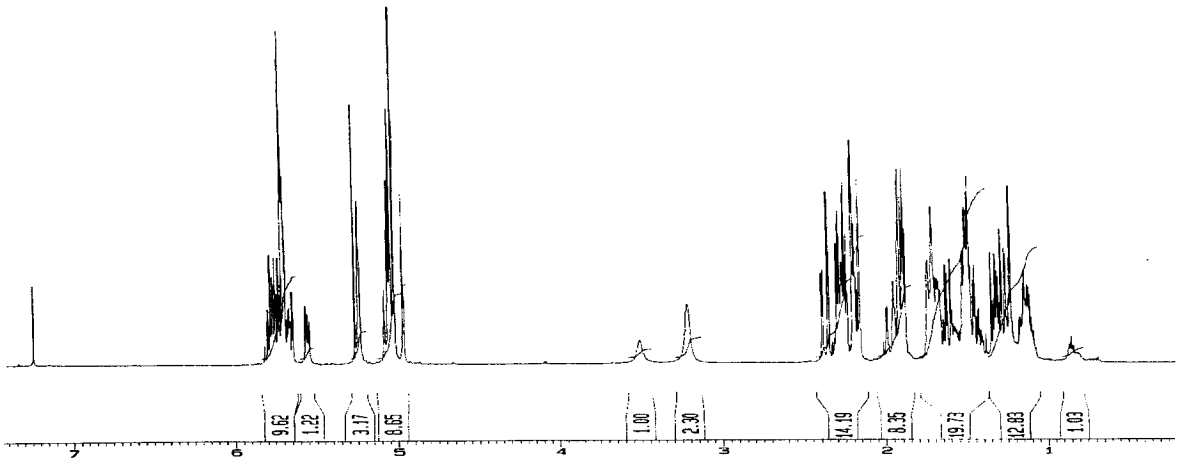
FTIR (neat, cm^{-1}) υ = 3510 (s), 3074.2, 3019, 2930, 2857, 2704, 1720 (s), 1436, 958, 915

HRMS (EI) Expected for $C_{14}H_{20}O_2$ [$(M)^+$]: 220.14633, Found 220.14522.

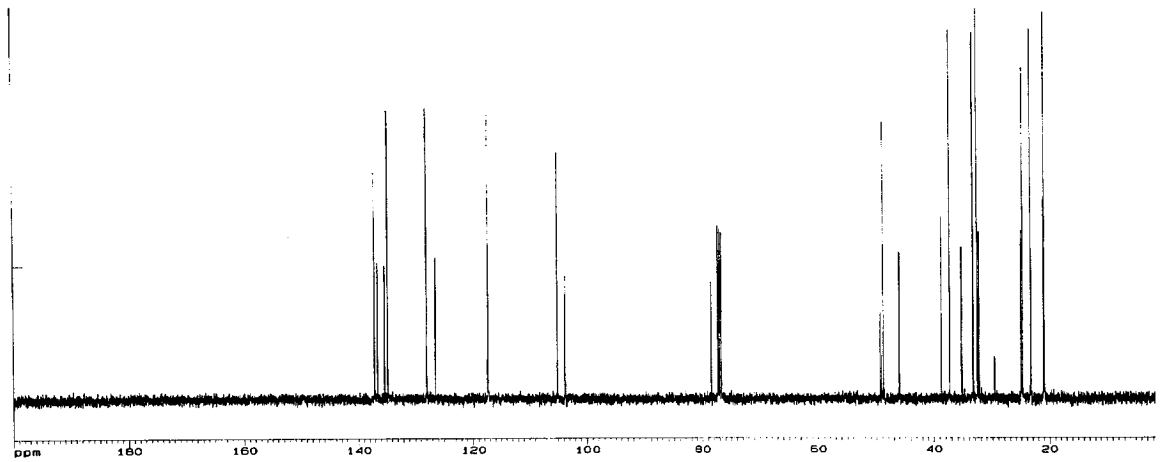


3.20

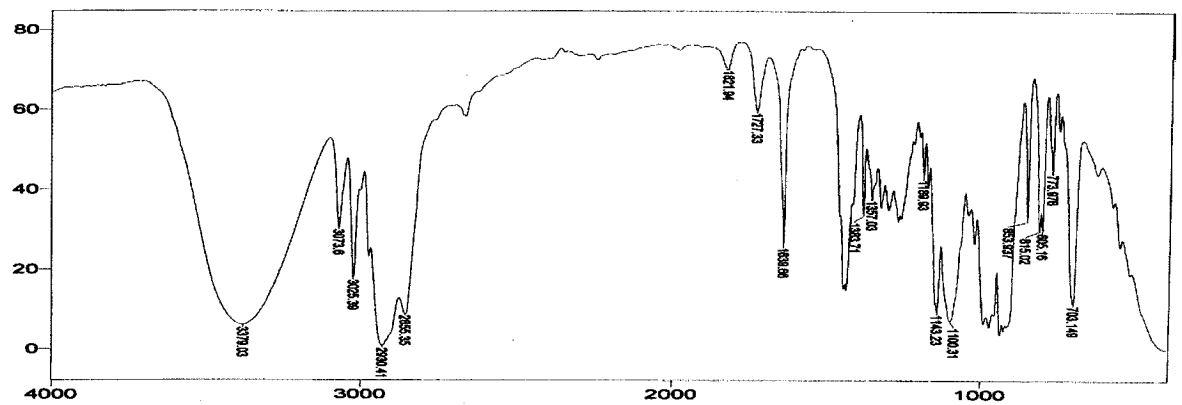
^{1}H NMR ($CDCl_3$, 300 MHz)

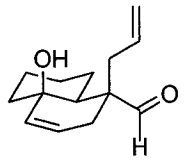


^{13}C NMR ($CDCl_3$, 75 MHz)



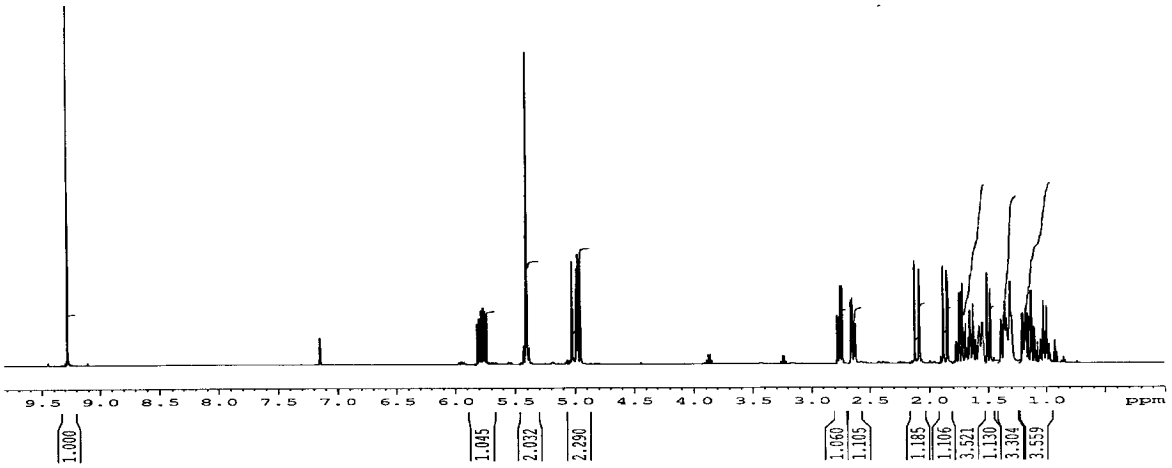
FTIR (neat)



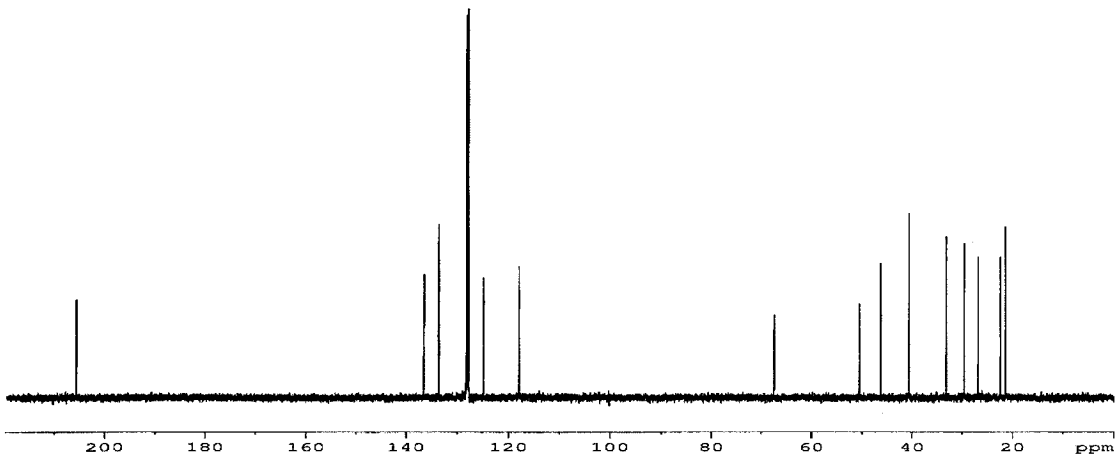


3.21

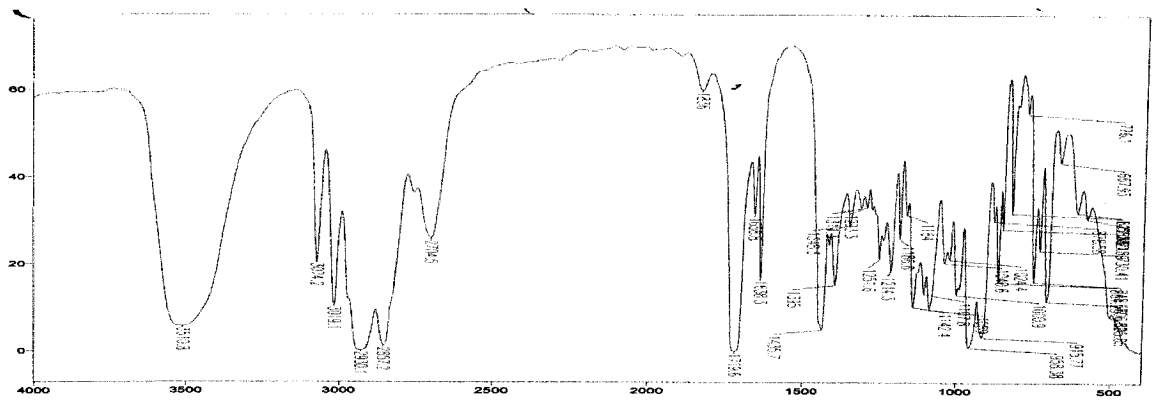
^{1}H NMR ($CDCl_3$, 500 MHz)

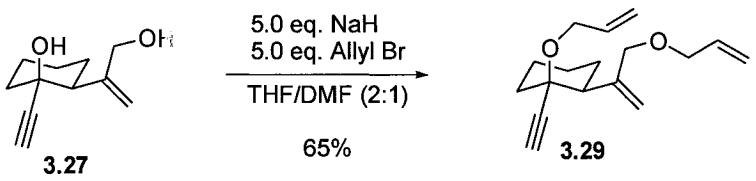


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





1-Allyloxy-2-(1-allyloxymethyl-vinyl)-1-ethynyl-cyclohexane (3.29). To a solution of the diol (37 mg, 0.204 mmol) in a mixture of THF (3 mL) and DMF (1 mL) was added allyl bromide (1.50 uL, 5 equiv.). After 5 min, sodium hydride (60% w/w in oil, 34 mg, 5 equiv.) was added, portionwise. The mixture was stirred for 1 hr, and quenched with sat'd $NH_4Cl_{(aq)}$. The mixture was extracted with diethyl ether (3 x 5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (5% EtOAc in Hexanes) to give the product (53 mg, 65%) as a colourless oil.

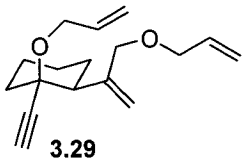
Data for **3.29**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.97-5.06 (m, 2H), 4.16-4.09 (m, 2H), 4.05-3.86 (m, 4H), 2.41 (s, 1H), 2.28 (dd, J = 3.5, 12.7 Hz, 1H), 2.24 (m, 1H), 1.84 (dd, J = 9.1, 12.7 Hz, 1H), 1.74-1.63 (m, 1H), 1.53-1.19 (m, 5H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 146.4 (C_4), 135.4 (CH), 135.0 (CH), 116.5 (CH_2), 115.2 (CH_2), 113.9 (CH_2), 84.9 (C_4), 73.8 (C_4), 73.8 (CH), 73.2 (CH_2), 70.8 (CH_2), 64.1 (CH_2), 51.0 (CH), 35.4 (CH_2), 27.0 (CH_2), 25.8 (CH_2), 20.4 (CH_2)

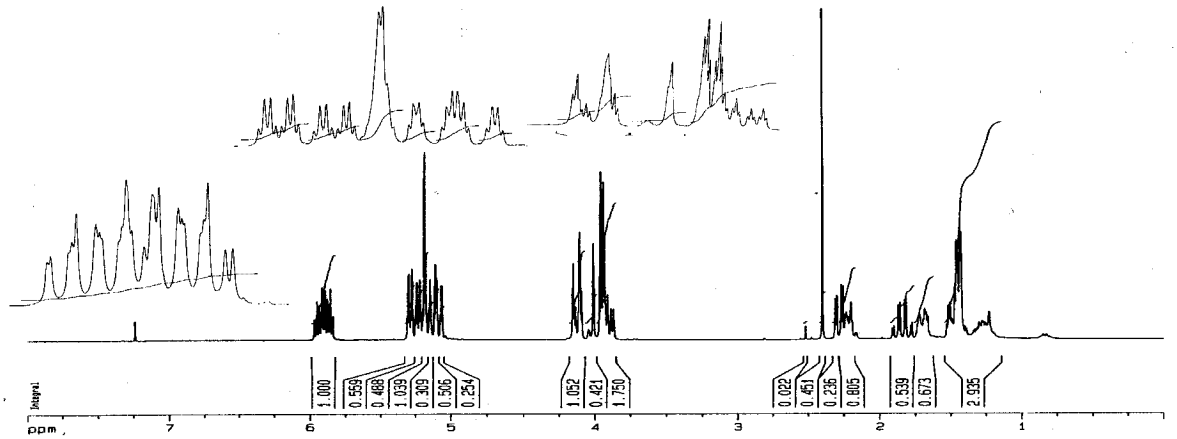
FTIR (neat, cm^{-1}) υ = 3304 (m), 3081 (w), 2936 (s), 2857 (s), 1646 (w), 1447 (m), 1139 (m), 1095 (m), 1060 (m), 919 (m) cm^{-1}

HRMS (EI) Expected for $C_{14}H_{19}O_2$ [(M-Allyl)$^+$]: 219.13851, found: 219.13953

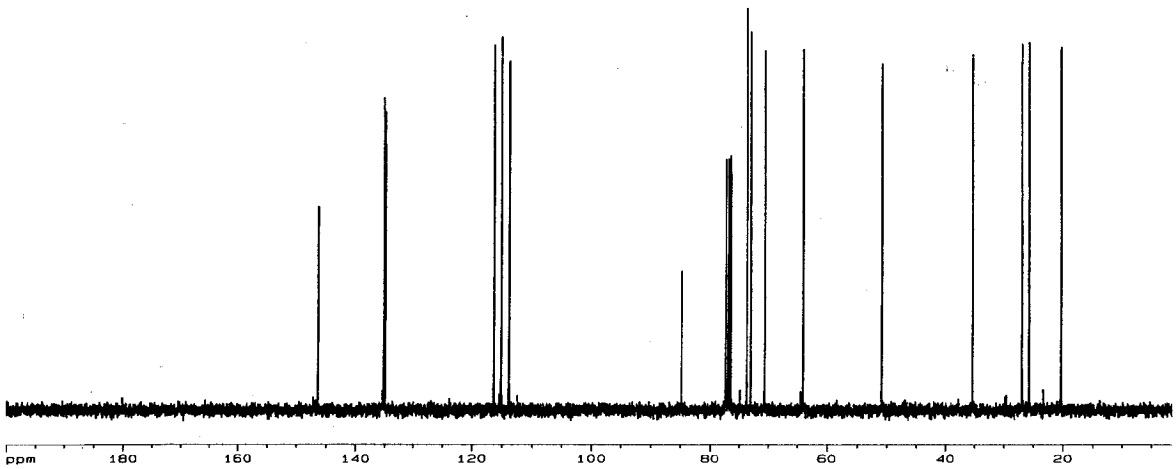


3.29

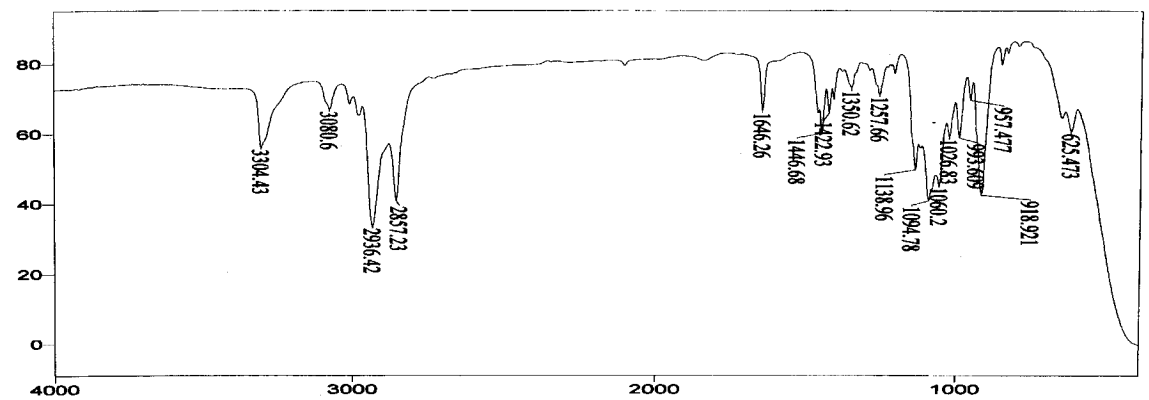
^{1}H NMR ($CDCl_3$, 500 MHz)

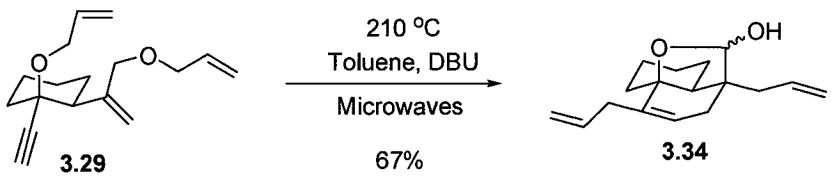


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





3.29 **3.34**

7,10-Diallyl-11-oxa-tricyclo[5.3.2.01,6]dodec-9-en-12-ol (3.34). A clean, dry, microwave cell fitted with 2 carboflons under argon was charged with **3.29** (32 mg, 0.123 mmol), toluene (18 mL), and DBU (50 uL, 0.34 mmol). The solution was degassed with bubbling argon for 15 minutes. The reaction was heated in the microwave (ramp to 210°C over 15 minutes, hold for 45 minutes), and allowed to cool. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (10% EtOAc in Hexanes) to give the lactol **3.24** as a mixture of stereoisomers (20.2 mg, 63% net yield), as a colorless oil.

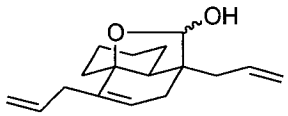
Data for **3.34**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.87-5.68 (m, 2H), 5.40-5.38 (m, 1H), 5.22 (d, J = 8.7 Hz, 1H), 5.09-4.94 (m, 4H), 3.02 (d, J = 8.7 Hz, 1H), 2.89-2.60 (m, 2H), 2.32-2.01 (m, 4H), 2.00-1.90 (m, 2H), 1.84-1.02 (m, 7H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 144.9 (C_4), 137.0 (CH), 134.7 (CH), 123.5 (CH), 117.4 (CH_2), 116.1 (CH_2), 105.7 (CH), 80.4 (C_4), 49.0 (C_4), 48.9 (CH), 37.3 (CH_2), 35.7 (CH_2), 32.7 (CH_2), 29.4 (CH_2), 24.4 (CH_2), 23.9 (CH_2), 21.0 (CH_2)

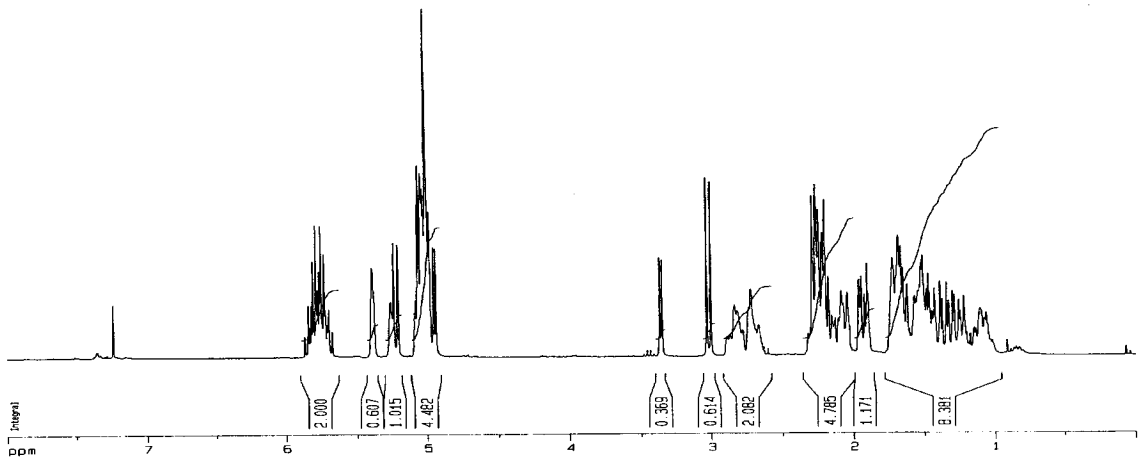
FTIR (neat, cm^{-1}) υ = 3400 (m), 3075 (m), 2932 (s), 2859 (m), 1640 (m), 1439 (m), 1101 (m), 990 (s), 912 (s), 812 (m) cm^{-1}

HRMS (EI) Expected for $C_{17}H_{22}O$ [$(M-H_2O)^+$]: 242.17489, found: 242.17061.

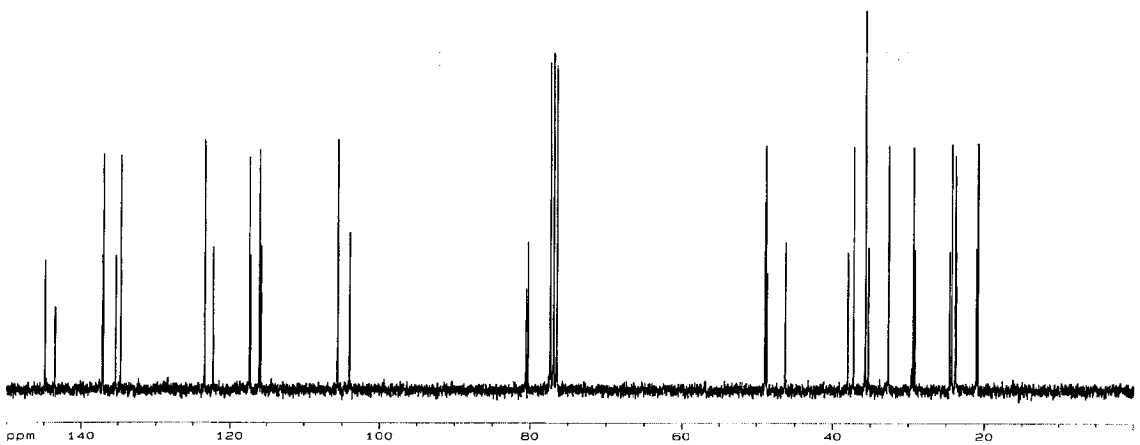


3.34

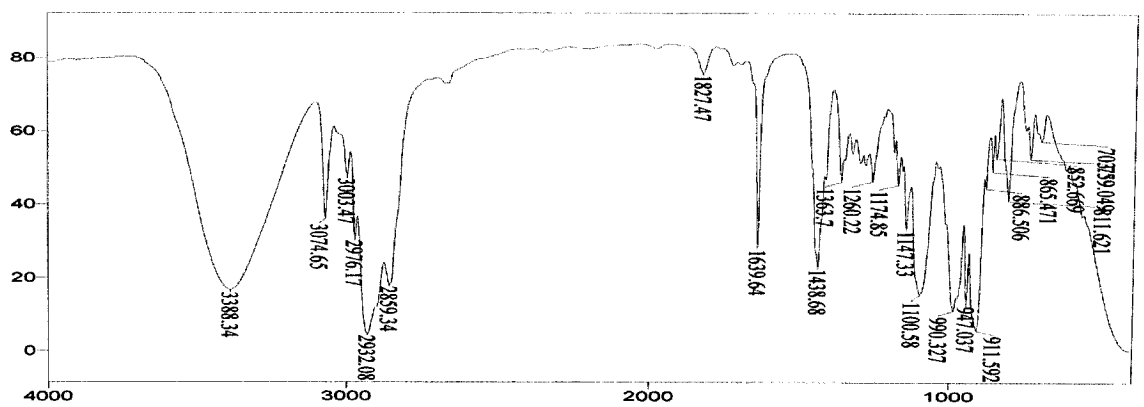
^{1}H NMR ($CDCl_3$, 300 MHz)

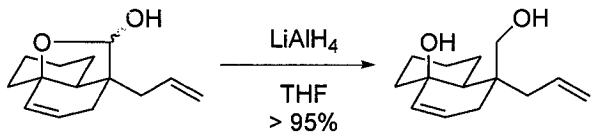


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.20 **3.46**

8-Allyl-8-hydroxymethyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.46). A solution of **3.20** (100 mg) in THF was stirred at RT under air, and $LiAlH_4$ (50 mg) was added. After the bubbling had subsided, the reaction was stirred under N_2 for 1.5 hr until it was deemed complete by TLC (approx. 1 hr). The mixture was cooled in an ice bath, and NH_4Cl(aq) was added very slowly. The crude was extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography to give **3.46** (97mg, >95%) as a white solid (mp: 62-64°C).

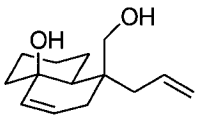
Data for **3.46**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.78-5.62 (m, 2H), 5.48 (d, J = 10.1 Hz, 1H), 5.08-4.92 (m, 2H), 4.20-3.95 (m, 2OH), 3.60 (d, J = 11.5 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 2.25-1.2 (m, 13H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 134.3 (CH), 134.5 (CH), 128.6 (CH), 118.8 (CH_2), 68.2 (C_4), 68.0 (CH_2), 48.2 (CH), 41.9 (CH_2), 40.0 (CH_2), 39.1 (C_4), 34.1 (CH_2), 27.4 (CH_2), 21.4 (CH_2), 20.8 (CH_2).

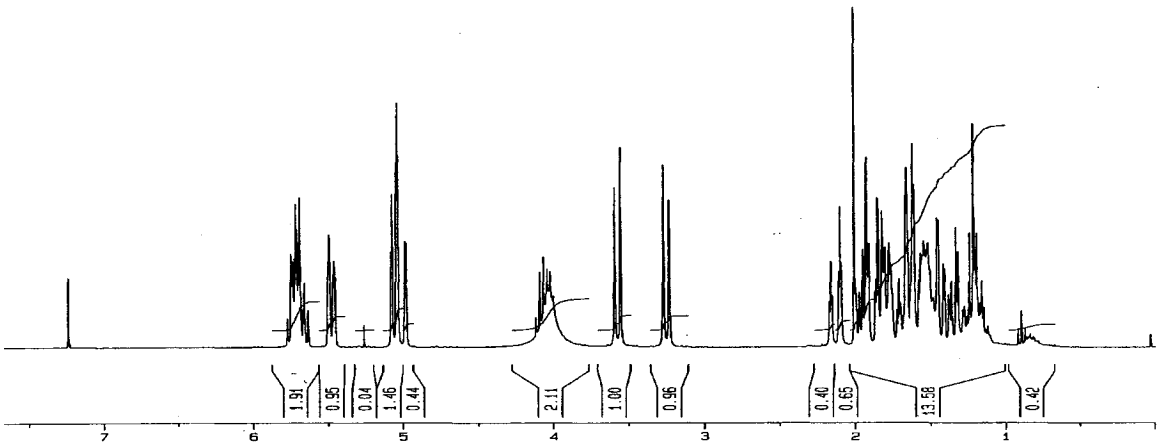
FTIR (neat, cm^{-1}) υ = 3414 (s), 2928 (s), 1439 (s), 957 (s), 938 (s), 911 (s)

HRMS (EI) Expected for $C_{14}H_{20}O$: 204.1514, found: 204.1490 (4.04%)

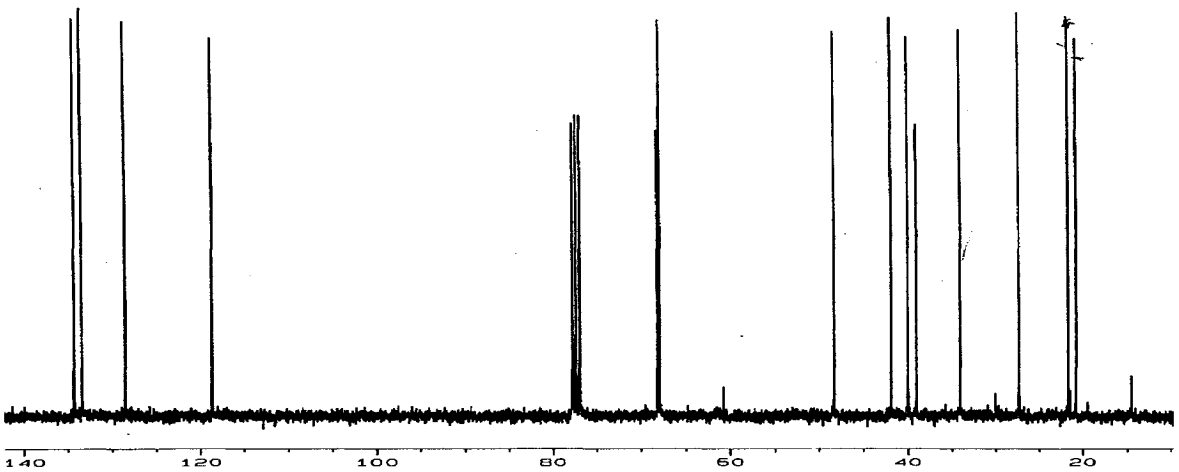


3.46

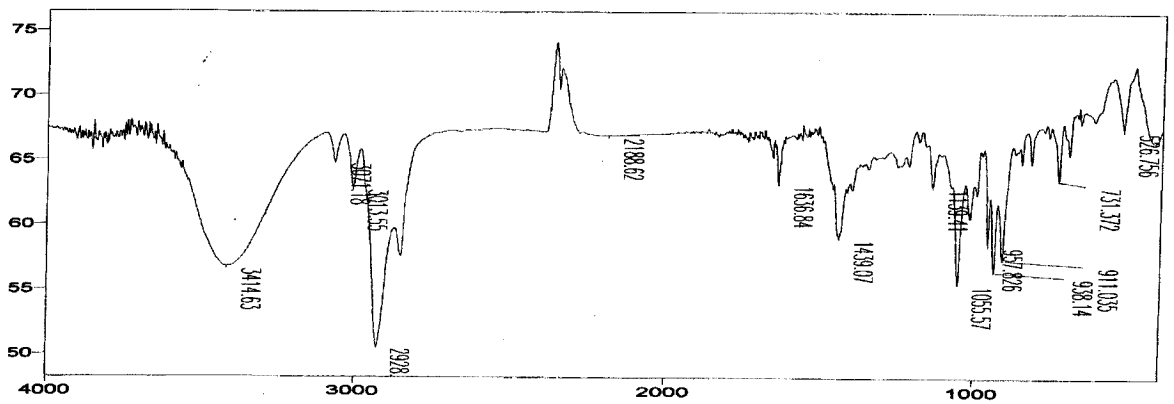
^{1}H NMR ($CDCl_3$, 500 MHz)

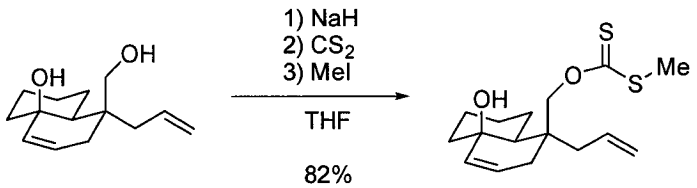


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





3.46 **3.49**

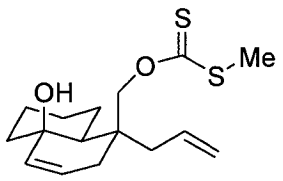
Dithiocarbonic acid O-(1-allyl-4a-hydroxy-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylmethyl) ester S-methyl ester (3.49). A solution of diol **3.46** (150 mg, 676 umol) in THF (5 mL) was stirred at rt, and NaH (60% w/w, 81 mg, 3 equiv.) was added in a single portion. After 10 minutes carbon disulfide (61 uL, 1.5 equiv.) was added, and the solution changed to a yellow-orange colour. Stirring was continued for 20 minutes and MeI (63 uL, 1.5 equiv.) was added. Following another 10 minutes, the reaction was quenched with aqueous $NH_4Cl_{(sat.)}$ (3 mL), extracted with ether (3x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography to give **3.49** as a yellow-orange oil (167 mg, 82%).

Data for **3.49**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.82-5.61 (m, 2H), 5.57-5.50 (m, 1H), 5.17-5.03 (m, 2H), 4.71 (s, 2H), 2.51 (s, 3H), 2.22-1.85 (m,5H), 1.76-1.02 (m, 11H)

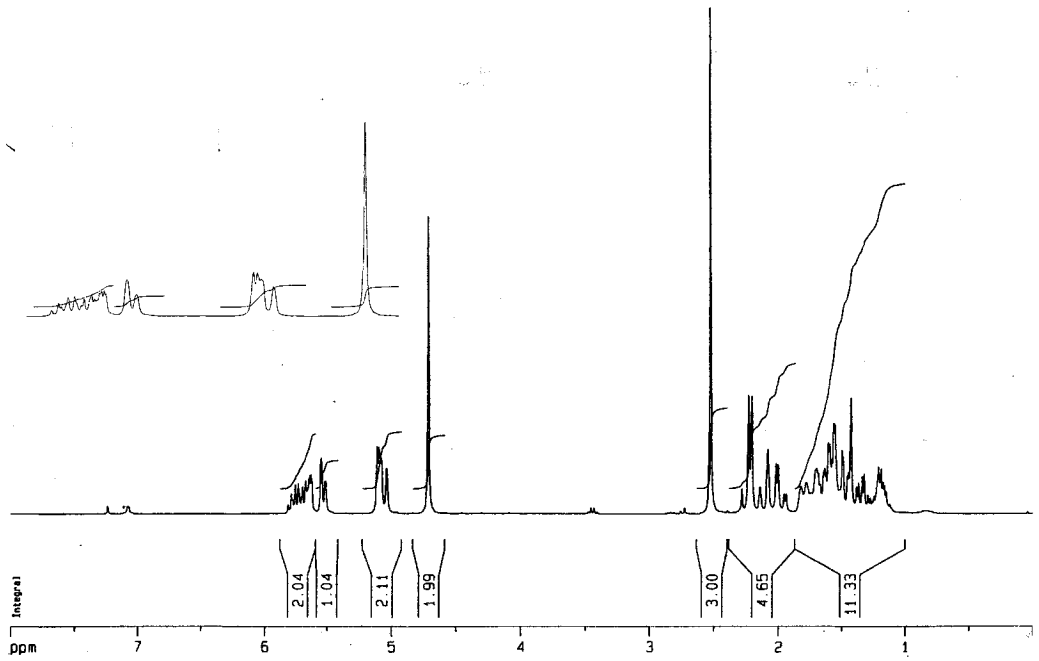
^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 215.5 (C=S), 133.6 (CH), 132.9 (CH), 128.9 (CH), 126.7 (CH_2), 77.6 (CH_2), 68.3 (C_4), 47.8 (CH), 40.2 (CH_2), 40.1 (CH_2), 38.1 (C_4), 32.8 (CH_2), 26.8 (CH_2), 21.2 (CH_2), 20.8 (CH_2), 18.9 (CH_3)

HRMS (EI, m/z) Expected for $C_{16}H_{24}O_2S_2$ [$(M-H_2O)^+$]: 294.11120, found: 294.1115 (0.6%)

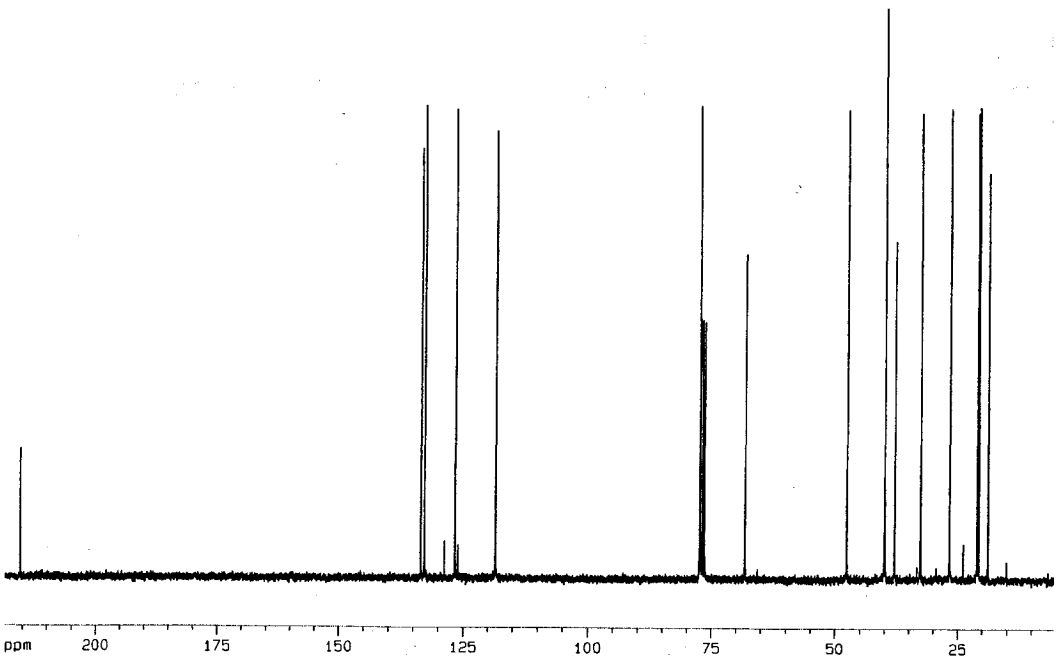


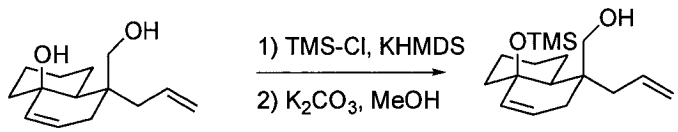
3.49

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



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





3.49 69% **3.54**

(1-Allyl-4a-trimethylsilanyloxy-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl)-methanol (3.54). A solution of **3.49** (550 mg, 2.48 mmol) in THF (100 mL) was stirred at 0°C, and freshly distilled chlorotrimethylsilane (1.3 mL, 4 equiv.) was added, followed by KHMDS (solid, 4 eq.) The reaction was stirred for 4 hr while allowing to warm to room temperature. The reaction was quenched with aqueous $NH_4Cl_{(sat.)}$, extracted with ether (3x), dried over $MgSO_4$ and concentrated to give a colourless light oil. The crude oil was used for the next without further purification. The oil was redissolved in MeOH (50 mL), and K_2CO_3 (300 mg, 1 equiv.) was added. This was stirred for 4 hr at 0°C. After the reaction was complete, the mixture was diluted with water (50 mL). Volatiles were removed *in vacuo*, and the remaining aqueous phase was extracted with dichloromethane (4 x 20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (5% EtOAc in Hexanes) to give **3.54** as a colourless oil. (506 mg, 69%).

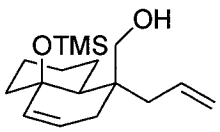
Data for **3.54**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.80-5.57 (m, 3H), 5.07 (s, 1H), 5.06-4.98 (m, 1H), 3.65 (dd, J = 5.7, 11.6 Hz, 1H), 3.25 (dd, J = 8.8, 11.6 Hz, 1H), 2.89 (dd, J = 5.7, 8.8 Hz, 1H), 2.17 (dd, J = 6.9, 13.4 Hz, 1H), 2.03 (dd, J = 7.9, 13.4 Hz, 1H), 1.95 (dt, J = 18.2, 2.2 Hz, 1H), 1.82-1.41 (m, 7H), 1.38-1.03 (3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 134.5 (CH), 132.6 (CH), 128.2 (CH), 118.0 (CH_2), 72.9 (C_4), 67.2 (CH_2), 50.4 (CH), 41.3 (CH_2), 39.5 (CH_2), 39.0 (CH_2), 33.8 (CH_2), 27.6 (CH_2), 22.3 (CH_2), 21.5 (CH_2), 2.4 (3 x CH_3).

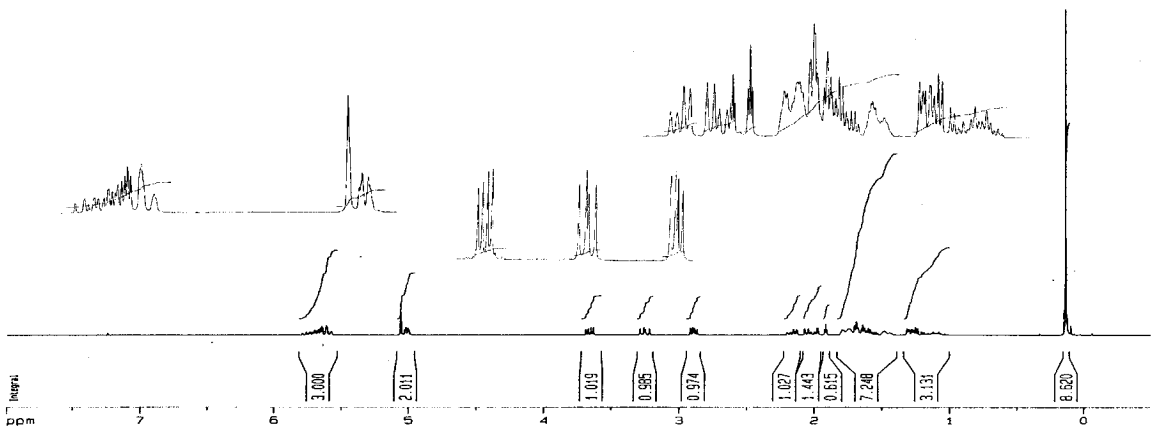
FTIR (neat, cm^{-1}) υ = 3456 (br), 2938 (s), 1445 (s), 1457 (s), 985 (s)

HRMS (EI) Expected for $C_{14}H_{25}O_2Si$ [$(M)^+$]: 253.1573, found: 253.1668

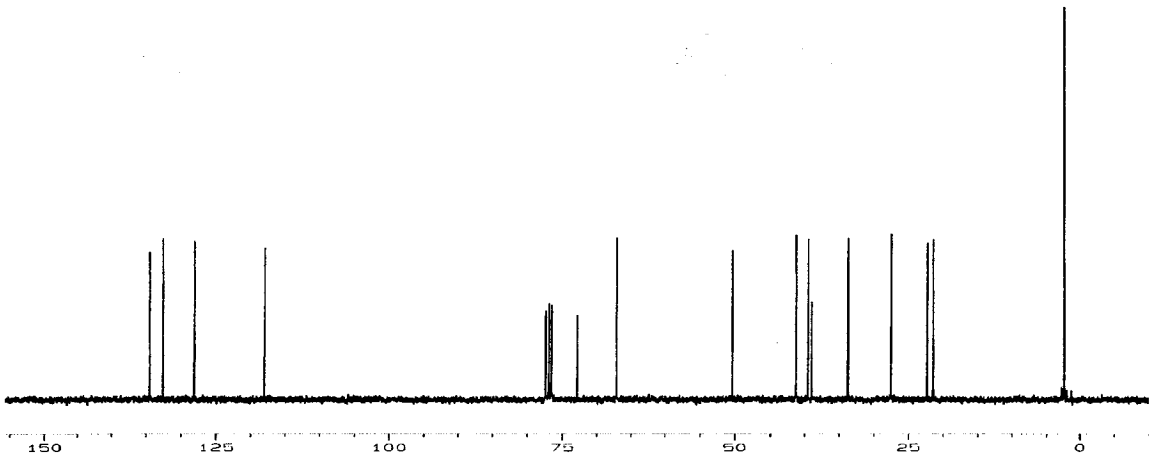


3.54

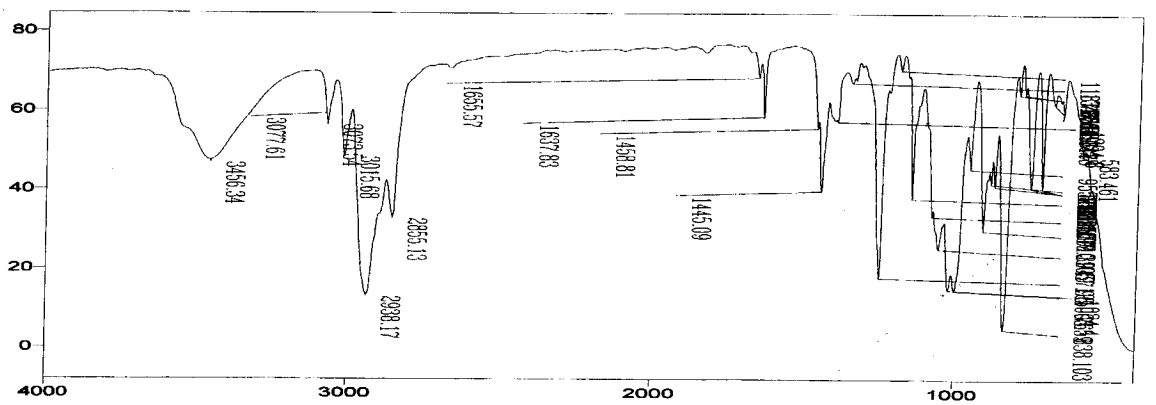
^{1}H NMR ($CDCl_3$, 300 MHz)

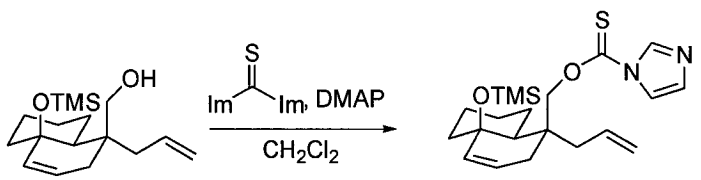


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)



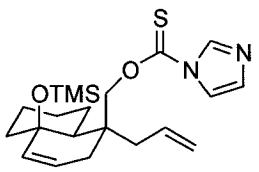


3.53 73% **3.56**

Imidazole-1-carbothioic acid O-(1-allyl-4a-trimethylsilanyloxy-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylmethyl) ester (3.56). A solution of alcohol **3.53** (35 mg, 119 umol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature, and thiocarbonyl diimidazole (64mg, 3.0 equiv.) and DMAP (29 mg, 2.0 equiv.) was added. The reaction was stirred for 24 hr. The volatiles were removed, and the residue was subjected to flash chromatography (10% EtOAc in Hexanes) to give **3.56** as a yellow foam (35 mg, 73%)

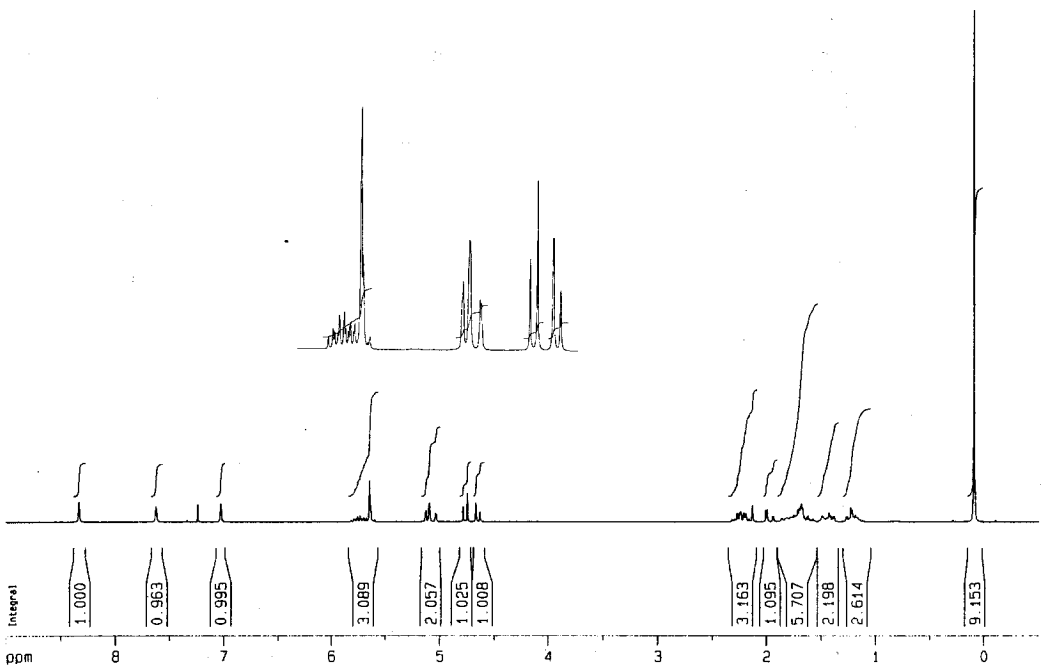
^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 8.33 (s, 1H), 8.63 (s, 1H), 7.02 (s, 1H), 5.72-5.51 (m, 3H), 5.12 (d, J = 9.1 Hz, 1H), 5.09 (dd, J = 16.1, 1.1 Hz, 1H), 4.76 (d, J = 11.2 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 2.62-2.12 (m, 3H), 1.97 (dd, J = 19 Hz, 4.0 Hz, 1H), 1.82-1.13 (m, 9H), 0.09 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 184.4 (C=S), 136.6(CH), 133.6 (CH), 133.3 (CH), 130.6 (CH), 125.8 (CH), 118.9 (CH_2), 117.9 (CH), 77.8 (CH_2), 71.5 (C_4), 49.3 (CH), 40.3 (CH_2), 39.5 (CH_2), 38.0 (CH_2), 33.0 (CH_2), 27.1 (CH_2), 21.4 (CH_2), 21.2 (CH_2), 2.5 (3 x CH_3)

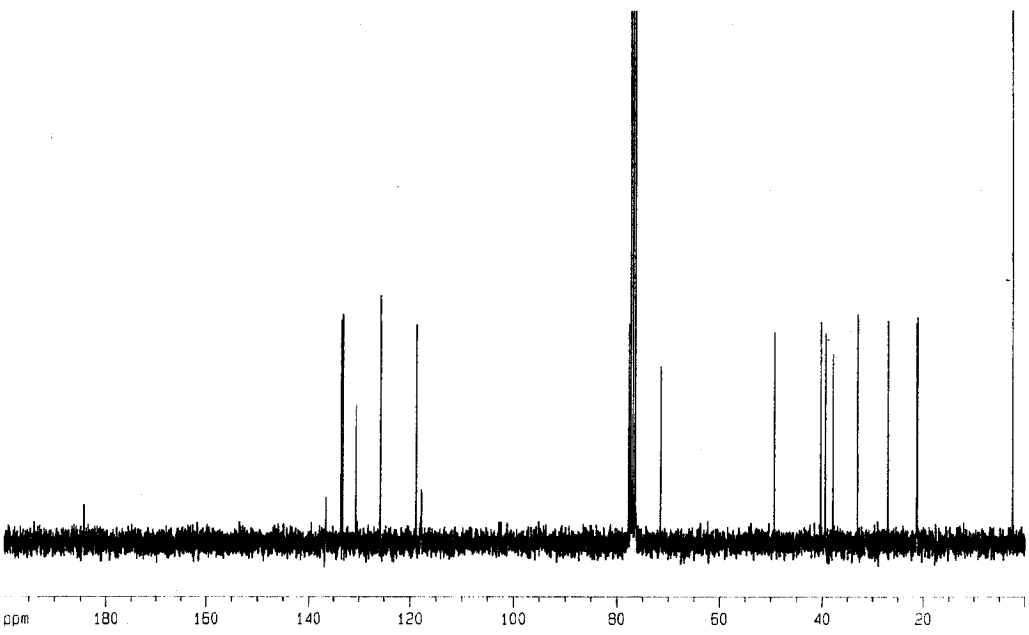


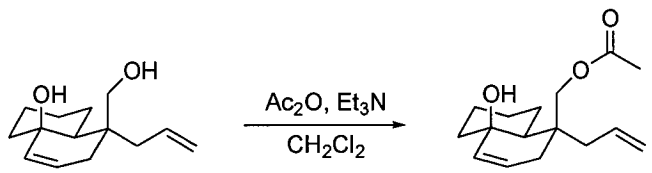
3.56

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



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





3.46 **3.59**

Acetic acid 1-allyl-4a-hydroxy-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylmethyl ester (3.59). A 50 mL roundbottom flask was charged with the diol **3.46** (328 mg, 1.48 mmol), DMAP (50 mg), and CH_2Cl_2 (15 mL). The mixture was stirred at rt and Et_3N (390 uL, 1.5 equiv.) was added, followed by acetic anhydride (225 uL, 1.3 equiv.). The mixture was stirred for 4 hr at room temperature. Once the starting material had been consumed (TLC), the reaction was concentrated and subjected to flash chromatography (20% EtOAc in Hexanes) to give **3.59** as a pale yellow oil (411 mg, 95%).

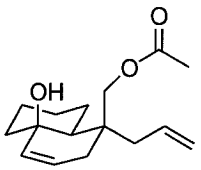
Data for **3.59**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.79-5.42 (m, 3H), 5.08-4.94 (m, 2H), 4.20 (d, J = 11.4Hz, 1H), 4.08 (d, J = 11.4 Hz, 1H), 2.08 (br d, J = 7.5 Hz, 2H), 1.97 (s, 3H), 1.87-1.04 (m, 11H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 171.2 (C=O), 134.2 (CH), 133.5 (CH), 127.0 (CH), 118.8 (CH_2), 68.5 (C_4), 67.9 (CH_2), 48.2 (CH), 40.7 (CH_2), 40.5 (CH_2), 37.8 (C_4), 33.1 (CH_2), 27.3 (CH_2), 21.8 (CH_2), 21.4 (CH_3), 21.0 (CH_2).

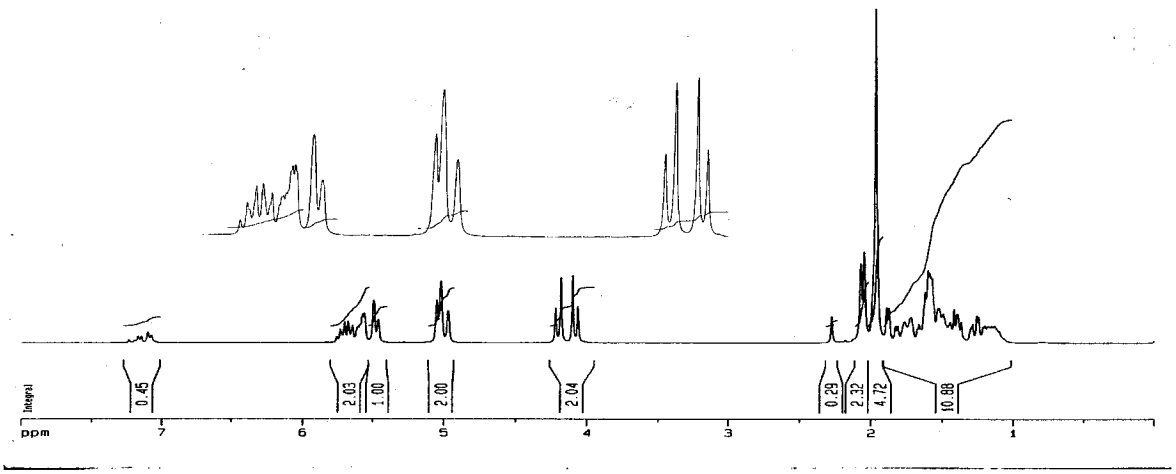
FTIR (neat, cm^{-1}) υ = 3508 (br), 3076 (s), 3015 (s), 2931 (s), 2851 (s), 1738 (s), 1722 (s), 1445 (s), 1386 (s), 1368 (s), 1249 (s), 1039 (m)

HRMS (EI) Expected for $C_{16}H_{20}O$ [(M-AcOH)$^+$]: 204.1514, found: 204.1535 (1.2%)

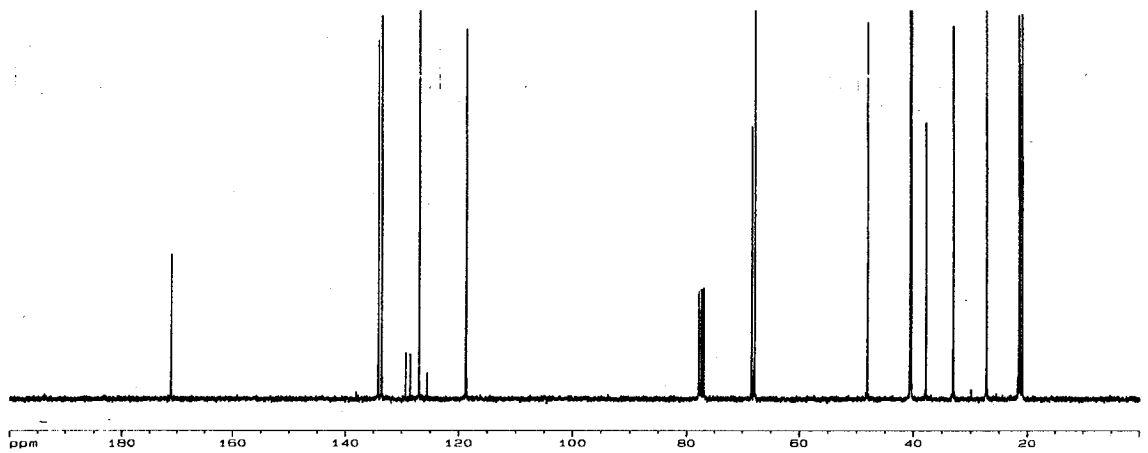


3.59

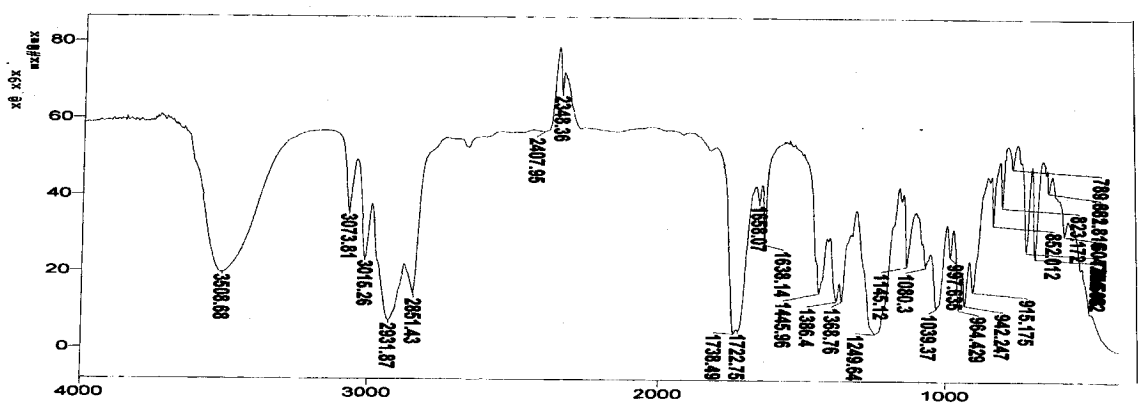
^{1}H NMR ($CDCl_3$, 300 MHz)

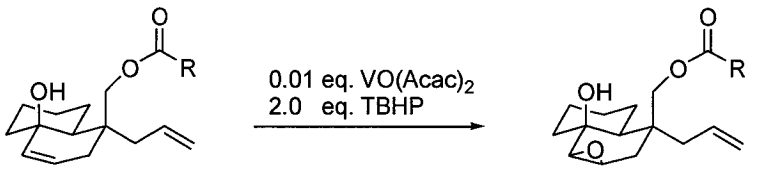


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.58 (R = CH_3)
3.60 (R = $C(CH_3)_3$)

3.62 (R = CH_3)
3.63 (R = $C(CH_3)_3$)

Acetic acid 3-allyl-7a-hydroxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.62) and **2,2-Dimethyl-propionic acid 3-allyl-7a-hydroxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.63)**. Representative procedure: A solution of pivaloate ester **3.63** (518 mg, 1.69 mmol) in toluene (17 mL) was stirred at room temperature and a solution of $VO(Acac)_2$ (4 mg in 1 mL toluene, 0.01 equiv.) was added, dropwise. t-BuOOH (70% in H_2O, 350 uL, 2.0 equiv.) was added to give a dark purple mixture. The reaction was heated to reflux for 2hr, and cooled to 0°C for 20 minutes. An aqueous solution of $NaI_{(sat.)}$ (3 mL) was added, and the mixture was shaken vigorously. $Na_2S_2O_3$ was added, and this was stirred at room temperature for 10 minutes (solution becomes clear). The organic phase was extracted with ethyl acetate (3 x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (20% EtOAc in Hexanes) to give **3.63** as a colourless oil (463 mg, 85%).

Data for **3.62**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.69-5.53 (m, 1H), 5.11-4.94 (m, 2H), 4.18 (d, J = 11.3 Hz, 1H), 3.97 (d, J = 11.3 Hz, 1H), 3.32 (br s, 1H), 2.94 (d, J = 3.8 Hz, 1H), 2.15-2.01 (m, 3H), 1.99 (s, 3H), 1.82-1.34 (m, 8H), 1.21-0.92 (m, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 171.3 (C=O), 133.7 (CH), 119.5 (CH_2), 68.9 (CH_2) 68.5 (C_4) 59.2 (CH), 56.1 (CH), 48.4 (CH_2), 41.3 (CH_2), 40.3 (C_4), 38.2 (CH_2), 30.4 (CH_2), 27.3 (CH_2), 21.7 (CH_2), 21.4 (CH_3), 21.1 (CH_2)

FTIR (neat, cm^{-1}) υ = 3500 (br), 3073 (m), 2934 (s), 2852 (s), 1737 (s), 1445 (s), 1387 (s), 1371 (s), 1249 (s), 1039 (m), 975 (m)

HRMS (EI) Expected for $C_{13}H_{19}O_4$ [(M-Allyl)$^+$]: 239.1283, found: 239.1242 (1.6%)

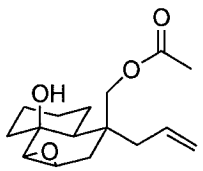
Data for **3.63:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.73-5.51 (m, 1H), 5.12-4.87 (m, 2H), 4.07 (d, J = 11.3 Hz, 1H), 4.00 (d, J = 11.3 Hz, 1H), 3.33 (br s, 1H), 2.92 (d, J = 3.4 Hz, 1H), 2.13-1.97 (m, 4H), 1.81-1.31 (m, 8H), 1.14 (s, 9H), 1.13-0.82 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 178.0 (C=O), 133.2 (CH), 118.9 (CH_2), 68.5 (CH_2), 68.0 (C_4), 58.8 (CH), 55.7 (CH), 47.9 (CH), 40.7 (CH_2), 39.8 (CH_2), 38.7 (C_4), 37.9 (CH_2), 30.1 (CH_2), 27.1 (3 x CH_3), 26.8 (CH_2), 21.3 (CH_2), 20.8 (CH_2).

