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THE SYNTHESIS OF HIGHLY OXYGENATED DECALIN COMPOUNDS

by

Kevin Richard Guertin

Submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry
McGill University
Montreal, Que., Canada
H3A 2K6

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THE SYNTHESIS OF HIGHLY OXYGENATED DECALIN COMPOUNDS

ABSTRACT

The Lewis acid catalysed tandem Michael-Claisen (4C+2C) annelation reaction of 1-trimethylsiloxy-1-methoxy-3-phenylthio-1,3-butadiene and 4,4-dimethyl-2-cyclohexen-1-one has been reexamined. The intermediate E and Z Michael adducts were cyclized under basic conditions to give the β-diketone 3-phenylthio-5,6,4a,8a-tetrahydro-5,5-dimethyl-(4H,7H)-naphthalen-1,8-dione. Angular methylation of this β-diketone under basic conditions was examined in detail, providing the *cis* angularly methylated product stereoselectively.

The *cis* ring junction stereochemistry of the β-diketone derivative mentioned above has been used advantageously to establish the C_8 (naphthalene numbering) α-hydroxyl stereochemistry required for the forskolin structure. A subsequent enolate oxidation / nucleophilic addition sequence was then used to stereoselectively install the C_1 and C_2 (naphthalene numbering) cis α,α-diol functionality also present in the forskolin structure. Subsequent functional group manipulations then provided 1,2,5,6,7,8,8a-heptahydro-1α,2α,4-trihydroxy-8α-(tert-butyldimethylsiloxy)-1β(1'-hexynyl)-2,5,5,8aβ-tetramethyl-naphthalen-3-one, a highly oxygenated α-diketone intermediate for the synthesis of forskolin.

A number of the decalin compounds leading to the α-diketone intermediate mentioned above, were tested for antifeedant activity against the spruce budworm *(Choristoneura fumiferana)*. Eleven of these compounds were found to be active and structure-activity relationships were examined.

SYNTHESE DE COMPOSÉS DÉCALINIQUES COMPORTANTS DE NOMBREUX ATOMES D'OXYGENE

RÉSUMÉ

On a réexaminé la réaction d'annélation en tandem de Michael et de Claisen (4C + 2C) catalysée par un acide de Lewis entre le 1-triméthylsiloxy-1-méthoxy-3-phénylthio-1,3-butadiène et la 4,4-diméthyl-2-cyclohexèn-1-one. Les intermediaires obtenus (les adduits de Michael E et Z) cyclisent en milieu basique pour former la β-dicétone 3-phénylthio-5,6,4a,8a-tétrahydro-5,5-diméthyl-(4H,7H)-naphthalèn-1,8-dione. La méthylation angulaire de cette dernière en milieu basique a également été examinée en detail: on obtient le produit de méthylation *cis* stéréosélectivement.

On a tiré parti de la stéréochimie *cis* de la jonction de cycle dans la β-dicétone mentionnée ci-dessus pour permettre l'hydroxylation stéréoselective du carbone C8 (numérotation du cycle de la naphthalène) requise dans la synthèse de la forskoline. La fonction α,α-diol *cis*, également présente dans la forskoline, a par la suite été introduite sur les atomes C_1 et C_2 par oxydation d'énolate suivie d'une addition nucléophile. Des manipulations fonctionnelles ultérieures ont conduit à l'obtention de la 1,2,5,6,7,8,8a-heptahydro-1a,2a,4-trihydroxy-8a-(tert-butyldiméthylsiloxy)-1b(1'-hexynyl)-2,5,5,8aβ-tétraméthylnaphthalèn-3-one, une a-dicétone intermédiaire pour la synthèse de la forskoline comportant de nombreux atomes d'oxygène.

Plusieurs des présurseurs décaliniques de l'α-dicétone mentionée ci-dessus ont été testés comme antiappétants chez la tordeuse des bourgeons de l'épinette (*Choristoneura fumiferana*). Onze de ces composés se sont révélés actifs: leurs relations structure-activité ont été examinées.

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I would like to sincerely thank Dr. Chan for his guidance, encouragement and patience thoughout my stay in his laboratory.

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Thank you all for making this thesis possible.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl
bp	boiling point
Bu	butyl
cat	catalyst
d	doublet
DA	Diels-Alder
DBB	dimethylboron bromide
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DIBALH	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAD	dimethylacetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
gem	geminal
h	hour (s)
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
Hz	hertz
INOC	intramolecular nitrile oxide cycloaddition
IR	infrared

NMR	nuclear magnetic resonance
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m	multiplet
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
min	minute (s)
MHz	megahertz
mp	melting point
MS	mass spectrometry
NBS	N-bromosuccinimide
NMO	N-methylmorpholine N-oxide monohydrate
nOe	nuclear Overhauser enhancement
Ph	phenyl
ppm	parts per million
PMB	*para*-methoxybenzyl
iPr	isopropyl
p-TSA	*para*-toluenesulphonic acid
ORTEP	Oak Ridge thermal elipsoid plot
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PPTS	pyridinium *para*-toluenesulphonate
pyr	pyridine
q	quartet

s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBAH	tetrabutylammonium hydroxide
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
tf	trifluoromethanesulphonate
THF	tetrahydrofuran
TMS	trimethylsilyl
TsOH	para-toluenesulphonic acid

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

Further utility of the tandem Michael-Claisen (4C+2C) annelation reaction in natural product synthesis has been demonstrated by the stereoselective construction of a highly functionalized (oxygenated) decalin intermediate 5.9 for the synthesis of forskolin 1.6.

New general methodology for the direct oxidation of enolates using dimethyldioxirane has been developed and successfully incorporated into our synthetic sequence leading to the advanced intermediate decalin compound 5.9. The methodology offers a number of advantages over existing methods for direct enolate oxidation. Most importantly, the mild nature of the dimethyldioxirane reagent prevents further oxidation of the α-hydroxy products, a problem frequently encountered with the other existing methods.

A number of the functionalized decalin intermediates prepared during the course of the synthetic work leading to 5.9 were tested for antifeedant activity against the spruce budworm *(Choristoneura fumiferana)*. Eleven of these compounds were found to be active when incorporated into the artificial diet at a concentration of 2000 ppm (0.2% wet weight).

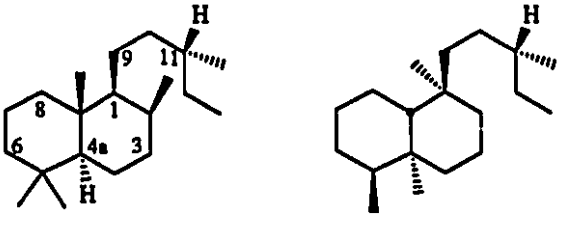
To my family,
for their encouragement.

CHAPTER 1

INTRODUCTION

1.1 Highly Oxygenated Bicyclic Diterpenoids: Classification and Biosynthetic Origins

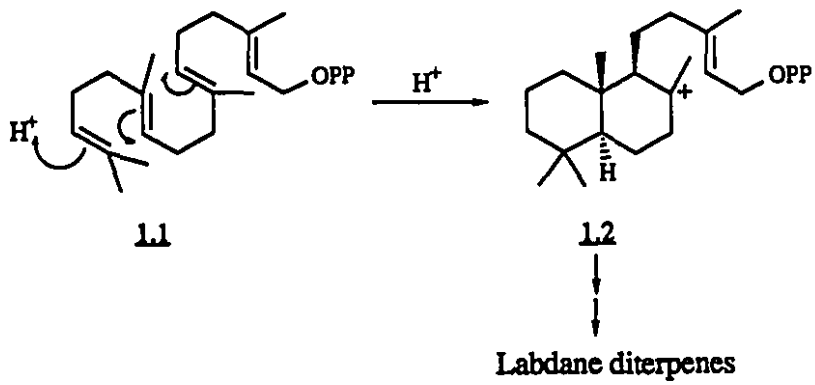
Bicyclic diterpenes represent a large number of the naturally occuring terpenes. They are generally classified into two main groups namely the labdanes and clerodanes, each containing a functionalized decalin ring skeleton (Figure 1.1).



Labdane Clerodane

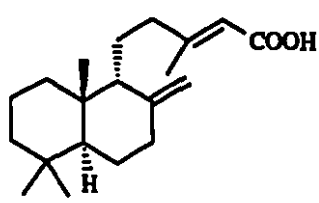
Figure 1.1

The labdane diterpenoids constitute the largest diterpene group and are widely distributed in nature; however, they are generally restricted to higher plants. In a biogenetic sense, labdane diterpenes (as well as most diterpenes) are believed to be derived from geranylgeraniol pyrophosphate (GGPP) 1.1 via a cationic polyene cyclization [1] (Scheme 1.1) to give an intermediate carbocation of general structure 1.2. Many simple labdane diterpenes such as copalol 1.3 [2], sclareol 1.4 [3], and manoyl oxide 1.5 [4] have either an olefin linkage involving the C_2 (naphthalene numbering) center or have oxygen function-



Scheme 1.1

ality on this carbon, further supporting the intermediacy of the carbocation 1.2 in the biogenetic pathway. Although manoyl oxide derivatives bearing a cyclic ether moiety are quite common, highly oxygenated labdane diterpenes such as forskolin 1.6, and related compounds 1.7, 1.8, 1.9 and 1.10 as well as erigerol 1.11, are rare.



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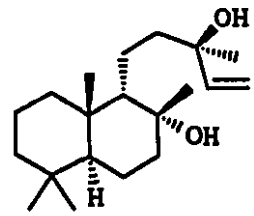

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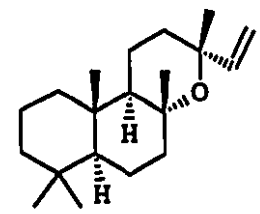

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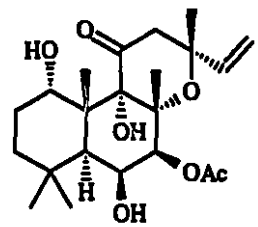

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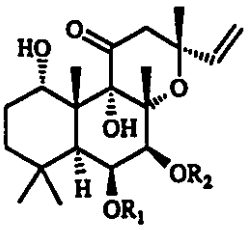
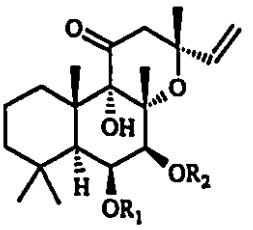
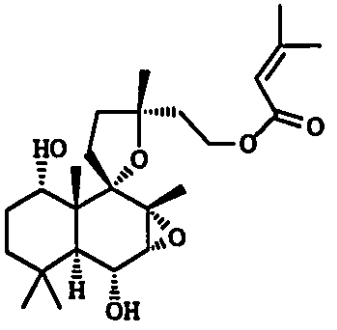


1.7 R_1 = Ac, R_2 = H
1.8 R_1 = R_2 = H



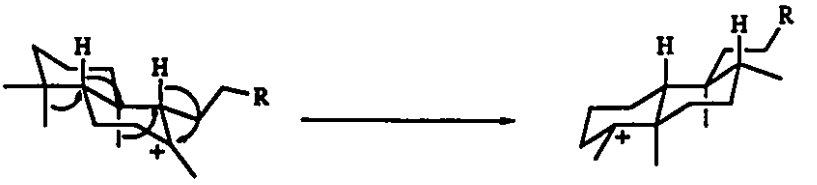
1.9 R_1 = H, R_2 = Ac
1.10 R_1 = R_2 = H



1.11

Forskolin 1.6 is a labdane diterpene isolated from the methanolic extracts of the roots (0.1% of the dry weight) of the Indian plant *Coleus forskohlii* Briq.(Labiatae) [5]. The structure and absolute configuration of 1.6 and related compounds 1.7, 1.8, 1.9 and 1.10 of the root extract were determined by extensive spectroscopic, chemical [6] and X-ray crystallographic techniques [7a,7b]. Recently, the absolute stereochemistry of 1.6 has been confirmed by applying the exiton chirality circular dichroism method [7c]. The structurally related labdane diterpene erigerol 1.11 was isolated from the aerial parts of *Erigeron philadelphicus* L. in very low yield. Its structure was determined by spectral data and X-ray analysis [8] and its total synthesis has recently been reported [9].

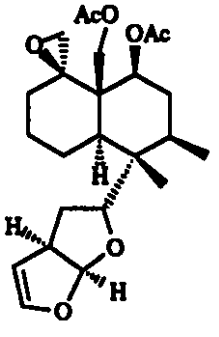
Clerodanes are bicyclic diterpenes which are believed to arise from their parent labdane precursors via a concerted backbone rearrangement involving sequential hydride and methyl shifts (Scheme 1.2) [10]. The highly oxygenated clerodane diterpene clerodin 1.12



Labdane type Clerodane type

Scheme 1.2

was first isolated from the roots of the indian bhat tree (*Clerodendron infortunatum* Linn) in 1936 [11] and later found to be the major constituent of the ground leaves and twigs [12] as well as the air-dried flowers [13]. Clerodin has also been isolated from the roots of *Clerodendron colebrookium* and *Clerodendron phlamoides* [14] and is considered to be the parent compound of over 650 clerodane diterpenes including the ajugarins I - III 1.13 - 1.15.



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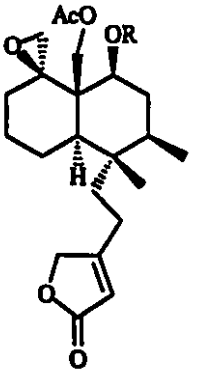
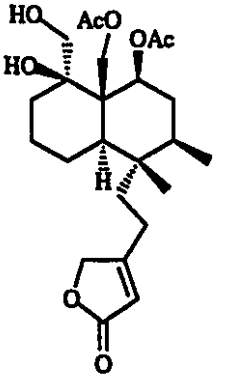


1.13 R = Ac
1.14 R = H



1.15

The highly oxygenated diterpenoids mentioned above represent challenging synthetic targets in that they pose a number of interesting stereochemical problems. In particular, close examination of the forskolin structure 1.6 reveals a rather simple molecular skeleton that accomodates a number of oxygenated groups. As a consequence of their stereochemistry, they generate a number of 1,3-diaxial interactions making their mode of introduction synthetically challenging. The interesting biological activity and therapeutic potential associated with 1.6 as well as its structural complexity have rendered forskolin a highly attractive target for synthetic organic chemists worldwide.

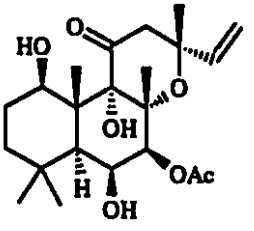
1.2 Approaches to the Functionalized Decalin Ring System of Forskolin

The highly oxygenated labdane diterpene forskolin 1.6 has been found to interact with a wide range of membrane proteins including adenylyl cyclase and the glucose transporter [15]. This produces significant cardiotonic effects due to its ability to interact directly with the catalytic subunit of the adenylate cyclase system [16] and increase intracellular cyclic AMP [17]. Forskolin increases cyclic AMP *in vivo*, which has prompted considerable investigation into its therapeutic potential in the treatment of a number of indications including glaucoma [18], asthma [19] and heart disease [20].

Although forskolin 1.6 displays interesting cardiotonic activity, poor aqueous solubility and insufficient metabolic stability are important limitations for clinical applications. In addition to the isolation and identification of the related compounds 1.7, 1.8, 1.9 and 1.10 of the root extract, numerous derivatives of forskolin have been prepared in order to address this problem. For example, analogs bearing different acyl groups on the 3β-, 4β- and 8α- (napthalene numbering) hydroxyl groups [21] as well as water-soluble derivatives have been prepared and tested for their ability to activate adenylyl cyclase [22]. Other halogenated derivatives, primarily for use in biochemical assays on forskolin binding

proteins have been synthesized. These include α-haloacetyl derivatives such as 4-(bromoacetyl)-4-desacetylforskolin and 4-(chloroacetyl)-4-desacetylforskolin [23] which irreversibly block the forskolin binding site on adenylyl cyclase. More recently, a number of 3β- and 4β-(aminoalkyl) carbamates of forskolin have been synthesized [24] and their binding affinities for adenylyl cyclase and the glucose transporter examined.

Vishwakarma and co-workers [25a] have reported the preparation of the unnatural forskolin epimers 1.16, 1.17 and 1.18 using Mitsunobu's inversion procedure. The same group has also reported that forskolin undergoes Lewis acid catalysed rearrangement to "spiroforskolin 1.19" [25b]. Treatment of forskolin with boron trifluoride etherate in benzene afforded 1.19 in 45% yield and when it was kept in methanol at room temperature for 3-4 days, it reverted back to natural forskolin.



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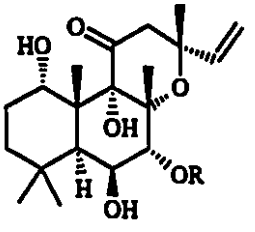
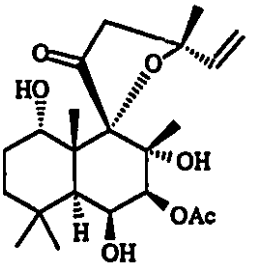


1.17 R = $COCF_3$
1.18 R = H



1.19

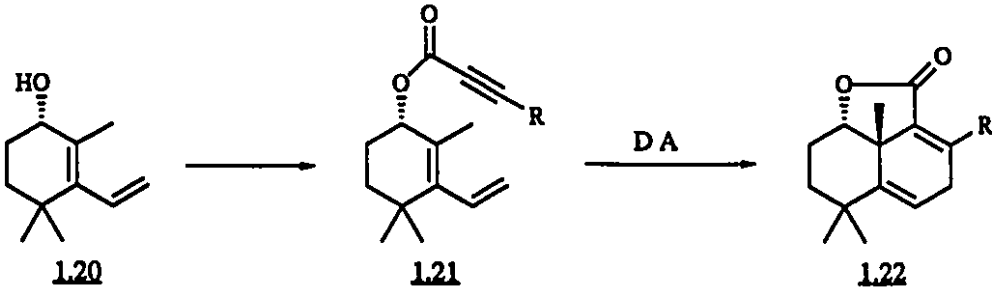
1.2.1 Some early approaches to 1.6

Since its isolation in 1977, forskolin 1.6 has been the subject of considerable synthetic effort. A number of reports have appeared on the synthesis of the AB or decalin ring skeleton as well as its total synthesis at the hands of Ziegler [26], Corey [27] and Ikegami [28]. Many of the early approaches to 1.6 have taken advantage of either the Intra and

Intermolecular Diels-Alder (DA) or the Intramolecular Nitrile Oxide Cycloaddition (INOC) strategies for the construction of the decalin ring system.

The Intramolecular Diels-Alder Strategy

In general, many of the intramolecular Diels-Alder approaches described to date utilize an acetylenic ester cycloaddition precursor 1.21 (readily available from the alcohol 1.20) which upon thermolysis, affords the corresponding cycloadducts 1.22 (Scheme 1.3).

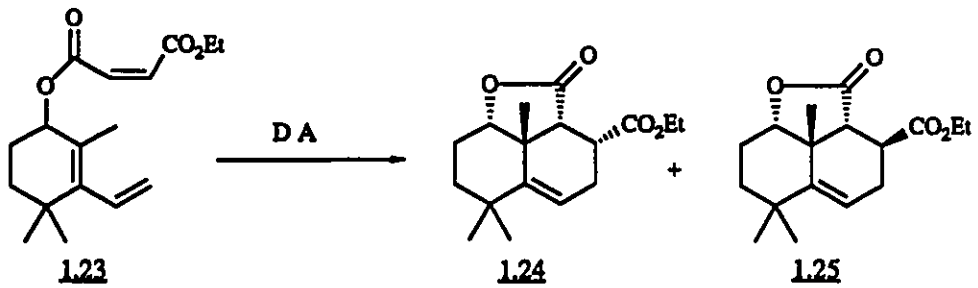


1.20 1.21 1.22

Scheme 1.3

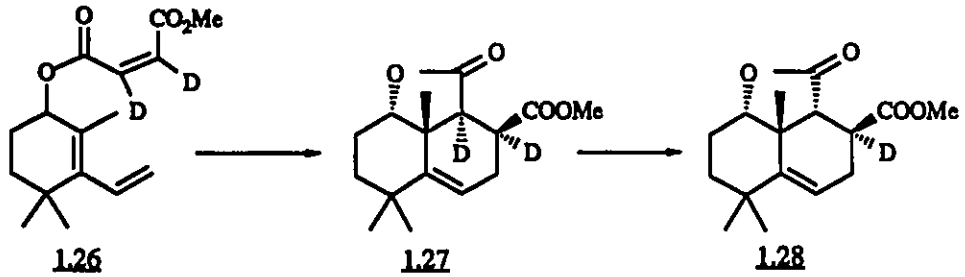
Perhaps the earliest approach to 1.6 was reported in 1984 by Jenkins and co-workers [29] who constructed the AB ring skeleton via intramolecular cycloaddition of the maleate 1.23 (Scheme 1.4). Thermolysis of 1.23 in benzene at 150°C produced a mixture of the two epimeric cycloadducts 1.24 and 1.25 in a ratio of 1:3 in favor of 1.25. The formation of an epimeric mixture at the carboethoxy bearing carbon was initially rationalized in terms of non-synchronous cyclization of a diradical intermediate in the double bond isomerization reaction. The stereochemical assignments of the lactones 1.24 and 1.25 were confirmed by X-ray crystallography and it was demonstrated by deuterium labelling studies that the apparent loss of the dienophile stereochemistry of 1.26 in forming 1.28 is due to the epimerization of the C_1 (naphthalene numbering) center of the strained lactone 1.27

(Scheme 1.5) [30].



1.23 1.24 1.25

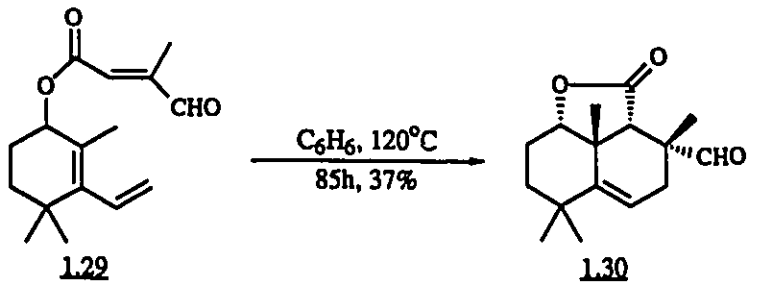
Scheme 1.4



1.26 1.27 1.28

Scheme 1.5

A similar intramolecular Diels-Alder strategy has been reported by Ziegler and coworkers who utilized the unsaturated aldehyde 1.29 in the cycloaddition step (Scheme 1.6). Thermolysis of 1.29 in benzene produced a single Diels-Alder adduct 1.30 in 37% yield with 55% recovered 1.29. The tricyclic cycloadduct 1.30 has been used successfully in a synthetic sequence to forskolin 1.6 (see section 1.2.2).

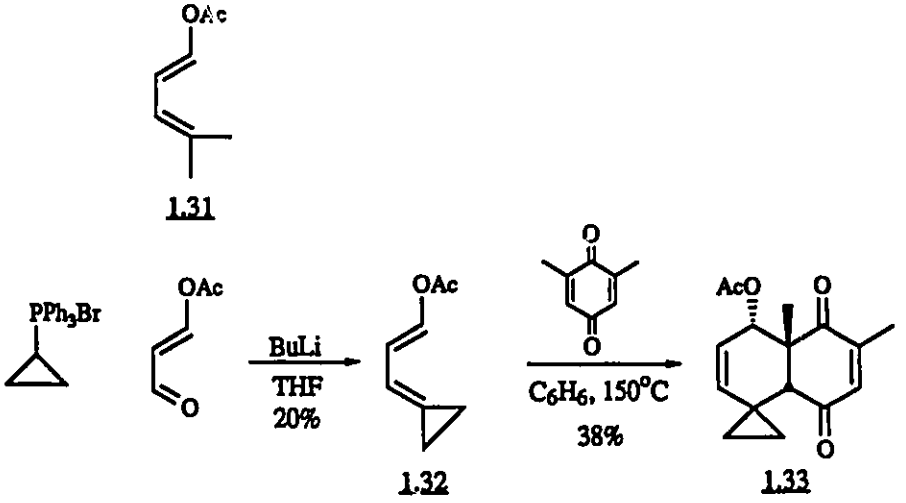


1.29 1.30

Scheme 1.6

The Intermolecular Diels-Alder Strategy

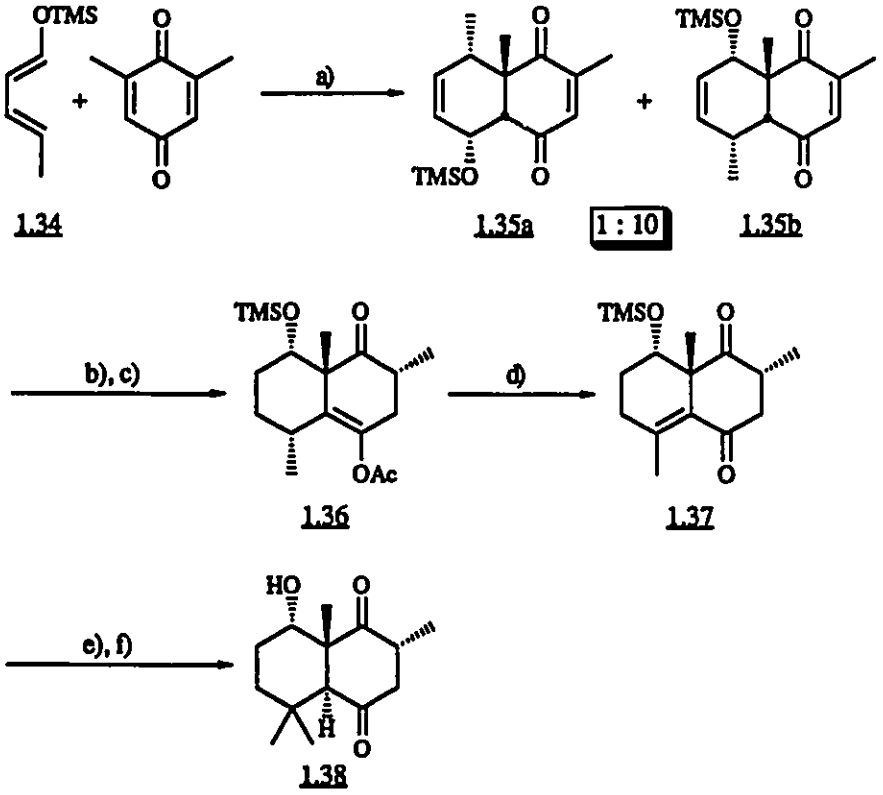
The intermolecular Diels-Alder (DA) cycloaddition strategy has also been used successfully for the construction of the AB ring system of forskolin 1.6. In an attempt to avoid the use of a hindered geminally substituted diene component such as 1.31 in the cycloaddition step, Snider and co-workers [31] prepared the diene 1.32 albeit in low yield (Scheme 1.7). Reaction of 1.32 and 2,6-dimethylbenzoquinone in benzene gave the cycloadduct 1.33 however the low overall yield for the two step sequence precluded further elaboration to forskolin.



1.31 1.32 1.33

Scheme 1.7

A similar intermolecular DA approach to 1.6 has been reported by Sih [32] and co-workers who utilized the 1,4-disubstituted diene 1.34 in the cycloaddition step. Thermolysis of 1.34 and 2,6-dimethylbenzoquinone in toluene at 120°C produced a regioisomeric mixture of cycloadducts 1.35a and 1.35b in good yield (Scheme 1.8). The use of the diene 1.34 allowed the incorporation of one of the C_5 (naphthalene numbering) methyl groups as well as the C_8 hydroxyl function.



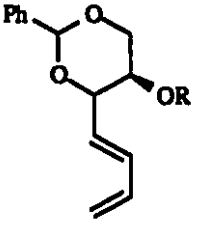
Reagents: a) PhMe, sealed tube, 120°C, 50%; b) H_2, Pd/C, EtOAc, 97%; c) $CH_2{=}C(Me)OAc$, TsOH, 94%; d) $PhSeO_2CCF_3$ then oxidative elimination, 57%; e) MeCu. BF_3, Bu_3P, 87%; f) NaOMe, MeOH, THF, r.t., 87%.

Scheme 1.8

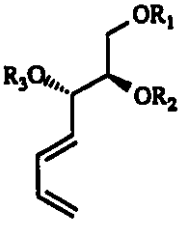
Hydrogenation of the major regioisomer 1.35b followed by enol acylation gave the enol

acetate 1.36. Selenation of 1.36 followed by oxidative elimination of the corresponding selenoxide provided the enone 1.37 in good overall yield. The remaining C_5 methyl group was then introduced via cuprate addition onto 1.37. Desilylation and epimerization of the ring junction was then carried out in one operation to give the β-hydroxy ketone 1.38.

Bhakuni and co-workers [33] have reported that the series of suitably protected dienes 1.39a - d and 1.40a - d (derived from D-glucose) undergo intermolecular Diels-Alder (DA) reaction with carbomethoxy-p-quinone to afford the corresponding cycloadducts in good yield. Accordingly, the cycloadduct 1.41 was produced from the diene 1.39a in good yield (Scheme 1.9).

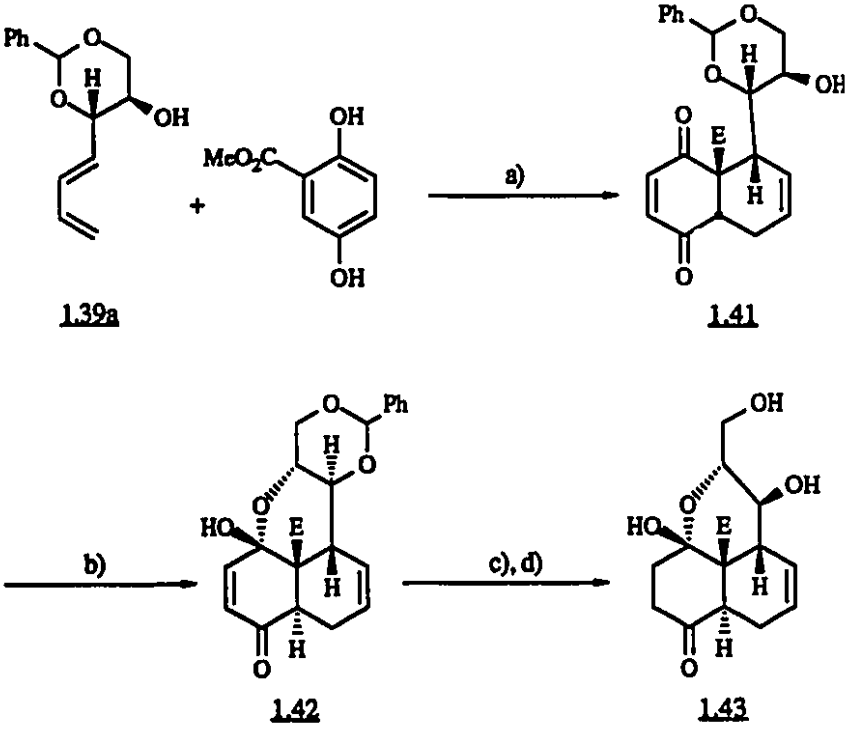


1.39a R = H
1.39b R = Ac
1.39c R = Ms
1.39d R = Me



1.40a $R_1 = R_2 = R_3 = Ac$
1.40b $R_1 = R_3 = Ac$; $R_2 = THP$
1.40c $R_1 = R_2 = R_3 = Me$
1.40d $R_1 = R_3 = Me$; $R_2 = THP$

Upon exposure to basic alumina, the cycloadduct 1.41 underwent epimerization and hemiketalization in one operation to give the trans ketone 1.42. Subsequent deprotection under acidic conditions provided the triol 1.43. Following the same sequence of reactions outlined in Scheme 1.9, the diene 1.40a was converted to the same triol 1.43 illustrating that the DA reaction followed the same stereo and regioselectivity for both diene series.



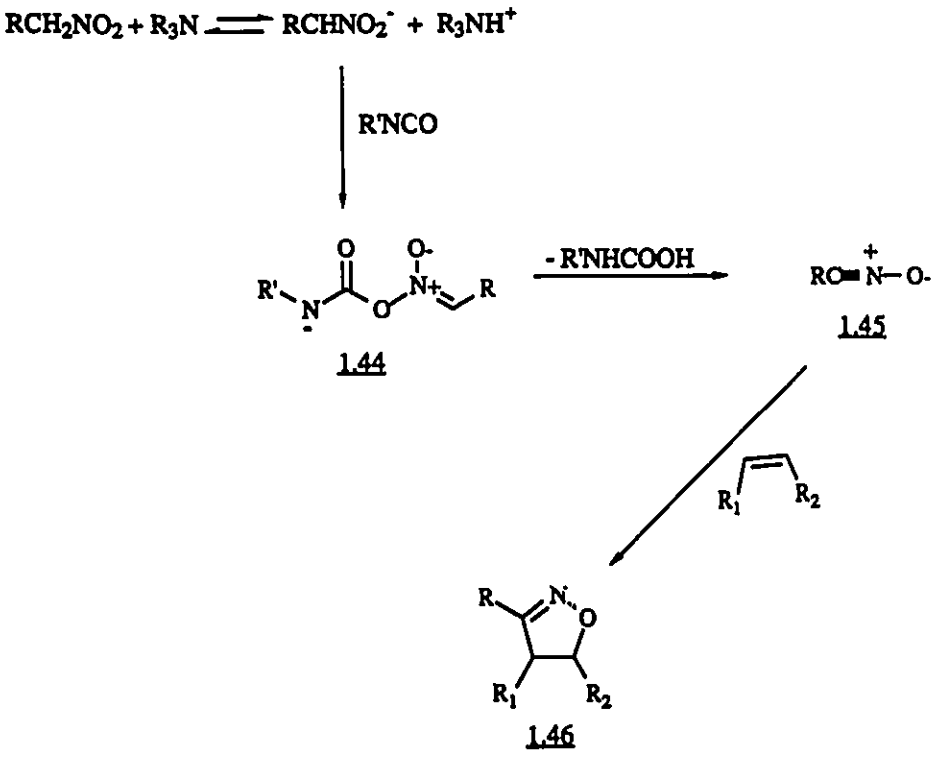
Reagents: a) Ag_2O, C_6H_6, r.t., 80%; b) basic Al_2O_3, 100%; c) Zn, HOAc; d) H_2O, HOAc, 80°C.