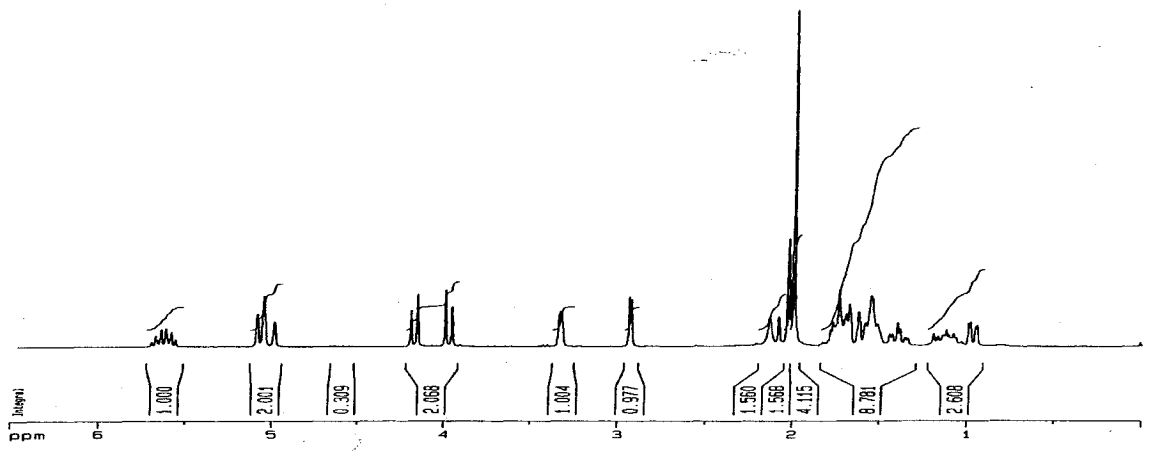
FTIR (neat, cm^{-1}) υ = 3512 (br), 3077 (m), 2968 (s), 2936 (s), 2872 (s), 1725 (s), 1480 (s), 1397 (m), 1285 (s), 1164 (s), 975 (s)

HRMS (EI) Expected for $C_{19}H_{30}O_4$ [$(M)^+$]: 322.2144, found: 322.2133 (0.6%)

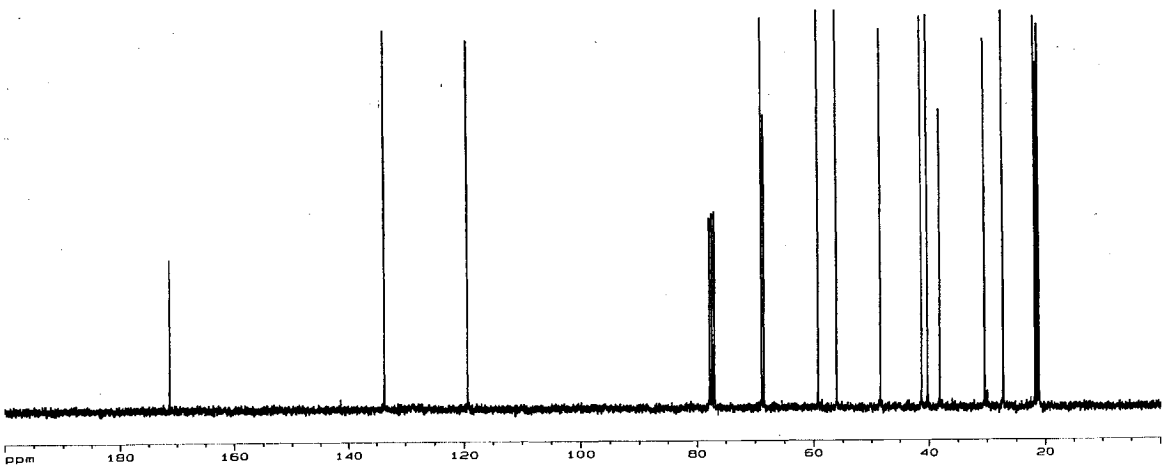


3.62

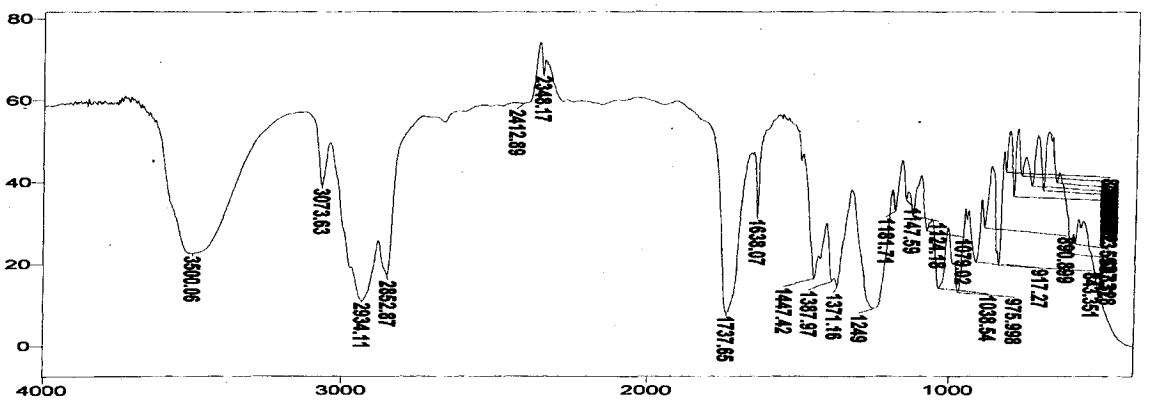
^{1}H NMR ($CDCl_3$, 300 MHz)

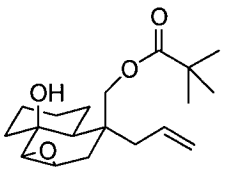


^{13}C NMR ($CDCl_3$, 75 MHz)



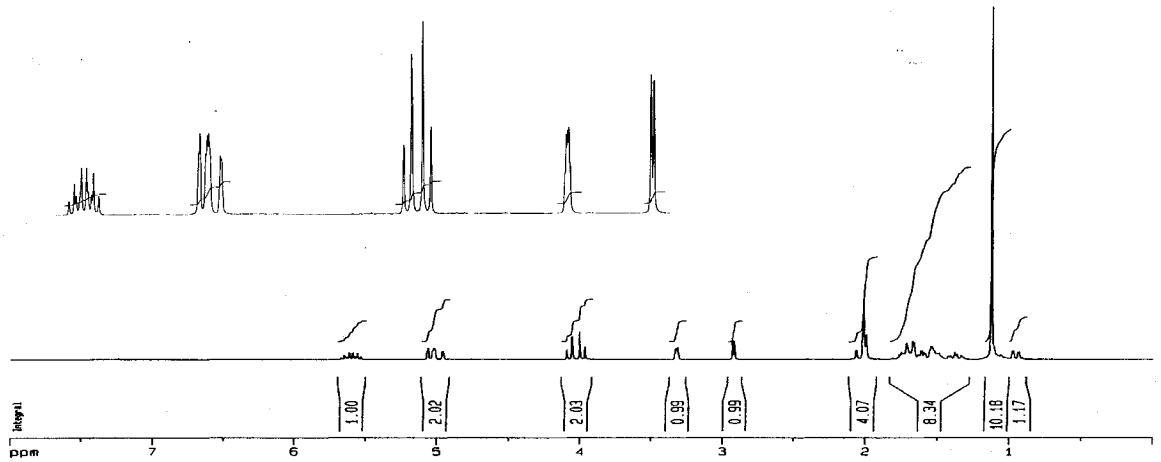
FTIR (neat)



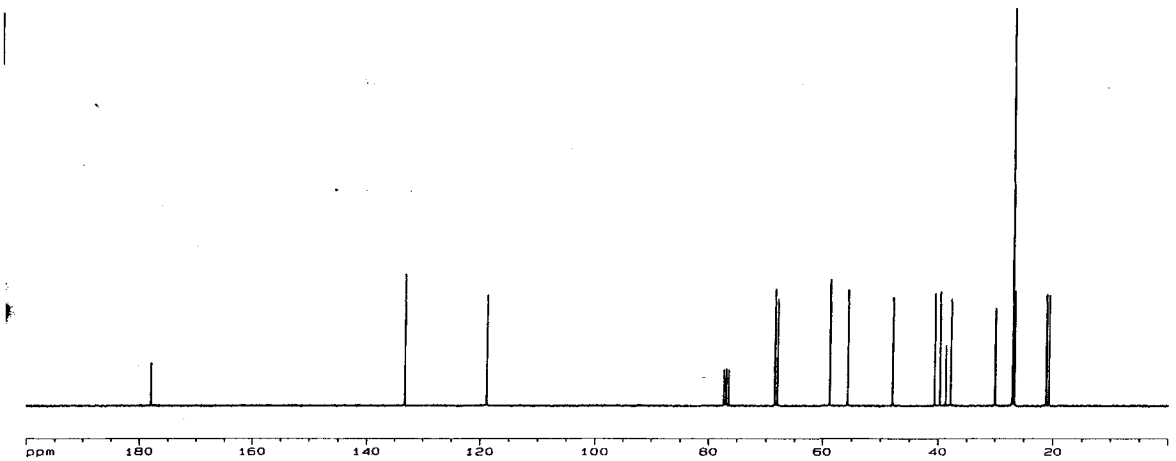


3.63

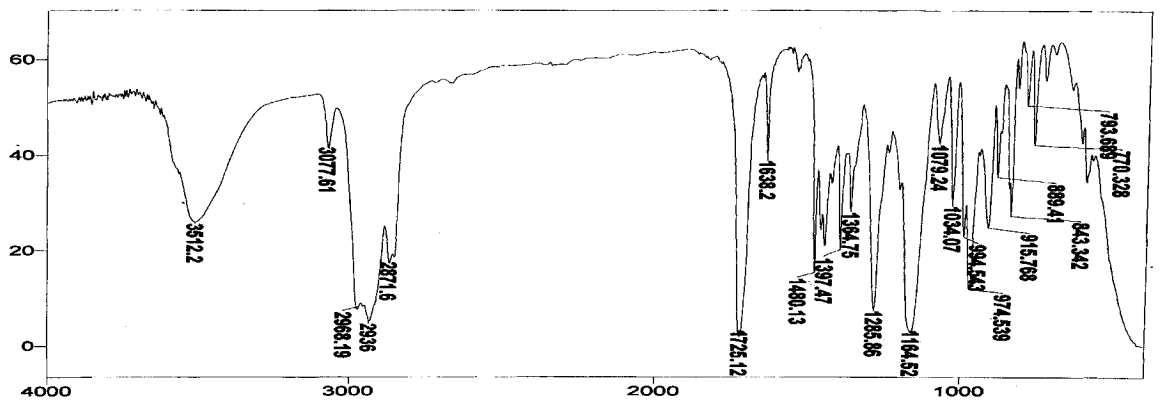
^{1}H NMR ($CDCl_3$, 300 MHz)

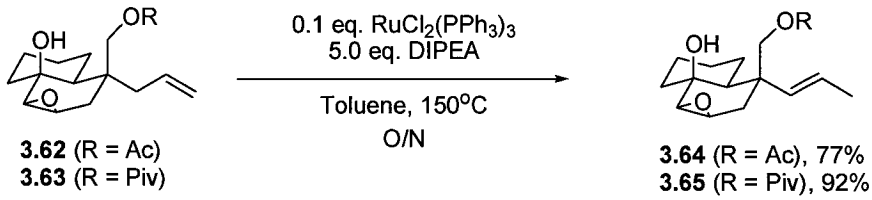


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.62 (R = Ac)
3.63 (R = Piv)

3.64 (R = Ac), 77%
3.65 (R = Piv), 92%

Acetic acid 7a-hydroxy-3-propenyl-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.64) and **2,2-Dimethyl-propionic acid 7a-hydroxy-3-propenyl-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.65)**. Representative procedure: A clean, dry resealable tube was charged with a solution of epoxide **3.63** (463 mg, 1.44 mmol), and DIPEA (1.25 mL, 5 equiv.) in toluene (15 mL). The catalyst bis-(triphenylphosphine)-rutheniumdichloride (52 mg, 0.05 equiv.) was added in a single portion, and the mixture was degassed by bubbling argon for 15 minutes. The tube was sealed, and placed in a wax bath held at 120°C for 48 hr. Once deemed complete (GC), the reaction was allowed to cool, and the volatiles removed *in vacuo*. The black residue was subjected to flash chromatography (0 to 25% EtOAc in Hexanes, 3 steps) to give **3.65** as a light yellow oil (424 mg, 92%)

Data for **3.64**:

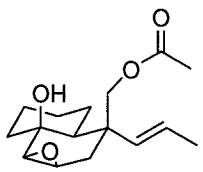
^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.32 (dq, J = 16.0, 6.0 Hz, 1H), 5.13 (d, J = 16.0 Hz, 1H), 4.30 (d, J = 11.3 Hz, 1H), 4.10 (d, J = 11.3 Hz, 1H), 3.35 (br s, 1H), 2.99 (d, J = 3.7 Hz, 1H), 2.31 (br d, J = 16 Hz, 1H), 2.01 (s, 3H), 1.82-1.76 (m, 3H), 1.65 (d, J = 6.0 Hz, 3H), 1.61-0.54 (m, 8H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 170.9 (C=O), 137.2 (CH), 123.5 (CH), 68.2 (C_4), 66.3 (CH_2), 58.7 (CH) 55.6 (CH), 51.2 (CH_3), 40.7 (C_4), 39.8 (CH_2), 32.2 (CH_2), 27.1 (CH_2) 21.4 21.1 (CH_2), 18.4 (CH_3), 15.2 (CH)

Data for **3.65**:

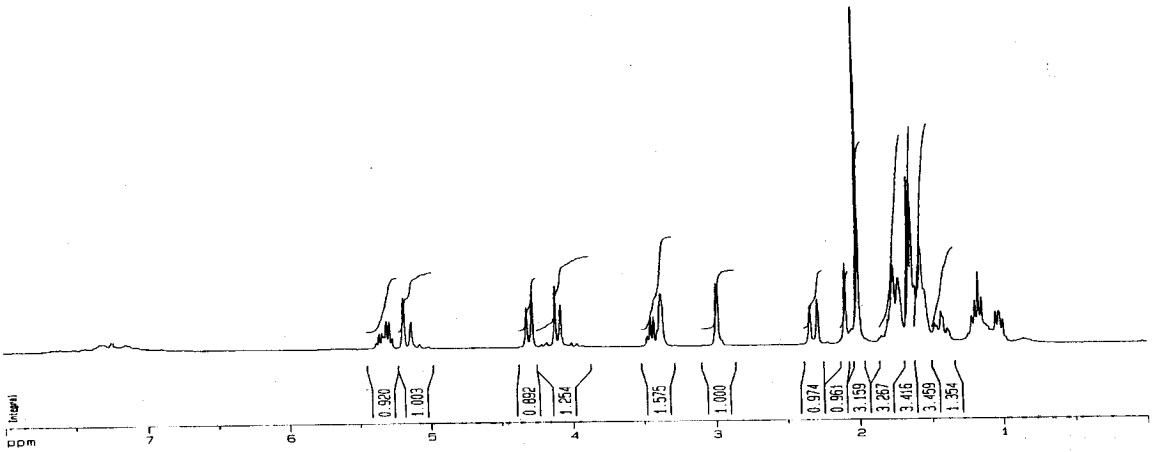
^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.42 (dq, J = 15.6, 5.4 Hz, 1H), 5.13 (d, J = 15.6 Hz, 1H), 4.23 (d, J = 11.3 Hz, 1H), 4.13 (d, J = 11.3 Hz, 1H), 3.45 (br s, 1H), 2.97 (d, J = 3.5 Hz, 1H), 2.31 (br d, J = 16 Hz, 1H), 2.01-1.59 (m, 3H), 1.58 (d, J = 5.4 Hz, 3H), 1.58-1.23 (m, 8H), 1.13 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 178.5 (C=O), 137.3 (CH), 123.7 (CH), 68.2 (C_4), 66.0 (CH_2), 58.8 (CH) 55.7 (CH), 51.0 (CH_3), 41.1 (CH_2), 40.7 (C_4), 38.7 (C_4), 31.9 (CH_2) 21.4 (CH_2), 27.0 (3 x CH_3), 21.5 (CH_2), 20.8 (CH_2), 18.2 (CH)

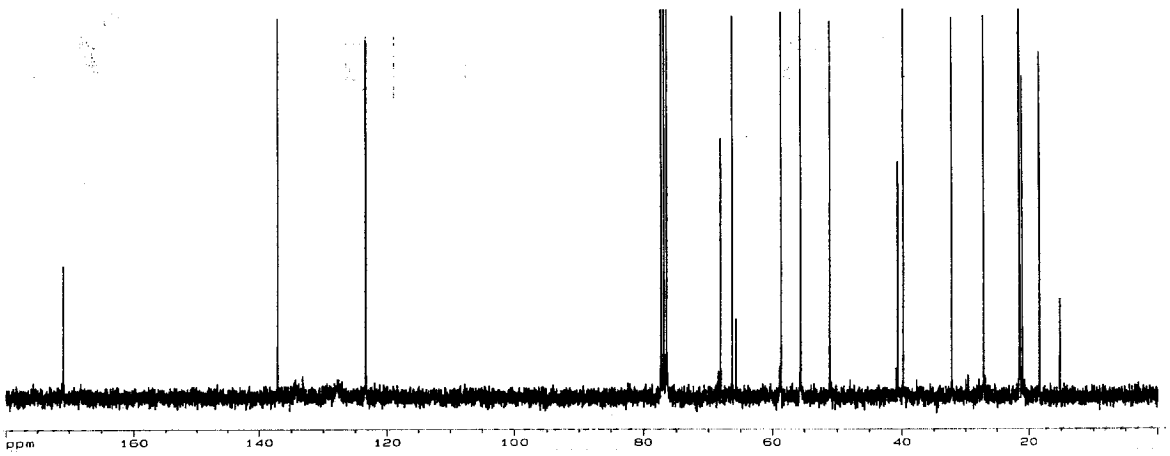


3.64

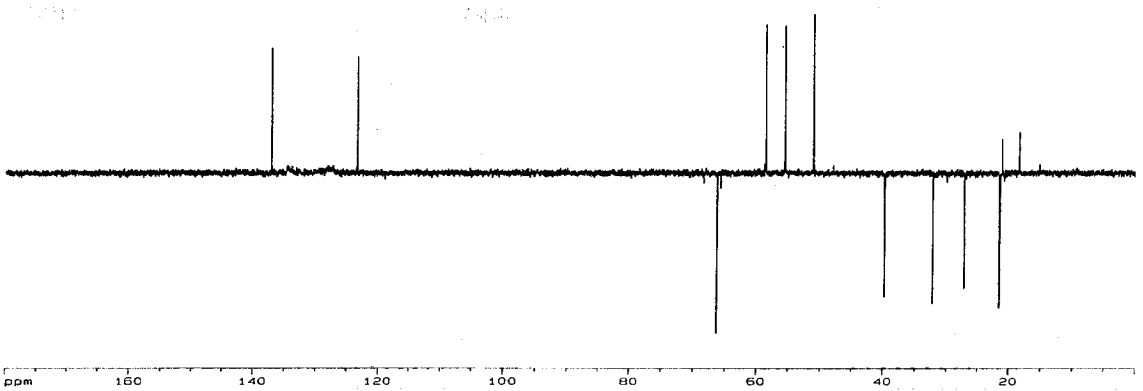
^{1}H NMR ($CDCl_3$, 300 MHz)

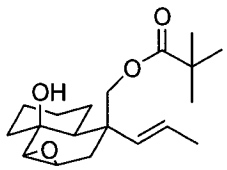


^{13}C NMR ($CDCl_3$, 75 MHz)



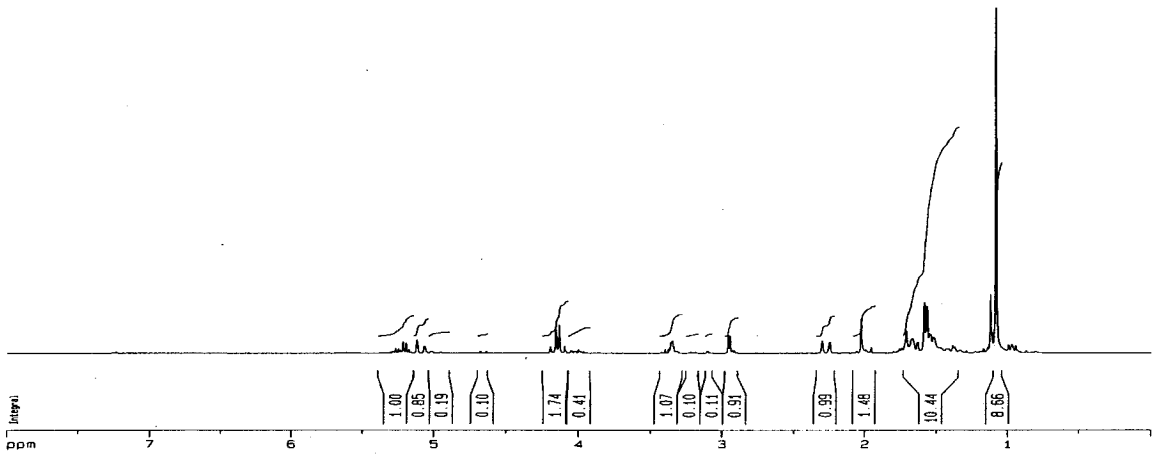
^{13}C DEPT135 ($CDCl_3$, 75 MHz)



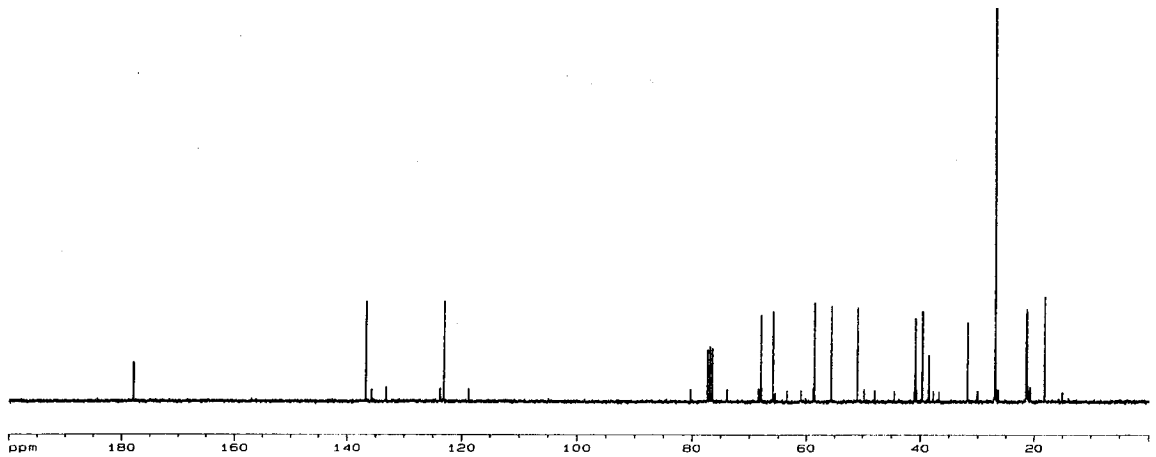


3.64

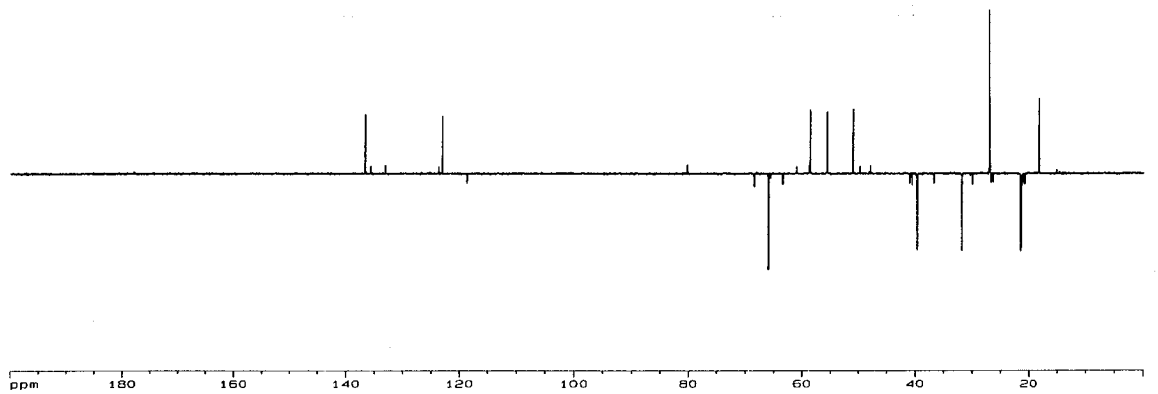
^{1}H NMR ($CDCl_3$, 300 MHz)

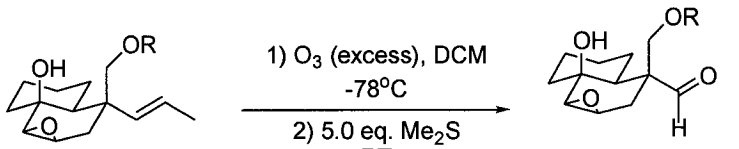


^{13}C NMR ($CDCl_3$, 75 MHz)



^{13}C DEPT135 ($CDCl_3$, 75 MHz)





3.64 (R = Ac), 77%
3.65 (R = Piv), 75%

3.66 (R = Ac), 37%
3.67 (R = Piv), 95%

Acetic acid 3-formyl-7a-hydroxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.66) and **2,2-Dimethyl-propionic acid 3-formyl-7a-hydroxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.67)**. Representative procedure: A solution of olefin **3.65** (424 mg, 1.31 mmol) in dichloromethane (30 mL) was cooled to -78°C under argon. A bubbler fitted to an OzoneLabs^{TM} generator was placed in the flask, and oxygen was passed through the solution as it was being cooled. Once cool, the current was switched on, and ozone was passed through the solution until steel-gray colour persisted (ca. 30 min). The current was switched off, and the bubbler removed. Argon was bubbled through the solution for 10 minutes, and DMS (1.0 mL, 10 equiv.) was added. The mixture was allowed to warm to room temperature and stirred for 1hr. The volatiles were removed uner reduced pressure, and the residue was subjected to flash chromatography (20 % EtOAc in Hexanes) to give **3.67** as sweet-smelling pale yellow oil (387 mg, 95%).

Data for **3.66**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 9.44 (s, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 3.44 (br s, 1H), 3.01 (d, J = 3.8 Hz, 1H), 2.25-2.02 (m, 3H), 1.90 (s, 3H), 1.85-1.62 (m, 4H), 1.60-1.05 (m, 5H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 204.5 (HC=O), 170.6 (C=O), 67.4 (CH_2), 64.1 (C_4), 58.4 (CH), 50.2 (C_4) 50.0 (CH), 47.2 (C_4), 27.0 (3 x CH_3), 26.3 (CH_2), 25.7 (CH_2), 21.9 (CH_2), 20.9 (CH_2), 20.7 (CH).

FTIR (neat, cm^{-1}) υ = 3501 (br s), 2937 (s), 2876 (s), 1727 (s), 1724 (s), 1251 (s), 1078 (s)

HRMS (EI) Expected for $C_{12}H_{16}O_3$ [$(M\text{-}AcOH)^+$]: 208.1099, found: 208.1082 (1.1 %)

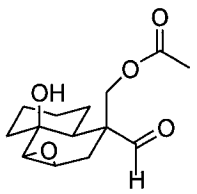
Data for **3.67**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 9.45 (s, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 3.45 (br s, 1H), 3.01 (d, J = 3.8 Hz, 1H), 2.20-1.62 (m, 7H), 1.49-1.13 (m, 6H), 1.08 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 204.6 (HC=O), 177.8 (C=O), 67.5 (CH_2), 64.2 (C_4), 58.5 (CH), 55.0 (CH), 50.1 (C_4), 47.4 (CH), 39.4 (CH), 38.6 (C_4), 26.9 (3 x CH_3), 26.2 (CH_2) 25.7 (CH_2), 21.8 (CH_2), 20.9 (CH_2),

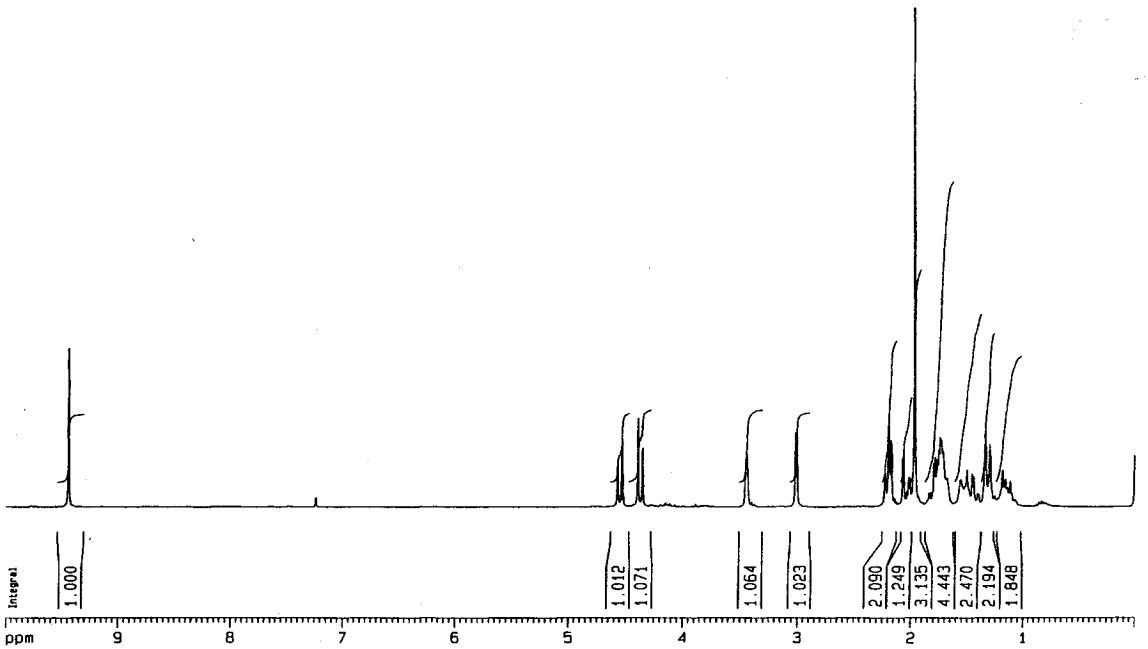
FTIR (neat, cm^{-1}) υ = 3507 (br s), 2974 (s), 2866 (s), 1727 (s), 1724 (s), 1480 (s), 1284 (s), 1158 (s), 977 (s)

HRMS (EI) Expected for $C_{12}H_{17}O_3$ [$(M\text{-}OPiv)^+$]: 209.1177, found: 208.1185 (0.6 %)

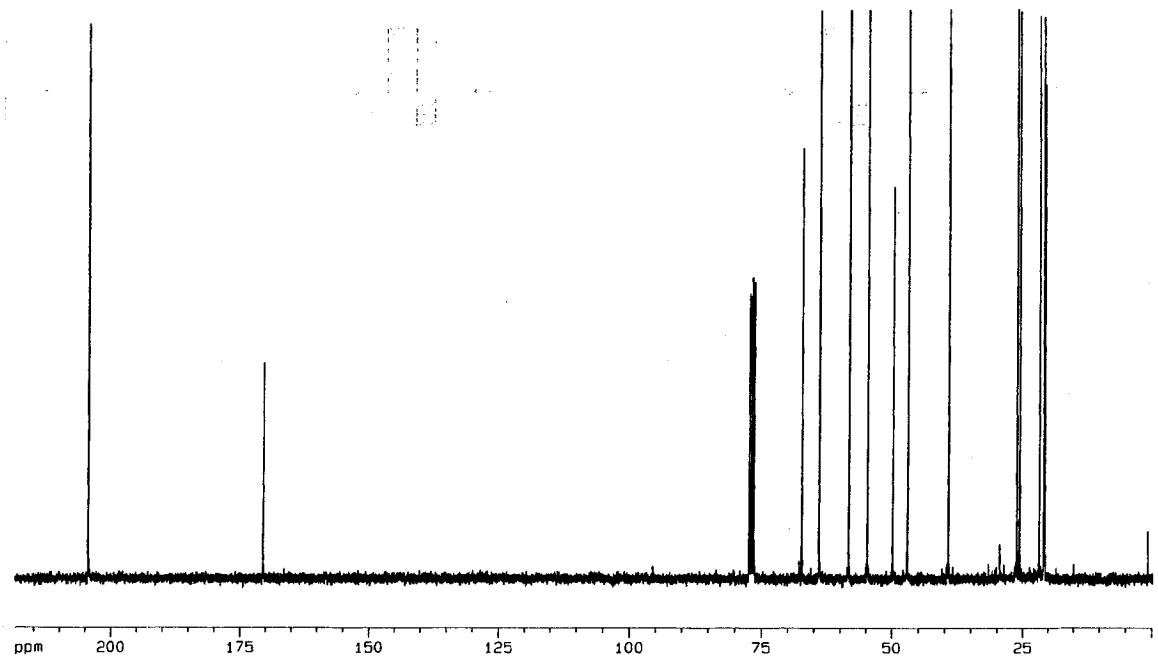


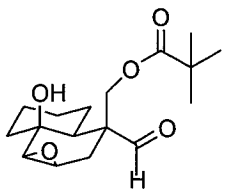
3.66

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



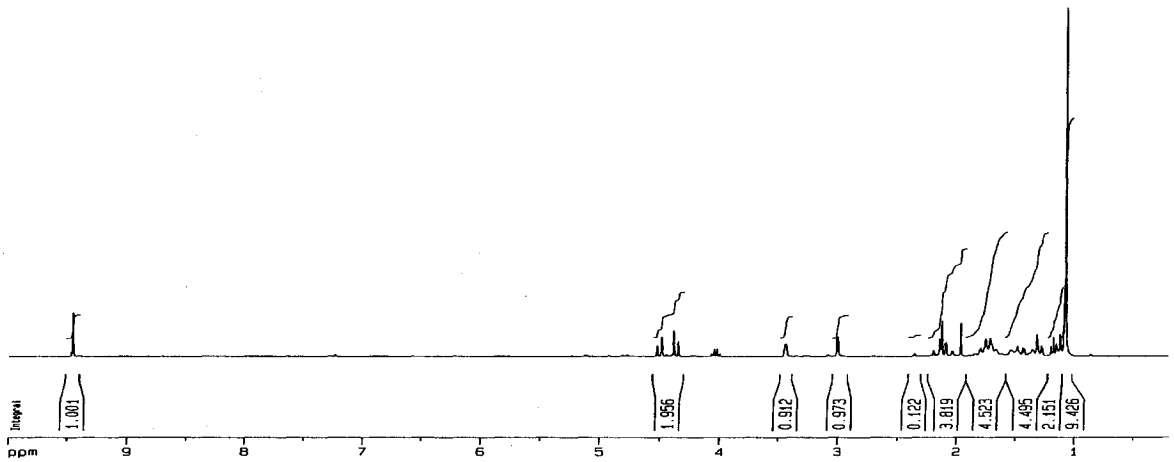
^{13}C NMR ($CDCl_3$, 75 MHz)



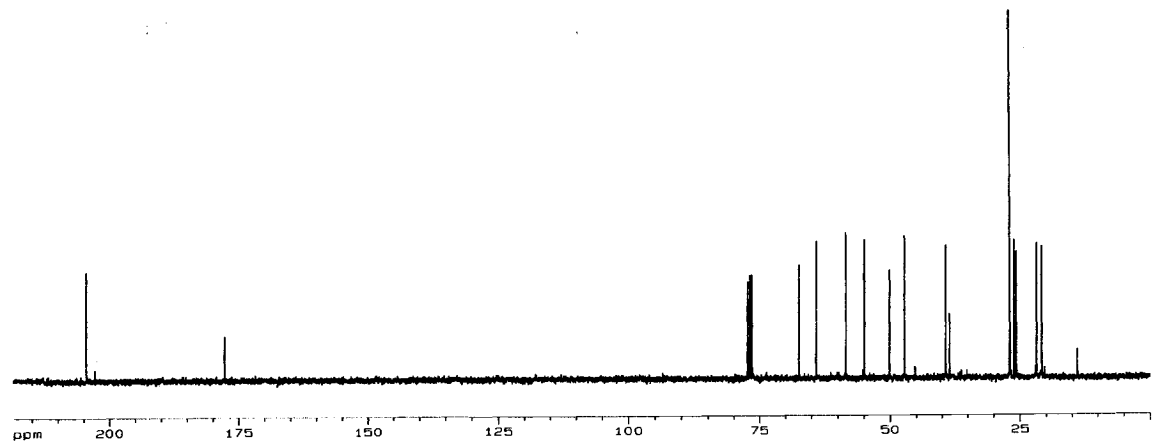


3.67

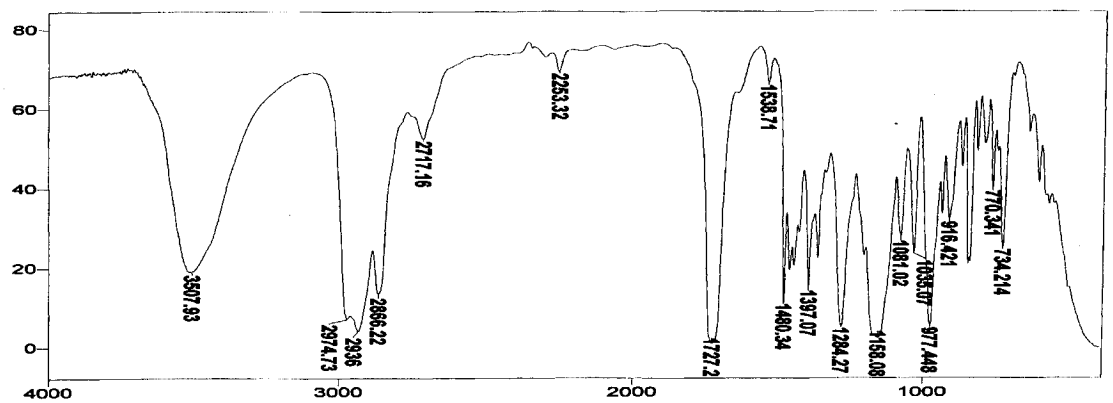
^{1}H NMR ($CDCl_3$, 300 MHz)

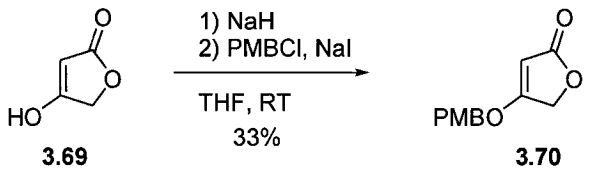


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





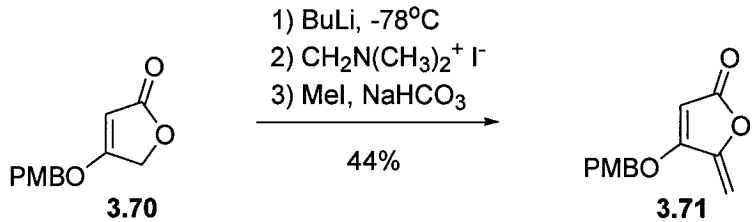
3.69 **3.70**

4-(4-Methoxy-benzyloxy)-5H-furan-2-one (3.70). A slurry of tetronic acid **3.69** (1.00g, 10 mmol) in THF (100 mL) was stirred at room temperature under argon. NaH (60% w/w, 2 equiv.) was added. Once the bubbling of H_2 had subsided, PMBCl (2.0 equiv.) and NaI (0.1 equiv.) were added. The reaction was allowed to stir overnight at room temperature. The following day, water (20 mL) was added, and the organic phase extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated. The residual solid was purified by flash chromatography (40% EtOAc in Hexanes) to give **3.70** as a white solid (730 mg, 33%).

Data for **3.70**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.27 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.14 (s, 1H), 4.96 (s, 2H), 4.59 (s, 2H), 3.78 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 178.9 (C_4), 173.4 (C_4), 160.1 (C_4), 129.5 (2 x CH), 125.6 (C_4), 114.1 (2 x CH), 89.3 (CH), 74.2 (CH_2), 67.8 (CH_2), 55.1 (CH_3)



3.70 **3.71**

4-(4-Methoxy-benzyloxy)-5-methylene-5H-furan-2-one (3.71). A clean, dry flask was flame dried and fitted with a magnetic stir bar. The flask was charged with THF (30 mL) under argon, and cooled to -78°C. BuLi (1.7M, 1.73mL, 1.3 equiv.) was added, and a solution of tetronate **3.70** (500 mg, 2.27 mmol, 1 equiv.) in THF (5 mL) was added very slowly. The solution assumed an orange-red colour, and was allowed to stir for 15 minutes. Eschenmoser's salt (2 eq, solid) was added in a single portion (by quickly removing the septum and replacing it), and the reaction was allowed to warm gradually to 0°C (over 2 hr).

MeI (3 equiv.) was added, and the reaction was allowed to stir overnight at room temperature. The following day $NaHCO_3$ (5g) was added, and allowed to stir for 2 hr. Addition of water (20 mL), extraction with ethyl acetate (3 x), drying over $MgSO_4$, and concentration gave a sticky foam that was purified by flash chromatography (10% EtOAc in hexanes) to give **3.71** as a sticky white foam (231 mg, 44%).

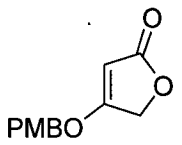
Data for **3.71**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.30 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.27 (br s, 1H), 5.02-4.98 (m, 4H), 3.79 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 168.3 (C_4), 168.2 (C_4), 160.1 (C_4), 129.8 (CH), 125.7 (C_4), 114.1 (CH), 92.4 (CH_2), 90.5 (CH), 74.0 (CH_2), 55.2 (CH_3)

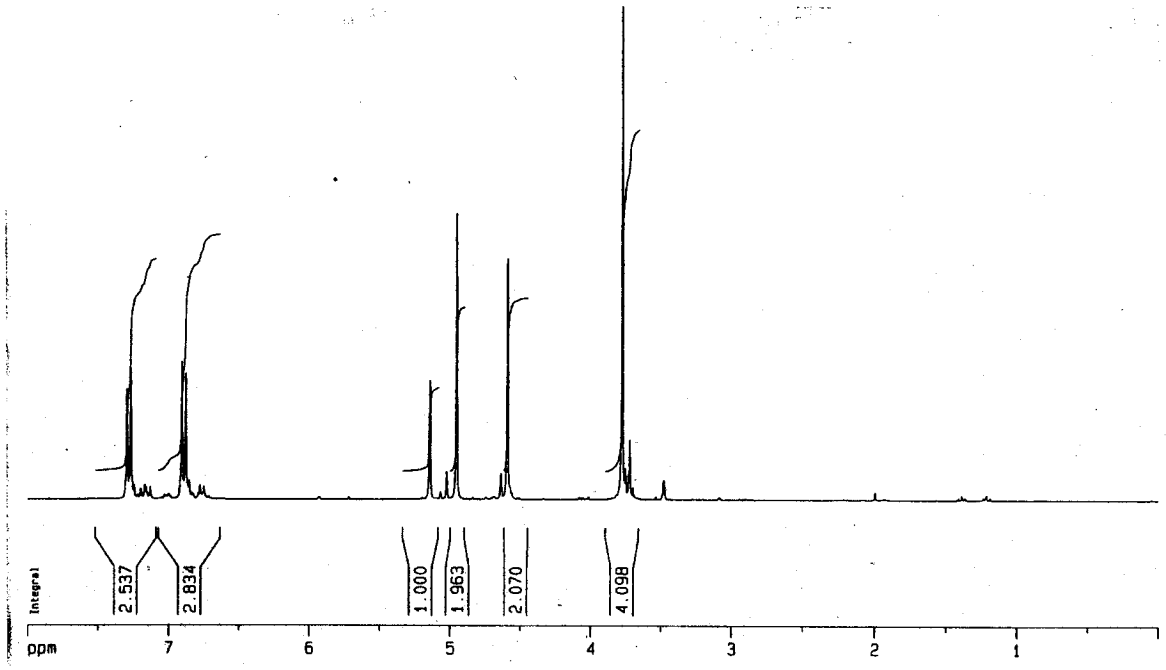
FTIR (neat, cm^{-1}) υ = 3133 (s), 2955 (s), 2884 (s), 1775 (s), 1742 (s), 1322 (m), 1242 (m), 958 (s), 917 (s)

HRMS (EI) Expected for $C_{13}H_{12}O_4$ $[(M)^+]$: 232.0736, found: 232.0734 (8.3 %)

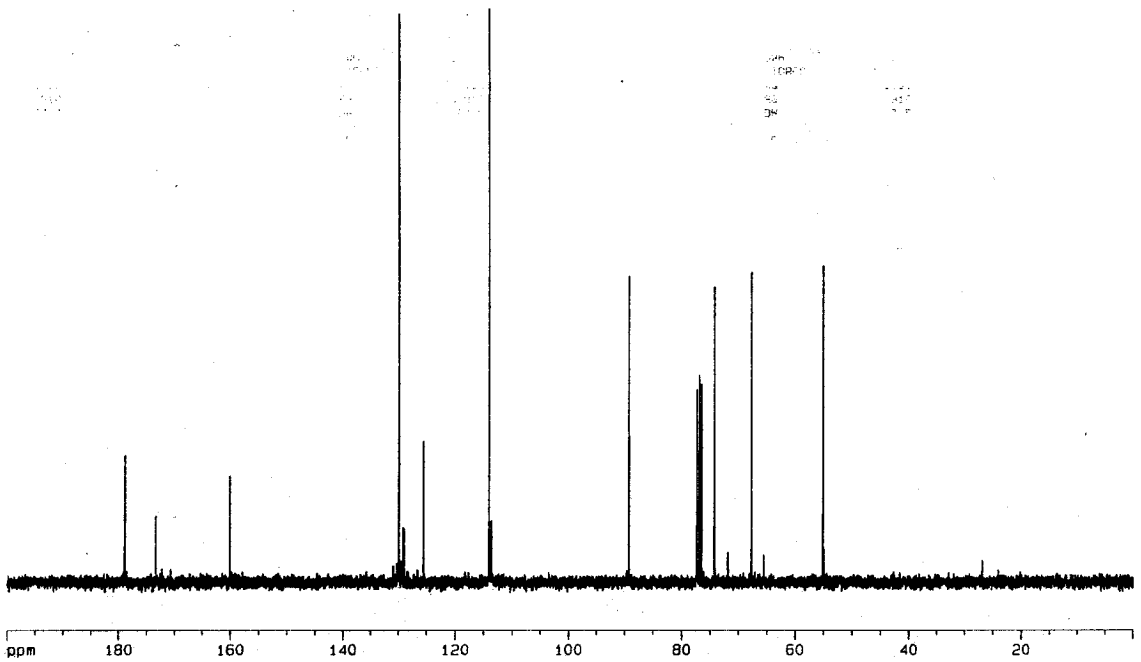


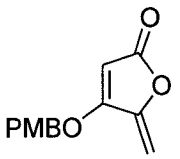
3.70

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



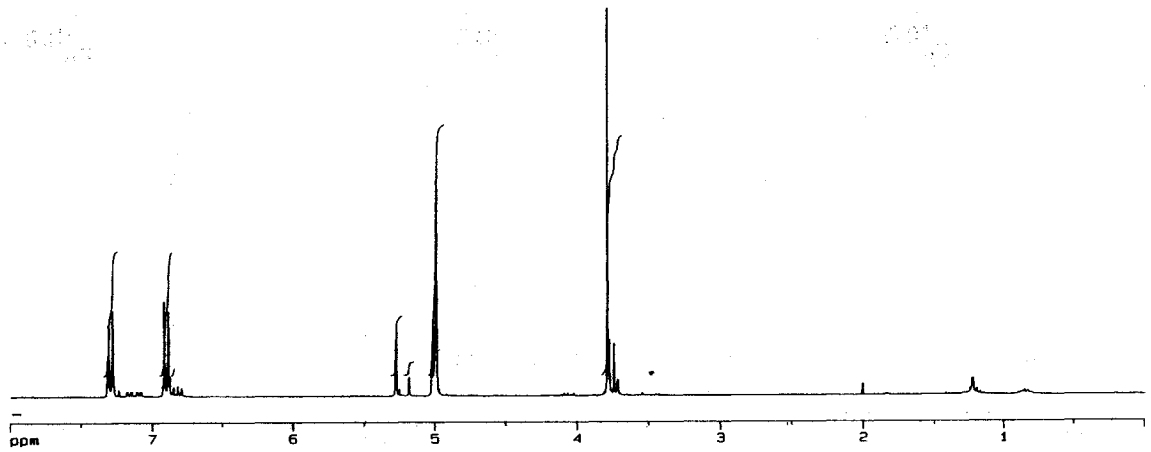
^{13}C NMR ($CDCl_3$, 75 MHz)



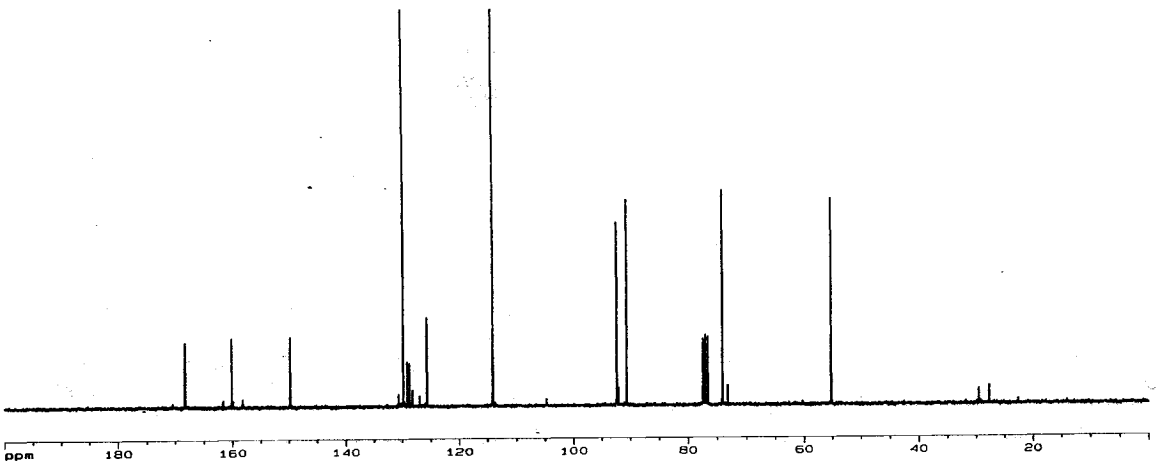


3.71

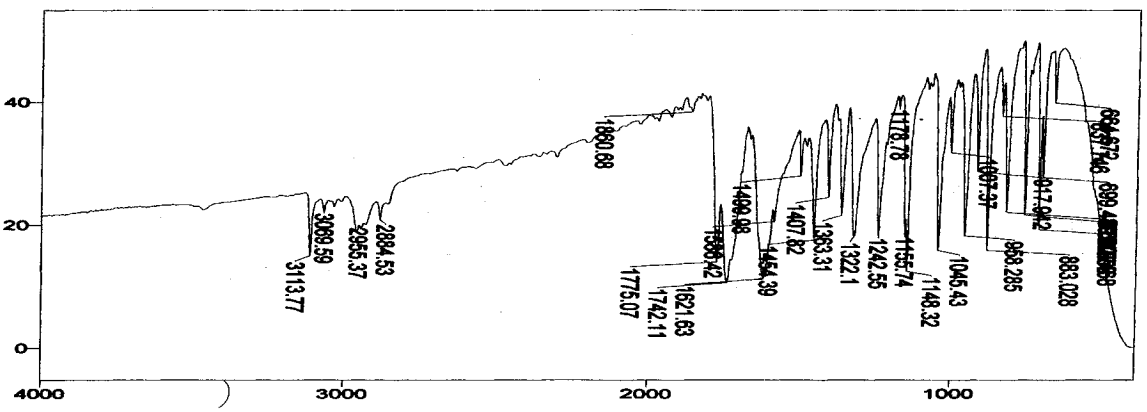
^{1}H NMR ($CDCl_3$, 300 MHz)



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

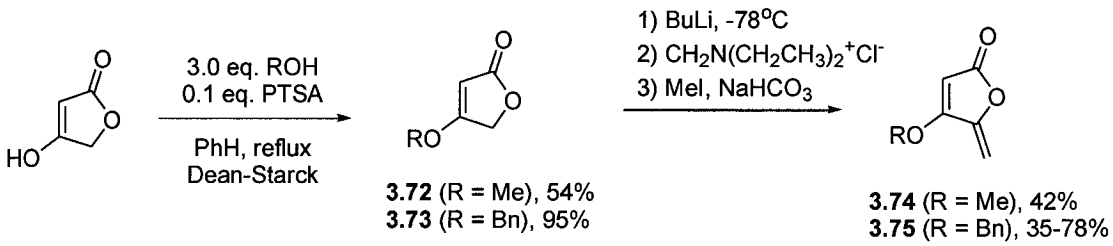


FTIR (neat)



Reagent Preparation: diethyl(methylene)ammonium chloride. Adaptation of procedure published by Duboudin et al.[92b] A clean, dry 500 mL flask fitted with a mechanical stirrer was charged with a mixture of diethylamine (103 mL, 1 mol), MeOH (81 mL, 2.5 equiv.) at 0°C. The stirrer was started and K_2CO_3 (165g, 1.5 equiv.) was added, portionwise over 15 minutes. Paraformaldehyde (24g, 1.0 equiv.) was added, and the mixture was allowed to stir overnight under air. The following day, the reaction mixture was diluted with hexanes (100 mL) and filtered. The crude was concentrated on the rotovap, and azeotroped with hexanes (2 x 100 mL) to give the product as a clear oil. (61.2 g, 65%). A clean dry 500 mL flask was charged with MeCN (200 mL) and trichloromethylsilane (CAUTION: This is NOT chlorotrimethylsilane it is trichloromethylsilane – the labels do look very similar - and is VERY hygroscopic) (70 mL, 1.1 equiv.). The mixture was placed in an oversized ice bath at 0°C, and the amine was added VERY slowly via pipette. A white solid should be noted immediately upon addition. The reaction was stirred for another 10 minutes, and was filtered under argon (with the aid of an inverted funnel and argon stream), washed with dry ether (3 x 50 mL) under argon, and transferred to the glovebox.

IMPORTANT: The mother liquor contains a large excess of trichloromethyl silane. This MUST be quenched by VERY SLOW addition of iPrOH (100 mL) at 0°C in the fume hood, followed by water (100 mL), and can then be disposed of accordingly.



4-methyloxy-2(5H)-furanone (3.72) and **4-benzyloxy-2(5H)-furanone (3.73)**. Representative procedure. A clean, dry flask was charged with tetronic acid (10.0g, 100

mmol), benzene (100 mL), benzyl alcohol (3 equiv.), and PTSA (0.1 equiv.). The flask was fitted with a dean-stark trap and heated to reflux overnight. The reaction mixture was diluted with ether (100 mL), and water (50 mL). The organic layer was extracted with ethyl acetate (3x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (40% EtOAc in Hexanes) to give the product **3.73** as a white solid (19.2g, 95%). Both **3.72** and **3.73** were identical to previously reported samples.[154]

4-Methoxy-5-methylene-5H-furan-2-one (3.74) and **4-benzyloxy-5-methylene-5H-furan-2-one (3.75)**. Representative procedure: A flame dried flask under argon fitted with a rubber septum and stirring bar was charged with THF (110 mL) and was cooled to -78°C. n-BuLi (13.0 mL, 1.4 equiv.) was added slowly, followed by a solution of benzyl ether **3.73** (4.66g, 1.0 equiv.) in THF (20 mL). The reaction was stirred for 30 minutes, and the diethyl-(methylene)-ammonium chloride (5.70g, 1.8 equiv.) was added as a solid in a single portion. The reaction was gradually allowed to warm to room temperature over 2hr. The reaction was quenched with $NH_4Cl_{(sat.)}$ and extracted (3 x). The combined organic phases were dried over $MgSO_4$ and concentrated carefully. The crude was redissolved in dichloromethane (100 mL), and MeI (3.22 mL, 2.0 equiv.) was added. The mixture was allowed to stir overnight at room temperature, and $NaHCO_3$ (8.8g, 5 equiv.) was added. Stirring was continued for a further 3hr, and water (40 mL) was added to the reaction mixture. The organic layer was extracted with dichloromethane (3 x), dried over $MgSO_4$ and concentrated VERY carefully (do NOT exceed 35°C). The crude was subjected to flash chromatography (40% Et_2O in Hexanes) to give **3.75** as a light yellow solid (3.7g, 65%). This solid is of insufficient purity for lithium chemistry and was recrystalized from MeOt-Bu (10 mL) in the freezer to give high quality off-white needles (2.7g, 48%).

Data for **3.75**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.37 (br s, 5H), 5.29 (s, 1H), 5.27 (br s, 1H), 5.11-4.98 (m, 4H)

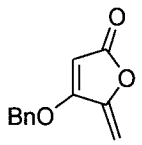
^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 168.1 (2 x C_4), 149.6 (C_4), 133.6 (C_4), 128.8 (CH), 128.6 (2 x CH), 127.7 (2 x CH), 92.3 (CH_2), 90.7 (CH), 73.9 (CH_2)

FTIR (neat, cm^{-1}) υ = 3114 (s), 3071 (m), 3019 (m), 2939 (s), 1782 (s), 1670 (s), 1607 (s), 1455 (s), 1239 (s), 958 (s), 882 (s)

HRMS (EI) Expected for $C_{12}H_{10}O_3$ [$(M)^+$]: 202.0630, found: 202.0630 (6.7 %)

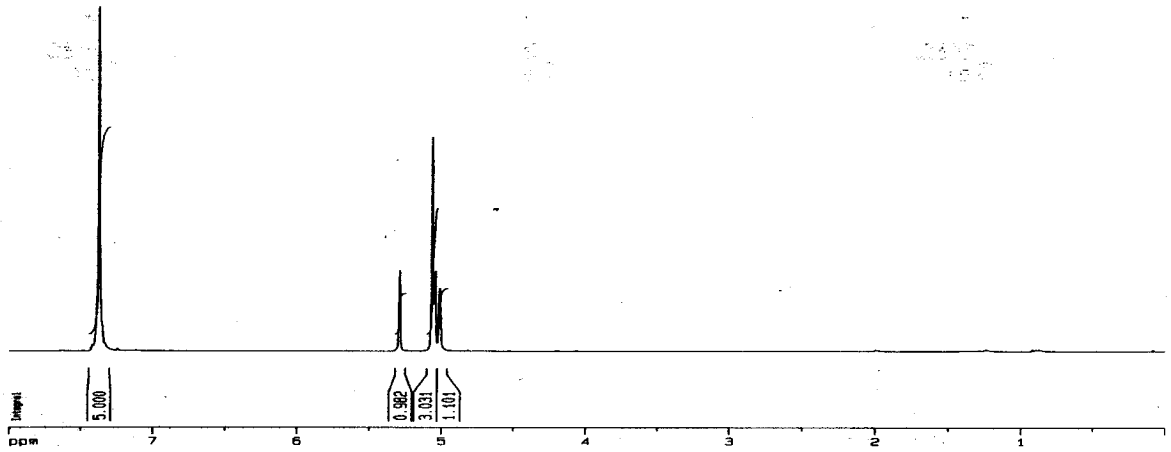
Data for **3.76**:

As described elsewhere.[155]

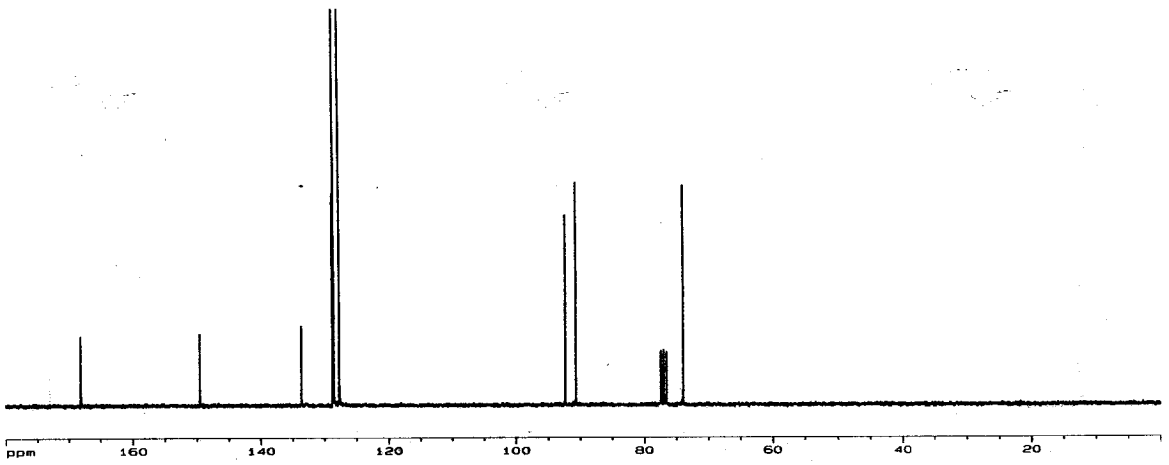


3.75

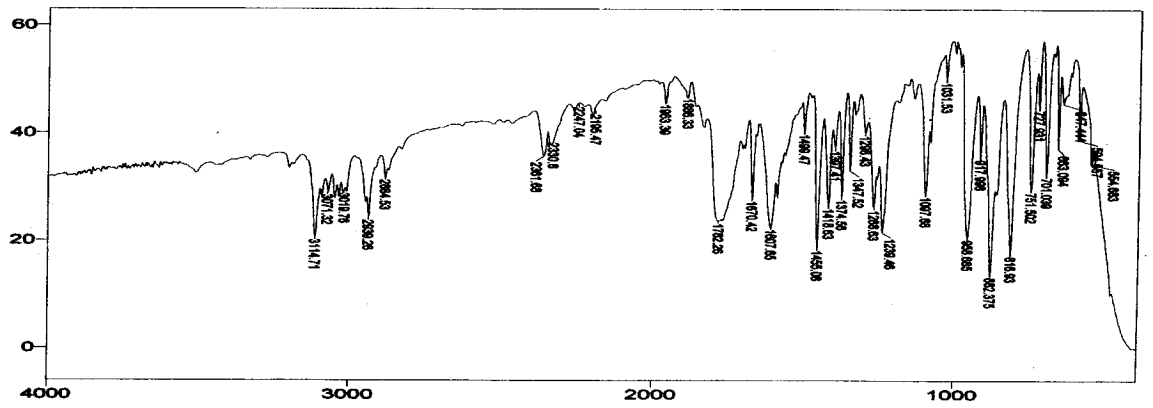
^{1}H NMR ($CDCl_3$, 300 MHz)

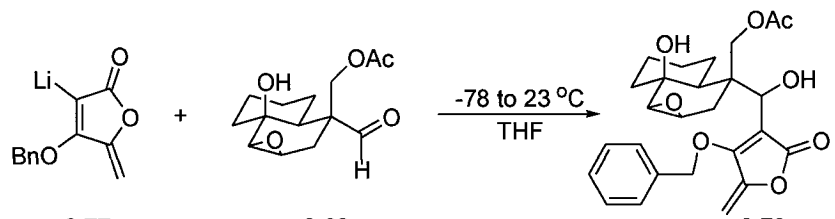


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.77 **3.66** **3.79**

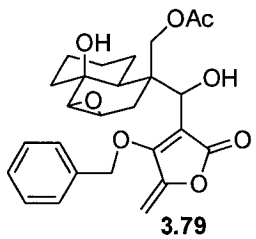
Acetic acid 3-[(4-benzyloxy-5-methylene-2-oxo-2,5-dihydro-furan-3-yl)-hydroxy-methyl]-7a-hydroxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-ylmethyl ester (3.79). A clean, dry 50 mL roundbottom flask was charged with freshly distilled N,N-diisopropyl amine (175 uL, 6.6 equiv.) and THF (10 mL). The mixture was cooled to -78°C and BuLi (2.5M, 450 uL, 6.0 equiv.) was added. After 5 min, a solution of the tetronate **3.75** (226 mg, 6.0 equiv.) in THF (3 mL) was added, dropwise. The solution assumed a red-orange colour. After 20 minutes stirring, a pre-cooled solution of the aldehyde **3.66** (50mg, 1.0 equiv.) was canulated. The reaction was stirred for 1hr at -78°C, and the colour of the mixture gradually became deep-red or black. The reaction was quenched cold with aqueous $NH_4Cl_{(sat.)}$ (3 mL), extracted with ether (3x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography *twice* (20% EtOAc/Hexanes) to give **3.79** as an orange foam (28 mg, 21%)

Data for **3.79**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.47-7.27 (m, 5H), 5.31 (d, J = 11.0 Hz, 1H), 5.20 (d, J = 11.0 Hz, 1H), 5.10 (d, J = 3.0 Hz, 1H), 4.99 (d, J = 3.0 Hz, 1H), 4.50 (s, 1H), 4.05-4.03 (m, 2H), 3.42-3.40 (m, 1H), 2.83 (d, J = 4.0 Hz, 1H), 1.95 (s, 3H), 1.87-1.05 (m, 13H + grease)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 170.7 (C_4), 167.5 (C_4), 165.2 (C_4), 149.6 (C_4), 135.1 (C_4), 128.8 (CH), 128.2 (2 x CH), 127.9 (2 x CH), 111.2 (C_4) 94.6 (CH_2), 80.1 (CH), 79.7 (CH), 77.2 (CH_2), 76.5 (CH), 69.7 (C_4), 64.5 (CH_2), 47.8 (C_4), 40.7 (CH_3), 37.9 (CH_2), 32.6 (CH_2), 29.7 (CH_2), 26.5 (CH_2), 22.5 (CH_2), 20.9 (CH)

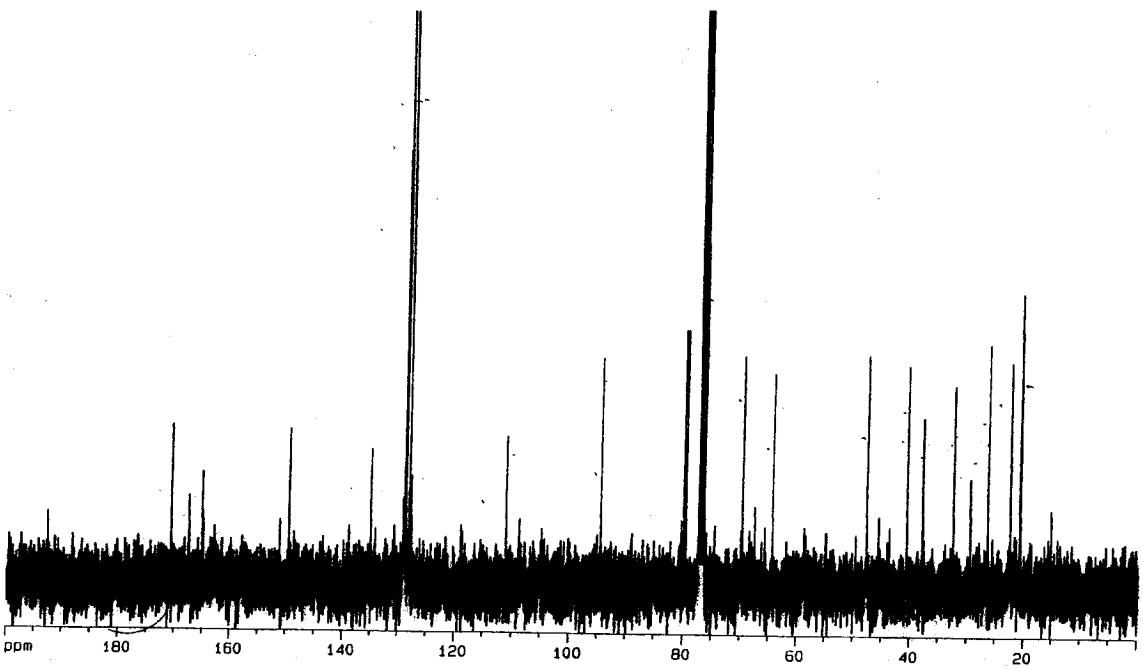
MS (EI) Expected for $C_{26}H_{30}O_8$: 470.2, found: 379 (M-Bn), 319, 180, 149, 133, 91

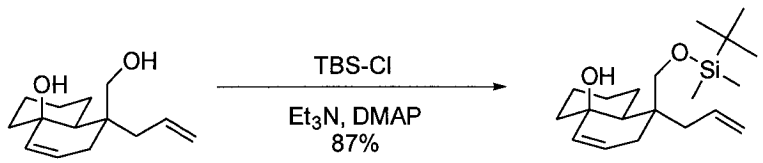


3.79

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

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





3.46 **3.87**

8-Allyl-8-(tert-butyl-dimethyl-silanyloxymethyl)-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.87). A solution of diol **3.46** (335 mg, 1.51 mmol) in distilled DMF (10.0 mL) was stirred at room temperature and TBDMSCl (275 mg, 1.2 equiv.), Et_3N (630 uL, 3.0 equiv.), and DMAP (20 mg, 0.1 equiv.) were added, sequentially. The reaction was stirred overnight at room temperature. The following day, the reaction was poured into 100 mL H_2O, extracted with ether (3 x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (10% EtOAc in Hexanes) to give **3.87** as a yellow oil (442 mg, 87%).

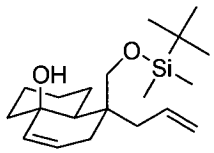
Data for **3.87**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.78-5.62 (m, 1H), 5.52 (ddd, J = 10.0, 4.8, 2.3 Hz, 1H), 5.44 (d, J = 10.2 Hz, 1H), 5.02 (dd, J = 10.2, 1.6 Hz, 1H), 4.95 (d, J = 16.9 Hz, 1H), 4.55 (d, 1.8 Hz, 1H), 3.63 (d, J = 10.6 Hz, 1H), 3.20 (d, J = 10.6 Hz, 1H), 2.05 (ddd, J = 18.3, 2.3, 2.3 Hz, 1H), 1.88 (dd, J = 13.8, 6.8 Hz, 1H), 1.82-1.53 (m, 6H), 1.49-1.30 (m, 3H), 1.25-1.02 (m, 2H), 0.81 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 113.9 (CH), 113.7 (CH), 126.2 (CH), 118.3 (CH_2), 67.7 (CH_2), 66.6 (C_4), 48.3 (CH), 41.5 (CH_2), 39.2 (CH_2), 38.5 (C_4), 33.6 (CH_2), 27.0 (CH_2), 25.7 (3 x CH_3), 21.2 (CH_2), 20.2 (CH_2), 18.0 (C_4), -5.6 (CH_3), -5.8 (CH_3).

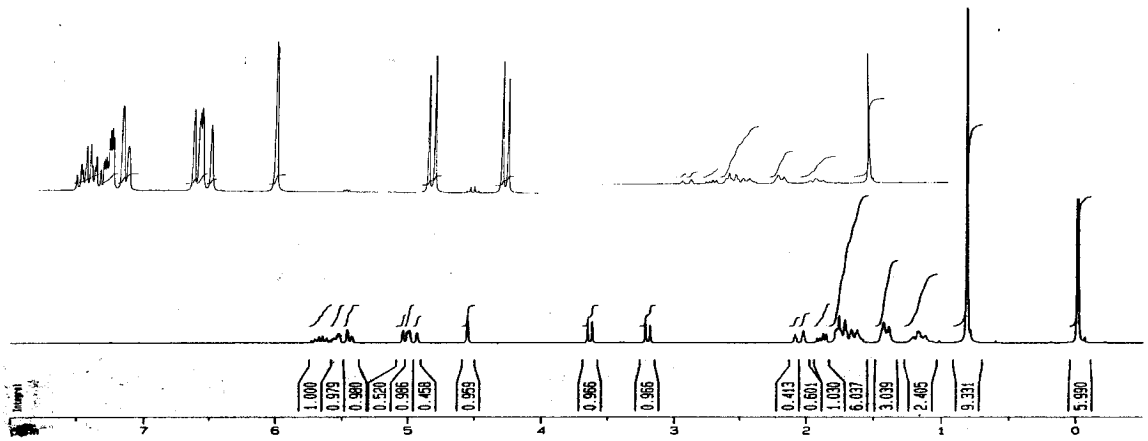
FTIR (neat, cm^{-1}) υ = 3427 (s), 3075 (w), 3015 (m), 2929 (s), 2856 (s), 1638 (w), 1446 (s)m 1254 (s), 1080 (s), 837 (m), 776 (m)

HRMS (EI) Expected for $C_{16}H_{27}O_2Si$ [$(M\text{-}tBu)^+$]: 279.1780, found: 279.1745 (0.9 %)

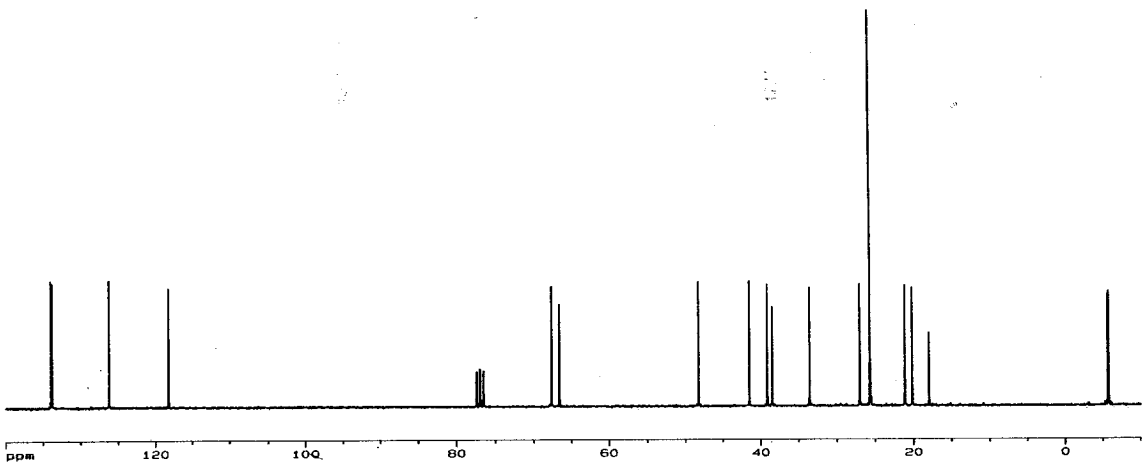


3.87

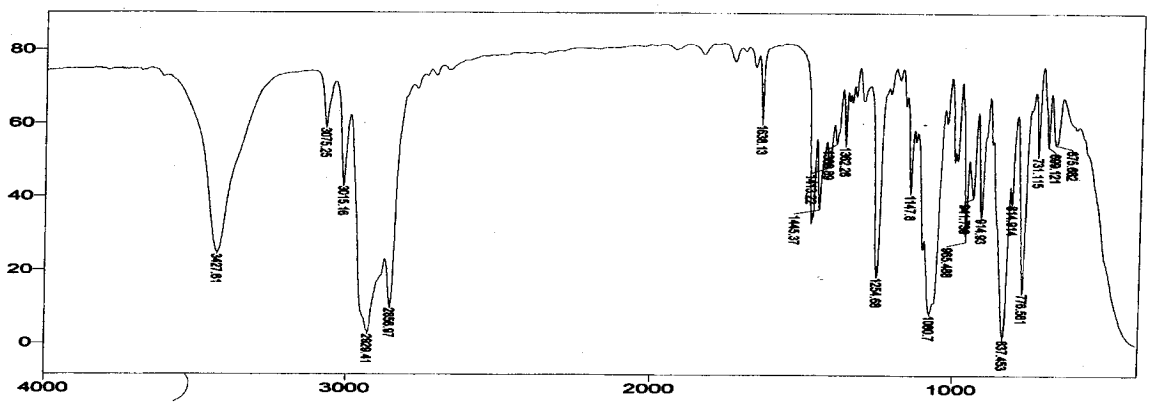
^{1}H NMR ($CDCl_3$, 300 MHz)

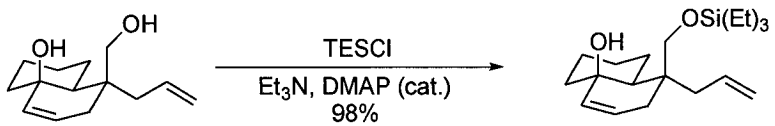


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.46 **3.88**

8-Allyl-8-triethylsilanyloxymethyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (3.88). To a solution of diol **3.46** (100 mg, 0.450 mmol), Et_3N (1.35 mmol), and DMAP (0.05 mmol) stirring at RT was added TESCl (0.600 mmol). A white precipitate was observed, after 2 hr stirring the reaction was diluted with 80 mL DCM, and washed once with $NaHCO_{3\,(satd)}$, dried over $MgSO_4$. The crude oil was subjected to flash chromatography (7% EtOAc in Hexane) which afforded **3.88** as a clear oil (149 mg, 98%).

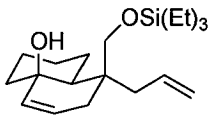
Data for **3.88**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} =5.76-5.55 (m, 2H), 5.49-5.45 (m, 1H), 5.04 (d, J = 10.3 Hz, 1H), 4.98 (d, J = 17.0 Hz, 1H), 4.74 (d, J = 1.8 Hz, 1H), 3.64 (d, J = 10.5 Hz, 1H), 3.21 (d, J = 10.5 Hz, 1H), 2.20-1.63 (m, 8H), 1.55-1.0 (m, 5H), 0.90 (t, J = 7.9 Hz, 9H), 0.55 (q, J = 7.9 Hz, Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 134.0 (CH), 133.8 (CH), 126.3 (CH), 118.3 (CH_2), 67.6 (CH_2), 66.5 (C_4), 48.3 (CH), 48.3 (CH_2), 41.6 (CH_2), 39.2 (CH_2), 38.6 (C_4), 33.7 (CH_2), 27.1 (CH_2), 21.2 (CH_2), 20.2 (CH_2), 6.6 (3 x CH_3), 4.0 (3 x CH_2).

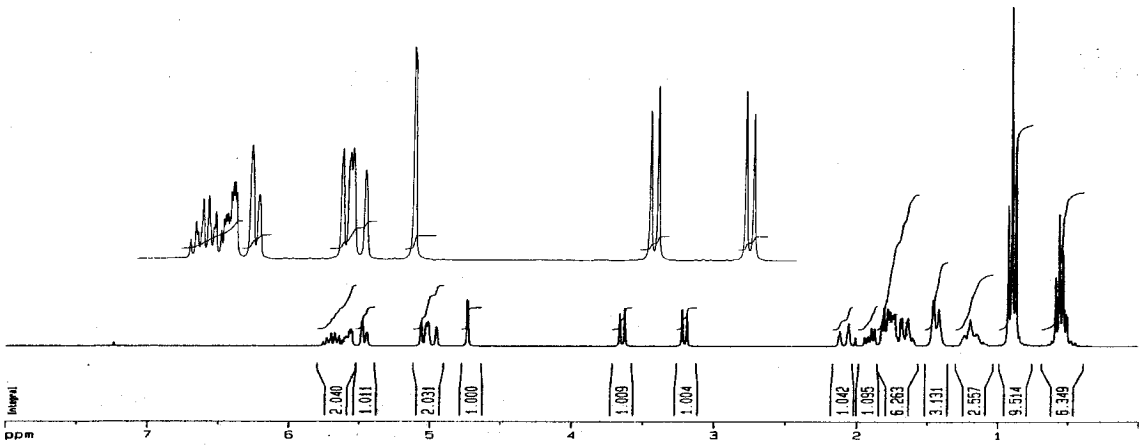
FTIR (neat, cm^{-1}) υ = 3424.6 (s), 3075.2 (w), 2935.9 (s), 1458 (m), 1445 (m), 1414 (m), 1080 (s).

HRMS (EI) Expected for $C_{17}H_{31}O_2Si$ [(M-Allyl)$^+$]: 295.2093, found: 295.2068 (1.0 %)

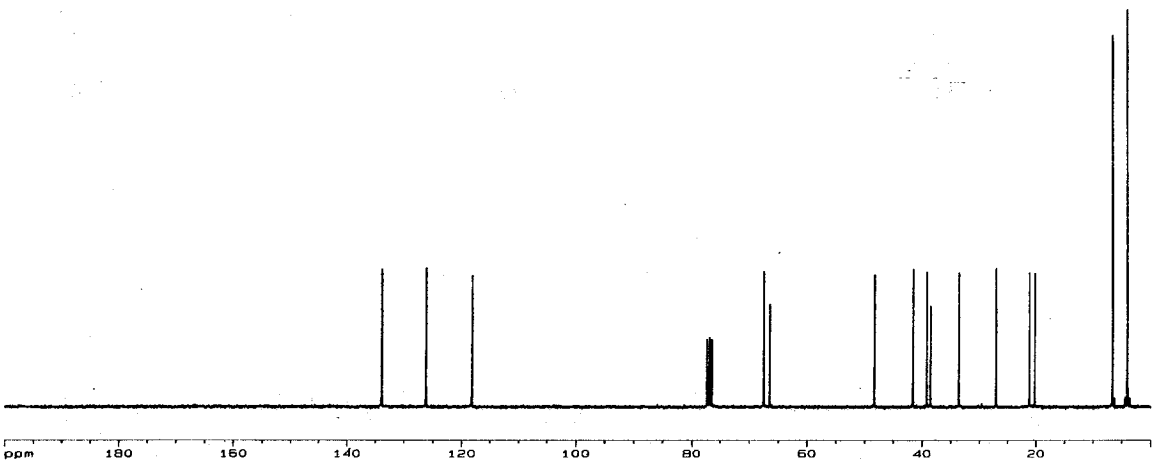


3.88

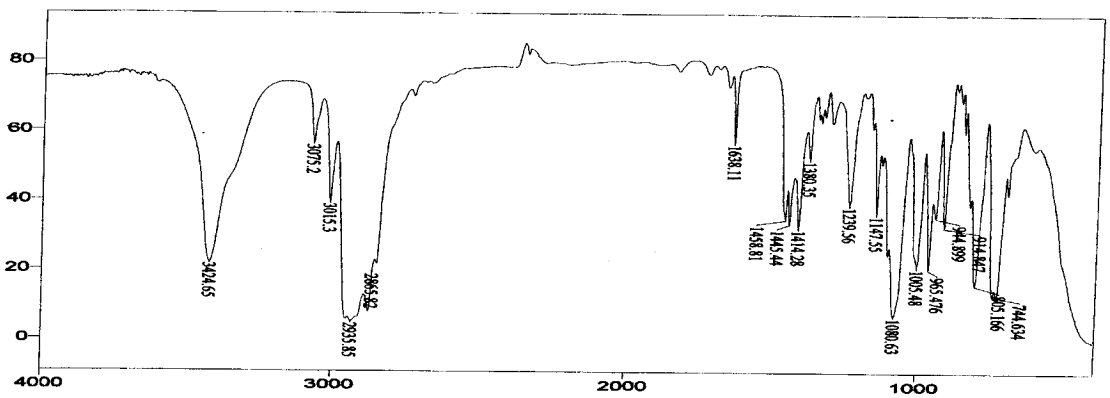
^{1}H NMR ($CDCl_3$, 300 MHz)

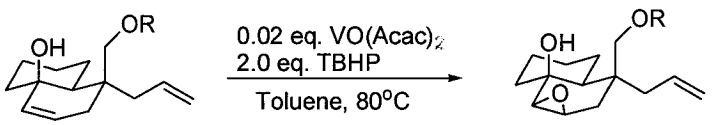


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.87 (R = TBMS)
3.88 (R = TES)

3.89 (R = TBMS), 78%
3.90 (R = TES), 77%

3-Allyl-3-(tert-butyl-dimethyl-silanyloxymethyl)-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (3.89) and 3-Allyl-3-triethylsilanyloxymethyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (3.90). Representative procedure: A clean, dry resealable pressure tube was charged with a solution of allylic alcohol **3.88** (149 mg, 0.440 mmol) in toluene (5 mL) and VO $(Acac)_2$ (2mg/mL in toluene, 0.004 mmol). To the slightly green solution was added t-BuOOH (70% in water, 120 uL, 0.88 mmol) and immediately the solution turned dark red-purple, which gradually faded to a slight orange. The mixture was heated to 110 °C for 7 Hr. The reaction was cooled to 0°C, and a solution of NaI was added and this was stirred for 10 minutes. $Na_2S_2O_3$ was added, and the organic layer was separated 3 x EtOAc (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography (15% EtOAc/Hexanes) afforded **3.90** as a clear oil (120 mg, 77%).

Data for **3.89**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.69-5.53 (m, 1H), 5.07-4.92 (m, 2H), 3.50 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 10.0 Hz, 1H), 3.22 (br s, 1H), 2.85 (d, J = 3.9 Hz, 1H), 2.65 (d, J = 1.2 Hz, 1H), 2.04-1.91 (m, 3H), 1.80-1.64 (m, 3H), 1.60-1.43 (m, 5H), 1.21-0.68 (m, 2H), 0.82 (s, 9H), -0.02 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 134.2 (CH), 118.3 (CH_2), 67.9 (C_4), 67.1 (CH_2), 58.7 (CH), 55.1 (CH), 47.9 (CH), 41.2 (CH_2), 39.6 (CH_2) 39.4 (C_4), 29.5 (CH_2), 26.9 (CH_2), 25.8 (3 x CH_3), 21.4 (CH_2), 20.8 (CH_2), 18.1 (C_4), -5.7 (CH_3), -5.8 (CH_3)

FTIR (neat, cm^{-1}) υ = 3451 (br s), 3074 (m), 2929 (s), 2855 (s), 1637 (m), 1470 (s), 1463 (s), 1447 (s), 1254 (s), 1085 (s), 972 (s), 857 (s), 837 (s).

HRMS (EI) Expected for $C_{16}H_{27}O_3Si$ [$(M\text{-}tBu)^+$]: 295.1730, found: 295.1753 (1.4 %)

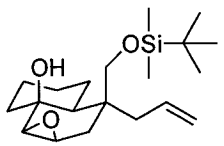
Data for **3.90**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.74-5.60 (m, 1H), 5.08-4.98 (m, 2H), 3.53 (d, J = 9.9 Hz, 1H), 3.35 (J = 9.9 Hz, 1H), 3.28 (br s, 1H), 2.90 (m, 2H), 2.21-1.83 (m, 3H), 1.80-1.51 (m, 7H), 1.49-1.05 (m, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.54 (q, J = 7.9 Hz, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 134.3 (CH), 118.5 (CH_2), 67.9 (C_4), 66.9 (CH_2), 58.8 (CH), 55.0 (CH), 47.9 (CH), 41.4 (CH_2), 39.6 (CH_2), 39.5 (C_4), 29.7 (CH_2), 27.0 (CH_2), 21.5 (CH_2), 20.8 (CH_2), 6.8 (3 x CH_3), 4.2 (3 x CH_2).

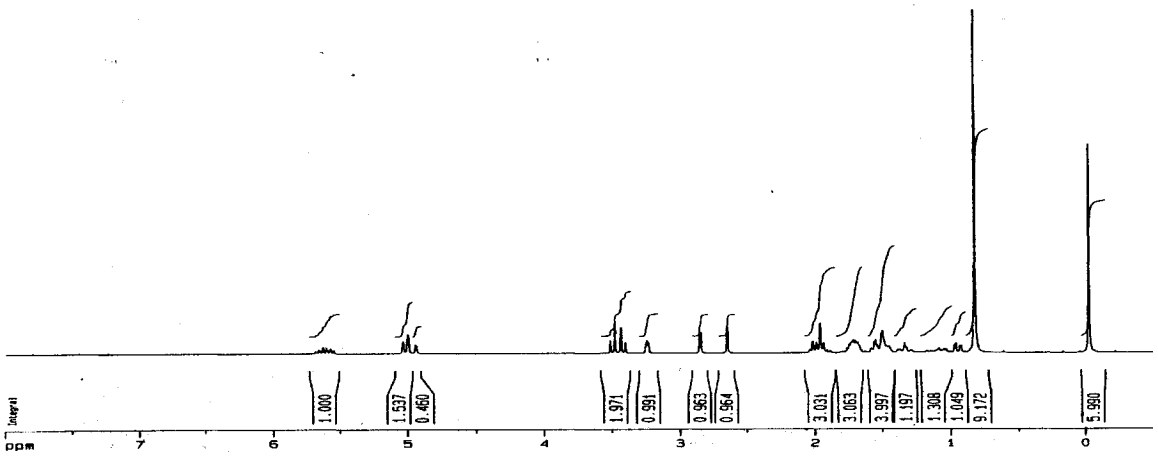
FTIR (neat, cm^{-1}) υ = 3423 (br s), 2936 (s), 2875 (s), 3074 (w), 1458 (m), 1447 (m), 1416 (m), 1086 (s)

HRMS (EI) Expected for $C_{20}H_{32}OSi$ $[(M-H_2O_2)^+]$: 318.2379, found: 318.2396 (7.2 %)

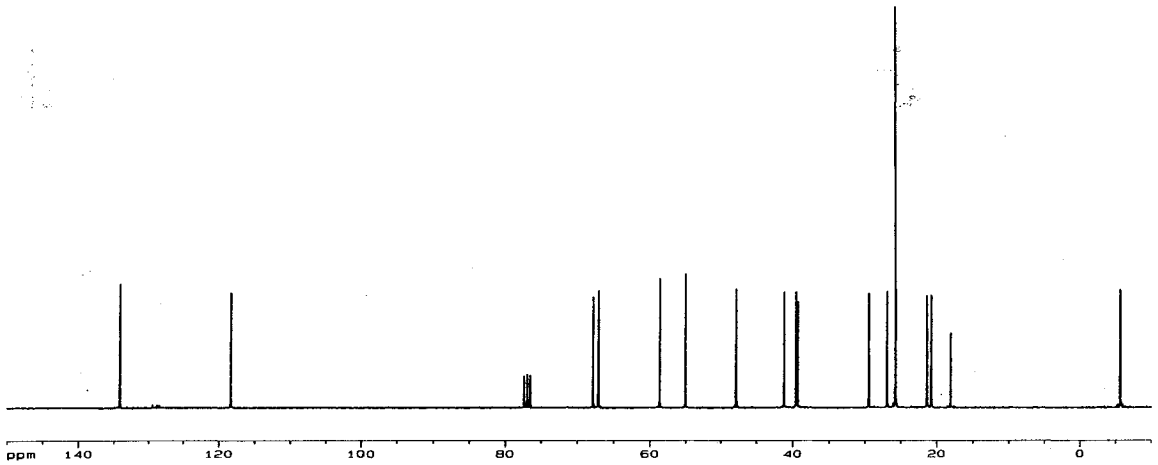


3.90

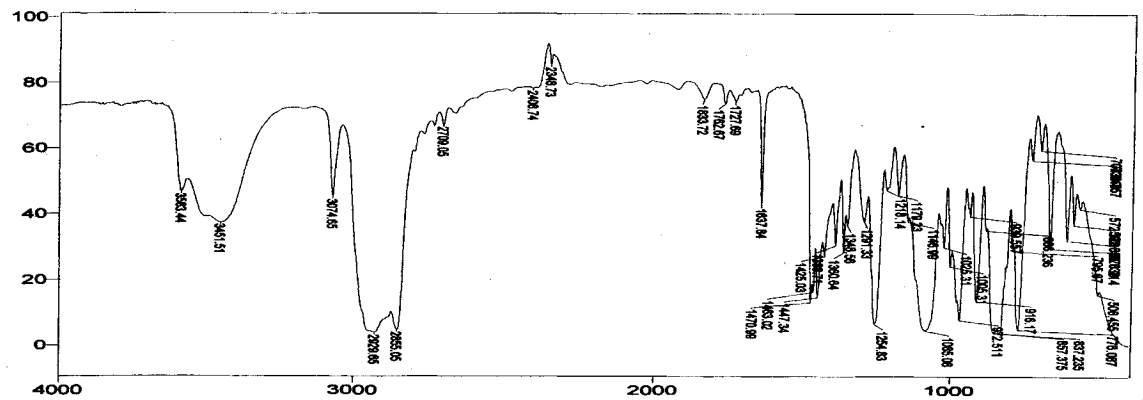
^{1}H NMR ($CDCl_3$, 300 MHz)

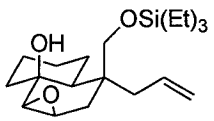


^{13}C NMR ($CDCl_3$, 75 MHz)



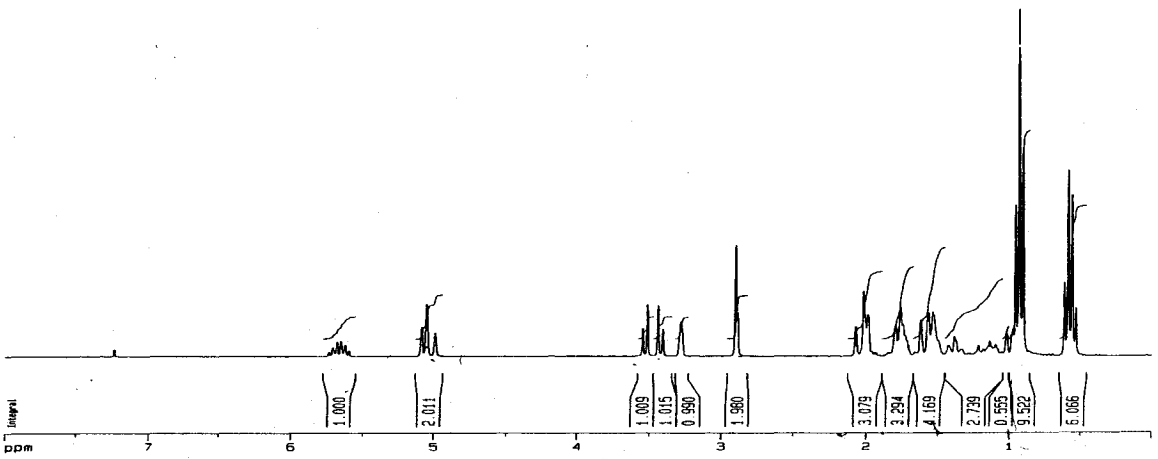
FTIR (neat)



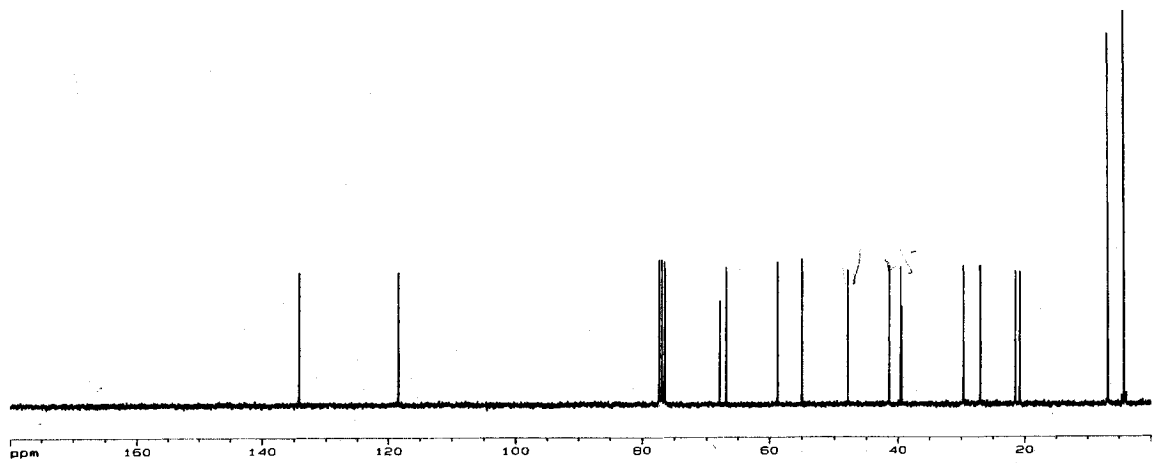


3.90

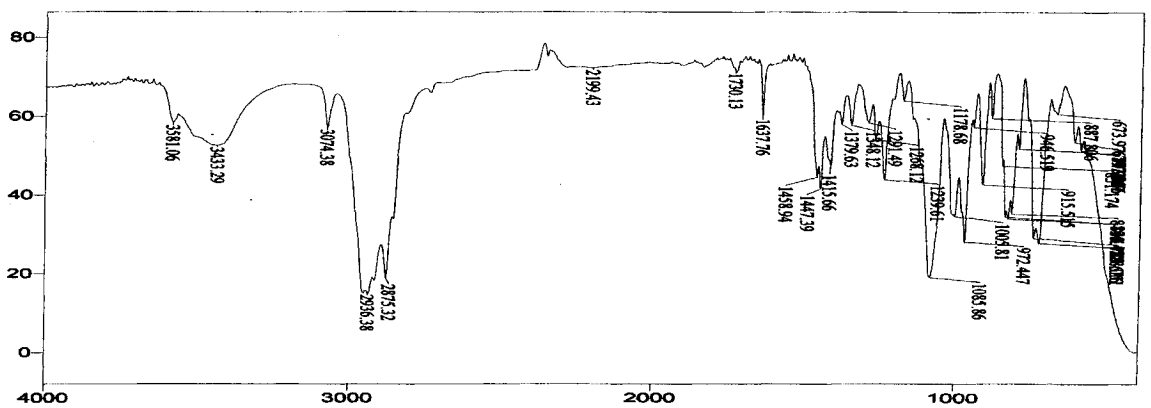
^{1}H NMR ($CDCl_3$, 300 MHz)

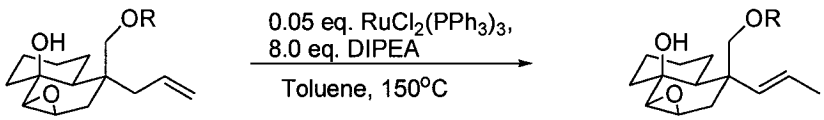


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.89 (R = TBMS)
3.90 (R = TES)

3.91 (R = TBMS), 85%
3.92 (R = TES), 92%

3-(tert-Butyl-dimethyl-silanyloxymethyl)-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (3.91) and **3-Propenyl-3-triethylsilanyloxymethyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (3.92).** Representative procedure: A solution of epoxide **3.89** (328 mg, 0.930 mmol) in dry toluene (15 mL) was placed in a resealable pressure tube, and dichlorobis(triphenylphosphine)ruthenium(II) (70 mg, 0.1 equiv) was added. The atmosphere over the solution was replaced with argon (3 vacuum cycles), and the tube was sealed. The tube was placed in a wax bath held at 150°C for 48 hr, or until deemed complete by GC analysis. After cooling, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography to give **3.91** as a thick yellow oil (279 mg, 85%).

Data for **3.91**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.29 (dq, J = 15.8, 5.8 Hz, 1H), 5.17 (dd, J = 15.8, 1.1 Hz, 1H), 3.59 (d, J = 10.1 Hz, 1H), 3.50 (d, J = 10.1 Hz, 1H), 3.24-3.22 (m, 1H), 3.01 (s, 1H), 2.85 (d, J = 3.9 Hz, 1H), 2.18 (dd, J = 1.5, 16.0 Hz, 1H), 1.82-1.63 (m, 3H), 1.58 (dd, J = 5.8, 1.1 Hz, 3H), 1.60-1.23 (m, 5H), 1.20-0.84 (m, 2H), 0.82 (s, 9H), -0.04 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 138.7 (CH), 122.3 (CH), 67.6 (C_4), 65.5 (CH_2), 58.4 (CH), 54.5 (CH), 50.8 (CH), 42.1 (C_4), 39.5 (CH_2), 32.2 (CH_2), 27.2 (CH_2), 25.8 (3 x CH_3), 21.6 (CH_2), 21.5 (CH_2), 18.3 (C_4), 18.1 (C_4), -5.6 (CH_3), -5.7 (CH_3),

FTIR (neat, cm^{-1}) υ = 3426 (s), 2931 (s), 2855 (s), 1447 (s), 1254 (s), 1091 (s), 971 (s), 852 (s), 775 (s)

HRMS (EI) Expected for $C_{16}H_{27}O_3Si$ $[(M\text{-}tBu)^+]$: 295.1730, found: 295.1716 (1.1%)

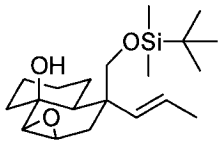
Data for **3.92**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 5.33 (dq, J = 16.0, 5.0 Hz, 1H), 5.20 (d, J = 16.0 Hz, 1H), 3.58 (d, J = 10.1Hz, 1H), 3.48 (d, J = 10.1 Hz, 1H), 3.30 (m, 1H), 3.24-3.26 (m, 1H), 2.87 (d, J = 3.9 Hz, 1H), 2.24-2.18 (m, 1H), 1.98-1.62 (m, 4H), 1.60 (d, J = 5.0 Hz, 3H), 1.58-1.01 (m, 7H), 0.92 (t, J = 7.6 Hz, 9H), 0.57 (q, J = 7.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 138.8 (CH), 122.3 (CH), 67.4 (CH), 65.2 (C_4), 58.4 (CH), 54.1 (CH), 50.9 (CH), 42.0 (C_4), 39.5 (CH_2), 32.5 (CH_2), 27.2 (CH_2), 21.5 (CH_2), 18.4 (CH), 6.7 (CH_3), 4.1 (CH_2).

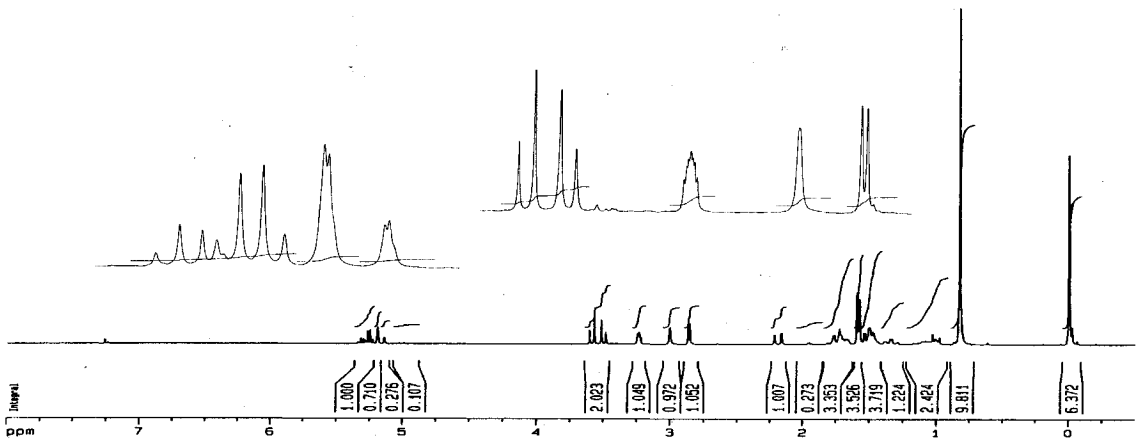
FTIR (neat, cm^{-1}) υ = 3410 (br s), 2936 (s), 1425 (s), 1088 (s), 971 (s), 852 (s), 775 (s)

HRMS (EI) Expected for $C_{20}H_{36}O_3Si$ [$(M)^+$]: 352.2434, found: 352.2411 (1.1%)

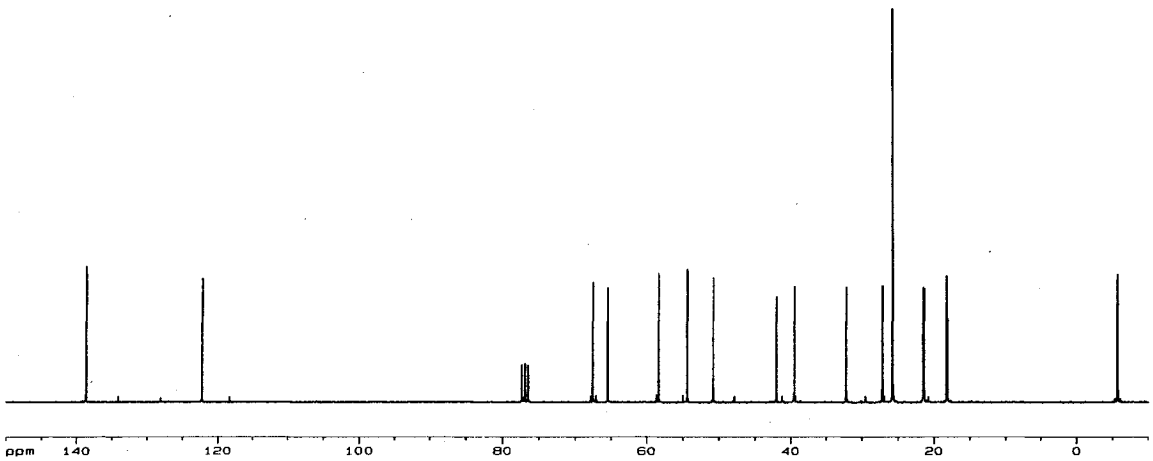


3.91

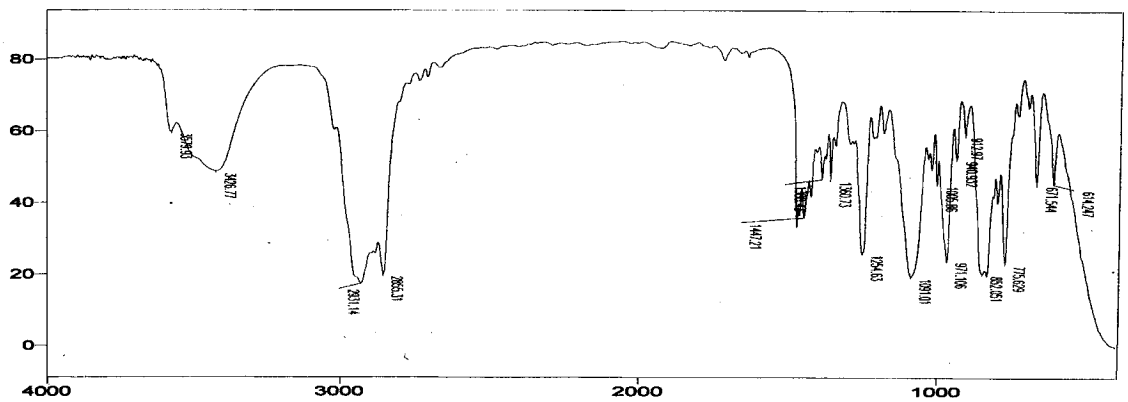
^{1}H NMR ($CDCl_3$, 300 MHz)

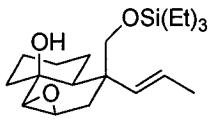


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)

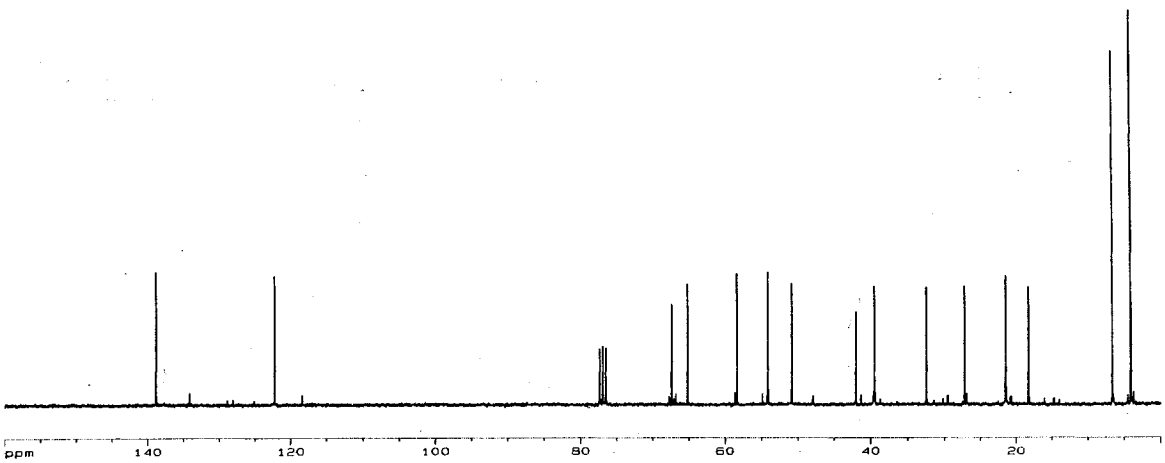




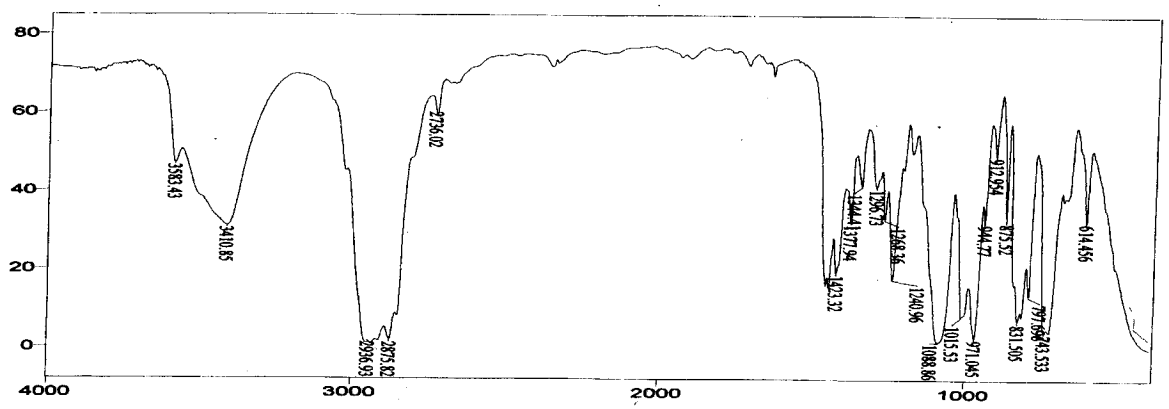
3.92

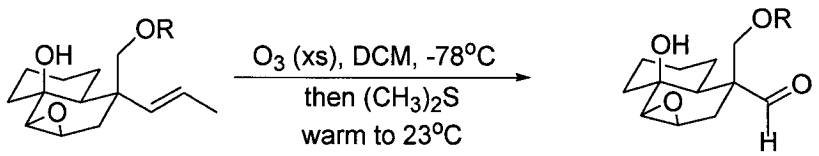
^{1}H NMR ($CDCl_3$, 300 MHz)

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



FTIR (neat)





3.91 (R = TBMS)
3.92 (R = TES)

3.93 (R = TBMS), 80%
3.94 (R = TES), 74%

3-(tert-Butyl-dimethyl-silanyloxymethyl)-7a-hydroxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (3.93) and **7a-Hydroxy-3-triethylsilanyloxymethy l-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (3.94)**. Representative procedure: A solution of epoxide **3.91** (122 mg, 0.347 mmol), in dichloromethane (9.0 mL) was cooled to -78°C. Ozone was passed through the solution via fritted bubbler until the steel-gray colour of ozone saturation persisted. The ozone bubbler was removed, and argon was bubbled through the solution for 10 minutes. DMS (200 uL, 5 equiv.) was added, and the mixture was allowed to warm to room temperature, and stirred for 60 minutes. The volatiles were removed under reduced pressure, and the residue was subjected to flash chromatography (30% EtOAc/Hexanes) to give **3.93** as a sweet-smelling clear oil that solidified upon standing in the fridge (94 mg, 80%).

Data for **3.93**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 9.52 (s, 1H), 3.98 (d, J = 10.2 Hz, 1H), 3.87 (d, J = 10.2 Hz, 1H), 3.40 (br s, 1H), 2.93 (d, J = 3.9 Hz, 1H), 2.20 (dd, J = 16.1, 1.3 Hz, 1H), 1.97 (dd, J = 16.1, 1.7 Hz, 1H), 1.60-1.31 (m, 7H), 1.24 (dd, J = 12.9, 2.7 Hz, 1H), 1.20-1.10 (m, 1H), 0.78 (s, 9H), -0.01 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 206.9 (HC=O), 67.4 (C_4), 62.7 (CH_2), 58.4 (CH), 55.1 (CH), 51.8 (C_4), 57.6 (CH), 39.1 (CH_2), 26.2 25.8 (2 x CH_3), 25.6 (CH_3), 25.2 (CH_2), 21.8 (CH_2), 21.0 (CH_2), 18.0 (C_4), -5.7 (2 x CH_3).

FTIR (neat, cm^{-1}) υ = 3501 (br s), 2930 (s), 2890 (s), 1727 (s), 1455 (s), 1254 (s), 1078 (s), 839 (s), 777 (s)

HRMS (EI) Expected for $C_{14}H_{23}O_4Si$ [$(M\text{-}tBu)^+$]: 283.13656, found: 283.13472 (6.2%)

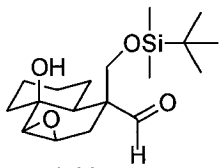
Data for **3.94**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 9.55 (s, 1H), 3.99 (d, J=10.2 Hz, 1H), 3.89 (d, J=10.2 Hz, 1H), 3.41 (br s, 1H), 2.95 (d, J=3.8 Hz, 1H), 2.44 (s, 1H), 2.27 (dd, J=8.7, 1.2 Hz, 1H), 1.98 (dd, J=8.9, 1.7 Hz, 1H), 1.89-1.01 (m, 10H), 0.92 (t, J = 7.8 Hz, 9H), 0.55 (q, J = 7.8 Hz, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 206.8 (HC=O), 67.4 (C4), 62.4 (CH), 58.5 (CH), 55.1 (CH), 51.8 (C_4), 47.6 (CH), 39.2 (CH_2), 26.3 (CH_2), 25.2 (CH_2), 21.9 (CH_2), 21.1 (CH_2), 6.6 (3 x CH_3), 4.1 (3 xCH_2).

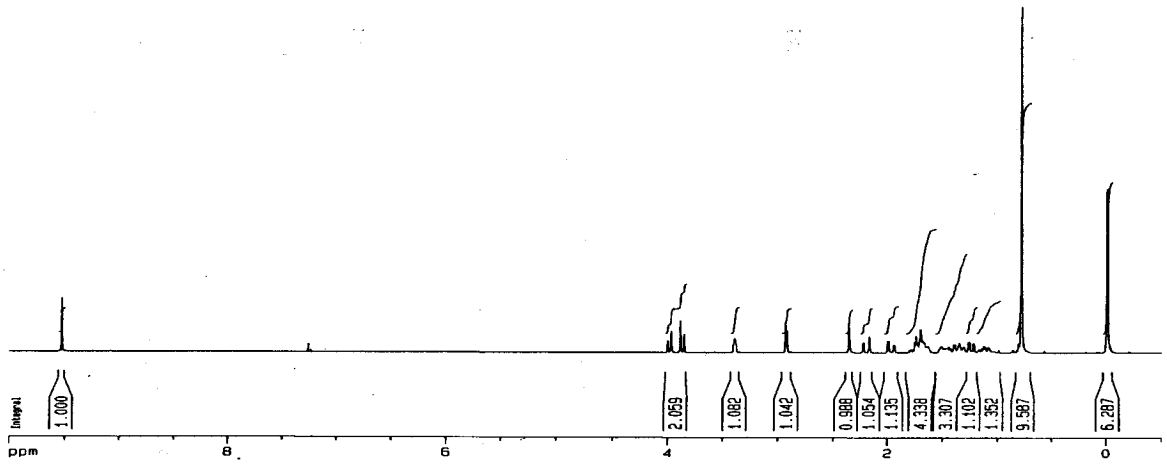
FTIR (neat, cm^{-1}) υ = 3501 (br s), 2937 (s), 2876 (s), 1727.5 (s), 1078 (s)

HRMS (EI) Expected for $C_{16}H_{27}O_4Si$ [$(M\text{-}Et)^+$]: 311.16885, found: 311.16885 (17.7%)

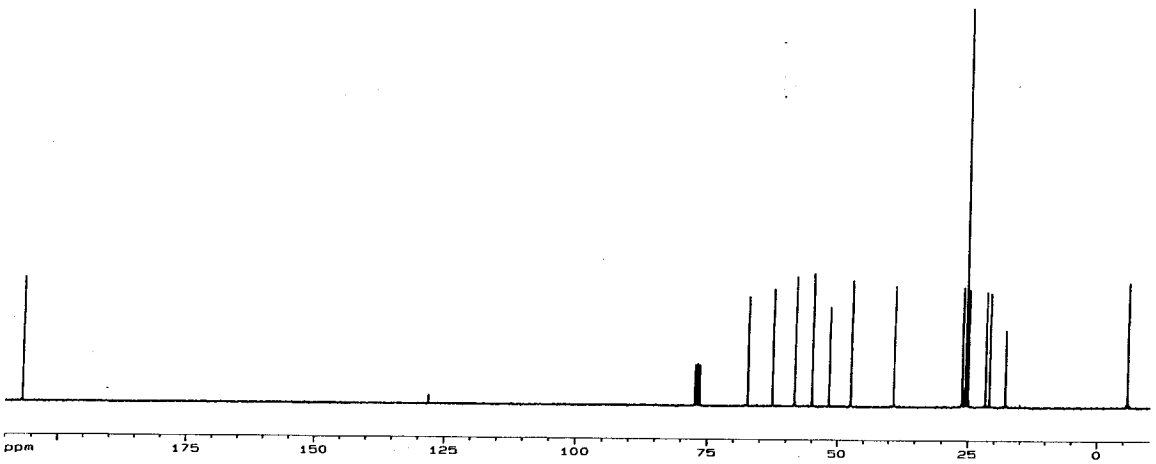


3.93

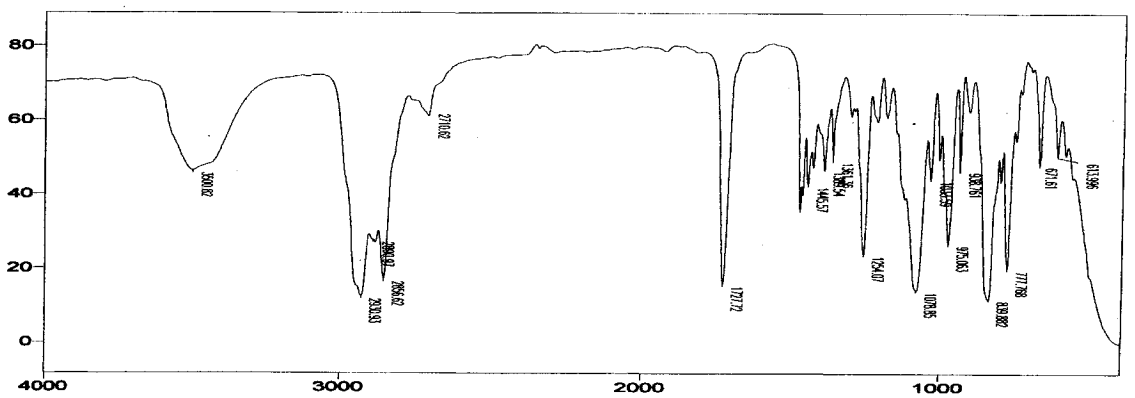
^{1}H NMR ($CDCl_3$, 300 MHz)

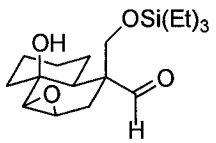


^{13}C NMR ($CDCl_3$, 75 MHz)



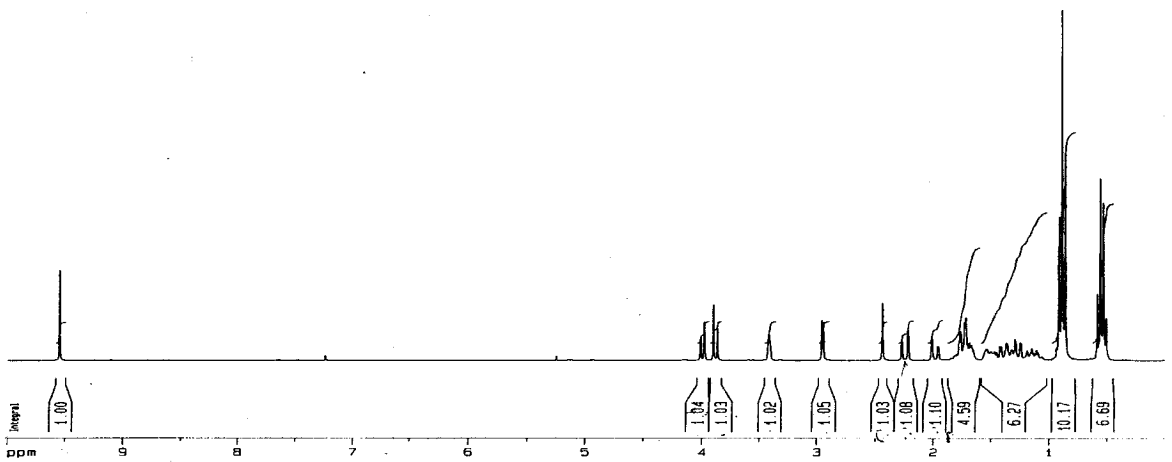
FTIR (neat)



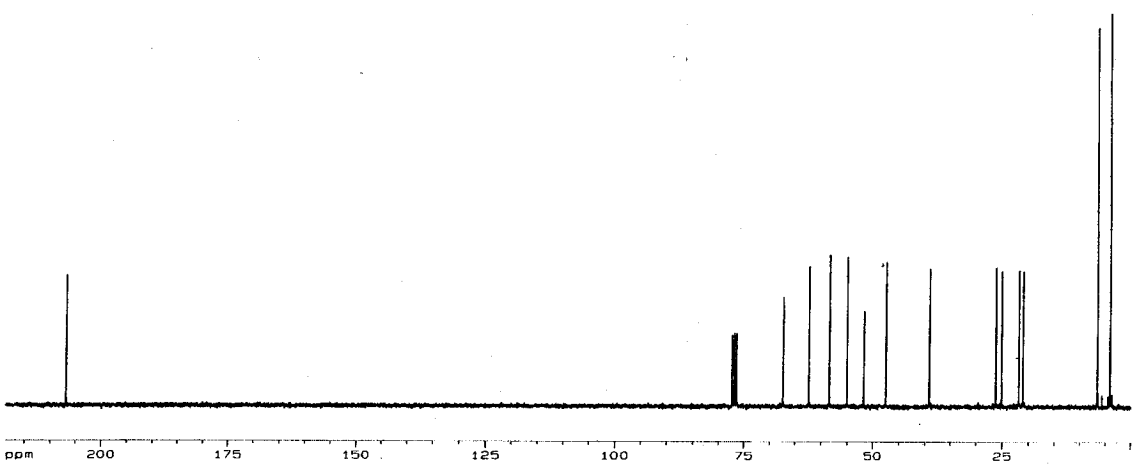


3.94

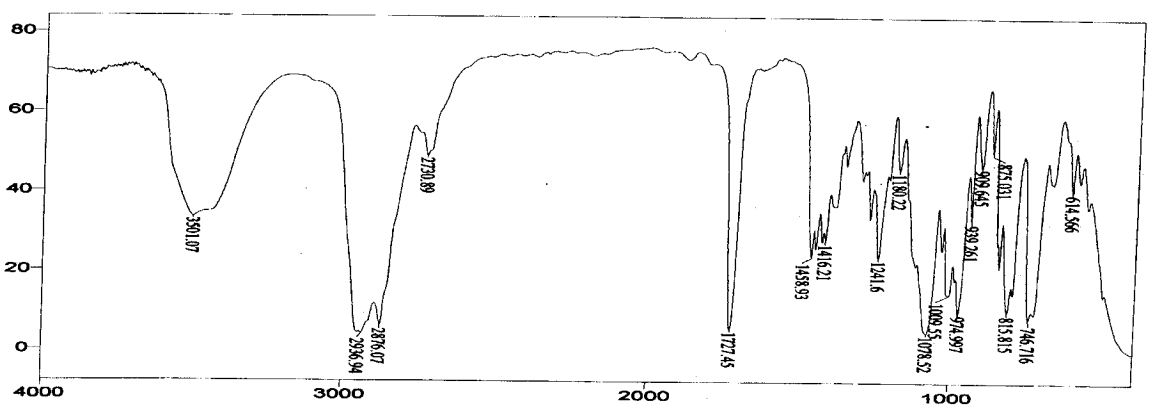
^{1}H NMR ($CDCl_3$, 300 MHz)

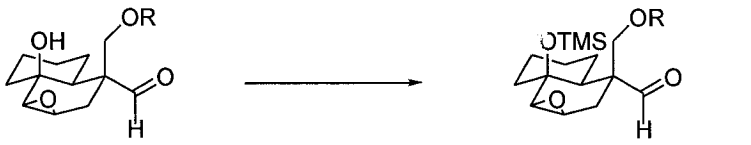


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.94 (R = TBMS)
3.95 (R = TES)

3.99 (R = TBMS)
3.100 (R = TES)

3-(tert-Butyl-dimethyl-silanyloxymethyl)-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (3.99) and **3-Triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (3.100)**. Representative procedure: A solution of aldehyde **3.94** (235mg, 691 umol) in dry THF (10 mL) under argon was stirred at 0°C, and trimethylchlorosilane (distilled over CaH_2 prior to use, 125 uL, 1.4 equiv.) was added, followed by KHMDS (192 mg, 1.4 equiv.). The mixture was stirred for 1.5 hr, quenched with aqueous $NH_4Cl_{(sat.)}$ (3 mL), and extracted with ether (3 x). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (5% Et_2O in Hexanes) that gave **3.99** as yellow oil which solidified upon standing in the freezer (275 mg, 89%).

Data for **3.99**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 9.67 (s, 1H), 4.14 (d, J = 10.3 Hz, 1H), 3.93 (d, J = 10.3 Hz, 1H), 3.35 (br s, 1H), 2.85 (d, J = 3.6 Hz, 1H), 2.27 (dd, J = 15.8, 1.0 Hz, 1H), 1.97 (br d, J = 15.8 Hz, 1H), 1.78-1.62 (m, 4H), 1.59-1.07 (m, 6H), 0.82 (s, 9H), 0.19 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} = 209.1 (HC=O), 72.1 (C_4), 62.6 (CH_2), 58.0 (CH), 54.6 (CH), 52.0 (C_4), 50.0 (CH), 36.3 (CH_2), 26.3 (CH_2), 25.7 (3 x CH_3), 25.1 (CH_2), 21.7 (CH_2), 21,4 (CH_2), 18.1 (C_4), 2.2 (3 x CH_3), -5.4 (CH_3), -5.5 (CH_3)

FTIR (neat, cm^{-1}) υ = 2951 (br s), 2857 (s), 1727 (s), 1472 (m), 1258 (s), 1251 (s), 1093 (s), 1076 (s), 1041 (s), 840 (s)

HRMS (EI) Expected for $C_{19}H_{35}O_4Si_2$ $[(M\text{-}tBu)^+]$: 355.1761, found: 355.1762 (5.7%)

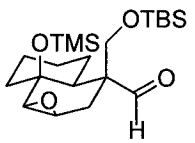
Data for **3.100**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 9.68 (s, 1H), 4.15 (d, J = 10.3 Hz, 1H), 3.94 (d, J = 10.3 Hz, 1H), 3.35 (br s, 1H), 2.85 (d, J = 3.6 Hz, 1H), 2.33 (d, J = 15.8 Hz, 1H), 1.97 (d, J = 15.8 Hz, 1H), 1.78-1.62 (m, 4H), 1.59-1.07 (m, 6H), 0.92 (t, J = 8.0 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H), 0.19 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} = 209.3 (HC=O), 72.1 (C_4), 62.3 (CH_2), 58.0 (CH), 54.6 (CH), 52.0 (C_4), 50.1 (CH), 26.3 (CH_2), 25.3 (CH_2), 21.6 (CH_2), 21.4 (CH_2), 6.7 (3 x CH_3), 4.65 (3 x CH_2), 2.40 (3 x CH_3)

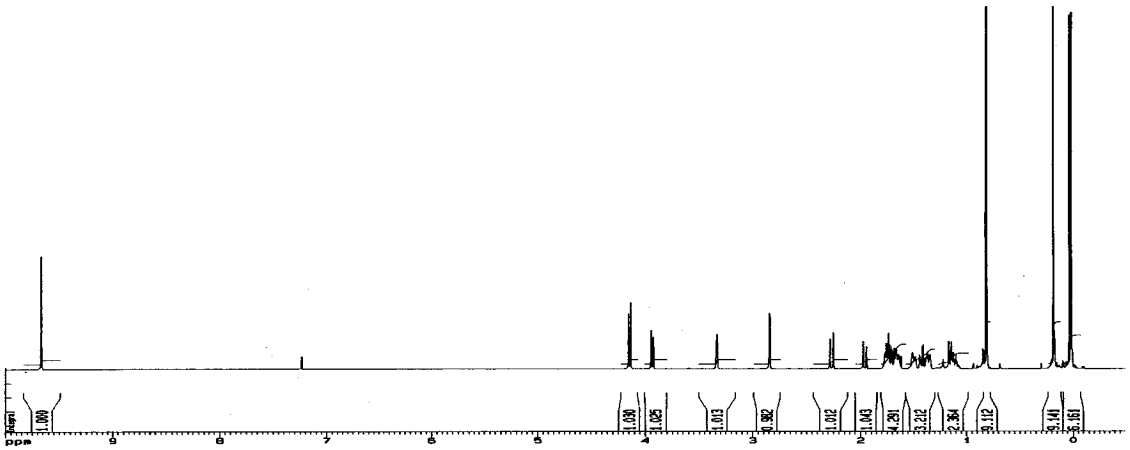
FTIR (neat, cm^{-1}) υ = 2951 (br s), 2876 (s), 1727 (s), 1441 (s), 1249 (s), 1093 (s), 1073 (s), 1041 (s), 840 (s)

HRMS (EI) Expected for $C_{19}H_{35}O_4Si_2$ [$(M\text{-}Et)^+$]: 383.2074, found: 383.2045 (2.7%)

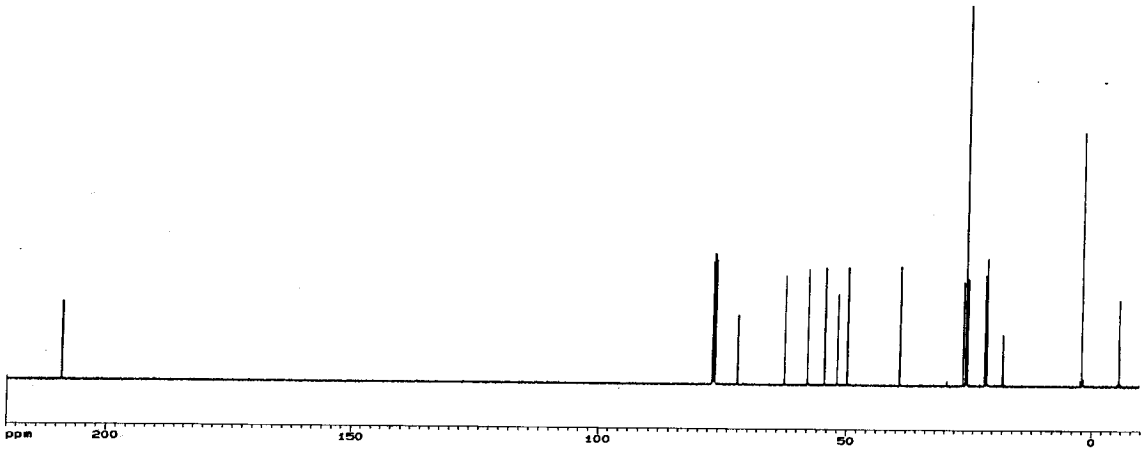


3.99

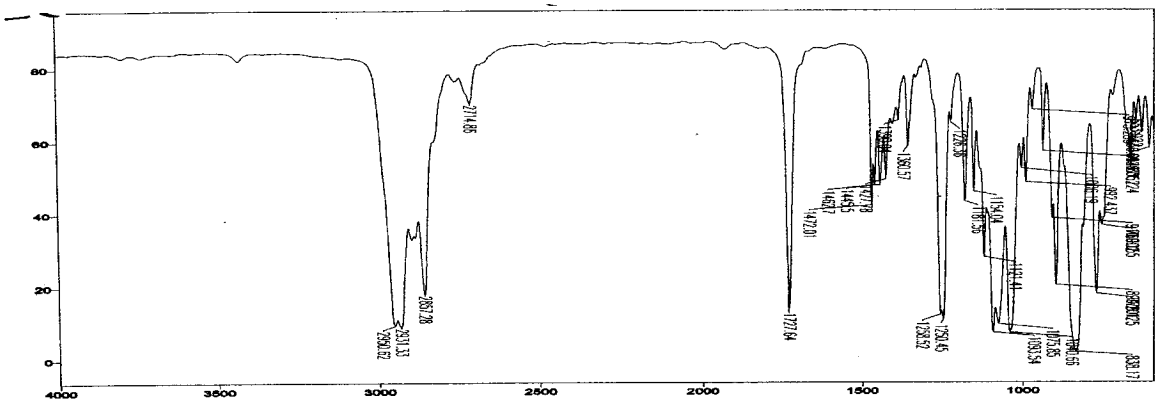
^{1}H NMR ($CDCl_3$, 500 MHz)

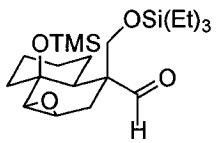


^{13}C NMR ($CDCl_3$, 125 MHz)



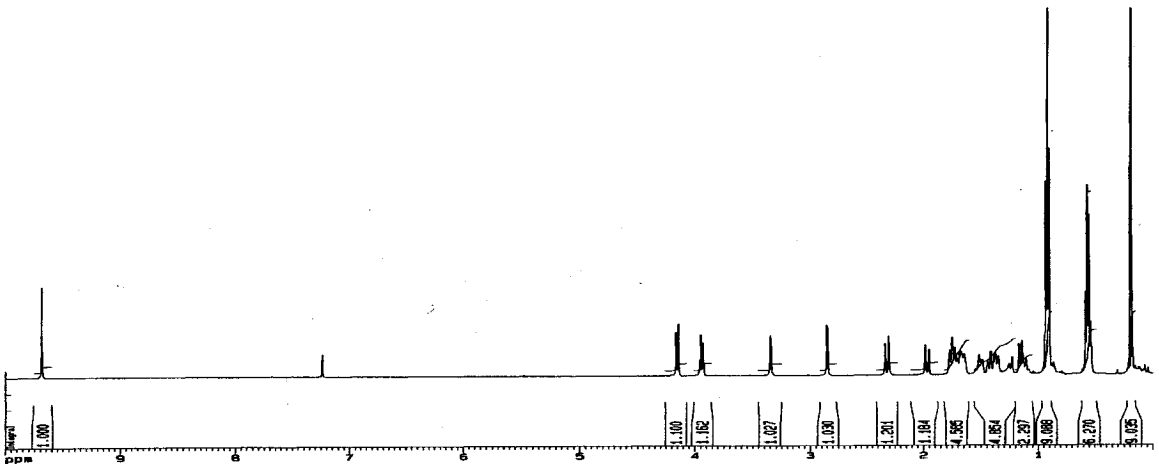
FTIR (neat)



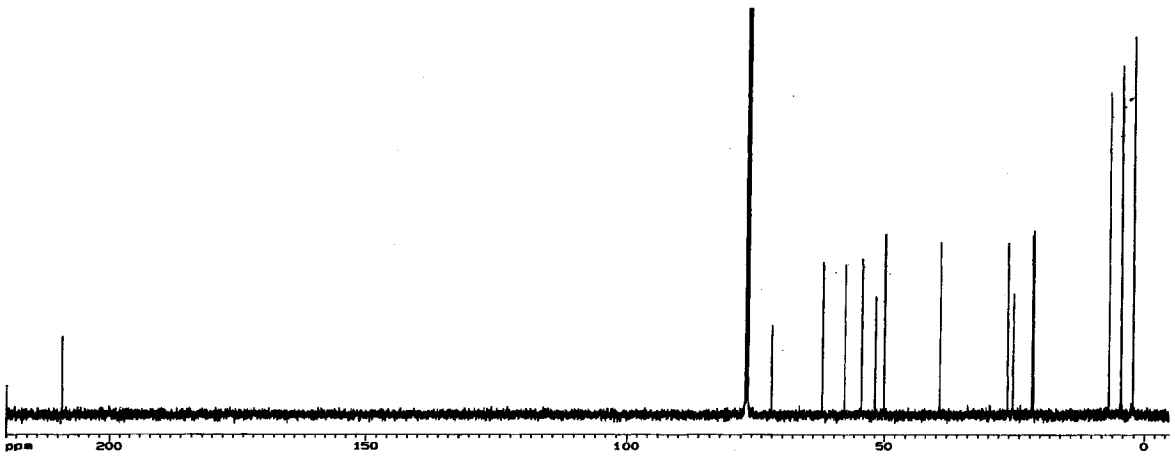


3.100

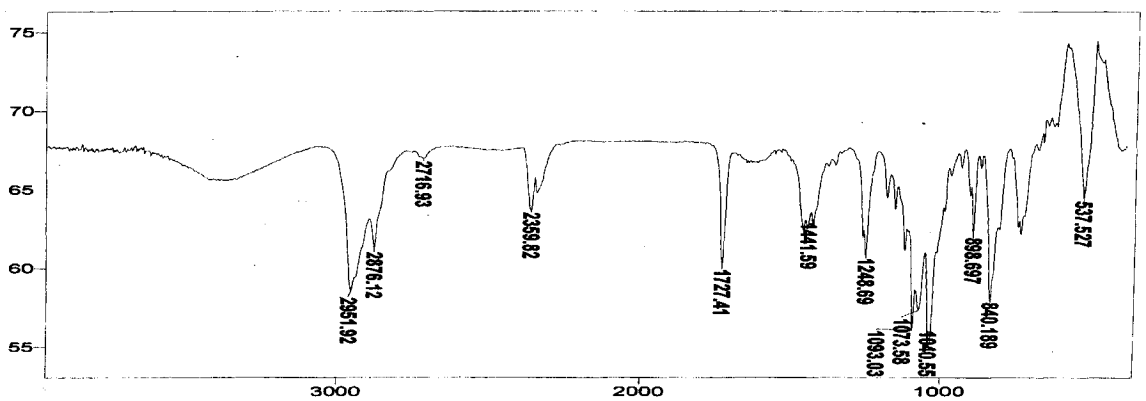
^{1}H NMR ($CDCl_3$, 500 MHz)

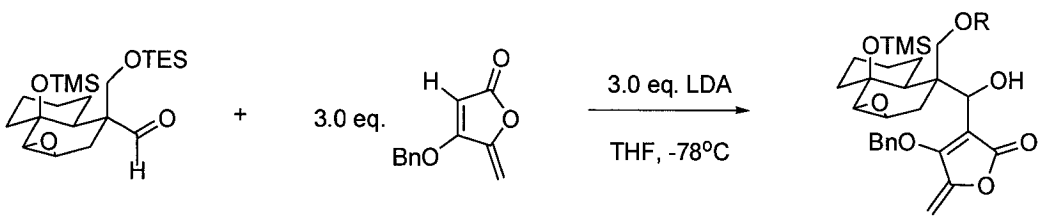


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





3.99 (R = TBMS)
3.100 (R = TES)

3.75

3.101 (R = TBMS, 38%)
3.102 (R = TES, 50%)

4-Benzyloxy-3-{[3-(tert-butyl-dimethyl-silanyloxymethyl)-7a-trimethyl silanyloxy-decahydro-1-oxa-cyclopropa [a]naphthalen-3-yl]-hydroxy-methyl}-5-methylene-5H-furan-2-one (3.101) and **4-Benzyloxy-3-[hydroxy-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a]naphthalen-3-yl)-methyl]-5-methylene-5H-furan-2-one (3.102).**

Representative procedure: LDA was prepared in the standard way by combining THF (2.4 mL), diisopropylamine (770 uL, 5.5 mmol), and BuLi (5.0 mmol) at -78°C. The solution was titrated at 0.91M with BHT and fluorene. A clean, dry 25 mL roundbottom flask was flame dried and backfilled with argon several times. The aldehyde **3.99** (23 mg, 109 umol) and tetronate (66 mg, 3 equiv.) were added, and the flask was again backfilled with argon several times. The mixture was dissolved in THF (5 mL) and cooled to -90°C. After 5 min, LDA (0.91M, 4 equiv.) was added, dropwise. The solution was allowed to warm to -78°C over 30 minutes, and gradually took on a red-orange colour. Once the reaction was deemed complete (TLC, capillary pre-treated with iPrOH), it was quenched with aqueous $NH_4Cl_{(sat)}$ (3 mL), and extracted with ether (3 x). The combined organic phases were dried over $MgSO_4$ and concentrated carefully (not to exceed 35°C). The residue was subjected to flash chromatography (0 to 50% Et_2O in hexanes) to give **3.101** as a thick yellow foam (25 mg, 38%).

Data for **3.100**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 7.43-7.32 (m, 5H), 5.32 (d, J = 11.2 Hz, 1H), 5.27 (d, J = 11.2 Hz, 1H), 5.07 (d, J = 2.9 Hz, 1H), 5.00 (d, J = 2.9 Hz, 1H), 4.71 (d, J = 7.7 Hz, 1H), 4.10 (d, J = 10.6 Hz, 1H), 3.50 (d, J = 10.6 Hz, 1H), 3.22-3.20 (m, 1H), 2.79 (d, J = 3.9 Hz, 1H), 2.13 (dd, J = 15.6, 2.1 Hz, 1H), 1.92 (dd, J = 15.6, 3.0 Hz, 1H), 1.83-1.60 (m, 4H), 1.58-1.13 (m, 5H), 0.82 (s, 9H), 0.17 (s, 9H), 0.02 (s, 6H)

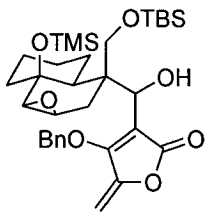
^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} = 169.3 (C_4), 161.9 (C_4), 149.6 (C_4), 135.2 (C_4), 128.8 (CH), 128.7 (2 x CH), 127.7 (2 x CH), 113.3 (C_4), 93.7 (CH_2), 75.4 (CH_2), 72.7 (C_4), 70.6 (CH), 64.9 (CH_2), 57.5 (CH), 53.8 (CH), 47.2 (CH), 46.3 (C_4), 40.1 (CH_2), 26.9 (CH_2), 26.0 (3 x CH_3), 25.4 (CH_2), 21.6 (CH_2), 21.2 (CH_2), 18.3 (C_4), 2.4 (3 x CH_3), -5.2 (CH_3), -5.3 (CH_3).

FTIR (neat, cm^{-1}) υ = 3490 (br s), 2951 (s), 2856 (s), 1766 (s), 1619 (s), 1243 (s), 1093 (s), 1036 (s), 834 (s)

HRMS (EI) Expected for $C_{29}H_{41}O_7Si_2$ [$(M\text{-}tBu)^+$]: 557.23906, found: 557.24181 (3.8%)

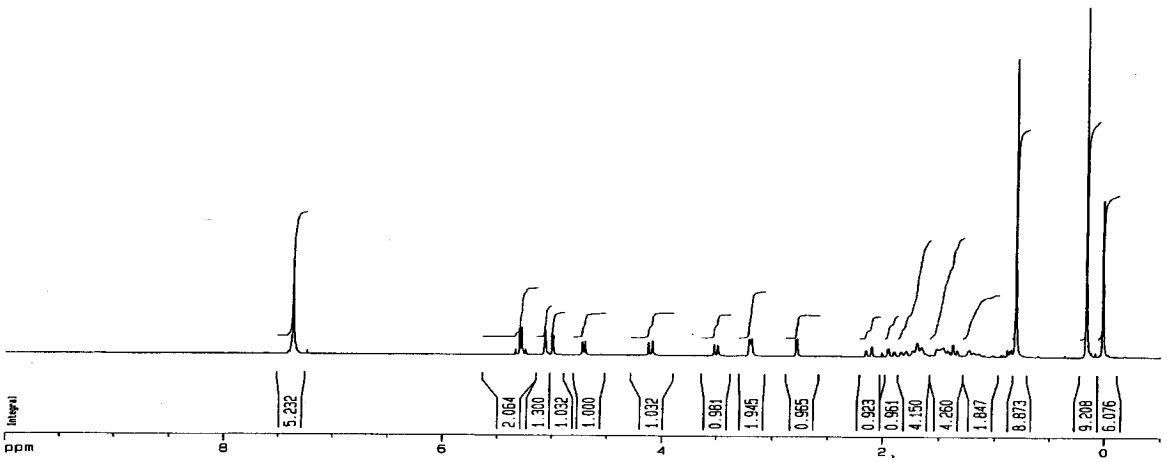
Data for **3.102**:

Used as a crude without further purification

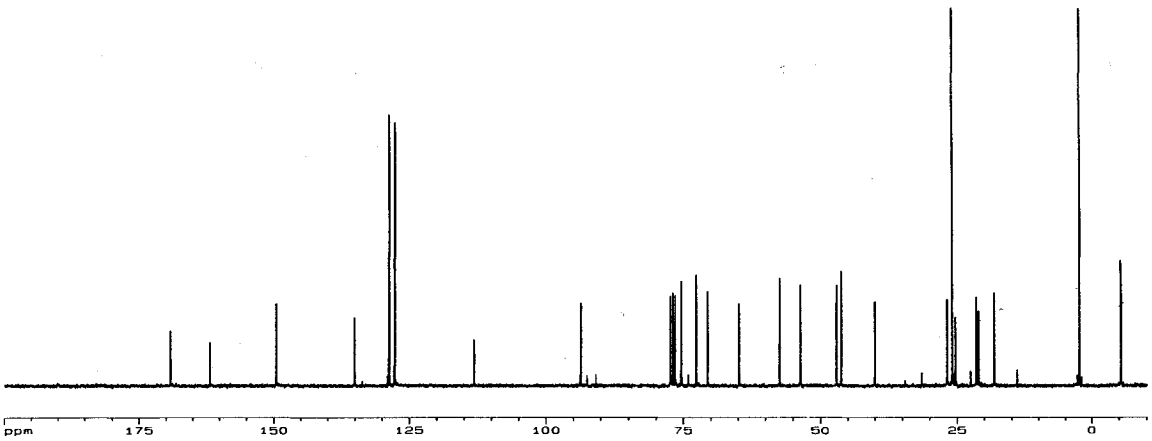


3.101

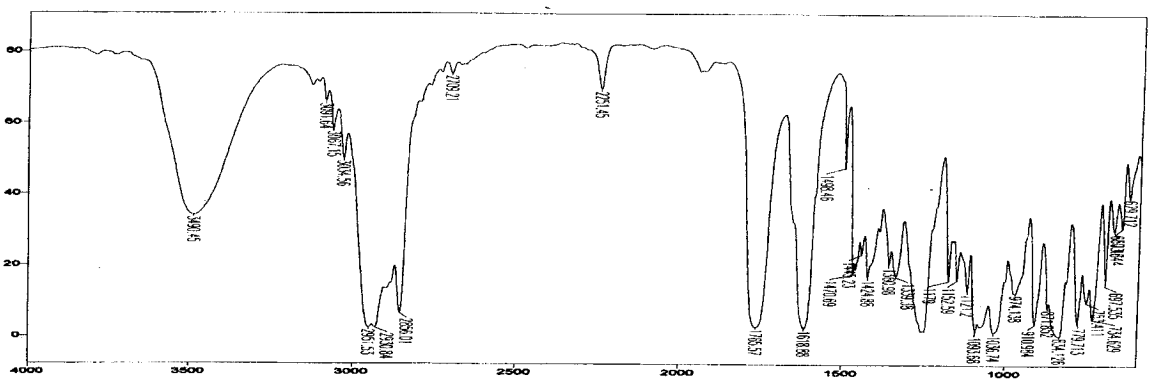
^{1}H NMR ($CDCl_3$, 500 MHz)

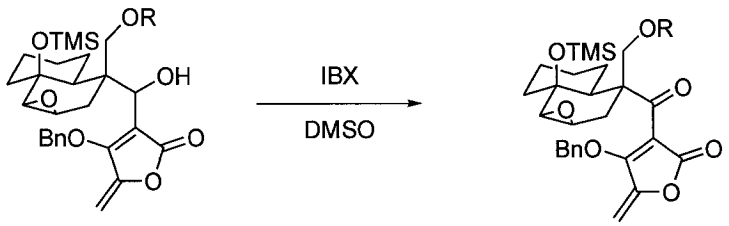


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





3.101 (R = TBMS)
3.102 (R = TES)

3.103 (R = TBMS, 47%)
3.104 (R = TES, 49%)

4-Benzyloxy-3-[3-(tert-butyl-dimethyl-silanyloxymethyl)-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl]-5-methylene-5H-furan-2-one (3.103) and **4-Benzyloxy-5-methylene-3-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (3.104)**. Representative procedure: A solution of alcohol **3.101** (100 mg) in DMSO (3.0 mL) was stirred at room temperature under air and IBX (92 mg, 3 equiv.) in DMSO (1.0 mL) was added. The reaction was allowed to stir for 2 hr, diluted with water (10 mL), and extracted with ether (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (20% Et_2O in Hexanes) to give **3.103** as a thick yellow foam (47 mg, 47%).

Data for **3.103**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.42-7.28 (m, 5H), 5.09 (d, J = 2.7 Hz, 1H), 5.05 (d, J = 2.7 Hz, 1H), 4.91 (d, J = 11.1 Hz, 1H), 4.89 (d, J = 11.1 Hz, 1H), 4.20 (br s, 2H), 3.37 (br s, 1H), 2.94 (d, J = 3.8 Hz, 1H), 2.78 (d, J = 15.0 Hz, 1H), 2.03 (dd, J = 14.5, 2.6 Hz, 1H), 1.97 (dd, J = 2.2, 11.4 Hz, 1H), 1.87-1.47 (m, 5H), 1.35-1.19 (m, 3H), 0.77 (s, 9H), 0.20 (s, 9H), -0.06 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 204.4 (C_4), 165.3 (C_4), 165.1 (C_4), 149.4 (C_4), 134.4 (C_4), 129.2 (CH), 128.8 (2 x CH), 128.7 (2 x CH), 109.0 (C_4), 94.2 (CH_2), 77.3 (CH_2), 72.5 (C_4), 62.1 (CH_2), 57.9 (CH), 57.8 (C_4), 54.5 (CH), 47.7 (CH), 40.0 (CH_2), 29.4 (CH_2), 26.6 (CH_2), 25.9 (3 x CH_3), 22.9 (CH_2), 21.5 (CH_2), 18.4 (C_4), 2.4 (3 x CH_3), -5.2 (2 x CH_3).

FTIR (neat, cm^{-1}) υ = 2951 (s), 2929 (s), 2855 (s), 1769 (s), 1678 (s), 1663 (s), 1596 (s), 1460 (m), 1422 (m), 1350 (s), 1283 (s), 1258 (s), 1250 (s), 1073 (m), 1034 (s), 910 (s), 838 (s)

HRMS (EI) Expected for $C_{29}H_{39}O_7Si_2$ $[(M\text{-}tBu)^+]$: 555.2234, found: 555.2224 (5.9%)

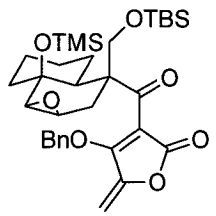
Data for **3.104**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.43-7.31 (m, 5H), 5.10 (d, J = 2.7 Hz, 1H), 5.07 (d, J = 2.7 Hz, 1H), 5.00 (d, J = 11.3 Hz, 1H), 4.87 (d, J = 11.3 Hz, 1H), 4.13 (d, J = 10.0 Hz, 1H), 4.05 (d, J = 10.0 Hz, 1H), 3.38 (br s, 1H), 2.94 (d, J = 3.8 Hz, 1H), 2.83 (d, J = 15.0 Hz, 1H), 2.10-2.00 (m, 2H), 1.84-1.51 (5H), 1.34-1.19 (m, 3H), 0.82 (t, J = 8.0 Hz, 9H), 0.42 (q, J = 8.0 Hz, 6H), 0.20 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 203.4 (C_4), 165.5 (C_4), 165.1 (C_4), 149.3 (C_4), 134.4 (C_4), 129.1 (CH), 128.7 (2 x CH), 128.6 (2 x CH), 108.6 (C_4), 94.2 (CH_2), 77.4 (CH_2), 72.5 (C_4), 61.5 (CH_2), 58.0 (CH), 57.6 (C_4), 54.4 (CH), 46.7 (CH), 40.1 (CH_2), 29.0 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 21.5 (CH_2), 6.7 (3 x CH_3), 4.0 (3 x CH_2), 2.3 (3 x CH_3).

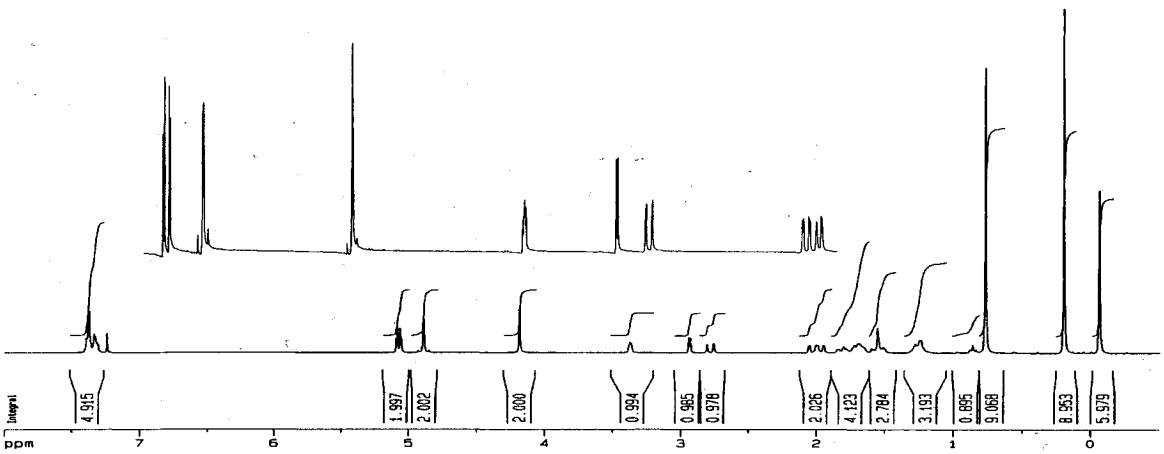
FTIR (neat, cm^{-1}) υ = 2952 (s), 1769 (s), 1673 (s), 1597 (s), 1459 (s), 1350 (s), 1283 (s), 1154 (s), 1037 (s), 911 (s), 840 (s), 747 (s)

HRMS (EI) Expected for $C_{31}H_{43}O_7Si_2$ $[(M\text{-}Et)^+]$: 583.25473, found: 583.25232 (4.2%)

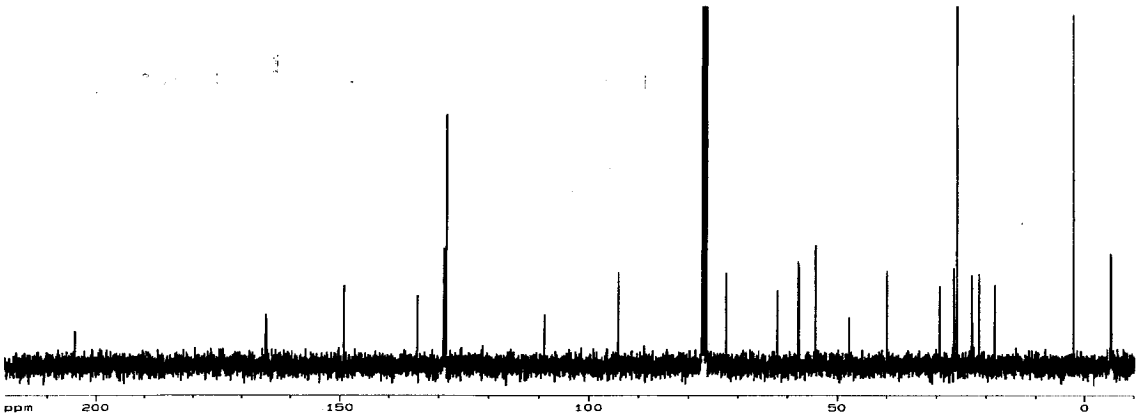


3.103

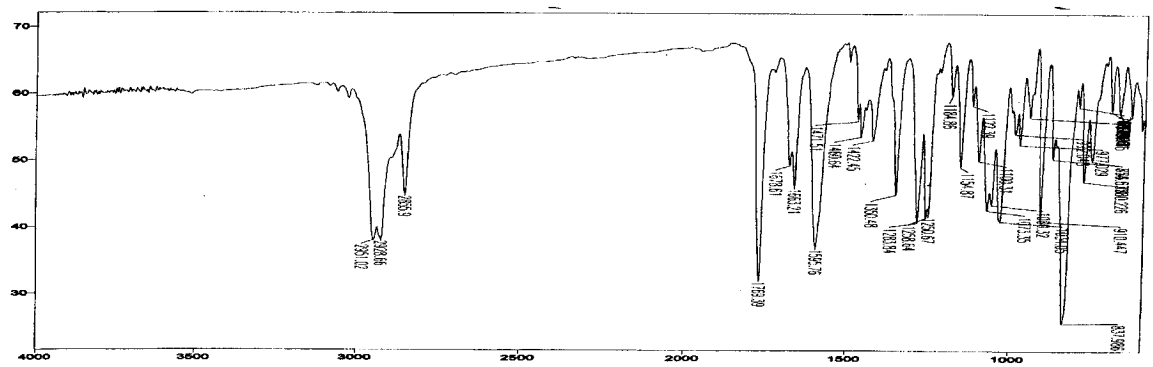
^{1}H NMR ($CDCl_3$, 300 MHz)

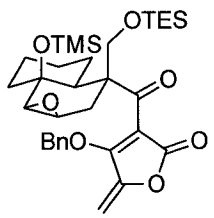


^{13}C NMR ($CDCl_3$, 75 MHz)



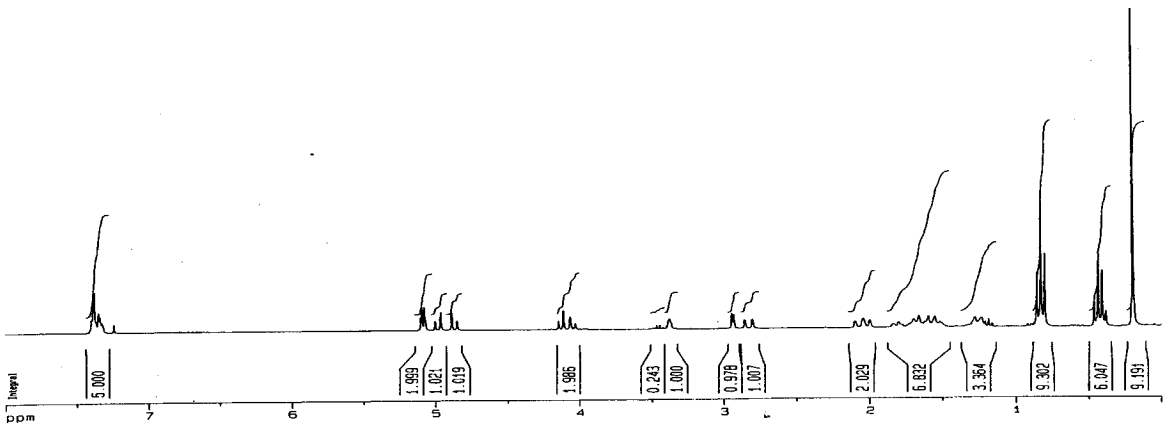
FTIR (neat)



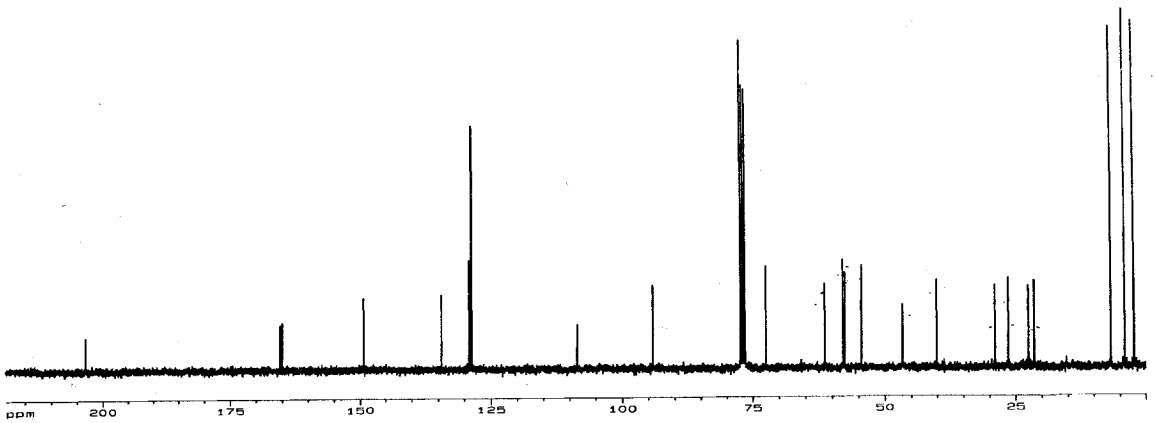


3.104

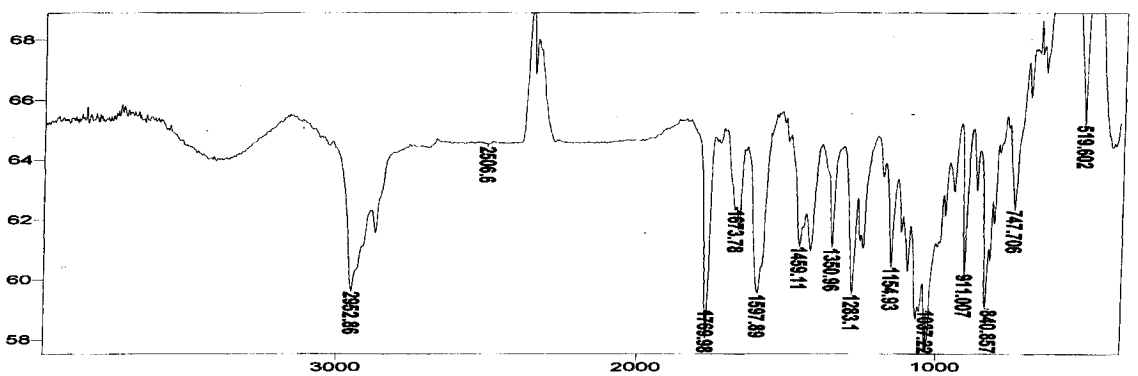
^{1}H NMR ($CDCl_3$, 300 MHz)

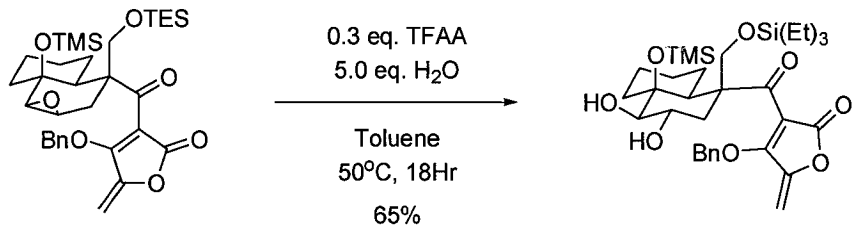


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.102 **3.107**

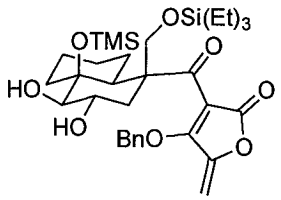
4-Benzyloxy-3-(3,4-dihydroxy-1-triethylsilanyloxymethyl-4a-trimethylsilanyloxy-decahydro-naphthalene-1-carbonyl)-5-methylene-5H-furan-2-one (3.107). A solution of **3.102** (7.2 mg, 11.4 umol) in toluene (1.0 mL) was stirred at room temperature, and trifluoroacetic acid (0.3 eq, solution in toluene) was added. The reaction was stirred for 10 minutes, and H_2O (5.0 eq in THF) was added, and the mixture was warmed to 50°C for 1 hr. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (40% EtOAc in Hexanes) to give **3.107** as a white powder (4.6 mg, 65%).