Scheme 1.9

The Intramolecular Nitrile Oxide Cycloaddition Strategy

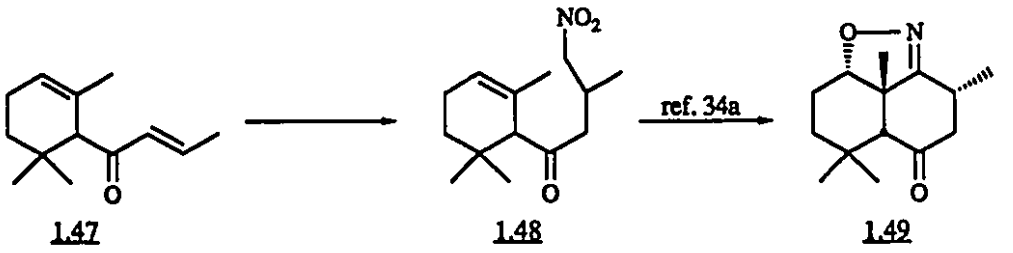
The intramolecular nitrile oxide cycloaddition or INOC reaction has also received considerable attention as an approach to the construction of the AB ring system of forskolin 1.6. In general, nitrile oxides may be generated from isocyanates and nitroalkanes according to Scheme 1.10 below [34a]. The intermediate adducts 1.44 decompose readily through proton transfer to give the corresponding nitrile oxides 1.45 and carbamic acid.

Alternatively, they may be generated from the corresponding oximes by oxidation with hypochlorite [34b]. Nitrile oxides of the type 1.45 are known to undergo [3+2] cycloaddition with a wide variety of olefins to give isoxazolines 1.46 which are valuable synthetic intermediates [35].



Scheme 1.10

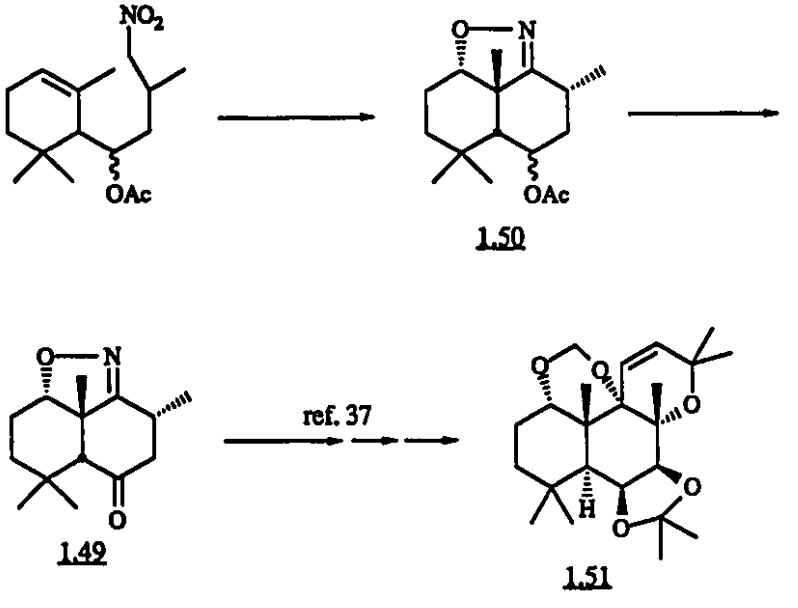
Barco and co-workers [36] have reported that the Michael adduct 1.48 (which is readily available from α-damascone 1.47) undergoes intramolecular nitrile oxide cycloaddition under the standard Mukaiyama conditions [34a] to give the cycloadduct 1.49, albeit in only 20% yield (Scheme 1.11).



1.47 1.48 1.49

Scheme 1.11

The corresponding acetate however, underwent smooth INOC to afford the cycloadducts 1.50 (bearing the cis ring junction stereochemistry) as an epimeric mixture in 90% yield (Scheme 1.12). Saponification of the acetate followed by Moffatt oxidation then provided the cycloadduct 1.49 which has been further elaborated to the model tricyclic system 1.51 although subsequent attempts to functionalize the olefin moiety of 1.51 failed [37].



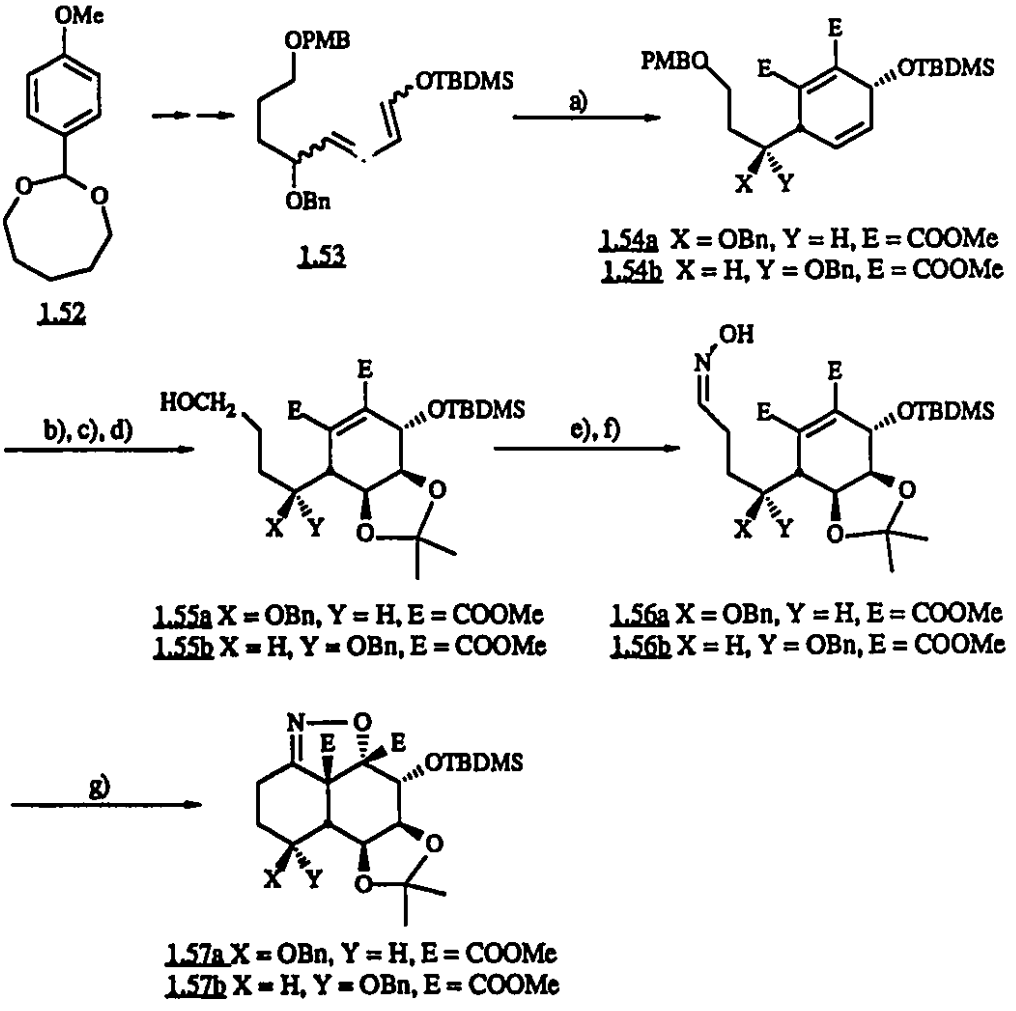
1.50

1.49 1.51

Scheme 1.12

Kozikowski [38] has recently reported a [(4+2)+(3+2)] tandem cycloaddition approach to the AB ring system of 1.6 which utilizes both the intermolecular DA and INOC strategies

(Scheme 1.13). The Diels-Alder cycloaddition precursor 1.53 was prepared from the acetal 1.52 in a six step sequence to afford a diene mixture (E,E-diene / other dienes = 2 / 1). Reaction of 1.53 with dimethylacetylenedicarboxylate (DMAD) afforded an isomeric mixture of DA cycloadducts 1.54 originating from the major E,E-diene. Subsequent osmylation of the disubstituted double bond of 1.54, protection of the diol as the acetonide and deprotection of the primary alcohol afforded 1.55. Oxidation of 1.55 to the aldehyde followed by oxime formation provided two INOC precursors 1.56 which underwent smooth cycloaddition under oxidative conditions to provide the key intermediate 1.57 in good yield.

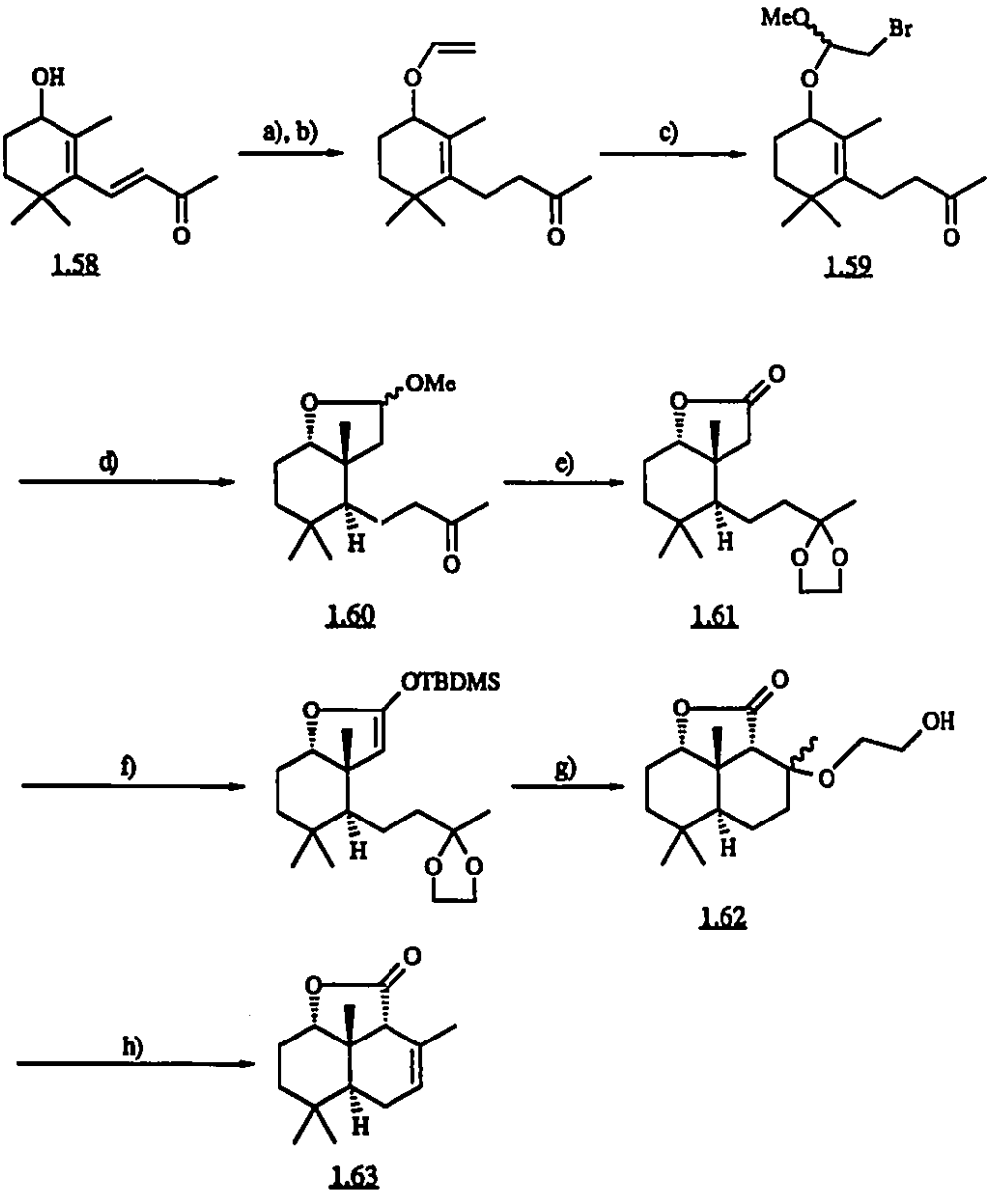


Reagents: a) DMAD, 120°C, 41%; b) OsO_4, NMO, Me_2CO, H_2O, r.t.; c) $Me_2C(OMe)_3$, PPTS, CH_2Cl_2, r.t., 70% over 2 steps; d) DDQ, CH_2Cl_2, H_2O, r.t., 83 - 95%; e) PCC, CH_2Cl_2, r.t., 88%; f) H_2NOH HCl, pyridine, r.t., 99%; g) NaOCl, xylenes, H_2O, 105 - 120°C, 66% 1.57a and 53% 1.57b .

Scheme 1.13

The Tandem Radical Cyclization / Intramolecular Mukaiyama Aldolization Approach

Utilizing a novel stereoselective radical cyclization and intramolecular aldolization sequence, Pattenden and co-workers [39] converted the bromoacetal 1.59 to the tricyclic



Reagents: a) Bu_3SnH, 95%; b) $EtOCH{=}CH_2$, $Hg(OAc)_2$, 57%; c) NBS, MeOH, -20°C, 98%; d) vitamin B_{12}, MeOH, $LiCLO_4$, -1.8V, r.t., then H_2CrO_4, 70%; e) $HOCH_2CH_2OH$, TsOH, 93%; f) LHMDS, TBDMSCl, -70°C to 0°C, 95%; g) $TiCl_4$, CH_2Cl_2, -78°C, 62%; h) KOH, MeOH, reflux, 82%.

Scheme 1.14

lactone 1.63 (Scheme 1.14). The bromoacetal 1.59 was prepared from hydroxy-β-ionone 1.58 via a three step sequence involving 1) conjugate reduction with tributyltin hydride, 2) trans-etherification with ethylvinyl ether in the presence of mercuric acetate and finally 3) bromination in methanol. The bromoacetal 1.59 underwent smooth radical mediated cyclization in the presence of electrochemically generated Co (I) to give the bicyclic acetal 1.60 which was oxidized (Jones reagent) and ketalized to give the lactone 1.61. Conversion of the lactone 1.61 to its enolsilyl ether under standard conditions followed by titanium tetrachloride promoted intramolecular aldolization gave the tricyclic lactone 1.62 as a mixture of diastereomers in good yield. Elimination of glycol from 1.62 by treatment with potassium methoxide in refluxing methanol afforded 1.63.

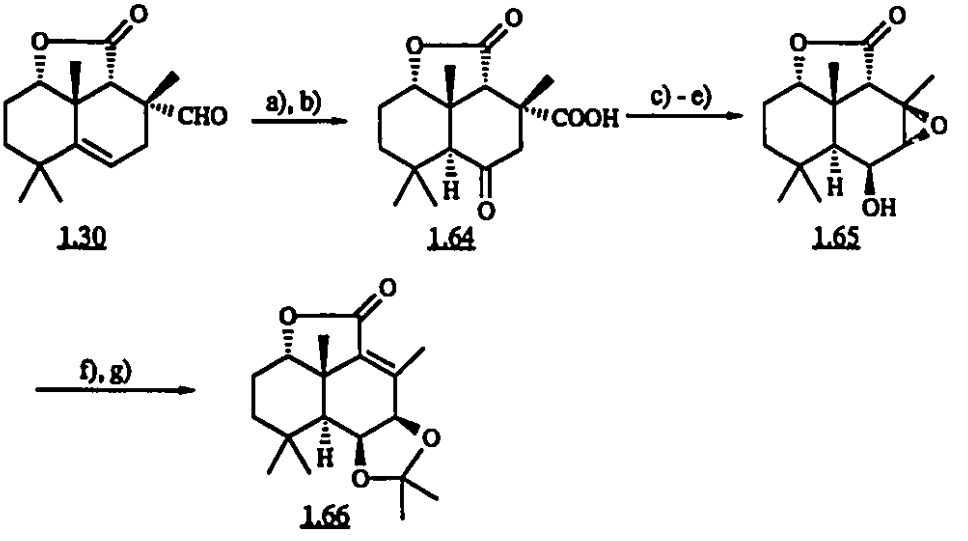
1.2.2 Total Syntheses of Forskolin

To date, three successful approaches to forskolin 1.6 have been reported [26, 27, 28]. An important feature which is common to each approach is the use of the intramolecular Diels-Alder cycloaddition strategy for the construction of the decalinic or AB ring skeleton. Furthermore, in each case, the construction of the C ring was postponed until the latter stages of the syntheses.

Ziegler's Synthesis of Forskolin

The initial stages of Ziegler's synthesis [26] of 1.6 involved the conversion of the Diels-Alder cycloadduct 1.30 to the lactone 1.66 by a seven step sequence as outlined in Scheme 1.15. Hydroboration of 1.30 followed by Jones oxidation and base catalysed

epimerization provided the keto-acid 1.64. Oxidative decarboxylation of 1.64 and subsequent 1,2-enone reduction provided an intermediate allylic alcohol which underwent directed epoxidation to give the epoxy alcohol 1.65 stereoselectively. Ring opening of the epoxide moiety with base provided a single diol which was protected as the acetonide 1.66.

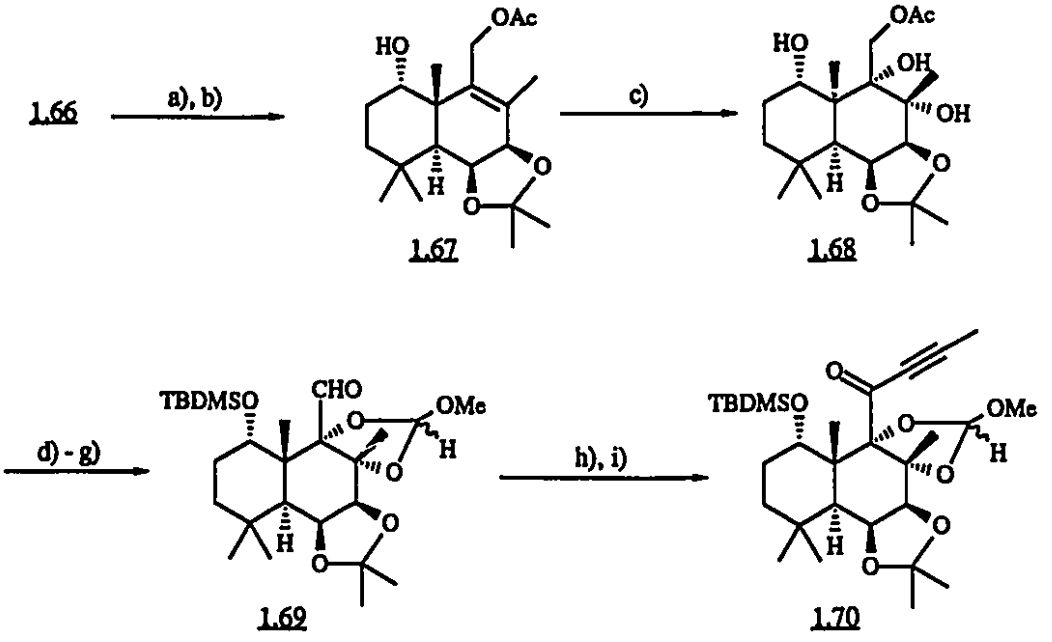


Reagents: a) BH_3.THF, 0°C, NaOOH; b) H_2CrO_4, 0°C, 60%; c) KOMe, MeOH, reflux, 95%; $Pb(OAc)_4$, pyridine, 95%; d) $LiBH_4$, Li_2CO_3, EtOH, 25°C, 52%; e) t-BuOOH, $VO(acac)_2$, CH_2Cl_2, 25°C, 95%; f) $LiNEt_2$, THF, -78°C to -25°C g) $Me_2C(OMe)_2$, TsOH, 25°C.

Scheme 1.15

The remaining cis C_1 and C_2 hydroxyl functionalities on the decalin ring system were installed by stereoselective osmylation of the allylic acetate 1.67 (prepared by the reduction of 1.66 and selective acetylation) to give the triol 1.68 (Scheme 1.16). Protection of the secondary hydroxyl of 1.68 as the TBDMS ether followed by the C_1, C_2 cis diol as the orthoformates gave, after saponification of the acetate and oxidation, the aldehydes 1.69.

Addition of 1-lithiopropyne to the major aldehyde followed by Collins oxidation of the

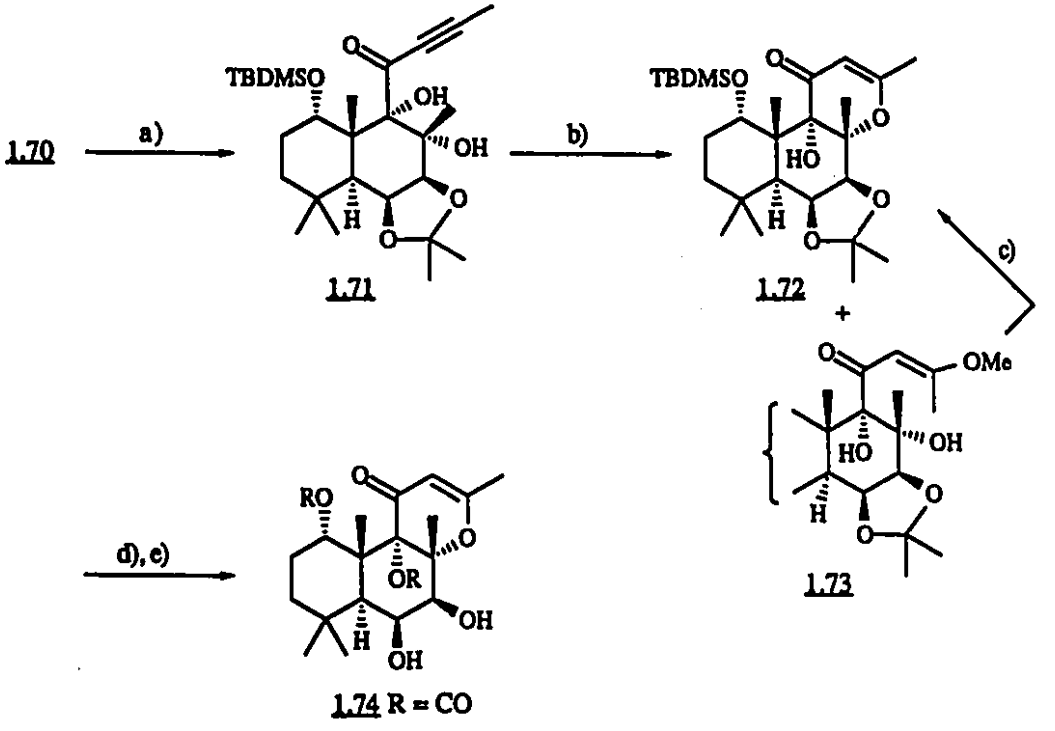


Reagents: a) LAH, Et_2O, 25°C, 1h; b) N-acetylimidazole, DBU, C_6H_6, 25°C, 1h, 95% from 1.66; c) OsO_4, pyridine, 25°C, then H_2S, 85%; d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2,0°C, 75%; e) neat $CH(OMe)_3$, TsOH, 25°C, 97%; f) KOH, MeOH, THF, 25°C; g) CrO_3.2pyr, CH_2Cl_2, 25°C, 88% over 2 steps; h) 1-lithiopropyne, THF, -10°C, 84%; i) CrO_3.2Pyr, CH_2Cl_2, 25°C, 94%.

Scheme 1.16

resulting propargyl alcohol gave the acetylenic ketone 1.70 which was converted to the dihydropyrone 1.74 in five steps as outlined in Scheme 1.17. Removal of the orthoformate protecting group then provided the diol 1.71 which underwent cyclization under basic conditions to produce a mixture of the dihydropyrone 1.72 and the E-vinologous ester 1.73 which could also be cyclized to 1.72 under acidic conditions in good overall yield. The

The dihydropyrone 1.72 was then desilylated, reacted with phosgene and deketalized to give the cyclic carbonate 1.74. Degradation studies of natural 1.6 afforded the same



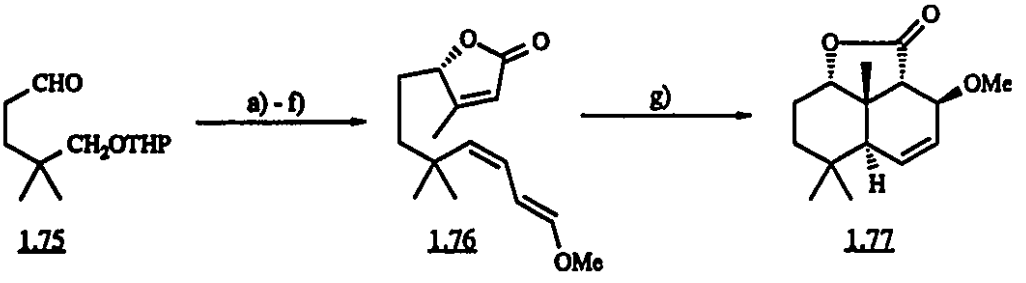
Reagents: a) 3N HCl, THF (1:25), 25°C then NH_3, MeOH, 25°C, 74%; b) KOMe, MeOH, 25°C, 44% 1.72 + 34% 1.73; c) TsOH, C_6H_6, 25°C, 97%; d) TBAF, THF, 25°C, 76% then $COCl_2$, pyridine, CH_2Cl_2, 0°C, 90%; e) 3N HCl / THF, 1:5, 50°C, 72%.

Scheme 1.17

dihydropyrone 1.74 which was converted back to 1.6 via a photochemical route [26b], thus culminating in a formal synthesis of forskolin 1.6. The photochemical route was developed in order to circumvent the conjugate vinyl addition step which appeared to be problematic.

Ikegami's Synthesis of Forskolin 1.6

Ikegami and co-workers [28] have also reported the total synthesis of forskolin 1.6 and also take advantage of the intramolecular Diels-Alder reaction for the construction of the AB ring skeleton. The cycloaddition precursor 1.76 was prepared in a six step sequence from the aldehyde 1.75 (Scheme 1.18)



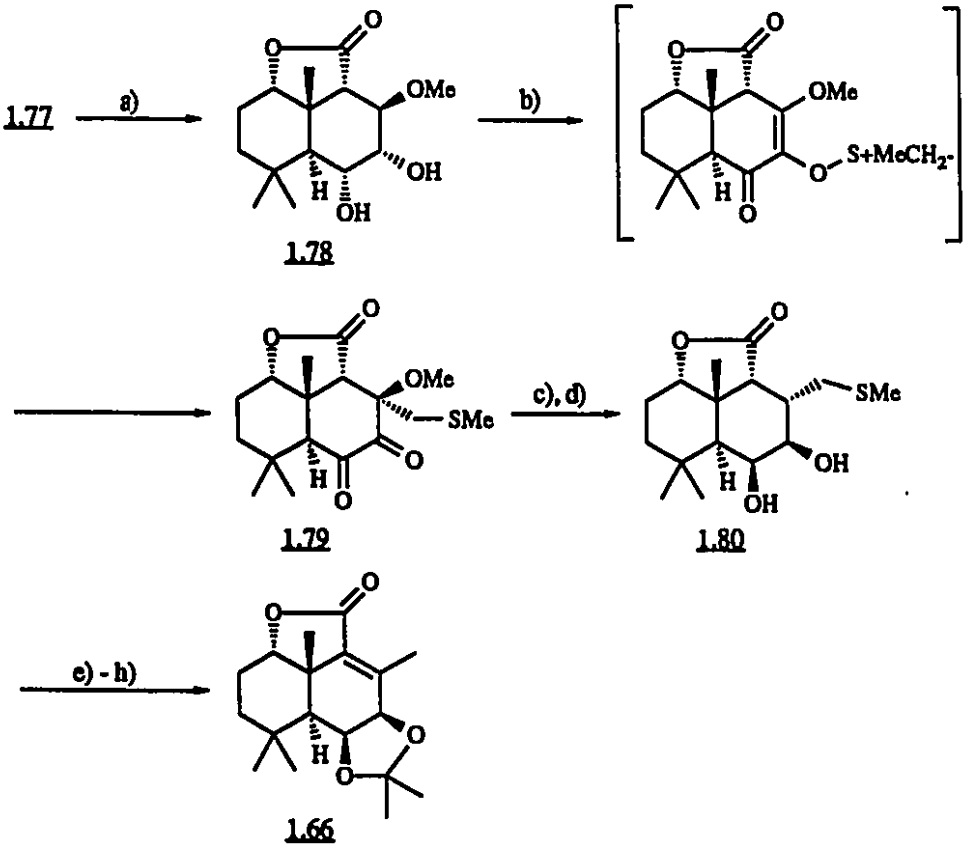
1.75 1.76 1.77

Reagents: a) LiC≡CCO$_2$Me, THF, -78°C, 91%; b) dihydropyran, TsOH, CH_2Cl_2, 0°C, 96%; c) $LiMe_2Cu$, THF, -70°C, 87%; d) TsOH, MeOH, 23°C, 90%; e) PCC, CH_2Cl_2, 23°C, 81%; f) MeOCH=$CHCH_2P^+PPh_3Br^-$, n-BuLi, THF, -25°C then -78°C to -25°C 76%; g) PhSH, PhMe, sealed tube, 220-230°C, 81%.

Scheme 1.18

The cis, trans diene 1.76 underwent tandem olefin isomerization / Diels-Alder reaction when thermolysis was carried out in the presence of thiophenol (as equilibrating catalyst) to give the adduct 1.77 as a single isomer in good yield. Subsequent stereoselective osmylation of the double bond of 1.77 gave the 3α, 4α-diol 1.78 whose stereochemistry was inverted by oxidation to the diketone 1.79 followed by stereoselective reduction to give the required 3β, 4β-diol 1.80 (Scheme 1.19). Formation of the acetonide followed by sulfoxide elimination and alkene isomerization gave the lactone 1.66, which was reduced

with LAH and tritylated to give 1.81 (Scheme 1.20). Stereoselective osmylation of 1.81 followed by protection of the secondary C_8 hydroxyl as the PMB ether gave 1.82. Detritylation of 1.82 followed by selective acetylation of the primary alcohol and orthoester

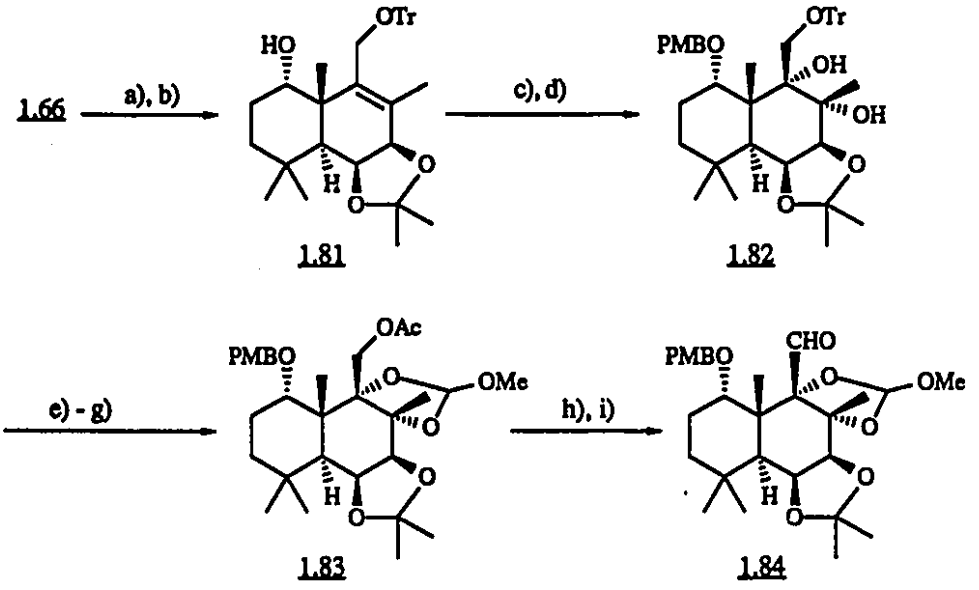


Reagents: a) OsO_4 (Cat.), NMO, pyridine, t-BuOH / H_2O (4:1), reflux, 90%; b) SO_3 - pyridine, Et_3N, DMSO, 20°C, 81%; c) NaTeH, EtOH, 23°C, 85%; d) t-BuNH_2. BH_3, MeOH, 23°C, 85%; e) $Me_2C(OMe)_2$, TsOH, C_6H_6, 23°C, 95%; f) MCPBA, CH_2Cl_2, -25°C, 94%; g) $CaCO_3$, Toluene, reflux, 68%; h) LiOMe, THF, 23°C, 92%.

Scheme 1.19

formation gave 1.83 in good overall yield. Reduction of the acetate and oxidation of the resulting alcohol gave the aldehyde 1.84 which differs from the Ziegler aldehyde 1.69 only

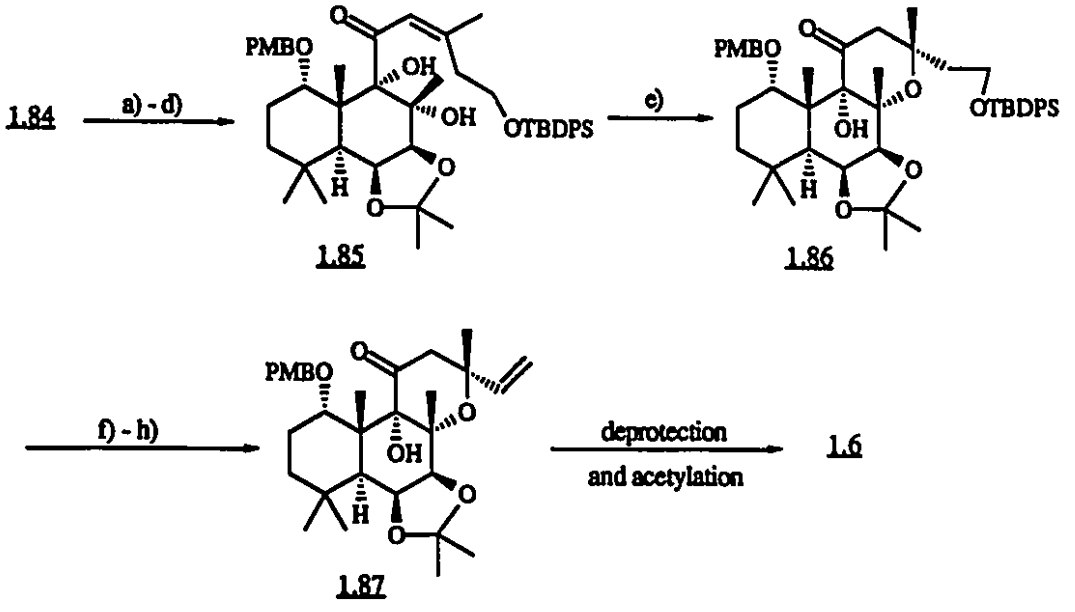
in the nature of the C_8 hydroxyl protecting group.



Reagents: a) LAH, Et_2O, reflux, 89%; b) TrCl, DMAP, $ClCH_2CH_2Cl$, reflux, 90%; c) OsO_4, pyridine, 20°C then H_2S, $CHCl_3$-Dioxane (1:1), 23°C, 83%; d) NaH, p-$MeOC_6H_4CH_2Cl$, HMPA, THF, 23°C, 91%; e) TsOH, $CHCl_3$-MeOH (2:1), 20°C, 95%; f) Ac_2O, pyridine, 20°C, 96%; g) $HC(OMe)_3$, TsOH, 20°C, 95%; h) LAH, Et_2O, 0°C, 95%; i) SO_3-pyridine, Et_3N, DMSO, 23°C, 78%.

Scheme 1.20

The final stages of the synthesis involved the construction of the pyrone ring as outlined in Scheme 1.21. Addition of 4-(tert-butyldiphenylsiloxy) butynyllithium to 1.84 followed by oxidation of the allylic alcohol, conjugate methyl addition and orthoformate hydrolysis gave the enone 1.85 which was cyclized efficiently to the pyrone 1.86 with phenylselenyl chloride and subsequent Raney nickel reduction. Desilylation of the primary alcohol followed by selenation and oxidative elimination provided the pyrone 1.87 which was deprotected under standard conditions and selectively acetylated to give 1.6.