Data for **3.107**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.43-7.28 (m, 5H), 5.12-5.07 (m, 2H), 5.08 (d, J = 11.3 Hz, 1H), 4.80 (d, J = 11.3 Hz, 1H), 4.13 (d, J = 10.1 Hz, 1H), 4.05 (d, 10.1 Hz, 1H), 3.84 (ddd, J = 11.5, 9.5, 4.5 Hz, 1H), 3.33 (d, J = 9.5 Hz, 1H), 2.65 (dd, J = 12.2, 4.5 Hz, 1H), 2.50 (dd, J = 9.0, 6.2 Hz, 1H), 2.19-1.67 (m, 3H), 1.60-1.32 (m, 4H), 1.30-1.02 (m, 4H), 0.81 (t, J = 8.0 Hz, 9H), 0.41 (q, J = 8.0 Hz, 6H), 0.18 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 200.6 (C_4), 166.2 (C_4), 165.8 (C_4), 149.3 (C_4), 134.3 (C_4), 129.2 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 107.8 (C_4), 94.6 (CH_2), 80.8 (CH), 79.1 (C_4), 77.7 (CH_2), 67.4 (CH), 59.9 (CH_2), 58.5 (C_4), 43.9 (CH), 35.4 (CH_2), 35.0 (CH_2), 26.1 (CH_2), 21.2 (CH_2), 21.1 (CH_2), 6.7 (3 x CH_3), 4.0 (3 x CH_2), 2.6 (3 x CH_3)

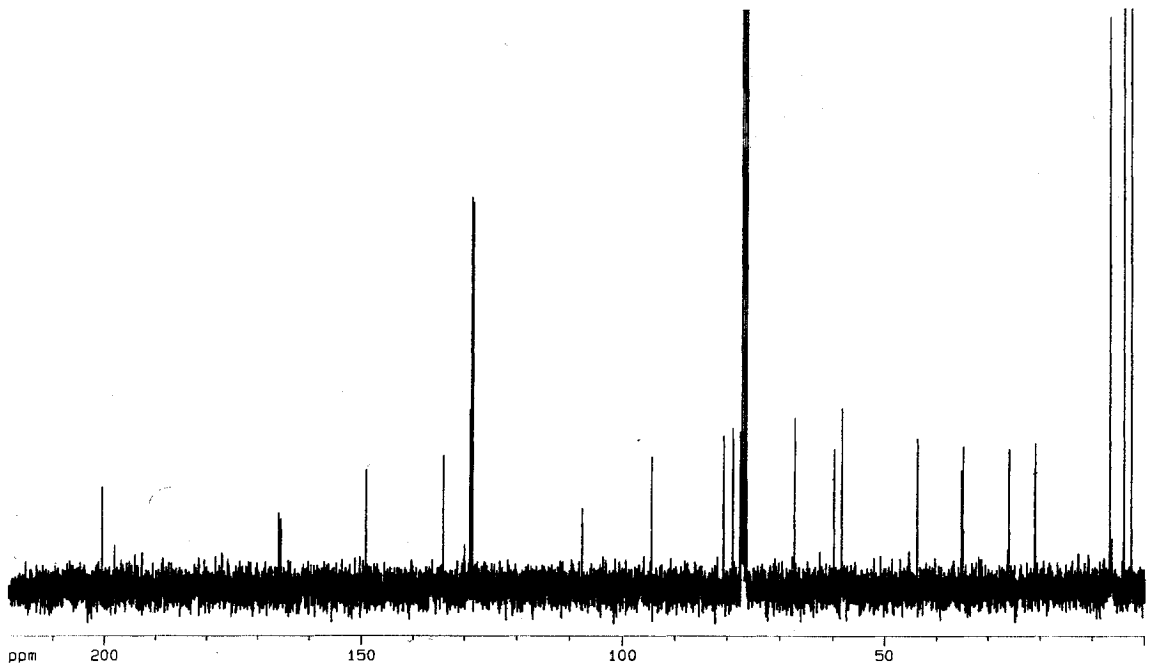
HRMS (EI) Expected for $C_{31}H_{45}O_8Si_2$ [$(M\text{-}Et)^+$]: 601.2653, found: 601.2623 (6.7%)

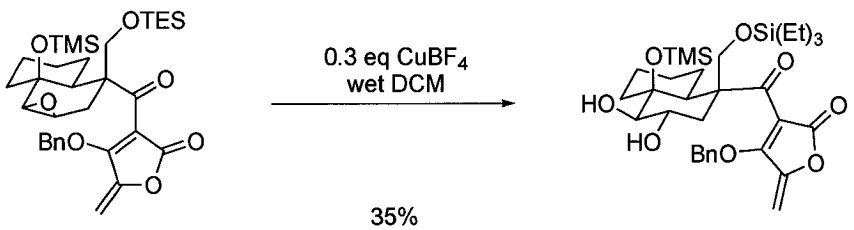


3.107

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

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



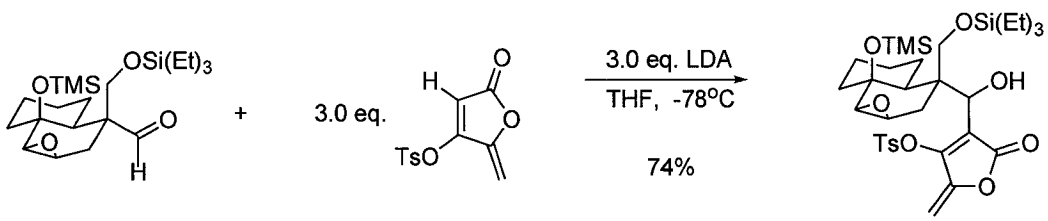


3.102 **3.107**

4-Benzyloxy-3-(3,4-dihydroxy-1-triethylsilanyloxymethyl-4a-trimethylsilanyloxy-decahydro-naphthalene-1-carbonyl)-5-methylene-5H-furan-2-one (3.107). A solution of the epoxide **3.102** (5 mg) in wet dichloromethane (1.0 mL) under air was stirred at room temperature, and $CuBF_4xH_2O$ (1 mg, 0.3 equiv.) was added. The reaction was allowed to stir for 6 hr, and placed directly on a silica gel column (40% EtOAc in Hexanes) to give **3.107** (1.8 mg, 35%) as a white powder.

Data for **3.107**:

As above



3.94 **3.119** **3.120**

Toluene-4-sulfonic acid 2-methylene-5-oxo-2,5-dihydro-furan-3-yl ester (3.119). Tosyl tetronate **3.119** was prepared from tetronic acid tosyl ester[156] with the same method as **3.75**, above. This compound is extremely sensitive to heat and light, possibly moisture, and polymerizes readily.

Toluene-4-sulfonic acid 4-[hydroxy-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalen-3-yl)-methyl]-2-methylene-5-oxo-2,5-dihydro-furan-3-yl ester (3.120). LDA was prepared in the standard way by combining THF (2.4 mL), diisopropylamine (770 uL, 5.5 mmol), and BuLi (5.0 mmol) at -78°C. The solution was titrated at 0.87 M with BHT and fluorene immediately prior to use. A clean, dry 100 mL roundbottom flask was flame dried and backfilled with argon several times. The aldehyde **3.94** (115 mg, 279 umol) and tetronate **3.119** (222 mg, 3 equiv.) were added, and the flask was again backfilled with argon several times. The mixture was dissolved in THF (15 mL) and cooled to -90°C. After 5 min, LDA (0.87M, 3.0 equiv.) was added, dropwise. The solution was allowed to warm to -78°C over 30 minutes, and immediately took on a dark-red/black colour. Once the reaction was deemed complete (TLC, capillary pre-treated with iPrOH), it was quenched with aqueous $NH_4Cl_{(sat)}$ (3 mL), and extracted with ether (3 x). The combined organic phases were dried over $MgSO_4$ and concentrated carefully (not to exceed 35°C). The residue was subjected to flash chromatography (0 to 30% Et_2O in hexanes) to give **3.120** as a thick yellow foam (139 mg, 38%).

Data for **3.119**:

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} = 7.84 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 5.97 (d, J = 1.8 Hz , 1H), 5.10 (dd, J = 3.1, 1.8 Hz, 1H), 5.00 (d, J = 3.1 Hz, 1H), 2.47 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 166.2 (C_4), 158.2 (C_4), 148.6 (C_4), 147.4 (C_4), 130.7 (C_4), 130.5 (2 x CH), 128.6 (2 x CH), 128.3 (C_4), 101.4 (CH), 94.8 (CH_2), 21.8 (CH_3)

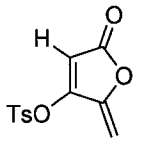
Data for **3.120**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.88 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 5.00 (d, J = 3.2 Hz, 1H), 4.55 (d, J = 3.0 Hz, 1H), 4.50 (d, J = 4.8 Hz, 1H), 4.09 (d, J = 10.5 Hz), 3.24 (br s, 1H), 3.18 (d, J = 10.5 Hz), 2.80 (d, J = 3.8 Hz, 1H), 2.61 (d, J = 4.8 Hz), 2.50 (s, 3H), 1.15 (d, J = 15.3 Hz), 1.05 (d, J = 15.2 Hz), 1.72-1.10 (m, 11H), 0.82-0.80 (m, 9H), 0.49-0.44 (m, 6H), 0.16 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz), δ_{ppm} = 166.7 (C_4), 151.4 (C_4), 148.9 (C_4), 146.8 (C_4), 132.2 (C_4), 130.2 (2 x CH), 128.6 (2 x CH), 125.8 (C_4), 94.9 (CH_2), 72.8 (C_4), 69.4 (CH), 63.2 (CH_2), 57.7 (CH), 54.6 (CH), 47.1 (C_4), 47.0 (CH), 40.1 (CH_2), 26.9 (CH_2), 23.9 (CH_2), 21.8 (CH_3), 21.6 (CH_2), 20.4 (CH_2), 14.1 (C_4), 6.7 (3 x CH_3), 3.98 (3 x CH_2), 2.3 (3 x CH_3)

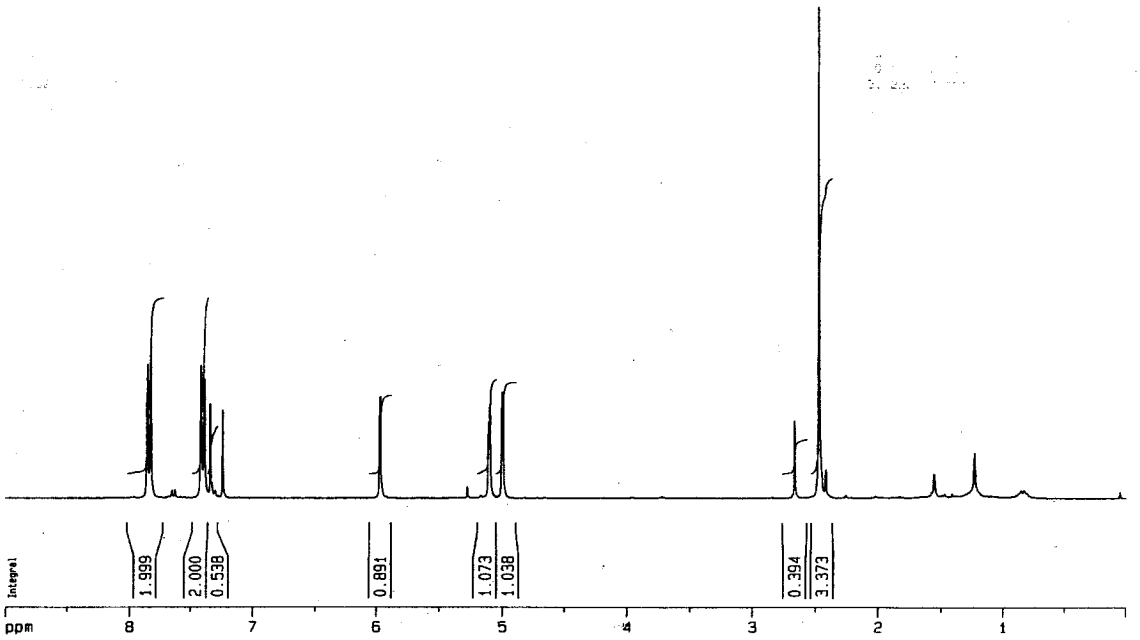
FTIR (FTIR, cm^{-1}) υ = 3352 (br, w), 2952 (s), 2876 (m), 1786 (s), 1642 (s), 1387 (s), 1089 (s), 1070 (s).

MS (CI, NH_3) Expected for $C_{33}H_{50}O_9SSi_2$ [$(M)^+$]: 678, found: 677 (0.6), 649 (48), 648 (27), 631 (15), 541 (28), 533 (16), 563 (30), 451 (20), 457 (45), 267 (74), 199 (47), 91 (83)

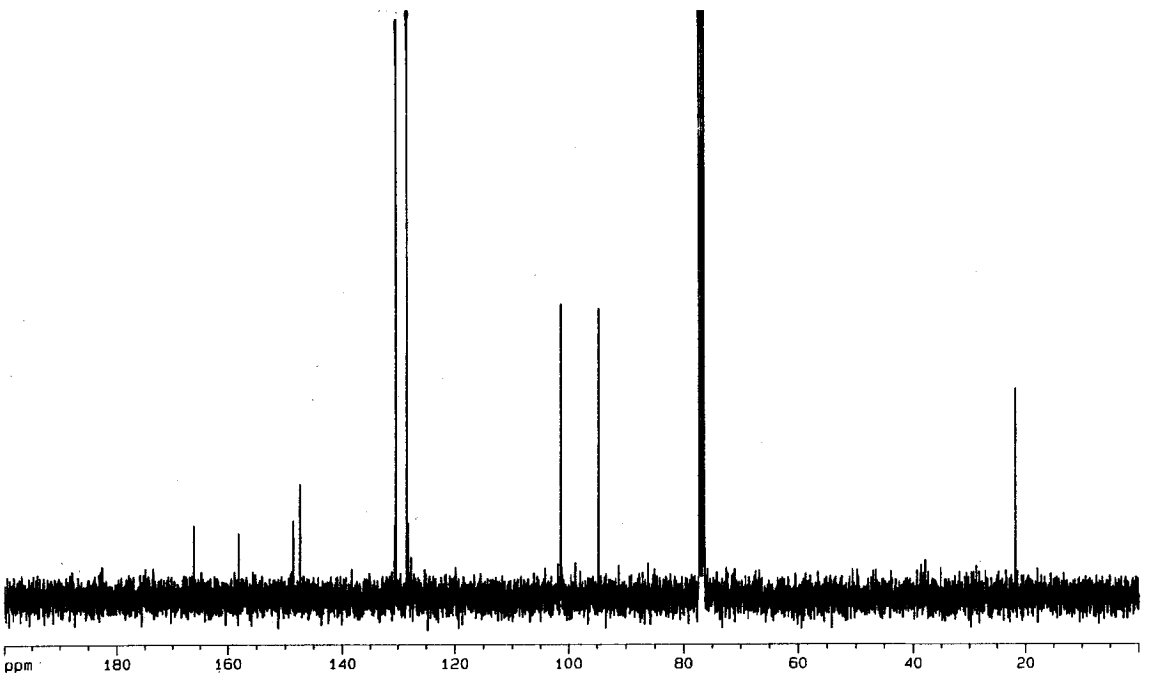


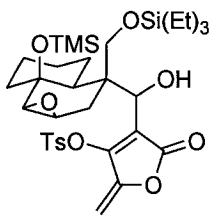
3.119

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



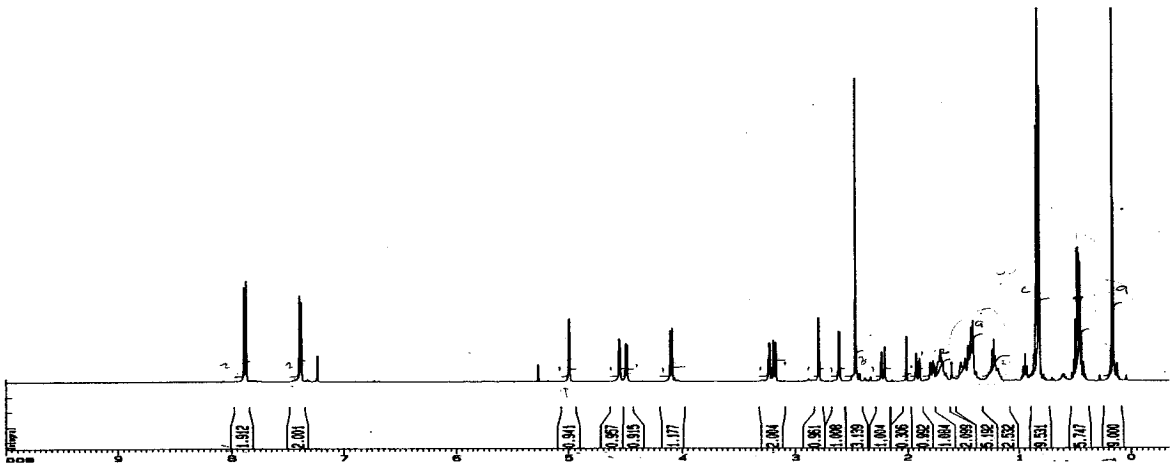
^{13}C NMR ($CDCl_3$, 75 MHz)



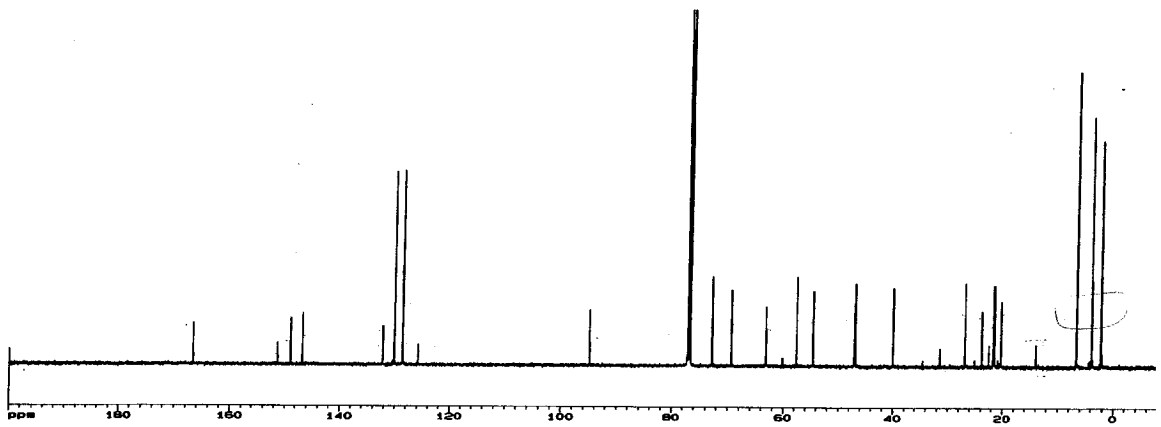


3.120

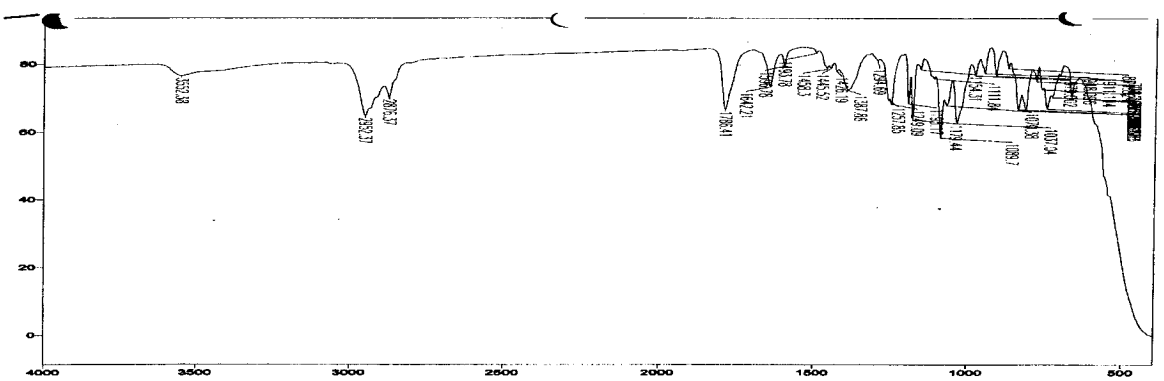
^{1}H NMR ($CDCl_3$, 500 MHz)

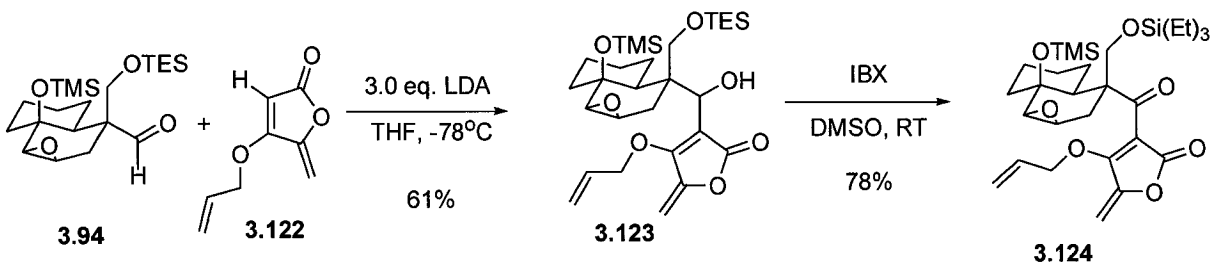


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4-Allyloxy-5-methylene-3-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (3.124). Allyl tetronate 4-Allyloxy-5-methylene-5H-furan-2-one (**3.122**) was prepared from known methods.[157] A solution of aldehyde **3.94** (100 mg) and tetronate **3.122** (130 mg, 3.0 equiv.) in THF (10 mL) was stirred at -78°C, and a freshly made and titrated solution of LDA (0.87M, 3.0 equiv.) was added, dropwise. The reaction was allowed to stir for 45 minutes, and quenched with aqueous $NH_4Cl_{(sat.)}$ (3 mL), followed by the usual workup. Flash chromatography (30% EtOAc in hexanes) gave **3.123** as an off-white foam (83 mg, 61%). A solution of the alcohol **3.123** (40 mg, 70.9 umol) in DMSO (1 mL) was stirred at room temperature and IBX (60 mg, 3 equiv.) was added in one portion. The reaction was allowed to stir overnight. In the morning, water (2 mL) was added, and the organic layer was extracted with ether (3 x 5 mL). After drying over $MgSO_4$ and removal of the volatiles, the residue was subjected to flash chromatography (10% Ether in Hexanes) to give the product **3.124** as a colorless oil. (24 mg, 60%)

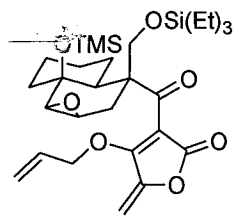
Data for **3.124**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 5.89-5.82 (m, 1H), 5.39 (dd, J = 17.1, 1.2 Hz, 1H), 5.32 (dd, J = 11.2, 1.2 Hz, 1H), 5.15 (d, J = 2.7 Hz, 1H), 5.09 (d, J = 2.7 Hz, 1H), 4.51 (dd, J = 12.5, 6.8 Hz, 1H), 4.37 (dd, J = 12.5, 5.3 Hz, 1H), 4.10 (d, J = 9.9 Hz, 1H), 4.00 (d, J = 9.9 Hz, 1H), 3.35 (br s, 1H), 2.91 (d, J = 3.8 Hz), 2.75 (dd, J = 15.1, 1.3 Hz, 1H), 2.10-1.85 (m, 2H), 1.83-1.46 (m, 7H), 1.36-1.19 (m, 1H), 0.89 (t, J = 7.9 Hz, 9H), 0.53 (q, J = 7.9 Hz, 6H), 0.19 (s, 9H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 202.9 (C_4), 165.4 (C_4), 164.8 (C_4), 130.9 (CH), 119.9 (CH_2), 108.3 (C_4), 94.0 (CH_2), 75.7 (CH_2), 72.6 (C_4), 61.5 (CH), 57.9 (CH), 57.5 (C_4), 54.4 (CH), 46.4 (CH), 40.1 (CH_2), 28.7 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 21.5 (CH_2), 6.7 (3 x CH_3), 4.1 (3 x CH_2), 2.3 (3 x CH_3).

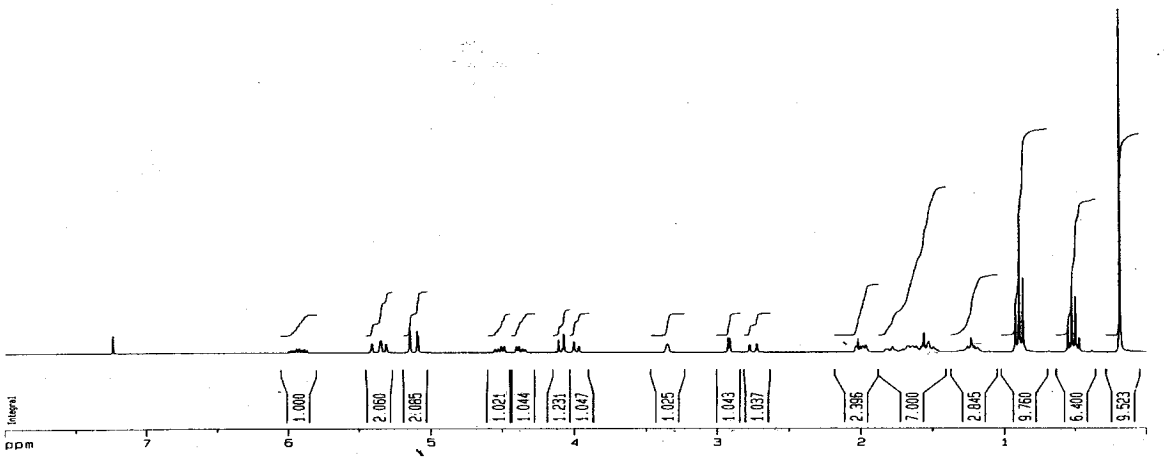
FTIR (neat, cm^{-1}) υ = 2951 (s), 2881 (m), 1771 (s), 1682 (m), 1660 (m), 1599 (s), 1282 (m), 1036 (s), 839 (s).

HRMS (EI) Expected for $C_{27}H_{41}O_7Si_2$ $[(M\text{-}Et)^+]$: 533.23908, found: 533.23737 (12.01%)

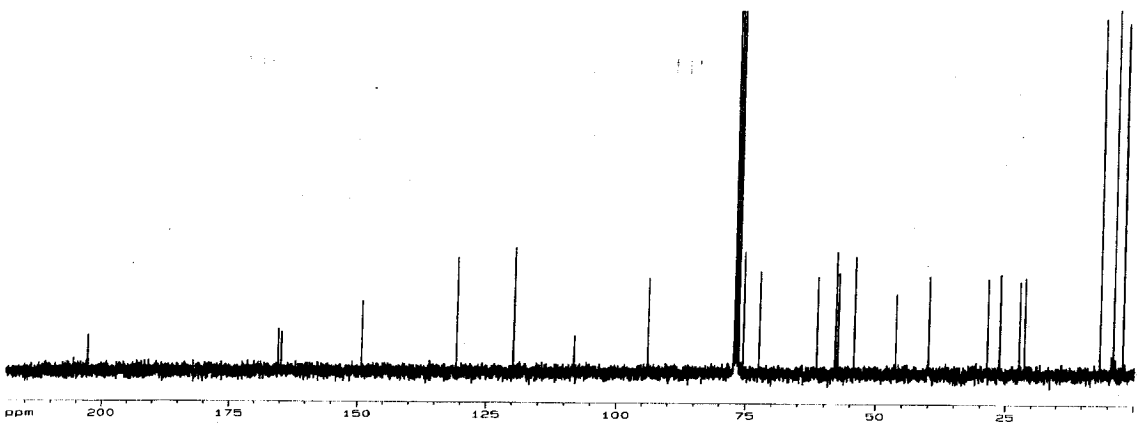


3.124

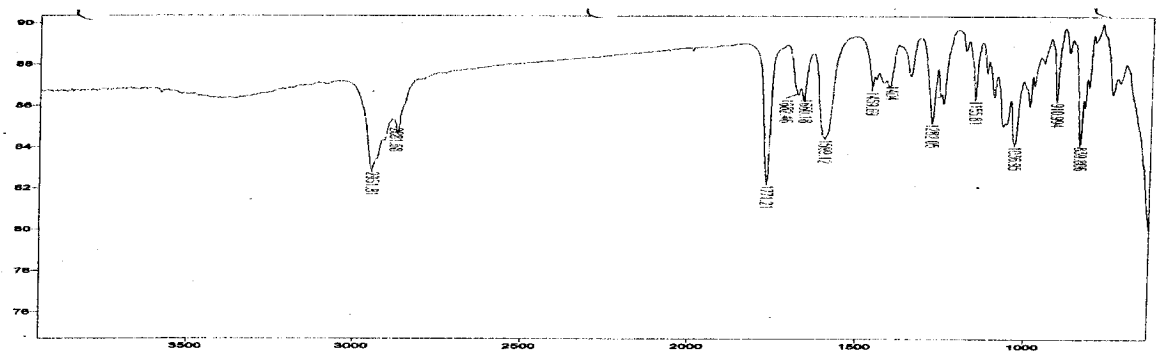
^{1}H NMR ($CDCl_3$, 300 MHz)

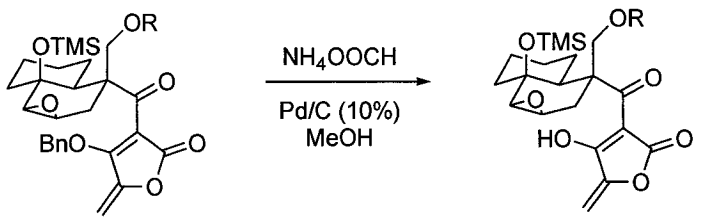


^{13}C NMR ($CDCl_3$, 75 MHz)



FTIR (neat)





3.103 (R = TBMS)
3.104 (R = TES)

3.127 (R = TBMS), 33%
3.108 (R = TES), 40%

3-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl]-4-hydroxy-5-methylene-5H-furan-2-one (3.103) and **4-Hydroxy-5-methylene-3-(3-triethylsilanyloxymethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (3.104)**. Representative procedure: A clean, dry, pressure tube was charged with ammonium formate (7.3 mg, 5 equiv.), the benzyl ether **3.103** (12 mg, 23 umol), and dry MeOH (3 mL). The reaction mixture was degassed with bubbling argon for 15 minutes, and allowed to stir until the ammonium formate had dissolved. Pd/C (10%) (1mg) was added in a single portion, and the reaction was heated to 40°C overnight. In the morning, the mixture was filtered through a plug of celite (with EtOAc wash) and concentrated. The residue was subjected to flash chromatography (40% EtOAc in Hexanes) to give **3.127** as a fine white powder (3.3 mg, 33%).

Data for **3.127**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.20 (d, J = 3.9 Hz, 1H), 4.98 (d, J = 3.9 Hz, 1H), 4.02 (br s, 2H), 3.39 (br s, 1H), 2.95 (d, J = 3.8 Hz, 1H), 2.71 (br d, J = 15.5 Hz, 1H), 2.29 (dd, J = 15.5, 2.9 Hz, 1H), 2.07 (br d, J = 12.5 Hz, 1H), 2.06-1.47 (m, 6H), 1.23-1.04 (m, 3H), 0.82 (s, 9H), 0.19 (s, 9H), 0.03 (s, 6H)

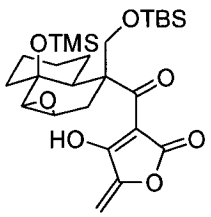
^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 201.3 (C_4), 201.0 (C_4), 165.9 (C_4), 163.3 (C_4), 148.5 (C_4), 92.0 (CH_2), 72.1 (C_4), 61.3 (CH_2), 58.1 (CH), 55.1 (C_4), 54.9 (CH), 40.2 (CH_2), 39.2 (CH), 27.0 (2 x CH_2), 25.8 (3 x CH_3), 22.6 (CH_2), 21.7 (CH_2), 18.1 (C_4), 2.3 (3 x CH_3), -5.2 (CH_3), -5.3 (CH_3)

Data for **3.108**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.21 (d, J = 3.9 Hz, 1H), 4.98 (d, J = 3.9 Hz, 1H), 3.99 (d, J = 9.7 Hz, 1H), 3.97 (d, J = 9.7 Hz, 1H), 3.42 (br s, 1H), 2.95 (d, J = 3.8 Hz, 1H), 2.70

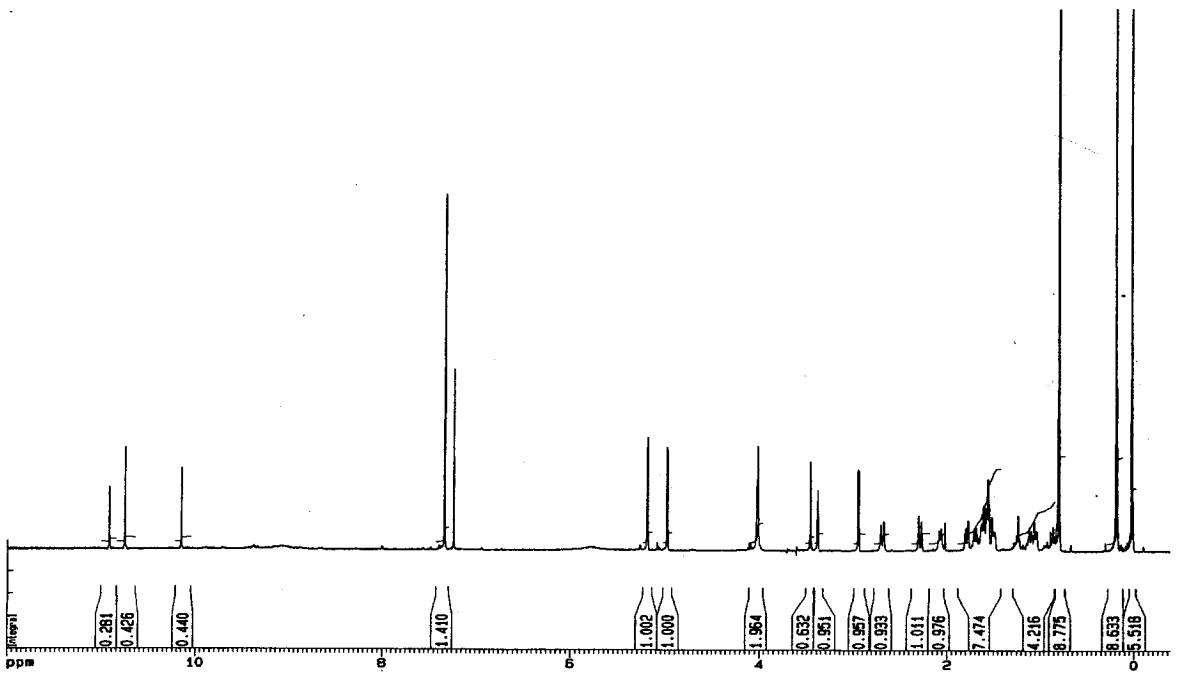
(d, J = 15.8 Hz, 1H), 2.34 (dd, J = 15.8, 2.8 Hz, 1H), 2.14 (br d, J = 12.0 Hz, 1H), 2.06-1.47 (m, 6H), 1.23-1.04 (m, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H), 0.18 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 201.0 (C_4), 166.1 (C_4), 163.7 (C_4), 148.5 (C_4), 140.8 (C_4), 92.4 (CH_2), 72.0 (C_4), 65.3 (CH_2), 60.9 (CH_2), 58.1 (CH), 55.0 (C_4), 54.9 (CH), 44.0 (CH), 40.1 (CH_2), 27.0 (CH_2), 22.4 (CH_2), 21.7 (CH_2), 6.9 (3 x CH_3), 4.5 (3 x CH_2), 2.2 (3 x CH_3).

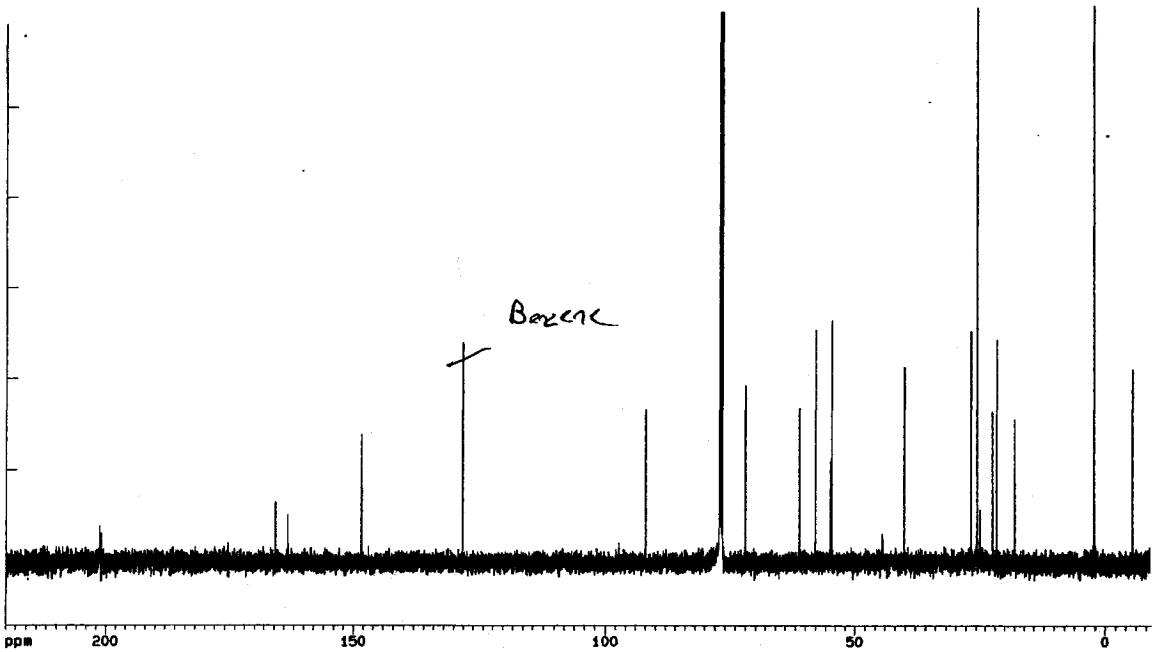


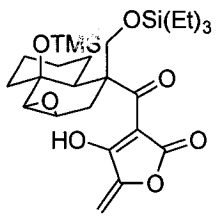
3.127

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



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

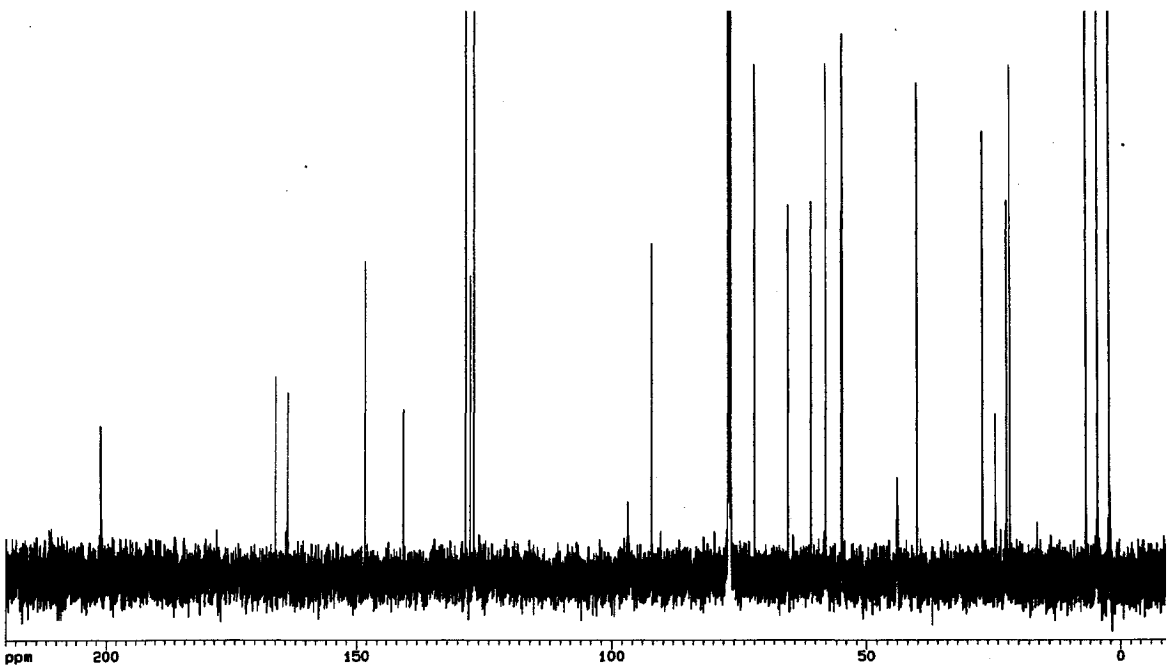


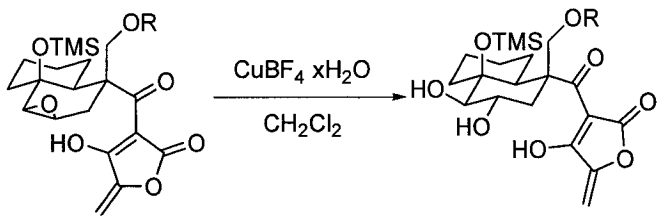


3.108

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

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





3.108 (R = TES)
3.127 (R = TBS)

3.128 (R = TES)
3.129 (R = TBS)

3-(3,4-Dihydroxy-1-triethylsilanyloxymethyl-4a-trimethylsilanyloxy-decahydro-naphthalene-1-carbonyl)-4-hydroxy-5-methylene-5H-furan-2-one (3.128) and **3-[1-(tert-Butyl-dimethyl-silanyloxymethyl)-3,4-dihydroxy-4a-trimethylsilanyloxy-decahydro-naphthalene-1-carbonyl]-4-hydroxy-5-methylene-5H-furan-2-one (3.129)**.

Representative procedure: A solution of epoxide **3.108** (15.0 mg, 29 umol) in wet dichloromethane (2.0 mL) was stirred at room temperature under air, and $CuBF_4xH_2O$ (16 mg, 2 equiv.) was added in a single portion. The mixture was stirred at room temperature for 12 hr, and once deemed complete (TLC), the reaction mixture was directly subjected to flash chromatography (80% EtOAc in Hexanes) to give **3.128** as a white powder (5.9 mg, 38%).

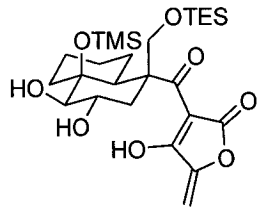
Data for **3.128**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.21 (d, J = 3.9 Hz, 1H), 4.98 (d, J = 3.9 Hz, 1H), 4.18 (d, J = 10.0 Hz, 1H), 4.10 (d, J = 10.0 Hz, 1H), 3.81 (ddd, J = 15.3, 10.1, 5.5 Hz, 1H), 3.62 (dd, J = 10.1, 1.4 Hz, 1H) 2.51 (dd, J = 12.3, 4.7 Hz, 1H), 2.42 (br s, 1H), 2.20-2.01 (m, 3H), 1.78-1.25 (m, 4H), 1.23-1.12 (m, 3H), 0.92 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H), 0.16 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 199.9 (C_4), 166.0 (C_4), 163.7 (C_4), 148.5 (C_4), 97.0 (C_4), 92.2 (CH_2), 79.8 (CH_2), 78.8 (CH), 68.2 (C_4), 59.5 (CH), 57.4 (CH_2), 43.7 (C_4), 35.4 (CH_2), 31.8 (CH), 29.7 (CH_2), 22.3 (CH_2), 21.2 (CH_2), 6.9 (3 x CH_3), 4.5 (3 x CH_2), 2.7 (3 x CH_3)

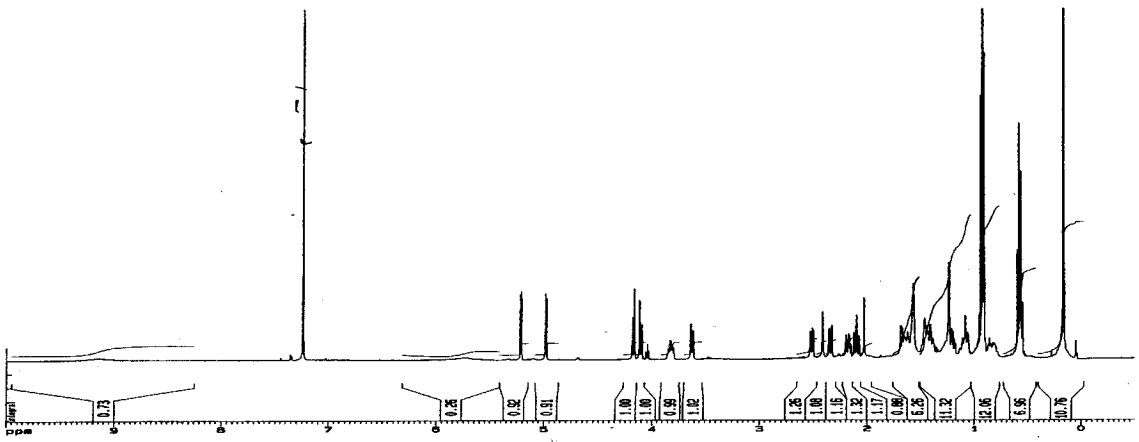
FTIR (neat, cm^{-1}) υ = 3387 (br s), 2958 (s), 2878 (s), 1739 (s), 1636 (s), 1467 (s), 1309 (s), 1247 (s), 1083 (s)

HRMS (EI) Expected for $C_{24}H_{39}O_8Si_2$ [$(M\text{-}Et)^+$]: 511.2183, found: 511.2167 (0.9%)

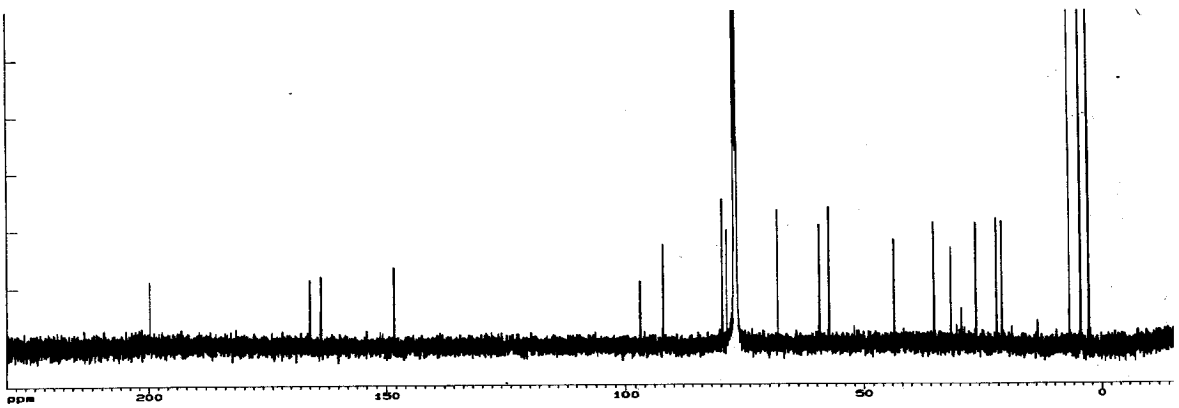


3.128

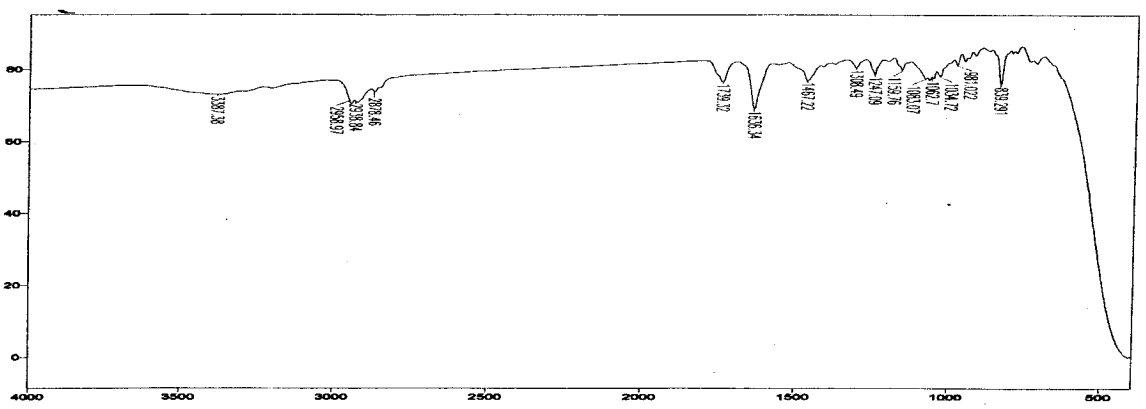
^{1}H NMR ($CDCl_3$, 500 MHz)

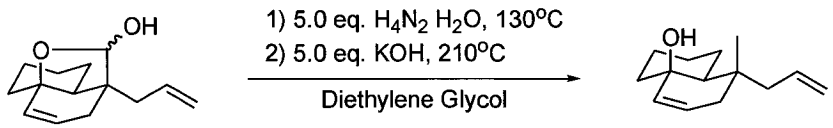


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





3.20 82-88% **4.1**

8-Allyl-8-methyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (4.1). A solution of the lactol **3.20** (1.62 g, 7.36 mmol) and diethylene glycol (37 mL) in a 250 mL roundbottom flask was degassed by placing under high vacuum, with stirring, for 45 minutes. Hydrazine hydrate (36.8 mmol) was added, and the flask was fitted with a reflux condenser. The atmosphere over the solution was replaced with argon (3 vac-refill cycles) and the mixture was heated to 130 °C for 1h. The reaction was cooled back to room temperature and KOH (74 mmol) was added in one portion. The reaction was heated to 210 °C for 3 hours and allowed to cool. Water (100 mL) and Et_2O (30 mL) was added. The biphasic mixture was allowed to stir 30 minutes. The organic phase was extracted with ether (5 x 30 mL), dried over $MgSO_4$ and concentrated. The crude oil was subjected to flash chromatography (5% Et_2O in Hexanes) to give **4.1** as a colourless oil (1.21g, 82%).

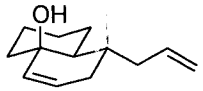
Data for **4.1**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.80-5.70 (m, 1H), 5.65 (ddd, J = 2.2, 5.4, 9.9 Hz, 1H), 5.54 (br d, J = 9.9 Hz, 1H), 5.07-4.98 (m, 2H), 2.13-2.02 (m, 2H), 1.95-1.87 (m, 1H), 1.84-1.77 (m, 1H), 1.73-1.47 (m, 6H), 1.35-1.17 (m, 4H), 0.95 (s, 3H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 134.8 (CH), 133.2 (CH), 127.4 (CH), 117.6 (CH_2), 69.1 (C_4) 48.7 (CH_2), 45.9 (CH), 40.1 (CH), 38.0 (CH), 34.0 (C_4), 26.7 (CH), 21.3 (CH_2), 21.3 (CH_2), 20.2 (CH_3)

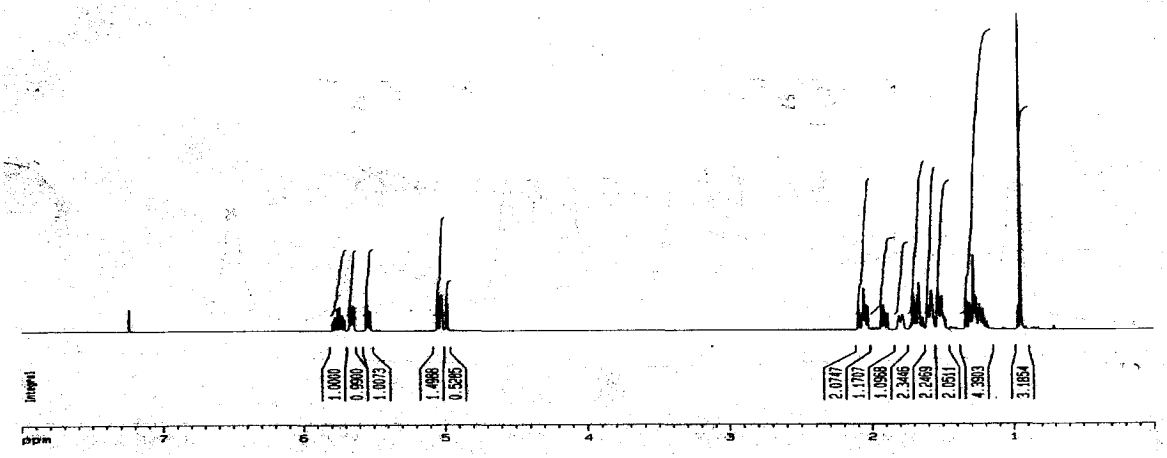
FTIR (neat, cm^{-1}) υ = 3485 (br s), 3073 (s), 3013 (s), 2931 (s), 1637 (m), 1445 (s), 1380 (m), 1142 (s), 995 (s), 939 (s), 913 (s).

HRMS (EI) Expected for $C_{14}H_{20}$ [$(M-H_2O)^+$]: 188.15650, found 188.15492 (3.4%)

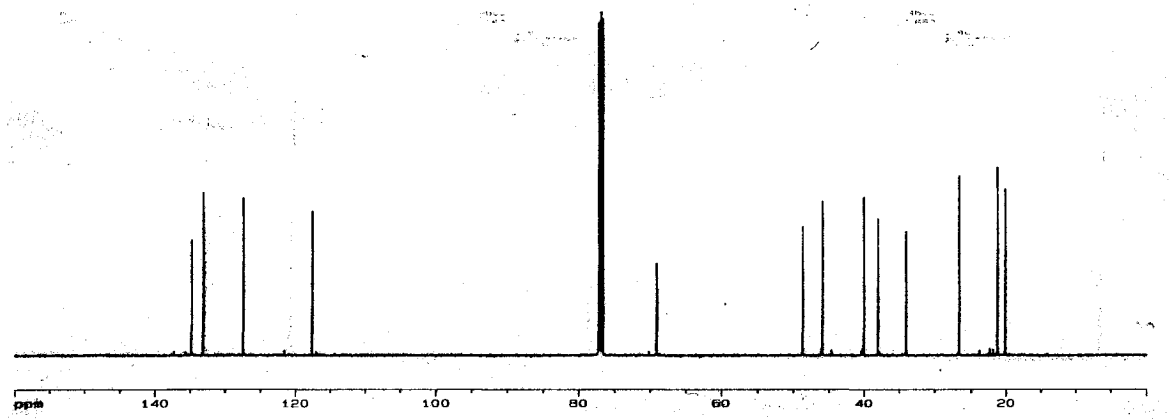


4.1

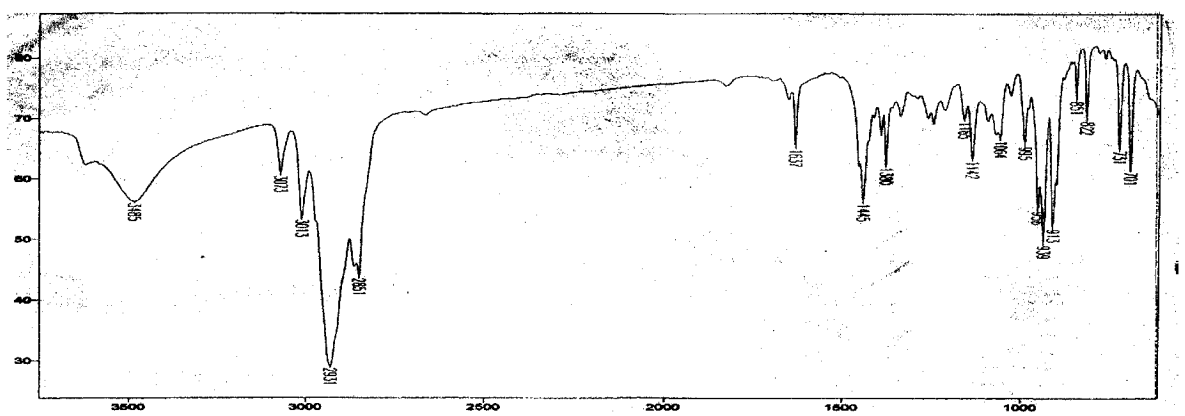
^{1}H NMR ($CDCl_3$, 500 MHz)

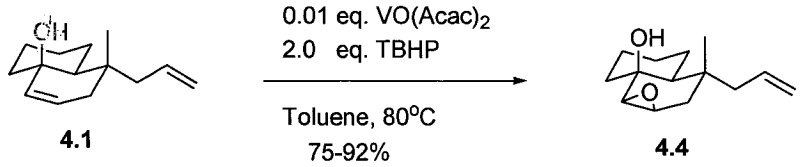


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.1 4.4

3-Allyl-3-methyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.4). A solution of the olefin **3.48** (1.48g, 7.36 mmol) in toluene (75 mL) was stirred at room temperature, and $VO(Acac)_2$ (75 mg, 0.29 mmol, 0.04 equiv.) was added. The mixture was sonicated briefly and allowed to stir for 1h until the catalyst had dissolved (to give a dark green solution). *tert*-butyl hydroperoxide (5-6M in Pentane, 15 mmol, 2 equiv.) was added.dropwise to give a deep purple mixture. The mixture was heated to 60-70 °C for 3 hr and allowed to cool. The reaction was diluted with ether (40 mL) and $NH_4Cl_{(aq)}$ (10 mL) was added. The organic phase was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (15% EtOAc in Hexanes) to give **3.148** as a light yellow oil (1.48g, 91%).

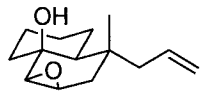
Data for **4.4**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 5.73-5.64 (m, 1H), 5.09-4.87 (m, 2H), 3.41 (ddd, J = 3.9. 2.1, 2.1 Hz, 1H), 3.0 (d, J = 3.9 Hz, 1H), 2.05 (br s, 1H), 1.95 (dd, J = 13.8, 6.70 Hz, 1H), 1.90-1.65 (m, 7H), 1.60-1.38 (m, 5H), 0.93 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} = 134.3 (CH), 118.3 (CH_2), 68.6 (C_4), 59.4 (C_4), 59.3 (CH), 56.6 (CH), 48.7 (CH), 47.4 (CH_2), 39.6 (CH_2), 34.9 (CH_2), 23.4 (CH), 21.5 (2 x CH_2), 20.2 (CH_3)

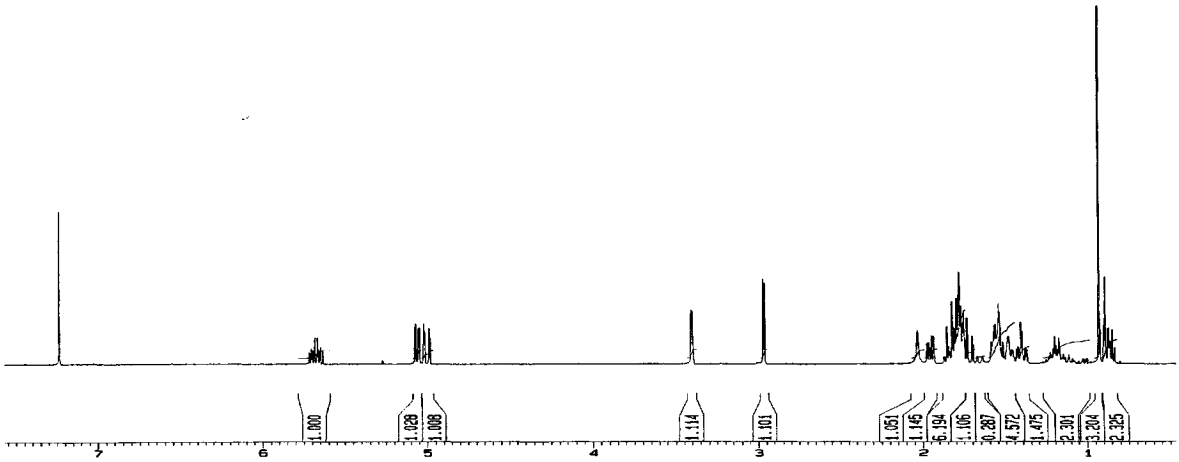
IR (FTIR, neat) υ = 3590 (br), 3073, 2933, 2850 1638, 1446, 973 cm^{-1};

HRMS (EI) Expected for $C_{14}H_{22}O_2$ [$(M)^+$]: 222.16198, found: 222.16007 (1.02%)

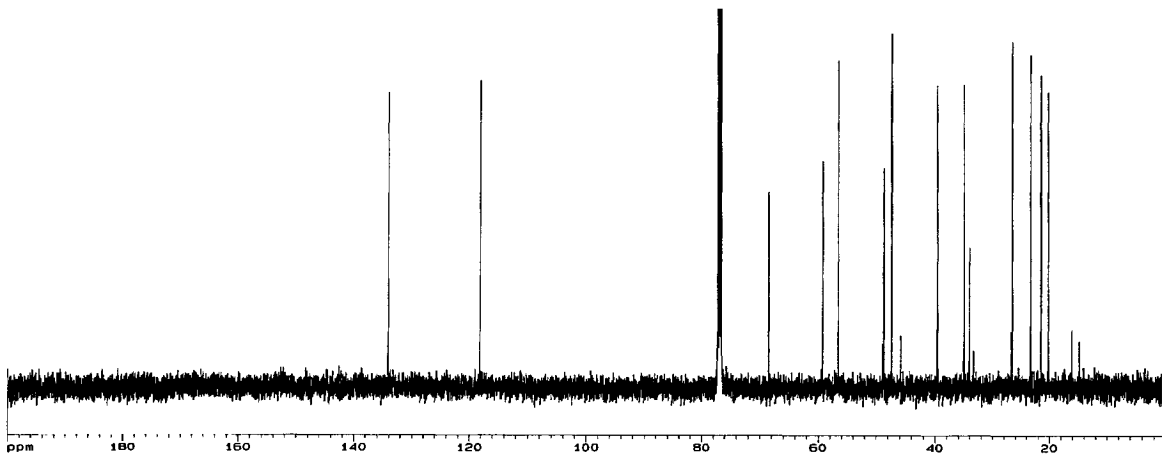


4.4

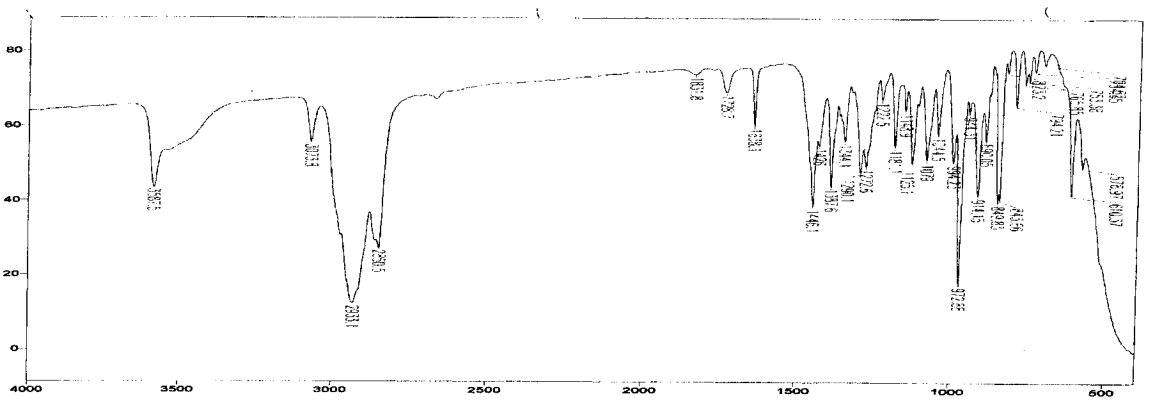
^{1}H NMR ($CDCl_3$, 500 MHz)

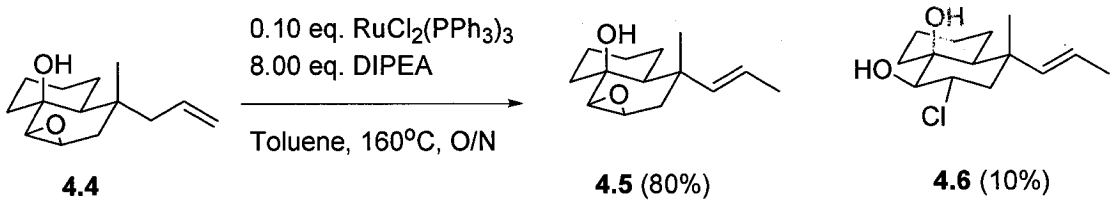


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.4 **4.5** (80%) **4.6** (10%)

3-Methyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.5) and **2-Chloro-4-methyl-4-propenyl-octahydro-naphthalene-1,8a-diol (4.6)**. A solution of the epoxide (1.040 g, 4.73 mmol) was stirred in dry toluene (47 mL) under argon, in a flask fitted with a reflux condeser. Hunig's Base (DIPEA, 6.6 mL, 8 equiv.) was added, followed by $RuCl_2(PPh_3)_3$ (90 mg, 0.02 equiv.). The mixture was heated to 140 °C for 18 hours (bath temp), and was followed by GC. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was subjected to column chromatography (0 to 15% gradient EtOAc in Hexane) to give olefin **3.149** (862 mg, 83%). Compound **3.150** was isolated in an analogous procedure utilizing 0.1 eq of $RuCl_2(PPh_3)_3$ to afford **3.150** as a colourless solid (10%).

Data for **3.149**:

^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 0.83-0.90 (m, 2H) 1.00 (s, 3H) 1.14-1.25 (m, 1H) 1.35-1.50 (m, 3H) 1.58-1.59 (m, 1H) 1.62 (dd, 3H, J=6.4, 1.6Hz) 1.67-1.84 (m, 4H) 1.93 (dd, 1H, J=15.7, 1.6 Hz) 2.04 (d, 1H, J=2.3 Hz) 2.98 (d, 1H, J=3.9 Hz) 3.38 (ddd, 1H J=3.9, ddd, J= 3.9, 3.8, 1.6 Hz) 5.10 (dd, 1H, J=15.5, 1.6 Hz) 5.26 (dt, 1H, J=15.5, 6.4 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 142.5 (CH), 121.9 (CH), 68.6 (C_4), 59.3 (CH), 56.4 (CH), 50.4 (CH), 39.6 (CH_2), 37.9 (C_4), 37.0 (CH_2), 26.9 (CH_2), 21.6 (CH_2) , 21.3 (CH_2), 20.0 (CH_3), 18.0 (CH_3).

FTIR (neat, cm^{-1}) υ = 3358 (br), 2934, 2851, 1446, 972.

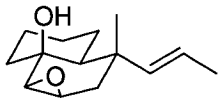
HRMS (EI) Expected for $C_{14}H_{22}O_2$ [$(M)^+$]: 222.16198, Found: 222.16022 (2.00%)

Data for **3.150**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.41-5.32 (m, 1H), 5.18 (dd, J = 1.4, 15.5 Hz, 1H), 4.27 (ddd, J = 4.2, 9.7, 13.8 Hz, 1H), 3.25 (dd, J = 9.7, 1.6 Hz, 1H), 2.62 (d, J = 2.2 Hz, 1H), 2.02 (d, J = 13.8 Hz, 1H), 1.92-1.85 (m, 2H), 1.67-1.63 (m, 2H), 1.63 (dd, J = 1.4, 6.4 Hz, 3H), 1.62-1.39 (m, 5H), 1.30-1.12 (m, 2H), 1.11 (s, 3H)

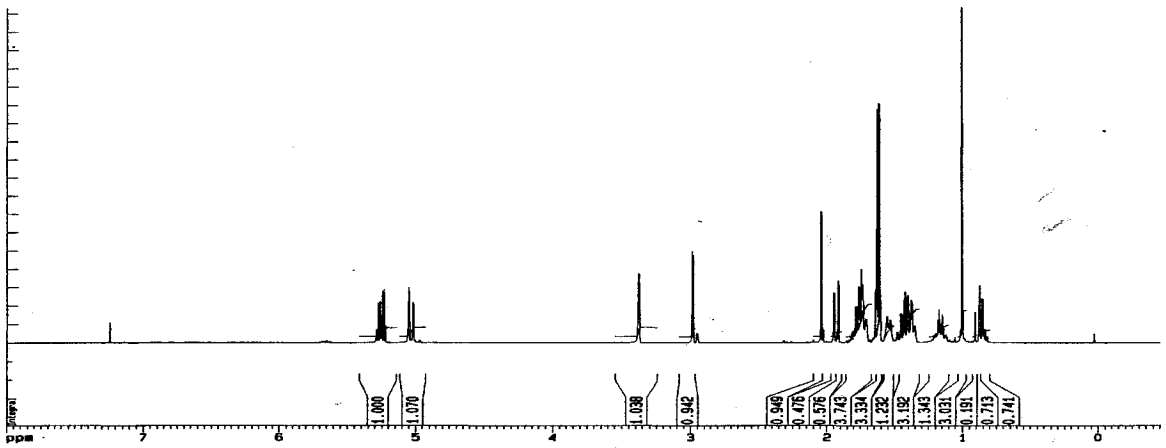
^{1}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 141.4 (CH), 122.4 (CH), 80.7 (CH), 74.2 (C_4), 62.3 (CH) 49.5 (CH), 48.1 (CH_2), 41.0 (C_4), 37.5 (CH_2), 26.4 (CH_2) 21.9 (CH_2), 21. (CH_2), 18.5 (CH_3), 18.1 (CH_3)

HRMS (EI) Expected for $C_{14}H_{23}O_2Cl$ [$(M)^+$]: 258.13866, found: 258.14030 (3.85%), 259.14316 (0.58%)

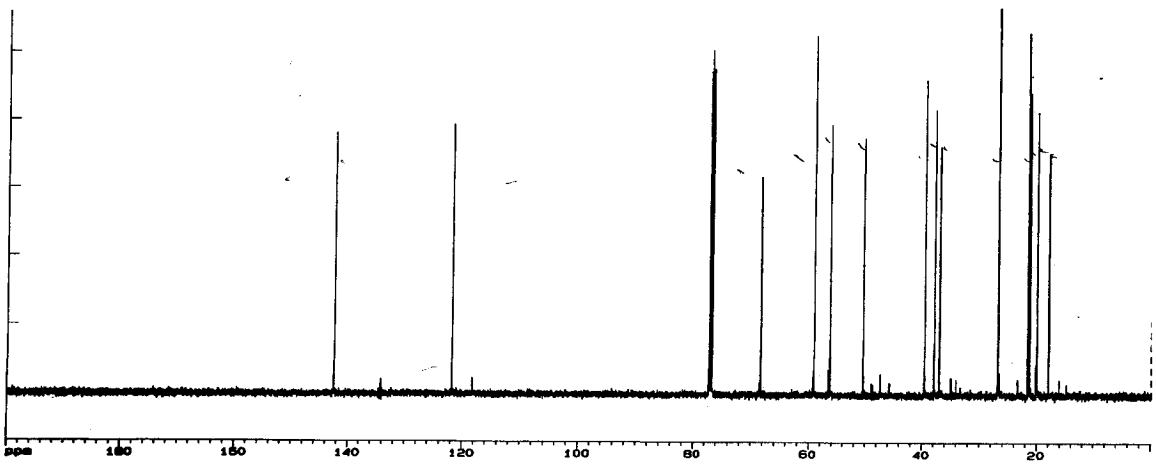


4.5

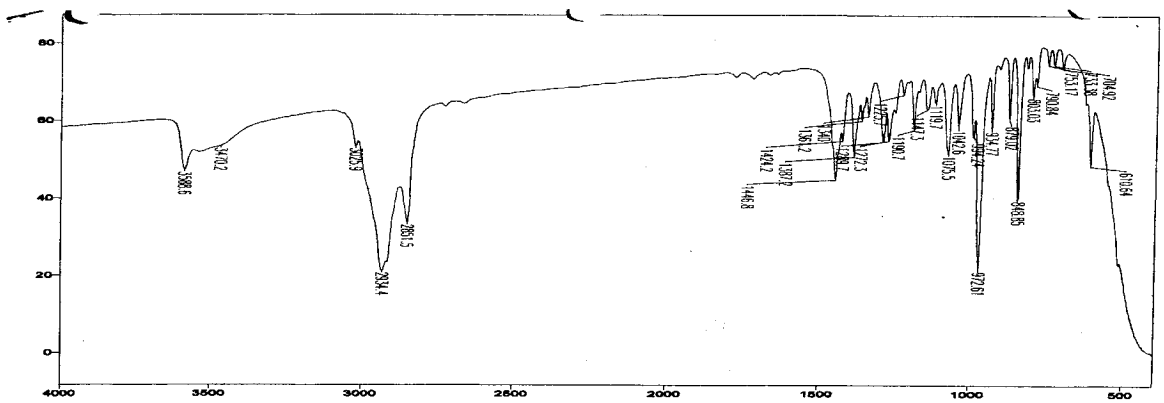
^{1}H NMR ($CDCl_3$, 500 MHz)

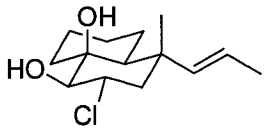


^{13}C NMR ($CDCl_3$, 125 MHz)



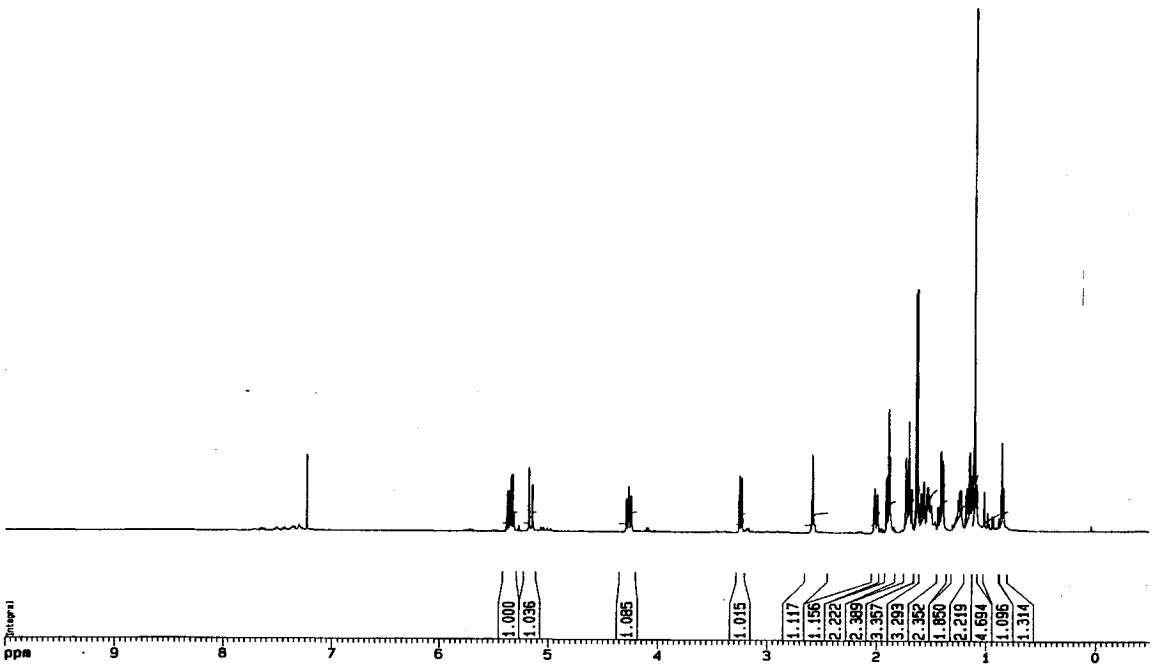
FTIR (neat)



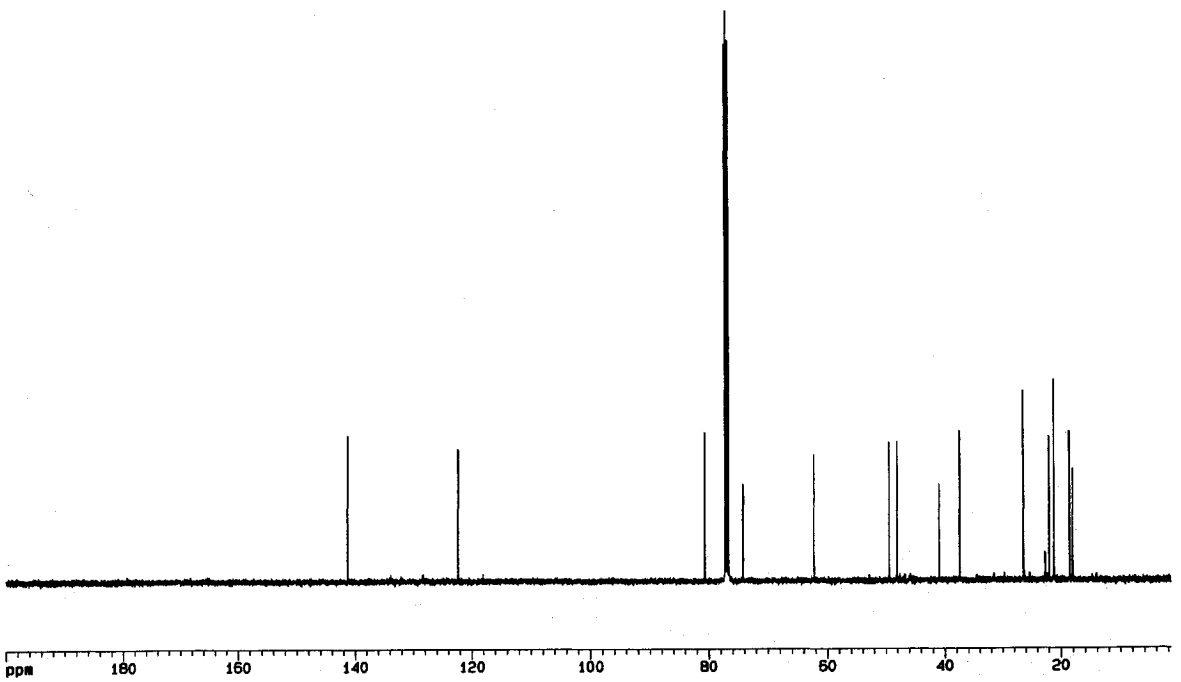


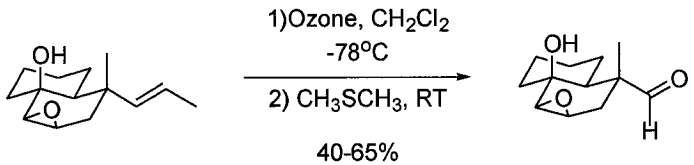
4.6

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



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





4.5 **4.7**

7a-Hydroxy-3-methyl-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (4.7). A clean, dry flask fitted with a magnetic stirring bar was charged with a solution of the olefin **4.5** (260 mg) in dichlormethane (10mL) and pyridine (0.5 mL). The solution was cooled to -78 °C under an argon atmosphere. Ozone was passed through the solution until the steel-gray colour persisted (approx 30 min). The reaction was sparged with argon, and DMS (400 uL, 5 equiv.) was added. The reaction was allowed to warm to room temperature over 2 hr, and concentrated. The residue was subjected to flash chromatography (20% EtOAc in Hexanes) to give the product **4.7** as a light yellow oil (210 mg, 85%)

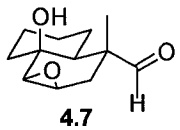
Data for **4.7**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 9.16 (s, 1H), 3.46-3.44 (ddd, 1H), 3.04 (d, J = 3.8 Hz, 1H), 2.07 (br s, 1H), 1.90-1.42 (m, 8H) 1.32-1.10 (m, 2H), 1.08 (s, 3H), 1.04-0.97 (m, 1H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 204.63 (CH), 67.39 (C_4), 58.72 (CH), 55.11 (CH), 46.61 (C_4), 45.31 (CH), 39.22 (CH_2), 30.23 (CH_2), 26.18 (CH_2), 22.30 (CH_2), 21.19 (CH_2), 15.92 (CH_3).

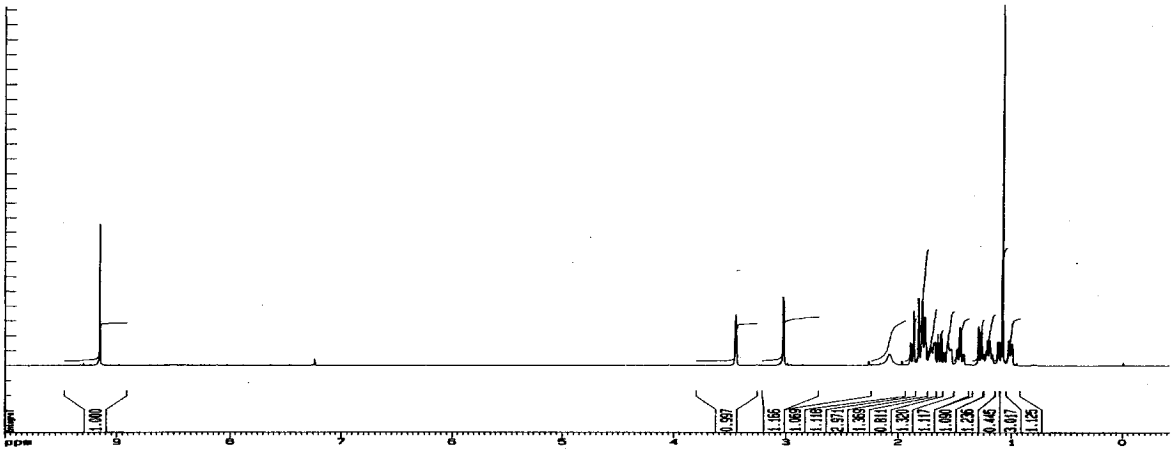
FTIR (neat, cm^{-1}) υ = 3347 (br), 2936, 2856, 1729, 974 cm^{-1}

HRMS (EI) Expected for $C_{12}H_{18}O_3$ [$(M)^+$]: 210.1256, Found: 210.1255

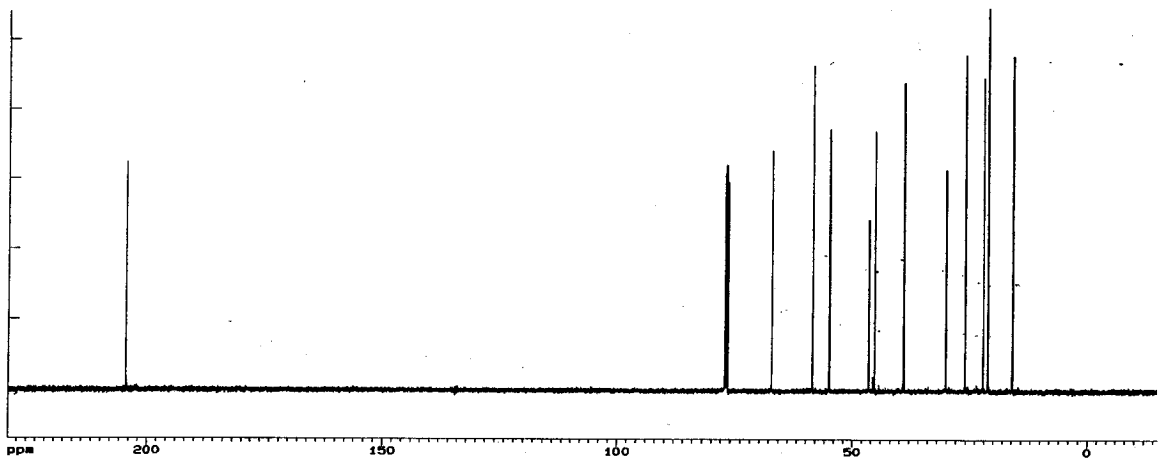


4.7

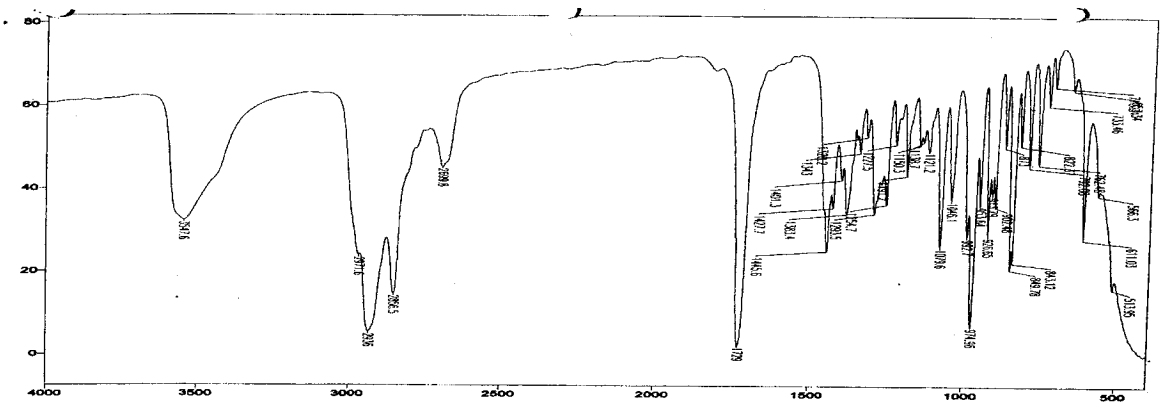
^{1}H NMR ($CDCl_3$, 500 MHz)

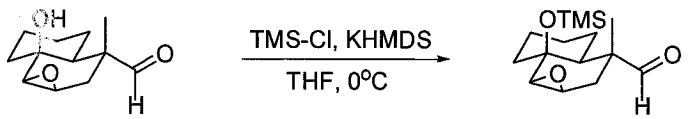


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.7 **4.10**

3-Methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbaldehyde (4.10). To a solution of the aldehyde **4.10** (283 mg, 1.37 mmol) in dry THF (25 mL) at 0°C was added KHMDS (550 mg, 2 equiv.) followed by TMSCl (350 uL, 2 equiv.). After 2 hr, the reaction was quenched with $NH_4Cl_{(sat)}$, ext w/ ether (3 x 10 mL), dried over $MgSO_4$ and concentrated. The residue was subjected to flash (20% EtOAc in Hexanes) to afford **4.10** as a colorless oil (268 mg, 60%)

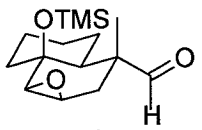
Data for **4.10**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 3.35 (br s, 1H), 2.93 (d, J = 3.7 Hz, 1H), 1.86 (dd, J = 15.4, 2.2 Hz, 1H), 1.90-1.60 (m, 6H), 1.58-1.13 (m, 2H + grease), 1.11 (s, 3H), 0.18 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 206.1 (CH=O), 71.5 (C_4), 58.1 (CH), 53.8 (CH), 47.2 (CH), 47.0 (C_4), 40.0 (CH_2), 31.1 (CH_2), 26.4 (CH_2), 22.3 (CH_2), 21.6 (CH_2), 15.6 (CH_3), (3 x CH_3).

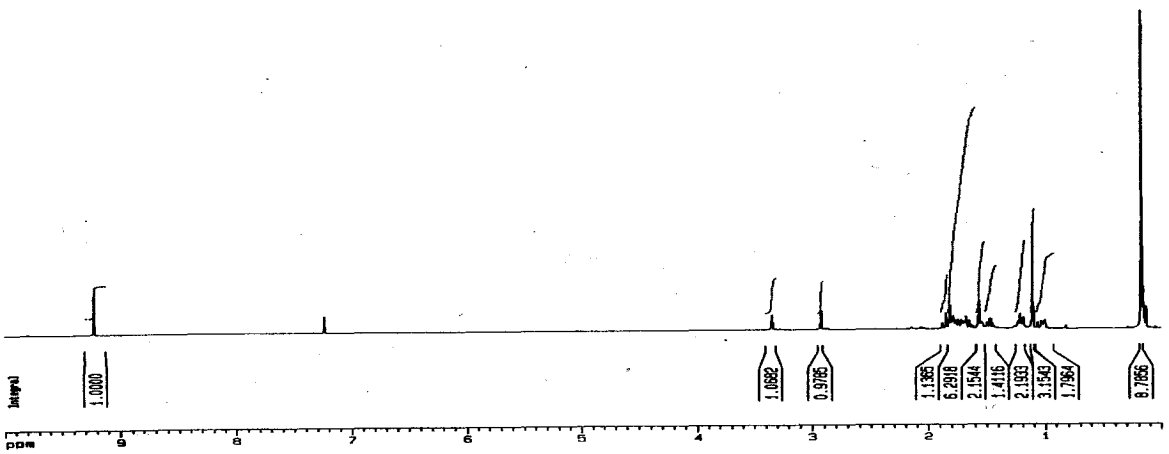
IR (FTIR, Neat) υ = 3209 (w), 2939 (s), 1248 (s), 1034 (s), 839 (s) cm^{-1}

HRMS (EI) Expected for $C_{14}H_{23}O_3Si$ $[(M-Me)^+]$: 268.14165, Found: 268.14355

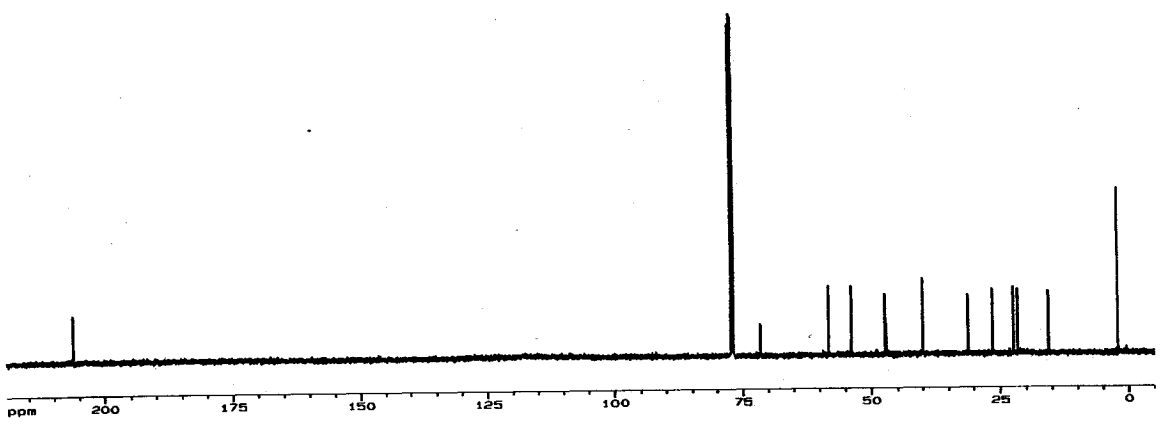


4.10

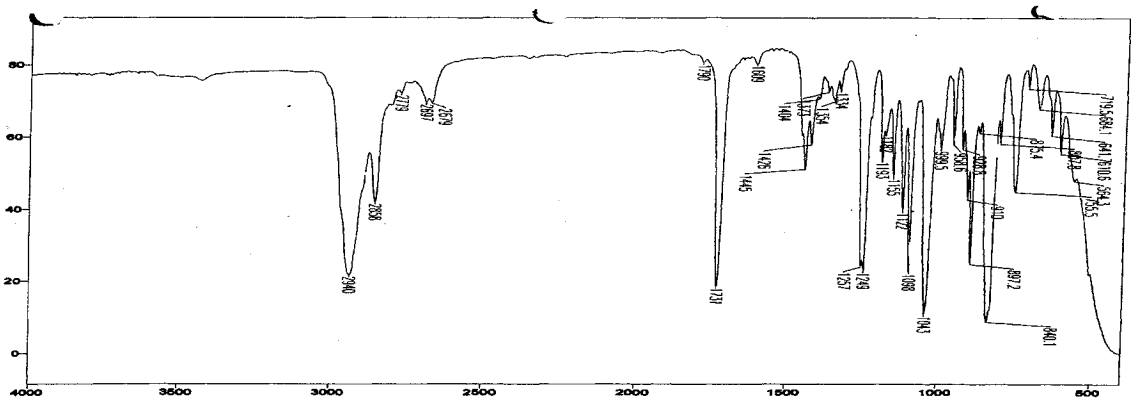
^{1}H NMR ($CDCl_3$, 500 MHz)

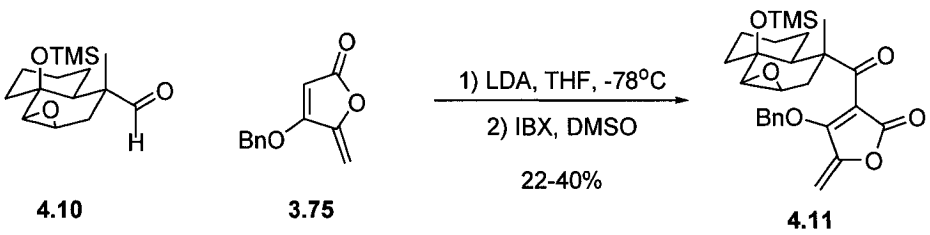


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.10 3.75 4.11

4-Benzyloxy-5-methylene-3-(3-methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (4.11). A mixture of **4.10** (95 mg, 490 umol) and tetronate **3.75** (297 mg, 3.0 equiv.) were placed in a (cool) flame-dried flask under argon. The mixture was dissolved in THF (5.0 mL) and cooled to -78°C. Freshly made and titrated LDA (0.95M in THF, 3.0 eq, titrated from BHT/Fluorene) was added, dropwise. After 15 minutes, the reaction was quenched with aqueous $NH_4Cl_{(sat.)}$ (3 mL), extracted with ether (3 x), dried over $MgSO_4$ and concentrated. The dark orange residue was passed through a pad of silica (100% Ether) and concentrated to give a yellow oil that was used for the next without further purification. The crude was redissolved in DMSO (3 mL) under air, and IBX (3.0 equiv.) was added, in a single portion. The reaction was allowed to stir for 3 hr at room temperature. The reaction mixture was then partitioned between water (20 mL) and ether (20 mL). The organic layer was extracted (2 x 10 mL), dried over $MgSO_4$ and concentrated. The residue was sugbjected to flash chromatography (0 to 15% EtOAc in Hexanes) to give **4.11** as a clear foam (44 mg, 22%).

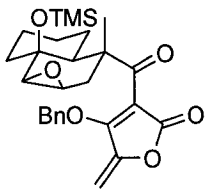
Data for **4.11**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 7.43-7.29 (m, 5H), 5.16 (d, J = 2.8 Hz, 1H), 5.13 (d, J = 2.8 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.94 (d, J = 10.8 Hz, 1H), 3.35 (br s, 1H), 2.95 (br d, J = 3.8 Hz, 1H), 2.33 (d, J = 14.2 Hz, 1H), 2.11 (dd, J = 14.1, 1.1 Hz, 1H), 1.89-1042 (m, 9H + grease), 1.38 (s, 3H), 0.17 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ_{ppm} = 207.0 (C_4), 165.3 (C_4), 165.2 (C_4), 134.1 (C_4), 129.2 (CH), 128.9 (2 x CH), 127.9 (2 x CH), 108.0 (C_4), 94.7 (CH_2), 76.6 (CH_2), 72.3 (C_4), 58.1 (CH), 54.3 (CH), 53.8 (CH), 51.3 (C_4), 47.2 (C_4), 40.0 (CH_2), 35.0 (CH_2), 26.4 (CH_2), 22.9 (CH_2), 21.6 (CH_2), 18.8 (CH_3), 2.2 (3 x CH_3)

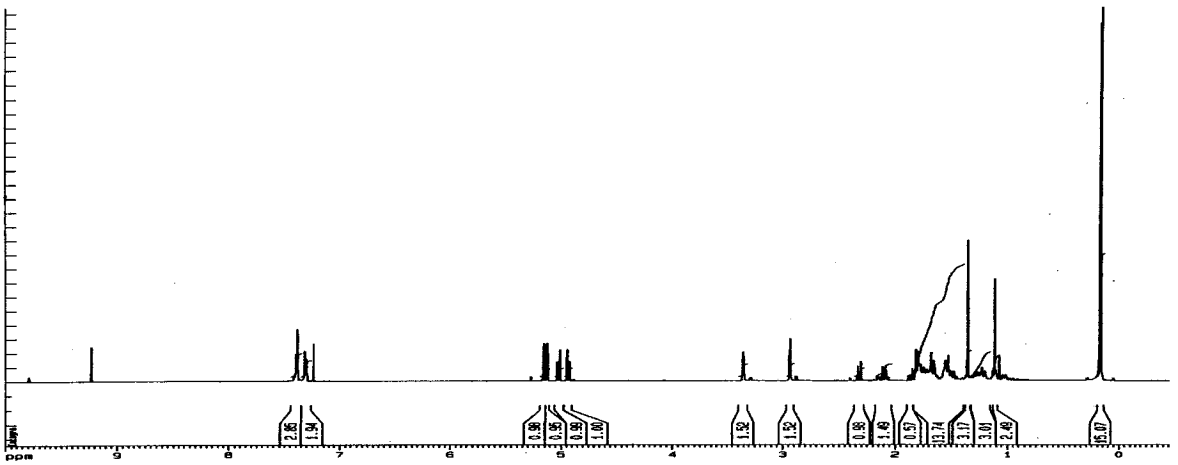
FTIR (neat, cm^{-1}) υ = 3182 (H_2O?), 2946 (s), 2838 (s), 2855, 1822, 1727 (s), 1640, 1143

HRMS (EI) Expected for $C_{20}H_{27}O_6Si$ [$(M\text{-}Bn)^+$]: 391.15769, Found: 391.1589 (1.2%)

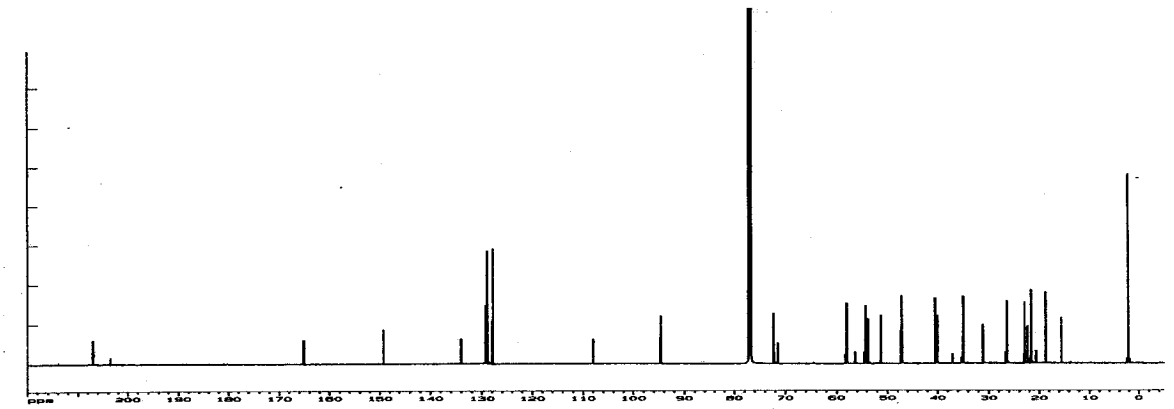


4.11

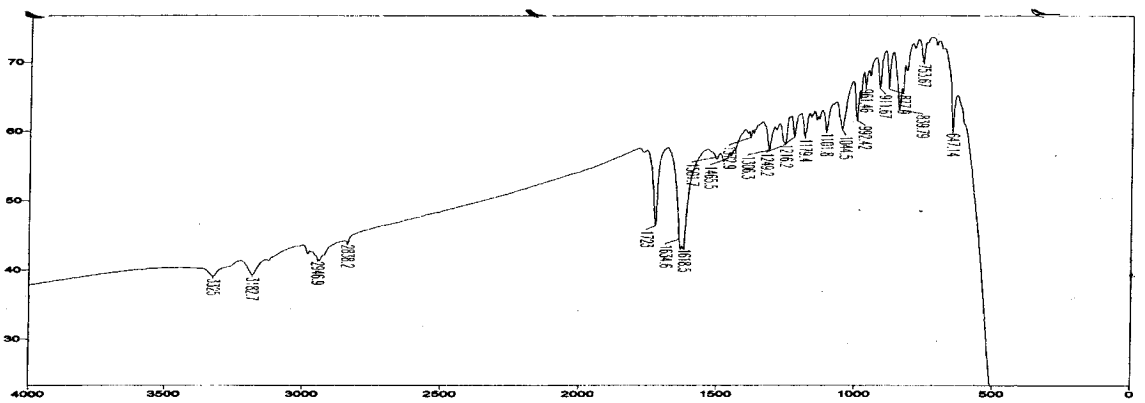
^{1}H NMR ($CDCl_3$, 500 MHz)

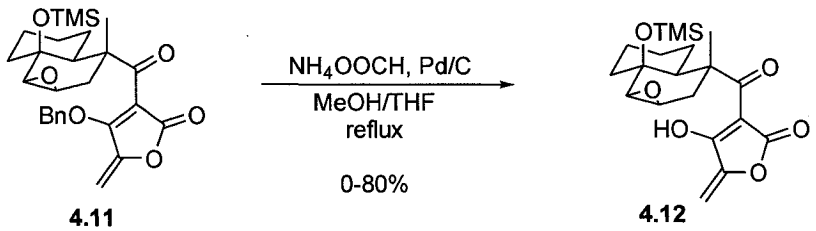


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.11 **4.12**

4-Hydroxy-5-methylene-3-(3-methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (4.12). A resealable pressure tube fitted with a magnetic stir bar was charged with a solution of the benzyl ether **4.11** (12 mg, 29 umol) and ammonium formate (9 mg, 5 equiv.) in MeOH (4.5 mL). Pd/C (10% Pd on C, 1 mg) was added in one portion. The tube was sealed, and the solution was heated to 50°C overnight (~18 hr). The reaction was diluted with ethyl acetate (10 mL) and filtered through a plug of celite. The volatiles were removed and the residue was subjected to flash chromatography (40% EtOAc in Hexanes) to give **4.12** as a white powder (8 mg, 73%).

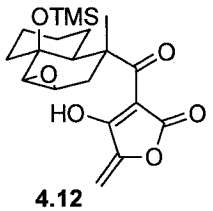
Data for **4.12**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.25 (d, J = 3.8 Hz, 1H), 5.01 (d, J = 3.8 Hz, 1H), 3.42 (ddd, J = 4.0, 3.8, 0.9 Hz, 1H), 3.01 (d, J = 3.8 Hz, 1H), 2.68 (dd, J = 15, 4.0 Hz, 1H), 2.40 (dd, J = 12.1 Hz, 0.9 Hz), 1.85-1.52 (m, 9H), 1.12 (s, 3H), 0.18 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 204.3 (C_4), 166.1 (C_4), 164.1 (C_4), 148.3 (C_4), 96.8 (C_4), 92.7 (CH_2), 71.7 (C_4), 58.6 (CH), 54.6 (CH), 49.3 (C_4), 43.2 (CH), 40.4 (CH_2), 31.1 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 18.7 (CH_3), 2.2 (3 x CH_3).

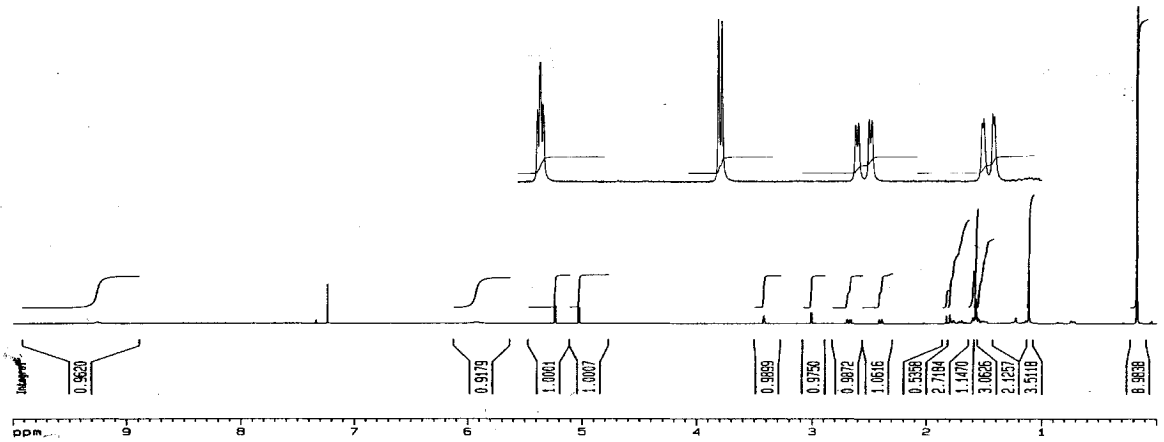
IR (FTIR, neat) υ =3325 (br), 3782 (br), 2946 (s), 2838 (m), 1723 (s), 1634 (s), 1618 (s), 1502 (m), 1306 (m), 1216 (s), 1044 (s), 992 (m) cm^{-1}

HRMS (EI) Expected for $C_{20}H_{28}O_6Si$ [$(M-H)^+$]: 391.15769, found: 391.1582 (1.1%)

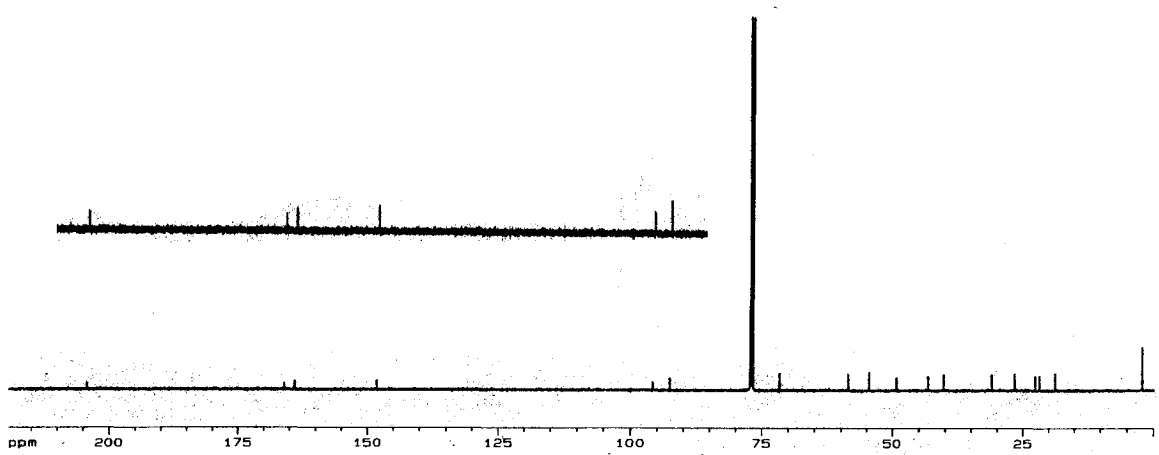


4.12

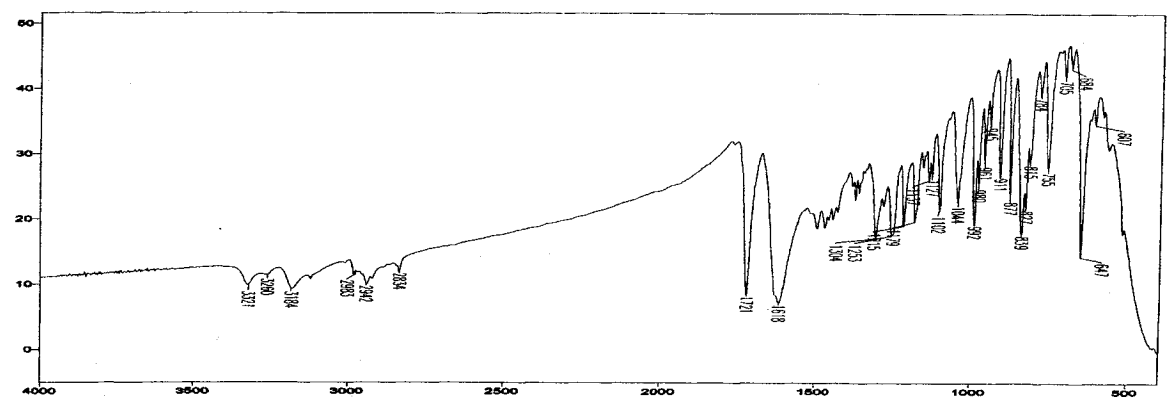
^{1}H NMR ($CDCl_3$, 500 MHz)

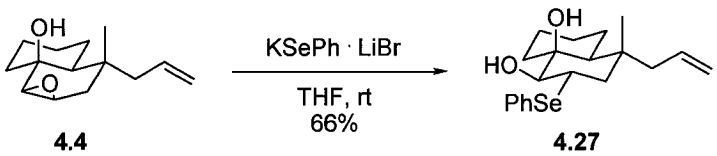


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.4 **4.27**

4-Allyl-4-methyl-2-phenylselanyl-octahydro-naphthalene-1,8a-diol (4.27). A dry 250 mL roundbottom flask was fitted with a magnetic stirring bar and charged with KBr (5 eq.). The flask was flame dried under high vacuum and the atmosphere replaced with argon. Diphenyl diselenide (702 mg, 0.50 equiv.) and KBr (1.60g, 3.0 equiv.) were placed in the flask, and the atmosphere was replaced with argon several times. The mixture was dissolved in THF (45 mL) and stirred at room temperature. $LiBH_4$ (2.0M in THF, 2.48 mL, 1.10 equiv.) was added, with some evolution of H_2 noted. After the yellow colour of the diselenide had vanished (~3 hr), a solution of epoxide **4.4** (4.5 mmol) was added. The reaction was allowed to stir 10 hr at room temperature. Once complete, the reaction was quenched with aqueous $NH_4Cl_{(sat.)}$, extracted with ether (3x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (0 to 20% EtOAc in hexanes) to give **4.29** as a thick, yellow oil (1.132g, 66%).

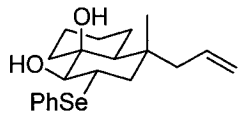
Data for **4.27**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.58-7.24 (m, 5H), 5.67-5.59 (m, 1H), 4.97 (d, J = 10.1 Hz, 1H), 4.91 (d, J = 17.0 Hz, 1H), 2.95-2.90 (m, 1H), 2.90 (d, J = 10.6 Hz, 1H), 1.99 (br d, J = 17.0 Hz), 1.90 (d, J = 7.4 Hz, 2H), 1.81 (dd, J = 13.4, 2.9 Hz, 1H), 1.70 (br d, J = 13.0 Hz, 1H), 1.67-1.40 (m, 6H), 1.13-1.04 (m, 2H), 1.01 (s, 3H), 1.00-0.93 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 136.0 (2 x CH), 134.2 (CH), 128.9 (2 x CH), 128.2 (CH), 125.5 (C QUAT.), 117.5 (CH_2), 73.7 (C QUAT.), 47.5 (CH), 46.7 (CH_2), 46.0 (CH), 44.0 (CH_2), 38.1 (C QUAT.), 37.7 (CH_2), 26.3 (CH_2), 21.3 (2 x CH_2), 21.0 (CH_3, CH_2).

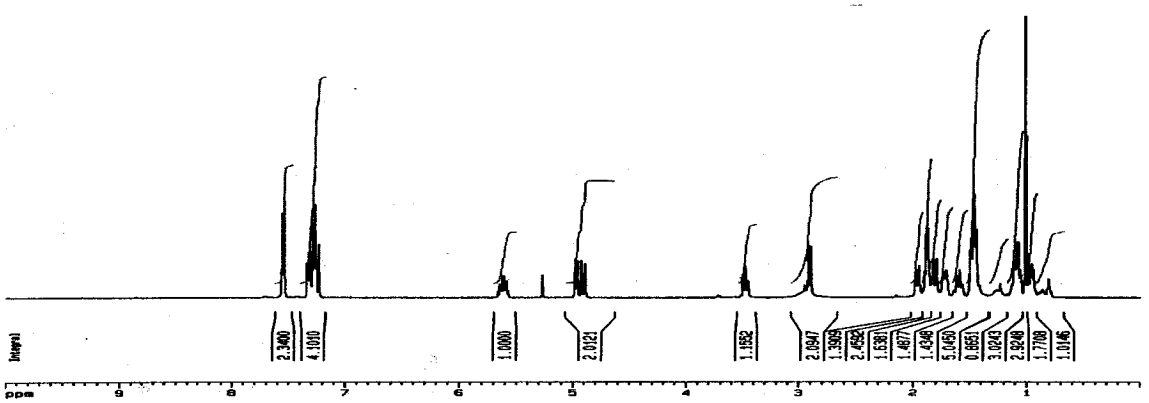
FTIR (neat, cm^{-1}) υ = 3492 (br s), 3071 (m), 2934 (s), 2856 (s), 1477, 1438, 1380 (m), 980.

HRMS (EI) Expected for $C_{20}H_{28}O_2Se$ [$(M)^+$]: 380.12545, found: 380.12681 (52.9%)

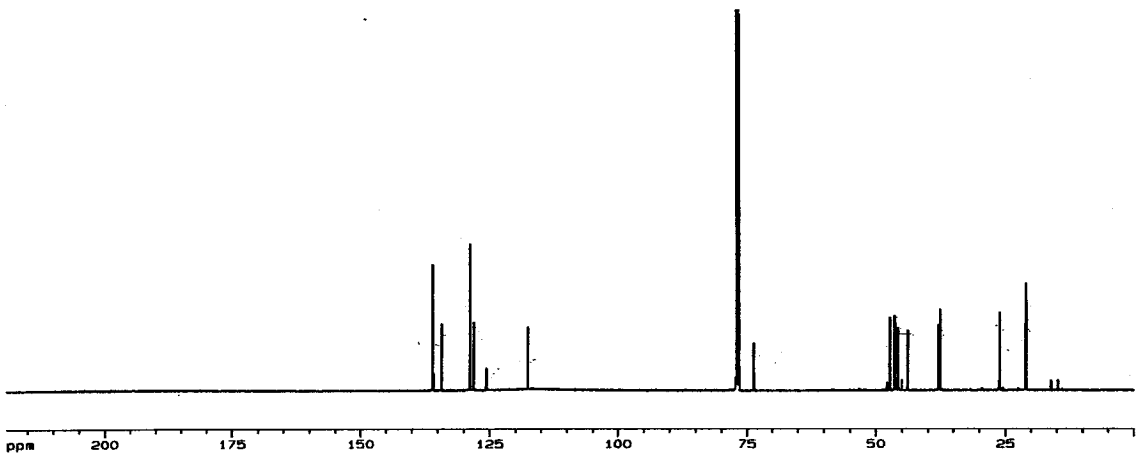


4.27

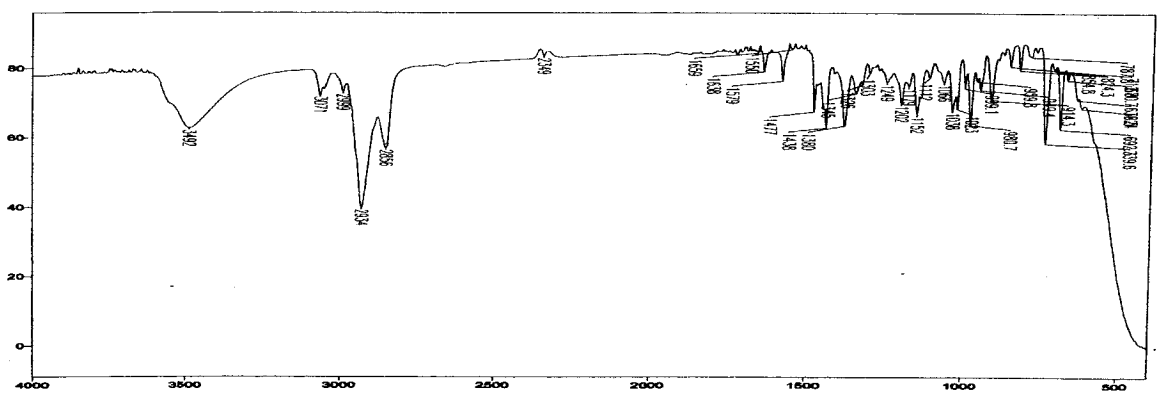
^{1}H NMR ($CDCl_3$, 500 MHz)

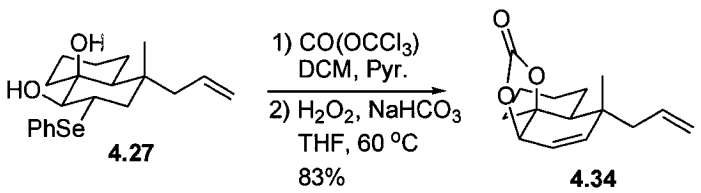


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





6-Allyl-6-methyl-6,6a,7,8,9,10-hexahydro-3aH-naphtho[1,8a-d][1,3]dioxol-2-one (4.34). A solution of selenide **4.27** (44 mg, 116 μmol) in DCM (3 mL) and Pyridine (100 μL) was stirred at 0°C. Triphosgene (35 mg, 1 equiv.) was added as a dichloromethane solution (1 mL). The reaction was allowed to warm to room temperature with stirring over 2 hr. The mixture was quenched with $NH_4Cl_{(sat.)}$, and extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were dried over $MgSO_4$ and concentrated. The crude carbonate was redissolved in THF (5 mL) and stirred at room temperature. $NaHCO_3$ (10 mg) was added, followed by H_2O_2 (30% in H_2O, 2 equiv.). The reaction was heated to 60°C for 1 hr, and allowed to cool. The mixture was partitioned between Ether (10 mL) and saturated ammonium chloride (5 mL). Extraction of the organic phase and drying over $MgSO_4$, followed by concentration gave a yellow oil that was subjected to flash chromatography (15% EtOAc in Hexanes) to give **4.34** as a clear oil (24.2mg, 83%).

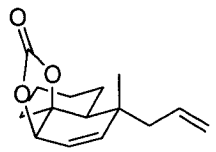
Data for **4.34**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.87 (d, J = 10.4 Hz, 1H), 5.61 (dd, J = 3.1, 10.4 Hz, 1H), 5.88-5.86 (m, 1H), 5.14 (d, J = 16.2 Hz, 1H), 5.04 (d, J = 10.2 Hz, 1H), 4.98 (d, J = 17.0 Hz, 1H) 4.52 (d, J = 3.1 Hz, 1H), 2.20-2.04 (m, 3H), 1.87-1.82 (m, 1H), 1.76-1.52 (m, 5H), 1.45-1.21 (m, 2H) 0.97 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 154.1 (C QUAT.), 143.2 (CH), 134.1 (CH), 119.3 (CH), 118.3 (CH_2), 83.5 (C QUAT.), 77.8 (CH), 45.2 (CH_2), 42.0 (CH), 37.4 (CH_2), 37.0 (C QUAT.), 25.5 (CH_2), 23.7 (CH_3), 22.4 (CH_2), 21.3 (CH_2).

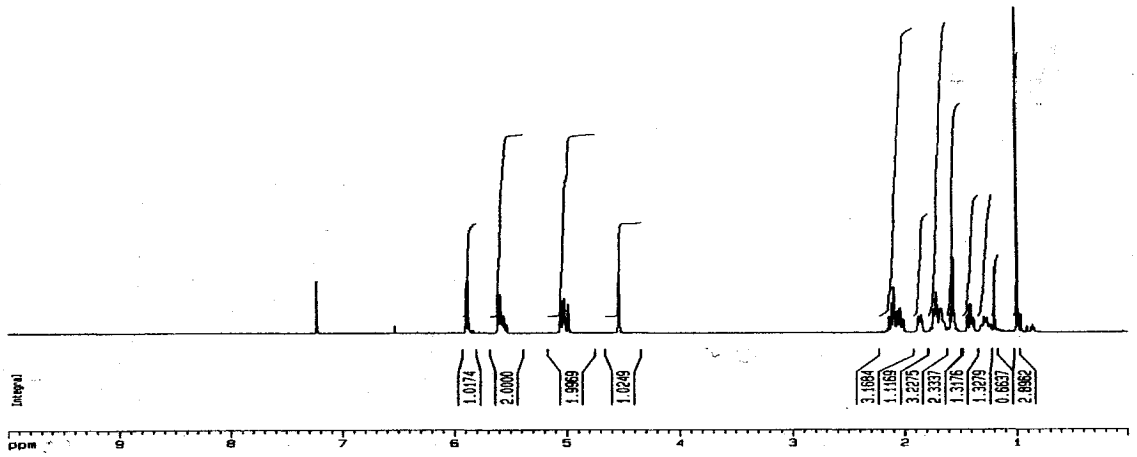
FTIR (neat, cm^{-1}) υ = 2939, 2866, 1797 (s), 1205, 1028, 1010.

HRMS (EI) Expected for $C_{12}H_{15}O_3$ [(M-Allyl)$^+$]: 207.10212, Found: 207.1002 (71.0%).

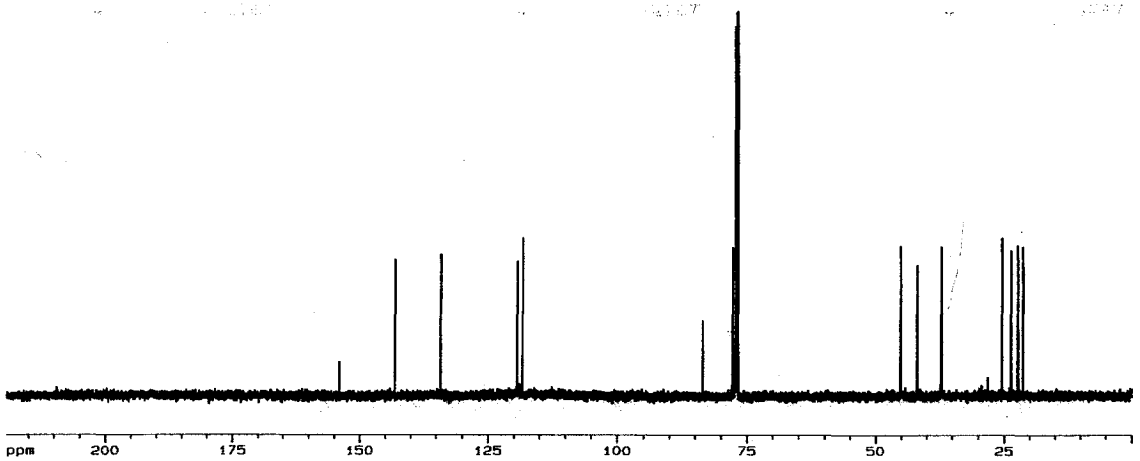


4.34

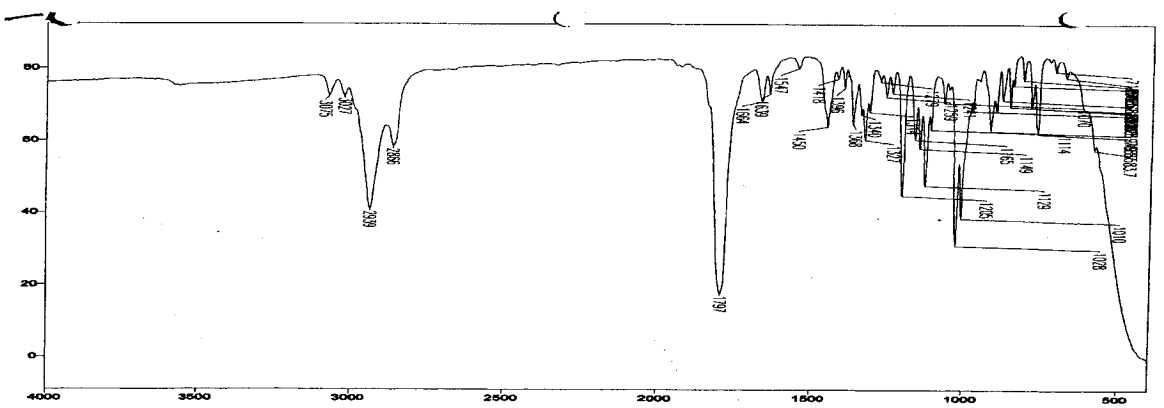
^{1}H NMR ($CDCl_3$, 500 MHz)

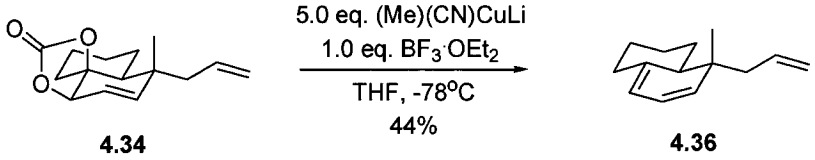


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.34 **4.36**

5-Allyl-5-methyl-1,2,3,4,4a,5-hexahydro-naphthalene (4.36). A slurry of CuCN (51 mg, 5 equiv.) in THF (5 mL) was cooled to -30 °C and MeLi (1.6M in THF, 706 uL, 10 equiv.) was added. After the solution became clear and colourless (5 min) the reaction was cooled to -78°C and BF_3-Etherate was added (15 uL, 3 equiv.) was added, followed by the carbonate **4.34** (28 mg) as a THF solution (1 mL). The reaction was allowed to stir 3 hr at -78°C, with monitoring by TLC. Once complete, the reaction was quenched with $NH_4Cl_{(sat)}$:NH_4OH (9:1), and extracted with ether. The residue was subjected to flash chromatography (100% Hexanes) to give **4.36** as a colourless oil (9.0 mg, 44%).

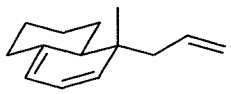
Data for **4.36**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm} = 5.82-5.78 (m, 1H), 5.70 (dd, J = 9.5, 5.4 Hz, 1H), 5.94 (d, J = 5.1 Hz, 1H), 5.27 (d, 9.6 Hz, 1H), 5.01-4.94 (m, 2H), 2.28-2.25 (m, 1H), 2.20 (dd, J = 7.4, 13.5 Hz, 1H) 2.05-1.92 (m, 3H) 1.82-1.55 (m, 3H) 1.40-1.22 (m, 3H) 0.90 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ_{ppm} = 143.5 (C QUAT.), 135.74 (CH), 133.5 (CH), 121.6 (CH), 116.7 (CH_2), 114.9 (CH), 46.59 (CH), 45.9 (CH_2), 37.0 (C QUAT.), 35.6 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 21.8 (CH_3).

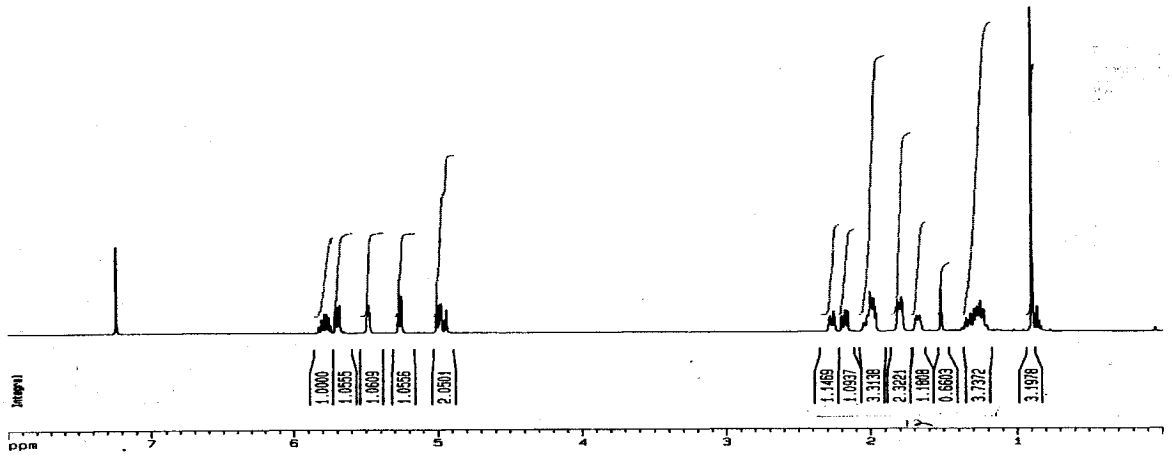
FTIR (neat, cm^{-1}) υ = 3072, 2929, 914.

HRMS (EI) Expected for $C_{14}H_{20}$ $[(M)^+]$: 188.1565, found: 188.1544

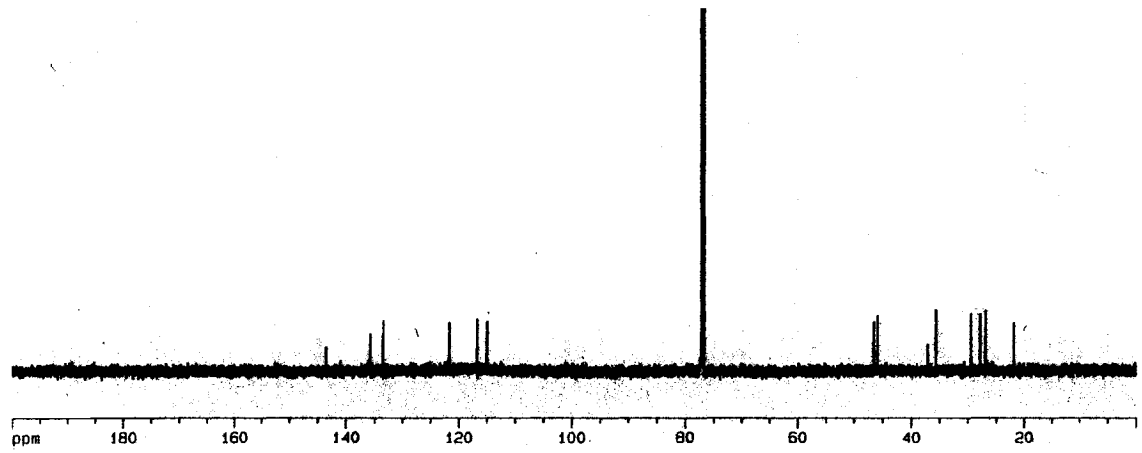


4.36

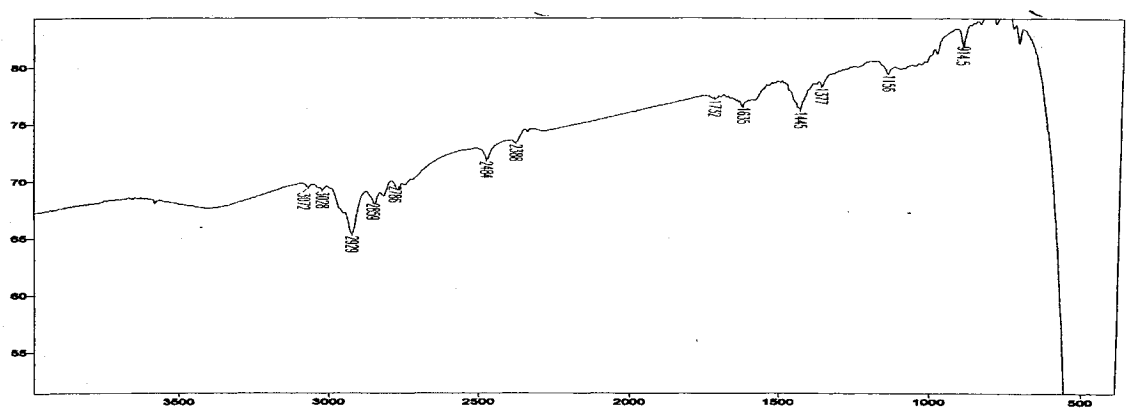
^{1}H NMR ($CDCl_3$, 500 MHz)

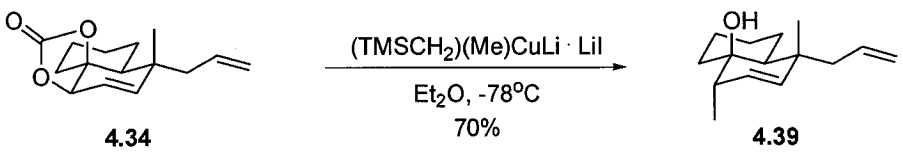


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.34 **4.39**

8-Allyl-5,8-dimethyl-1,3,4,5,8,8a-hexahydro-2H-naphthalen-4a-ol (4.39). A solution of CuI (483 mg, 3 equiv.) in Et_2O (8 mL) was cooled to -78°C and trimethylsilylmethyllithium (240 mg, 3 equiv.) was added as an ether solution (2 mL), followed by Methyllithium (1.6M in Ether, 3 equiv.). The cuprate was annealed at -30 °C briefly and recooled to -78°, and the carbonate **4.34** (199 mg, 1 equiv.) was added via canula and rinse (2 mL THF). The rx was stirred for 1 hr, while allowing to warm to -20° C, followed by quench with $NH_4Cl_{(sat.)}$ and workup as usual. Flash chromatography (0 to 10% EtOAc in Hex.) gave **4.39** as a light yellow oil (131 mg, 70%)

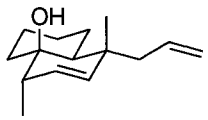
Data for **4.39**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.70-5.63 (dddd, 1H), 5.61 (dd, J = 10.2, 5.5 Hz, 1H), 5.36 (d, J = 10.2 Hz, 1H) 5.01-4.93 (m, 2H) 2.05-1.92 (m, 3H), 1.75-1.38 (m, 10H), 1.00 (s, 3H), 0.89 (d, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 135.9 (CH), 135.5 (CH), 128.6 (CH), 117.0 (CH_2), 73.4 (C QUAT.), 46.2 (CH_2), 44.4 (CH), 42.2 (CH), 39.5 (CH), 37.9 (CH_2), 26.5 (CH_2), 24.5 (CH_3), 22.7 (CH_2), 21.8 (CH_2), 18.00 (CH_3).

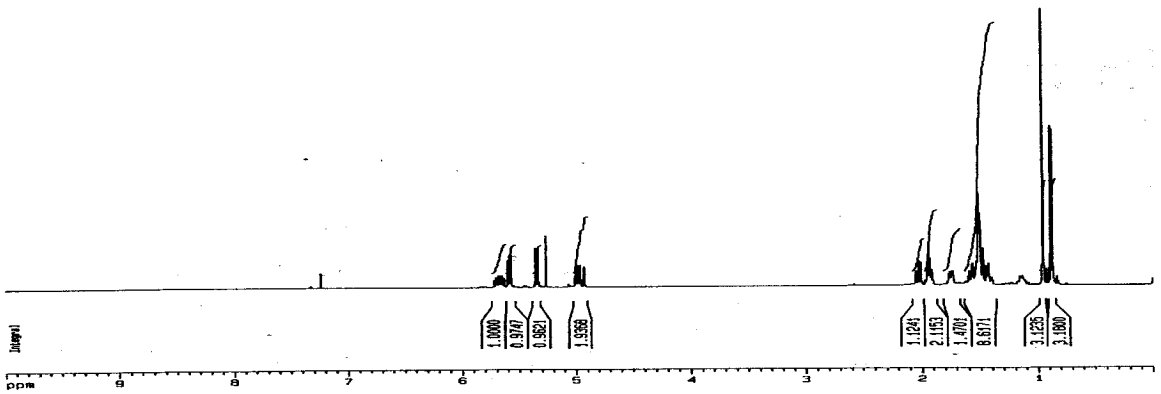
FTIR (neat, cm^{-1}) υ = 3494, 3073, 2931, 912

HRMS (EI) Expected for $C_{15}H_{22}$ [$(M-H_2O)^+$]: 202.1722, Found: 202.1712

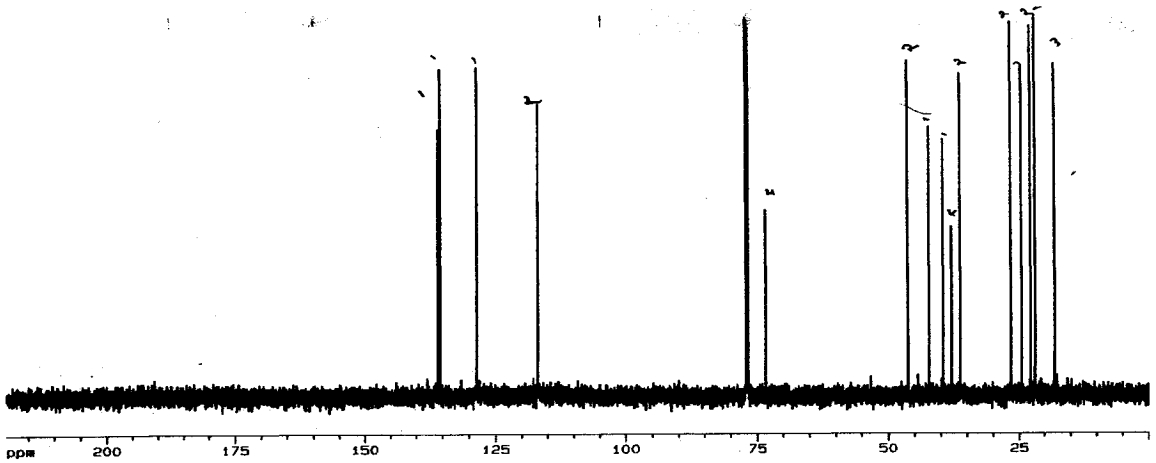


4.39

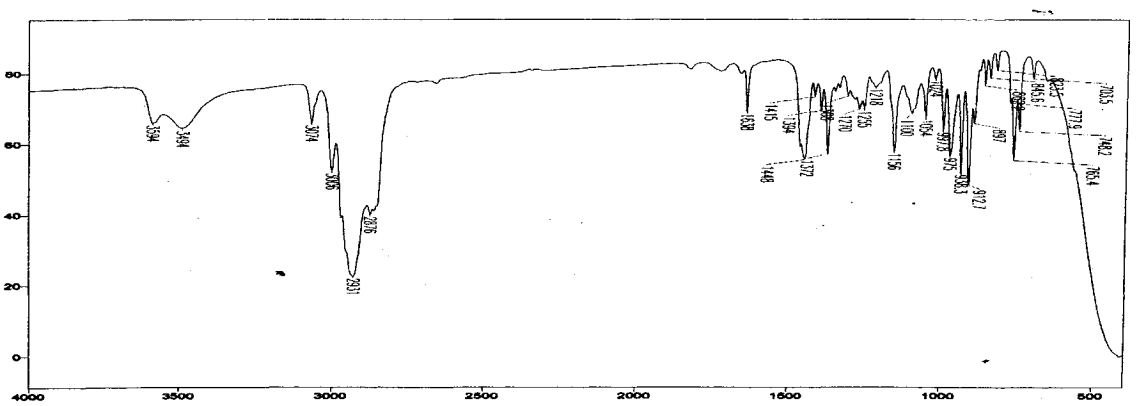
^{1}H NMR ($CDCl_3$, 500 MHz)

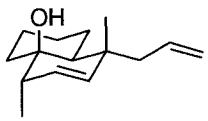


^{13}C NMR ($CDCl_3$, 125 MHz)



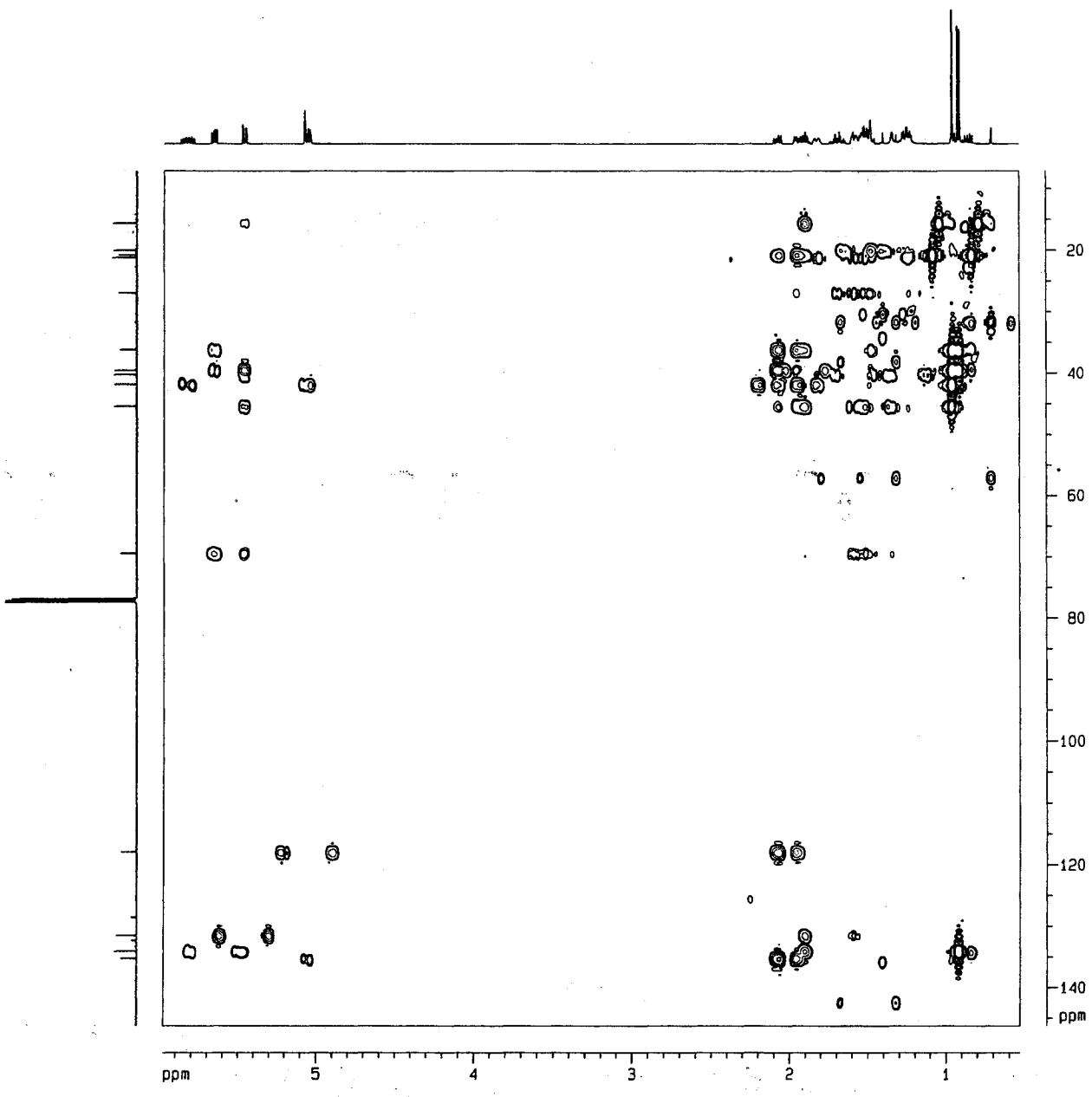
FTIR (neat)

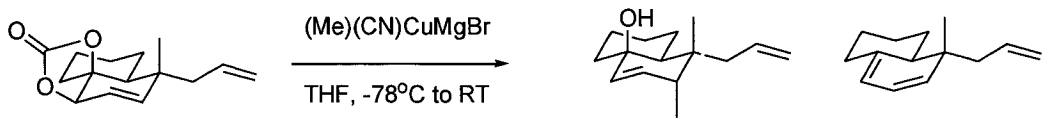




4.39

HMBC ($CDCl_3$)





4.34 **4.40** (64%) **4.36** (12%)

8-Allyl-7,8-dimethyl-1,3,4,7,8,8a-hexahydro-2H-naphthalen-4a-ol (4.40). A slurry of CuCN (1.06 g, 5 equiv.) in dry THF (120 mL) under argon was cooled to -78°C, and MeMgBr (3M in Et_2O, 3.97 mL, 5 equiv.) was added. The aspect of the mixture subtly changed from dull gray to bright white, as the mixture was allowed to stir for 45 minutes. The carbonate **4.34** (590 mg, 2.38 mmol) was added dropwise via syringe as a solution in dry THF (10 mL). No more dry ice was added to the cooling bath, and the reaction was allowed to warm gradually to room temperature over ~ 4hr. Stirring was continued overnight (18hr), and the reaction was quenched with $NH_4Cl_{(sat.)}/NH_4OH$ (9:1). Air was bubbled through the mixture for 1 hr with vigorous stirring (to oxidize excess copper and aid with separation of the layers), and heterogeneous mixture was filtered. The organic layer was extracted with Et_2O (4 x 20 mL), dried over $MgSO_4$, and concentrated. The crude oil was subjected to flash chromatography (15% EtOAc in Hexanes) to give **4.40** as a pale yellow oil (360 mg, 64%), and **4.36** (72 mg, 12%).

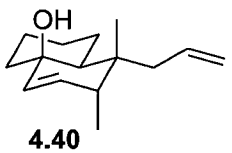
Data for **4.40**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} =5.88-5.78 (m, 1H), 5.66 (dd, J = 4.2, 14.1 Hz, 1H), 5.46 (d, J = 9.9 Hz, 1H), 5.09-5.07 (m, 1H), 5.07-5.04 (m, 1H), 2.06 (dd, J = 8.0, 14.1 Hz, 1H) 1.98-1.86 (m, 3H), 1.86-1.81 m, 1H) 1.75-1.20 (m, 7H), 0.96 (d, J = 0.75 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 135.2 (CH), 134.2 (CH), 131.4 (CH), 117.9 (CH2), 69.4 (C4), 45.3 (CH), 41.8 (CH2), 40.2 (CH2), 39.5 (CH2), 36.1 (C4), 26.9 (CH2), 21.1 (CH2), 20.7 (CH) 19.9 (CH3), 15.5 (CH3).

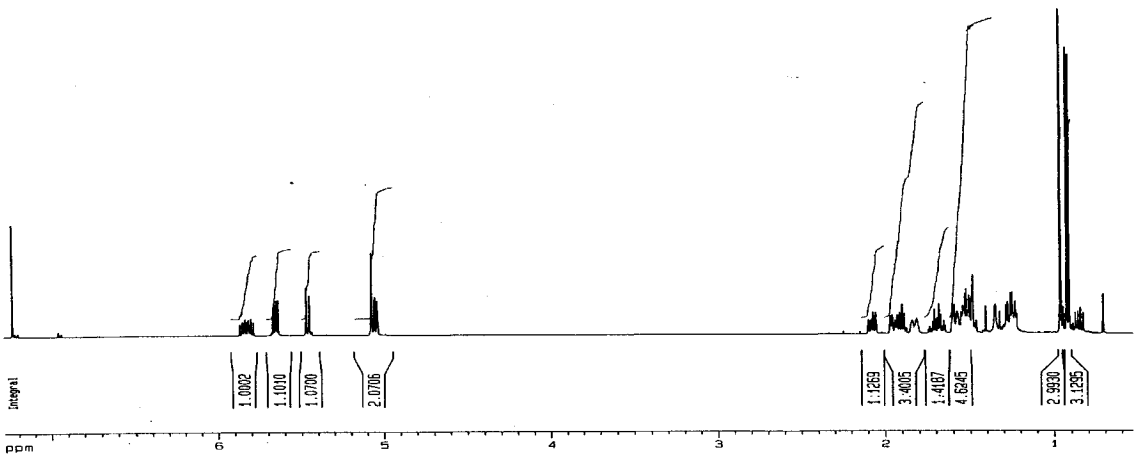
FTIR (neat, cm^{-1}) υ = 3485 (br), 3073 (m), 3008 (m), 2932 (s), 2874 (s), 1456 (s), 1442 (s), 1373 (s), 955 (m), 941 (s).