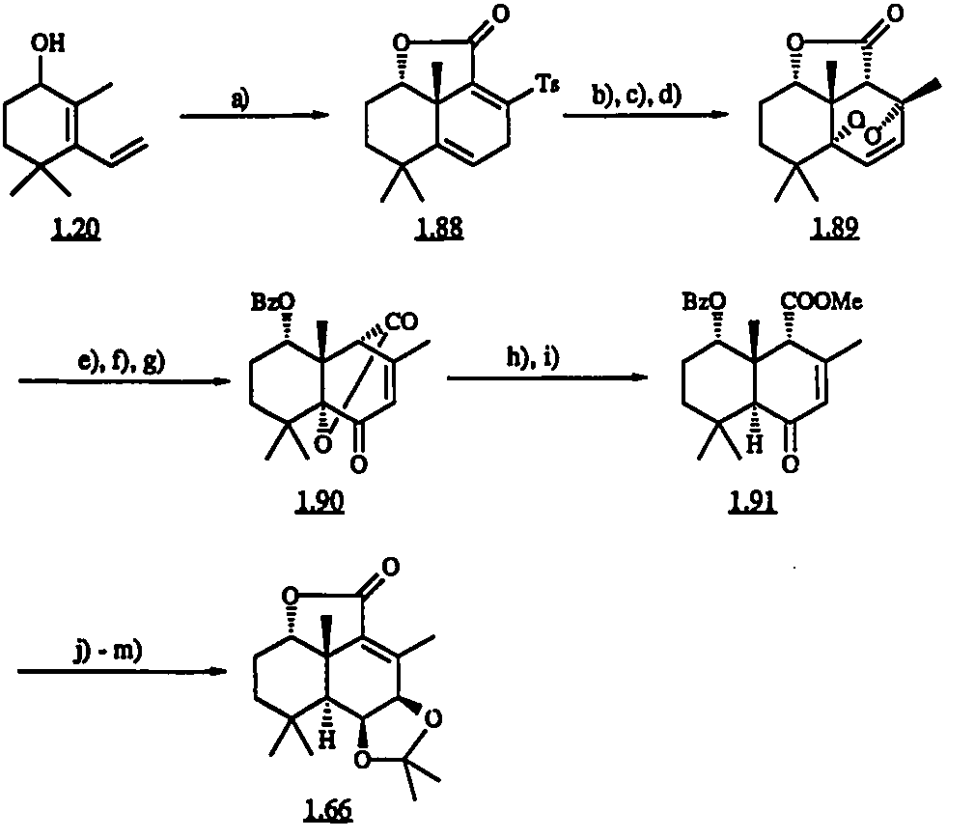
Reagents: a) $LiC{\equiv}CCH_2CH_2OSi\text{-}t\text{-}BuPh_2$, THF, -78°C to 20°C, 83%; b) MnO_2, C_6H_6, 23°C, 79%; c) $LiMe_2Cu$, Et_2O, -78°C, 93%; d) 3N HCl - THF (1:40), 23°C then 0.2 N KOH - THF - MeOH (1:4:4), 23°C, 95%; e) PhSeCl, CH_2Cl_2, 0°C then Ra-Ni (W - 2), EtOH, reflux, 78%; f) TBAF, THF, 23°C, 97%; g) $o\text{-}O_2NC_6H_4SeCN$, Bu_3P, THF, 23°C, 89%; h) 30% H_2O_2, CH_2Cl_2, 18°C, 84%.

Scheme 1.21

Corey's Synthesis of Forskolin 1.6

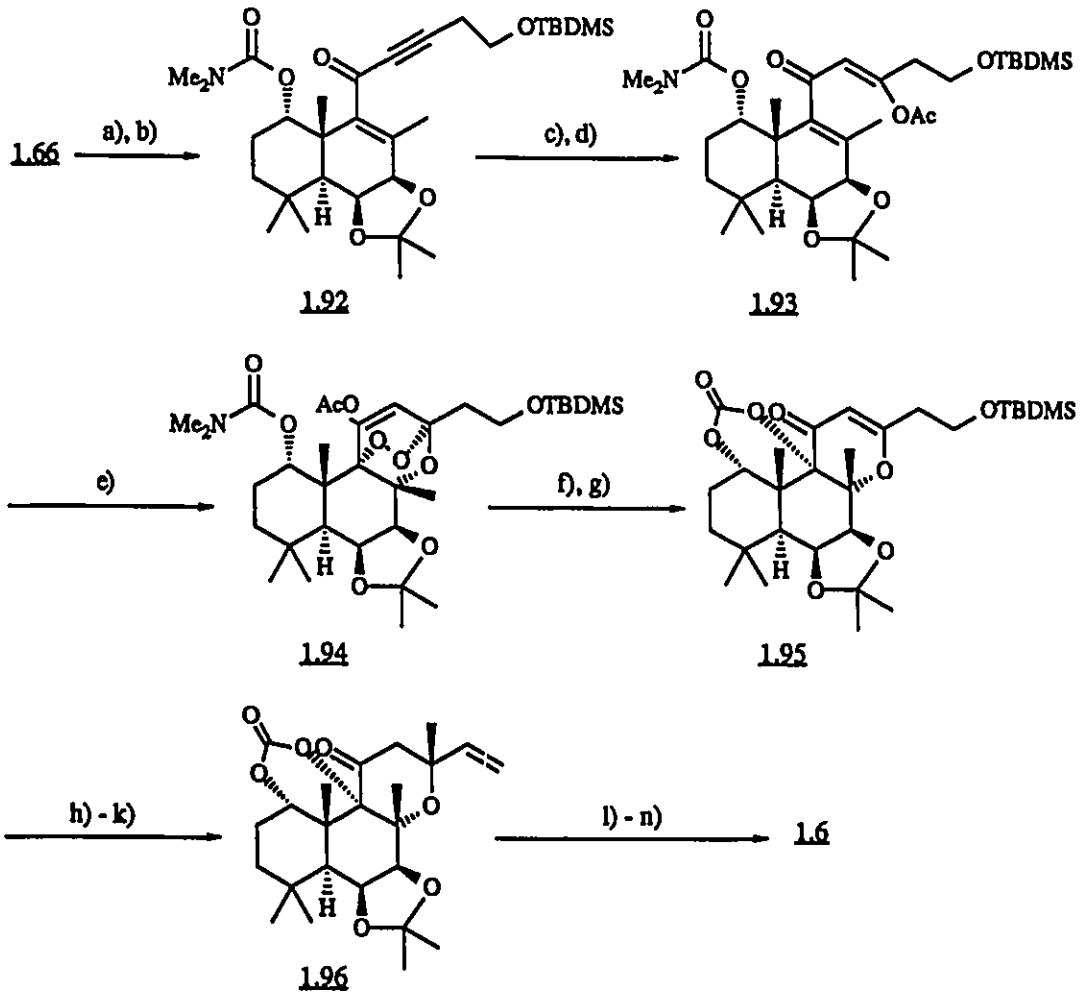
Corey and coworkers [27] have recently reported, what amounts to, an enantioselective synthesis of forskolin 1.6. Racemic alcohol 1.20 (later prepared in optically pure form) was converted to the cycloadduct 1.88 in good yield by reaction with 3-*p*-toluenesulfonyl-propynoic acid (Scheme 1.22). Displacement of the tosyl group with lithium dimethyl cuprate and boron trifluoride etherate followed by diene isomerization and endoperoxide formation gave 1.89 in good overall yield. Reduction of the hydroperoxide with Al / Hg amalgam followed by benzoylation of the secondary hydroxyl group and PCC oxidation

provided the enone 1.90. Reductive cleavage of the lactone followed by esterification with diazomethane then provided the enone 1.91. Stereoselective reduction of the enone moiety and subsequent epoxidation and opening of the epoxide ring under equilibrating conditions provided a diol which was protected as the acetonide 1.66. Interestingly, the acetonide 1.66 is a key intermediate which is also common to both the Ziegler and Ikegami syntheses.



Reagents: a) Ts-▬-COOH, $CHCl_3$, 23°C, 72%; b) Me_2CuLi, BF_3. OEt_2, -35°C to 0°C, 76%;c) DBN, 23°C; d) O_2, hv, $CHCl_3$, methylene blue, 0°C, 95% over 2 steps; e) Al - Hg,THF, H_2O, 23°C, 97%; f) Bz_2O, pyridine, DMAP, $ClCH_2CH_2Cl$, 50°C, 85%; g) PCC, $ClCH_2CH_2Cl$, 80 - 90°C, 60%; h)Al - Hg, THF, H_2O, 20°C, 85%; i) CH_2N_2, Et_2O, 99%; j) DIBALH, PhMe, -78°C, 80%; k) t - BuOOH, $Mo(CO)_6$, PhH, 68°C; l) KOH, MeOH, 23 °C; m) $Me_2C(OMe)_2$, Me_2CO, TsOH, 23°C.

Scheme 1.22



Reagents: a) LiC≡C(CH$_2$)$_2$OTBDMS, THF, 0°C, 80%; b) Me$_2$NCOCl, 2,6-lutidine, AgOTf, CH$_2$Cl$_2$, 23°C, 60%; c) K$_2$CO$_3$, THF, HOCH$_2$CH$_2$OH, 23°C then (CO$_2$H)$_2$, H$_2$O, Me$_2$CO, 60°C; d) i) TBDMSCl, imidazole, DMF, 23°C; ii) TlOEt, 23°C, then AcCl, -78°C to -45°C, 60% over 3 steps; e) O$_2$, hv, CHCl$_3$, 10°C, methylene blue, 55 - 63%; f) NaOEt, Bu$_3$P, EtOH, 0°C, 80%; g) HOAc, Ac$_2$O, 100 - 105°C, sealed tube; h) MeCu . Bu$_3$P, BF$_3$. OEt$_2$, Et$_2$O, -78°C to -50°C, 85%; i) HF, CH$_3$CN, H$_2$O, 0°C; j) o-O$_2$N-C$_6$H$_4$SeCN, Bu$_3$P, THF, 0°C; k) H$_2$O$_2$, THF, 23°C, 90%; l) H$_2$NCONHNH$_2$, HOAc, H$_2$O, 70°C, 95%; m) LiOH, THF, H$_2$O, i-PrOH, 23°C, 95%; n) Ac$_2$O, pyridine, 0°C, 90%.

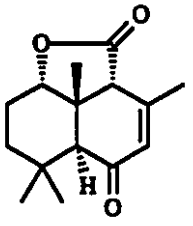
Scheme 1.23

The lactone 1.66 was ethynylated and the secondary hydroxyl group was protected as the carbamate 1.92 (Scheme 1.23). Conjugate addition of glycol to 1.92 followed by acid

hydrolysis, resilylation of the primary alcohol and O-acetylation of the intermediate β-diketone gave the corresponding enol acetate 1.93. Photocyclization of 1.93 and 4 + 2 cycloaddition of singlet oxygen gave the endoperoxide 1.94 which was converted to the dihydropyrone 1.95 by β-elimination, hydroperoxide reduction and finally cyclic carbonate formation under acidic conditions. Conjugate methyl addition followed by desilylation of the primary alcohol and oxidative elimination of the corresponding selenoxide gave 1.96. Removal of the carbonate and acetonide protecting groups followed by selective acetylation of the C_3 (naphthalene numbering) hydroxyl provided forskolin 1.6 in good overall yield.

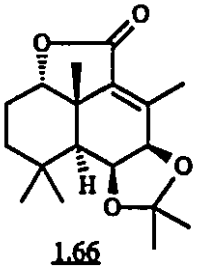
1.2.3 Formal Syntheses of Forskolin 1.6

In addition to the total syntheses of forskolin described earlier, several groups have reported the formal or abbreviated synthesis of 1.6. In general, the formal synthetic approaches focus on the preparation of the known functionalized lactones 1.102 and 1.66 as well as the aldehyde 1.69 previously encountered in the syntheses of Ziegler, Corey and Ikegami.



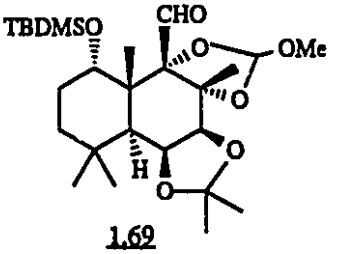
1.102

Key Intermediate in Ziegler and Corey Syntheses



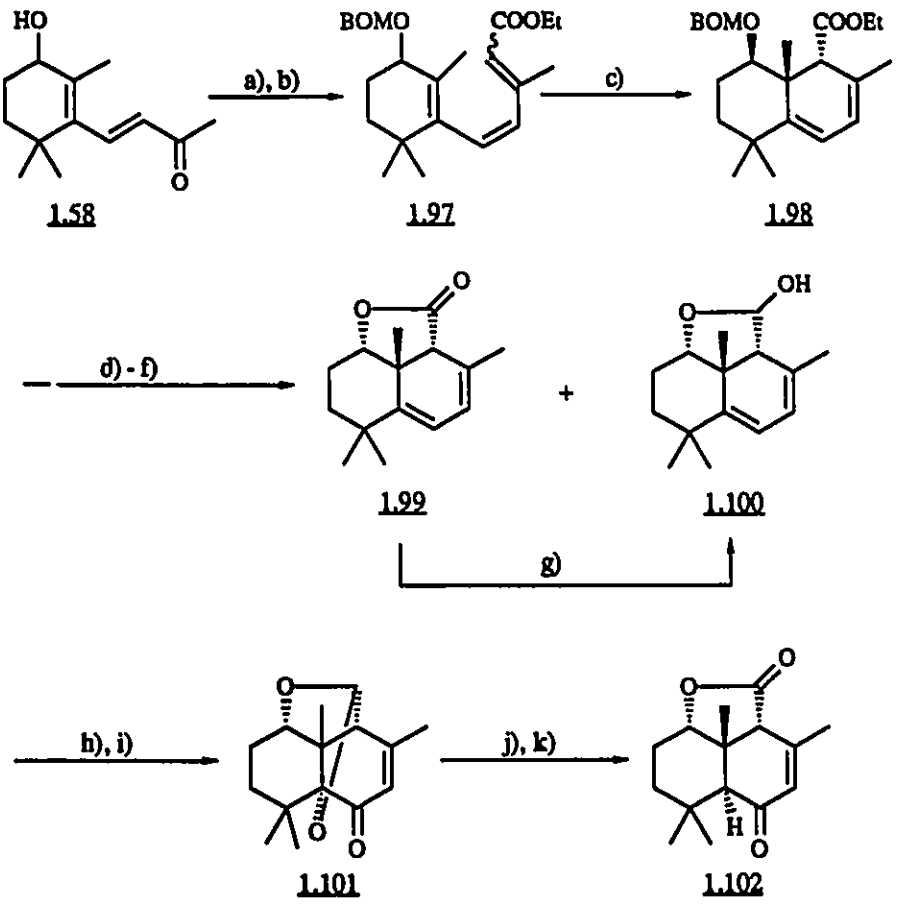
1.66

Key intermediate in Ziegler, Corey and Ikegami Syntheses



1.69

Key Intermediate in Ziegler Synthesis



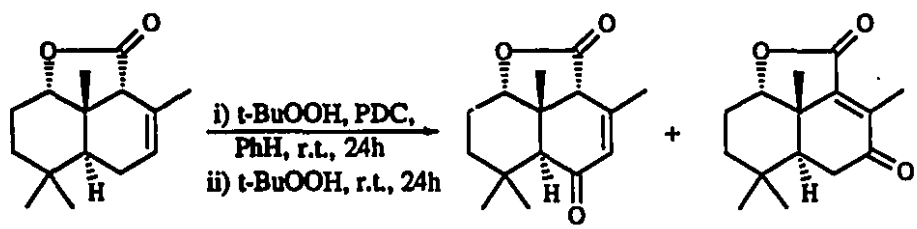
Reagents: a) $PhCH_2OCH_2Cl$, iPr_2EtN, CH_2Cl_2; b) $(iPr_2O)P(O)CH_2CO_2Et$, NaH, THF, reflux; c) N,N-dimethylaniline, 240°C; d) Raney-Ni (W-2), EtOH, r.t., 80%; e) PCC, CH_2Cl_2; f) $NaBH_4$, EtOH, 80% over 2 steps; g) LAH, Et_2O, 0°C, 97%; h) t-BuOOH, $VO(acac)_2$, PhH; i) PCC, CH_2Cl_2, 77%; j) Na, anthracene, THF, 83%; k) PCC, CH_2Cl_2, 80%.

Scheme 1.24

Cha and co-workers [40] have reported the synthesis of the key enone 1.102 and further elaboration to the lactone 1.66. The key step in their synthesis of 1.102 involves the thermolysis of the triene ester 1.97 (readily available from hydroxy-β-ionone) to give the bicyclic ester 1.98 (Scheme 1.24). Removal of the BOM protecting group followed by inversion of the C_8 hydroxyl stereochemistry by a standard oxidation / reduction sequence

provided a 3 : 1 mixture of the lactone 1.99 and the corresponding lactol 1.100 respectively. The lactone was further reduced to give the lactol 1.100. Regioselective epoxidation followed by 1,3-oxidative rearrangement gave the enone 1.101 in good yield. Reductive cleavage of the bridging acetal followed by oxidation of the resulting lactol gave the known enone 1.102 with the trans ring junction stereochemistry.

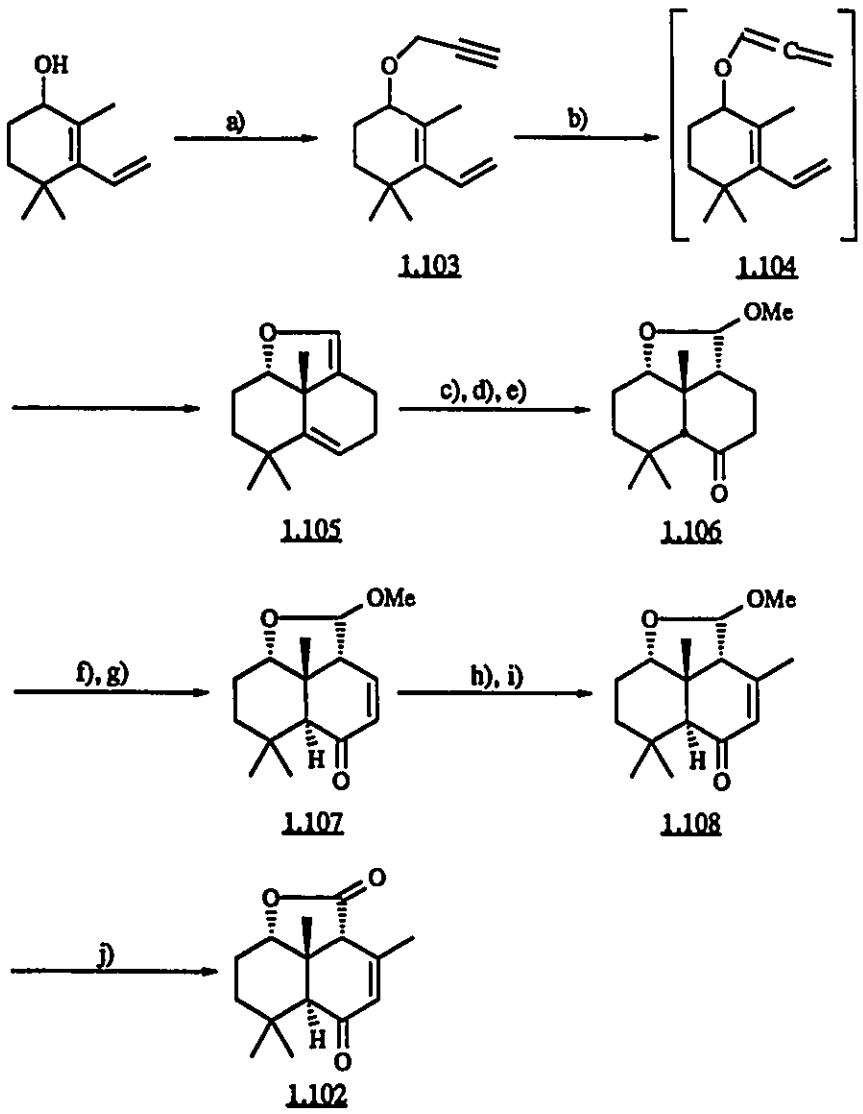
Pattenden and co-workers [39] have synthesized the key enone 1.102 by oxidation of the lactone 1.63 albeit in poor yield (Scheme 1.25). The lactone 1.63 was prepared via a tandem radical cyclization / intramolecular Mukaiyama aldolization strategy as outlined in Scheme 1.14. Apparently, the low yield of the enone 1.102 is a consequence of the steric hindrance at the C_4 (naphthalene numbering) carbon.



1.63 → 1.102 (34%) + (37%)

Scheme 1.25

Recently, Kanematsu *et al.* [41] reported the synthesis of 1.102 via a novel intramolecular Diels-Alder cycloaddition reaction of the allenyl ether 1.104 which was produced in situ by base catalysed isomerization of the propargyl ether precursor 1.103 (Scheme 1.26). Cycloaddition proceeded smoothly to give the tricyclic ether 1.105 in quantitative yield.



Reagents: a) BuLi, HMPA, THF then $BrCH_2C{\equiv}CH$, 0°C, 83%; b) KOt - Bu, t - BuOH, reflux, 100%; c) MeOH, CSA, 0°C, 100%; d) BH_3 . THF, 0°C, NaOH, H_2O_2, 74%; e) PCC, celite, CH_2Cl_2, 0°C; f) NaOMe, MeOH, reflux, 98% (2 steps); g) LDA, THF, -78°C, PhSeCl, -78°C to r.t., then H_2O_2, pyr., CH_2Cl_2, 0°C, 80%; h) Me_2CuLi, Et_2O, -20°C; i) PhSeCl, -78°C to r.t. then H_2O_2, pyr., CH_2Cl_2, 0°C, 71%; j) m-CPBA, BF_3 . OEt_2, CH_2Cl_2, 0°C.

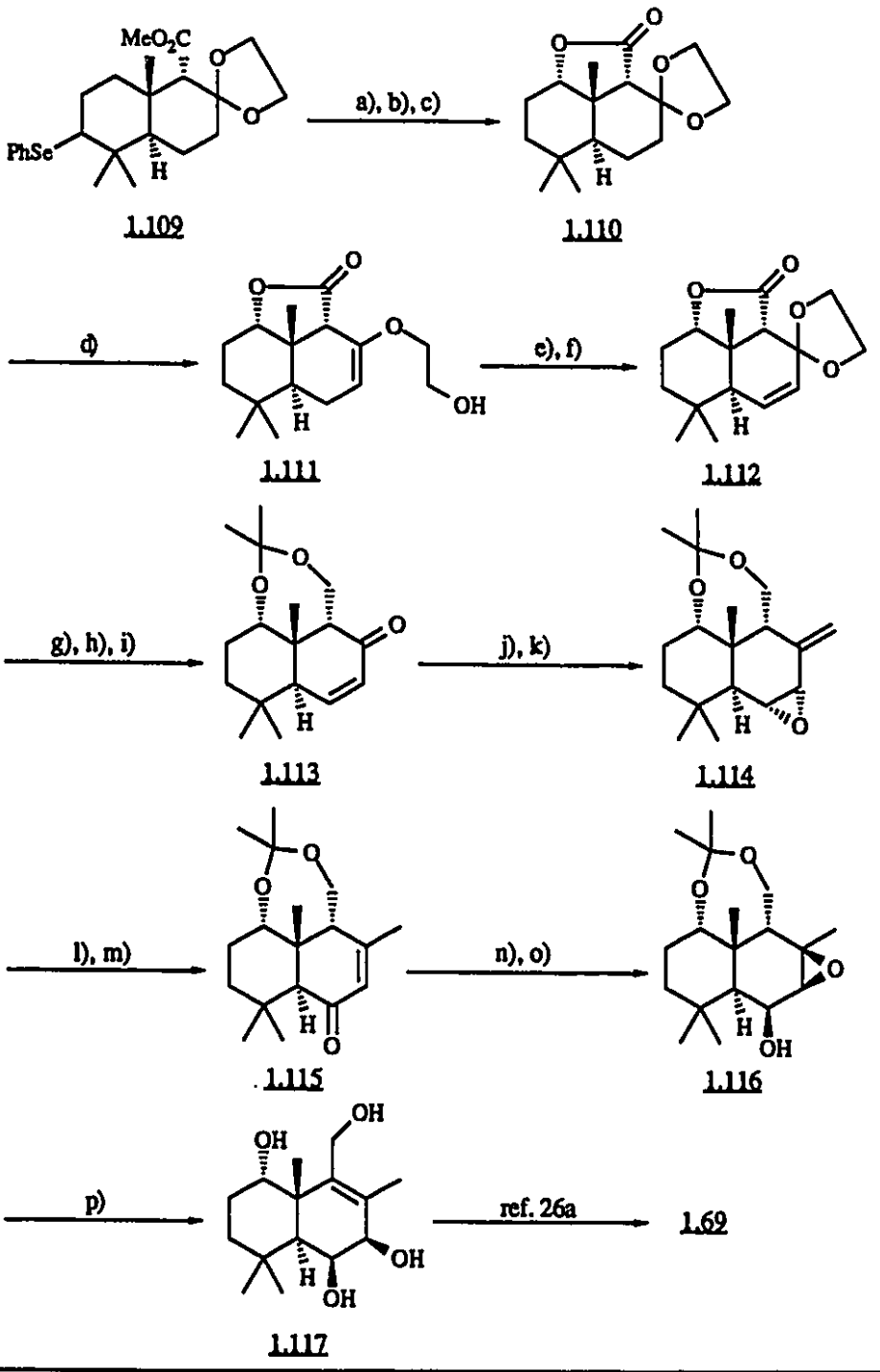
Scheme 1.26

Acid catalysed addition of methanol to 1.105 followed by hydroboration and PCC oxidation gave the ketone 1.106 which was epimerized and oxidized to the trans-enone

1.107 using standard selenoxide elimination chemistry. Conjugate methyl addition followed by reoxidation provided 1.108. Oxidation of the acetal moiety by reaction with m-chloroperoxybenzoic acid catalysed by boron trifluoride etherate afforded the Ziegler / Corey enone 1.102 in good overall yield.

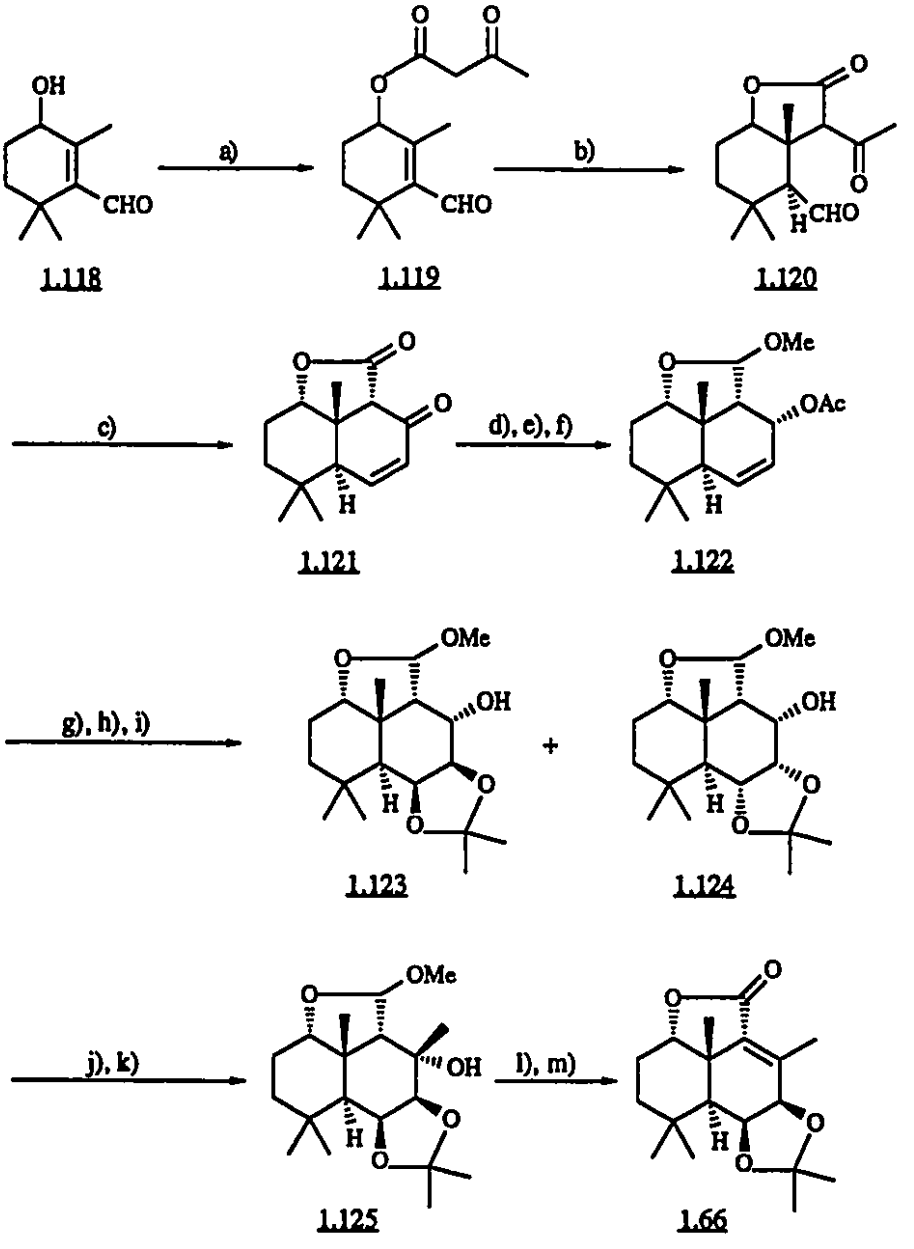
Nicolaou [42] has reported the synthesis of the key Ziegler aldehyde 1.69 starting from the bicyclic selenide 1.109 which was prepared via a cation mediated polyene cyclization reaction (Scheme 1.27). Selenoxide elimination of followed by allylic oxidation with selenium dioxide and subsequent hydrogenation over rhodium catalyst gave the lactone 1.110. Regioselective opening of the dioxolane moiety with aluminum amide base gave the enol ether 1.111 which was converted to the alkene 1.112 by reaction with phenylselenyl chloride and subsequent selenoxide elimination. Reduction of 1.112 followed by deketalization provided a diol which was protected as the acetonide 1.113. Epoxidation of the enone followed by Wittig methylenation gave the allylic epoxide 1.114 which underwent rearrangement under Lewis acid conditions and double bond isomerization under basic conditions to give the enone 1.115. Reduction of 1.115 followed by hydroxyl directed epoxidation of the resulting allylic alcohol gave 1.116 in good yield. Exposure of to dimethoxypropane under acidic conditions produced the acetonide 1.117 via regioselective opening of the epoxide moiety. Following a sequence essentially the same as Ziegler (see Scheme 1.16), the acetonide 1.117 was further elaborated to the key aldehyde 1.69.

Ruveda and co-workers [43] have reported the synthesis of the key lactone 1.66 via an intramolecular Michael / aldol strategy as outlined in (Scheme 1.28). Reaction of the hydroxyaldehyde 1.118 with diketene gave the β-ketoester 1.119. Intramolecular Michael addition under basic conditions then provided 1.120. Acid catalysed intramolecular aldol condensation of 1.120 gave the enone 1.121 in good overall yield.



Reagents: a) O_3, CH_2Cl_2, -78°C then iPr_2NH, CCl_4, reflux, 97%; b) SeO_2, dioxane, reflux, 90%; c) H_2, Rh / C, 25°C, 95%; d) $AlMe_3$, iPr_2NH, CH_2Cl_2, 25°C, 93%; e) PhSeCl, Et_2iPrNH, CH_2Cl_2, 25°C, 95%; f) O_3, CH_2Cl_2, -78°C then iPr_2NH, CCl_4, reflux, 97%; g) LAH, THF, 0°C then 25°C, 94%; h) HCl, THF, 25°C, 100%; i) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 25°C, 92%; j) H_2O_2, NaOH, MeOH, 10°C, 87%; k) $Ph_3P^+MeBr^-$, BuLi, THF, 0°C, 95%; l) $BF_3.OEt_2$, CH_2Cl_2, -78°C, 84%; m) K_2CO_3, MeOH, 25°C, 100%; n) DIBAL, THF, -78°C, 89%; o) $VO(acac)_2$, t-BuOOH, benzene, reflux, 40% + 53% 1.115; p) $Me_2C(OMe)_2$, PPTS, MeOH, 75°C, 73%.

Scheme 1.27

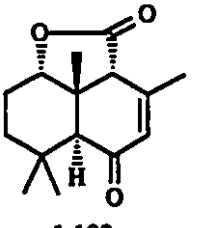


Reagents: a) diketene; b) K_2CO_3, EtOH; c) TsOH, benzene, r.t.; d) $NaBH_4$, $CeCl_3.7H_2O$, CH_2Cl_2, EtOH, -78°C to -20°C; e) MeOH, TsOH, 20°C; f) Ac_2O, DMAP, CH_2Cl_2, 55 - 60% overall from 1.121; g) OsO_4, pyridine, 20°C; h) $Me_2C(OMe)_2$, TsOH; i) K_2CO_3, MeOH, 20°C, 70 - 75% overall from 1.122; j) PDC, CH_2Cl_2, 20°C, 100%; k) MeMgI, Et_2O, 20°C; l) Jones reagent, acetone, 20°C; m) $SOCl_2$, pyridine, 0°C, 100%.

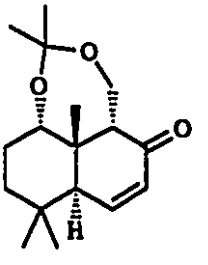
Scheme 1.28

Reduction of 1.121 with sodium borohydride and cerium (III) chloride gave a mixture of hemiacetals which were treated with acidic methanol and then acetylated to give the acetate 1.122 . Stereoselective osmylation of 1.122 gave a 3 : 1 mixture of diols which were protected as the acetonides and saponified to give the alcohols 1.123 and 1.124. Oxidation of the major alcohol 1.123 to the ketone followed by exposure to excess methylmagnesium iodide gave the tertiary alcohol 1.125 in good yield. Final linkage with the Ziegler, Corey and Ikegami lactone 1.66 was achieved by Jones oxidation followed by dehydration of the β-hydroxylactone with thionyl chloride in pyridine.

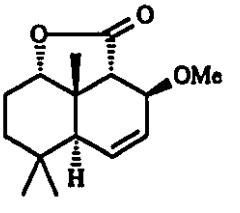
The enone 1.121 proved to be a versatile intermediate for the synthesis of forskolin 1.6 and the same group has reported the preparation of the key Ziegler / Corey enone 1.102 as well as the enone 1.113 and lactone 1.77 previously utilized by Nicolaou [42] and Ikegami [28] respectively in their approaches to forskolin.