HRMS (EI) Calc for $C_{15}H_{24}O_1$ [$(M)^+$]: 220.18272, Found: 220.18232 (2.74%).

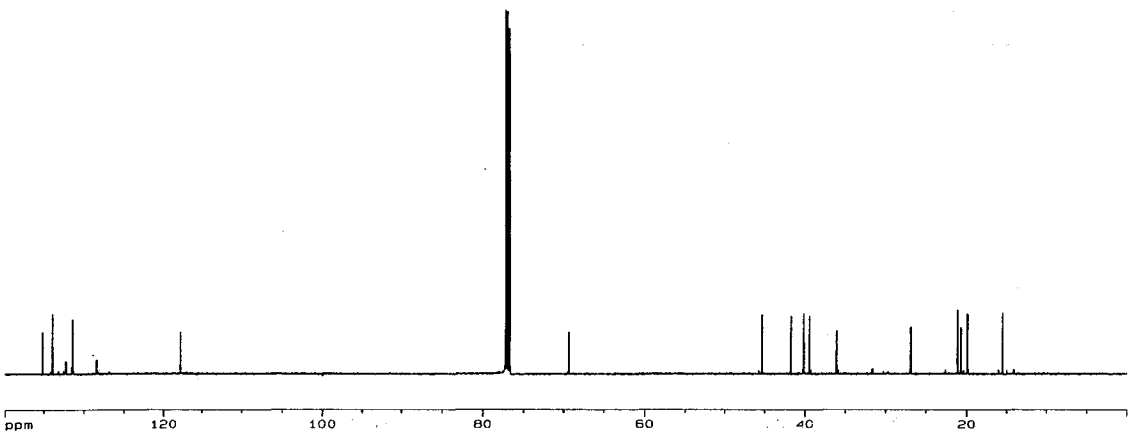


4.40

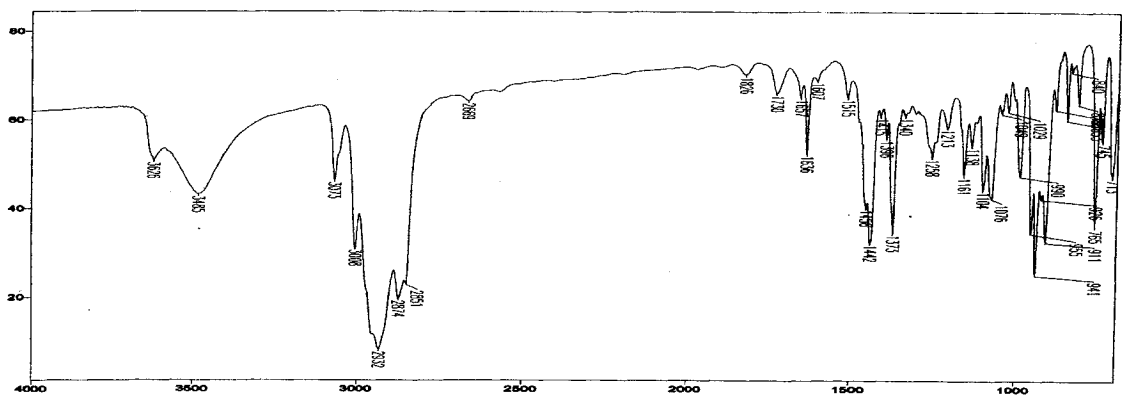
^{1}H NMR ($CDCl_3$, 500 MHz)

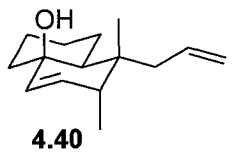


^{13}C NMR ($CDCl_3$, 125 MHz)



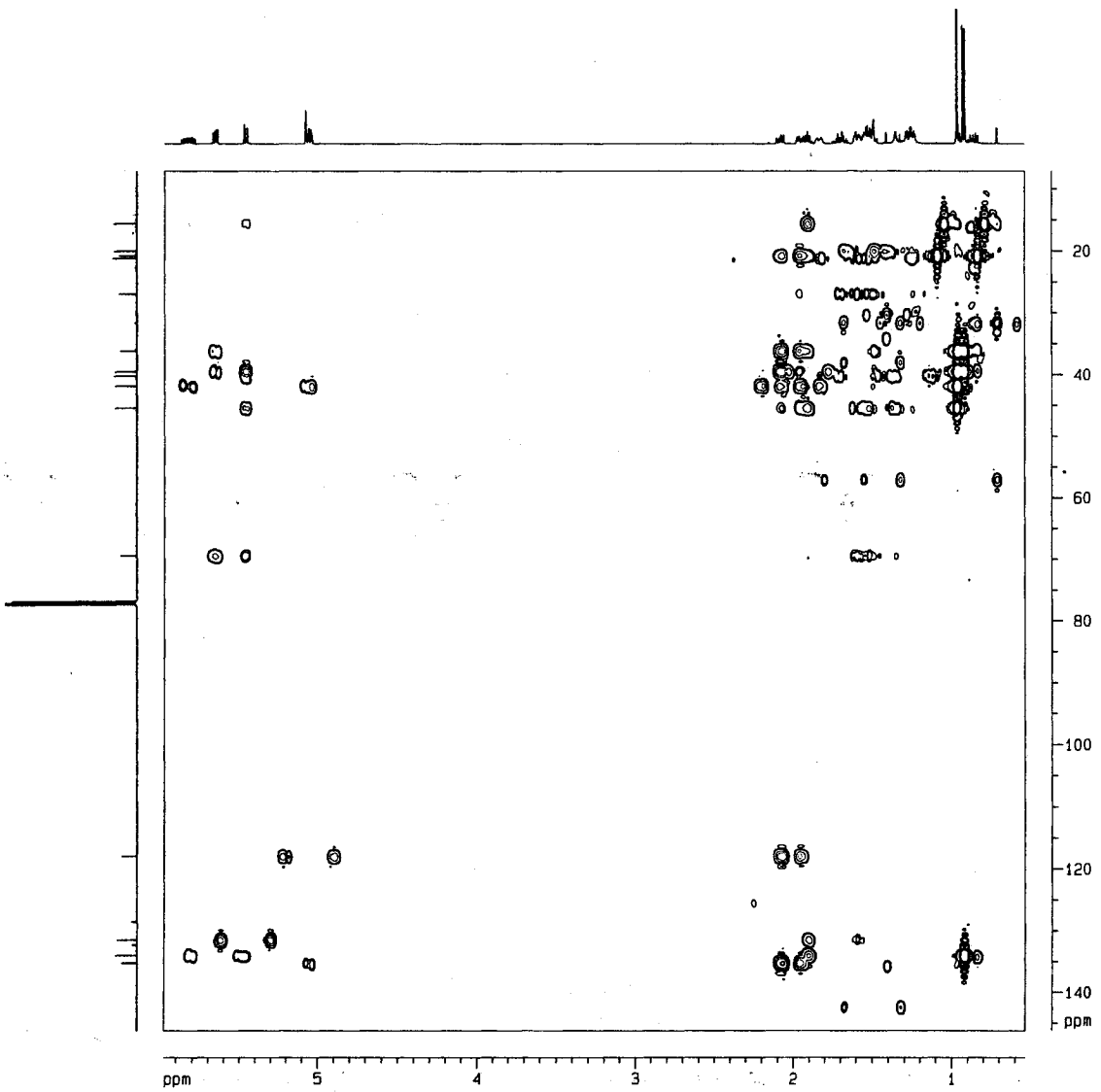
FTIR (neat)

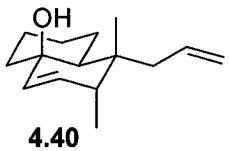




4.40

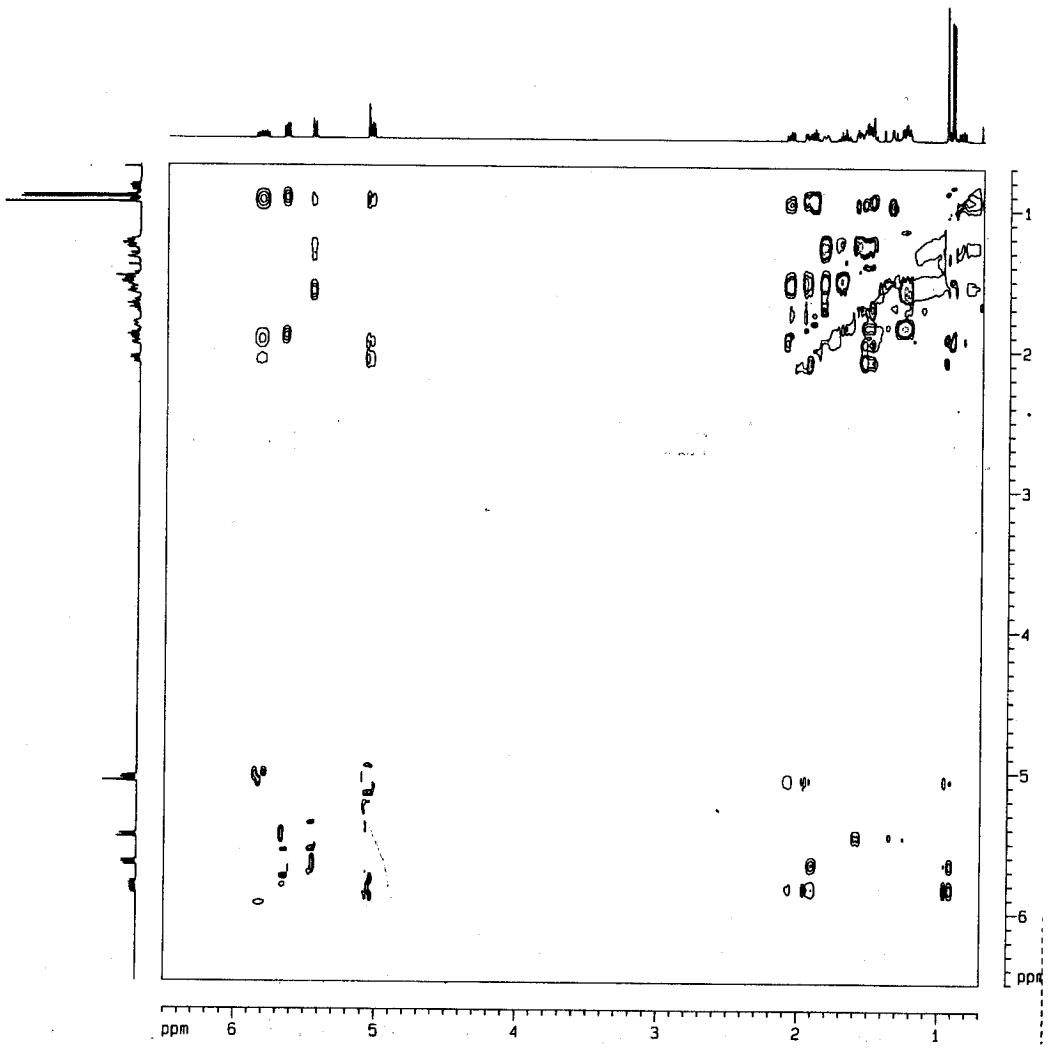
HMBC ($CDCl_3$)

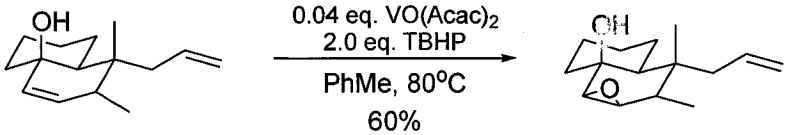




4.40

^{1}H NOESY ($CDCl_3$)





4.40 **4.41**

3-Allyl-2,3-dimethyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (19). A solution of the allylic alcohol **4.40** (39 mg, 177 umol) in toluene (17 mL) was stirred at room temperature and $VO(Acac)_2$ (2.2 mg, 0.05 equiv.) was added. After the catalyst had dissolved, TBHP (5-6M in pentane, 60 uL, 2.0 equiv.) was added and the green solution became dark purple. The mixture was heated to 60 °C for 1 hr, and allowed to cool. A mixture of aqueous brine and Na_2SO_3 (sat'd, 1:1) were added, and stirred briefly prior to extraction with EtOAc (3 x 5 mL), drying over $MgSO_4$ and concentrating *in vacuo*. The residue was purified by flash chromatography (10% EtOAc / Hexanes) to give **4.41** as a pale yellow oil (28 mg, 68%).

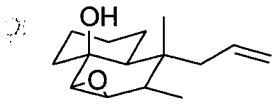
Data for **4.41**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.84-5.74 (m, 1H), 5.12-5.03 (m, 2H), 3.18 (dd, J = 2.1, 3.7 Hz, 1H), 2.96 (d, J = 3.8 Hz), 2.07-2.03 (m, 2H), 1.95 (dd, J = 7.6, 14.1 Hz), 1.85-1.72 (m, 4H), 1.59-1.15 (m, 8H), 1.07 (dd, J = 2.7, 12.3 Hz, 1H), 1.01 (d, J = 4.5 Hz, 3H), 1.01 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 134.7 (CH), 118.2 (CH_2), 68.8 (C QUAT.), 61.4 (CH), 58.7 (CH), 45.4 (CH), 43.8 (CH_2), 39.5 (CH_2), 35.9 (C QUAT.), 35.2 (CH_2), 26.9 (CH_2), 21.4 (CH_2), 21.2 (CH_3), 20.0 (CH) 12.93 (CH_3).

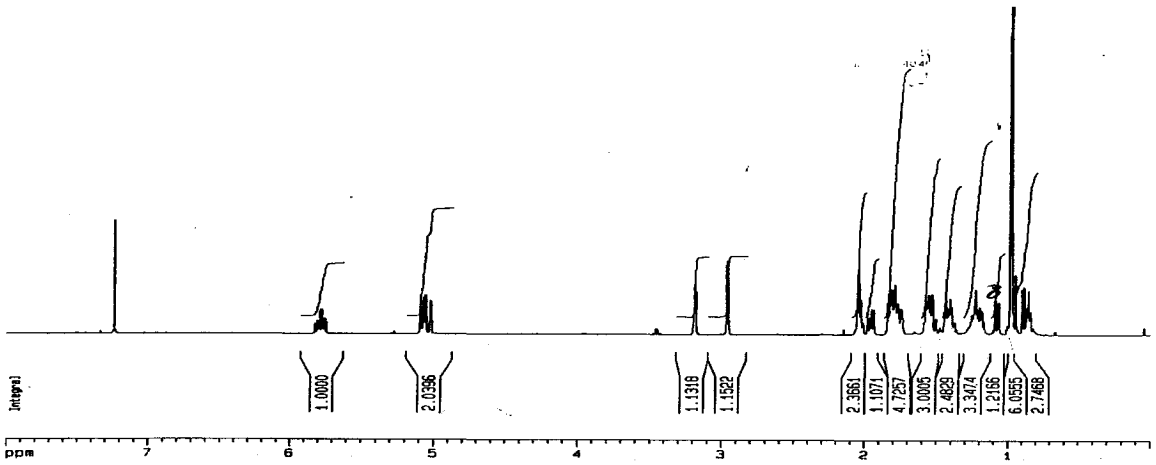
FTIR (neat, cm^{-1}) υ = 3500 (br), 3074, 2933, 1724, 1637, 1445, 1380, 973.

HRMS (EI) Calc for $C_{15}H_{24}O_2$ [$(M)^+$]: 236.17763, Found: 236.17663 (2.74%).

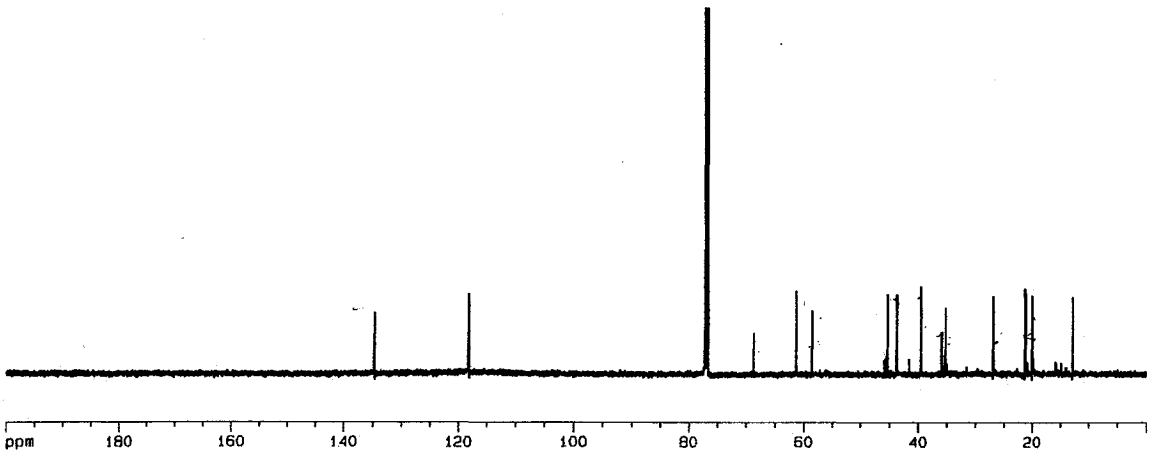


4.41

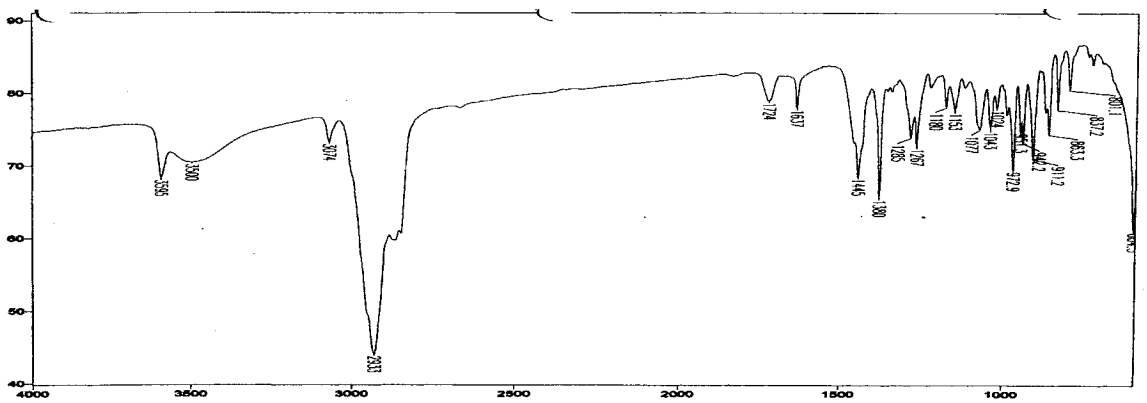
^{1}H NMR ($CDCl_3$, 500 MHz)

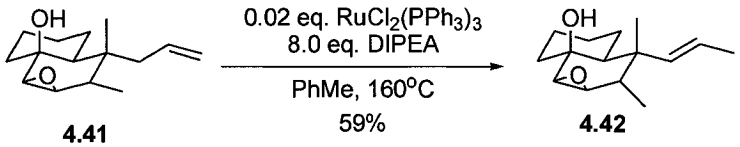


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.41 **4.42**

2,3-Dimethyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.42). A solution of the epoxide **4.41** (520 mg, 2.37 mmol) was stirred in toluene (23 mL) under argon in a flask fitted with a reflux condeser at room temperature. Hunig's Base (DIPEA, 3.3 mL, 8.0 equiv.) was added, followed by $RuCl_2(PPh_3)_3$ (45 mg, 0.02 equiv.). The mixture was heated to 160 °C for 18 hours, and was followed by GC. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was subjected to column chromatography (0 to 15% gradient EtOAc in hexanes) to give olefin **4.42** (307 mg, 59%) as a clear oil.

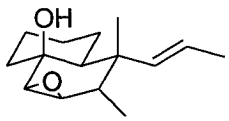
Data for **4.42**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.27 (dq, J = 15.7, 6.3 Hz, 1H), 5.14 (dd, J = 1.5, 15.7 Hz, 1H), 3.21 (dd, J = 1.7, 3.9 Hz, 1H), 3.02 (d, J = 3.9 Hz, 1H), 2.10-2.02 (m, 1H), 1.97 (dq, J = 1.7, 7.5 Hz, 1H) 1.85-1.73 (m, 3H), 1.67 (dd, J = 1.5, 6.3 Hz, 3H) 1.55 (s, 3H), 1.50-1.40 (m, 2H), 1.30-1.04 (m, 4H), 0.96 (d, J = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 140.5 (CH), 122.1 (CH), 68.8 (C_4), 61.7 (CH), 59.0 (CH), 45.5 (CH), 39.5 (CH_2), 39.0 (CH), 38.7 (C_4), 27.0 (CH_2), 21.7 (CH_2), 21.4 (CH_2), 20.8 (CH_3), 18.2 (CH_3), 14.4 (CH_3),.

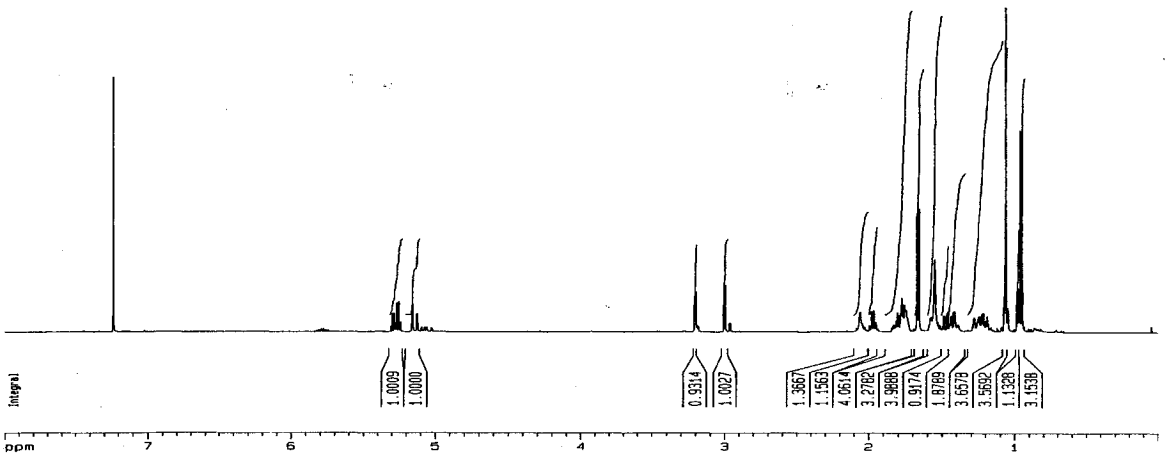
FTIR (neat, cm^{-1}) υ = 3593 (br, s), 2933 (s), 2853 (s), 1446 (s), 1376 (s), 1075 (s), 974 (s) 861 (s).

HRMS (EI) Expected for $C_{15}H_{24}O_2$ [$(M)^+$]: 236.17763, Found: 236.17660 (2.2%)

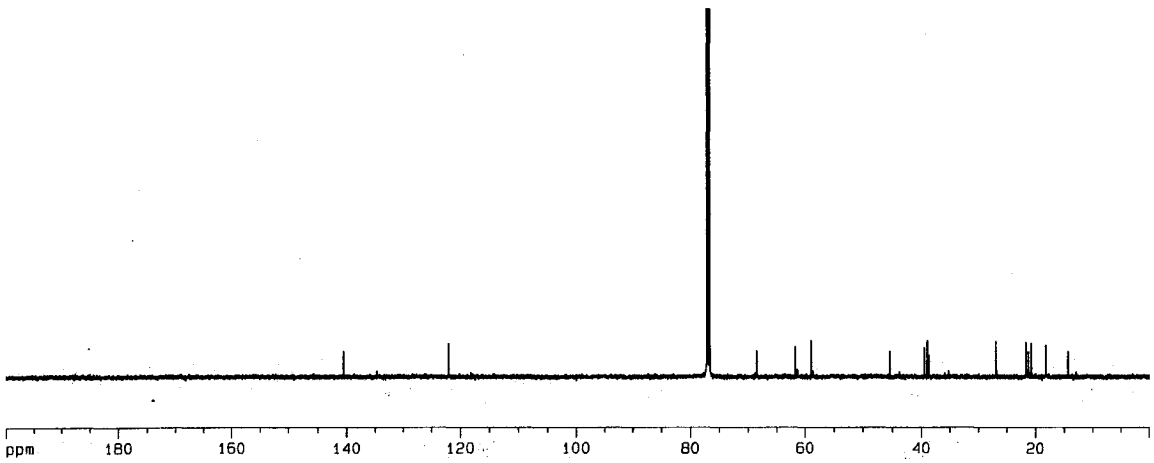


4.42

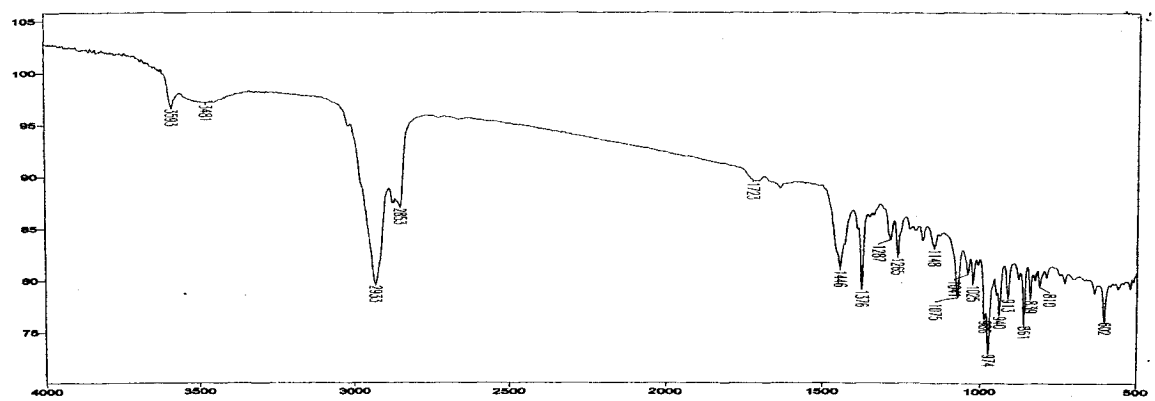
^{1}H NMR ($CDCl_3$, 500 MHz)

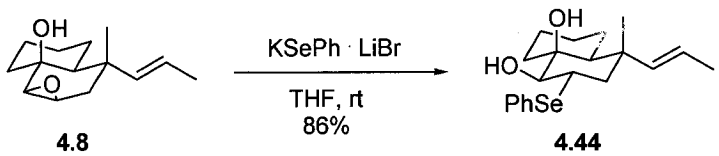


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.8 **4.44**

4-Methyl-2-phenylselanyl-4-propenyl-octahydro-naphthalene-1,8a-diol (4.44). A dry 250 mL roundbottom flask was fitted with a magnetic stirring bar and charged with KBr (5 equiv.). The flask was flame dried under high vacuum and the atmosphere replaced with argon. After cooling, diphenyl diselenide (1.28 g, 4.02 mmol, 0.6 equiv.), and THF (70 mL) were added to give a canary yellow solution. $LiBH_4$ (2M in THF, 4.70 mL, 1.4 equiv.) was added, with slow evolution of H_2 noted. After the solution became colorless or white (1 hr), a solution of the epoxide **4.8** (1.42 g, 6.72 mmol) was added. After 2 hours, the reaction was deemed complete by TLC (20% Et_2O/Hexanes as eluent). The reaction was quenched by slow addition of $NH_4Cl_{(aq)}$ and the organic layers were extracted with ether (3 x 20 mL). Drying over $MgSO_4$ and removal of the volatiles afforded a thick yellow sludge that was subjected to flash chromatography (0 to 20% Et_2O in Hexanes) to give the selenide **4.44** as a thick, clear colourless oil (2.10 g, 86%).

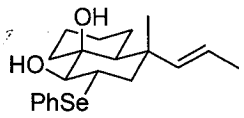
Data for **4.44**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.58-7.55 (m, 2H), 7.35-7.25 (m, 3H), 7.32 (dq, J = 15.5, 6.4 Hz, 1H) 5.06 (dd, J = 15.5, 1.4 Hz, 1H), 3.50 (ddd, J = 13.4, 10.8, 3.4 Hz, 1H), 2.98 (d, J = 10.8 Hz, 1H) 1.97-1.92 (m, 2H), 1.85 (dd, J = 13.4, 3.4, 1H) Hz, 1.70-1.61 (m, 1H) 1.61 (dd, J = 6.4, 1.4 Hz, 3H), 1.57-1.24 (m, 6H), 1.11 (s, 3H), 1.11-0.85 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 141.92 (CH), 136.28 (CH), 129.08 (CH), 128.34 (CH), 125.47 (C QUAT.), 122.00 (CH), 77.25 (CH), 73.52 (C QUAT.), 49.21 (CH), 46.39 (CH_2), 45.77 (CH), 40.88 (CH), 37.81 (CH_2), 26.43 (CH_2), 22.09 (CH_2), 21.42 (CH_2), 18.33 (CH_3), 18.13 (CH_3).

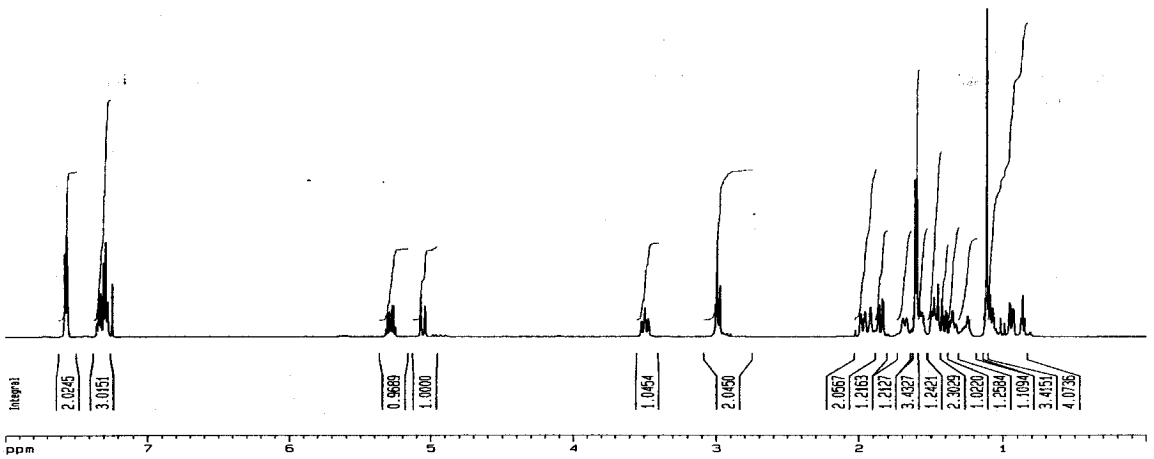
FTIR (neat, cm^{-1}) υ = 3503 (br), 3061, 3026, 2933, 2851, 978 cm^{-1}.

HRMS (EI) Expected for $C_{20}H_{28}O_2Se_1$ [$(M)^+$]: 380.1254, found: 380.1272 (40.1%)

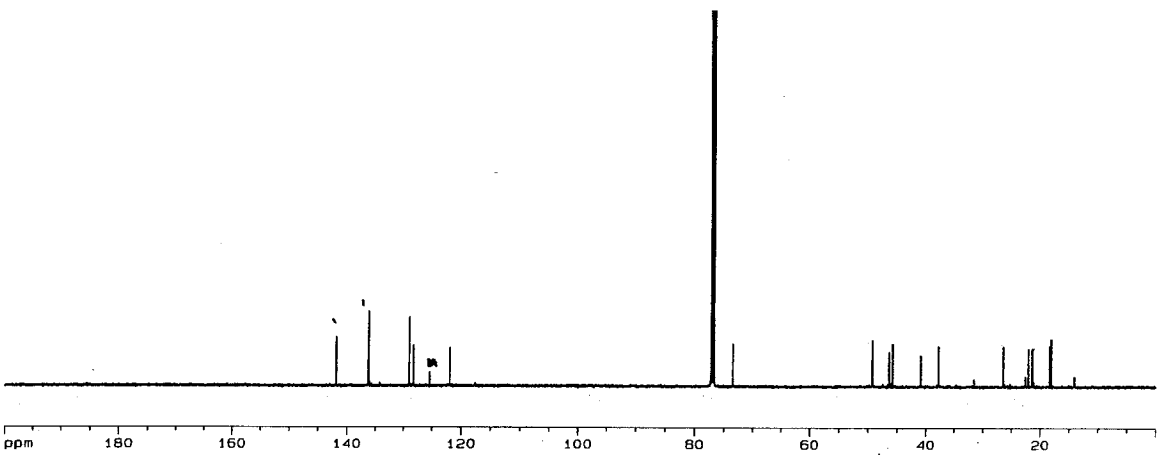


4.44

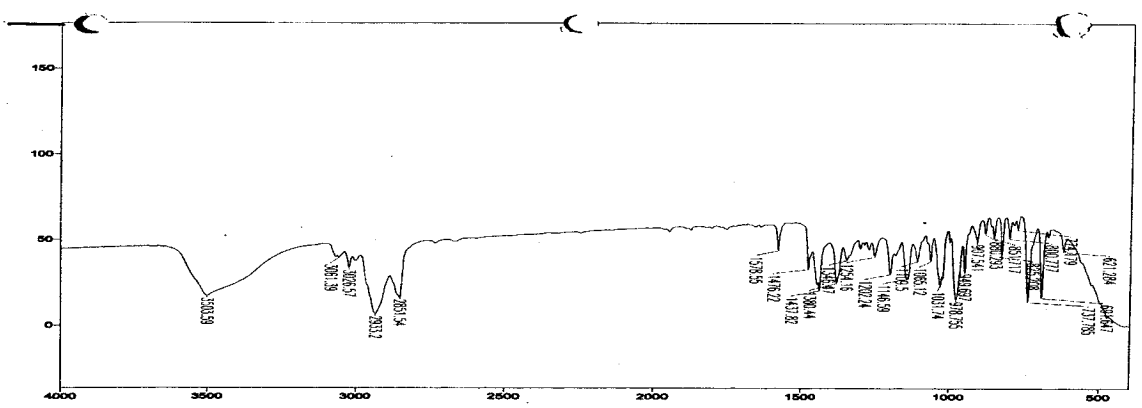
^{1}H NMR ($CDCl_3$, 500 MHz)

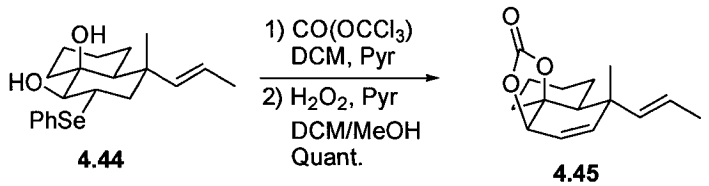


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.44 **4.45**

6-Allyl-6-methyl-6,6a,7,8,9,10-hexahydro-3aH-naphtho[1,8a-d][1,3]dioxol-2-one (4.45). To a solution of triphosgene (1.26 g, 1 equiv.) in dichloromethane (50 mL) under argon was added Pyridine (3.45 mL, 10equiv.) and cooled to 0 °C. After stirring for several minutes, a white-yellow precipitate formed, and diol **4.44** (1.68 g, 4.42 mmol) was added via canula and rinse (15 mL CH_2Cl_2). The reaction was stirred for 3 hr while being allowed to come to room temperature. The reaction mixture was re-cooled to 0 °C and Methanol (65 mL) was added, followed by H_2O_2 (30% in H_2O, 877 uL, 2 equiv.). This was stirred for 1 hr until the starting material had disappeared by TLC (rF of the starting material is 0.6 in 20% EtOAc/Hex, the oxidized selenide appears at the baseline). The oxidation was halted by the addition of water (100 mL), and the organic phase was extracted with dichloromethane (4 x 20mL). The combined organic phases were dried over $MgSO_4$ and concentrated to leave a dark orange oily residue. The residue was redissolved in benzene (60 mL) and pyridine was added (3.45 mL, 10equiv.). The mixture was heated to 50-60 °C for one hour, the volatiles were removed, and the crude was subjected to flash chromatography (0 to 15% EtOAc/Hex) to give **4.45** as light orange-red oil (1.10 g, quant).

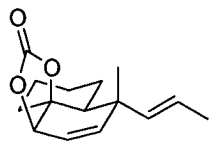
Data for **4.45**:

^{1}H NMR (500 MHz, $CDCl_3$) 5.82 (d, J = 10.3 Hz, 1H), 5.57 (dd, J = 10.3, 3.1 Hz, 1H), 5.42 (dq, J = 15.5, 6.4 Hz), 5.26 (dd, J = 15.5, 1.6 Hz), 4.59 (d, J = 3.1 Hz, 1H), 2.10-2.05 (m, 1H), 1.89-1.80 (m, 1H), 1.77-1.66 (m, 2H), 1.66 (dd, J = 6.4, 1.6 Hz) 1.60-1.35 (m, 4H), 1.30-1.25 (m, 1H), 1.07 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 154.1 (O-(CO)-O), 143.1 (CH), 138.5 (CH), 124.3 (CH), 118.3 (CH), 83.1 (C QUAT.), 77.8 (CH), 45.6 (CH), 39.3 (C QUAT.), 37.3 (CH_2), 25.6 (CH_2), 23.0 (CH_2), 21.4 (CH_2), 21.0 (CH_3), 18.1 (CH_3)

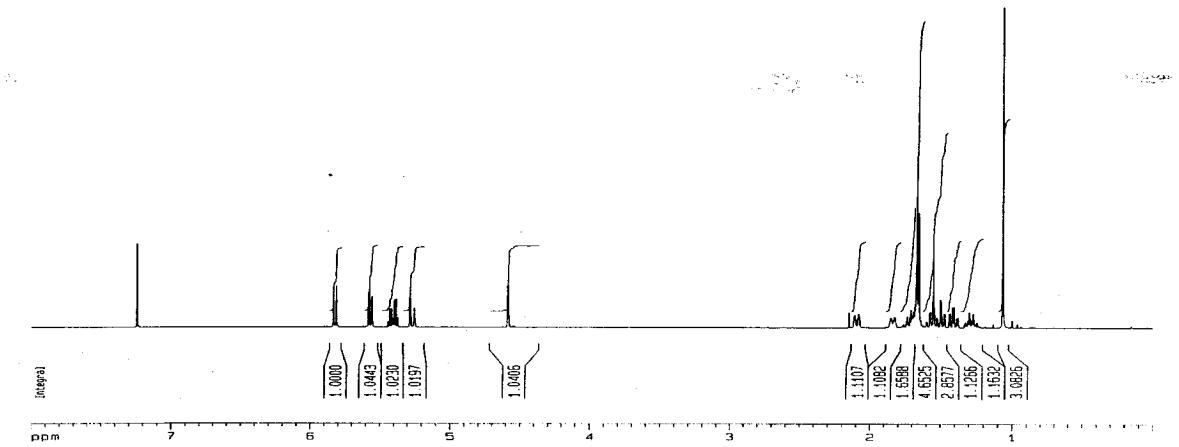
FTIR (neat, cm^{-1}) υ =3027 (m), 2939 (s), 2865 (m), 1801 (s), 1449 (m), 1205 (s), 1011 (s), 1027 (s).

HRMS (EI) Expected for $C_{15}H_{20}O_3$ [$(M)^+$]: 248.14125, found: 248.14130 (40.1%).

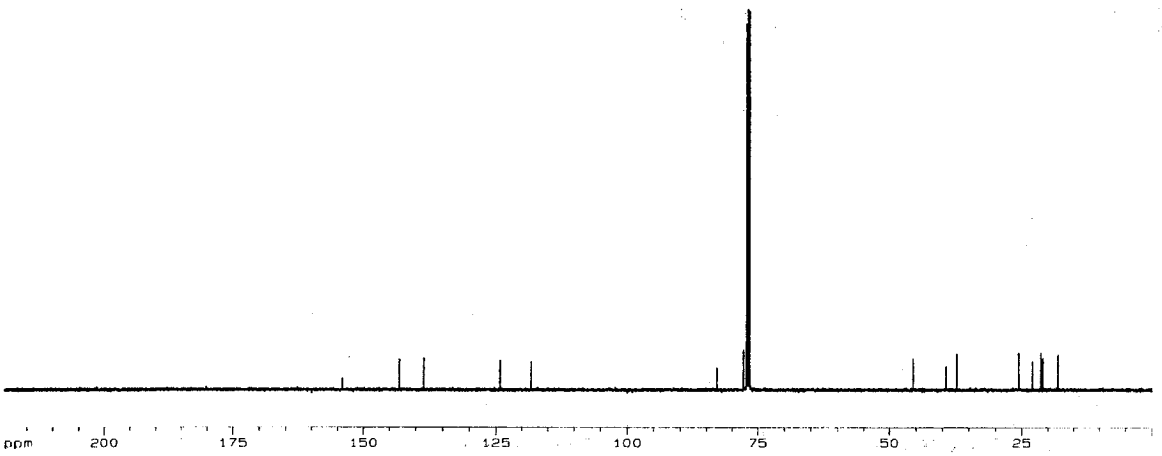


4.45

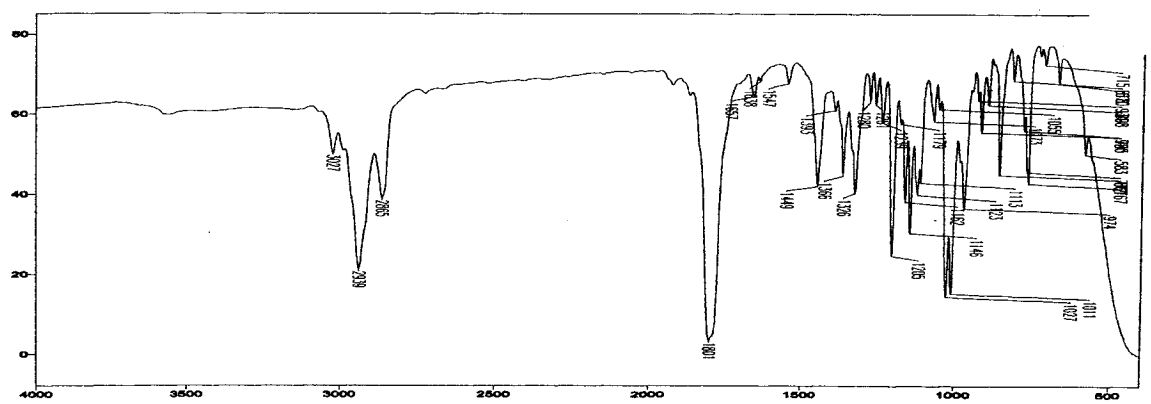
^{1}H NMR ($CDCl_3$, 500 MHz)

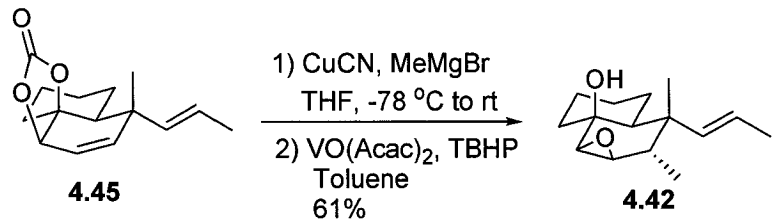


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)



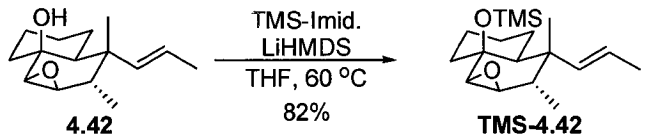


4.45 **4.42**

2,3-Dimethyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-ol (4.42). A dry 500 mL flask under argon was fitted with a magnetic sturring bar, and charged with CuCN (1.50 g, 5 equiv.). Dry THF (volume made so 0.1 M in Cu, 140 mL) was added and the slurry was cooled to -78°C. MeMgBr (3M in Ether, 5.58 mL, 5 equiv.) was added and stirring was continued for 45 minutes. Noticeably, the dull-gray colour of the copper cyanide slurry brightens to a bleached white colour as stirring is continued. A solution of the allylic carbonate **22** (830 mg, 3.35 mmol) in dry THF (20 mL) was added dropwise. No more dry ice was added to the cold bath, and the reaction was allowed to come to room temperature overnight (18hr). The cuprate was quenched with saturated $NH_4Cl_{(aq)}$: NH_4OH (8:1) (30 mL), and allowed to stir under air for 2 hours (or until the organic layer is clear and the aqueous layer was clear blue – you can hasten this by bubbling compressed air through the solution). The organic layers were extracted with ether (3 x 30 mL), combined, and washed with brine (2 x 30 mL). After drying over $MgSO_4$ and removal of the volatiles, the remaining yellow oil was purified to give. The procedure for epoxidation used was identical above (see compound **11** or **19**), but was completed after only 45 minutes. Purification by flash chromatography (0 to 15% Ether in Hexanes) afforded the epoxide **20** (482 mg, 61%) as a colourless oil.

Data for **4.42**:

As above



2,3-Dimethyl-3-propenyl-octahydro-1-oxa-cyclopropa[a]naphthalen-7a-yloxy)-trimethyl-silane (TMS-4.42). A solution of free alcohol **4.42** (660 mg, 2.80 mmol) in dry THF (30 mL) was stirred at room temperature under argon and TMS Imidazole (820 uL, 2 equiv.) was added, followed by LiHMDS (solid, 450 mg, 1 equiv.) in one portion. The mixture was heated to reflux for 1hr and allowed to cool. To quench, silica was added to the reaction mixture (~ 1 g) and the volatiles were removed on rotovap and hi-vac. The residual powder was subjected to flash chromatography (0 to 5% Et_2O in Hexanes) to give the product as a yellow oil (712 mg, 82%).

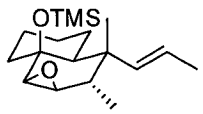
Data for TMS-**4.42**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.25 (dq, J = 15.6, 6.2 Hz, 1H), 5.16 (dd, J = 15.6, 1.2 Hz, 1H), 3.04 (dd, J = 3.8, 1.5 Hz, 1H), 2.87 (d, J=3.8 Hz), 1.92-1.65 (m, 4H), 1.65 (dd, J = 6.2, 1.2 Hz, 3H), 1.65-1.34 (m, 4H), 1.33-1.12 (m, 2H), 1.03 (s, 3H), 0.93 (d, J= 10.0 Hz, 3H), 0.16 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 141.32 (CH), 121.04 (CH), 72.276 (C QUAT.), 60.47 (CH), 58.26 (CH), 46.89 (CH), 40.319 (CH), 39.56 (CH_2), 38.76 (CH), 27.12 (CH_2), 27.96 (CH_2), 21.31(CH_2), 20.20 (CH), 18.23 (CH_3), 14.52 (CH_3), 2.21 (3 x CH_3).

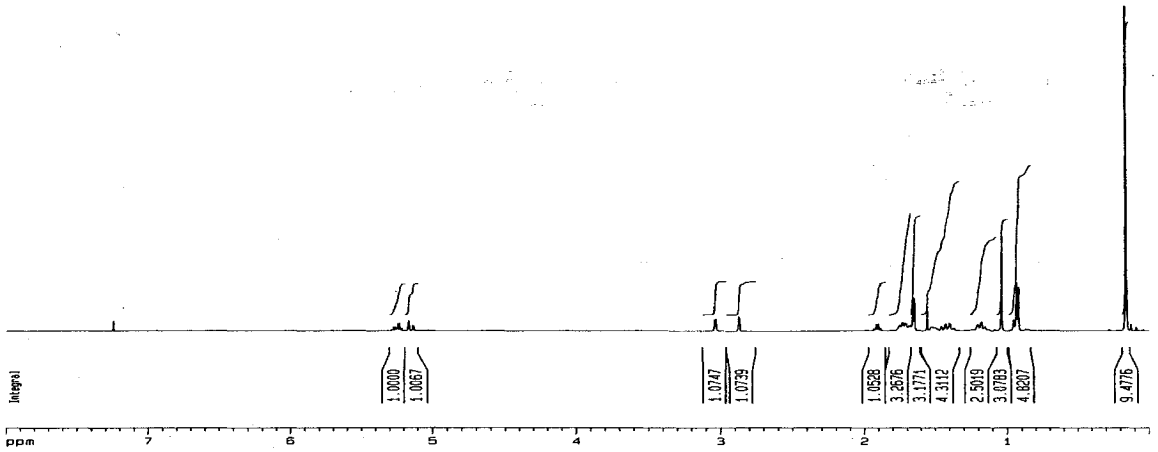
FTIR (neat, cm^{-1}) υ = 3209 (w), 2939 (s), 1248 (s), 1034 (s), 839 (s).

HRMS (EI) Expected for $C_{18}H_{32}O_2Si$ [$(M)^+$]: 308.2172, Found: 308.2170

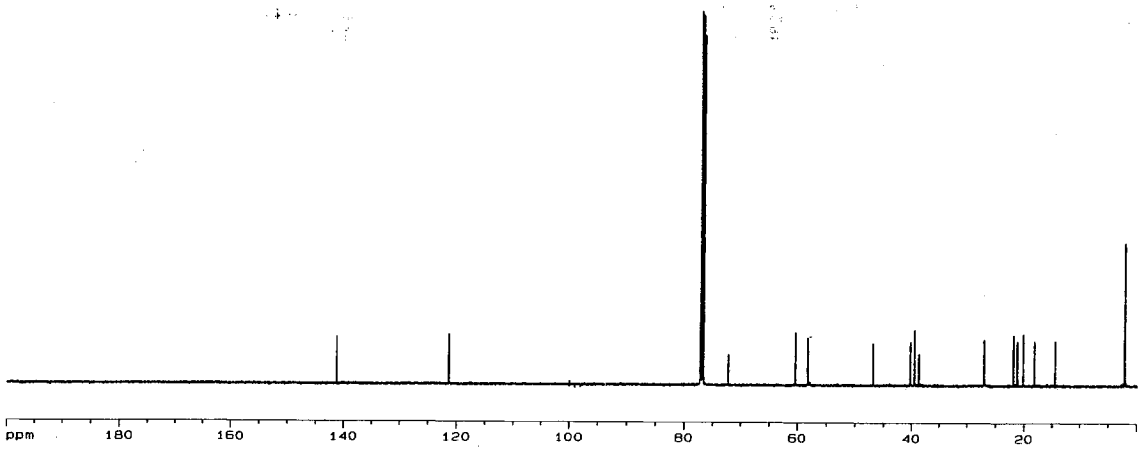


TMS-4.42

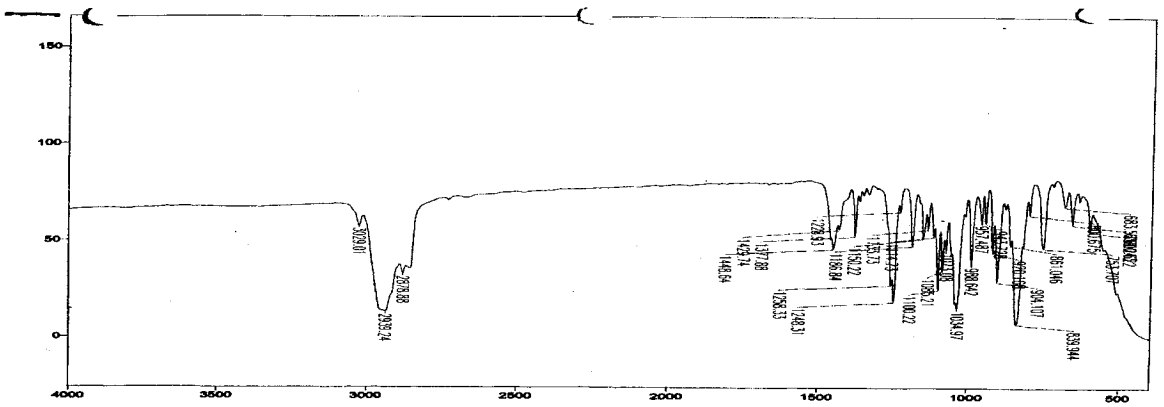
^{1}H NMR ($CDCl_3$, 500 MHz)

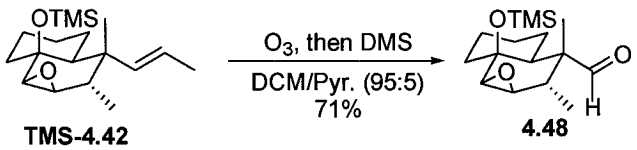


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carbaldehyde (4.48). A clean dry flask was charged with olefin **TMS-4.42** (538 mg, 1.72 mmol), dichloromethane (17 mL) and Pyridine (850 uL). The solution was bubbled with oxygen while being cooled to -78°C. Once cool, the current was switched on and ozone was generated until the steel-gray ozone colour persisted (approx. 30 minutes). The solution was sparged with Argon for 20 minutes and DMS (5 equiv.) was added. The reaction was allowed to warm to room temperature, and brine (5 mL) was added. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$ and concentrated. The crude was subjected to flash chromatography (0 to 20% EtOAc in Hexanes) to give the aldehyde **4.48** as a thick colourless oil (360 mg, 71%).

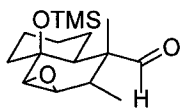
Data for **4.48**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 9.35 (s, 1H), 3.03 (dd, J = 3.7, 1.4 Hz, 1 H), 2.94 (d, J = 3.7 Hz, 1H), 2.19 (dq, J = 7.5, 1.1 Hz, 1 H), 1.90-1.65 (m, 3H), 1.64-1.40 (m, 4H), 1.29-1.20 (m, 2H), 1.1 (s, 3H), 1.00 (d, J = 7.5 Hz, 3H), 0.16 (s, 9 H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 207.8 (CH), 71.6 (C QUAT.), 59.8 (CH), 58.1 (CH), 48.3 (C QUAT.), 42.7 (CH), 40.0 (CH_2), 35.9 (CH), 26.5 (CH_2), 21.8 (CH_2), 21.7 (CH_2), 16.6 (CH_3), 13.6 (CH_3), 2.1 (3 x CH_3).

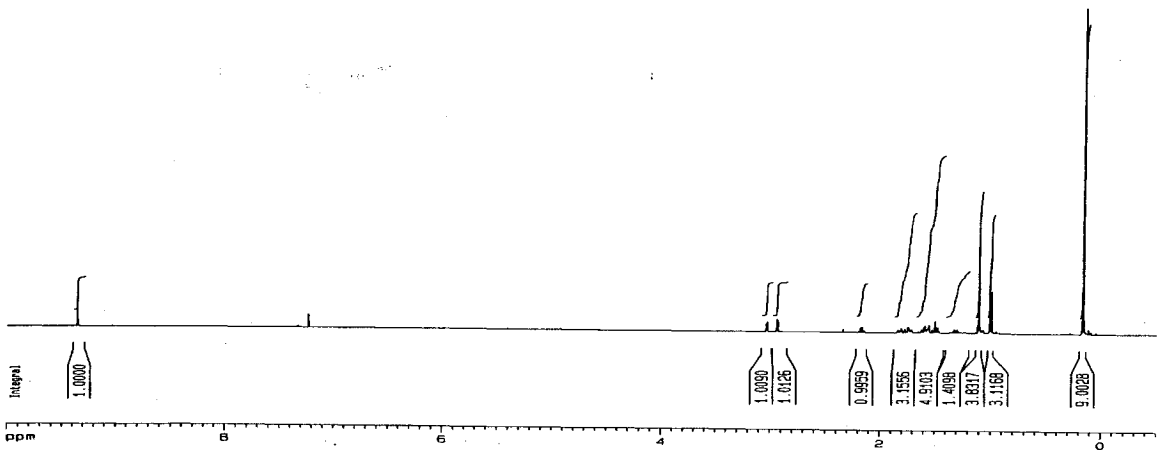
FTIR (neat, cm^{-1}) υ = 2945 (s), 2859 (m), 1727 (s), 1445 (m), 1248 (s), 1031 (s), 839 (s).

HRMS (EI) Expected for $C_{16}H_{28}O_3Si$ [$(M)^+$]: 296.18077, found: 296.17800.

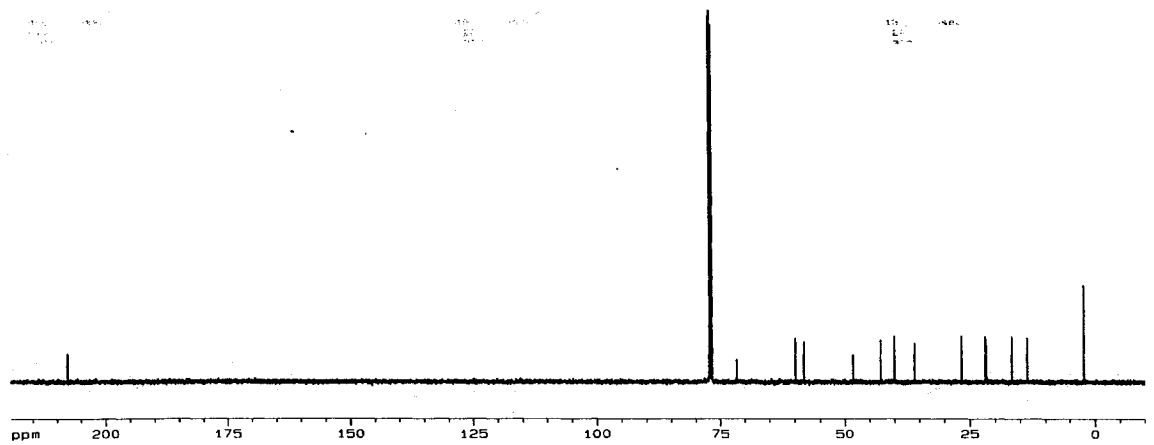


4.48

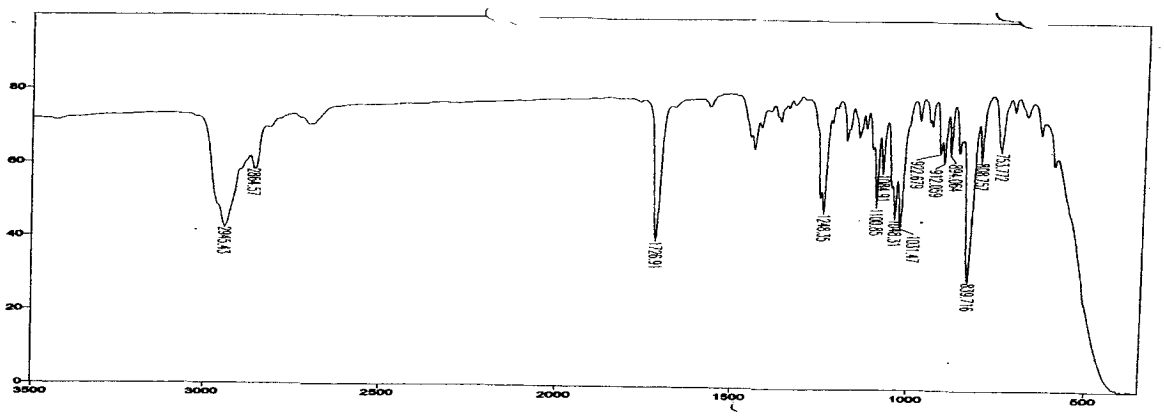
^{1}H NMR ($CDCl_3$, 500 MHz)

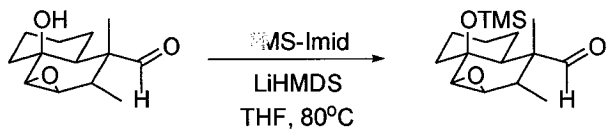


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)



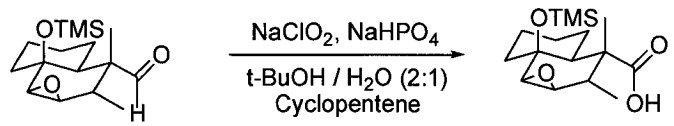


4.43 **4.48**

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carbaldehyde (2a). A solution of the aldehyde **4.43** (132 mg, 590 umol) in dry THF (5 mL) under argon was stirred at room temperature, and trimethylsilyl imidazole (2.0 equiv.) was added, followed by LiHMDS (2.0 equiv.). The flask was fitted with a reflux condenser, and heated to 80°C for 2hr. After cooling, silica gel (1g) was poured into the flask, and the volatiles were removed under reduced pressure. Flash chromatography (5% EtOAc in hexanes) of the powder gave **4.48** as a thick colourless oil (144 mg, 83%).

Data for **4.48**:

As above



4.48 80% **4.61**

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] aphthalene-3-carboxylic acid (4.61). A solution of **4.48** (76 mg, 257 umol) in t-BuOH (2 mL) and H2O (1 mL) was stirred at 0 °C and NaH_2PO_4 (308 mg, 10 equiv.) was added. Once the solid had dissolved, cyclopentene (100 uL) was added followed by $NaClO_2$ (140 mg, 6 equiv.). The reaction was stirred vigorously. After 30 minutes, the reaction was allowed to warm to ambient temperature, and stirred for another 30 min. The reaction mixture was returned to an ice bath, and a mixture of Na2SO3(sat.) and Brine (1:1, 5 mL) was added. The organic phase was extracted with EtOAc (3 x 5 mL), dried over MgSO4 and concentrated. The crude was passed through a pad of silica (40%EtOAc in Hexanes) to give **4.61** as a white powder. (63 mg, 85%).

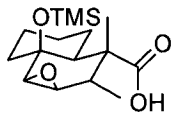
Data for **4.61**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 3.05 (dd, J = 2.1, 3.9 Hz, 1H), 2.92 (d, J = 3.9 Hz, 1H), 2.14 (dq, J = 2.1, 7.5 Hz, 1H), 1.90-1.55 (m, 6H), 1.50-1.35 (m, 4H), 1.25 (s, 3H), 0.98 (d, J = 7.4 Hz, 3H), 0.15 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 182.3, 71.9, 58.9, 58.0, 48.2, 45.7, 40.3, 37.2, 26.6, 23.7, 21.8, 19.0, 15.2, 2.6

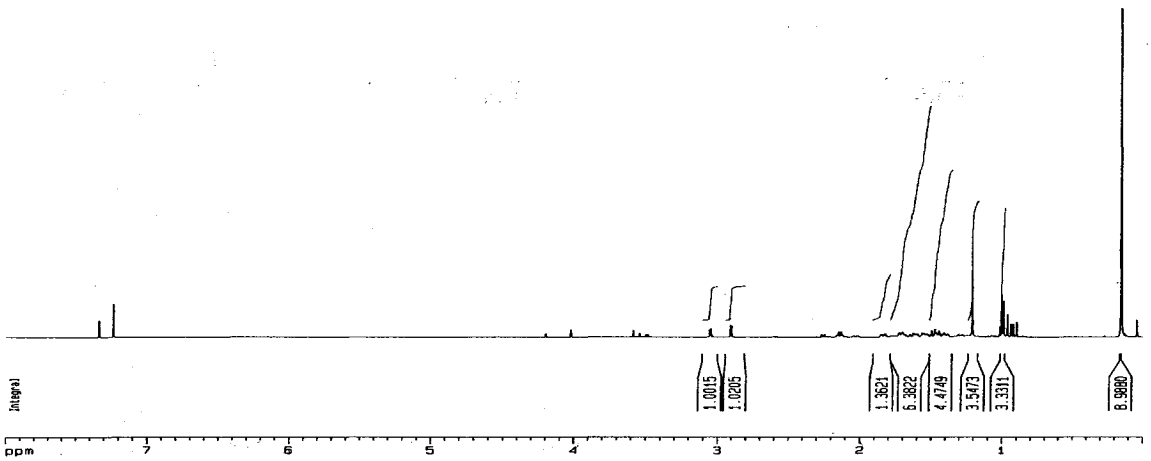
FTIR (neat, cm^{-1}) υ = 3429 (br), 2946 (s), 2858 (m), 1698

HRMS (EI) Expected for $C_{16}H_{28}O_4Si$ [$(M)^+$]: 312.17569, found: 312.17211 (1.4%).

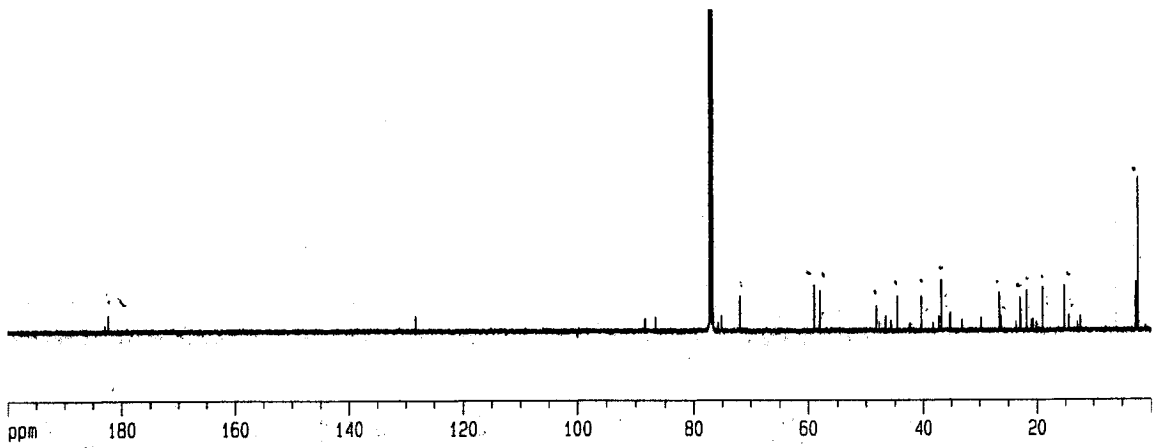


4.61

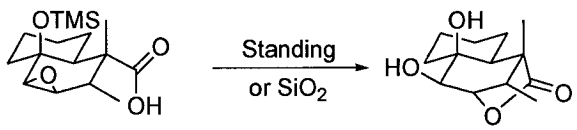
^{1}H NMR ($CDCl_3$, 500 MHz)



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



FTIR (neat)



4.61 **4.69**

7,8-Dihydroxy-1,12-dimethyl-10-oxa-tricyclo[7.2.1.02,7]dodecan-11-one (4.69). Upon standing or repurifying **4.61**, compound **4.69** is frequently isolated (same rF in 40% EtOAc/Hexanes).

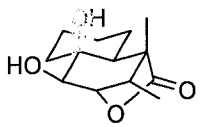
Data for **4.69**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 4.02 (br s, 1H), 3.59 (br s, 1H), 3.49 (q, J = 7.1 Hz, 1H), 2.11-2.03 (m, 2H), 1.80-1.73 (m, 1H), 1.65-1.45 (m, 5H), 1.27-1.18 (m, 2H), 0.97 (s, 3H), 0.94 (d, J = 7.1 Hz, 3H), 0.15 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 182.8 (C=O), 68.6 (CH), 75.2 (CH), 71.3 (C_4), 46.5 (CH), 45.7 (C_4), 37.2 (CH_2), 35.2 (CH), 26.4 (CH_2), 22.7 (CH_2), 20.7 (CH_2), 14.3 (CH_3), 12.3 (CH_3), 2.6 (3 x CH_3)

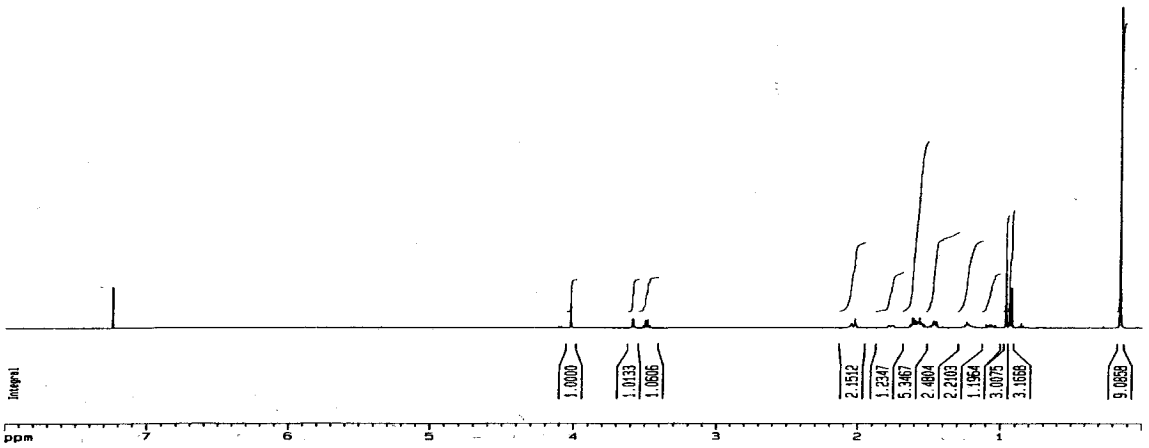
FTIR (neat, cm^{-1}) υ = 3465 (br s), 2941 (s), 2876 (s), 1758 (s), 1457 (s), 1445 (s), 1052 (s)

HRMS (EI) Expected for $C_{16}H_{28}O_4Si$ [$(M)^+$]: 312.17569, found: 312.17336 (1.4%).

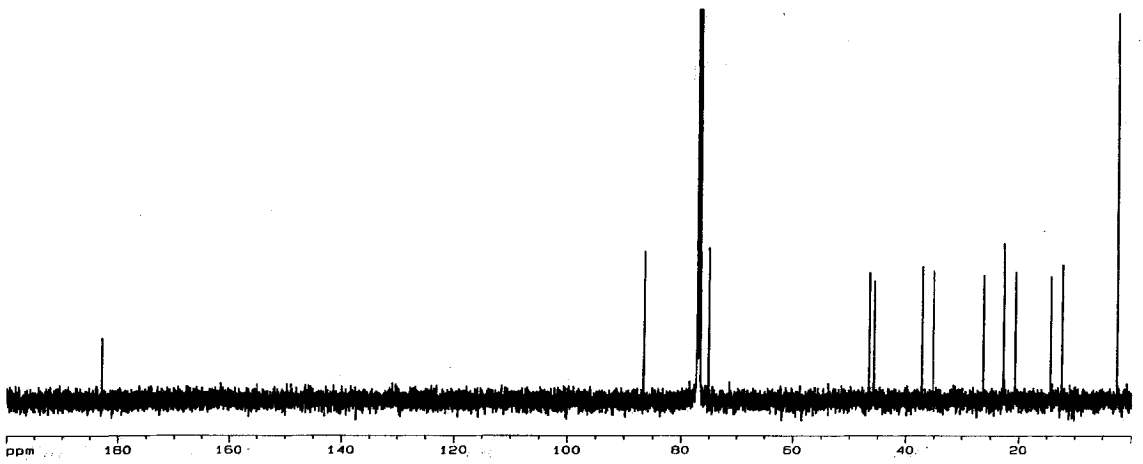


4.69

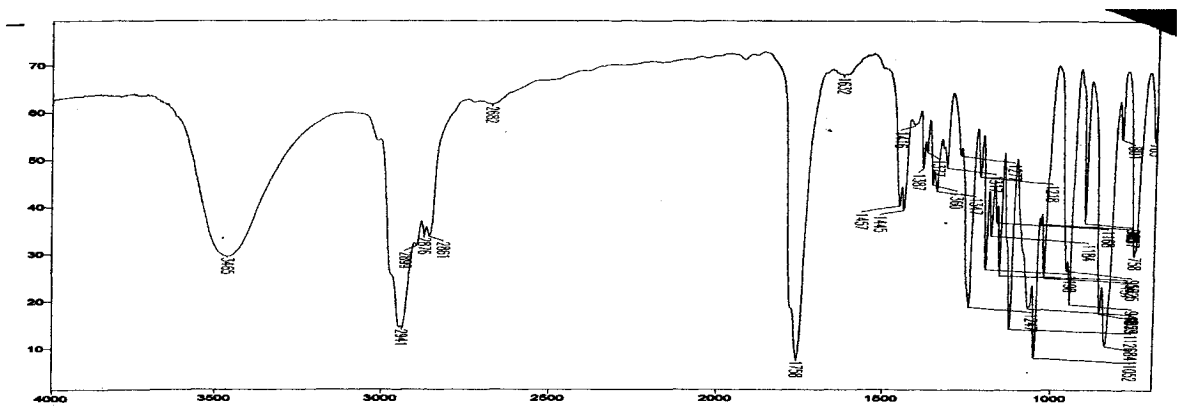
^{1}H NMR ($CDCl_3$, 500 MHz)

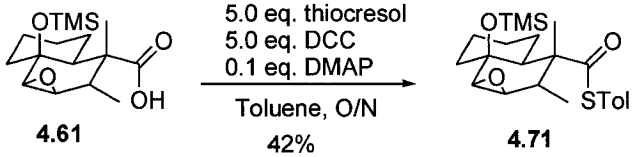


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.61 42% **4.71**

2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a]naphthalene-3-carbothioic acid S-p-tolyl ester (4.71). A solution of acid **4.61** (63 mg) in Toluene (5 mL) was stirred at room temperature and dicyclohexyl carbodiimide (1M in CH_2Cl_2, 5 equiv.) was added,dropwise, followed by thiocresol (50 mg, 2 equiv.) and DMAP (1 mg). The reaction was stirred atambient temperature for 18 h, and diluted with ether (10 mL). The mixture was filtered through a sintered glass filter. The organic phase was washed with water (2 x 2 mL) and brine (1 x 2 mL).The layer was dried over $MgSO_4$ and concentrated. The residue was subjected to flashchromatography (0 to 10% Et_2O in Hexanes) to afford **4.71** as a thick yellow oil. (38 mg, 46%)

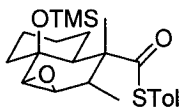
Data for **4.71**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.26-1.15 (m, 5H), 3.10 (dd, J = 1.9, 3.8 Hz, 1H), 2.89 (d, J =3.8 Hz, 1H), 2.34 (s, 3H), 2.26 (dq, J = 1.8, 7.4 Hz, 1H), 1.92-1.55 (m, 9H), 1.46 (s, 3H), 0.95 (d, J = 7.4 Hz, 3H), 0.17 (s, 9 H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 204.1 (C_4), 139.4 (C_4), 134.9 (CH), 134.8 (CH), 130.0 (CH), 129.9 (CH), 124.8 (C_4), 72.3 (C_4), 59.6 (CH), 58.0 (CH_3), 55.7 (C_4), 45.0 (CH), 40.2 (CH_2), 37.7 (CH), 26.6 (CH_2), 22.5 (CH_2), 21.8 (CH_2), 21.3 (CH), 19.5 (CH_3), 15.3 (CH_3), 2.2 (3 x CH_3)

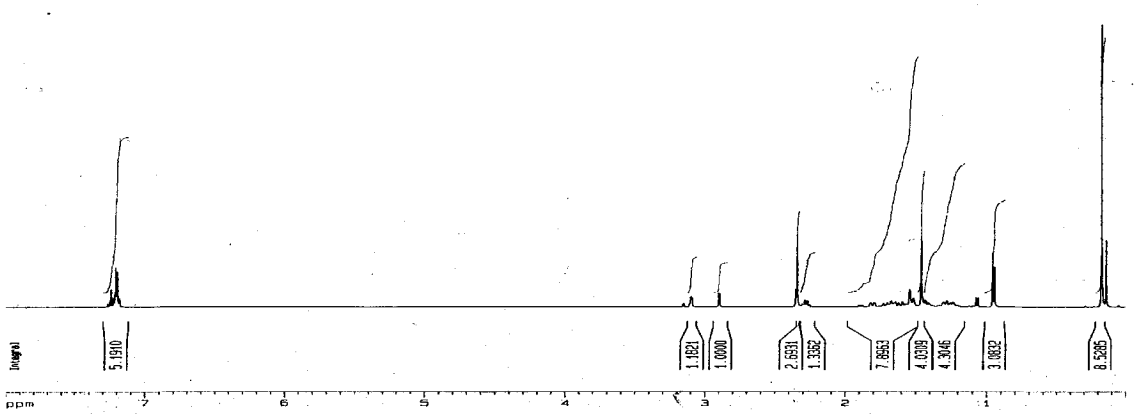
FTIR (neat, cm^{-1}) υ = 2943 (s), 2857 (m), 1696 (s), 1445 (m), 1258 (s), 1247 (s), 1108 (s), 838 (s)

HRMS (EI) $C_{16}H_{27}O_3Si$ [(M-STol)+]: 295.1730, found: 295.1737 (3.7%)

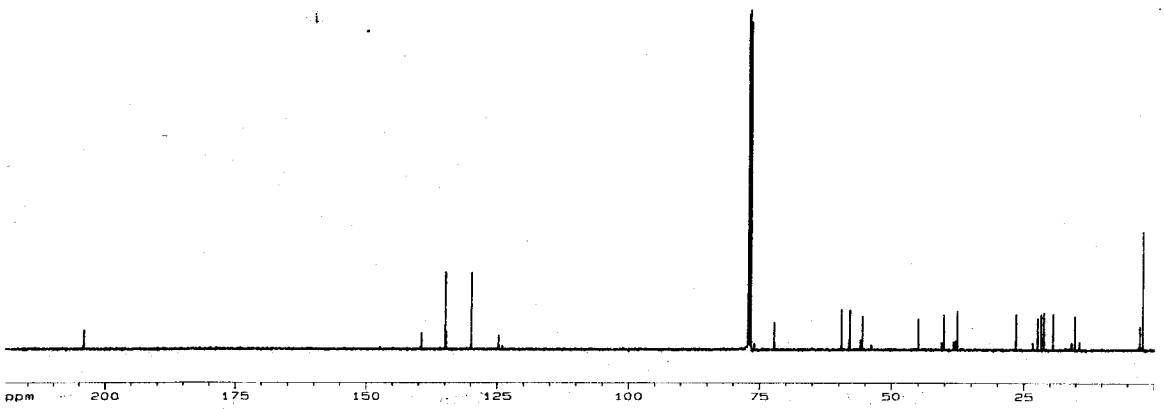


4.71

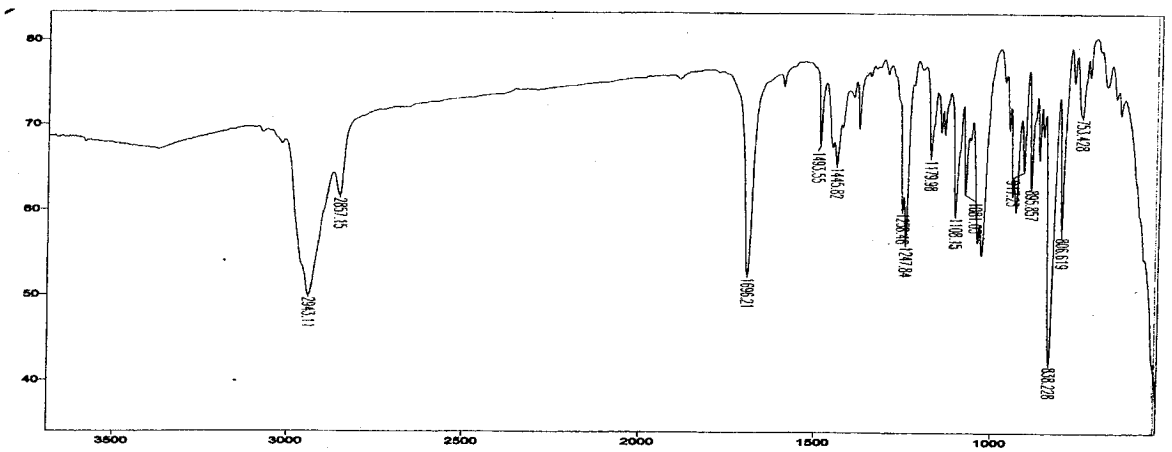
^{1}H NMR ($CDCl_3$, 500 MHz)

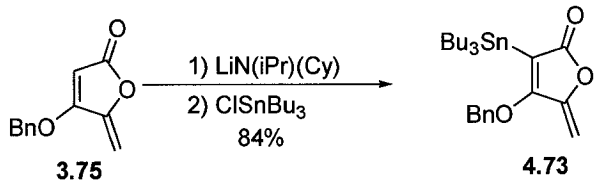


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





3.75 **4.73**

4-Benzyloxy-5-methylene-3-tributylstannanyl-5H-furan-2-one (4.73). A clean, dry 50 mL roundbottom flask fitted with a magnetic stirrer was flame-dried and filled with argon. Isopropylcyclohexylamine (140 uL, 1.5 equiv.) and THF (10 mL) were added. The flask was cooled to -78°C and t-BuLi (1.7M, 503 uL, 1.5 equiv.) was added. The reaction was allowed to stir for 10 minutes, and a solution of tetronate **3.75** (115 mg, 1.0 equiv.) in THF (3 mL) was added dropwise via syringe. The reaction was allowed to stir 10 minutes, and $SnBu_3Cl$ (180 uL, 1.2 equiv.) was added. The reaction was gradually allowed to warm to 0°C over 1 hr, quenched with $NH_4Cl_{(aq)}$, extracted with ether (3 x), dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (2% EtOAc in Hexanes) to give **4.73** as a pale yellow oil. (235 mg, 84%).

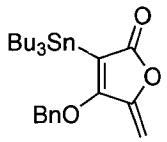
Data for **4.71**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.42-7.35 (m, 5H), 5.04 (br s, 2H), 4.92 (br s, 2H), 1.55-1.47 (m, 7 H), 1.32-1.10 (m, 11H), 0.87 (t, J = 7.3 Hz, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 174.9 (C_4), 173.8 (C_4), 156.0 (C_4), 151.3 (C_4), 134.7 (C_4), 128.8 (3 x CH), 127.5 (2 x CH), 125.2 (C_4), 121.3 (C_4), 89.8 (CH_2), 73.7 (CH_2), 28.9 (3 x CH_2), 27.2 (3 x CH_2), 13.6 (3 x CH_2), 11.9 (3 x CH_3)

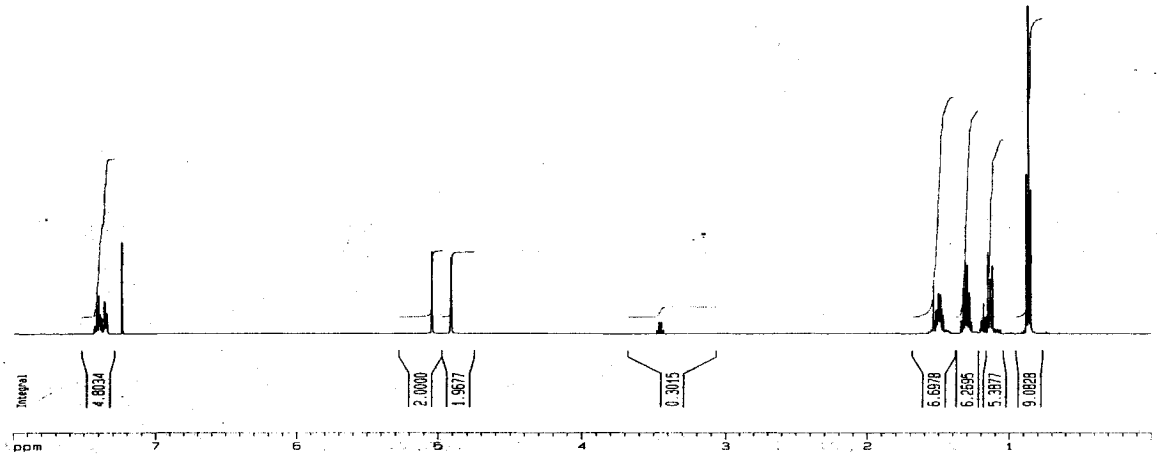
FTIR (neat, cm^{-1}) υ = 2956 (s), 2923 (s), 2871 (s), 1748 (s), 1661 (s), 1565 (s), 1456 (s), 1249 (s), 974 (s)

HRMS (EI) $C_{20}H_{27}O_3Sn$ [$(M-Bu)^+$]: 435.08922, found: 435.11638 (64.1%)

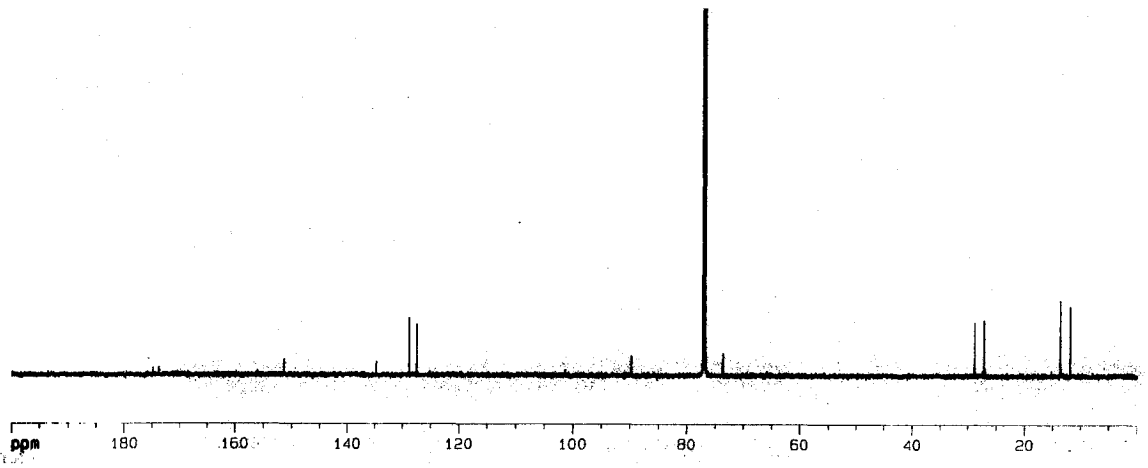


4.73

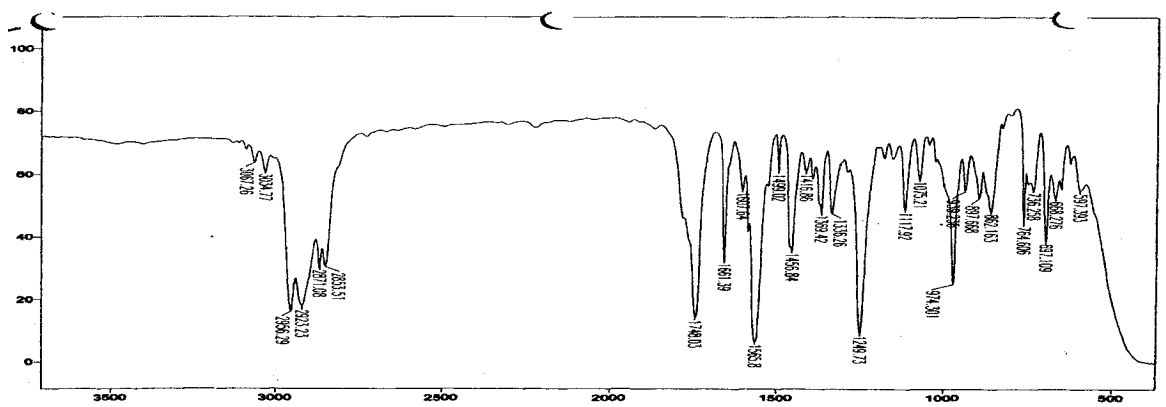
^{1}H NMR ($CDCl_3$, 500 MHz)

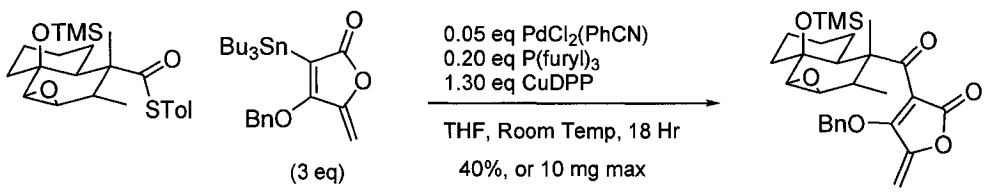


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.71 **4.73** **4.50**

4-Benzyloxy-3-(2,3-dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5-methylene-5H-furan-2-one (4.50). A clean flame-dried flask under Ar was charged with tri-2-furylphosphine (2.2 mg, 0.2 equiv.), Dichloro(benzonitrile)Palladium(II) (1.0 mg, 0.05 equiv.), and Copper (I) Diphenylphosphinate (CuDPP, 17mg, 1.3 equiv.). A solution of the thioester **4.71** (20.0 mg, 48 mmol, 1 equiv.) and the stannane **4.73** (119 mg, 5 equiv.) in dry degassed THF (2.0 mL) was added. The yellow reaction was allowed to stir overnight at room temperature. In the morning, the black-brown mixture was diluted with ether (5 mL), filtered through a plug of celite, and washed with $NH_4Cl_{(aq)}/NH_4OH$ solution (1:1, 2 x 10 mL). After drying over $MgSO_4$ and concentrating, the residue was subjected to flash chromatography (0 to 8% Et_2O in Hexanes) to give the product as a colourless foam (10.6 mg, 40%). Note that this compound has identical spectral properties to that prepared via alkylation-oxidation.

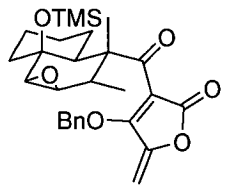
Data for **4.50**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.43-7.30 (m, 5H), 5.34 (d, J = 11.2 Hz, 1H), 5.13 (d, J = 2.7 Hz, 1H), 5.10 (d, J = 2.7 Hz, 1H), 4.69 (d, J = 11.2 Hz, 1H), 3.20 (dq, J = 1.6, 7.3 Hz, 1H), 3.14 (dd, J = 1.6, 3.8 Hz), 2.91 (d, J = 3.8 Hz), 1.82-1.55 (m, 7H), 1.45 (s, 3H), 1.42-1.32 (m, 2H), 0.90 (d, J = 7.3 Hz), 0.17 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 204.6 (C_4), 116.2 (C_4), 165.1 (C_4), 149.2 (C_4), 134.3 (C_4), 129.1 (2 x CH), 128.8 (CH), 127.8 (2 x CH), 108.8 (C_4), 94.2 (CH_2), 77.4 (CH_2), 72.4 (C_4), 60.5 (CH), 57.8 (CH), 53.8 (C_4), 43.8 (CH), 40.5 (CH_2), 33.7 (CH), 26.6 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 19.6 (CH_3), 15.5 (CH_3), 2.18 (3 x CH_3)

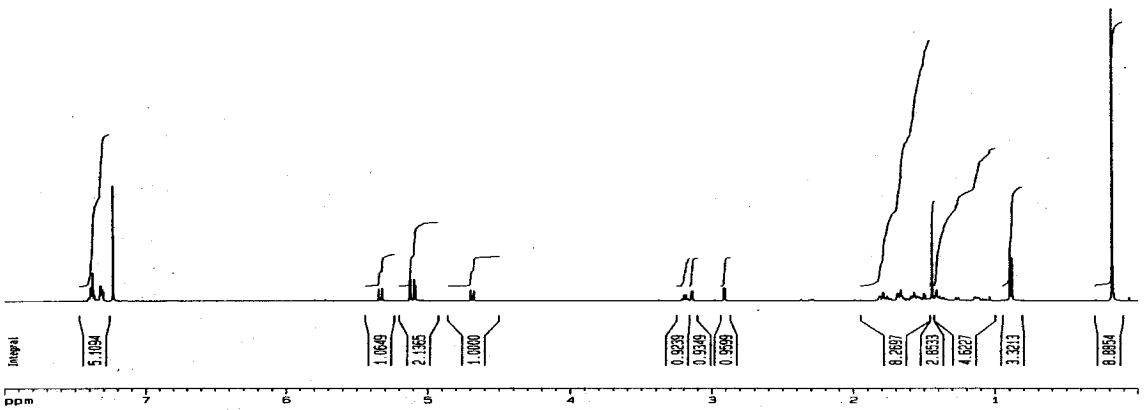
IR (FTIR, neat) υ = 3372 (br, m), 2940 (s), 1772 (s), 1661 (m), 1578 (s), 1290 (s), 1025 (m), 838 (m) cm^{-1}

HRMS (EI) Expected for $C_{21}H_{29}O_6Si$ [$(M - CH_2Ph)^+$]: 405.1733, found: 405.1647 (0.9%)

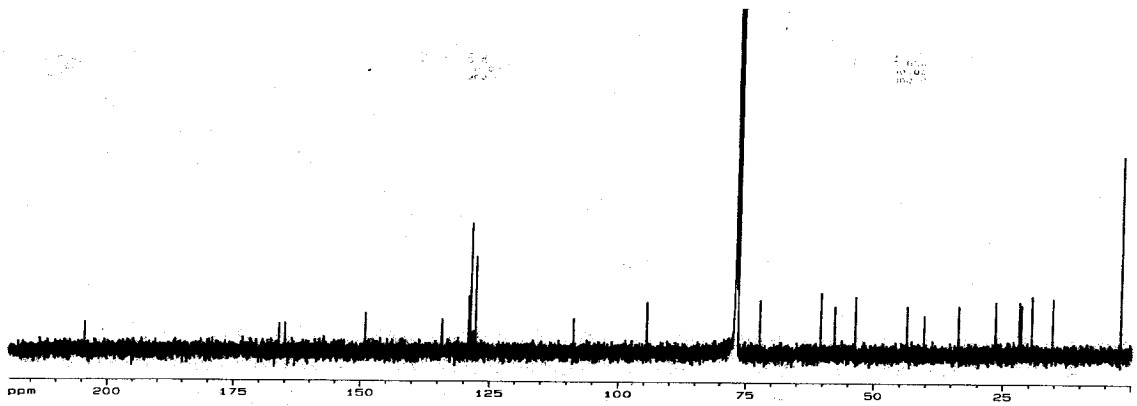


4.50

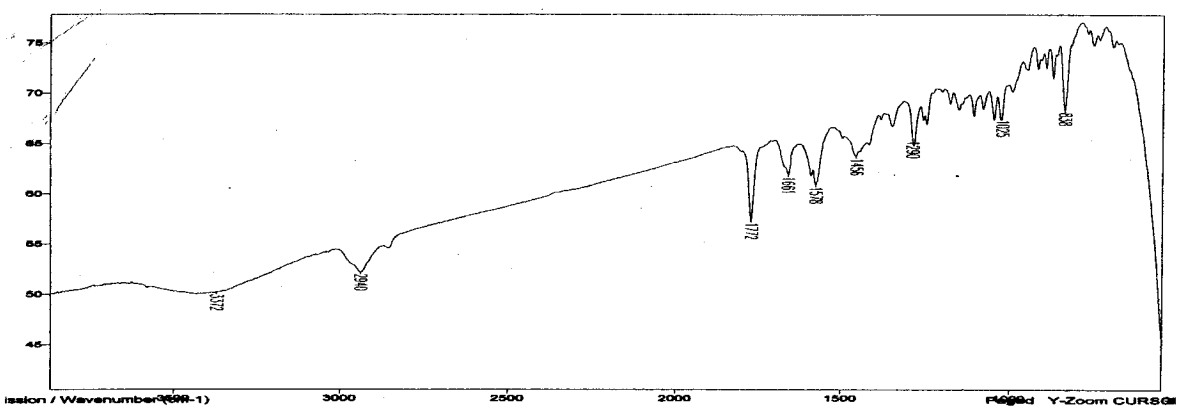
^{1}H NMR ($CDCl_3$, 500 MHz)

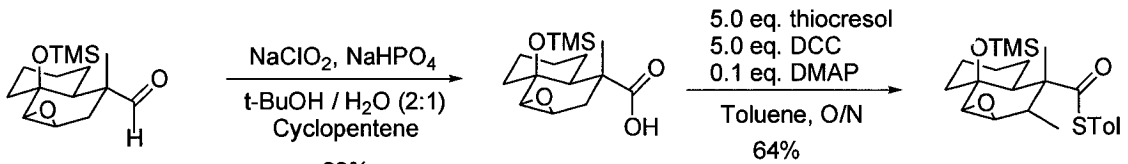


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)





4.10 **4.74-acid** **4.74**

3-Methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carboxylic acid (4.74). See procedure for **4.61** and **4.71**, above.

Data for **4.74**-acid:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 3.35-3.30 (m, 1H), 2.94 (d, J = 3.7 Hz, 1H), 2.25 (dd, J = 15.3, 2.4 Hz, 1H), 2.12 (dd, J = 15.3, 1.4 Hz, 1H), 1.82-1.63 (m, 4H), 1.58-1.39 (m, 3H), 1.29-1.20 (m, 3H), 1.16 (s, 3H), 0.17 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 184.4 (C=O), 71.7 (C_4), 58.1 (CH), 54.1 (CH), 48.7 (CH), 45.3 (C_4), 40.2 (CH_2), 34.9 (CH_2), 26.5 (CH_2), 22.8 (CH_2), 21.6 (CH_2), 17.8 (CH_2), 2.1 (3 x CH_3)

FTIR (neat, cm^{-1}) υ = 3000 (v. br), 2927 (s), 1693 (s), 1256 (s), 1246 (s), 1181 (m), 838 (s)

HRMS (EI) Expected for $C_{15}H_{26}O_4Si$ [$(M)^+$]: 298.16004, found: 298.16024 (6.6%).

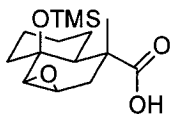
Data for **4.74**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 7.22-7.18 (m, 4H), 3.35-3.33 (m, 1H), 2.94 (d, J = 3.8 Hz, 1H), 2.35 (s, 3H), 2.18 (dd, J = 15.5, 2.5 Hz, 1H), 1.52 (dd, J = 15.5, 1.4 Hz, 1H), 1.85-1.64 (m, 5H), 1.58-1.42 (m, 4H), 1.42 (s, 3H), 0.18 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 207.0 (C=O), 139.4 (C_4), 134.8 (2 x CH), 129.9 (2 x CH), 124.7 (C_4), 72.2 (C_4), 58.1 (CH), 54.4 (CH), 52.8 (C_4), 49.9 (CH), 40.2 (CH_2), 36.0 (CH_2), 26.4 (CH_2), 22.3 (CH_2), 21.6 (CH_2), 21.3 (CH_3), 18.1 (CH_3), 2.129 (3 x CH_3)

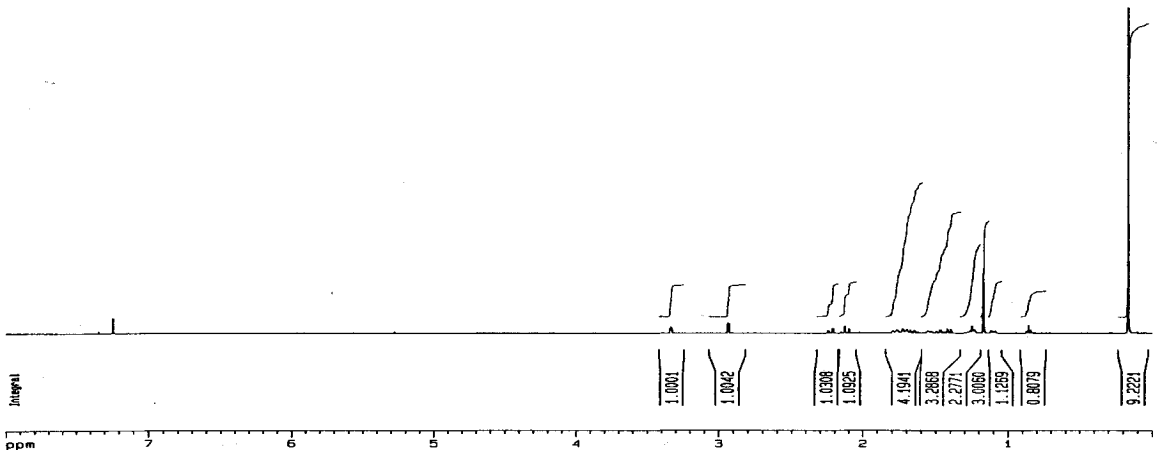
FTIR (neat, cm^{-1}) υ = 2935 (s), 2857 (m), 1687 (s), 1493 (m), 1444 (m), 1257 (s), 1247 (s), 1094 (s), 1040 (s), 837 (s)

HRMS (EI) Expected for $C_{22}H_{32}O_3S$ [$(M)^+$]: 404.18414, found: 404.1825 (1.0%).

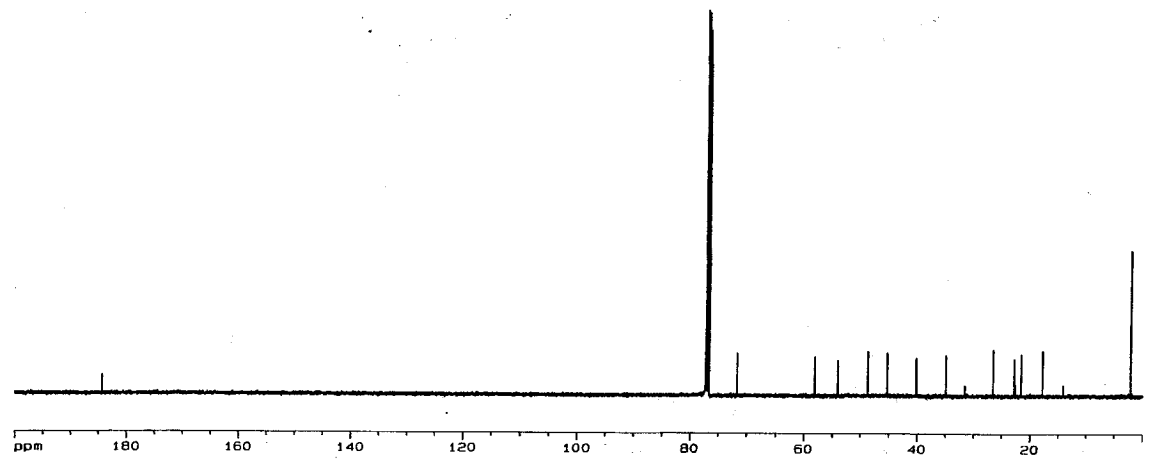


4.74-acid

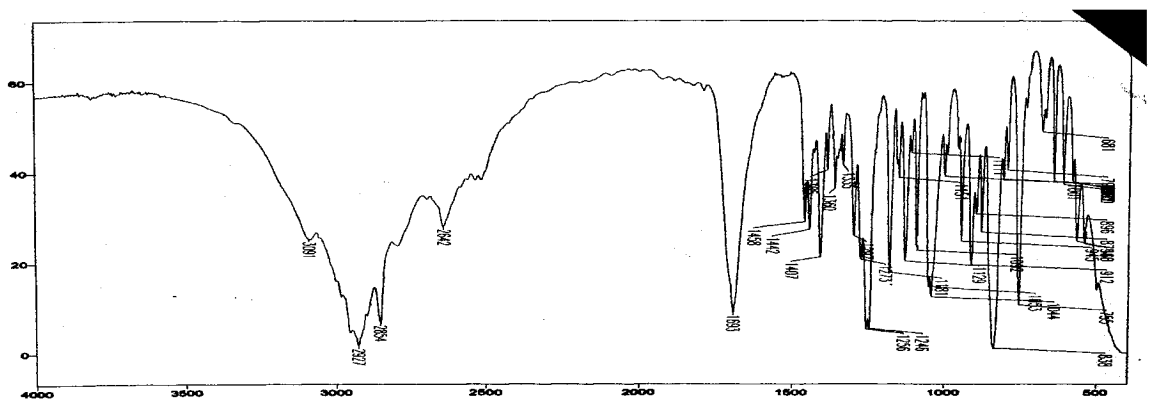
^{1}H NMR ($CDCl_3$, 500 MHz)

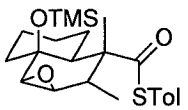


^{13}C NMR ($CDCl_3$, 125 MHz)



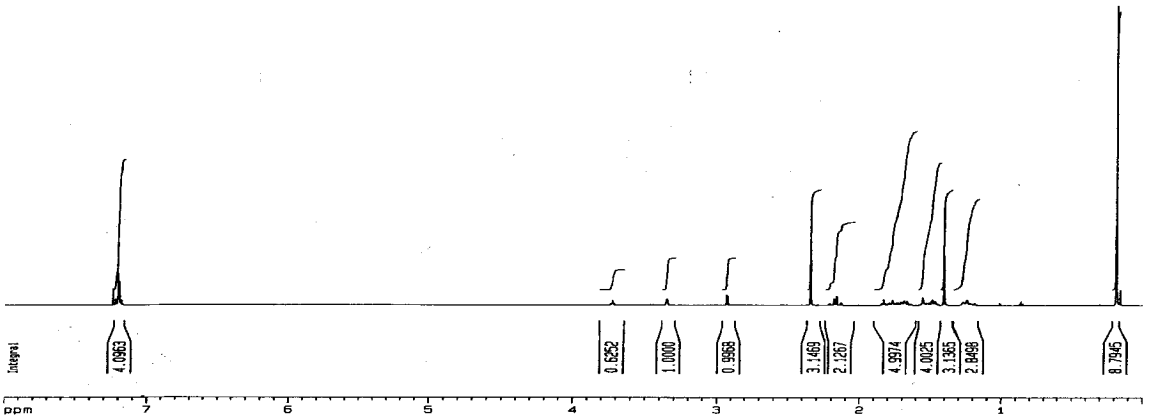
FTIR (neat)



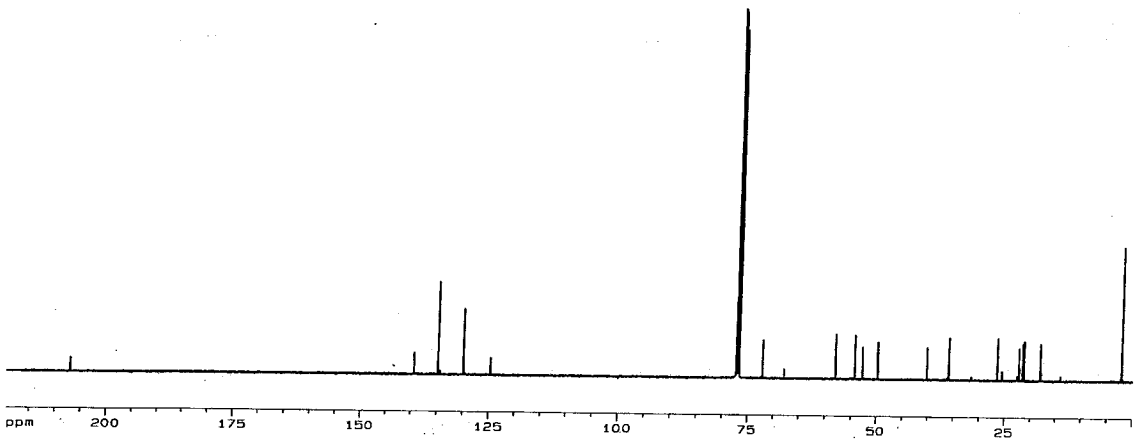


4.74

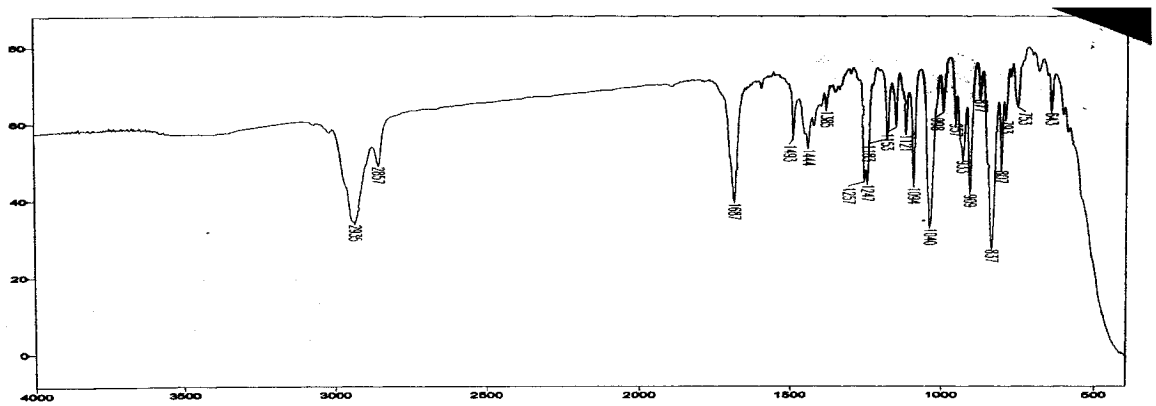
^{1}H NMR ($CDCl_3$, 500 MHz)

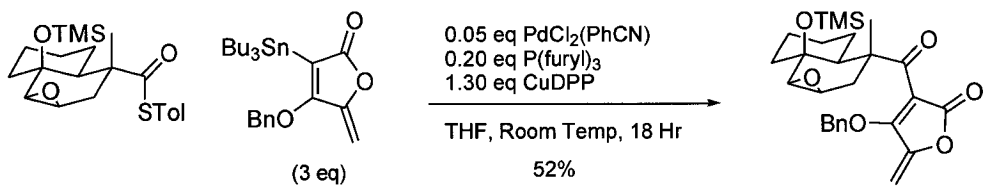


^{13}C NMR ($CDCl_3$, 125 MHz)



FTIR (neat)



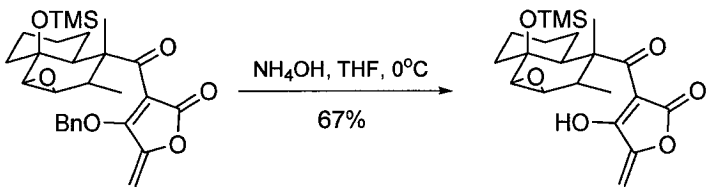


4.74 **4.73** **4.11**

4-Benzyloxy-5-methylene-3-(3-methyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa[a]naphthalene-3-carbonyl)-5H-furan-2-one (4.11). A clean, dry 50 mL roundbottom flask was flame-dried and refilled with argon. The flask was charged with trifuryl phosphine (2.4 mg, 0.20 equiv.), CuDPP (110 mg, 2 equiv.), and dichloro(bis)benzonitrile palladium (II) (1.0 mg, 0.05 equiv.). The flask was fitted with a balloon, and a THF (5 mL) solution of the thioester **4.74** (70 mg, 173 umol) and stannane **4.73** (254 mg , 3 equiv.) were added, dropwise. The reaction was allowed to stir overnight (18 hr) at room temperature. In the morning, the mixture was diluted with ether (10 mL), filtered through celite, and concentrated. The residue was subjected to flash chromatography (0 to 20% EtOAc in Hexanes) to give **4.11** as a yellow solid (43mg, 52%).

Data for **4.11**:

As above



4.50 **4.51**

3-(2,3-Dimethyl-7a-trimethylsilanyloxy-decahydro-1-oxa-cyclopropa [a] naphthalene-3-carbonyl)-4-hydroxy-5-methylene-5H-furan-2-one (4.51). A solution of **4.51** (5.0 mg, 12.1 umol) in undistilled THF (2.0 mL) under air was stirred at 0°C, and 2 drops of saturated ammonium hydroxide (~100 uL) was added. After stirring for 30 minutes, the reaction mixture was diluted with ether (3 mL) and water (0.5 mL). The organic layer was extracted once, dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (40% EtOAc in Hexanes) to give **4.51** as a white film (3.2 mg, 67%).

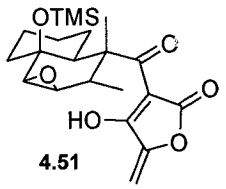
Data for **4.51**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} = 5.20 (d, J = 4.0 Hz, 1H), 4.97 (d, J = 4.0 Hz, 1H), 3.28 (br s, 1H), 3.10 (dd, J = 3.7, 1.6 Hz, 1H), 2.89 (d, J = 3.7 Hz, 1H), 1.80-1.45 (m, 10H + grease), 1.42 (s, 3H), 0.78 (d, 7.4 Hz, 1H), 0.18 (s, 9H)

^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm} = 203.6 (C_4), 165.3 (C_4), 163.1 (C_4), 154.7 (C_4), 148.4 (C_4), 97.7 (C_4), 92.1 (CH_2), 72.5 (C_4), 60.6 (CH), 57.7 (CH), 51.7 (C_4), 43.5 (CH), 40.7 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 22.5 (CH_2), 22.0 (CH_2), 14.9 (CH_3), 13.6 (CH_3), 2.2 (3 x CH_3)

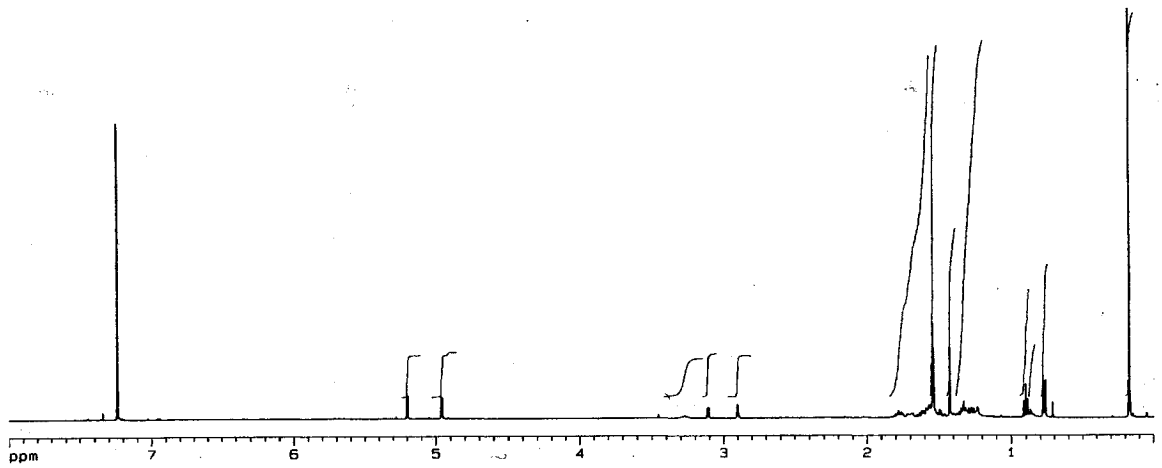
FTIR (neat, cm^{-1}) υ = 3370 (s), 3265 (s), 3209 (s), 2931 (s), 1731 (s), 1633 (s), 1618 (s), 1462 (s), 1258 (s), 1242 (s), 1080 (s), 840 (s)

MS (EI, m/z) = 435, 393, 354, 322, 269, 251, 210, 149, 91, 57

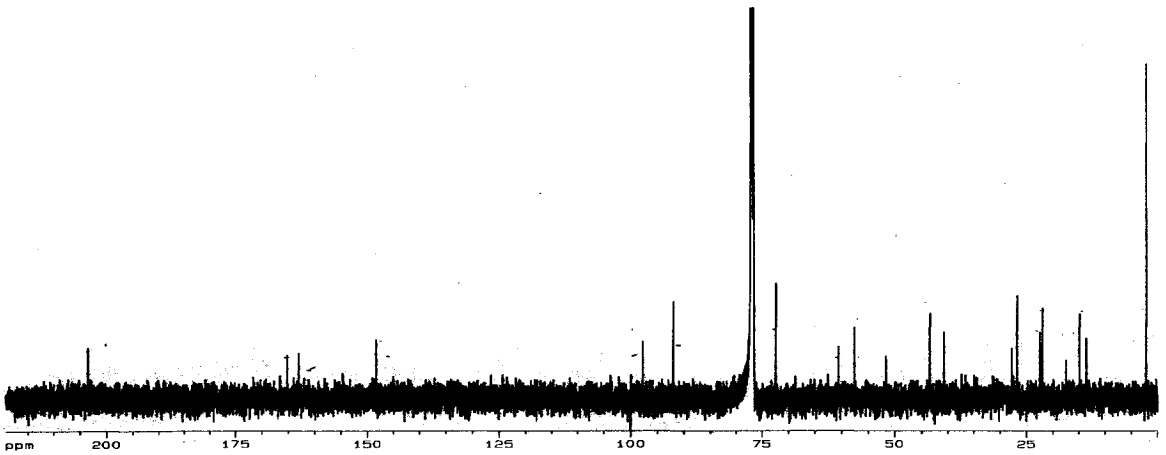


4.51

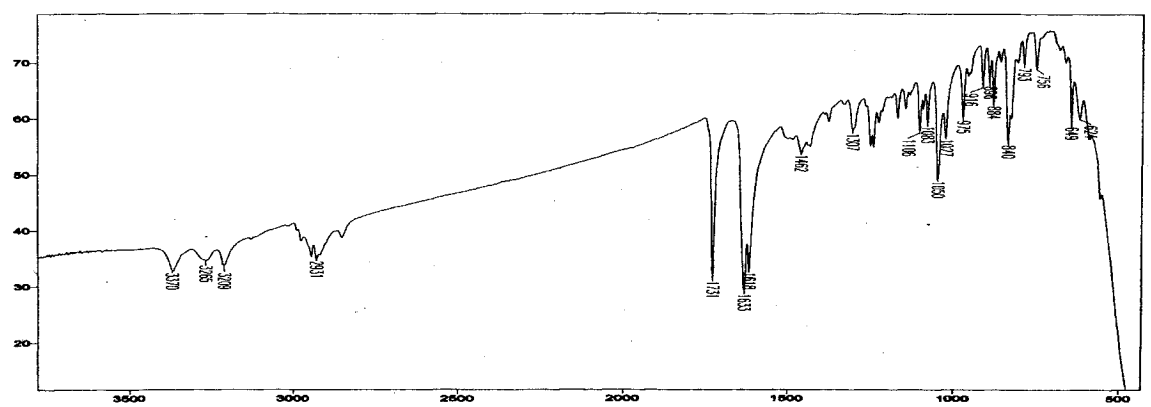
^{1}H NMR ($CDCl_3$, 500 MHz)



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



FTIR (neat)



X-ray Data

2.16

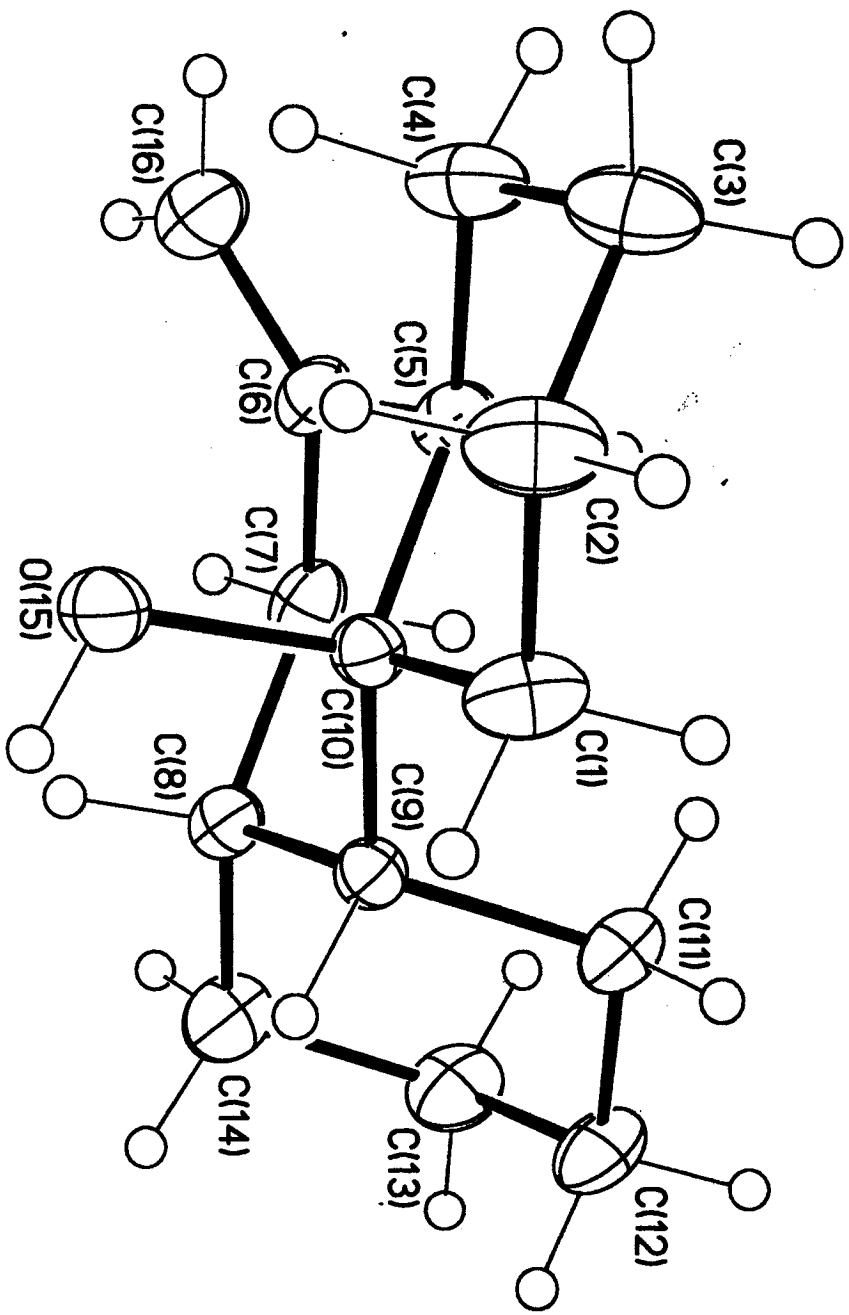


Table 6.1 - Crystal data and structure refinement for ***2.16***

Identification code	lb001
Empirical formula	C15 H24 O
Formula weight	220.34
Temperature	237(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.543(3) A alpha = 68.37(3) deg. b = 9.692(2) A beta = 80.53(4) deg. c = 11.306(6) A gamma = 76.26(4) deg.
Volume	645.1(5) A^3
Z, Calculated density	2, 1.134 Mg/m^3
Absorption coefficient	0.068 mm^-1
F(000)	244
Crystal size	0.3 x 0.1 x 0.1 mm
Theta range for data collection	2.45 to 20.82 deg.
Limiting indices	-6<=h<=6, -8<=k<=9, 0<=l<=10
Reflections collected / unique	1726 / 1048 [R(int) = 0.0521]
Completeness to theta = 20.82	77.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1048 / 0 / 146
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0532, wR2 = 0.1699
R indices (all data)	R1 = 0.0656, wR2 = 0.1904
Extinction coefficient	0.16(3)
Largest diff. peak and hole	0.177 and -0.235 e.A^-3

Table 6.2 - Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for ***2.16***

	x	y	z	U(eq)
C(1)	3994(6)	3410(4)	6543(5)	48(1)
C(2)	4396(7)	1694(5)	6898(7)	54(2)
C(3)	3951(7)	942(5)	8312(6)	53(2)
C(4)	1697(7)	1568(4)	8762(5)	50(1)
C(5)	1224(6)	3306(4)	8397(6)	35(2)
C(6)	-1000(6)	3997(4)	8798(4)	38(1)
C(7)	-1442(6)	5709(5)	8415(6)	42(2)
C(8)	-912(6)	6516(4)	6987(6)	35(1)
C(9)	1375(5)	5848(4)	6607(4)	30(1)
C(10)	1752(5)	4100(4)	6963(5)	30(1)
C(11)	2971(6)	6357(4)	7144(5)	40(1)
C(12)	2537(6)	8083(4)	6721(5)	49(1)
C(13)	270(6)	8746(4)	7123(5)	51(2)
C(14)	-1315(6)	8239(4)	6608(5)	49(1)
O(15)	277(4)	3813(3)	6283(3)	46(1)
C(16)	-2486(7)	3226(5)	9363(4)	53(2)

Table 6.3 - Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for ***2.16***

	x	y	z	U(eq)
H(1A)	4244	3869	5615	57
H(1B)	5013	3668	6935	57
H(2A)	3489	1429	6439	64
H(2B)	5869	1329	6642	64
H(3A)	4965	1115	8767	64
H(3B)	4127	-151	8514	64
H(4A)	1486	1105	9692	60
H(4B)	691	1278	8386	60
H(5A)	2193	3545	8849	42
H(7A)	-614	5991	8907	50
H(7B)	-2939	6057	8636	50
H(8A)	-1851	6278	6515	42
H(9A)	1591	6281	5665	36
H(11A)	2849	5924	8079	48
H(11B)	4411	5992	6834	48
H(12A)	2788	8501	5790	59
H(12B)	3530	8391	7092	59
H(13A)	51	8412	8057	61
H(13B)	54	9853	6796	61
H(14A)	-1228	8697	5675	59
H(14B)	-2745	8595	6939	59
H(15A)	119	4506	5584	69
H(16C)	-3853	3729	9539	64
H(16A)	-2190	2167	9595	64

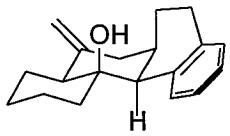
Table 6.4 - Bond lengths (Å) and angles (deg.) for ***2.16***

C(1)-C(2)	1.526(5)
C(1)-C(10)	1.537(5)
C(2)-C(3)	1.503(7)
C(3)-C(4)	1.535(6)
C(4)-C(5)	1.545(5)
C(5)-C(6)	1.521(5)
C(5)-C(10)	1.537(6)
C(6)-C(16)	1.304(6)
C(6)-C(7)	1.519(5)
C(7)-C(8)	1.534(6)
C(8)-C(14)	1.531(5)
C(8)-C(9)	1.542(5)
C(9)-C(11)	1.542(5)
C(9)-C(10)	1.557(5)
C(10)-O(15)	1.459(4)
C(11)-C(12)	1.528(5)
C(12)-C(13)	1.536(5)
C(13)-C(14)	1.520(5)
C(2)-C(1)-C(10)	114.0(3)
C(3)-C(2)-C(1)	110.6(4)
C(2)-C(3)-C(4)	110.9(4)
C(3)-C(4)-C(5)	113.1(3)
C(6)-C(5)-C(10)	109.8(3)
C(6)-C(5)-C(4)	115.6(3)
C(10)-C(5)-C(4)	111.6(3)
C(16)-C(6)-C(7)	120.9(4)
C(16)-C(6)-C(5)	124.2(4)
C(7)-C(6)-C(5)	114.8(3)
C(6)-C(7)-C(8)	113.2(3)
C(14)-C(8)-C(7)	113.1(3)
C(14)-C(8)-C(9)	112.6(3)
C(7)-C(8)-C(9)	109.0(3)
C(11)-C(9)-C(8)	111.0(3)
C(11)-C(9)-C(10)	113.0(3)
C(8)-C(9)-C(10)	112.2(3)
O(15)-C(10)-C(5)	107.2(3)
O(15)-C(10)-C(1)	107.7(3)
C(5)-C(10)-C(1)	110.4(3)
O(15)-C(10)-C(9)	106.3(3)
C(5)-C(10)-C(9)	111.6(3)
C(1)-C(10)-C(9)	113.3(3)
C(12)-C(11)-C(9)	109.8(3)
C(11)-C(12)-C(13)	112.8(3)
C(14)-C(13)-C(12)	110.5(3)
C(13)-C(14)-C(8)	111.7(3)

Symmetry transformations used to generate equivalent atoms:

Table 6.5– Anisotropic displacement parameters (A^2 x 10^3) for ***2.16***

	U11	U22	U33	U23	U13	U12
C(1)	53(3)	38(2)	48(4)	-14(2)	14(2)	-14(2)
C(2)	68(3)	35(3)	51(6)	-17(3)	13(3)	-8(2)
C(3)	78(3)	27(2)	48(6)	-10(3)	1(3)	-6(2)
C(4)	76(3)	36(2)	35(4)	-7(2)	5(2)	-22(2)
C(5)	42(2)	39(2)	28(5)	-14(3)	2(2)	-18(2)
C(6)	39(2)	47(3)	34(4)	-17(2)	1(2)	-21(2)
C(7)	30(2)	53(3)	48(6)	-24(3)	3(2)	-13(2)
C(8)	33(2)	34(2)	38(5)	-10(3)	-2(2)	-11(2)
C(9)	34(2)	35(2)	24(4)	-10(2)	-1(2)	-12(2)
C(10)	37(2)	30(2)	24(5)	-8(3)	-4(2)	-11(2)
C(11)	35(2)	39(2)	51(4)	-18(2)	1(2)	-14(2)
C(12)	50(3)	40(2)	66(4)	-21(3)	-1(2)	-22(2)
C(13)	57(3)	32(2)	66(4)	-21(2)	-3(2)	-9(2)
C(14)	40(2)	39(2)	65(5)	-18(2)	-2(2)	-5(2)
O(15)	73(2)	43(2)	29(3)	-8(2)	-12(2)	-27(1)
C(16)	50(3)	54(3)	57(5)	-17(3)	-1(3)	-19(2)


OH
H

2.27

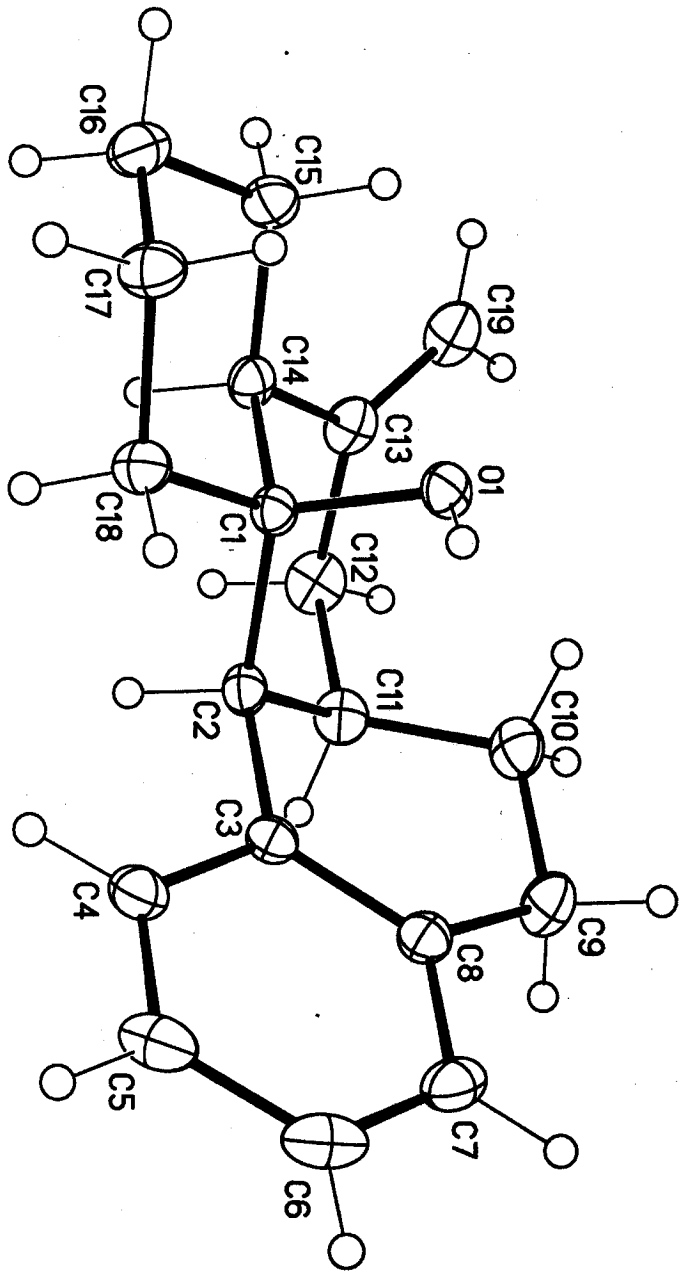

C16
C15
C17
C19
C14
C13
O1
C18
C1
C12
C11
C10
C2
C3
C4
C8
C9
C5
C7
C6

Table 6.6 – Crystal data and structure refinement for **2.27**

Identification code	lb003
Empirical formula	C19 H24 O
Formula weight	268.38
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 11.2989(12) A alpha = 90 deg. b = 14.9499(15) A beta = 98.083(2) de c = 17.7862(18) A gamma = 90 deg.
Volume	2974.6(5) A^3
Z, Calculated density	8, 1.199 Mg/m^3
Absorption coefficient	0.072 mm^-1
F(000)	1168
Crystal size	0.4 x 0.3 x 0.1 mm
Theta range for data collection	1.79 to 28.81 deg.
Limiting indices	-15<=h<=14, 0<=k<=20, 0<=l<=22
Reflections collected / unique	23323 / 7150 [R(int) = 0.0555]
Completeness to theta = 28.81	91.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7150 / 0 / 363
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1131
R indices (all data)	R1 = 0.0621, wR2 = 0.1186
Largest diff. peak and hole	0.237 and -0.243 e.A^-3

Table 6.7 – Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2 x 10^3) for 2.27

	x	y	z	U(eq)
O(1)	5553(1)	2445(1)	1912(1)	30(1)
O(2)	7718(1)	1681(1)	1368(1)	29(1)
C(1)	4414(1)	2229(1)	1496(1)	25(1)
C(2)	4228(1)	2671(1)	690(1)	27(1)
C(3)	5155(1)	2377(1)	201(1)	27(1)
C(4)	5034(1)	1553(1)	-175(1)	35(1)
C(5)	5881(1)	1245(1)	-601(1)	42(1)
C(6)	6875(1)	1763(1)	-667(1)	44(1)
C(7)	6990(1)	2593(1)	-327(1)	39(1)
C(8)	6133(1)	2919(1)	104(1)	31(1)
C(9)	6254(1)	3865(1)	403(1)	43(1)
C(10)	5381(1)	4119(1)	948(1)	38(1)
C(11)	4154(1)	3701(1)	708(1)	33(1)
C(12)	3229(1)	4014(1)	1206(1)	42(1)
C(13)	3462(1)	3609(1)	1984(1)	34(1)
C(14)	3468(1)	2599(1)	1970(1)	29(1)
C(15)	3572(1)	2156(1)	2748(1)	35(1)
C(16)	3408(1)	1150(1)	2673(1)	38(1)
C(17)	4320(1)	753(1)	2216(1)	36(1)
C(18)	4273(1)	1207(1)	1443(1)	31(1)
C(19)	3638(1)	4093(1)	2614(1)	45(1)
C(20)	8778(1)	1139(1)	1529(1)	25(1)
C(21)	9934(1)	1733(1)	1642(1)	27(1)
C(22)	10082(1)	2305(1)	955(1)	28(1)
C(23)	10522(1)	1932(1)	325(1)	36(1)
C(24)	10654(1)	2430(1)	-312(1)	44(1)
C(25)	10346(1)	3328(1)	-338(1)	46(1)
C(26)	9951(1)	3713(1)	285(1)	42(1)
C(27)	9831(1)	3223(1)	939(1)	33(1)
C(28)	9558(1)	3723(1)	1629(1)	43(1)
C(29)	9258(1)	3132(1)	2271(1)	37(1)
C(30)	10067(1)	2311(1)	2365(1)	33(1)
C(31)	9878(1)	1765(1)	3068(1)	37(1)
C(32)	8718(1)	1258(1)	2937(1)	32(1)
C(33)	8661(1)	626(1)	2273(1)	29(1)
C(34)	7602(1)	-19(1)	2176(1)	36(1)
C(35)	7701(1)	-686(1)	1540(1)	41(1)
C(36)	7758(1)	-189(1)	802(1)	35(1)
C(37)	8806(1)	464(1)	880(1)	30(1)
C(38)	7861(1)	1372(1)	3360(1)	47(1)

U(equiv.) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 6.8 – Bond lengths (Å) and angles (deg.) for **2.27**

O(1)-C(1)	1.4290(13)
O(2)-C(20)	1.4410(12)
C(1)-C(18)	1.5366(15)
C(1)-C(14)	1.5528(15)
C(1)-C(2)	1.5651(15)
C(2)-C(3)	1.5180(16)
C(2)-C(11)	1.5421(16)
C(3)-C(4)	1.3986(16)
C(3)-C(8)	1.4013(16)
C(4)-C(5)	1.3803(18)
C(5)-C(6)	1.382(2)
C(6)-C(7)	1.380(2)
C(7)-C(8)	1.4026(17)
C(8)-C(9)	1.5100(18)
C(9)-C(10)	1.5251(19)
C(10)-C(11)	1.5258(17)
C(11)-C(12)	1.5352(18)
C(12)-C(13)	1.4999(19)
C(13)-C(19)	1.3247(18)
C(13)-C(14)	1.5096(16)
C(14)-C(15)	1.5240(16)
C(15)-C(16)	1.5189(18)
C(16)-C(17)	1.5204(17)
C(17)-C(18)	1.5274(16)
C(20)-C(37)	1.5378(16)
C(20)-C(33)	1.5505(15)
C(20)-C(21)	1.5684(15)
C(21)-C(22)	1.5193(16)
C(21)-C(30)	1.5382(16)
C(22)-C(27)	1.4006(17)
C(22)-C(23)	1.4037(16)
C(23)-C(24)	1.3809(18)
C(24)-C(25)	1.385(2)
C(25)-C(26)	1.378(2)
C(26)-C(27)	1.3973(17)
C(27)-C(28)	1.5070(17)
C(28)-C(29)	1.5196(18)
C(29)-C(30)	1.5246(18)
C(30)-C(31)	1.5330(17)
C(31)-C(32)	1.5029(17)
C(32)-C(38)	1.3196(17)
C(32)-C(33)	1.5069(17)
C(33)-C(34)	1.5281(16)
C(34)-C(35)	1.5237(18)
C(35)-C(36)	1.5176(18)
C(36)-C(37)	1.5254(16)

O(1)-C(1)-C(18)	109.56(9)
O(1)-C(1)-C(14)	106.09(9)
C(18)-C(1)-C(14)	108.36(9)
O(1)-C(1)-C(2)	111.89(8)
C(18)-C(1)-C(2)	111.35(9)
C(14)-C(1)-C(2)	109.39(9)
C(3)-C(2)-C(11)	110.18(9)
C(3)-C(2)-C(1)	112.83(9)
C(11)-C(2)-C(1)	113.80(9)
C(4)-C(3)-C(8)	118.42(11)
C(4)-C(3)-C(2)	120.05(10)
C(8)-C(3)-C(2)	121.53(10)
C(5)-C(4)-C(3)	121.82(12)
C(4)-C(5)-C(6)	119.66(13)
C(7)-C(6)-C(5)	119.55(12)
C(6)-C(7)-C(8)	121.51(12)
C(3)-C(8)-C(7)	118.91(12)
C(3)-C(8)-C(9)	122.12(11)
C(7)-C(8)-C(9)	118.84(11)
C(8)-C(9)-C(10)	115.05(10)
C(11)-C(10)-C(9)	111.30(11)
C(10)-C(11)-C(12)	112.26(11)
C(10)-C(11)-C(2)	111.44(10)
C(12)-C(11)-C(2)	111.11(10)
C(13)-C(12)-C(11)	111.31(10)
C(19)-C(13)-C(12)	122.98(12)
C(19)-C(13)-C(14)	124.12(12)
C(12)-C(13)-C(14)	112.90(11)
C(13)-C(14)-C(15)	114.76(10)
C(13)-C(14)-C(1)	111.79(9)
C(15)-C(14)-C(1)	111.51(9)
C(16)-C(15)-C(14)	111.00(10)
C(15)-C(16)-C(17)	110.43(10)
C(16)-C(17)-C(18)	111.64(10)
C(17)-C(18)-C(1)	113.30(10)
O(2)-C(20)-C(37)	108.91(9)
O(2)-C(20)-C(33)	106.23(8)
C(37)-C(20)-C(33)	109.20(9)
O(2)-C(20)-C(21)	111.18(9)
C(37)-C(20)-C(21)	111.31(9)
C(33)-C(20)-C(21)	109.88(9)
C(22)-C(21)-C(30)	110.28(10)
C(22)-C(21)-C(20)	113.52(9)
C(30)-C(21)-C(20)	113.99(9)
C(27)-C(22)-C(23)	117.71(11)
C(27)-C(22)-C(21)	121.59(10)
C(23)-C(22)-C(21)	120.65(11)
C(24)-C(23)-C(22)	122.17(12)
C(23)-C(24)-C(25)	119.64(13)
C(26)-C(25)-C(24)	119.07(13)
C(25)-C(26)-C(27)	122.00(13)
C(26)-C(27)-C(22)	119.28(12)
C(26)-C(27)-C(28)	118.23(11)
C(22)-C(27)-C(28)	122.19(11)
C(27)-C(28)-C(29)	114.62(11)
C(28)-C(29)-C(30)	110.88(10)
C(29)-C(30)-C(31)	111.52(10)
C(29)-C(30)-C(21)	111.99(10)
C(31)-C(30)-C(21)	111.96(10)
C(32)-C(31)-C(30)	111.11(10)
C(38)-C(32)-C(31)	122.71(12)
C(38)-C(32)-C(33)	125.06(12)
C(31)-C(32)-C(33)	112.23(10)
C(32)-C(33)-C(34)	115.55(10)
C(32)-C(33)-C(20)	111.01(10)
C(34)-C(33)-C(20)	112.03(9)
C(35)-C(34)-C(33)	111.03(10)
C(36)-C(35)-C(34)	109.76(11)
C(35)-C(36)-C(37)	111.15(10)
C(36)-C(37)-C(20)	113.01(9)

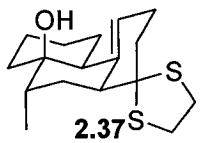
Symmetry transformations used to generate equivalent atoms:

Table 6.9 – Anisotropic displacement parameters (A^2 x 10^3) for **2.27**

	U11	U22	U33	U23	U13	U12
O(1)	21(1)	39(1)	30(1)	-3(1)	3(1)	2(1)
O(2)	25(1)	37(1)	26(1)	3(1)	3(1)	8(1)
C(1)	22(1)	27(1)	25(1)	-1(1)	3(1)	0(1)
C(2)	24(1)	27(1)	28(1)	0(1)	0(1)	-2(1)
C(3)	29(1)	30(1)	22(1)	4(1)	1(1)	0(1)
C(4)	43(1)	35(1)	25(1)	0(1)	4(1)	-3(1)
C(5)	62(1)	38(1)	28(1)	0(1)	10(1)	7(1)
C(6)	49(1)	55(1)	31(1)	9(1)	14(1)	16(1)
C(7)	32(1)	53(1)	31(1)	13(1)	7(1)	0(1)
C(8)	30(1)	36(1)	25(1)	7(1)	0(1)	-1(1)
C(9)	41(1)	38(1)	50(1)	2(1)	8(1)	-12(1)
C(10)	44(1)	26(1)	44(1)	-1(1)	4(1)	-5(1)
C(11)	34(1)	28(1)	36(1)	4(1)	2(1)	4(1)
C(12)	39(1)	32(1)	54(1)	3(1)	7(1)	11(1)
C(13)	26(1)	33(1)	46(1)	-3(1)	11(1)	4(1)
C(14)	22(1)	32(1)	32(1)	-3(1)	6(1)	0(1)
C(15)	31(1)	43(1)	31(1)	-2(1)	10(1)	0(1)
C(16)	37(1)	42(1)	36(1)	8(1)	9(1)	-2(1)
C(17)	45(1)	31(1)	34(1)	6(1)	9(1)	2(1)
C(18)	37(1)	27(1)	30(1)	0(1)	8(1)	1(1)
C(19)	42(1)	37(1)	60(1)	-12(1)	20(1)	-2(1)
C(20)	22(1)	30(1)	25(1)	1(1)	4(1)	5(1)
C(21)	23(1)	34(1)	26(1)	-2(1)	4(1)	3(1)
C(22)	23(1)	35(1)	28(1)	-3(1)	4(1)	-5(1)
C(23)	34(1)	42(1)	34(1)	-4(1)	11(1)	-4(1)
C(24)	43(1)	58(1)	33(1)	-5(1)	15(1)	-9(1)
C(25)	47(1)	55(1)	36(1)	8(1)	9(1)	-14(1)
C(26)	45(1)	36(1)	43(1)	3(1)	6(1)	-11(1)
C(27)	30(1)	35(1)	34(1)	-4(1)	4(1)	-7(1)
C(28)	53(1)	34(1)	42(1)	-8(1)	10(1)	-2(1)
C(29)	40(1)	39(1)	33(1)	-11(1)	7(1)	0(1)
C(30)	28(1)	42(1)	28(1)	-6(1)	2(1)	-3(1)
C(31)	36(1)	49(1)	25(1)	-3(1)	1(1)	2(1)
C(32)	32(1)	41(1)	24(1)	4(1)	2(1)	5(1)
C(33)	25(1)	36(1)	27(1)	3(1)	4(1)	4(1)
C(34)	33(1)	43(1)	33(1)	6(1)	8(1)	-3(1)
C(35)	42(1)	37(1)	43(1)	1(1)	8(1)	-8(1)
C(36)	36(1)	36(1)	34(1)	-6(1)	6(1)	-4(1)
C(37)	29(1)	33(1)	28(1)	-3(1)	7(1)	1(1)
C(38)	45(1)	65(1)	32(1)	-5(1)	11(1)	1(1)

Table 6.10 – Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **2.27**

	x	y	z	U(eq)
H(1)	6080	2147	1745	45
H(2)	7679	1892	934	44
H(2A)	3446	2457	432	32
H(4)	4358	1199	-136	41
H(5)	5783	687	-845	51
H(6)	7469	1550	-943	53
H(7)	7657	2949	-384	46
H(9A)	6141	4277	-30	52
H(9B)	7070	3948	663	52
H(10A)	5697	3917	1461	46
H(10B)	5301	4771	960	46
H(11)	3873	3903	184	40
H(12A)	3258	4668	1249	50
H(12B)	2427	3846	965	50
H(14)	2680	2418	1696	34
H(15A)	4359	2286	3033	41
H(15B)	2964	2403	3031	41
H(16A)	2599	1017	2421	45
H(16B)	3504	878	3179	45
H(17A)	4164	112	2141	44
H(17B)	5123	822	2500	44
H(18A)	3508	1066	1134	37
H(18B)	4911	962	1183	37
H(19A)	3619	4721	2584	54
H(19B)	3780	3809	3089	54
H(21)	10618	1313	1706	33
H(23)	10733	1324	337	43
H(24)	10951	2161	-725	52
H(25)	10407	3669	-775	55
H(26)	9755	4325	269	50
H(28A)	8883	4126	1476	51
H(28B)	10251	4093	1821	51
H(29A)	8422	2940	2163	45
H(29B)	9355	3474	2746	45
H(30)	10901	2531	2449	39
H(31A)	10541	1344	3189	44
H(31B)	9874	2168	3502	44
H(33)	9384	247	2375	35
H(34A)	7576	-343	2652	43
H(34B)	6857	320	2059	43
H(35A)	8423	-1050	1667	49
H(35B)	7007	-1086	1481	49
H(36A)	7011	140	658	42
H(36B)	7844	-620	398	42
H(37A)	8796	791	402	36
H(37B)	9555	124	970	36
H(38A)	7962	1784	3764	56
H(38B)	7149	1041	3259	56


OH
S
2.37
S

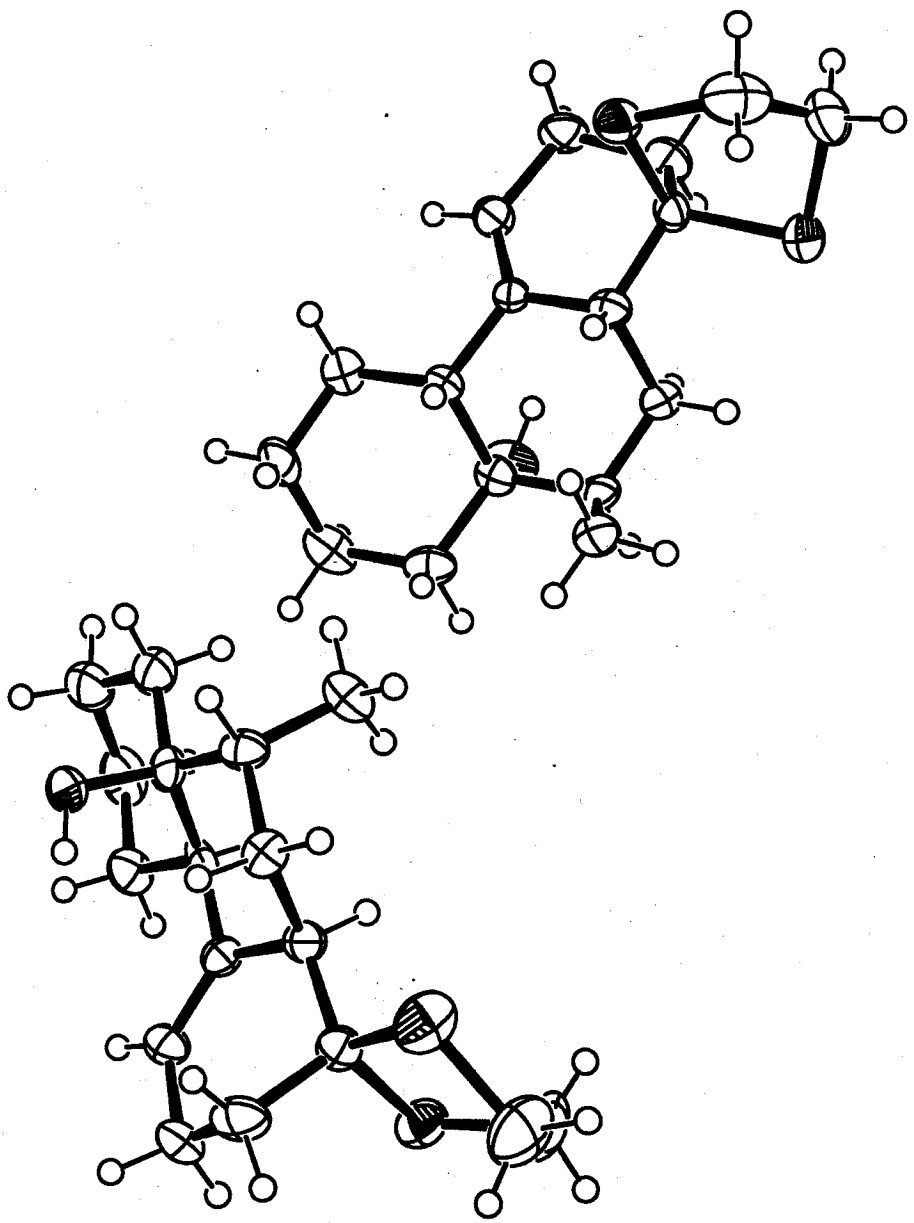


Table 6.11 - Atomic Coordinates and anisotropic displacement parameters for ***2.37***