1.102

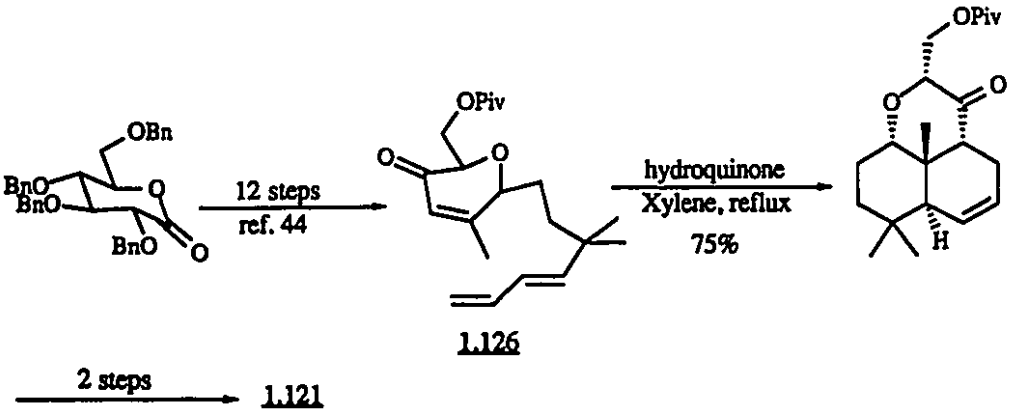


1.113



1.77

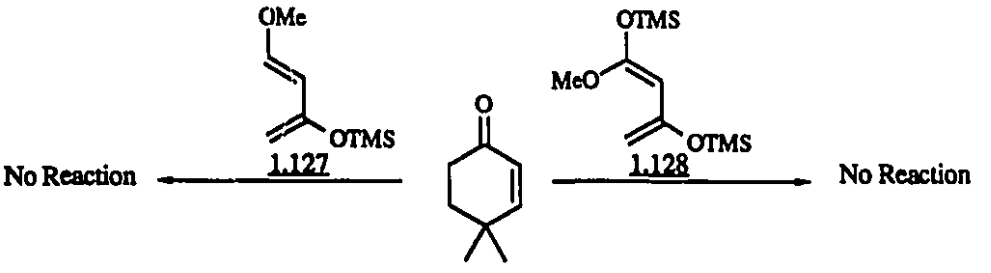
Most recently, Fraser-Reid *et al.* [44] have prepared Ruveda's lactone 1.121 via an intramolecular Diels-Alder reaction of the sugar derived diene 1.126 in good yield (Scheme 1.29).



Scheme 1.29

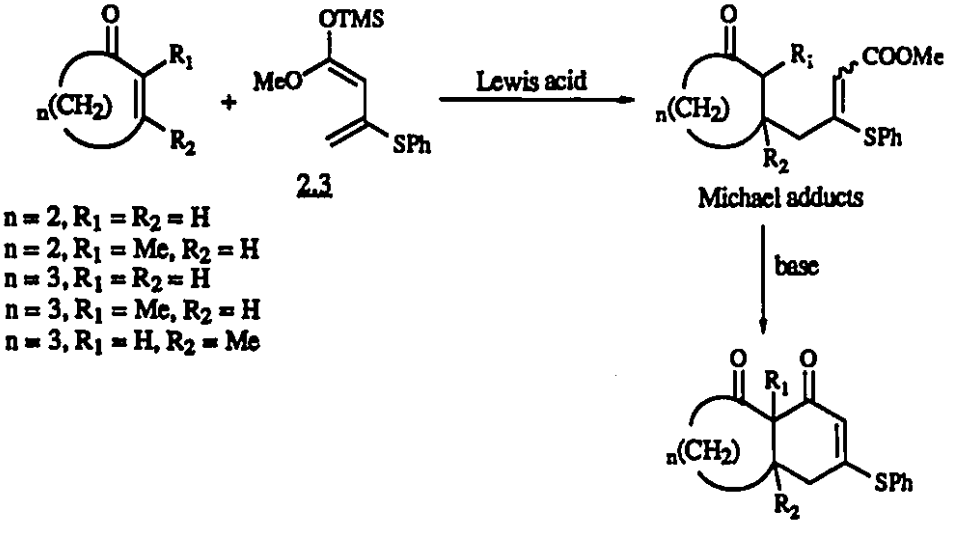
1.3 The Tandem Michael - Claisen Condensation

Annulation reactions leading to six membered rings are very important in organic synthesis. The classical strategies for the formation of six membered rings include the Diels-Alder reaction and the Robinson annulation. Although these approaches have been and continue to be employed in organic synthesis, there are certain limitations associated with them. For example, in the Diels-Alder reaction, cyclohexenone reacts with most dienes to give the corresponding adducts in good yield. On the other hand, 2- or 3-substituted cyclohexenones react sluggisly or not at all. Furthermore, it has recently been reported [45] that all attempts to add the electron rich dienes 1.127 and 1.128 to 4,4-dimethyl-2-cyclohexen-1-one have been completely unsuccessful (Scheme 1.30).

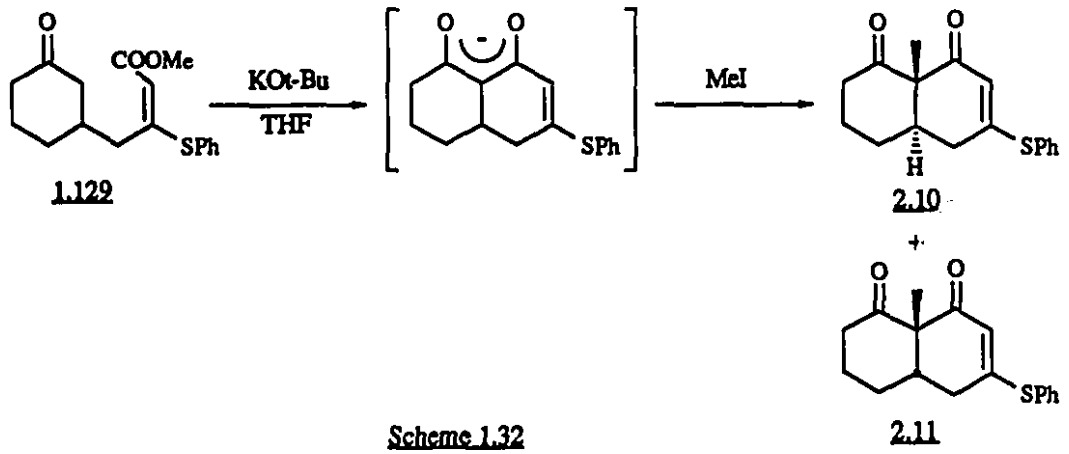


Scheme 1.30

Recently, Chan and Prasad [46] have reported that 3-(phenylthio)-1-(trimethylsiloxy)-1-methoxy-1,3-butadiene 2.3 reacts with a number of Michael acceptors under Lewis acid conditions to give the Michael adducts in good yield (Scheme 1.31). Clearly, the diene reacts exclusively at its δ-position and in a 1,4-fashion with the enone components. The intermediate E Michael adducts may then be cyclized under basic conditions to give annulated products in good yield. The isomeric Z Michael adducts may also be cyclized by exposure to lithium thiophenoxide in refluxing THF.



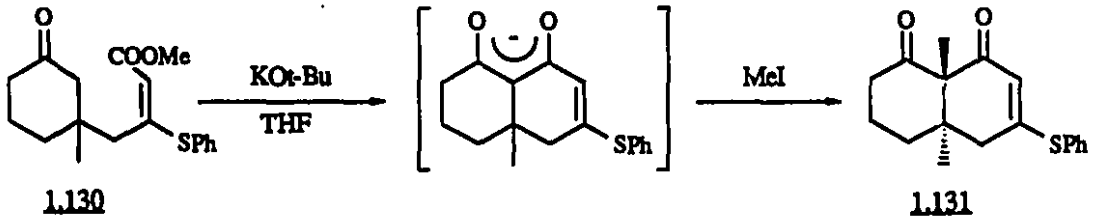
Scheme 1.31



1.129 2.10 + 2.11

Scheme 1.32

Although the overall sequence is equivalent to the Diels-Alder 4 + 2 cycloaddition reaction, it offers certain advantages, as the ring junction stereochemistry may be controlled by the tandem sequence. For example, Claisen cyclization of the E Michael adduct 1.129 with potassium t-butoxide followed by quenching with methyl iodide provides the *trans* and *cis* angularly methylated diketones 2.10 and 2.11 in a ratio of 9 : 4 respectively (Scheme 1.32). Similarly, cyclization of the E Michael adduct 1.130 with potassium t-butoxide followed by quenching with methyl iodide gives the *trans* compound 1.131 stereoselectively, whose ring junction stereochemistry was established by nOe experiments (Scheme 1.33).

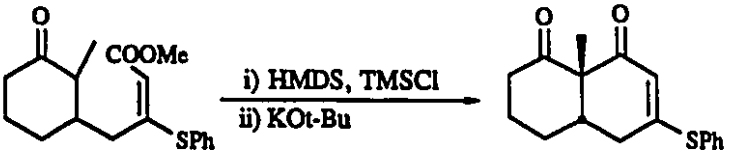


1.130 1.131

Scheme 1.33

On the other hand, Claisen cyclization of the E Michael adduct 2.19 provides the *cis*

annulated compound 2.20 exclusively.



2.19 2.20

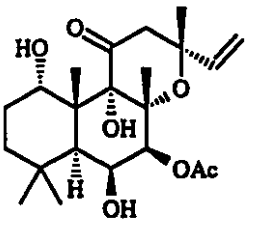
Scheme 1.34

The bicyclic ketones obtained by the tandem Michael-Claisen sequence are interesting in a sense that they contain three carbonyl groups, one of which is masked as the enol thio ether function, thereby providing a useful entry into a number of multifunctional targets.

1.4 Proposed Research

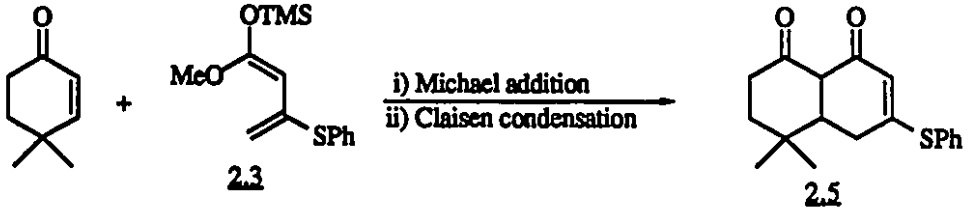
As outlined in the previous section, the utility of the tandem Michael-Claisen condensation for the construction of cyclic compounds has been demonstrated. The methodology has been extended to the synthesis of the 8a-methyl decalin as well as the hydrindane ring systems and the total synthesis of two sesquiterpenes namely aristolone and fukinone has been accomplished [47].

Of particular interest is the extension of this methodology to the stereoselective construction of the functionalized decalin ring system of of the labdane diterpene forskolin 1.6. A number of other natural products such as erigerol 1.11, clerodin 1.12, and the ajugarins I - III 1.13 - 1.15 (see Section 1.1) also contain a highly oxygenated decalin ring skeleton and as such, may in principle, be constructed by the tandem Michael-Claisen approach.



1.6

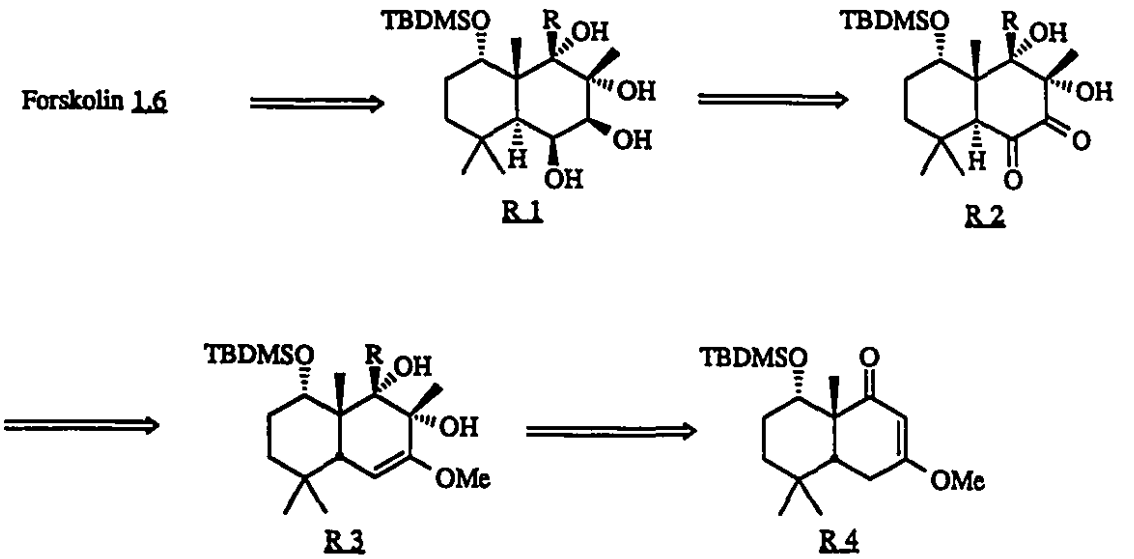
Condensation of the diene component 2.3 with 4,4-dimethyl-2-cyclohexen-1-one would give the corresponding Michael adducts which may be cyclized under basic conditions to give the decalone 2.5 in analogy to the Michael-Claisen sequence outlined in the previous section (Section 1.3).



2.3 2.5

In order to elaborate the decalone 2.5 to the functionalized ring system of forskolin 1.6. a number of important issues must be addressed. It is important to examine the angular methylation of 2.5 in order to determine whether the decalin ring junction stereochemistry can be controlled to give the *cis* isomer selectively. The second question relates to the ability of the *cis* ring junction stereochemistry to control the stereochemistry of the C_1, C_2 and C_8 (naphthalene numbering) centers. Finally, it is also important to examine the problem of converting *cis* ring junction to the thermodynamically more stable *trans* stereochemistry. The *trans* ring junction stereochemistry may then be used advantageously to establish the β-stereochemistry of the C_3 and C_4 (naphthalene numbering) hydroxyl groups.

Retro-synthetic Analysis of Forskolin



The retro-synthetic scheme outlined above, reveals that forskolin 1.6 may be derived from the tetrol R1 which in turn may be derived from the diketone R2. Further analysis reveals the retro-synthetic intermediate diol R3 bearing an enol ether or masked carbonyl function. The alkyl group (R) in the diol structure R3 may be either alkenyl or alkynyl and simply functions as a masked aldehyde group. Finally, the diol R3 may be traced back to the β-methoxy enone R4 having the *cis* ring junction stereochemistry.

The retro-synthetic intermediate diketone R2 represents a highly oxygenated decalin intermediate for the synthesis of forskolin 1.6 and thus will be the final target of the present study.

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CHAPTER 2

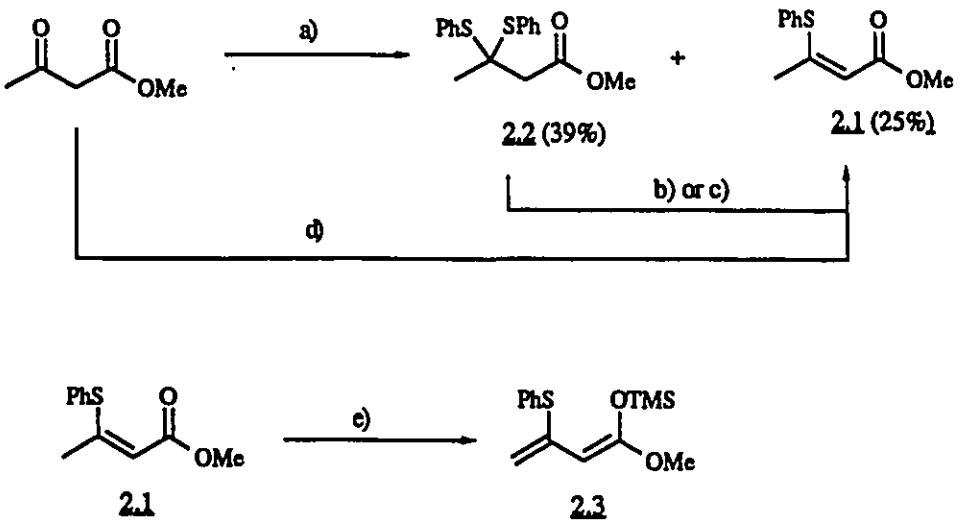
CONSTRUCTION OF THE AB RING SYSTEM OF FORSKOLIN USING THE TANDEM MICHAEL-CLAISEN STRATEGY

2.1 Introduction

As outlined in Chapter 1, the diene 2.3 was found to react in a Michael fashion under Lewis acid conditions with a number of α,β-unsaturated ketones, furnishing the corresponding Michael adducts in good yield [1]. The Michael adducts could in turn be cyclized under basic conditions (Claisen cyclization) to give cyclic products. In order to apply this methodology to the construction of the decalin ring system of forskolin 1.6, it is necessary to utilize specifically the enone 4,4-dimethyl-2-cyclohexen-1-one for the Michael addition step. Herein, we detail the synthesis of the diketone 2.5 using the tandem Michael-Claisen annulation sequence and examine the introduction of the angular methyl group. Further synthetic transformations of 2.6 are then carried out leading to our retrosynthetic intermediate enone R4 (see Section 1.4, Chapter 1).

2.2 Synthesis of the Diene Component

The vinyl sulfide 2.1 was prepared from methylacetoacetate according to the literature procedure [1], however the thioketal 2.2 was generally isolated as the major product in 39% yield. Conversion of the thioketal 2.2 back to the vinyl sulfide 2.1 could be achieved by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at reflux temperature (Scheme 2.1). Alternatively, exposure of 2.2 to mercuric trifluoroacetate and lithium carbonate in acetonitrile [2a] gave 2.1 in good yield; however, separation of the product from the mercuric salts proved to be quite difficult.



Reagents: a) P_2O_5, PhSH, CH_2Cl_2, r.t., 73%; b) $Hg(OCOCF_3)_2$, Li_2CO_3, CH_3CN, 70%; c) DBU, CH_2Cl_2, reflux, 75%; d) PhSH, p-TSA, toluene, reflux, 46% + 16% recovered PhSH; e) LDA, TMS Chloride, -78°C 100%.

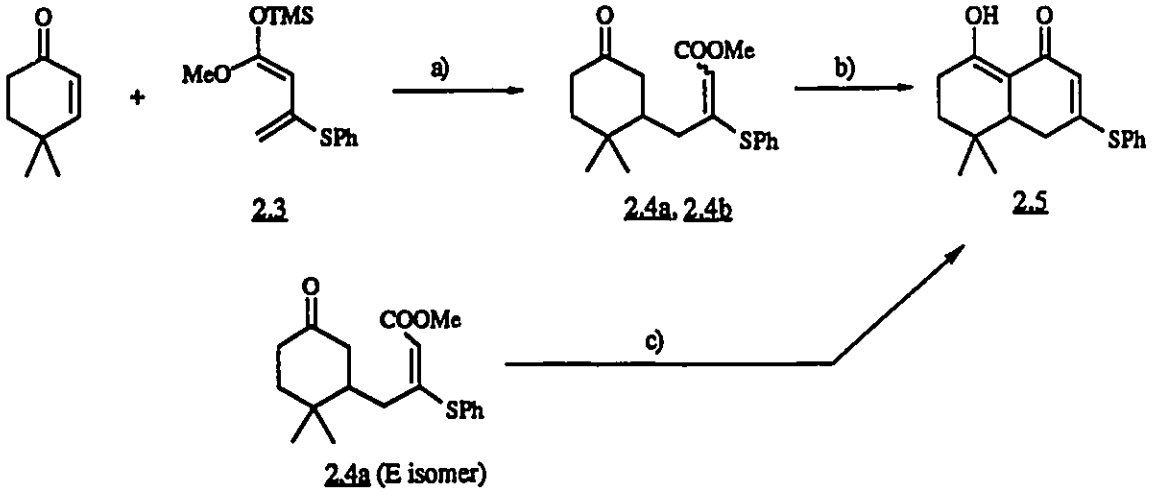
Scheme 2.1

Alternatively, 2.1 could be prepared from methylacetoacetate, thiophenol and acid catalyst under Dean-Stark conditions in good yield (Scheme 2.1) [2b].

The enol silyl ether 2.3 was prepared according to the literature procedure [1] with only a slight modification. In order to effect complete conversion of the vinyl sulphide 2.1 to the enol silyl ether 2.3, it was deprotonated with lithium diisopropylamide (LDA) in the presence of the trimethylsilyl chloride (TMSCl) in order to immediately quench the enolate as it was formed. The enol silyl ether could then be isolated in essentially quantitative yield (Scheme 2.1). The stereochemistry of 2.3 was assigned to be Z as reported previously [1]. With relatively easy access to the enol silyl ether 2.3 established, the Michael-Claisen annulation sequence was then examined.

2.3 The Michael-Claisen Annulation sequence : An entry into the Decalin Ring Skeleton of Forskolin

Exposure of the diene 2.3 to 4,4-dimethyl-2-cyclohexen-1-one under titanium tetrachloride ($TiCl_4$) conditions delivered the Michael adducts 2.4a and 2.4b as a mixture of E and Z isomers in reasonably good yield (E : Z = 4 : 1) [1]. Claisen cyclization of the major E isomer 2.4a could be achieved under basic conditions by treatment with potassium t-butoxide in t-butanol to give the decalone 2.5 in good yield (Scheme 2.2).



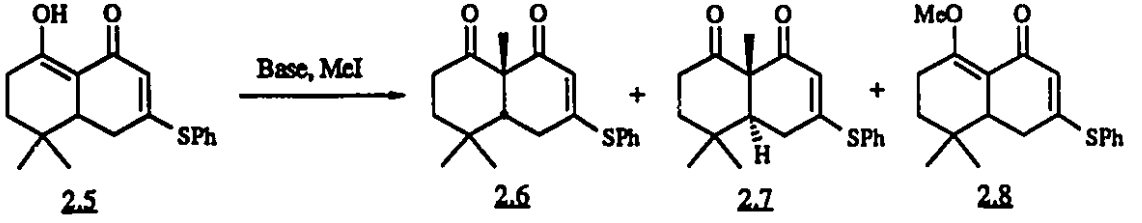
Reagents: a) $TiCl_4$, CH_2Cl_2, -78°C, 60%; b) PhSLi, THF, reflux, 67%; c) KOt-Bu, t-butanol, 40°C, 85%

Scheme 2.2

Cyclization of 2.4a was immediately evident by the absence of a methoxy signal in the ^1H NMR spectrum. Cyclization could also be conducted in THF [1], however the yield of the decalone 2.5 was quite variable (ie: 35 - 70%). t-Butanol was found to be the solvent of choice for this reaction, delivering the decalone 2.5 cleanly and in reproducible yield. Alternatively, the E / Z mixture of 2.4 could be cyclized to 2.5 by refluxing lithium thiophenoxide in THF as reported previously [1] in good yield (67%).

2.4 Angular Methylation of The Decalone 2.5

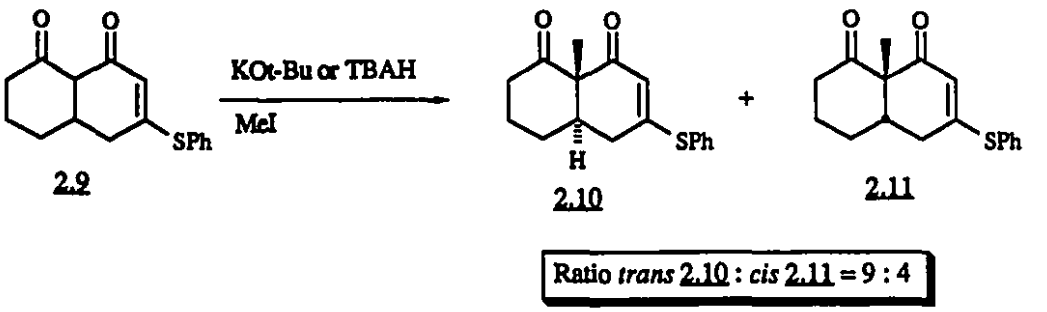
Due to the presence of the angular methyl group in decalin ring structure of forskolin and a number of decalinic natural products, methylation of the decalone 2.5 was examined under a variety of conditions. Three possible isomers may be envisioned for the alkylation of the decalone 2.5 under basic conditions, the *cis* and *trans* C-alkyl products 2.6 and 2.7 as well as the O-alkyl product 2.8 (Scheme 2.3).



2.5 2.6 2.7 2.8

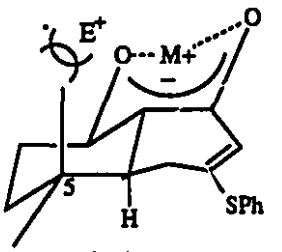
Scheme 2.3

The yields as well as the selectivities of the methylation reaction of 2.5 are given in Table 2.1. In each case, the *cis* isomer predominates over the *trans*, with ratios ranging from a low of 1.1 : 1 to a high of 7 : 1. The preferred formation of the *cis* isomer 2.6 over the *trans* 2.7 in the alkylation of 2.5 under basic conditions is somewhat unexpected. It was previously found that in the methylation of the parent decalone 2.9 using either tetrabutylammonium hydroxide (TBAH) or potassium tert-butoxide (KOtBu) as base, the *trans* isomer 2.10 was formed preferentially over the *cis* 2.11 in a ratio of 9 : 4 (Scheme 2.4) [1]. The preferred formation of the *cis* isomer 2.6 may be attributed to the steric effect of the C_5 (naphthalene numbering) axial methyl of the anion 2.12 on the approaching electrophile in forming 2.7. When the metal ion (M^+) is larger and less coordinating (ie: K^+, Cs^+, Bu_4N^+) to the anion than Li^+ or the solvent more polar (ie: CH_3CN) relatively more of the *trans* isomer 2.7 is formed because in the transition state, the electrophile (E^+) is further away and less subject to the steric effect.



2.9 2.10 2.11

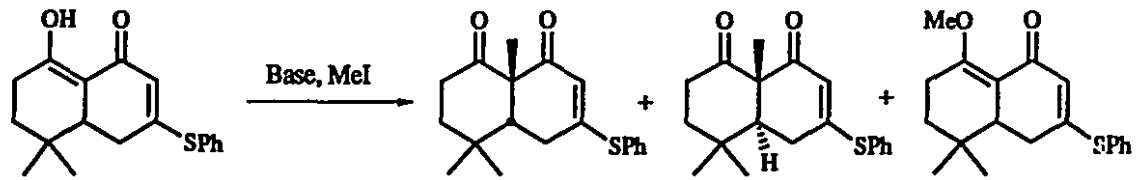
Scheme 2.4



2.12

A convenient one pot procedure for the direct conversion of the E Michael adduct 2.4a to the alkylated products 2.6, 2.7 and 2.8 was found by quenching the reaction mixture with methyl iodide (MeI) rather than water as outlined in Scheme 2.5. Thus when the Claisen cyclization reaction of the E Michael adduct 2.4a was conducted in THF and the enolate quenched with MeI, the C-alkyl products 2.6 and 2.7 were obtained in a ratio of 2:1 in about 50% yield. The O-alkyl product 2.8 was obtained in 14% yield. Optimum yield of the C-alkyl products 2.6 and 2.7 could be achieved when this cyclization / alkylation sequence was carried out in t-butanol (t-BuOH) as solvent (ie: 75% , ratio 2.6 : 2.7 = 2 : 1 ; yield of 2.8 = 4%). It is interesting to note that solvent polarity (ie: t-BuOH vs. THF) has little or no effect on the ratio of the C-alkyl products in this particular case whereas in the direct alkylation of 2.5 under basic conditions solvent polarity plays an important role (see Table 2.1).

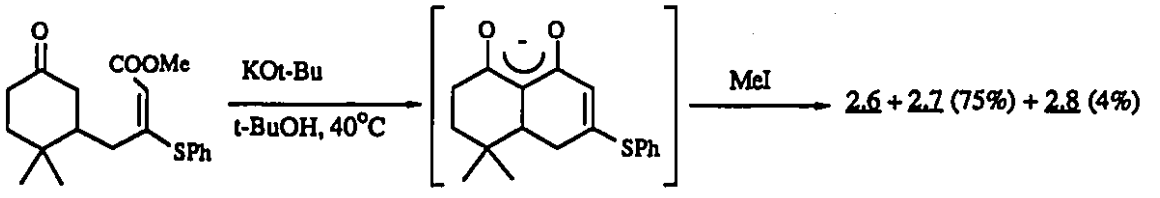
Table 2.1 : Angular Methylation of the dione 2.5



2.5 2.6 2.7 2.8

Conditions	Temp (°C)	Time (h)	[a] % Yield 2.6 and 2.7	[b] Ratio 2.6 : 2.7	[a] % Yield 2.8	[a] % Recov. 2.5
BuLi, -78°C / CH_3I, THF	50	262	50	4.2:1	2	13
Li_2CO_3 / THF / CH_3I	66	96	0	--	0	95
Na_2CO_3 / THF / CH_3I	66	94	0	--	0	95
Na_2CO_3 / CH_3CN / CH_3I	82	216	0	--	0	90
K_2CO_3 / CH_3CN / CH_3I	82	26	63	1.2:1	28	0
Cs_2CO_3 / CH_3CN / CH_3I	82	4	56	1.2:1	24	4
Cs_2CO_3 / THF / CH_3I	66	72	49	2.0:1	11	0
Ag_2O / CH_3CN / CH_3I	82	75	19	4.0:1	20	39
Bu_4NOH / C_6H_6 / CH_3I	80	141	22	1.1:1	1	46
i) TlOEt / C_6H_6, ii) CH_3I	42	216	15	7:1	5	32

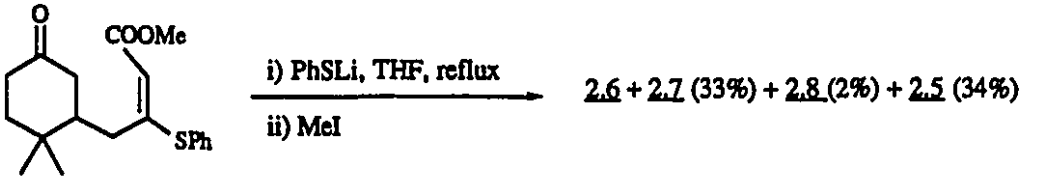
[a] Refers to isolated yield (after chromatography). [b] Ratios were determined from the ^1H NMR spectrum of the crude reaction mixture.



2.4a
E isomer

Scheme 2.5

Taking this cyclization / alkylation sequence one step further, it was also possible to directly cyclize and alkylate the E / Z mixture of the Michael adducts 2.4a and 2.4b albeit in relatively poor yield. Thus, exposure of 2.4a and 2.4b to lithium thiophenoxide (PhSLi) followed by quenching with methyl iodide delivered the C-alkyl products 2.6 and 2.7 in a ratio of 4:1 in 33% yield, the O-alkyl product 2.8 in 2% yield as well as a substantial amount (34%) of the decalone 2.5 (Scheme 2.6).

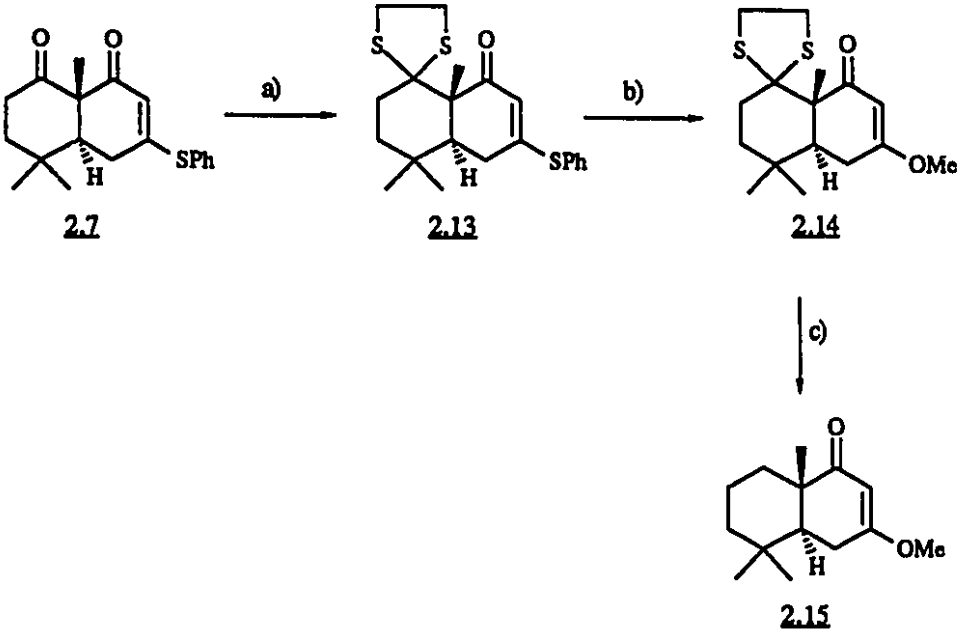


2.4a, 2.4b
4 : 1 E / Z Mixture

Scheme 2.6

The assignment of the *trans* stereochemistry to the decalone 2.7 is based on chemical correlation according to Scheme 2.7. Compound 2.7 was thioketalized with ethanedithiol to give 2.13. Conjugate addition of methoxide to the enone 2.13 delivered the methoxy compound 2.14. Reductive removal of the thioketal moiety of 2.14 with Raney nickel gave the known compound 2.15 [4] with the *trans* ring junction stereochemistry. With the *trans* stereochemistry of 2.7 established, the isomeric decalone 2.6 must have the *cis* stereochemistry. Further confirmatory evidence of the *cis* ring junction stereochemistry of

2.6 was obtained by X-ray crystallography (see section 2.5).

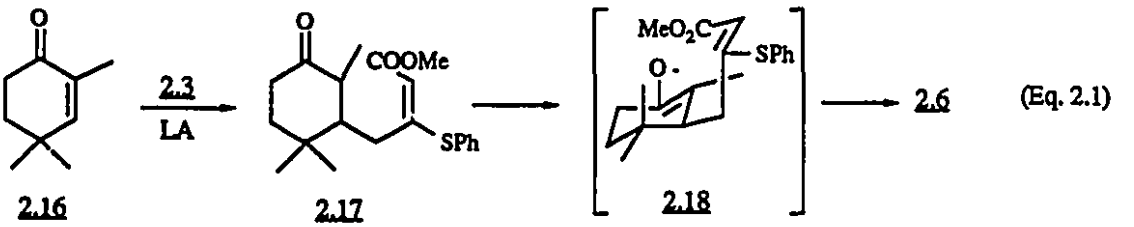


2.7 2.13 2.14 2.15

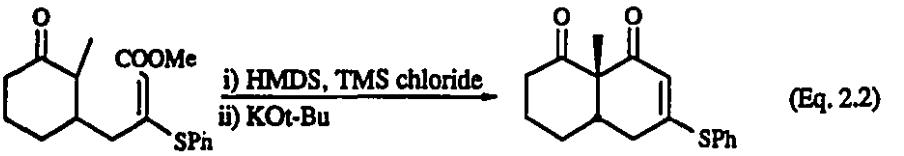
Reagents: a) ethanedithiol, p-TSA, benzene, reflux, 100%; b) MeONa, MeOH, reflux, 24h, 60%; c) Raney nickel, ethanol, reflux, 6h, 85%

Scheme 2.7

In an attempt to improve the selectivity of the angular methylation and to alleviate completely the problem of O-alkylation, we decided to examine the use of the α-methylated enone 2.16 in the Michael addition step. Cyclization of the intermediate E adduct 2.17 was expected to deliver the *cis* decalone 2.6 selectively, since the electrophile (COOMe) would prefer to approach the enolate in an axial fashion as depicted in 2.18 (Eq.2.1). Indeed, this *cis* selectivity has been observed previously for similar methylated Michael adducts, however lacking the gem dimethyl substituents at C5. For example, cyclization of the E Michael adduct 2.19 was carried out in a two step sequence, namely formation of the enol silyl ether with TMSCl and hexamethyldisilazane (HMDS) and Claisen cyclization with potassium t-butoxide to give the *cis* isomer 2.20 exclusively (Eq.2.2) [3].

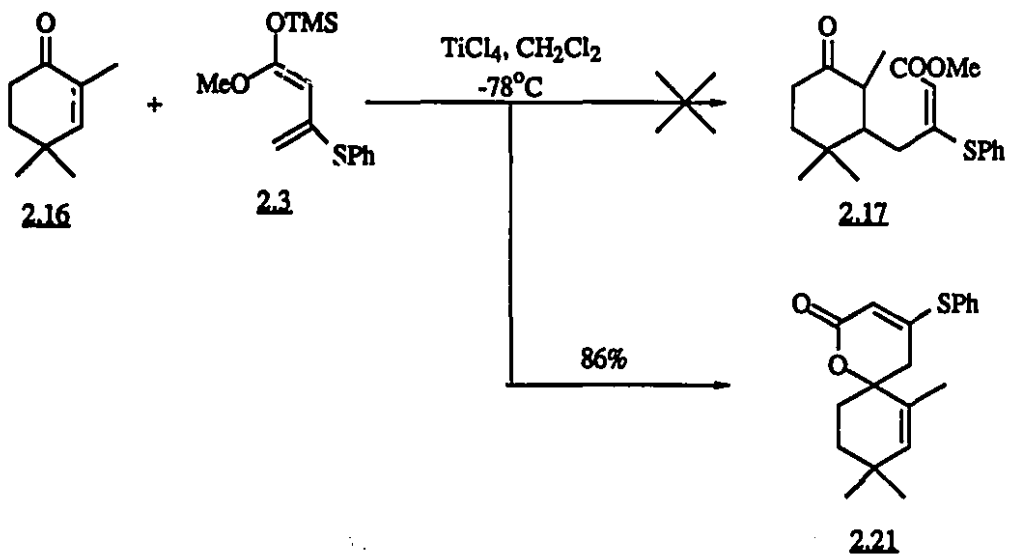


2.16 2.17 2.18



2.19 2.20

The required enone 2.16 was readily prepared in good yield using the enamine chemistry of Stork [5]. Unfortunately, exposure of 2.16 to our diene component 2.3 under $TiCl_4$ conditions did not provide any of the expected Michael adduct 2.17. Instead, 1, 2-addition occurred with cyclization affording the spirolactone 2.21 in 86% yield (Scheme 2.8).



2.16 2.3 2.17 2.21

Scheme 2.8

The structure 2.21 was proposed based on the absence of a methoxy and doublet methyl signal in the ^1H NMR spectrum. The DEPT NMR spectrum was also consistent with the proposed structure, showing $3CH_2$, $3CH_3$, 5CH and 6 quaternary carbon signals. The outcome of the reaction appeared to be independant of the Lewis acid used. A series of other Lewis acids were surveyed as outlined in Table 2.2 however, only 1,2-addition was observed in each case.

Table 2.2: Effect of the Lewis Acid on the Reaction of 2.16 and 2.3.

Run No.	Lewis Acid (Equiv.)	Time(h)	[a]% Yield 2.21	Temperature(^oC)
1	$AlCl_3$ (1.0)	2	67	-78
2	BF_3 Et_2O (1.0)	2	70	-78
3	$(i\text{-}Bu)_2AlCl$ (1.0)	2.5	69	-78

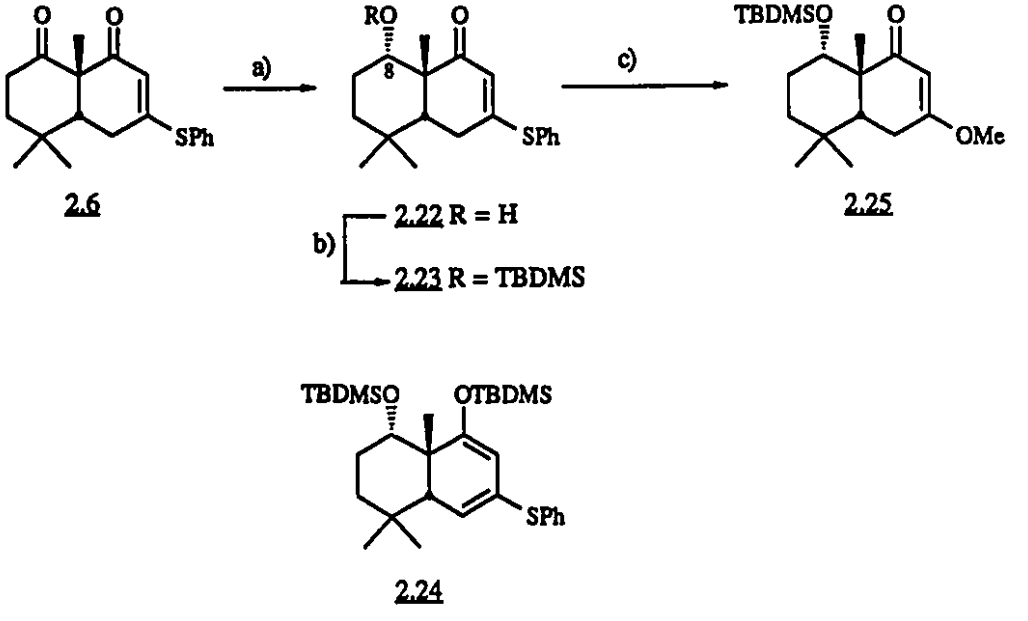
[a] Refers to isolated yield (after chromatography).

The propensity of 2.3 to undergo 1,2-addition in its reaction with the enone 2.16 under Lewis acid conditions is not entirely unexpected. Presumably, the steric effect of the three methyl groups as well as the electron releasing effect of the α-methyl group render 2.16 unreactive as a Michael acceptor under the experimental conditions.

2.5 Functional Group Manipulations: Conversion to the Retro-Synthetic Intermediate Enone 2.25 (R4)

With relatively easy access to the *cis* decalone 2.6 established, a synthetic route to the retro-synthetic intermediate β-methoxy enone 2.25 (R4) was sought. Thus, the non-conjugated carbonyl group of 2.6 was selectively reduced from the less hindered β-face

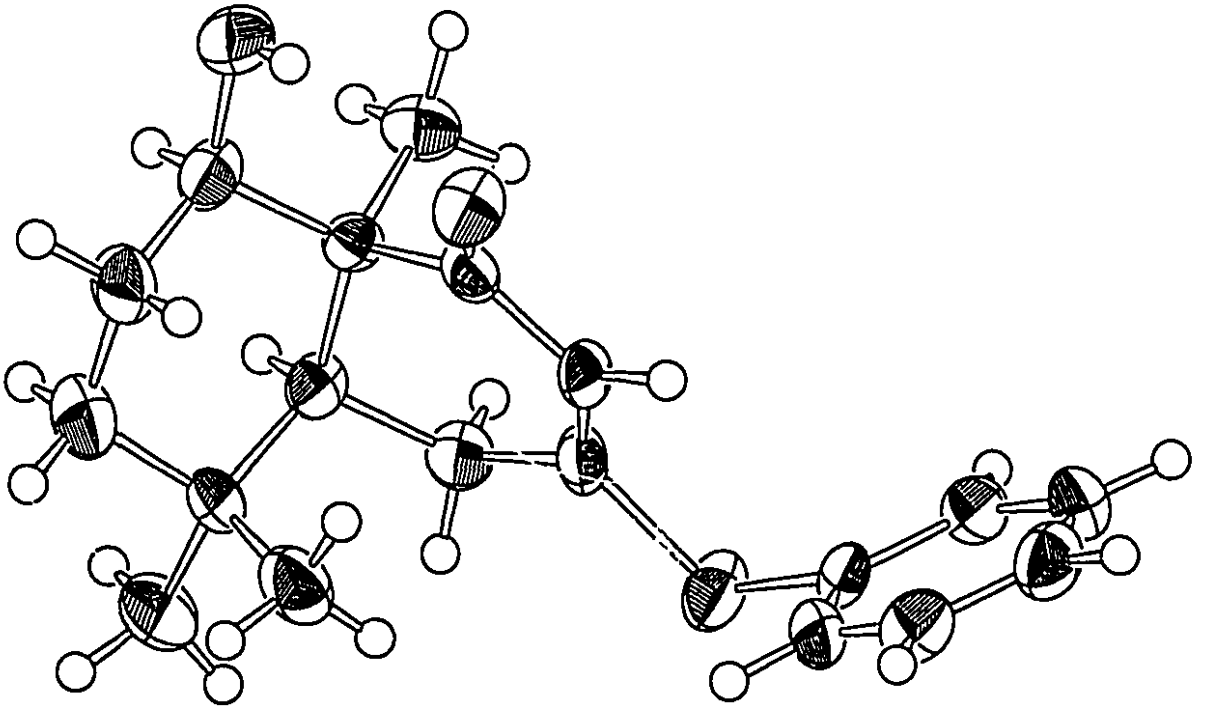
with the bulky reducing agent $LiAlH(Ot\text{-}Bu)_3$ to give the equatorial alcohol 2.22, as a single diastereomer, in essentially quantitative yield (Scheme 2.9). The reduction could also be performed with sodium borohydride in methanol at 0°C, however the reaction frequently did not go to completion and some of the diketone 2.6 was recovered. The stereochemistry of the hydroxyl group of 2.22 was initially assigned on the basis of ^1H NMR. The C_8 methine signal at 3.15 ppm showed both large (10.6 Hz) and small (4.6 Hz) coupling constants expected of an axial hydrogen.

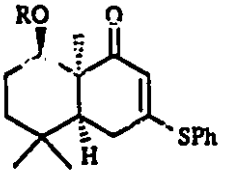


Reagents: a) $LiAlH(Ot\text{-}Bu)_3$, THF, -20°C, 21.5h, 100%; b) TBDMS triflate, 2,6-lutidine, CH_2Cl_2, r.t., 5h, 77%; c) MeONa, MeOH, reflux, 83-96%.

Scheme 2.9

Further confirmatory evidence of the structure of 2.22 was determined by single crystal X-ray diffraction. The ORTEP diagram 1 of 2.22 reveals the expected *cis* ring junction stereochemistry and the equatorial orientation of the C_8 hydroxyl group. Furthermore, the X-ray data revealed that the unit cell of the selected crystal contained only one enantiomer,





2.22

absolute configuration

ORTEP Diagram 1

the absolute configuration as depicted in the ORTEP diagram. This observation suggests that 2.22 crystallizes in two different enantiomeric forms. An attempt was made to manually separate the two enantiomers by examination of the crystals under a microscope, however, the crystals appeared to be similar in size and shape and there did not appear to be any distinguishing features between the two crystalline enantiomeric forms.

Protection of the hindered hydroxyl group of 2.22 was achieved using the standard 2,6-lutidine / t-butyldimethylsilyl (TBDMS) triflate conditions [6] to give the silyl ether 2.23 in 77% yield (Scheme 2.9). This reaction appeared to be reproducible on a small scale (ie: approx. 1 mmol) however, in several larger scale runs, a significant quantity (ca. 30 - 50%) of the enol silyl ether 2.24 was obtained at the expense of 2.23. This result however was not problematic since 2.24 could be easily converted back to 2.23 in high yield by mild acid hydrolysis (see Experimental section). Other attempts at hydroxyl protection such as TBDMS chloride / imidazole / N,N-dimethylformamide (DMF) and $AgNO_3$ / TBDMS Chloride / THF failed and only starting material was recovered in each case. Replacement of the thiophenyl group by a methoxy group was accomplished by refluxing with sodium methoxide in methanol to give the enone 2.25 which is our retrosynthetic intermediate R4 (see Section 1.4, Chapter 1) in good yield.

References

1. See ref. 46 in Chapter 1.

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CHAPTER 3

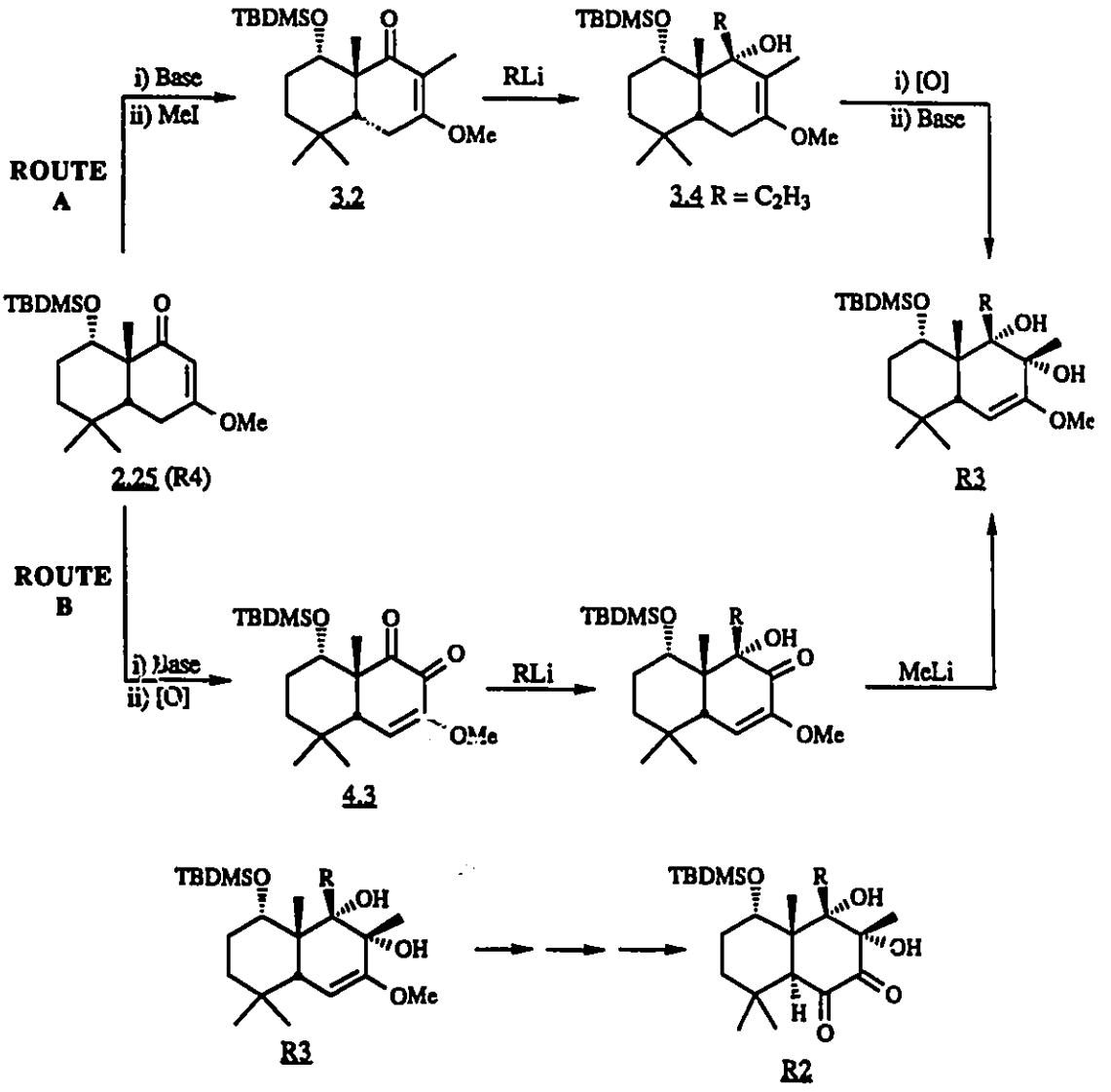
SYNTHETIC APPROACHES TO THE RETRO-SYNTHETIC INTERMEDIATE DIKETONE R2 AND UNEXPECTED STEREOCHEMICAL RESULTS

3.1 Introduction

With the β-methoxy enone intermediate 2.25 (R4) in hand, a stereoselective route to the retro-synthetic intermediate diketone R2 was sought in order to complete the functionalized decalin ring system of forskolin 1.6. Initially, two obvious routes to the required diketone R2 were envisioned, each involving the intermediacy of the diol R3 as outlined in Scheme 3.1.

The first route (Route A) requires the regioselective methylation of 2.25 followed by stereoselective 1,2-addition of a suitably masked aldehyde equivalent to the carbonyl group of 3.2. Hydroxyl directed epoxidation of the enol ether moiety of 3.4 followed by ring opening of the epoxide was then expected to give the key diol R3 stereoselectivity.

In contrast, the alternate Route B requires the regioselective oxidation of 2.25 to the diketone 4.3 followed by tandem stereo and regioselective addition of methyl and masked aldehyde equivalents to each carbonyl group. Initially, we elected to pursue the methylation, nucleophilic addition and epoxidation sequence (Route A) outlined in Scheme 3.1. Thus, our efforts to prepare the retro-synthetic intermediate diol R3 via Route A are described here.



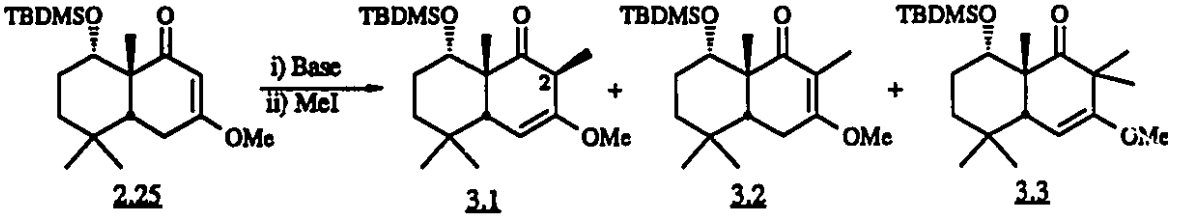
Scheme 3.1

3.2 Attempted Synthesis of the Intermediate diol R3 Via Route A

In order to convert the methoxy enone 2.25 to the diol R3 for further elaboration to the retro-synthetic intermediate diketone R2, it was necessary to establish conditions for the mono-methylation of 2.25. Thus, deprotonation of 2.25 with lithium diisopropylamide (LDA) in THF / HMPA followed by quenching the enolate with methyl iodide and warming to room temperature gave, after chromatography, the mono-alkylated products

3.1 and 3.2 as well as the dialkyl product 3.3 in 23%, 36% and 29% yield respectively (Table 3.1). The methylated products 3.1, 3.2 and 3.3 were readily distinguished from one another by IR and ^{1}H NMR. The α-methyl product 3.1 displayed a double quartet at 2.74 ppm (J = 1.3, 6.9 Hz) corresponding to the C_2 (naphthalene numbering) allylic methine proton, as well as a doublet methyl signal at 1.27 ppm (J = 6.9 Hz). Furthermore, in the IR spectrum, the carbonyl group appeared at 1716 cm^{-1} as expected. In contrast, the ^{1}H NMR spectrum of 3.2 revealed a methyl singlet at 1.65 ppm which is at considerably

Table 3.1 : α-Methylation of the enone 2.25



Enolate Generation Conditions[a]	Alkylation Temp. (°C)	% Yield[b] 3.1	% Yield[b] 3.2	% Yield[b] 3.3	%Recovered[b] 2.25
i) LDA, THF ii) MeI	-78 to r.t	0	0	0	95
i) LDA, ether, HMPA ii) MeI	-78 to r.t.	0	0	0	100
i) LDA, THF, HMPA ii) MeI	-78 to r.t.	23	36	29	0
i) LDA, THF, HMPA ii) MeI	-78 to -60	75	0	0	15

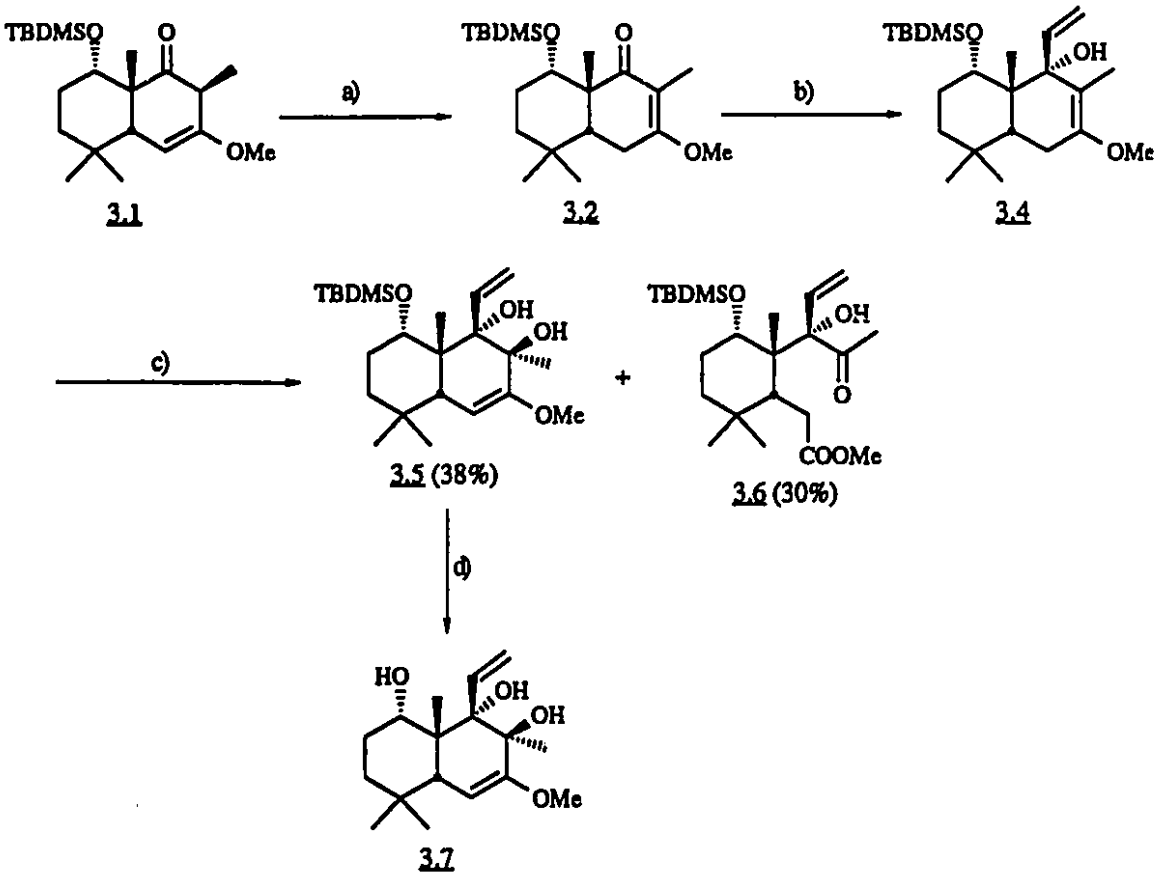
[a] The enolate was generated with 3 equiv. of LDA in the appropriate solvent at -78°C for 1h. [b] Refers to isolated yield (after chromatography).

lower field than that of 3.1. The IR spectrum revealed a carbonyl stretching frequency of 1634 cm^{-1} characteristic of the β-methoxy enone functionality. The ^{1}H NMR spectrum of the dialkyl product 3.3 revealed five (5) methyl singlets at 1.39, 1.22, 1.20, 0.88 and 0.60

ppm in contrast to the four (4) signals observed for both 3.1 and 3.2.

As shown in Table 3.1, HMPA is essential for successful generation of the enolate. Furthermore, no deprotonation occurs when diethyl ether is used as solvent in place of THF, only starting material is recovered. In all cases, methylation did not proceed at -78°C and product mixtures were obtained when the reaction mixtures were allowed to warm to room temperature. Optimum conditions for the selective formation of 3.1 were LDA (3.0 eq.), HMPA (5.0 eq.) in THF at -78°C for 1h followed by MeI (2.7 eq.) and warming to -60°C, however, a substantial amount (ca. 15 - 20%) of the starting enone 2.25 was frequently recovered. Later, lithium hexamethyldisilazide (LHMDS) was found to be superior to LDA for the generation of the enolate of 2.25 resulting in essentially complete deprotonation with only a slight excess of base required (see Chapter 4).

The α-methyl ketone 3.1 could be smoothly isomerized to the α,β-unsaturated enone 3.2 by refluxing in sodium methoxide / methanol (Scheme 3.2). Exposure of the enone 3.2 to vinyllithium [1] in ether at room temperature gave the labile allylic alcohol 3.4 as a single isomer in good yield. The stereochemistry of 3.4 was proposed based on presumed attack of the vinyl anion from the less hindered convex face of 3.2. The vinyl anion was chosen for the addition onto 3.2 in order to minimize regioselectivity problems in the subsequent epoxidation step. Clearly, one expects the electron rich enol ether double bond of 3.4 to be considerably more reactive towards electrophiles than its vinyl counterpart.



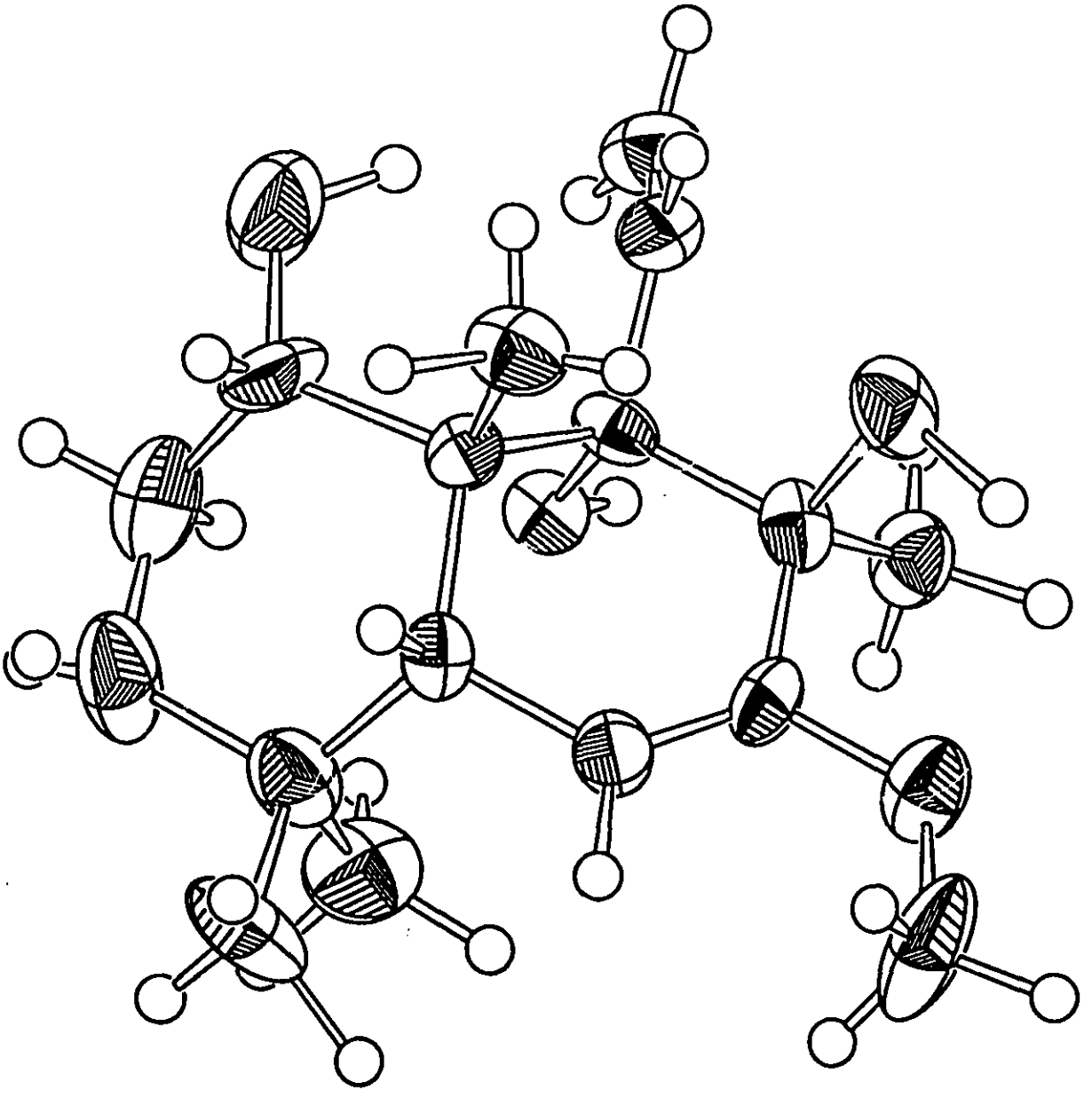
3.1 3.2 3.4

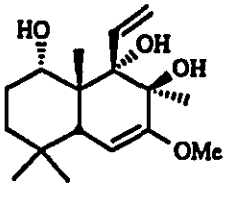
3.5 (38%) 3.6 (30%) 3.7

Reagents: a) MeONa, MeOH, reflux, 2h, 95%; b) C_2H_3Li, ether, 0°C to r.t., 30 min., 79%; c) MCPBA, Na_2CO_3(aq.), CH_2Cl_2, 0°C to r.t; d) TBAF, THF, r.t., 3h, 91%.

Scheme 3.2

Epoxidation of the enol ether moiety of 3.4 with m-chloroperoxybenzoic acid (MCPBA) buffered with aqueous sodium carbonate delivered the oily diol 3.5 (38%) and a substantial quantity (30%) of what appeared to be, the cleavage product 3.6. The silyl protecting group of 3.5 was then cleaved with tetrabutylammonium fluoride (TBAF) in THF delivering the crystalline triol 3.7 in 96% yield, whose structure was confirmed by single crystal X-ray diffraction as shown in the ORTEP diagram 2. The X-ray data revealed that two independant molecules (conformers) differing in the conformation of the A ring (ie: the ring bearing the 2° hydroxyl group) were present in the unit cell.





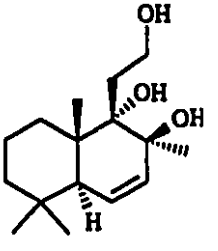
3.7

ORTEP Diagram 2

The stereochemistry of the diol product 3.5 is consistent with the preferred approach of the peroxyacid from the less hindered convex face of 3.4. The apparent inability of the allylic hydroxyl group to participate in directing epoxidation to the more hindered α-face of 3.4 is presumably due to the steric congestion imparted by the folded nature of the decalin ring system .

Attempts to suppress the formation of the cleavage product 3.6 by varying the amount of sodium carbonate buffer and the temperature were unsuccessful and only 3.5 and 3.6 were obtained in each case. However, epoxidation of 3.4 with the mild peroxide reagent, dimethyldioxirane [2], delivered the diol 3.5 in 79% yield without formation of any cleavage product 3.6. Due to our inability to obtain the desired retro-synthetic intermediate diol R3 by this epoxidation sequence, we decided to abandon this approach and examine the alternative Route B (see Scheme 3.1).

In passing, although this approach was not successful for the synthesis of the retro-synthetic intermediate diol R3, it may well be useful in the synthesis of the natural product isoalbrassitriol 3.8 [3] where the *trans* relationship of the tertiary hydroxyl functionalities is required.



3.8

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2. a) Murray, R.W; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. b) Murray, R.W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335. c) Adam, W.; Chan, Y.Y.; Cremer, D.; Gauss, J.; Schentzow, O.; Schindler, M. *J. Org Chem.* **1987**, *52*, 2800.

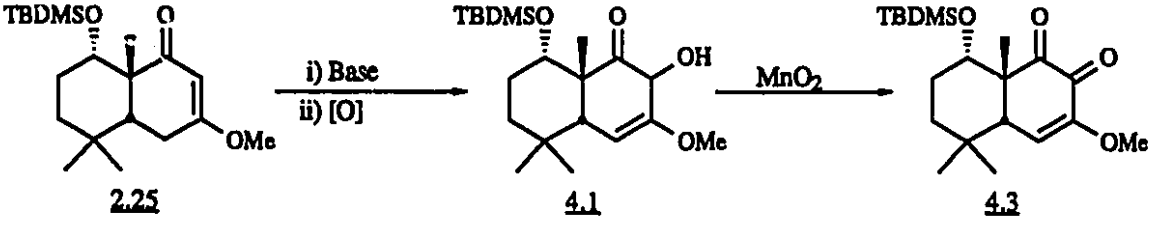
3. Ayer, W.A.; Pena-Rodriguez, L.M. *J. Nat. Prod.* **1987**, *50*, 408.

CHAPTER 4

ATTEMPTED SYNTHESIS OF THE RETRO-SYNTHETIC INTERMEDIATE DIKETONE R2 VIA ROUTE B(PRELIMINARY INVESTIGATION)

4.1 Introduction

In order to utilize Route B for the construction of the advanced intermediate diketone R2, conditions for the regioselective oxidation of the enone 2.25 to the diketone 4.3 had to be established first. It was thought that this transformation could be achieved in a two step sequence, namely, regioselective enolate oxidation to give the acyloin 4.1, followed by oxidation to the diketone 4.3 with manganese dioxide (Scheme 4.1). Subsequent methyl and functionalized carbanion additions to each carbonyl group of 4.3 was expected to provide a useful stereoselective entry to the functionalized decalin ring system of forskolin 1.6. Herein, we describe the preparation of the diketone 4.3 using novel enolate oxidation methodology and our initial attempts at further elaboration of 4.3 to the retro-synthetic intermediate diketone R2.



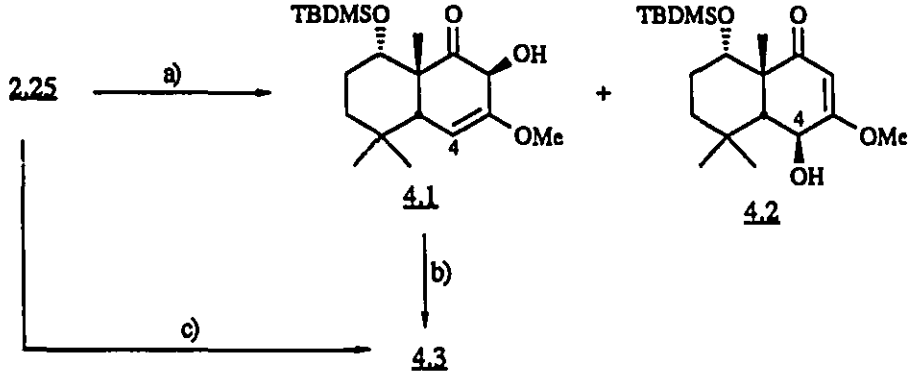
2.25 4.1 4.3

Scheme 4.1

4.2 Initial Attempts at Enolate Oxidation of 2.25

The enolate of 2.25 was generated with LDA and HMPA in THF at -78°C as described

previously (see Chapter 3, Table 3.1 and accompanying text). Direct oxidation of the enolate of 2.25 with Vedejs' MoOPH [1] reagent gave none of the expected α-hydroxy product 4.1. Instead, over-oxidation occurred to give the α-diketone 4.3 albeit in low yield, along with a considerable quantity (48%) of recovered 2.25 (Scheme 4.2). The poor yield and material balance in this reaction as well as difficulties encountered in product isolation led us to examine other routes to the desired acyloin product 4.1.