			Coordinates			Uij					
Num	Label	SFAC									
1	C1	1	0.746	0.76	0.083	0.035	0.028	0.026	0.001	-0.016	-0.011
2	C2	1	0.621	0.877	0.071	0.035	0.039	0.034	0.005	-0.015	-0.011
3	C3	1	0.597	0.976	0.135	0.045	0.023	0.04	0.008	-0.015	-0.009
4	C4	1	0.598	0.929	0.235	0.035	0.027	0.029	-0.001	-0.009	-0.009
5	C5	1	0.648	0.815	0.26	0.026	0.027	0.021	0	-0.004	-0.015
6	C6	1	0.636	0.769	0.361	0.023	0.026	0.022	0.002	-0.007	-0.008
7	C7	1	0.589	0.661	0.437	0.03	0.032	0.036	-0.003	-0.012	-0.005
8	C8	1	0.586	0.605	0.536	0.054	0.035	0.025	-0.005	-0.012	-0.008
9	C9	1	0.484	0.74	0.567	0.037	0.045	0.032	0.002	-0.008	-0.003
10	C10	1	0.531	0.646	0.484	0.029	0.037	0.042	0.006	-0.006	-0.014
11	C11	1	0.538	0.596	0.392	0.021	0.033	0.03	0.004	-0.012	-0.009
12	C12	1	0.593	0.596	0.319	0.033	0.036	0.042	0.008	-0.015	-0.024
13	C13	1	0.606	0.649	0.217	0.037	0.032	0.033	0.003	-0.012	-0.019
14	C14	1	0.711	0.716	0.188	0.025	0.033	0.031	0.005	-0.01	-0.014
15	C15	1	0.737	0.469	0.32	0.052	0.031	0.037	0.002	-0.013	-0.018
16	C16	1	0.916	0.681	-0.096	0.064	0.052	0.031	-0.009	-0.007	-0.021
17	C17	1	1.024	0.69	-0.054	0.044	0.043	0.057	-0.001	0.007	-0.009
18	C18	1	0.934	0.059	0.732	0.031	0.027	0.037	0.002	-0.016	-0.006
19	C19	1	0.979	0.026	0.823	0.042	0.037	0.057	0.018	-0.028	-0.015
20	C20	1	0.85	0.087	0.91	0.062	0.046	0.035	0.015	-0.028	-0.026
21	C21	1	0.77	0.217	0.881	0.037	0.037	0.025	0.003	-0.005	-0.016
22	C22	1	0.783	0.266	0.803	0.026	0.031	0.03	0.002	-0.008	-0.017
23	C23	1	0.712	0.4	0.783	0.027	0.042	0.015	0	-0.009	-0.015
24	C24	1	0.599	0.477	0.869	0.033	0.037	0.028	-0.005	-0.003	-0.008
25	C25	1	0.53	0.606	0.839	0.048	0.045	0.038	-0.018	-0.006	-0.001
26	C26	1	0.646	0.658	0.789	0.072	0.04	0.045	0.006	-0.029	-0.018
27	C27	1	0.766	0.579	0.705	0.047	0.035	0.041	0	-0.019	-0.015
28	C28	1	0.832	0.448	0.732	0.036	0.034	0.035	0.002	-0.021	-0.017
29	C29	1	0.947	0.373	0.642	0.027	0.035	0.036	0.008	-0.01	-0.016
30	C30	1	1.009	0.239	0.667	0.024	0.032	0.037	-0.003	-0.006	-0.01
31	C31	1	0.883	0.194	0.713	0.029	0.031	0.032	0.004	-0.013	-0.014
32	C32	1	0.893	0.394	0.554	0.045	0.052	0.028	0.003	-0.01	-0.018
33	C33	1	1.031	-0.141	0.628	0.071	0.045	0.08	-0.021	-0.012	-0.014
34	C34	1	0.865	-0.086	0.646	0.099	0.078	0.085	-0.016	-0.016	-0.06
35	H1	2	0.388	0.818	0.349	0.059	0	0	0	0	0
36	H2	2	0.932	0.379	0.824	0.059	0	0	0	0	0
37	H2a	2	0.644	0.904	0.004	0.045	0	0	0	0	0
38	H2b	2	0.529	0.864	0.068	0.045	0	0	0	0	0
39	H3a	2	0.675	1.008	0.106	0.046	0	0	0	0	0
40	H3b	2	0.502	1.043	0.138	0.046	0	0	0	0	0
41	H4a	2	0.561	0.986	0.284	0.036	0	0	0	0	0
42	H6a	2	0.737	0.711	0.36	0.029	0	0	0	0	0
43	H7a	2	0.657	0.903	0.417	0.041	0	0	0	0	0
44	H7b	2	0.49	0.921	0.44	0.041	0	0	0	0	0
45	H8a	2	0.556	0.866	0.582	0.049	0	0	0	0	0
46	H8b	2	0.688	0.748	0.534	0.049	0	0	0	0	0
47	H9a	2	0.485	0.702	0.63	0.052	0	0	0	0	0
48	H9b	2	0.382	0.798	0.573	0.052	0	0	0	0	0
49	H10a	2	0.628	0.585	0.493	0.045	0	0	0	0	0
50	H10b	2	0.461	0.607	0.514	0.045	0	0	0	0	0
51	H12a	2	0.515	0.564	0.336	0.04	0	0	0	0	0
52	H13a	2	0.506	0.704	0.214	0.038	0	0	0	0	0
53	H13b	2	0.644	0.584	0.171	0.038	0	0	0	0	0
54	H14a	2	0.808	0.658	0.197	0.034	0	0	0	0	0
55	H15a	2	0.729	0.457	0.385	0.06	0	0	0	0	0
56	H15b	2	0.819	0.515	0.297	0.06	0	0	0	0	0
57	H15c	2	0.756	0.427	0.276	0.06	0	0	0	0	0
58	H16a	2	0.968	0.617	-0.144	0.061	0	0	0	0	0
59	H16b	2	0.869	0.757	-0.126	0.061	0	0	0	0	0
60	H17a	2	1.069	0.725	-0.102	0.069	0	0	0	0	0
61	H17b	2	1.085	0.61	-0.035	0.069	0	0	0	0	0
62	H19a	2	1.015	-0.061	0.833	0.052	0	0	0	0	0
63	H19b	2	1.061	0.051	0.816	0.052	0	0	0	0	0
64	H20a	2	0.782	0.047	0.928	0.053	0	0	0	0	0
65	H20b	2	0.887	0.08	0.964	0.053	0	0	0	0	0
66	H21a	2	0.706	0.268	0.944	0.04	0	0	0	0	0
67	H23a	2	0.659	0.406	0.737	0.032	0	0	0	0	0
68	H24a	2	0.521	0.446	0.9	0.043	0	0	0	0	0
69	H24b	2	0.647	0.473	0.918	0.043	0	0	0	0	0
70	H25a	2	0.459	0.654	0.896	0.059	0	0	0	0	0
71	H25b	2	0.475	0.61	0.795	0.059	0	0	0	0	0
72	H26a	2	0.598	0.739	0.765	0.062	0	0	0	0	0
73	H26b	2	0.69	0.664	0.835	0.062	0	0	0	0	0
74	H27a	2	0.723	0.586	0.654	0.048	0	0	0	0	0
75	H27b	2	0.845	0.609	0.679	0.048	0	0	0	0	0
76	H29a	2	1.031	0.396	0.622	0.039	0	0	0	0	0
77	H30a	2	1.085	0.226	0.712	0.038	0	0	0	0	0
78	H30b	2	1.077	0.194	0.606	0.038	0	0	0	0	0
79	H31a	2	0.824	0.215	0.668	0.036	0	0	0	0	0
80	H32a	2	0.971	0.343	0.501	0.064	0	0	0	0	0
81	H32b	2	0.865	0.477	0.534	0.064	0	0	0	0	0
82	H32c	2	0.807	0.373	0.571	0.064	0	0	0	0	0
83	H33a	2	1.063	-0.183	0.587	0.063	0	0	0	0	0
84	H33b	2	1.058	-0.198	0.68	0.063	0	0	0	0	0
85	H34a	2	0.827	-0.149	0.658	0.067	0	0	0	0	0
86	H34b	2	0.843	-0.04	0.589	0.067	0	0	0	0	0
87	O1	3	0.389	0.774	0.398	0.022	0.041	0.044	0.0108	-0.0124	-0.005
88	O2	3	0.911	0.445	0.796	0.051	0.041	0.042	0.011	-0.031	-0.024
89	S1	4	0.781	0.646	0.002	0.0543	0.0424	0.0325	-0.0067	-0.0082	-0.023
90	S2	4	0.919	0.786	0.051	0.0377	0.0433	0.0357	0.0035	-0.0102	-0.022
91	S3	4	1.064	-0.021	0.626	0.0406	0.0399	0.0816	-0.012	-0.0043	-0.009
92	S4	4	0.781	0.011	0.749	0.041	0.0397	0.0523	0.0026	-0.0166	-0.021

Table 6.12 - Calculated bond lengths (Å) for ***2.37***

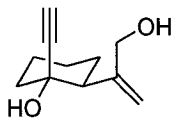
A	B	Dist
C(1)	C(2)	1.525
C(1)	C(14)	1.532
C(1)	S(1)	1.823
C(1)	S(2)	1.851
C(2)	H(2a)	0.979
C(2)	H(2b)	0.98
C(2)	C(1)	1.525
C(2)	C(3)	1.529
C(3)	H(3a)	0.98
C(3)	H(3b)	0.98
C(3)	C(4)	1.51
C(3)	C(2)	1.529
C(4)	H(4a)	0.94
C(4)	C(5)	1.319
C(4)	C(3)	1.51
C(5)	C(4)	1.319
C(5)	C(6)	1.498
C(5)	C(14)	1.51
C(6)	H(6a)	0.98
C(6)	C(5)	1.498
C(6)	C(7)	1.519
C(6)	C(11)	1.535
C(7)	H(7b)	0.98
C(7)	H(7a)	0.982
C(7)	C(8)	1.518
C(7)	C(6)	1.519
C(8)	H(8b)	0.98
C(8)	H(8a)	0.98
C(8)	C(9)	1.518
C(8)	C(7)	1.518
C(9)	H(9b)	0.98
C(9)	H(9a)	0.98
C(9)	C(8)	1.518
C(9)	C(10)	1.517
C(10)	H(10a)	0.98
C(10)	H(10b)	0.98
C(10)	C(9)	1.517
C(10)	C(11)	1.522
C(11)	O(1)	1.433
C(11)	C(10)	1.522
C(11)	C(6)	1.535
C(11)	C(12)	1.547
C(12)	H(12a)	0.98
C(12)	C(15)	1.531
C(12)	C(13)	1.533
C(12)	C(11)	1.547
C(13)	H(13b)	0.979
C(13)	H(13a)	0.98
C(13)	C(12)	1.533
C(13)	C(14)	1.544
C(14)	H(14a)	0.98
C(14)	C(5)	1.51
C(14)	C(1)	1.532
C(14)	C(13)	1.544
C(15)	H(15c)	0.969
C(15)	H(15a)	0.969
C(15)	H(15b)	0.97
C(15)	C(12)	1.531
C(16)	H(16b)	0.98
C(16)	H(16a)	0.98
C(16)	C(17)	1.508
C(16)	S(1)	1.787
C(17)	H(17b)	0.979
C(17)	H(17a)	0.98
C(17)	C(16)	1.508
C(17)	S(2)	1.808
C(18)	C(19)	1.528
C(18)	C(31)	1.528
C(18)	S(3)	1.833
C(18)	S(4)	1.857
C(19)	H(19a)	0.98
C(19)	H(19b)	0.98
C(19)	C(20)	1.511
C(19)	C(18)	1.528
C(20)	H(20b)	0.98
C(20)	H(20a)	0.98
C(20)	C(21)	1.485
C(20)	C(19)	1.511
C(21)	H(21a)	0.94
C(21)	C(22)	1.332
C(21)	C(20)	1.485
C(22)	C(21)	1.332
C(22)	C(31)	1.499
C(22)	C(23)	1.521
C(23)	H(23a)	0.99
C(23)	C(22)	1.521
C(23)	C(24)	1.527
C(23)	C(28)	1.528
C(24)	H(24a)	0.979
C(24)	H(24b)	0.98
C(24)	C(25)	1.508
C(24)	C(23)	1.527
C(25)	H(25b)	0.98
C(25)	H(25a)	0.98
C(25)	C(24)	1.508
C(25)	C(26)	1.52
C(26)	H(26a)	0.979
C(26)	H(26b)	0.979
C(26)	C(25)	1.52
C(26)	C(27)	1.525
C(27)	H(27b)	0.979
C(27)	H(27a)	0.98
C(27)	C(26)	1.525
C(27)	C(28)	1.525
C(28)	O(2)	1.441
C(28)	C(27)	1.525
C(28)	C(23)	1.528
C(28)	C(29)	1.544
C(29)	H(29a)	0.99
C(29)	C(30)	1.529
C(29)	C(32)	1.541
C(29)	C(28)	1.544
C(30)	H(30a)	0.98
C(30)	H(30b)	0.98
C(30)	C(29)	1.529
C(30)	C(31)	1.546
C(31)	H(31a)	0.982
C(31)	C(22)	1.499
C(31)	C(18)	1.528
C(31)	C(30)	1.546
C(32)	H(32b)	0.97
C(32)	H(32c)	0.97
C(32)	H(32a)	0.97
C(32)	C(29)	1.541
C(33)	H(33a)	0.98
C(33)	H(33b)	0.98
C(33)	C(34)	1.514
C(33)	S(3)	1.799
C(34)	H(34b)	0.98
C(34)	H(34a)	0.98
C(34)	C(33)	1.514
C(34)	S(4)	1.801
H(1)	O(1)	0.83
H(2)	O(2)	0.829
H(2a)	C(2)	0.979
H(2b)	C(2)	0.98
H(3a)	C(3)	0.98
H(3b)	C(3)	0.98
H(4a)	C(4)	0.94
H(6a)	C(6)	0.98
H(7a)	C(7)	0.982
H(7b)	C(7)	0.98
H(8a)	C(8)	0.98
H(8b)	C(8)	0.98
H(9a)	C(9)	0.98
H(9b)	C(9)	0.98
H(10a	) C(10)	0.98
H(10b	) C(10)	0.98
H(12a	) C(12)	0.98
H(13a	) C(13)	0.98
H(13b	) C(13)	0.979
H(14a	) C(14)	0.98
H(15a	) C(15)	0.969
H(15b	) C(15)	0.97
H(15c	) C(15)	0.969
H(16a	) C(16)	0.98
H(16b	) C(16)	0.98
H(17a	) C(17)	0.98
H(17b	) C(17)	0.979
H(19a	) C(19)	0.98
H(19b	) C(19)	0.98
H(20a	) C(20)	0.98
H(20b	) C(20)	0.98
H(21a	) C(21)	0.94
H(23a	) C(23)	0.99
H(24a	) C(24)	0.979
H(24b	) C(24)	0.98
H(25a	) C(25)	0.98
H(25b	) C(25)	0.98
H(26a	) C(26)	0.979
H(26b	) C(26)	0.979
H(27a	) C(27)	0.98
H(27b	) C(27)	0.979
H(29a	) C(29)	0.99
H(30a	) C(30)	0.98
H(30b	) C(30)	0.98
H(31a	) C(31)	0.982
H(32a	) C(32)	0.97
H(32b	) C(32)	0.97
H(32c	) C(32)	0.97
H(33a	) C(33)	0.98
H(33b	) C(33)	0.98
H(34a	) C(34)	0.98
H(34b	) C(34)	0.98
O(1)	H(1)	0.83
O(1)	C(11)	1.433
O(2)	H(2)	0.829
O(2)	C(28)	1.441
S(1)	C(16)	1.787
S(1)	C(1)	1.823
S(2)	C(17)	1.808
S(2)	C(1)	1.851
S(3)	C(33)	1.799
S(3)	C(18)	1.833
S(4)	C(34)	1.801
S(4)	C(18)	1.857

Table 6.13 Calculated bond angles (deg.) for ***2.37***

A	B	C	Angle
C2	C1	C14	110.66
C2	C1	S1	111.08
C2	C1	S2	108.32
C14	C1	S1	110.23
C14	C1	S2	108.89
S1	C1	S2	106.77
H2a	C2	H2b	106
H2a	C2	C1	109.4
H2a	C2	C3	109.42
H2b	C2	C1	109.33
H2b	C2	C3	109.43
C1	C2	C3	111.2
H3a	C3	H3b	106.03
H3a	C3	C4	108.42
H3a	C3	C2	109.34
H3b	C3	C4	109.41
H3b	C3	C2	109.37
C4	C3	C2	111.21
H4a	C4	C5	117.47
H4a	C4	C3	117.47
C5	C4	C3	125.09
C4	C5	C6	124.83
C4	C5	C14	122
C6	C5	C14	112.95
H6a	C6	C5	108.15
H6a	C6	C7	108.17
H6a	C6	C11	108.13
C5	C6	C7	116.25
C5	C6	C11	110.45
C7	C6	C11	110.97
H7b	C7	H7a	107.8
H7b	C7	C6	108.17
H7b	C7	C8	108.22
H7a	C7	C6	108.04
H7a	C7	C8	109.2
C6	C7	C8	112.31
H8b	C8	H8a	108.18
H8b	C8	C9	109.75
H8b	C8	C7	108.74
H8a	C8	C9	108.72
H8a	C8	C7	108.81
C9	C8	C7	109.61
H9b	C9	H9a	108.23
H9b	C9	C8	108.82
H9b	C9	C10	108.74
H9a	C9	C8	109.71
H9a	C9	C10	109.7
C8	C9	C10	109.82
H10a	C10	H10b	107.66
H10a	C10	C9	108.97
H10a	C10	C11	108.86
H10b	C10	C9	108.93
H10b	C10	C11	108.89
C9	C10	C11	113.35
O1	C11	C10	106.02
O1	C11	C6	110.12
O1	C11	C12	108.46
C10	C11	C6	110.56
C10	C11	C12	111.34
C6	C11	C12	111.13
H12a	C12	C15	106.64
H12a	C12	C13	108.67
H12a	C12	C11	108.6
C15	C12	C13	110.2
C15	C12	C11	110.03
C13	C12	C11	110.16
H13b	C13	H13a	106.09
H13b	C13	C12	109.47
H13b	C13	C14	109.41
H13a	C13	C12	109.42
H13a	C13	C14	109.4
C12	C13	C14	111
H14a	C14	C5	106.71
H14a	C14	C1	106.67
H14a	C14	C13	106.64
C5	C14	C1	112.86
C5	C14	C13	107.54
C1	C14	C13	115.87
H15c	C15	H15a	109.49
H15c	C15	H15b	109.49
H15c	C15	C12	109.51
H15a	C15	H15b	109.41
H15a	C15	C12	109.47
H15b	C15	C12	109.46
H16b	C16	H16a	106.81
H16b	C16	C17	110.46
H16b	C16	S1	110.39
H16a	C16	C17	110.42
H16a	C16	S1	110.4
C17	C16	S1	108.56
H17b	C17	H17a	108.39
H17b	C17	C16	109.96
H17b	C17	S2	110.09
H17a	C17	C16	109.96
H17a	C17	S2	110.04
C16	C17	S2	108.39
C19	C18	C31	110.12
C19	C18	S3	112.04
C19	C18	S4	107.99
C31	C18	S3	109.89
C31	C18	S4	110.32
S3	C18	S4	106.81
H19a	C19	H19b	108.03
H19a	C19	C20	109.45
H19a	C19	C18	109.45
H19b	C19	C20	109.52
H19b	C19	C18	109.42
C20	C19	C18	110.93
H20b	C20	H20a	107.91
H20b	C20	C21	109.14
H20b	C20	C19	109.21
H20a	C20	C21	109.27
H20a	C20	C19	109.25
C21	C20	C19	111.97
H21a	C21	C22	118.15
H21a	C21	C20	118.25
C22	C21	C20	123.6
C21	C22	C31	122.73
C21	C22	C23	123.98
C31	C22	C23	113
H23a	C23	C22	108.46
H23a	C23	C24	108.43
H23a	C23	C28	108.39
C22	C23	C24	116.19
C22	C23	C28	110.14
C24	C23	C28	110.63
H24a	C24	H24b	108.09
H24a	C24	C25	109.44
H24a	C24	C23	109.45
H24b	C24	C25	109.38
H24b	C24	C23	109.34
C25	C24	C23	111.09
H25b	C25	H25a	108.01
H25b	C25	C24	109.27
H25b	C25	C26	109.3
H25a	C25	C24	109.3
H25a	C25	C26	109.3
C24	C25	C26	111.8
H26a	C26	H26b	108.16
H26a	C26	C25	109.43
H26a	C26	C27	109.52
H26b	C26	C25	109.41
H26b	C26	C27	109.48
C25	C26	C27	110.8
H27b	C27	H27a	107.65
H27b	C27	C28	108.78
H27b	C27	C26	108.78
H27a	C27	C28	108.71
H27a	C27	C26	108.73
C28	C27	C26	114.04
O2	C28	C27	104.72
O2	C28	C23	110.06
O2	C28	C29	107.71
C27	C28	C23	111.27
C27	C28	C29	111.11
C23	C28	C29	111.68
H29a	C29	C30	108.28
H29a	C29	C32	108.21
H29a	C29	C28	108.39
C30	C29	C32	110.47
C30	C29	C28	111.72
C32	C29	C28	115.14
H30a	C30	H30b	106.12
H30a	C30	C29	109.5
H30a	C30	C31	109.51
H30b	C30	C29	109.54
H30b	C30	C31	109.58
C29	C30	C31	110.55
H31a	C31	C22	107.18
H31a	C31	C18	107.14
H31a	C31	C30	107.19
C22	C31	C18	112.85
C22	C31	C30	107.44
C18	C31	C30	114.86
H32b	C32	H32c	109.5
H32b	C32	H32a	109.41
H32b	C32	C29	109.43
H32c	C32	H32a	109.46
H32c	C32	C29	109.53
H32a	C32	C29	109.5
H33a	C33	H33b	106.83
H33a	C33	C34	110.38
H33a	C33	S3	110.48
H33b	C33	C34	110.4
H33b	C33	S3	110.41
C34	C33	S3	106.55
H34b	C34	H34a	108.41
H34b	C34	C33	110.09
H34b	C34	S4	110.11
H34a	C34	C33	110.09
H34a	C34	S4	110.11
C33	C34	S4	108.04
H1	O1	C11	109.45
H2	O2	C28	109.51
C16	S1	C1	98.17
C17	S2	C1	98.43
C33	S3	C18	97.74
C34	S4	C18	98.09

Table 6.14 – RMS displacements for ***2.37***

Atom	min	mid	max	min	mid	max
C1	0.1396	0.1679	0.1941	0.01956	0.02819	0.03769
C2	0.1635	0.1942	0.2137	0.02672	0.03771	0.04567
C3	0.1396	0.2073	0.2274	0.0195	0.04296	0.05169
C4	0.1631	0.1708	0.198	0.02659	0.02916	0.03922
C5	0.1341	0.1519	0.176	0.01798	0.02308	0.03099
C6	0.1445	0.1511	0.1727	0.02089	0.02283	0.02984
C7	0.16	0.1858	0.2076	0.02561	0.03454	0.04311
C8	0.15	0.1873	0.2552	0.02249	0.03508	0.06515
C9	0.176	0.1779	0.2618	0.03096	0.03165	0.06856
C10	0.1633	0.1799	0.2313	0.02667	0.03235	0.05351
C11	0.1328	0.1697	0.1935	0.01759	0.0288	0.03744
C12	0.1303	0.1861	0.2202	0.01699	0.03462	0.0485
C13	0.1581	0.1797	0.198	0.02499	0.03229	0.03922
C14	0.1496	0.1841	0.1942	0.02243	0.02693	0.03771
C15	0.1701	0.1936	0.2311	0.02892	0.03749	0.05341
C16	0.1666	0.233	0.2655	0.02774	0.05431	0.07047
C17	0.1776	0.2131	0.308	0.03154	0.0454	0.09484
C18	0.1529	0.1802	0.1976	0.02337	0.03249	0.03903
C19	0.1516	0.2033	0.2611	0.02297	0.04135	0.06819
C20	0.1472	0.2132	0.2558	0.02167	0.04543	0.06541
C21	0.1496	0.1929	0.2021	0.02243	0.03723	0.04083
C22	0.1357	0.1745	0.1828	0.0184	0.03046	0.03343
C23	0.1128	0.16	0.2054	0.01271	0.0256	0.04219
C24	0.1536	0.1836	0.2184	0.0237	0.03749	0.04882
C25	0.1504	0.2237	0.274	0.02262	0.05004	0.07508
C26	0.1826	0.2117	0.2761	0.03341	0.0448	0.07625
C27	0.1658	0.1889	0.2229	0.0345	0.03569	0.04968
C28	0.1344	0.1806	0.2081	0.01807	0.03262	0.04329
C29	0.1501	0.1714	0.2119	0.02253	0.02937	0.04489
C30	0.1546	0.1791	0.196	0.02391	0.03209	0.03843
C31	0.1575	0.1854	0.1899	0.02481	0.02735	0.03608
C32	0.166	0.2143	0.2346	0.02755	0.04594	0.05506
C33	0.1662	0.2812	0.3057	0.03543	0.07907	0.09346
C34	0.1727	0.2623	0.3444	0.02983	0.0688	0.11859
H1	0.1	0.1	0.1	0.01	0.01	0.01
H2	0.1	0.1	0.1	0.01	0.01	0.01
H2a	0.1	0.1	0.1	0.01	0.01	0.01
H2b	0.1	0.1	0.1	0.01	0.01	0.01
H3a	0.1	0.1	0.1	0.01	0.01	0.01
H3b	0.1	0.1	0.1	0.01	0.01	0.01
H4a	0.1	0.1	0.1	0.01	0.01	0.01
H6a	0.1	0.1	0.1	0.01	0.01	0.01
H7a	0.1	0.1	0.1	0.01	0.01	0.01
H7b	0.1	0.1	0.1	0.01	0.01	0.01
H8a	0.1	0.1	0.1	0.01	0.01	0.01
H8b	0.1	0.1	0.1	0.01	0.01	0.01
H9a	0.1	0.1	0.1	0.01	0.01	0.01
H9b	0.1	0.1	0.1	0.01	0.01	0.01
H10a	0.1	0.1	0.1	0.01	0.01	0.01
H10b	0.1	0.1	0.1	0.01	0.01	0.01
H12a	0.1	0.1	0.1	0.01	0.01	0.01
H13a	0.1	0.1	0.1	0.01	0.01	0.01
H13b	0.1	0.1	0.1	0.01	0.01	0.01
H14a	0.1	0.1	0.1	0.01	0.01	0.01
H15a	0.1	0.1	0.1	0.01	0.01	0.01
H15b	0.1	0.1	0.1	0.01	0.01	0.01
H15c	0.1	0.1	0.1	0.01	0.01	0.01
H16a	0.1	0.1	0.1	0.01	0.01	0.01
H16b	0.1	0.1	0.1	0.01	0.01	0.01
H17a	0.1	0.1	0.1	0.01	0.01	0.01
H17b	0.1	0.1	0.1	0.01	0.01	0.01
H19a	0.1	0.1	0.1	0.01	0.01	0.01
H19b	0.1	0.1	0.1	0.01	0.01	0.01
H20a	0.1	0.1	0.1	0.01	0.01	0.01
H20b	0.1	0.1	0.1	0.01	0.01	0.01
H21a	0.1	0.1	0.1	0.01	0.01	0.01
H23a	0.1	0.1	0.1	0.01	0.01	0.01
H24a	0.1	0.1	0.1	0.01	0.01	0.01
H24b	0.1	0.1	0.1	0.01	0.01	0.01
H25a	0.1	0.1	0.1	0.01	0.01	0.01
H25b	0.1	0.1	0.1	0.01	0.01	0.01
H26a	0.1	0.1	0.1	0.01	0.01	0.01
H26b	0.1	0.1	0.1	0.01	0.01	0.01
H27a	0.1	0.1	0.1	0.01	0.01	0.01
H27b	0.1	0.1	0.1	0.01	0.01	0.01
H29a	0.1	0.1	0.1	0.01	0.01	0.01
H30a	0.1	0.1	0.1	0.01	0.01	0.01
H30b	0.1	0.1	0.1	0.01	0.01	0.01
H31a	0.1	0.1	0.1	0.01	0.01	0.01
H32a	0.1	0.1	0.1	0.01	0.01	0.01
H32b	0.1	0.1	0.1	0.01	0.01	0.01
H32c	0.1	0.1	0.1	0.01	0.01	0.01
H33a	0.1	0.1	0.1	0.01	0.01	0.01
H33b	0.1	0.1	0.1	0.01	0.01	0.01
H34a	0.1	0.1	0.1	0.01	0.01	0.01
H34b	0.1	0.1	0.1	0.01	0.01	0.01
O1	0.1395	0.1885	0.2513	0.01864	0.03554	0.06314
O2	0.1475	0.1858	0.248	0.02175	0.03453	0.06152
S1	0.1677	0.2007	0.2422	0.02811	0.04028	0.05865
S2	0.1725	0.1944	0.2135	0.02975	0.03781	0.04557
S3	0.1774	0.2273	0.2686	0.03147	0.05166	0.07215
S4	0.1785	0.2057	0.2305	0.03188	0.0423	0.05312



3.27b

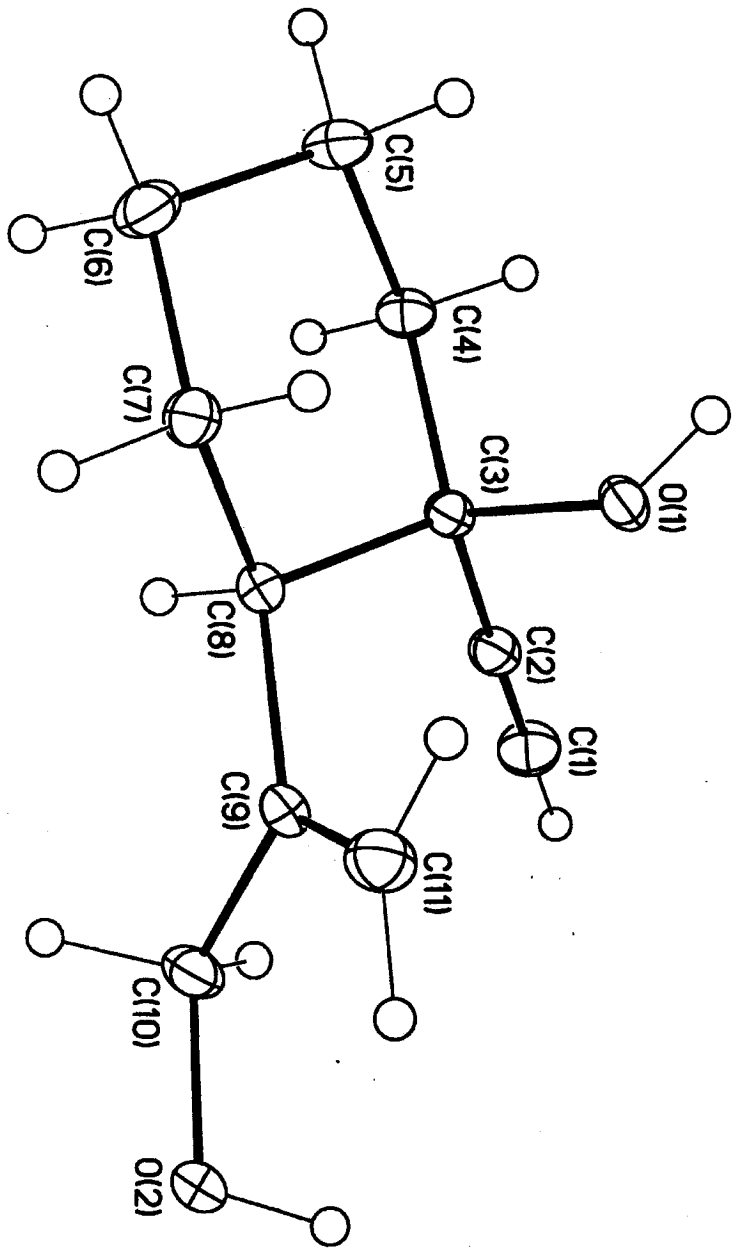


Table 6.15 - Crystal data and structure refinement for ***3.27b***

Identification code	lb2004
Empirical formula	C11 H16 O2
Formula weight	180.24
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 11.6110(12) A alpha = 90 deg. b = 7.9013(8) A beta = 115.877(2) deg c = 12.1569(13) A gamma = 90 deg.
Volume	1003.47(18) A^3
Z, Calculated density	4, 1.193 Mg/m^3
Absorption coefficient	0.080 mm^-1
F(000)	392
Crystal size	0.30 x 0.20 x 0.10 mm
Theta range for data collection	1.95 to 28.91 deg.
Limiting indices	-15<=h<=15, -10<=k<=10, -15<=l<=15
Reflections collected / unique	7161 / 2339 [R(int) = 0.0179]
Completeness to theta = 28.91	88.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000000 and 0.924062
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2339 / 0 / 182
Goodness-of-fit on F^2	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0952
R indices (all data)	R1 = 0.0424, wR2 = 0.1003
Largest diff. peak and hole	0.238 and -0.220 e.A^-3

*Table 6.16 - Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **3.27b***

	x	y	z	U(eq)
O(1)	3618(1)	7227(1)	2273(1)	21(1)
O(2)	3914(1)	740(1)	2174(1)	29(1)
C(1)	3358(1)	5413(2)	-396(1)	29(1)
C(2)	3011(1)	5848(1)	349(1)	22(1)
C(3)	2566(1)	6442(1)	1259(1)	18(1)
C(4)	1452(1)	7704(1)	625(1)	23(1)
C(5)	848(1)	8303(1)	1453(1)	28(1)
C(6)	422(1)	6799(2)	1982(1)	30(1)
C(7)	1546(1)	5596(1)	2645(1)	25(1)
C(8)	2103(1)	4927(1)	1787(1)	19(1)
C(9)	3126(1)	3577(1)	2392(1)	21(1)
C(10)	3014(1)	2065(1)	1590(1)	28(1)
C(11)	4011(1)	3692(1)	3544(1)	29(1)

*Table 6.17 - Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for **3.27b***

	x	y	z	U(eq)
H(1A)	3649(18)	5050(20)	-990(18)	65(5)
H(1B)	3680(14)	8280(20)	2113(14)	43(4)
H(2A)	4670(17)	1120(20)	2292(15)	52(5)
H(4A)	1759(13)	8677(19)	311(12)	33(3)
H(4B)	809(13)	7142(16)	-98(12)	27(3)
H(5A)	124(14)	9055(18)	985(13)	35(4)
H(5B)	1470(14)	9024(18)	2131(14)	37(4)
H(6A)	-302(15)	6141(19)	1326(14)	42(4)
H(6B)	110(14)	7184(19)	2567(13)	39(4)
H(7A)	1277(13)	4609(19)	2975(13)	37(4)
H(7B)	2210(12)	6213(16)	3346(12)	25(3)
H(8A)	1408(12)	4403(16)	1040(12)	24(3)
H(10A)	2140(15)	1550(18)	1337(13)	40(4)
H(10B)	3058(14)	2409(19)	828(14)	38(4)
H(11A)	4046(13)	4685(18)	4052(13)	36(4)
H(11B)	4642(13)	2813(18)	3919(12)	35(3)

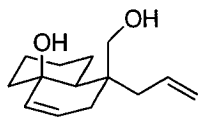
Table 6.18 – Bond lengths (Å) and angles (deg.) for ***3.27b***

O(1)-C(3)	1.4421(11)
O(1)-H(1B)	0.865(17)
O(2)-C(10)	1.4296(12)
O(2)-H(2A)	0.878(17)
C(1)-C(2)	1.1905(16)
C(1)-H(1A)	0.97(2)
C(2)-C(3)	1.4863(14)
C(3)-C(4)	1.5469(13)
C(3)-C(8)	1.5607(13)
C(4)-C(5)	1.5316(15)
C(4)-H(4A)	0.991(15)
C(4)-H(4B)	0.977(13)
C(5)-C(6)	1.5323(16)
C(5)-H(5A)	0.983(14)
C(5)-H(5B)	1.003(15)
C(6)-C(7)	1.5295(15)
C(6)-H(6A)	1.014(15)
C(6)-H(6B)	0.977(15)
C(7)-C(8)	1.5408(14)
C(7)-H(7A)	0.988(15)
C(7)-H(7B)	0.992(13)
C(8)-C(9)	1.5251(13)
C(8)-H(8A)	1.004(13)
C(9)-C(11)	1.3297(15)
C(9)-C(10)	1.5120(14)
C(10)-H(10A)	1.008(16)
C(10)-H(10B)	0.988(15)
C(11)-H(11A)	0.989(15)
C(11)-H(11B)	0.967(14)

C(3)-O(1)-H(1B)	110.2(10)
C(10)-O(2)-H(2A)	107.1(11)
C(2)-C(1)-H(1A)	179.1(12)
C(1)-C(2)-C(3)	178.27(11)
O(1)-C(3)-C(2)	109.41(8)
O(1)-C(3)-C(4)	111.13(7)
C(2)-C(3)-C(4)	108.61(8)
O(1)-C(3)-C(8)	107.05(7)
C(2)-C(3)-C(8)	111.01(8)
C(4)-C(3)-C(8)	109.64(8)
C(5)-C(4)-C(3)	113.25(8)
C(5)-C(4)-H(4A)	111.0(8)
C(3)-C(4)-H(4A)	109.2(8)
C(5)-C(4)-H(4B)	110.1(8)
C(3)-C(4)-H(4B)	107.4(8)
H(4A)-C(4)-H(4B)	105.5(11)
C(6)-C(5)-C(4)	111.15(9)
C(6)-C(5)-H(5A)	111.1(8)
C(4)-C(5)-H(5A)	109.1(9)
C(6)-C(5)-H(5B)	110.1(8)
C(4)-C(5)-H(5B)	110.1(8)
H(5A)-C(5)-H(5B)	105.1(11)
C(7)-C(6)-C(5)	110.23(9)
C(7)-C(6)-H(6A)	108.6(8)
C(5)-C(6)-H(6A)	112.1(9)
C(7)-C(6)-H(6B)	108.2(9)
C(5)-C(6)-H(6B)	110.8(9)
H(6A)-C(6)-H(6B)	106.7(12)
C(6)-C(7)-C(8)	111.72(9)
C(6)-C(7)-H(7A)	110.9(8)
C(8)-C(7)-H(7A)	107.7(8)
C(6)-C(7)-H(7B)	108.1(7)
C(8)-C(7)-H(7B)	110.6(7)
H(7A)-C(7)-H(7B)	107.7(11)
C(9)-C(8)-C(7)	112.44(8)
C(9)-C(8)-C(3)	113.52(8)
C(7)-C(8)-C(3)	109.73(8)
C(9)-C(8)-H(8A)	107.3(7)
C(7)-C(8)-H(8A)	110.2(7)
C(3)-C(8)-H(8A)	103.2(7)
C(11)-C(9)-C(10)	122.84(9)
C(11)-C(9)-C(8)	122.78(9)
C(10)-C(9)-C(8)	114.33(8)
O(2)-C(10)-C(9)	114.80(9)
O(2)-C(10)-H(10A)	106.0(8)
C(9)-C(10)-H(10A)	107.9(8)
O(2)-C(10)-H(10B)	110.0(9)
C(9)-C(10)-H(10B)	111.3(9)
H(10A)-C(10)-H(10B)	106.4(12)
C(9)-C(11)-H(11A)	120.9(8)
C(9)-C(11)-H(11B)	121.8(8)
H(11A)-C(11)-H(11B)	117.3(12)

Table 6.19 - Anisotropic displacement parameters (A^2 x 10^3) for ***3.27b***

	U11	U22	U33	U23	U13	U12
O(1)	23(1)	15(1)	24(1)	-2(1)	9(1)	-3(1)
O(2)	26(1)	15(1)	48(1)	2(1)	16(1)	1(1)
C(1)	33(1)	31(1)	27(1)	-1(1)	16(1)	3(1)
C(2)	24(1)	19(1)	24(1)	1(1)	10(1)	1(1)
C(3)	20(1)	16(1)	20(1)	-1(1)	9(1)	0(1)
C(4)	25(1)	21(1)	24(1)	3(1)	10(1)	5(1)
C(5)	29(1)	26(1)	31(1)	3(1)	15(1)	10(1)
C(6)	26(1)	33(1)	36(1)	1(1)	19(1)	6(1)
C(7)	27(1)	23(1)	30(1)	2(1)	18(1)	1(1)
C(8)	18(1)	16(1)	22(1)	-1(1)	9(1)	-2(1)
C(9)	22(1)	15(1)	28(1)	1(1)	12(1)	-1(1)
C(10)	30(1)	16(1)	33(1)	-1(1)	11(1)	2(1)
C(11)	29(1)	25(1)	30(1)	2(1)	9(1)	4(1)


OH
OH

3.46

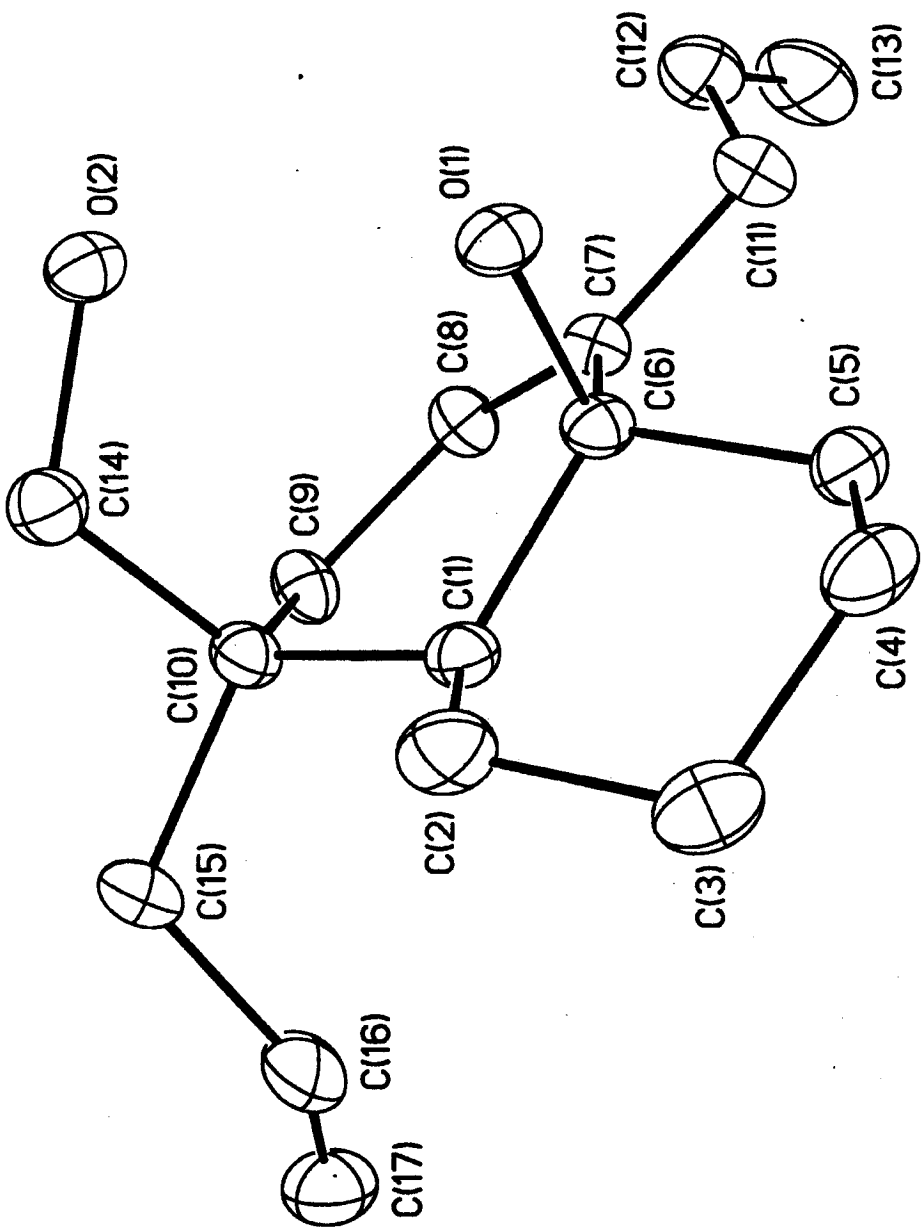

C(12)
C(13)
O(2)
O(1)
C(11)
C(7)
C(8)
C(6)
C(5)
C(14)
C(9)
C(1)
C(4)
C(10)
C(2)
C(3)
C(15)
C(16)
C(17)

Table 6.20 - Crystal data and structure refinement for ***3.46***

Identification code	lb2001
Empirical formula	C17 H24 O2
Formula weight	260.36
Temperature	203(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 9.587(4) A alpha = 90 deg. b = 8.403(4) A beta = 110.36(6) deg. c = 10.290(4) A gamma = 90 deg.
Volume	777.2(6) A^3
Z, Calculated density	2, 1.113 Mg/m^3
Absorption coefficient	0.071 mm^-1
F(000)	284
Crystal size	0.10 x 0.10 x 0.10 mm
Theta range for data collection	2.11 to 28.66 deg.
Limiting indices	-12<=h<=11, -9<=k<=9, 0<=l<=13
Reflections collected / unique	2240 / 2229 [R(int) = 0.0713]
Completeness to theta = 28.66	78.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2229 / 2 / 177
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0740, wR2 = 0.1924
R indices (all data)	R1 = 0.0850, wR2 = 0.2043
Absolute structure parameter	1(2)
Extinction coefficient	0.040(14)
Largest diff. peak and hole	0.380 and -0.279 e.A^-3

Table 6.21 - Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for ***3.46***

	x	y	z	U(eq)
O(1)	8982(2)	3566(3)	5008(3)	34(1)
O(2)	9900(2)	1322(4)	3684(3)	34(1)
C(1)	6625(3)	2405(5)	3412(3)	30(1)
C(2)	6329(4)	3920(6)	2535(4)	44(1)
C(3)	5503(4)	5127(6)	3079(5)	49(1)
C(4)	6367(4)	5524(6)	4587(5)	43(1)
C(5)	6785(4)	4039(5)	5491(4)	35(1)
C(6)	7604(3)	2797(5)	4933(4)	29(1)
C(7)	7984(3)	1302(5)	5828(3)	29(1)
C(8)	7811(4)	-151(5)	5260(4)	33(1)
C(9)	7220(4)	-506(5)	3744(4)	34(1)
C(10)	7113(4)	931(5)	2785(4)	31(1)
C(11)	8627(4)	1554(6)	7385(4)	38(1)
C(12)	9389(5)	127(7)	8190(4)	48(1)
C(13)	8987(6)	-642(8)	9088(5)	69(2)
C(14)	8579(4)	1141(6)	2495(4)	37(1)
C(15)	5952(4)	512(7)	1314(4)	50(1)
C(16)	4354(5)	510(9)	1256(5)	77(2)
C(17)	3362(10)	-358(15)	980(11)	58(2)
C(16')	4354(5)	510(9)	1256(5)	77(2)
C(17')	3250(9)	997(14)	505(11)	58(2)

Table 6.22 - Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for ***3.46***

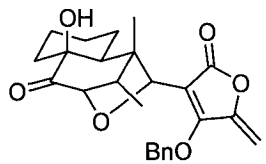
	x	y	z	U(eq)
H(1A)	9434	2996	4627	50
H(2A)	9762	2014	4202	51
H(1B)	5645	2112	3461	36
H(2B)	7277	4375	2553	52
H(2C)	5740	3658	1572	52
H(3A)	4524	4702	2997	58
H(3B)	5350	6099	2520	58
H(4A)	5763	6224	4940	52
H(4B)	7275	6101	4645	52
H(5A)	5878	3560	5553	42
H(5B)	7419	4348	6429	42
H(8A)	8086	-1023	5868	39
H(9A)	6226	-972	3515	41
H(9B)	7860	-1311	3548	41
H(11A)	9341	2435	7580	46
H(11B)	7821	1871	7710	46
H(12A)	10239	-244	8028	58
H(13A)	8143	-314	9284	82
H(13B)	9537	-1530	9546	82
H(14A)	8707	215	1969	45
H(14B)	8478	2078	1902	45
H(16A)	4094	1506	1521	93
H(17A)	3465	-1401	697	69
H(17B)	2451	-23	1040	69
H(16B)	4237	-16	2018	93
H(17C)	3229	1547	-297	69
H(17D)	2367	846	692	69

Table 6.23 - Bond lengths (Å) and angles (deg.) for ***3.46***

O(1)-C(6)	1.449(4)
O(2)-C(14)	1.430(4)
C(1)-C(2)	1.529(6)
C(1)-C(10)	1.543(6)
C(1)-C(6)	1.554(5)
C(2)-C(3)	1.510(7)
C(3)-C(4)	1.520(7)
C(4)-C(5)	1.524(6)
C(5)-C(6)	1.533(5)
C(6)-C(7)	1.525(6)
C(7)-C(8)	1.338(6)
C(7)-C(11)	1.518(5)
C(8)-C(9)	1.492(5)
C(9)-C(10)	1.540(6)
C(10)-C(14)	1.545(5)
C(10)-C(15)	1.575(5)
C(11)-C(12)	1.496(6)
C(12)-C(13)	1.291(7)
C(15)-C(16)	1.512(6)
C(16)-C(17)	1.153(11)
C(2)-C(1)-C(10)	116.3(3)
C(2)-C(1)-C(6)	109.9(4)
C(10)-C(1)-C(6)	115.3(3)
C(3)-C(2)-C(1)	110.8(3)
C(2)-C(3)-C(4)	110.8(3)
C(3)-C(4)-C(5)	112.2(4)
C(4)-C(5)-C(6)	112.9(3)
O(1)-C(6)-C(7)	108.3(3)
O(1)-C(6)-C(5)	104.6(3)
C(7)-C(6)-C(5)	112.4(3)
O(1)-C(6)-C(1)	111.6(3)
C(7)-C(6)-C(1)	111.5(3)
C(5)-C(6)-C(1)	108.2(3)
C(8)-C(7)-C(11)	122.1(4)
C(8)-C(7)-C(6)	121.4(3)
C(11)-C(7)-C(6)	116.5(4)
C(7)-C(8)-C(9)	125.7(4)
C(8)-C(9)-C(10)	115.4(3)
C(9)-C(10)-C(14)	110.6(3)
C(9)-C(10)-C(1)	108.9(3)
C(14)-C(10)-C(1)	114.7(3)
C(9)-C(10)-C(15)	108.0(3)
C(14)-C(10)-C(15)	103.1(3)
C(1)-C(10)-C(15)	111.5(3)
C(12)-C(11)-C(7)	114.4(4)
C(13)-C(12)-C(11)	126.0(5)
O(2)-C(14)-C(10)	116.2(3)
C(16)-C(15)-C(10)	113.9(3)
C(17)-C(16)-C(15)	138.4(8)

Table 6.24 - Anisotropic displacement parameters ($A^2 \times 10^3$) for ***3.46***

	U11	U22	U33	U23	U13	U12
O(1)	26(1)	25(2)	47(2)	-5(1)	10(1)	-4(1)
O(2)	29(1)	31(2)	41(1)	-3(1)	9(1)	1(1)
C(1)	24(1)	34(3)	31(2)	0(2)	8(1)	-3(1)
C(2)	40(2)	46(3)	41(2)	14(2)	8(2)	9(2)
C(3)	39(2)	45(3)	57(3)	11(2)	11(2)	7(2)
C(4)	34(2)	31(3)	62(3)	-1(2)	13(2)	7(2)
C(5)	32(2)	28(3)	43(2)	-6(2)	12(1)	-1(2)
C(6)	25(1)	25(2)	33(2)	-3(2)	7(1)	-3(1)
C(7)	27(1)	31(2)	26(2)	-2(2)	7(1)	0(2)
C(8)	39(2)	30(3)	29(2)	2(2)	12(1)	-1(2)
C(9)	42(2)	28(3)	33(2)	-8(2)	13(1)	-7(2)
C(10)	30(2)	32(3)	28(2)	-4(2)	7(1)	-4(1)
C(11)	42(2)	37(3)	31(2)	-2(2)	7(1)	-5(2)
C(12)	46(2)	58(4)	33(2)	8(2)	4(2)	6(2)
C(13)	76(3)	82(5)	35(2)	11(3)	3(2)	7(3)
C(14)	36(2)	42(3)	34(2)	4(2)	12(1)	-1(2)
C(15)	38(2)	73(4)	30(2)	-11(2)	1(2)	-5(2)
C(16)	42(2)	139(6)	45(3)	-39(3)	9(2)	-17(3)
C(17)	41(3)	61(6)	61(4)	-11(4)	5(3)	-3(4)
C(16')	42(2)	139(6)	45(3)	-39(3)	9(2)	-17(3)
C(17')	41(3)	61(6)	61(4)	-11(4)	5(3)	-3(4)



4.68

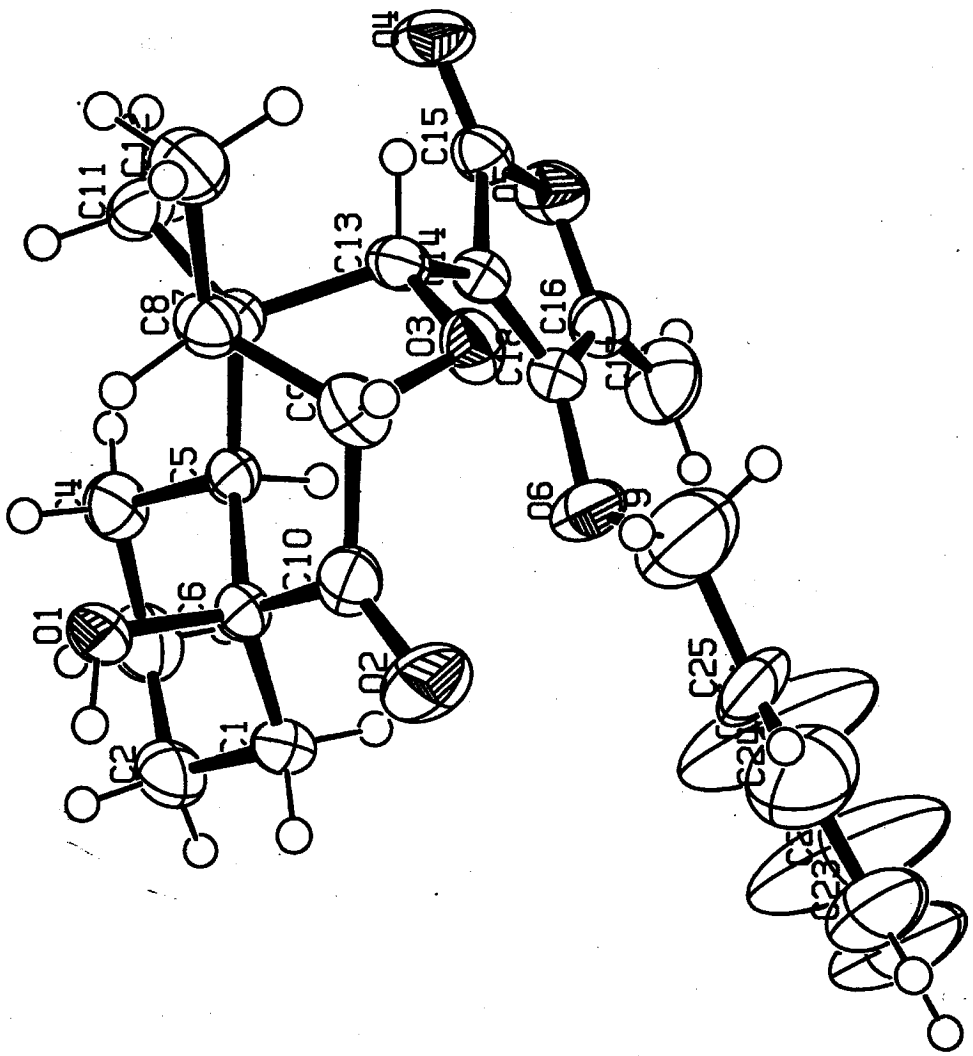


Table 5.25 - Atomic Coordinates and anisotropic displacement parameters for ***4.68***

			Coordinates			Uij					
Num	Label	SFAC									
1	C1	1	0.205	0.417	0.244	0.0477	0.0288	0.0363	0.0091	0.0038	0.0022
2	C2	1	0.292	0.309	0.197	0.0622	0.0341	0.0513	0.0093	-0.0026	0.019
3	C3	1	0.454	0.398	0.154	0.0585	0.0488	0.0625	0.0052	0.0103	0.0308
4	C4	1	0.395	0.506	0.103	0.0408	0.0386	0.0438	0.0041	0.0134	0.0139
5	C5	1	0.315	0.615	0.154	0.0287	0.0276	0.0256	0.0035	0.0021	0.0034
6	C6	1	0.139	0.514	0.188	0.0311	0.0279	0.0269	0.0026	0.0016	0.0003
7	C7	1	0.284	0.754	0.116	0.0304	0.0278	0.0279	0.0044	0.003	0.0036
8	C8	1	0.064	0.734	0.101	0.0322	0.0291	0.0377	0.0047	-0.0013	0.0082
9	C9	1	0.03	0.753	0.189	0.0257	0.0349	0.0478	0.0024	0.0071	0.0067
10	C10	1	0.028	0.812	0.227	0.0285	0.0379	0.0337	0.0032	0.0053	0.0009
11	C11	1	0.384	0.786	0.042	0.0425	0.0437	0.034	0.0135	0.0092	0.0046
12	C12	1	0.009	0.851	0.056	0.05	0.0417	0.0506	0.0079	-0.0081	0.0161
13	C13	1	0.351	0.902	0.183	0.0343	0.0253	0.0364	0.0088	0.0041	0.0061
14	C14	1	0.548	0.947	0.233	0.0356	0.0244	0.0322	0.0046	0.0049	0.0034
15	C15	1	0.713	1.059	0.207	0.0345	0.027	0.0395	0.0048	0.0007	0.0012
16	C16	1	0.831	0.968	0.319	0.0461	0.0386	0.0396	0.0027	-0.0007	0.0133
17	C17	1	0.963	0.983	0.376	0.0857	0.078	0.0537	0.0071	-0.0103	0.0302
18	C18	1	0.621	0.909	0.301	0.0448	0.0266	0.034	0.006	0.0083	0.0064
19	C19	1	0.403	0.849	0.396	0.1043	0.1136	0.0684	0.0287	0.0206	0.0211
20	C20	1	0.545	0.738	0.504	0.1046	0.3695	0.1887	0.1965	0.0347	0.0235
21	C21	1	0.535	0.672	0.573	0.1064	0.3781	0.1902	0.2021	0.0253	-0.0045
22	C22	1	0.363	0.629	0.605	0.1114	0.1721	0.0791	0.0728	0.0046	-0.0301
23	C23	1	0.2	0.654	0.567	0.1565	0.0904	0.081	0.0378	0.0716	0.0411
24	C24	1	0.21	0.72	0.498	0.1939	0.1049	0.0993	0.0427	0.0539	0.0885
25	C25	1	0.382	0.762	0.466	0.1389	0.0786	0.0297	0.0068	0.0297	-0.0208
26	H1a	2	0.095	0.356	0.267	0.0451	0	0	0	0	0
27	H1b	2	0.303	0.486	0.288	0.0451	0	0	0	0	0
28	H1c	-2	0.074	0.338	0.136	0.0516	0	0	0	0	0
29	H2a	2	0.344	0.254	0.234	0.059	0	0	0	0	0
30	H2b	2	0.19	0.232	0.157	0.059	0	0	0	0	0
31	H3a	2	0.494	0.325	0.12	0.0679	0	0	0	0	0
32	H3b	2	0.566	0.46	0.195	0.0679	0	0	0	0	0
33	H4a	2	0.508	0.567	0.081	0.0493	0	0	0	0	0
34	H4b	2	0.295	0.444	0.057	0.0493	0	0	0	0	0
35	H5a	2	0.417	0.664	0.202	0.032	0	0	0	0	0
36	H8a	-2	0.011	0.628	0.073	0.0396	0	0	0	0	0
37	H9a	-2	0.089	0.779	0.195	0.0433	0	0	0	0	0
38	H11a	2	0.359	0.872	0.022	0.0602	0	0	0	0	0
39	H11b	2	0.335	0.695	0.001	0.0602	0	0	0	0	0
40	H11c	2	0.523	0.811	0.058	0.0602	0	0	0	0	0
41	H12a	-2	0.131	0.828	0.05	0.0713	0	0	0	0	0
42	H12b	2	0.049	0.845	0.003	0.0713	0	0	0	0	0
43	H12c	2	0.073	0.954	0.087	0.0713	0	0	0	0	0
44	H13a	2	0.347	0.99	0.157	0.0384	0	0	0	0	0
45	H17a	2	1.094	1.041	0.377	0.079	0	0	0	0	0
46	H17b	2	0.927	0.922	0.416	0.079	0	0	0	0	0
47	H19a	2	0.276	0.822	0.362	0.1145	0	0	0	0	0
48	H19b	2	0.45	0.96	0.416	0.1145	0	0	0	0	0
49	H20a	2	0.661	0.767	0.482	0.2651	0	0	0	0	0
50	H21a	2	0.645	0.655	0.598	0.2699	0	0	0	0	0
51	H22a	2	0.356	0.584	0.652	0.145	0	0	0	0	0
52	H23a	2	0.084	0.625	0.589	0.1311	0	0	0	0	0
53	H24a	2	0.1	0.737	0.473	0.1593	0	0	0	0	0
54	O1	-3	0.003	0.414	0.12	0.0368	0.0286	0.0378	0.0052	0.0005	-0.0047
55	O2	-3	0.058	0.579	0.283	0.0635	0.0666	0.0557	0.0216	0.0361	0.0167
56	O3	3	0.202	0.875	0.234	0.0354	0.035	0.0416	-0.0019	0.0099	0.0051
57	O4	3	0.719	1.13	0.152	0.0495	0.0426	0.0545	0.0247	0.0046	-0.0014
58	O5	3	0.881	1.079	0.259	0.0342	0.0418	0.0538	0.0127	0.0002	0.0009
59	O6	3	0.533	0.81	0.348	0.0723	0.0532	0.0424	0.0234	0.0212	0.023

Table 6.26 - Calculated bond lengths (Å) for **2.37**

A	B	Dist
C1	H1a	0.98
C1	H1b	0.98
C1	C6	1.527
C1	C2	1.532
C2	H2a	0.98
C2	H2b	0.98
C2	C3	1.525
C2	C1	1.532
C3	H3b	0.98
C3	H3a	0.98
C3	C2	1.525
C3	C4	1.537
C4	H4a	0.98
C4	H4b	0.98
C4	C3	1.537
C4	C5	1.538
C5	H5a	0.99
C5	C4	1.538
C5	C6	1.553
C5	C7	1.58
C6	O1	1.453
C6	C1	1.527
C6	C10	1.539
C6	C5	1.553
C7	C11	1.528
C7	C8	1.56
C7	C13	1.567
C7	C5	1.58
C8	H8a	0.99
C8	C12	1.529
C8	C9	1.529
C8	C7	1.56
C9	H9a	0.99
C9	O3	1.461
C9	C10	1.52
C9	C8	1.529
C10	O2	1.212
C10	C9	1.52
C10	C6	1.539
C11	H11a	0.97
C11	H11b	0.97
C11	H11c	0.97
C11	C7	1.528
C12	H12a	0.97
C12	H12b	0.97
C12	H12c	0.97
C12	C8	1.529
C13	H13a	0.99
C13	O3	1.441
C13	C14	1.501
C13	C7	1.567
C14	C16	1.352
C14	C15	1.472
C14	C13	1.501
C15	O4	1.206
C15	O5	1.364
C15	C14	1.472
C16	C17	1.313
C16	O5	1.396
C16	C18	1.461
C17	H17a	0.94
C17	H17b	0.94
C17	C16	1.313
C18	O6	1.35
C18	C14	1.352
C18	C16	1.461
C19	H19a	0.98
C19	H19b	0.98
C19	O6	1.41
C19	C25	1.508
C20	H20a	0.94
C20	C21	1.39
C20	C25	1.39
C21	H21a	0.94
C21	C20	1.39
C21	C22	1.39
C22	H22a	0.94
C22	C21	1.39
C22	C23	1.39
C23	H23a	0.94
C23	C22	1.39
C23	C24	1.39
C24	H24a	0.94
C24	C23	1.39
C24	C25	1.39
C25	C20	1.39
C25	C24	1.39
C25	C19	1.508
H1a	C1	0.98
H1b	C1	0.98
H1c	O1	0.83
H2a	C2	0.98
H2b	C2	0.98
H3a	C3	0.98
H3b	C3	0.98
H4a	C4	0.98
H4b	C4	0.98
H5a	C5	0.99
H8a	C8	0.99
H9a	C9	0.99
H11a	C11	0.97
H11b	C11	0.97
H11c	C11	0.97
H12a	C12	0.97
H12b	C12	0.97
H12c	C12	0.97
H13a	C13	0.99
H17a	C17	0.94
H17b	C17	0.94
H19a	C19	0.98
H19b	C19	0.98
H20a	C20	0.94
H21a	C21	0.94
H22a	C22	0.94
H23a	C23	0.94
H24a	C24	0.94
O1	H1c	0.83
O1	C6	1.453
O2	C10	1.212
O3	C13	1.441
O3	C9	1.461
O4	C15	1.206
O5	C15	1.364
O5	C16	1.396
O6	C18	1.35
O6	C19	1.41

Table 6.27 - Calculated bond angles (deg.) for 2.37

A	B	C	Angle
H1a	C1	H1b	108.14
H1a	C1	C6	109.63
H1a	C1	C2	109.62
H1b	C1	C6	109.62
H1b	C1	C2	109.63
C6	C1	C2	110.18
H2a	C2	H2b	107.99
H2a	C2	C3	109.37
H2a	C2	C1	109.37
H2b	C2	C3	109.36
H2b	C2	C1	109.37
C3	C2	C1	111.31
H3b	C3	H3a	107.72
H3b	C3	C2	108.89
H3b	C3	C4	108.89
H3a	C3	C2	108.89
H3a	C3	C4	108.89
C2	C3	C4	113.41
H4a	C4	H4b	108.13
H4a	C4	C3	109.59
H4a	C4	C5	109.59
H4b	C4	C3	109.59
H4b	C4	C5	109.6
C3	C4	C5	110.3
H5a	C5	C4	104.86
H5a	C5	C6	104.86
H5a	C5	C7	104.86
C4	C5	C6	107.89
C4	C5	C7	117.61
C6	C5	C7	115.41
O1	C6	C1	110.22
O1	C6	C10	102.79
O1	C6	C5	108.58
C1	C6	C10	113.64
C1	C6	C5	109.7
C10	C6	C5	111.63
C11	C7	C6	113.71
C11	C7	C13	111.02
C11	C7	C5	113.7
C6	C7	C13	97.74
C6	C7	C5	110.31
C13	C7	C5	109.19
H8a	C8	C12	109.75
H8a	C8	C9	109.74
H8a	C8	C7	109.75
C12	C8	C9	112.3
C12	C8	C7	116.25
C9	C8	C7	98.51
H9a	C9	O3	111.26
H9a	C9	C10	111.26
H9a	C9	C8	111.27
O3	C9	C10	104.14
O3	C9	C8	106.11
C10	C9	C8	112.46
O2	C10	C9	122.18
O2	C10	C6	123.07
C9	C10	C6	114.74
H11a	C11	H11b	109.47
H11a	C11	H11c	109.47
H11a	C11	C7	109.48
H11b	C11	H11c	109.47
H11b	C11	C7	109.47
H11c	C11	C7	109.47
H12a	C12	H12b	109.47
H12a	C12	H12c	109.47
H12a	C12	C8	109.48
H12b	C12	H12c	109.47
H12b	C12	C8	109.47
H12c	C12	C8	109.47
H13a	C13	O3	107.49
H13a	C13	C14	107.49
H13a	C13	C7	107.49
O3	C13	C14	110.68
O3	C13	C7	104.95
C14	C13	C7	118.27
C18	C14	C15	105.77
C18	C14	C13	135.37
C15	C14	C13	118.86
O4	C15	O5	120.22
O4	C15	C14	130.48
O5	C15	C14	109.29
C17	C16	O5	121
C17	C16	C18	131.87
O5	C16	C18	107.1
H17a	C17	H17b	120
H17a	C17	C16	120
H17b	C17	C16	120
O6	C18	C14	130.18
O6	C18	C16	119.96
C14	C18	C16	109.81
H19a	C19	H19b	108.1
H19a	C19	O6	109.55
H19a	C19	C25	109.54
H19b	C19	O6	109.55
H19b	C19	C25	109.54
O6	C19	C25	110.52
H20a	C20	C21	120
H20a	C20	C25	120
C21	C20	C25	120
H21a	C21	C20	120
H21a	C21	C22	120
C20	C21	C22	120
H22a	C22	C21	120
H22a	C22	C23	120
C21	C22	C23	120
H23a	C23	C22	120
H23a	C23	C24	120
C22	C23	C24	120
H24a	C24	C23	120
H24a	C24	C25	120
C23	C24	C25	120
C20	C25	C24	120
C20	C25	C19	118.66
C24	C25	C19	121.08
H1c	O1	C6	109.47
C13	O3	C9	107.88
C15	O5	C16	107.96
C18	O6	C19	119.3

Table 6.28 – RMS displacements for 2.37

Atom	min	mid	max	min	mid	max
C1	0.1582	0.1901	0.2427	0.02501	0.03614	0.05891
C2	0.1721	0.215	0.2678	0.02961	0.04623	0.07174
C3	0.1811	0.2488	0.2583	0.0328	0.06191	0.06672
C4	0.1791	0.1985	0.2247	0.03206	0.03939	0.05047
C5	0.1499	0.1627	0.1893	0.02248	0.02648	0.03582
C6	0.147	0.1685	0.21	0.0216	0.0284	0.04409
C7	0.1561	0.1677	0.1966	0.02436	0.02813	0.03867
C8	0.167	0.1752	0.209	0.02788	0.03068	0.0437
C9	0.158	0.1897	0.2256	0.02497	0.03599	0.05091
C10	0.1563	0.1828	0.2246	0.02442	0.03341	0.05046
C11	0.1613	0.201	0.2417	0.02601	0.04041	0.05841
C12	0.1845	0.2055	0.2635	0.03403	0.04222	0.06942
C13	0.1525	0.1858	0.201	0.02326	0.03452	0.0404
C14	0.1513	0.1797	0.2052	0.02288	0.03228	0.04211
C15	0.1522	0.1958	0.218	0.02315	0.03833	0.04753
C16	0.1868	0.202	0.2287	0.03489	0.04079	0.05229
C17	0.1982	0.2678	0.2962	0.03927	0.07169	0.08771
C18	0.1602	0.1828	0.2228	0.02567	0.03343	0.04962
C19	0.2436	0.3153	0.3652	0.05934	0.09942	0.13341
C20	0.2477	0.3428	0.6927	0.06138	0.11752	0.4798
C21	0.2367	0.3502	0.7175	0.05602	0.12265	0.51486
C22	0.1982	0.2984	0.5278	0.0393	0.08904	0.27859
C23	0.1975	0.3024	0.423	0.03899	0.09144	0.17896
C24	0.2576	0.2937	0.4512	0.06634	0.08623	0.20356
C25	0.1449	0.2442	0.4496	0.021	0.05961	0.20215
H1a	0.1	0.1	0.1	0.01	0.01	0.01
H1b	0.1	0.1	0.1	0.01	0.01	0.01
H1c	0.1	0.1	0.1	0.01	0.01	0.01
H2a	0.1	0.1	0.1	0.01	0.01	0.01
H2b	0.1	0.1	0.1	0.01	0.01	0.01
H3a	0.1	0.1	0.1	0.01	0.01	0.01
H3b	0.1	0.1	0.1	0.01	0.01	0.01
H4a	0.1	0.1	0.1	0.01	0.01	0.01
H4b	0.1	0.1	0.1	0.01	0.01	0.01
H5a	0.1	0.1	0.1	0.01	0.01	0.01
H8a	0.1	0.1	0.1	0.01	0.01	0.01
H9a	0.1	0.1	0.1	0.01	0.01	0.01
H11a	0.1	0.1	0.1	0.01	0.01	0.01
H11b	0.1	0.1	0.1	0.01	0.01	0.01
H11c	0.1	0.1	0.1	0.01	0.01	0.01
H12a	0.1	0.1	0.1	0.01	0.01	0.01
H12b	0.1	0.1	0.1	0.01	0.01	0.01
H12c	0.1	0.1	0.1	0.01	0.01	0.01
H13a	0.1	0.1	0.1	0.01	0.01	0.01
H17a	0.1	0.1	0.1	0.01	0.01	0.01
H17b	0.1	0.1	0.1	0.01	0.01	0.01
H19a	0.1	0.1	0.1	0.01	0.01	0.01
H19b	0.1	0.1	0.1	0.01	0.01	0.01
H20a	0.1	0.1	0.1	0.01	0.01	0.01
H21a	0.1	0.1	0.1	0.01	0.01	0.01
H22a	0.1	0.1	0.1	0.01	0.01	0.01
H23a	0.1	0.1	0.1	0.01	0.01	0.01
H24a	0.1	0.1	0.1	0.01	0.01	0.01
O1	0.143	0.1941	0.2402	0.02044	0.03767	0.05772
O2	0.1602	0.2653	0.2902	0.02567	0.07039	0.08423
O3	0.1728	0.1822	0.2348	0.02986	0.03319	0.05515
O4	0.1582	0.2216	0.2854	0.0244	0.04912	0.08145
O5	0.1689	0.2127	0.2545	0.02851	0.04523	0.06476
O6	0.1658	0.2384	0.2741	0.02749	0.05683	0.07512

Glossary of Abbreviations

Ac	acetate
acac	acetoacetonate
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
BuLi	n-butyllithium
cat.	catalyst or catalytic
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DHP	dihydrofuran
DIBAL-H	diisobutylaluminumhydride
DIPEA	N,N,N-diisopropylethyl amine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E^+	electrophile
equiv	equivalents
Et	ethyl
GC	gas chromatography
GC/MS	gas chromatography coupled to mass spectrometry
HMPA	hexamethylphosphoramide

HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrum
Im	imidazole
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithiumdiisopropylamide
LICA	lithiumcyclohexylisopropylamide
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
mp	melting point
ms	molecular sieves
NMO	N-methylmorpholine oxide
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OTf	trifluoromethylsulfonate
OTs	toluenesulfonate
ox.	oxidation
PCC	pyridiniumchlorochromate
PG	protecting group
Ph	phenyl
Piv	pivaoyl $(CH_3)_3C$-CO
ppm	parts per million
PTSA	para toluenesulfonic acid
pyr	pyridine
quant.	quantitative yield (i.e. >98%)
rF	"to-Front" ratio = analyte elution distance / solvent elution distance
s-BuLi	*sec* butyllithium
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBMS	*tert*-butyldimethyl silyl
TBS	*tert*-butyldimethyl silyl
t-BuLi	*tert* butyllithium

TFA	trifluoroacetic acid
TFAA	trifluoro acetic anhydride
TFP	trifuryl phosphine
THF	tetrahydrofuran
TMS	trimethylsilyl
tol	toluene
TPAP	tetrapropylammonium perruthenate
xs	excess

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