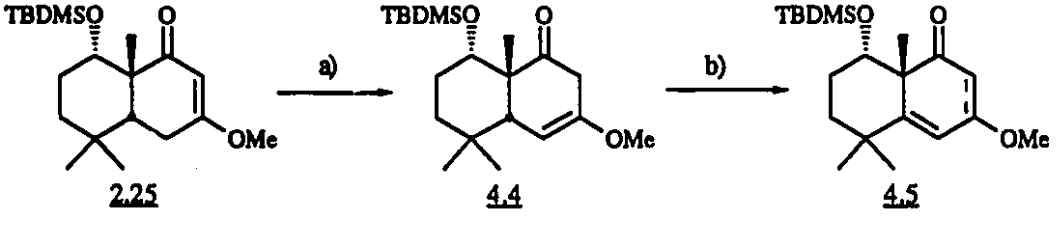
Reagents: a) LHMDS, HMPA, THF, -78°C, 1h, then 2-benzenesulphonyl-3-phenyl-oxaziridine, -78°C, 30 min, 96%; b) MnO_2, pentane, r.t, 2h, 95%; c) LDA, HMPA, -78°C, 1h, then MoOPh, -78°C to r.t., 15.5h, 8%.

Scheme 4.2

We then turned our attention to the oxaziridine methodology recently described by Davis [2]. The enolate of 2.25 was generated with the stronger base lithium hexamethyldisilazide (LHMDS) and HMPA in THF in order to minimize recovery of 2.25. Reaction of the enolate with 2-benzenesulfonyl-3-phenyloxaziridine at -78°C gave the α- and γ- hydroxy products 4.1 and 4.2 as single diastereomers in 30% and 66% yield respectively (Scheme 4.2). As expected, the use of LHMDS (1.3 Equiv.) allowed efficient and essentially quantitative generation of the enolate at -78°C, and as such, none of the starting enone 2.25 was recovered.

The hydroxyl groups of 4.1 and 4.2 are likely to have the β–stereochemistry which is expected for the approach of the oxaziridine reagent from the less hindered convex face of the enolate. The isomeric alcohols 4.1 and 4.2 were easily distinguished based on their spectroscopic data. The ^{1}H NMR spectrum of 4.1 revealed a doublet at 4.94 ppm corresponding to the enol ether (C_4) proton. The IR spectrum revealed a carbonyl stretching band at 1722 cm^{-1}, consistent with the acyloin functionality. In contrast, the regioisomeric product 4.2 displayed a carbonyl band at 1636 cm^{-1} and the enol ether (C_2) proton appeared at lower field (5.26 ppm) in the ^{1}H NMR spectrum. The α-hydroxy product 4.1 was then smoothly oxidized to the α-diketone 4.3 by manganese dioxide in pentane in 95% yield (Scheme 4.2).

In an attempt to improve the yield of the α-hydroxy product 4.1, we have tried to regioselectively introduce a hydroxyl or keto group α to the carbonyl of 2.25 using the selenium dioxide approach outlined in Scheme 4.3. Thus, quenching the enolate derived from 2.25 with water at -78°C cleanly afforded the deconjugated enone 4.4 in 95% yield. Exposure of 4.4 to selenium dioxide in refluxing dioxane gave exclusively the enone 4.5 in 88% yield. The ^{1}H NMR spectrum of 4.5 revealed two (2) doublet olefin signals at 6.08 and 5.29 ppm which were mutually coupled (^{4}J = 1.8 Hz), consistent with the dienone structure.

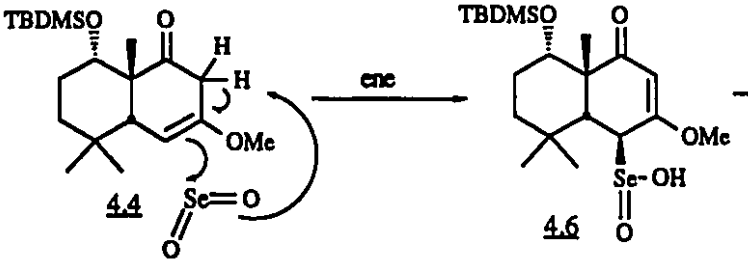


2.25 4.4 4.5

Reagents: a) LHMDS, HMPA, THF, -78°C, 1h, then H_2O quench, 95%; b) SeO_2, dioxane reflux, 30 min., 88%.

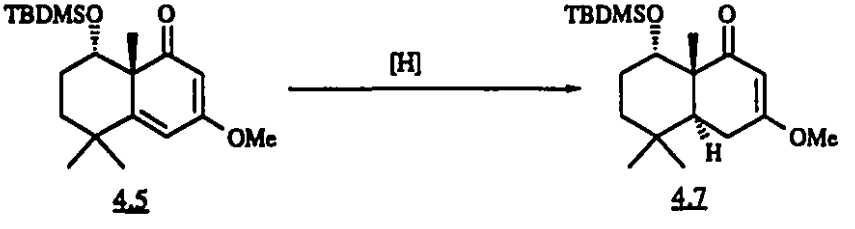
Scheme 4.3

Mechanistically, one can explain the formation of 4.5 by initial ene-type reaction of selenium dioxide to give the intermediate selenic acid 4.6 which then undergoes syn-elimination (rather than [2,3]-sigmatropic rearrangement) to give 4.5 (Eq. 4.1).



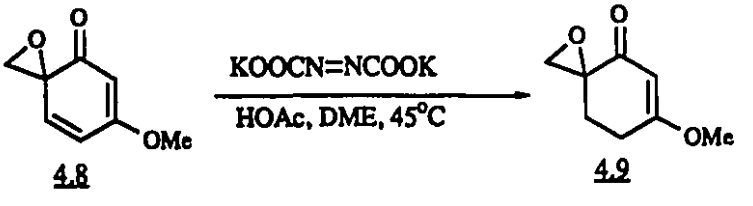
(Eq.4.1)

Although none of the desired α-hydroxy product was isolated in this reaction, this deconjugation / oxidation sequence may well be useful as a method to convert the *cis* ring junction stereoisomer 2.25 to the thermodynamically more stable *trans* isomer 4.7. This would require the selective hydrogenation or reduction of the trisubstituted double bond of 4.5 (Eq. 4.2).



(Eq. 4.2)

Indeed, in their synthesis of Ovalicin, Corey and coworkers [3] were able to selectively reduce the disubstituted double bond of 4.8 with diimide to give 4.9, leaving the β-methoxyenone functionality intact (Eq. 4.3).



(Eq. 4.3)

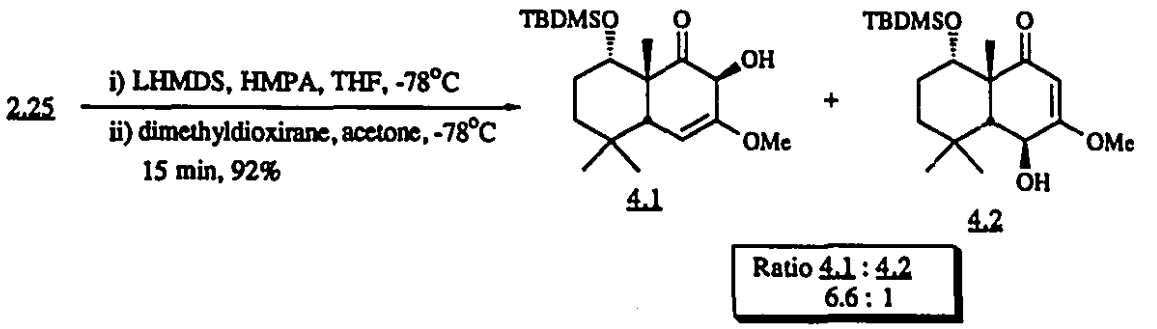
In view of the lack of regioselectivity obtained in the oxidation of the enolate of 2.25 with oxaziridine and the poor yield / material balance encountered in the MoOPH oxidation, it seemed important to develop new methodology which would allow smooth regioselective oxidation of the enolate of 2.25 to give the α-hydroxy compound 4.1 .

4.3 Enolate Oxidation With Dimethyldioxirane : New General Methodology For The Formation of α-Hydroxy Carbonyl Compounds

Recently, dimethyldioxirane [4] has been shown to be a mild selective oxidant converting enol ethers [5], γ-methylene-γ-butyrolactones [6], sugar-derived dihydropyrans [7], α,β-unsaturated ketones, esters and acids [8], enol silyl ethers [9], and aflatoxin B_1 [10], to their corresponding epoxides, polycyclic arenes [11], to their oxides and allenes [12], to their dioxides. The remarkably mild nature and high efficiency of this reagent in forming the labile epoxides mentioned above led us to examine its use in the oxidation of the enolate of 2.25.

Dimethyldioxirane (as a solution in acetone) was prepared according to the small scale literature procedure [4c]. In general, the concentrations of the solutions were determined to be in the range of 0.05 - 0.10 M.

When the enolate of 2.25 was treated a slight molar excess (1.4 Equiv.) of anhydrous dimethyldioxirane solution in acetone (inverse addition, ie: the enolate solution in THF at -78°C was added dropwise via cannula to the dimethyldioxirane solution also at -78°C) we were very pleased to discover that the α- and γ-hydroxy products 4.1 and 4.2 could be isolated as single diastereomers in a ratio of 6.6 : 1 and in 92% yield (Scheme 4.4).

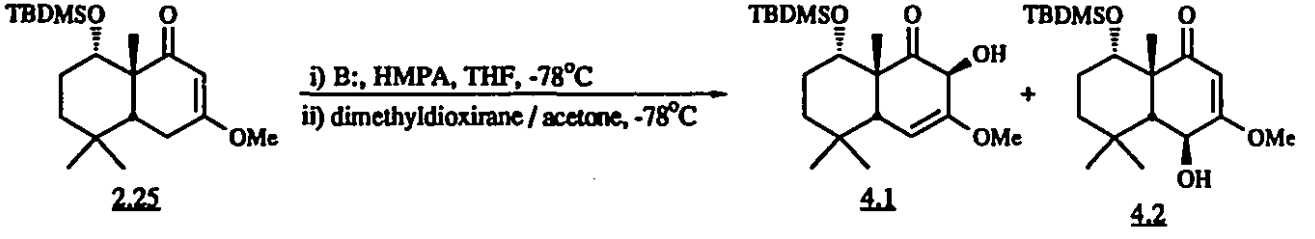


Scheme 4.4

Remarkably, the reaction appeared to be very rapid and clean at -78°C affording only 4.1 and 4.2. No products resulting from condensation of the enolate of 2.25 with acetone could be detected. Furthermore, little or no starting enone 2.25 or the deconjugated derivative 4.4 were recovered (ie: < 5%) suggesting that, in this case, the oxidation of the enolate of 2.25 by dimethyldioxirane is considerably faster than the proton transfer reaction with acetone.

Interestingly, in the oxidation of the enolate of 2.25, the α / γ selectivity appeared to vary according to the steric size and / or strength of the amide base used for the generation of the enolate. For example, when the enolate of 2.25 was generated with LDA and then quenched with dimethyldioxirane solution at -78°C, the α / γ ratio was found to be 4 : 1 in favor of the α-isomer 4.1. On the other hand, when the less hindered base lithium diethylamide was used, the α / γ ratio changed markedly to 1 : 1.3 in favor of the γ product 4.2 (Table 4.1). It would appear that LHMDS is the base of choice allowing efficient

Table 4.1: The Effect of the Base on the Ratio of 4.1 : 4.2 (ratio of α/γ)



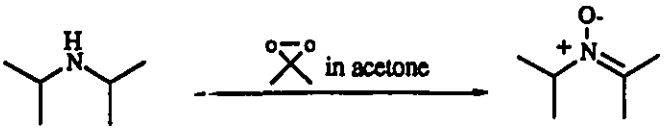
Base (B:)	Temp.(ºC)	[a] % Yield 4.1, 4.2	[b] ratio 4.1 : 4.2	[a] % Yield 4.4	[a] % Recovered 2.25
iPr_2NLi	-78	75	4 : 1	17	0
Et_2NLi	-78	67	1 : 1.3	10	17
$(Me_3Si)_2NLi$	-78	92	6.6 : 1	0	0

[a] Refers to isolated yield (after chromatography). [b] Ratios were determined from the ^1H NMR spectrum of the crude reaction mixtures

deprotonation and high regioselectivity in the oxidation step.

A number of other commercially available ketones were also examined in order to probe the generality of this new oxidation methodology (Table 4.2). In general, despite taking all precautions to exclude moisture from these reactions, some of the starting ketone was recovered in the cases of compounds 4.10a, 4.11a, 4.12a and 4.13a. This is presumably due to the competing proton transfer reaction between the enolates and acetone. The amount of recovery however, could be minimized using the inverse addition technique (Method A).

Although no products resulting from aldol condensation with acetone could be detected in these reactions, there appeared to be a minor but detectable side product which was common to each reaction. This would suggest that either acetone, LDA or diisopropylamine were involved. Indeed, the common product that was produced was identified as the nitrone 4.14 resulting from oxidation of diisopropylamine by excess dimethyldioxirane (Eq. 4.4). The identity of 4.14 was confirmed by comparison with an authentic sample prepared by oxidation of diisopropylamine according to the literature procedure [13].

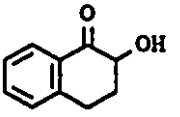
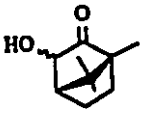
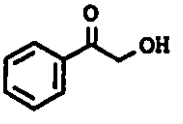
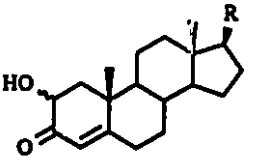


(Eq. 4.4)

4.14

In comparing the oxidations of α-tetralone 4.10a, camphor 4.11a, cholestenone 4.13a and our β-methoxyenone 2.25, the chemical yields are clearly superior to the MoOPH method (Method C). In the case of cholestenone 4.13a, the α-hydroxy product is derived, as expected, from the kinetic enolate in regiochemistry. Moderate stereoselectivity is

Table 4.2: Enolate oxidation with dimethyldioxirane[a]

Carbonyl Compound	Oxid.[b] Method	Oxid. Temp.(oC)	Time (min)	Product	% Yield [c]	Recovered Carbonyl [c] Compound (%)	Other [c] % Yield
α-tetralone 4.10a	A	-78	10	 4.10b	82	8	-
	B	-78	20	4.10b	52	31	-
	C[d]	-22	-	4.10b	48	0	-
Camphor 4.11a	A	-78	15	 4.11b	74[e]	18	-
	B	-78	30	4.11b	50[e]	39	-
	C[d]	-22	10	4.11b	70[f]	15	-
Acetophenone 4.12a	A	-78	30	 4.12b	77	4	-
Cholestenone 4.13a	A	-78	10	 4.13b	60[g]	26	-
	C[d]	-	-	4.13b	40[g]	0	-

[a] dimethyldioxirane solutions in acetone were prepared (small scale) and standardized (thioanisole assay) according to the procedure of Adam and co-workers (ref.4c) and dried over 3A molecular sieves for 2 days at -20°C before using. [b] Method A : inverse addition (see text). Method B: regular addition (ie: the DD solution in acetone at -78°C is added dropwise to the enolate in THF at -78°C). Method C : The MoOPH reagent (approx. 1.5 equiv.) is added to the enolate in THF at -78°C and then warmed to the specified temperature. [c] Refers to isolated yield (after chromatography). [d] These results were taken from ref. 1 . Cholestenone was oxidized using inverse MoOPH addition. [e] Mixture of 2 diastereomers (exo : endo = 2.2 : 1). [f] Reported as a single diastereomer (see ref.1). [g] Mixture of 2 diastereomers, stereochemistry not determined.

observed for derivatives 4.11b (2.2 : 1, exo : endo) and 4.13b (2 : 1 mixture of diastereomers, stereochemistry not determined).

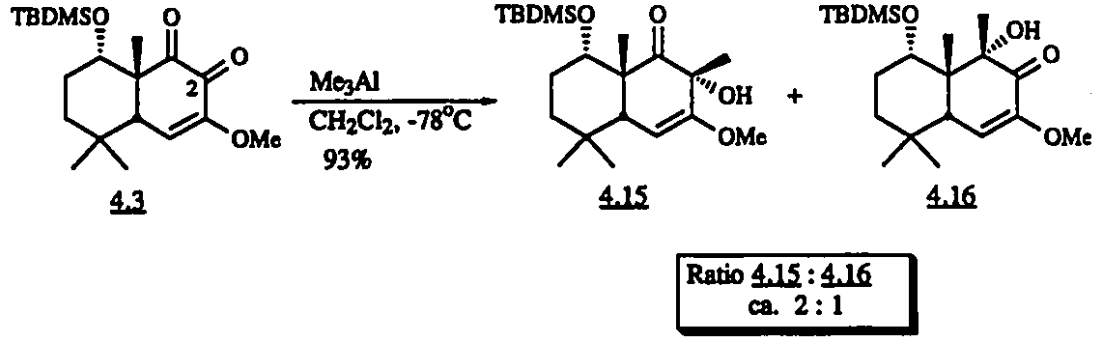
In general, there are a number of limitations associated with the MoOPH methodology. The reagent is highly toxic and requires careful handling. Only limited success is achieved in the oxidation of methyl ketones, as aldol self-condensation is often a problem [1]. Furthermore, over-oxidation of the acyloin products is quite common and sometimes the corresponding diketones are the predominant species [1]. It is not possible to efficiently oxidize the enolates of β-diketones or β-ketoesters with MoOPH, presumably due to chelation with the molybdenum species which resists oxidation [1].

This new method for the oxidation of enolates offers several advantages over the MoOPH method. The reagent (dimethyldioxirane) is easily prepared and safe to use, it oxidizes methyl ketones (see compound 4.12a in Table 4.2) efficiently and the absence of a metallic component suggests that it may be used effectively for the oxidation of β-diketone and β-ketoester enolate systems. Furthermore, the mild nature of the reagent ensures that further oxidation of the acyloin products to the α-diketones is effectively suppressed. In none of the cases examined (Table 4.2) were α-diketone products ever detected. With a selective and efficient pathway to the α-diketone 4.3 developed, further studies directed towards the retro-synthetic intermediate diketone R2 were then undertaken.

4.4 Attempted Elaboration of the Diketone 4.3 to the Diketone R2: An Unexpected Stereochemical Outcome

The reactivity of the two carbonyl groups of 4.3 towards alkyllithium reagents was examined in order to determine whether or not carbonyl differentiation could be easily achieved. Thus, exposure of 4.3 to vinyllithium [14] in THF at r.t. gave the C_2

(naphthalene numbering) addition compound as a single isomer albeit in low yield. This preliminary result seemed to suggest that the C_2 enone carbonyl is considerably more reactive and less sterically hindered. Keeping this in mind, reaction of 4.3 with trimethylaluminum (Me_3Al) in CH_2Cl_2 at -78°C afforded a ca. 2 : 1 mixture of the allylic alcohol 4.15 and the other α-hydroxy enone regioisomer 4.16 as single diastereomers in 93% yield (Scheme 4.5).



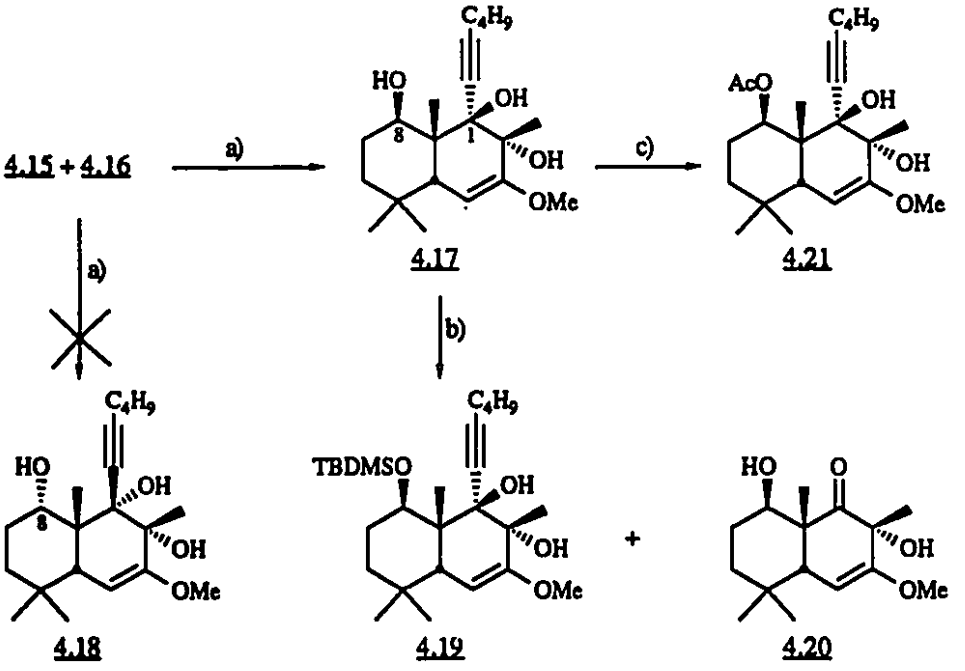
Scheme 4.5

The ratio of 4.15 : 4.16 however, was not reproducible in many cases and appeared to favor 4.15 on a small scale (ie: ratio 4.15 : 4.16 = 12 : 1) or when the trimethylaluminum solution was added rapidly to the enone solution at -78°C. Slow dropwise addition of the trimethylaluminum solution to the enone at -78°C (over a 10-15 min. period) gave essentially a 1 : 1 mixture of the regioisomers on a 300 mg scale. Furthermore, separation of the two regioisomers by flash chromatography proved to be quite tedious, as their R_f values were very close in a variety of solvent systems.

After two chromatographic separations, we were able to separate the desired regioisomer 4.15 although it was frequently contaminated with approximately 5 - 10% of 4.16. With a reasonably pure sample of 4.15 in hand, attempts were then made to add

various functionalized carbanions to the remaining carbonyl group. Unfortunately, even under forcing conditions, we were unable to effect addition of either vinyllithium [14], vinyl magnesium bromide, lithium acetylide-ethylene diamine complex [15] or 1-lithio-1-methoxy allene [16] and only the starting ketone 4.15 was recovered in each case. The seemingly inert nature of the ketone 4.15 to vinyl anions is presumably due to the steric influence of the 1,3-diaxial methyl groups. However, exposure of the crude (ca. 2 : 1 mixture) of 4.15 and 4.16 to an excess of the less sterically demanding carbanion 1-lithio-1-hexyne in THF at reflux temperature afforded a single product in 82% yield, which was tentatively assigned the triol structure 4.17. Initially, the expected isomeric structure 4.18 was assigned on the basis of ^{1}H NMR (Scheme 4.6). The C_8 (naphthalene numbering) methine proton at 4.49 ppm appeared as a doublet of doublet of doublet with both large (11.1 Hz) and small (4.8 Hz) vicinal couplings as well as a small hydroxyl coupling (2.2 Hz) expected of an axial hydrogen. If the tentatively assigned structure 4.17 is indeed correct, there must be a greater population of the conformer A in solution ($CDCl_3$) at room temperature in order to account for the large and small vicinal couplings observed for the C_8 methine proton (Figure 4.1).

Since we did not know for certain the stereochemistry of the triol product and spectroscopic data appeared to be compatible with the expected structure 4.18, we proceeded with the subsequent reaction steps. *Indeed, it was only through conversion of this triol to the crystalline tetrol 4.30 that the errant stereochemistries were determined and the structure 4.18 could be ruled out. Consequently, the triol product was tentatively assigned the isomeric structure 4.17.*



Reagents: a) excess 1-lithio-1-hexyne, THF, reflux, 4h, 80%; b) TBDMS triflate, 2,6-lutidine CH_2Cl_2, r.t.; c) Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, reflux, 7 days, 89%.

Scheme 4.6

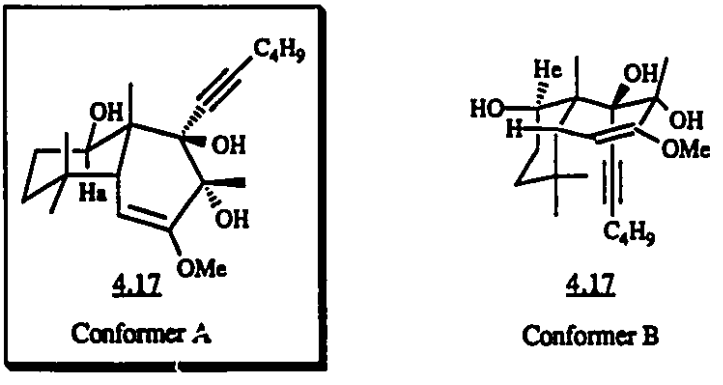


Figure 4.1

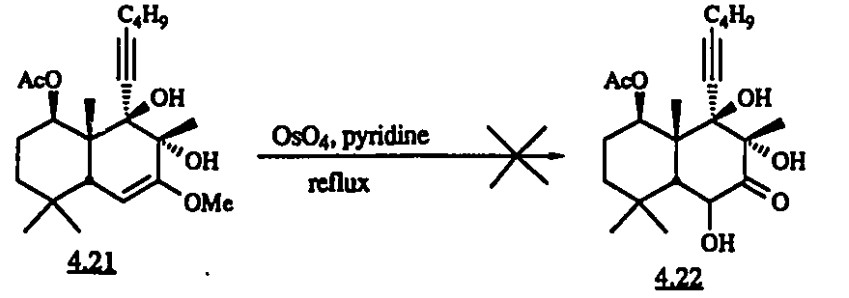
It is worth noting at this stage that the formation of only one triol (ie: 4.17) in high yield (80%) in the reaction of 4.15 and 4.16 (ca. 2 : 1 mixture) with the hexynyl carbanion,

suggests that the minor isomer 4.16 undergoes α-ketol rearrangement to 4.15 prior to acetylide addition. This statement is based on the observation that when a 1 : 1.3 mixture of 4.15 and 4.16 was subjected to the same conditions, the triol 4.17 was isolated exclusively in 71% yield. Similarly, when a 12 : 1 mixture of 4.15 and 4.16 was utlilized, the same triol 4.17 was isolated in 81% yield.

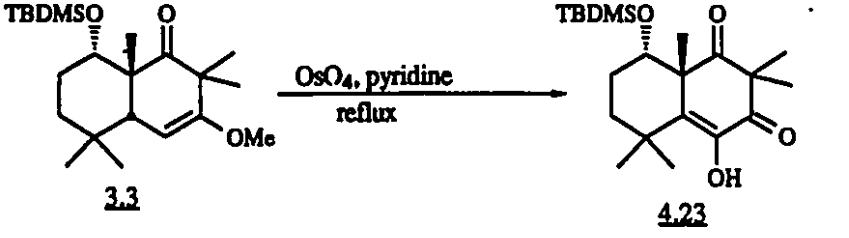
Selective protection of the secondary hydroxyl group of 4.17 as the t-butyldimethylsilyl (TBDMS) ether was then attempted under a variety of conditions (ie: TBDMS chloride / imidazole / DMF at 40°C and 80°C and TBDMS chloride / silver nitrate) however only unreacted triol was recovered in each case. When silylation was attempted with TBDMS trifluoromethanesulfonate and 2,6-lutidine [17], some of the silylated product 4.19 appeared to have formed as determined from the crude ^{1}H NMR spectrum, however contaminated by a considerable quantity (approximately 33%) of what appeared to be, the retro-addition product 4.20. Attempted separation of 4.19 and 4.20 by silica gel chromatography led to complete decomposition of the presumed silyl ether 4.19. All attempts to suppress the formation of 4.20 by altering the base strength or temperature were unsuccessful and at best, a 3 : 1 mixture could be obtained (Scheme 4.6). To this end, smooth selective acetylation of 4.17 could be achieved with acetic anhydride / pyridine and 4-dimethylaminopyridine (DMAP) to give the mono-acetate 4.21 in 89% yield.

Our initial attempts to convert the enol ether moiety of 4.21 to the corresponding diketone function were unsuccessful. For example, stoichiometric osmylation of 4.21 with osmium tetroxide in pyridine failed to provide any of the required acyloin product 4.22 even under forcing (reflux) conditions (Eq. 4.5). We were, however, able to prepare the diketone 4.23 of the model enol ether 3.3 under these conditions, albeit in low yield (Eq. 4.6). The ^{1}H NMR spectrum of 4.23 revealed that the diketone moiety is completely enolic in $CDCl_3$ as indicated by the presence of an exchangeable hydroxyl singlet at 6.60 ppm.

The drastic conditions required to osmylate 3.3 as well as the seemingly inert nature of 4.21 suggests that their enol ether moieties are in incredibly sterically encumbered environments.



4.21 4.22 (Eq. 4.5)



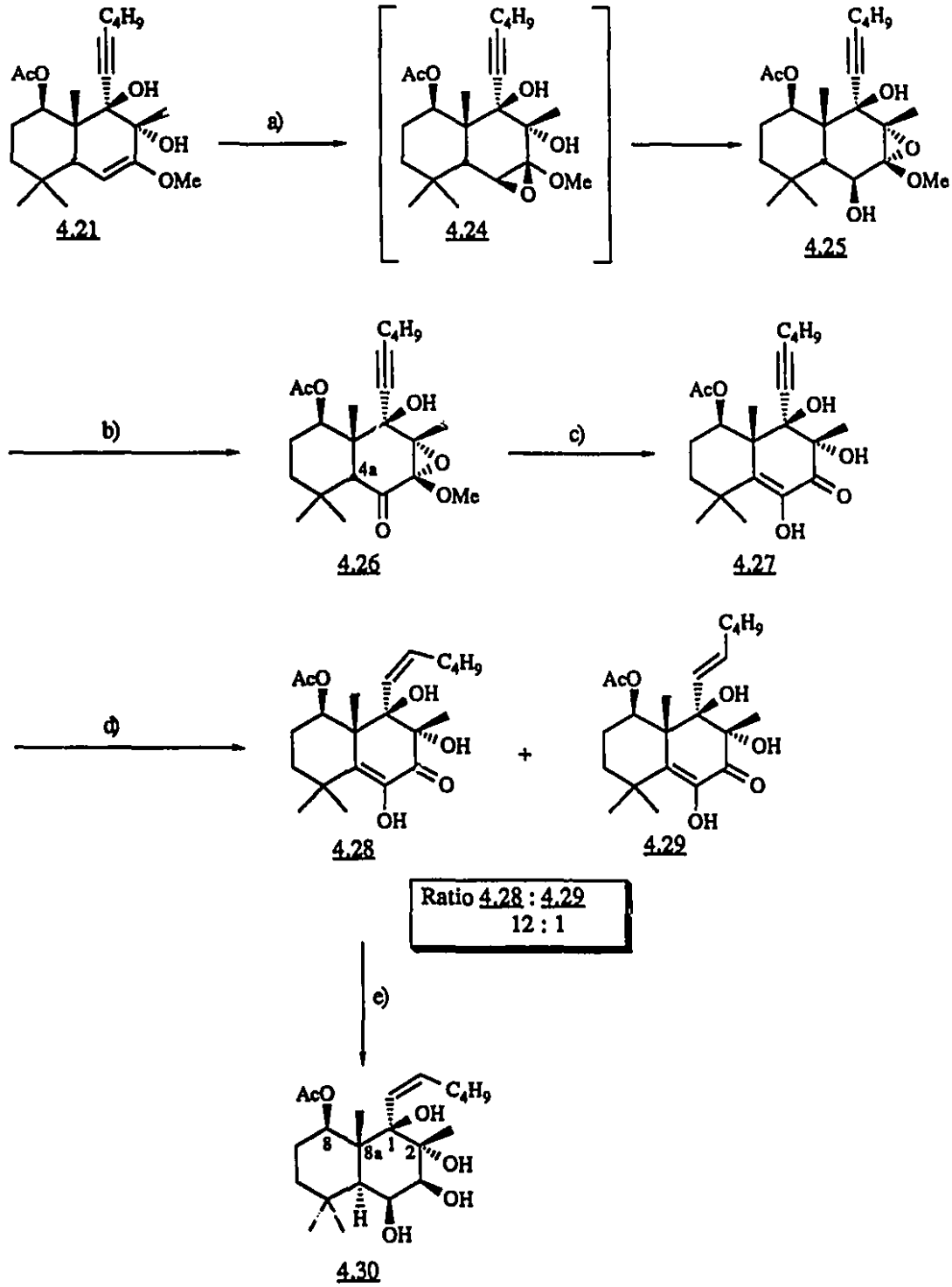
3.3 4.23 (Eq. 4.6)

24% + 49% unreacted 3.3

The enol ether 4.21 could be converted to the α-diketone 4.27 efficiently by a three step sequence as outlined in Scheme 4.7. Epoxidation of the enol ether moiety of 4.21 with dimethyldioxirane [5] gave a single labile epoxy ether 4.25 (resulting from Payne rearrangement of the initially formed epoxy ether 4.24) in essentially quantitative yield. It was found that when the dimethyldioxirane reagent concentration was less than about 0.06M (as determined by thioanisole assay) the isomeric epoxy ether 4.24 was formed almost exclusively in quantitative yield. This however, did not cause any problems since both 4.24 and 4.25 could be converted to the epoxy ketone 4.26 in the subsequent oxidation step. The epoxide stereochemistry of 4.24 or 4.25 was not determined, however the approach of the dioxirane reagent from the less hindered convex face of 4.21 is expected.

Oxidation of 4.25 with sodium acetate buffered pyridinium chlorochromate (PCC) [18] afforded the epoxy ketone 4.26 in 65% yield together with a small amount of recovered 4.25. The ^{1}H NMR spectrum of 4.26 showed a singlet at 2.39 ppm corresponding to the C_{4a} ring junction proton. The IR spectrum revealed two (2) carbonyl absorptions at 1737 cm^{-1} and 1711 cm^{-1} corresponding to the acetate and cyclic ketone groups respectively. It should be noted that other common oxidation methods such as Swern [19], pyridinium dichromate (PDC) [20], PCC on alumina [21], barium manganate [22] or chromium oxide / pyridine (Collins method) proved to be inferior for the oxidation of 4.25.

Cleavage of the epoxy ether function of 4.26 with dimethylboron bromide (DBB) [23] in the presence of triethylamine (TEA) afforded the solid α-diketone 4.27 in good yield which exists exclusively as the enol tautomer in deuterated chloroform (Scheme 4.7). An attempt was made to obtain crystals suitable for X-ray crystallographic analysis however 4.27 seemed to crystallize in the form of fine plates from a variety of solvents. The ^{1}H NMR spectrum of 4.27 revealed an exchangeable hydroxyl singlet at 6.34 ppm, analogous to that previously observed for the diketone 4.23. The presence of TEA was found to be crucial



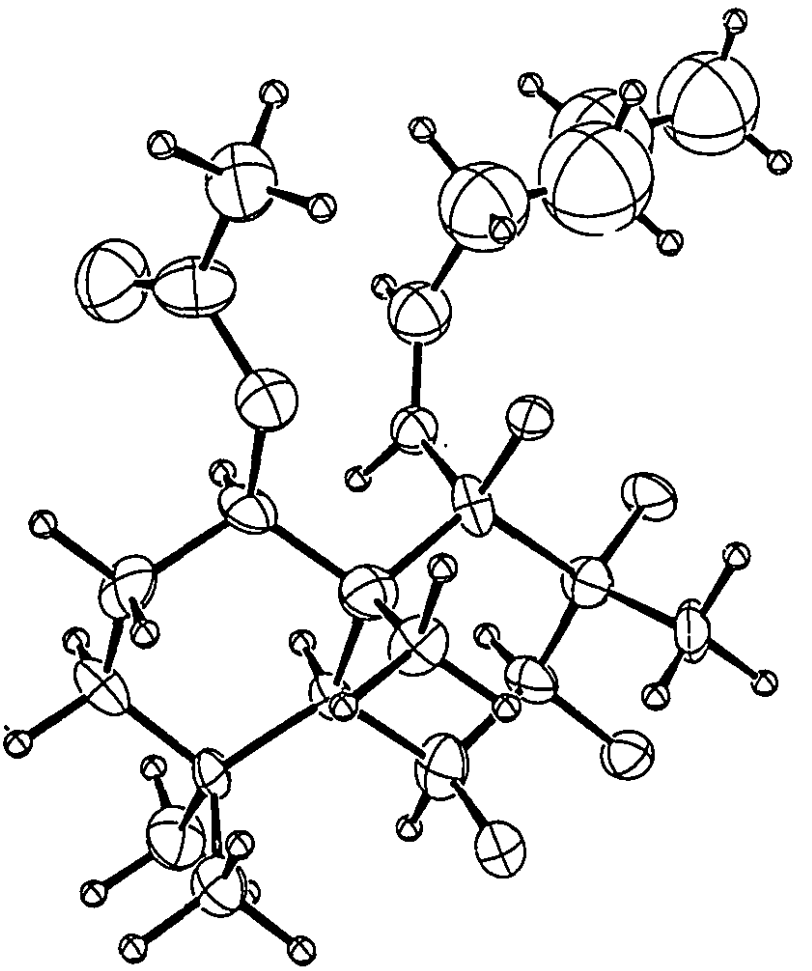
Reagents: a) dimethyldioxirane, acetone, CH_2Cl_2, r.t., 1h, 100%; b) PCC, NaOAc, CH_2Cl_2, r.t., 26h, 65% + 7% recovered 4.25; c) Me_2BBr, Et_3N, CH_2Cl_2, -78°C, then 0°C, 10 min., 83 - 96%; d) H_2 (1 atm.), Pd / C, ethanol, r.t, 1h, 98%; e) t-$BuNH_2$ BH_3, THF, reflux, 24h, 52%.

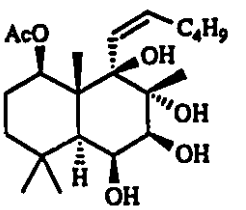
Scheme 4.7

for the success of this reaction. For example, when the reaction was carried out using 1 equivalent of DBB and only 0.1 equivalent of TEA as acid scavenger, none of the desired α-diketone 4.27 was produced. Instead, a labile compound lacking a methoxy group was obtained, however it could not be isolated for identification purposes. On the other hand, when equimolar quantities of DBB and TEA were present, the starting epoxyketone 4.26 was recovered unchanged. Other common reagents and conditions for ether cleavage such as PhSLi / DMF / 100°C, LiI / $ZnBr_2$ or $TiCl_4$ / LiI were also examined. Unfortunately, only complex product mixtures or recovered starting material were obtained.

Hydrogenation of the carbon-carbon triple bond of 4.27 using 10% palladium on carbon (Pd / C) as catalyst afforded the oily E- and Z- allylic alcohols 4.29 and 4.28 in a ratio of 1 : 12 in 98% yield which were easily separated at this stage. The major Z allylic alcohol 4.28 was clearly distinguished from its isomeric counterpart 4.29 on the basis of ^1H NMR. The olefin signal of the major isomer 4.28 at 5.24 ppm appeared as a doublet with a relatively small coupling constant (7.3 Hz) suggesting a *cis* or Z geometry about the double bond. On the other hand, the analogous proton of the minor isomer 4.29 at 5.49 ppm showed a large coupling constant (ie: 15.3 Hz) in support of the E or *trans* double bond geometry. It was found that Lindlar's catalyst was incapable of catalyzing the hydrogenation of 4.27 under similar conditions and only starting material was recovered.

Stereoselective reduction of the α-diketone moiety of the major Z- allylic alcohol 4.28 with borane-*tert*-butylamine complex [24], gave the crystalline tetrol 4.30 in 52% yield (Scheme 4.7) whose structure was confirmed by single crystal X-ray diffraction as shown in ORTEP diagram 3. The ORTEP diagram 3 reveals that the tetrol 4.30 has the incorrect stereochemistry at the C_1 and C_8 (naphthalene numbering) carbons. For the forskolin structure 1.6, the α-OH stereochemistry at both C_1 and C_8 is required. It would seem that the incorrect structure 4.30 is a consequence of the stereochemical outcome of the acetylide

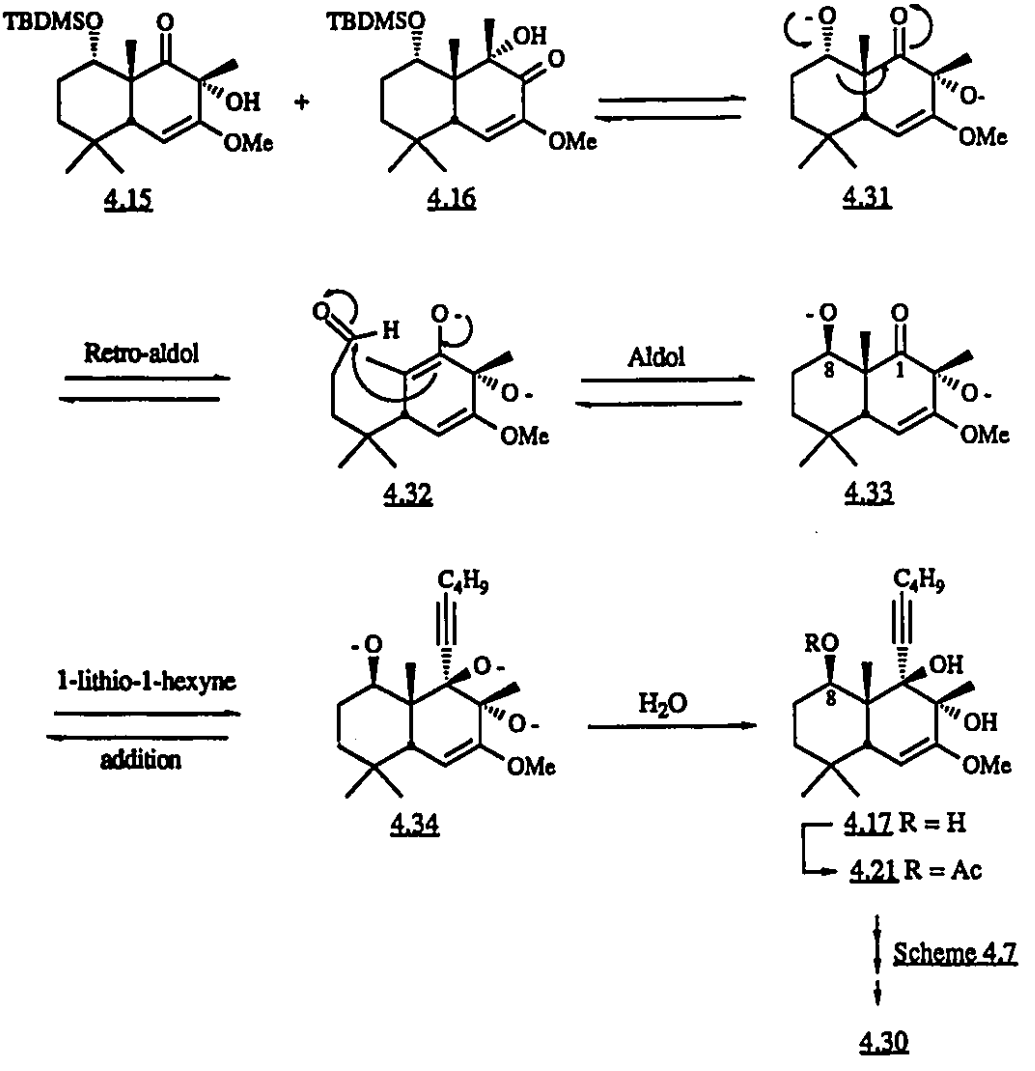




4.30

ORTEP Diagram 3

addition reaction on the isomeric mixture of 4.15 and 4.16. One possible explanation for the formation of 4.30 is outlined in Scheme 4.8 .

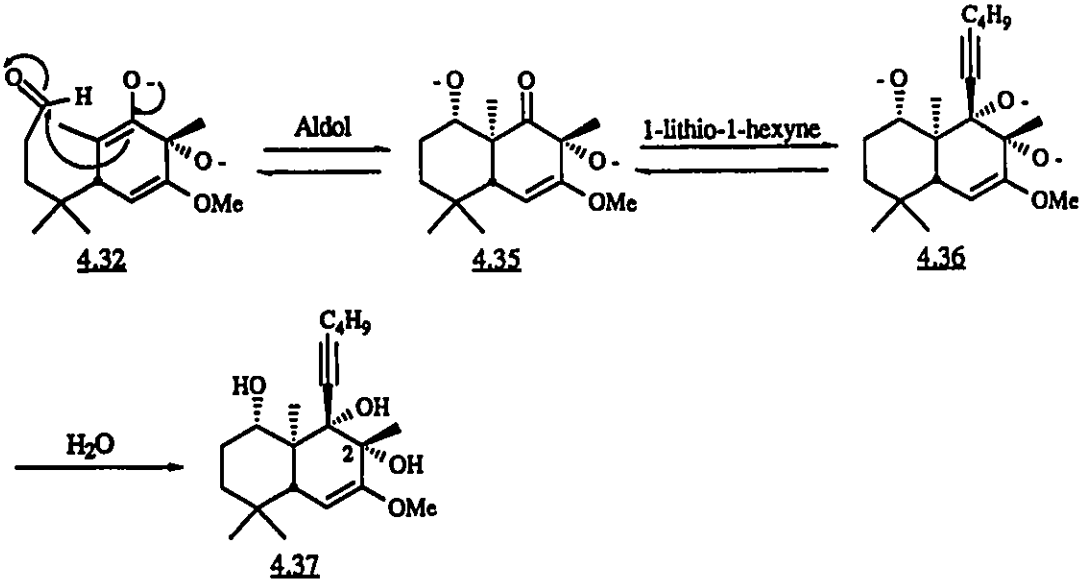


Scheme 4.8

In the reaction of 4.15 and 4.16 with 1-lithio-1-hexyne in THF under reflux conditions, the silyl protecting group is removed first. As a consequence, the resulting β-alkoxy ketone 4.31 may then undergo a retro-aldol ring opening to give the intermediate aldehyde 4.32 which then recyclizes via intramolecular aldol condensation to give the β-alkoxy ketone 4.33 with the *cis* stereochemistry at the ring junction. In order to satisfy the C_8 β-

acetoxy stereochemistry in the tetrol structure 4.30, the C_8 hydroxyl group must adopt a β–orientation as a result of the recyclization of 4.32. Finally, the acetylide carbanion would then add from the concave face of 4.33 to give 4.17 thus establishing the observed C_1 stereochemistry of the tetrol 4.30.

An alternative explanation for the formation of 4.30 from the mixture of ketones 4.15 and 4.16 is outlined in Scheme 4.9 below. In this particular case, the same aldehyde intermediate 4.32 (produced via retro-aldol opening of 4.31) may then recyclize to give the intermediate β-alkoxy ketone 4.35 bearing a *trans* (rather than *cis*) ring junction stereochemistry. Addition of the hexynyl carbanion from the less hindered β-face of 4.35 would then give a triol of structure 4.37. The pathway leading to 4.37 as outlined in Scheme 4.9, does not however, explain the fact that the C_{8a} and C_2 methyl groups of the tetrol 4.30 have a *cis* 1,3 relationship. This would require the epimerization of the C_2



4.32 4.35 4.36 4.37

Scheme 4.9

stereocenter to give the β-OH stereochemistry. It is unclear to us at what stage this

epimerization may be occurring, however the fact that the C_2 hydroxyl group is tertiary suggests that epimerization may be facile under mildly acidic conditions. In the conversion of the diol 4.21 to the tetrol 4.30 (see Scheme 4.7) a number of the reagents used (ie: PCC, dimethylboron bromide and dimethyldioxirane) are acidic in nature and either of these reagents may well be responsible for the C_2 epimerization. In our opinion however, the mechanism leading to the triol structure 4.17 presented in Scheme 4.8 appears to be more likely as it does not require the epimerization of the C_2 stereocenter.

It is important to note, at this point, the *trans* ring junction stereochemistry of the tetrol 4.30. In the reduction of the diketone 4.28 with *tert*-butylamine borane complex, one expects hydride delivery to occur from the less hindered α-face of the diketone 4.28 (see Scheme 4.7). Although 4.28 seems to exist exclusively as the enol tautomer in $CDCl_3$, presumably, in equilibrium, there is a small amount of the keto tautomer (with the thermodynamically more stable *trans* ring junction stereochemistry) which undergoes stereoselective reduction from the α-face (anti to the C_2, C_5 and C_{8a} axial methyl groups) thus shifting the equilibrium in favor of the corresponding tetrol 4.30. Alternatively, if the C_3 carbonyl of the enol tautomer is reduced first (again from the α-face) the remaining C_4 carbonyl may ketonize to give the *trans* ring junction stereochemistry prior to its own reduction.

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CHAPTER 5

SYNTHESIS OF THE RETRO-SYNTHETIC INTERMEDIATE DIKETONE R2 VIA ROUTE B (MODIFIED STRATEGY)

5.1 Introduction

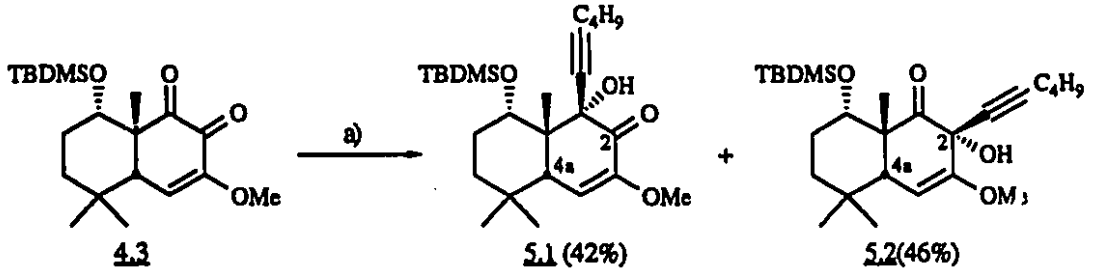
As outlined in the previous chapter, the addition of 1-lithio-1-hexyne to the mixture of ketones 4.15 and 4.16 resulted in the formation of a single triol product whose structure was assigned to be 4.17 based on correlation with the crystalline tetrol compound 4.30. Clearly, it is the loss of the C_8 silyl protecting group of 4.15 that triggers the retro-aldol / aldol sequence which is ultimately responsible for the errant C_1 and C_8 stereochemistries of the triol 4.17 and thus, the tetrol 4.30.

An alternate or modified route was then undertaken in order to establish the correct C_1 and C_8 (naphthalene numbering) stereochemistries of the diketone structure R2. We attempted to correct these stereochemistries by entering the acetylide carbanion prior to the methyl carbanion. This was expected to allow retention of the C_8 silyl protecting group of 4.15 and consequently, elimination of the retro-aldol problem. Herein, we describe the synthesis of the retrosynthetic intermediate diketone R2 using this modified strategy.

5.2 Execution of The Modified Strategy For The Synthesis of The Diketone R2 (5.9)

Addition of an excess of 1-lithio-1-hexyne to a solution of the diketone 4.3 in toluene at -78°C gave, upon warming to 0°C, a 1 : 1 mixture of the regioisomeric adducts 5.1 and 5.2 in good yield (Scheme 5.1). The two adducts were readily distinguished from one another by ^1H NMR. The enol ether proton of 5.2 appears as a doublet at 4.85 ppm and is coupled to the adjacent C_{4a} (naphthalene numbering) ring junction proton at 1.99

ppm (J= 6.6 Hz). In contrast, the analogous proton signals of 5.1 appear at 5.75 and 2.44 ppm respectively. The apparent downfield shifts observed for 5.1 may be attributed to the deshielding effect of the C_2 carbonyl group, which is not present in the case of 5.2.



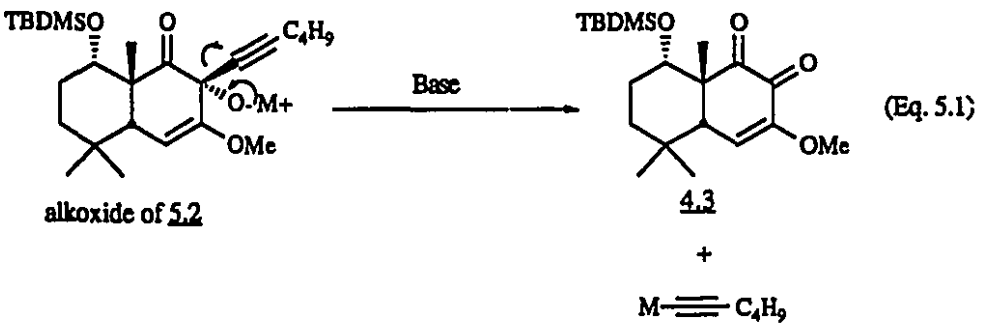
4.3 5.1 (42%) 5.2(46%)

Scheme 5.1

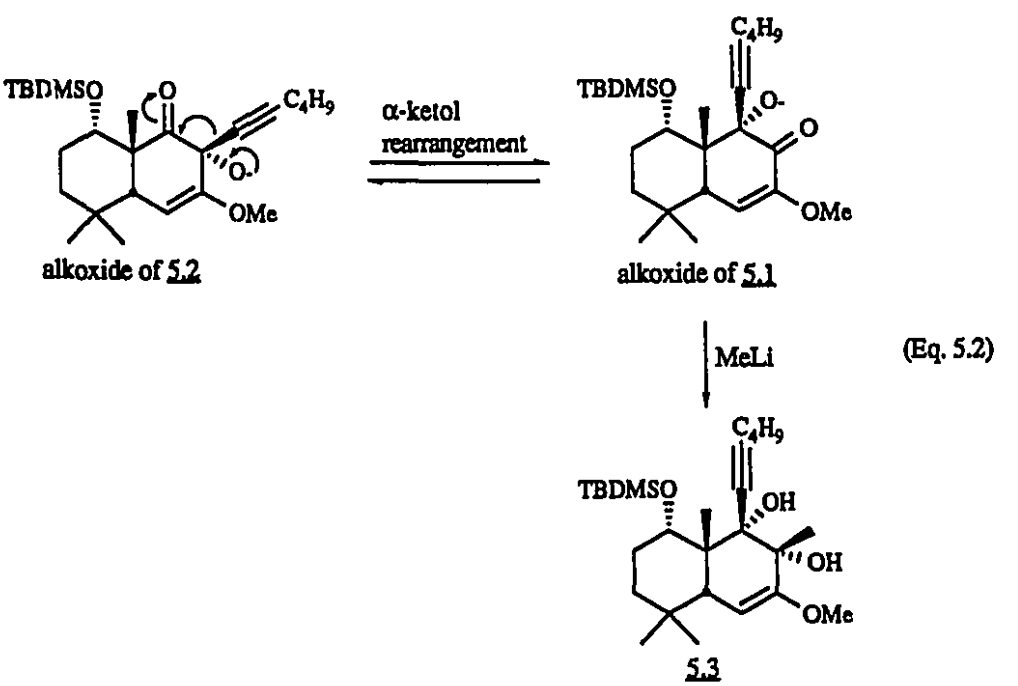
The ratio of the two adducts of 5.1 and 5.2 appeared to depend on the solvent in which the reaction was conducted. For example, when the reaction was carried out in either THF or diethyl ether, the ratio was found to be about 2.5 : 1 in favor of 5.2 as determined by ^1H NMR. The addition of either $MgBr_2$ OEt_2 or HMPA gave a 3 : 1 mixture when THF was used as solvent. Furthermore, in the case of toluene, added N,N,N',N'-tetramethylethylenediamine (TMEDA, 20%) produced a 16 : 1 ratio of regioisomers, once again in favor of 5.2. The choice of solvent for this particular reaction seemed to be quite limited, as the starting diketone 4.3 is almost completely insoluble in hydrocarbon solvents such as hexanes and pentane.

In an attempt to improve the yield of the desired adduct 5.1 we decided to examine the base induced retro-addition and α-ketol rearrangement of the acetylenic alcohol function of 5.2. In principle, under basic conditions, the adduct 5.2 may expel the acetylide function regenerating the diketone precursor 4.3. If the acetylide carbanion is then trapped by a suitable electrophile, it then may not add back onto the diketone 4.3 (Eq. 5.1). We have

tried various conditions such as sodium methoxide in methanol (catalytic and stoichiometric), refluxing triethylamine, TBDMS triflate / 2,6-lutidine in CH_2Cl_2 as well as acetic anhydride / pyridine / DMAP however only complex product mixtures or recovered starting material were obtained and none of the diketone 4.3 was ever detected. Alternatively, it was thought that 5.2 may undergo α-ketol rearrangement to give the corresponding alkoxide of 5.1 which can be trapped by methyllithium to give the diol 5.3



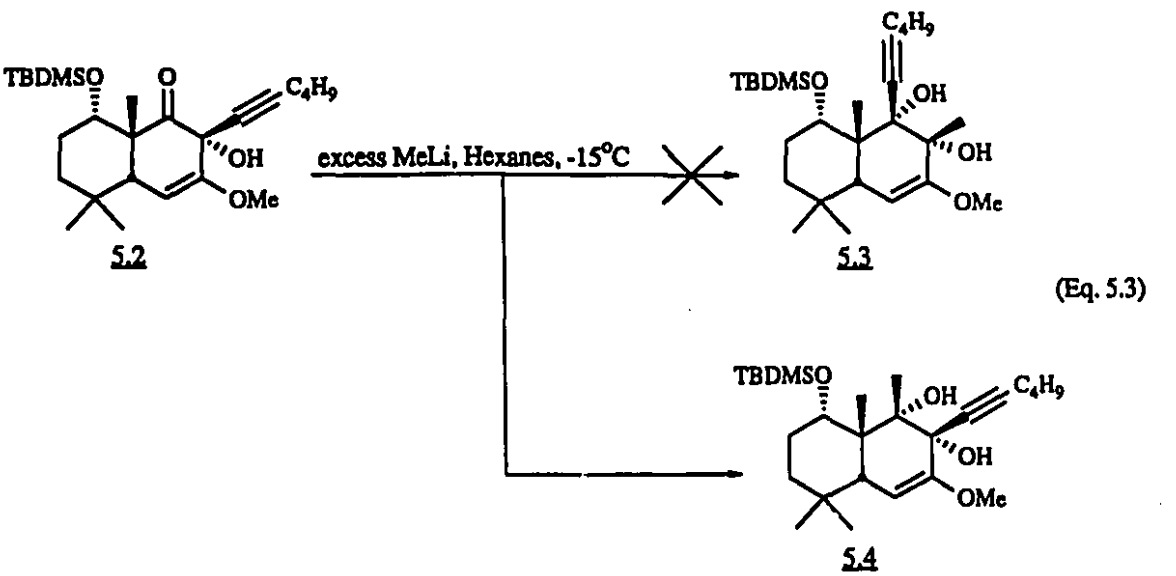
(Eq. 5.1)



(Eq. 5.2)

(R3) stereoselectively in one operation (Eq. 5.2). Indeed, we have already observed this

type of rearrangement in the reaction of the acetylenic carbanion with the isomeric mixture of 4.15 and 4.16 (see Chapter 4, Scheme 4.6 and accompanying text). Unfortunately, exposure of 5.2 to excess methyllithium in hexanes at -15°C gave the isomeric diol 5.4 as a single diastereomer in 52% yield along with 20% recovered 5.2 (Eq. 5.3)



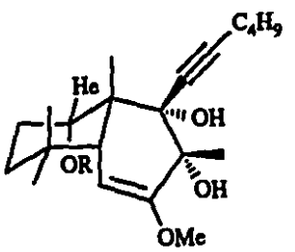
5.2 5.3 5.4

(Eq. 5.3)

Despite the poor regioselectivity encountered in the addition of the acetylide carbanion to the diketone 4.3 and our inability to utilize the regioisomer 5.2, the subsequent methyl addition step was examined. Reaction of the enone 5.1 with methyllithium in hexanes at -15°C cleanly afforded the oily diol 5.3 in 77% isolated yield (Scheme 5.2). A considerable amount of silyl cleavage was observed when the reaction was conducted in either THF or diethyl ether thus precluding their use as solvent. In the ^{1}H NMR spectrum of 5.3 the C_8 methine proton at 4.04 ppm appears as a doublet with only one small coupling constant (J= 3.5 Hz) suggesting that it is likely to be equatorial. The multiplicity of the methine signal as well as the magnitude of the coupling constant would suggest that there is a greater population of the conformer 5.5 in solution at room temperature. In contrast, if 5.3 had the conformation as depicted in 5.6 exclusively, the methine signal

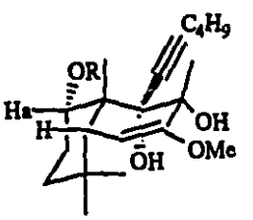
would show both large and small coupling constants characteristic of an axial proton (H_a).

Desilylation of 5.3 with TBAF in THF delivered the crystalline triol 4.18 whose structure was confirmed by single crystal X-ray diffraction (see ORTEP diagram 4). The ORTEP diagram 4 reveals the expected α-orientation of the three hydroxyl groups of 4.18. With the stereochemistry of the C_1, C_2 and C_8 stereocenters firmly established the remaining three step protocol for the conversion of the enol ether 5.3 to the diketone structure 5.9 was attempted (Scheme 5.2).



5.5 R = TBDMS

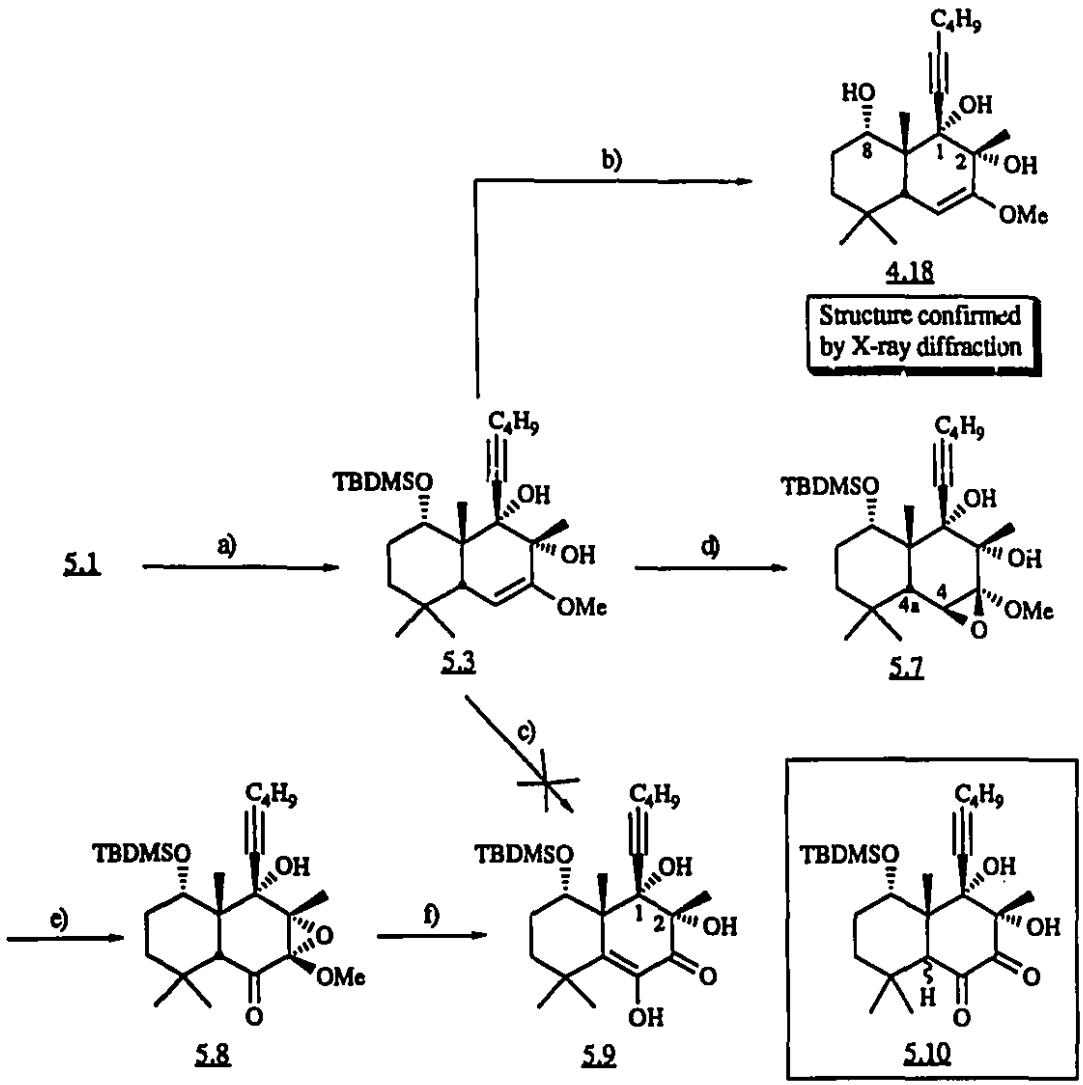
J_{He} = two small vicinal couplings



5.6 R = TBDMS

J_{Ha} = Large and small vicinal couplings

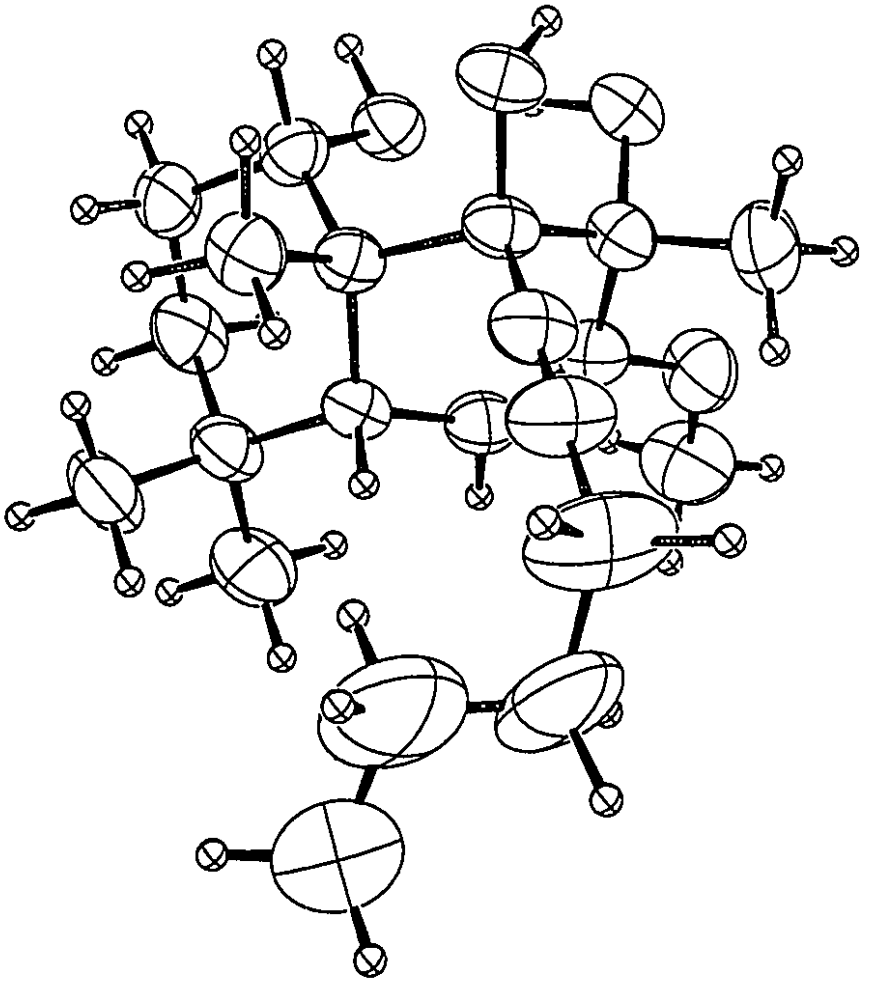
Epoxidation of the enol ether moiety of 5.3 with dimethyldioxirane [1] in acetone / CH_2Cl_2 at room temperature provided a single labile epoxy ether 5.7 in quantitative yield (Scheme 5.2). In the ^1H NMR spectrum of 5.7 the C_4 epoxide methine proton appears as a singlet (no coupling to either the ring junction or hydroxy protons) suggesting the structure 5.7 rather than its corresponding Payne rearrangement counterpart. The crude product appeared to be quite pure by ^1H NMR and was used without further purification for the subsequent oxidation step. In passing, we note that the enol ether 5.3 was stable to osmium tetroxide in pyridine at reflux temperature in contrast to the model compound 3.3 which reacted to give the diketone 4.23, although sluggishly (see Equation 4.6, Chapter 4).

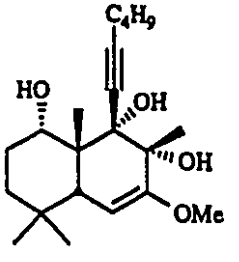


Reagents: a) MeLi, hexanes, -15°C, 1.5h, 77%; b) TBAF,THF, r.t., 15 min., 96%; c) OsO_4, pyridine, reflux, 31h; d) dimethyldioxirane, acetone / CH_2Cl_2, r.t., 1h, 100%; e) oxalyl chloride, DMSO, CH_2Cl_2, -78°C, 45 min. then TEA, -78°C to r.t., 30 min.; f) Me_2BBr, Et_3N, iPr_2O, -84°C then 0°C, 15 min., 35% from 5.7;

Scheme 5.2

Unfortunately, attempted oxidation of 5.7 to the epoxy ketone 5.8 under the conditions previously optimized for the oxidation of 4.25 to 4.26 (see Chapter 4, Scheme 4.7 and accompanying text) resulted in a complex mixture of products from which no 5.8 could be





4.18

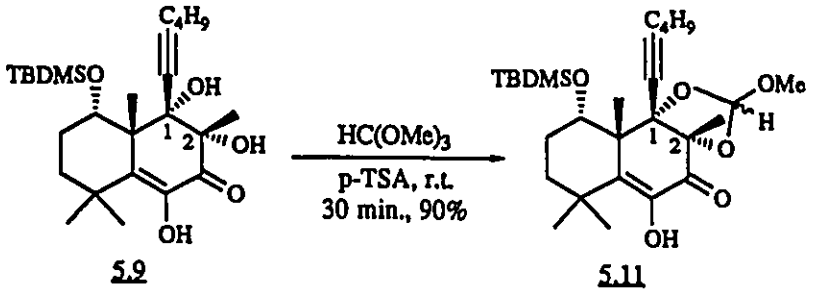
ORTEP Diagram 4

detected by ^{1}H NMR of the crude reaction mixture. In fact, a number of chromium based oxidation systems were examined (ie: PCC / mol.sieves [2], PCC / alumina [3], PDC in DMF and chromium oxide / pyridine) however, only complicated product mixtures or recovered starting material were obtained in each case. Other metal based reagent systems such as tetra-propylammonium perruthenate (TPAP) / 4-methylmorpholine N-oxide (NMO) / mol.sieves [4], activated MnO_2 and SmI_2 / 2-butanone [5] proved ineffective and only starting material was recovered. To this end, we were able to obtain 5.8 by Swern oxidation [6] (crude yield = 100%, > 60% pure as judged by ^{1}H NMR), however, it could not be purified by chromatography without considerable loss of material (Scheme 5.2). For example, when the crude product was subjected to chromatography on silica gel, a 3 : 1 mixture of products was obtained, the major component being the epoxy ketone 5.8 albeit in low yield (ie: 29% yield as determined by ^{1}H NMR). The minor component (not observed in the crude ^{1}H NMR spectrum), was not identified, however ^{1}H NMR and MS data suggested that it may be isomeric with 5.8. For this reason, the crude epoxy ketone 5.8 was used for subsequent reactions without further purification.

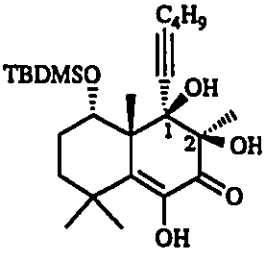
Cleavage of the epoxy ketone 5.8 was then attempted with dimethylboron bromide [7] as previously described for the preparation of the diketone 4.27 (see Chapter 4, Scheme 4.7 and accompanying text). Unfortunately, under these conditions, an exceedingly complex product mixture was obtained and none of the desired diketone 5.9 could be detected. We suspected that the reaction conditions were too vigorous, even at low temperature, since all attempts to moderate the reaction by decreasing the reaction temperature (ie: -84°C, -60°C, -47°C and -23°C) or amount of triethylamine were completely unsuccessful. It has been reported, that dimethylboron bromide can be used effectively for the selective cleavage of either dimethyl acetal, MEM or MOM ethers in the presence of acetonides when diethyl ether (or possibly another ether) is present in the reaction mixture. Presumably, the ether acts as a new coordinating ligand which effectively competes with the substrate for the

boron reagent, thus slowing the overall reaction and amplifying the reactivity difference between acetonides and the more reactive acetals [7]. It was hoped that this approach would decrease or moderate the activity of the dimethylboron bromide to allow cleavage of the labile epoxy ether function of 5.8 (without TBDMS ether cleavage) and suppress any subsequent side reactions which may be occurring. Therefore, we were very pleased to discover that when the diketone was treated with dimethylboron bromide (3 Equiv.) and triethylamine (1 Equiv.) in diisopropyl ether at -84°C and then warmed to 0°C, the corresponding diketone 5.9 was formed in 35% isolated yield (unoptimized) from 5.7 (Scheme 5.2). Unfortunately, 5.9 appeared to be quite labile and the chromatographic purification step was, in part, responsible for the low yield. In addition to 5.9 another labile product lacking a methoxy group (previously unobserved on tlc of the crude reaction mixture) was obtained after chromatography on silica gel, however it was contaminated with at least two other minor components. Although it could not be further purified for characterization purposes, we have tentatively assigned the major product the corresponding tautomeric structure 5.10.

At this stage, with limited material available, we decided that it was important to demonstrate the *cis* stereochemistry of the C_1 and C_2 hydroxyl groups. This task was accomplished by protection of the diol functionality as the orthoformates 5.11. Thus, exposure of 5.9 to excess trimethylorthoformate with p-TSA catalyst [8] afforded 5.11 as a 9 : 1 mixture of diastereomers (Eq. 5.4). The incorporation of the CH(OMe) functionality into the parent structure 5.9 was immediately evident by ^{1}H NMR [major isomer: 5.56 ppm (s, 1H), 3.38 ppm (s, 3H)]. While the formation of 5.11 establishes the *cis* diol stereochemistry of 5.9, it does not rule out the isomeric structure 5.12, which may also form the corresponding orthoformates under these conditions. In our opinion however, the isomeric diol 5.12 is unlikely to be formed in the sequence outlined in Scheme 5.2, as this would require the epimerization of both the C_1 and C_2 stereocenters.



5.9 5.11 (Eq. 5.4)

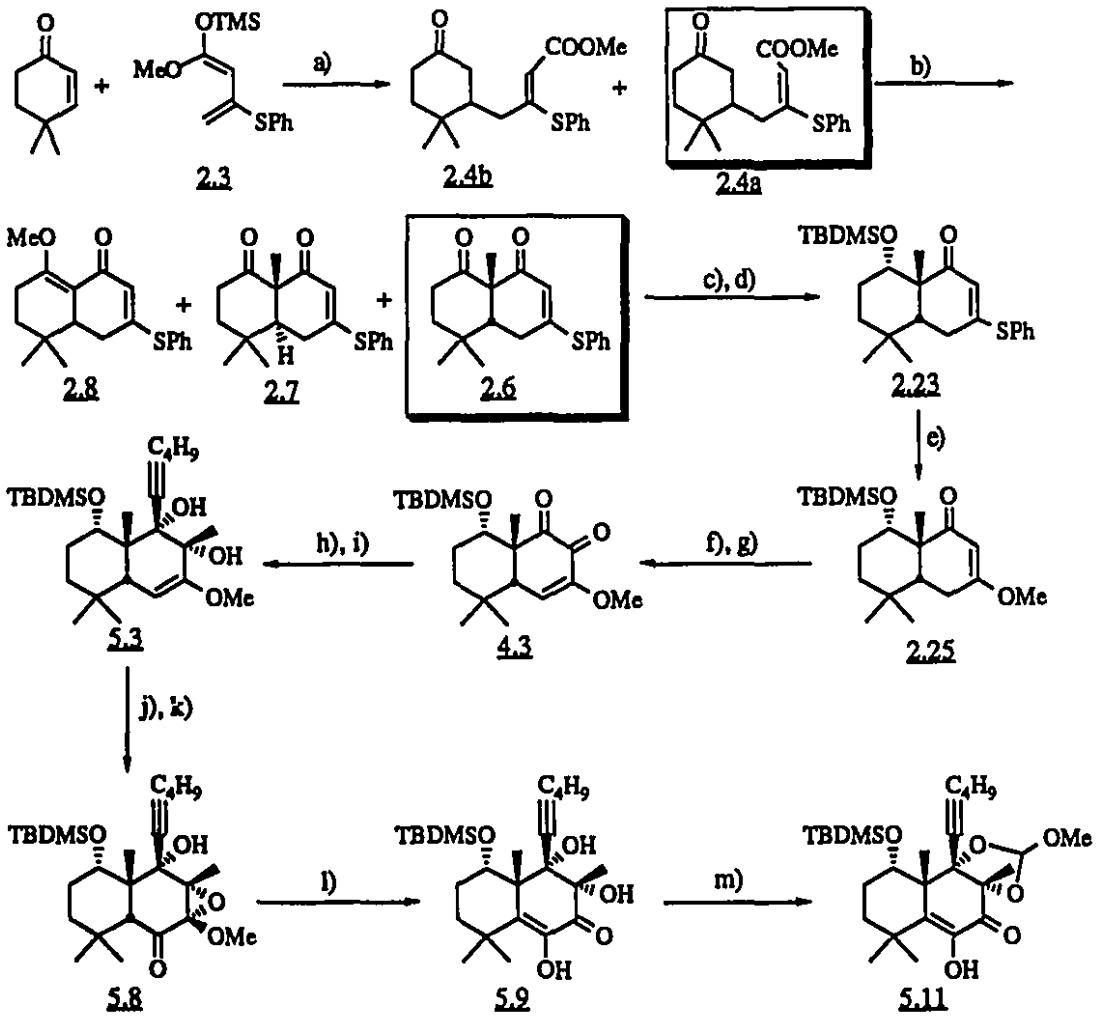


5.12

The final overall synthetic pathway leading to the diketone 5.9 from our diene component 2.3 is outlined in Scheme 5.3. The overall sequence involves twelve synthetic steps and proceeds with complete stereoselectivity for establishing the C_1, C_2 and C_8 (naphthalene numbering) hydroxyl stereochemistries of the diketone 5.9 (R2). Noteworthy or novel transformations include the regioselective enolate oxidation of 2.25 as well as the chemoselective cleavage of the labile epoxy ether function of 5.8. The high efficiency of dimethyldioxirane in epoxidizing the enol ether moiety of 5.3 is also worth noting.

The main problems associated with the overall synthetic sequence leading to 5.9 include the modest stereoselectivity and chemical yield observed in the angular methylation of 2.5 as well as the lack of regioselectivity in the addition of the hexynyl carbanion to the diketone 4.3. Despite these minor problems, the sequence has considerable potential for the synthesis of forskolin 1.6. One possible approach would involve the conversion of the orthoformates 5.11 to the aldehyde 1.69 as outlined in Scheme 5.4. The aldehyde 1.69

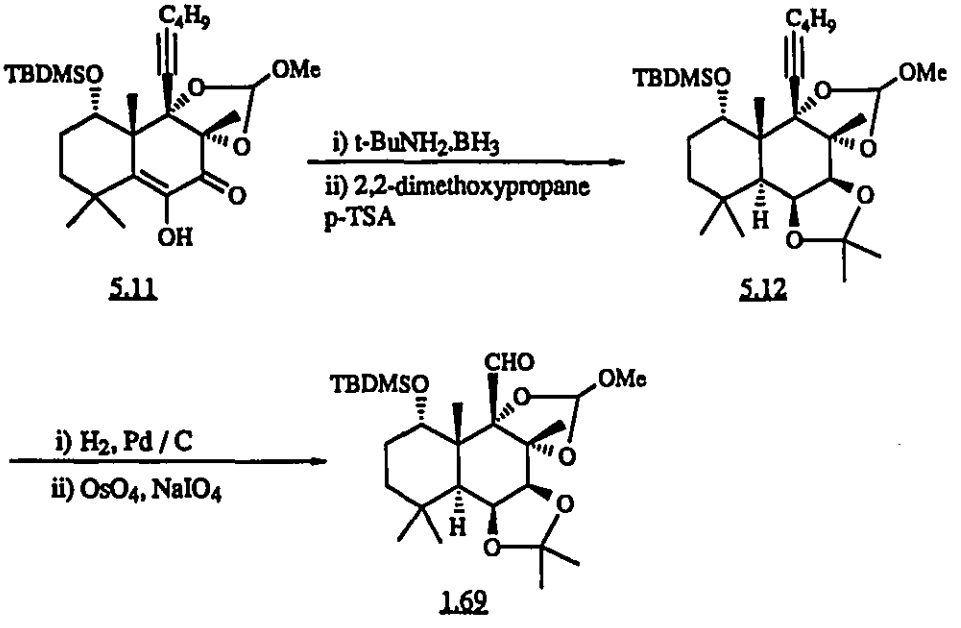
was previously utlilized by Ziegler and co-workers [8] in their synthesis of forskolin. Reduction of the α-diketone function of 5.11 with borane-tert-butylamine complex is expected to provide the 3β,4β-diol stereoselectively in analogy to the α-diketone 4.28.



Reagents: a) $TiCl_4$, CH_2Cl_2, -78°C, 60%; b) KOt-Bu, t-BuOH, 40°C then MeI; 79%; c) $LiAl(Ot\text{-}Bu)_3$, THF, -20°C, 100%; d) TBDMS triflate, 2,6-lutidine, CH_2Cl_2, r.t., 77%; e) MeONa, MeOH, reflux, 83 - 96%; f) LHMDS, HMPA, THF, -78°C then dimethyldioxirane, -78°C, 80%; g) MnO_2, pentane, r.t., 95%; h) 1-lithio-1-hexyne, toluene, -78°C to 0°C, 42%; i) MeLi, hexanes, -15°C, 77%; j) dimethyldioxirane, acetone / CH_2Cl_2, r.t., 100%; k) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C then Et_3N, -78°C to r.t.; l) Me_2BBr, Et_3N, iPr_2O, -84°C to 0°C, 35% from 5.3; m) $HC(OMe)_3$, p-TSA, r.t., 90%.

Scheme 5.3

which presumably underwent stereoselective reduction from the less hindered α-face to give the corresponding tetrol 4.30 (see Chapter 4, Scheme 4.7 and accompanying text). Protection of the resulting *cis* diol function as the acetonide would then give 5.12. Hydrogenation of the triple bond of 5.12 with palladium on carbon (see Chapter 4, Scheme 4.7 and accompanying text) would afford the corresponding allylic ether, which upon oxidative cleavage of the double bond would give the key Ziegler aldehyde(s) 1.69.



5.11 5.12 1.69

Scheme 5.4

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CHAPTER 6

HIGHLY OXYGENATED DECALIN COMPOUNDS AS POTENTIAL SPRUCE BUDWORM (*Choristoneura fumiferana*) ANTIFEEDANTS: STRUCTURE-ACTIVITY RELATIONSHIPS

6.1 Introduction

The spruce budworm, *Chorisotoneura fumiferana*, is an insect pest that infests the fir and spruce forests of North America. The budworm larvae feed on a number of conifers including, among others, balsam fir (*Abies balsamea* [L.] Mill.), white spruce (*Picea glauca* [Moench] Voss) and red spruce (*Picea rubens* Sarg). The spruce budworm has a one year lifecycle (Figure 6.1). Female moths deposit their eggs on the undersides of the needles of the host tree in July and the eggs usually hatch in about 10 days. In May of the following year, second instar larvae emerge from their hibernacula. By late May, third-instar larvae begin to feed on newly opened shoots and consume the greatest amount of foliage during their sixth instar development stage in early June. As a result, a budworm outbreak inflicts extensive damage to the forest resource and has a devastating impact on the Canadian pulp and paper industry. Furthermore, the forest destroyed by the budworm requires many years to return to its normal status.

Up to now, efforts to control the spruce budworm population have relied heavily on the spraying of chemical insecticides such as Fenotrothion or the microbial insecticide *Bacillus thuringiensis* (BT). In an environmental sense, the use of insecticide sprays is undesirable as they are generally toxic and may result in contamination of food supplies. The efficacy of BT against the spruce budworm under field conditions is subject to a number of conditions and recently, insect resistance has been reported [1].

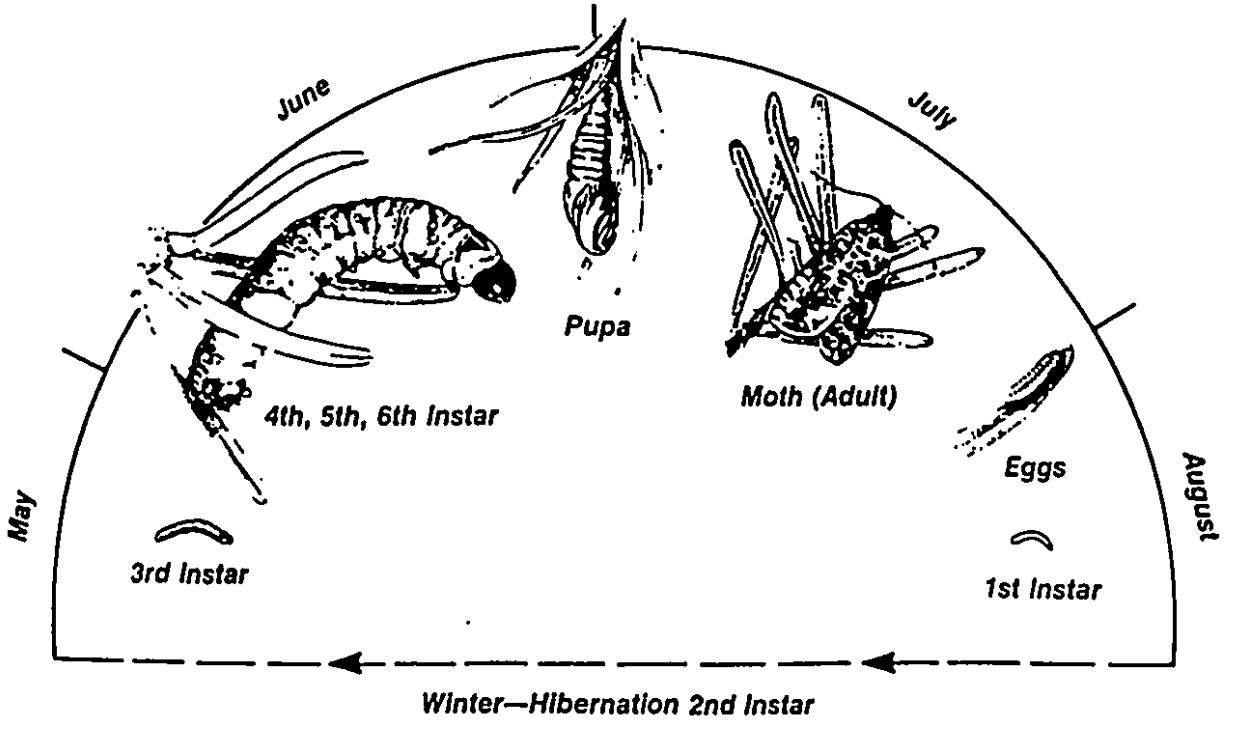
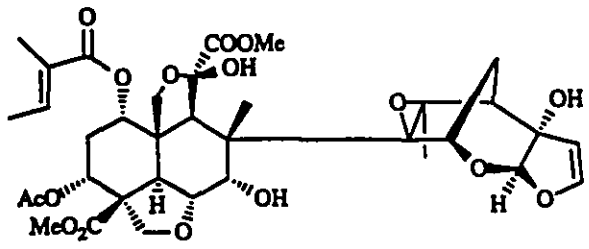


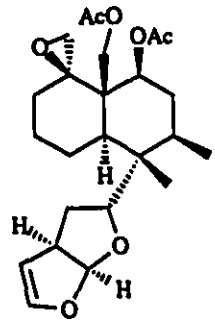
Figure 6.1

A strategy that has been considered for pest control is to employ antifeedants to interfere with the feeding behavior of insects. The approach may offer distinct advantages over the conventional methods of pest control as antifeedant could protect current year foliage while leading indirectly to budworm mortality, without being generally toxic [2].

In screening programs, a number of natural products such as azadirachtin 6.1 [3], clerodin 1.12 [4] and Nic-1 6.2 [5] have been found to exhibit pronounced antifeedant activity. For the spruce budworm [6], an active compound, specionin 6.3 [7] has been isolated from the leaves of *Catalpa speciosa warder (Bignoniaceae)*. The total synthesis of specionin has recently been reported [8].



6.1



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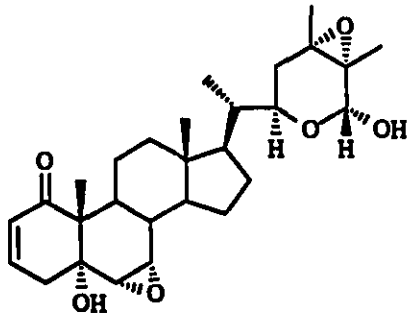

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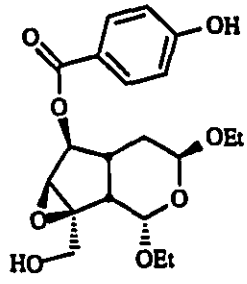

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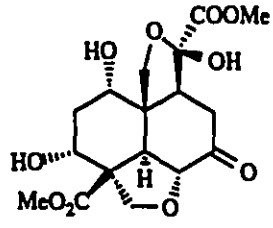

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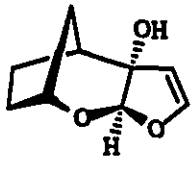

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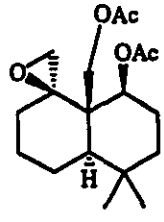

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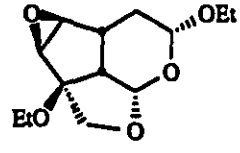
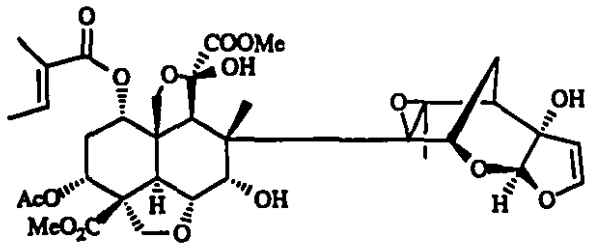


6.7

Although their carbon skeletons or presumed biogenetic origin may differ widely, most insect antifeedants discovered up to now share a common feature, namely, they are polyoxygenated molecules. The synthetic compounds 6.5 and 6.6 which share common structures with azadirachtin 6.1 [9] and clerodin 1.12 [10] were found to exhibit antifeedant activity. In the case of the spruce budworm, the iridoid derivative 6.7 was found to exhibit moderate but definate antifeedant activity [11].

The known antifeedant azadirachtin 6.1 is a naturally occuring tetranortriterpene isolated from the neem tree *Azadirachta indica* (A. juss). Recently, the structure of 6.1 was



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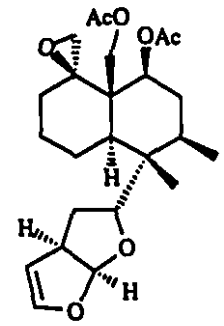

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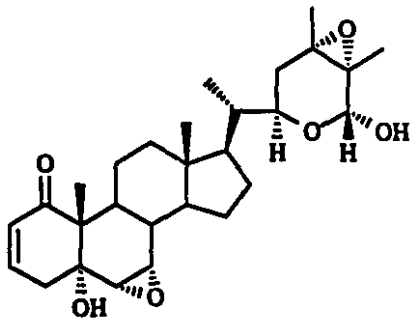

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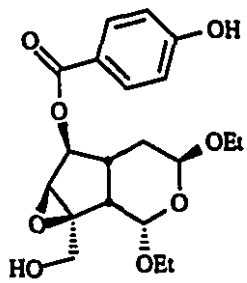

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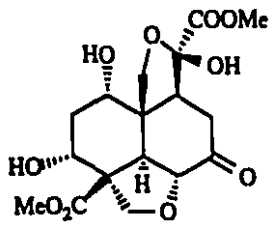

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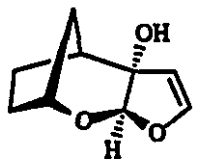

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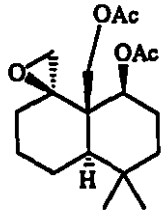

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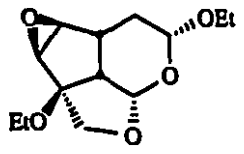

6.7

Although their carbon skeletons or presumed biogenetic origin may differ widely, most insect antifeedants discovered up to now share a common feature, namely, they are polyoxygenated molecules. The synthetic compounds 6.5 and 6.6 which share common structures with azadirachtin 6.1 [9] and clerodin 1.12 [10] were found to exhibit antifeedant activity. In the case of the spruce budworm, the iridoid derivative 6.7 was found to exhibit moderate but definate antifeedant activity [11].

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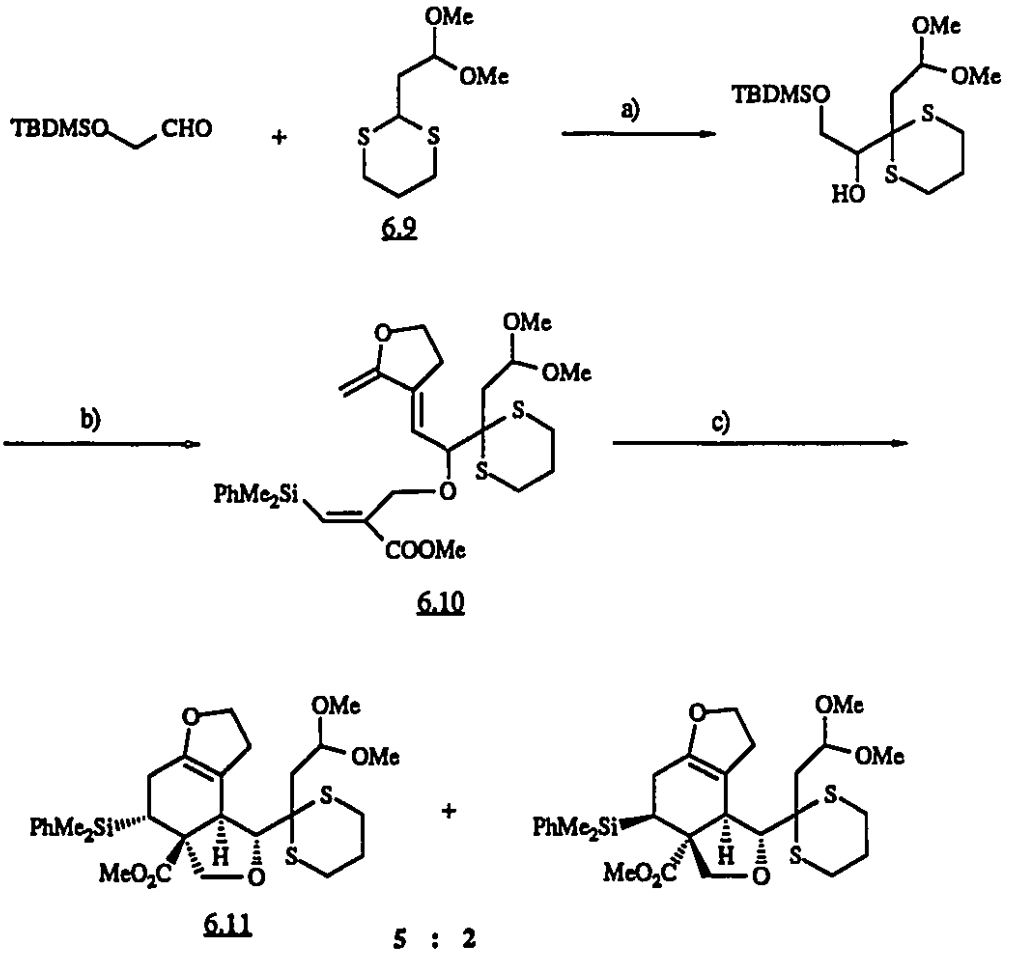
Due to the structural complexity of azadirachtin 6.1 as well as its potent antifeedant activity, it is not surprising that this target has been the subject of considerable synthetic effort. Indeed, the advanced intermediates 6.4, and 6.5 representing the decalin and cyclic acetal fragments have been prepared [9]. Furthermore, structural modification and degradative studies of azadirachtin 6.1 have also been performed.

As outlined in Scheme 6.2 an important key step involving intramolecular Diels-Alder cycloaddition was utilized for the construction of the oxygenated decalin fragment 6.4 of the parent structure 6.1. The key bicyclic intermediate 6.11 was prepared efficiently in a seven step sequence starting from the acetal 6.9 . The critical intramolecular Diels-Alder cycloaddition of 6.10 proceeded to give only two of the four possible diastereomeric products with good endo stereoselectivity. The phenyldimethylsilyl group was found to be a critical element favoring the formation of the required endo adduct 6.11.



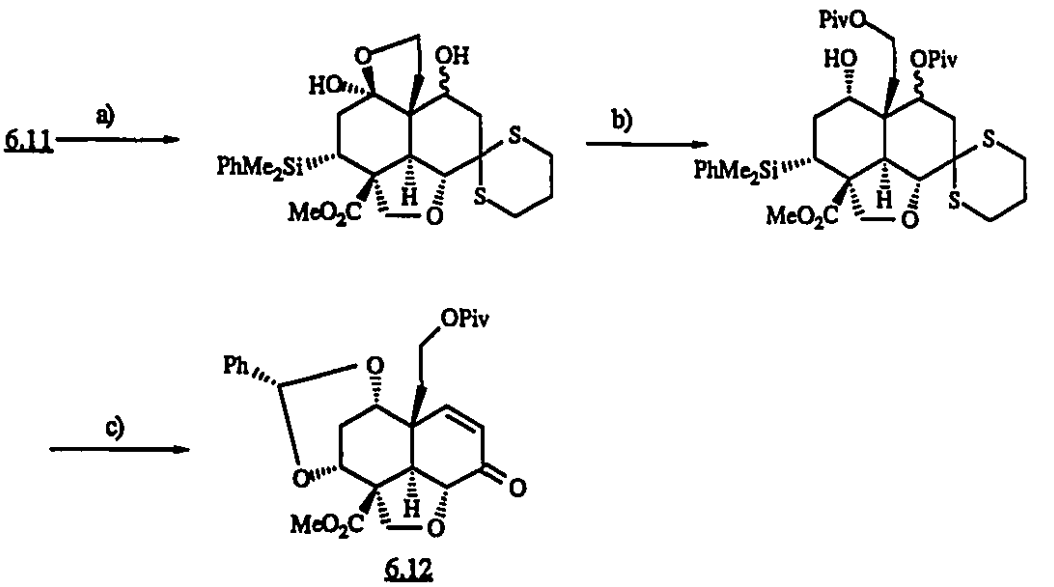
Reagents: a) BuLi, TMEDA, 54%; b) i) KH, Methyl-E-2-(bromomethyl)-3-(dimethylphenylsilyl) propenate, 60%, ii) HF, pyridine, 86%, iii) $(COCl)_2$, DMSO, Et_3N, -78°C, 93%, iv) LiCl, DIPEA, Diethylphosphonobutyrolactone, DMF, 68%, v) Tebbe reagent, pyridine, -40°C; c) Toluene, 85°C.

Scheme 6.2

Cyclization of 6.11 was achieved by a key acid catalysed aldol type condensation step. Pivoylation, stereoselective reduction, dithiane removal, elimination and oxidative cleavage of the phenyldimethylsilyl group provided a diol which was protected as the benzylidene acetal 6.12 (Scheme 6.3).

The furan ring was installed via a novel ring contraction process as outlined in Scheme 6.4. The enone 6.12 was reduced with L-selectride and the resulting alcohol silylated. The

The furan ring was installed via a novel ring contraction process as outlined in Scheme 6.4. The enone 6.12 was readily converted to the cyanoacetic ester 6.13 by a standard series of steps involving depivolylation of the primary hydroxyl, oxidation to the aldehyde

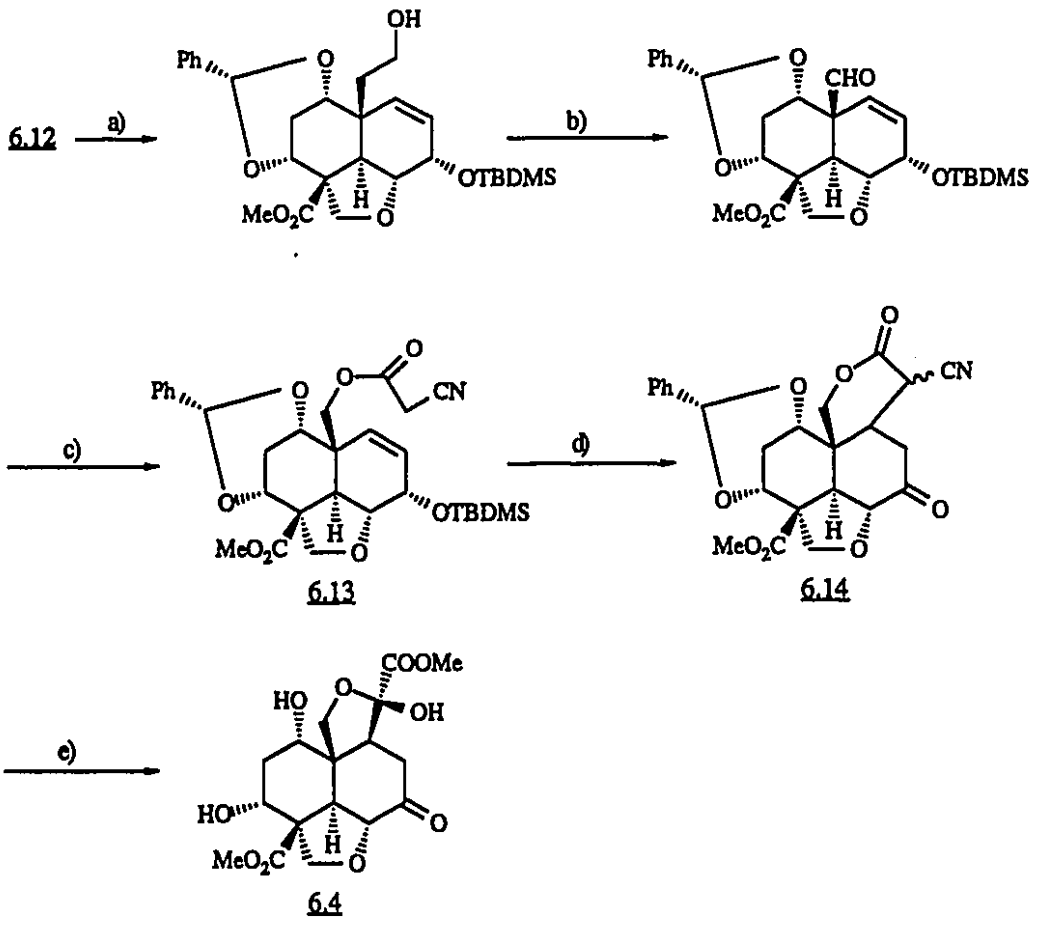


6.12

Reagents: a) p - TSA, MeCN, H_2O, 55°C, 63%; b) i) Pivaloyl chloride, pyridine, DMAP, 89%; ii) $NaBH_4$, THF / MeOH, 96%; c) i) MeI, MeCN, 100%; ii) DBU, 92%; iii) $Hg(O_2CCF_3)_2$, TFA - HOAc then CH_3CO_3H, 85%; iv) PhCHO, PPTS, C_6H_6, 94%.

Scheme 6.3

followed by ozonolysis of the corresponding enolsilyl ether reduction of the resulting aldehyde and cyanoacetylation. Desilylation of the allylic hydroxyl followed by oxidation with PDC provided an enone which underwent smooth intra-molecular Michael cyclization upon treatment with DBU to give the α-cyano lactone 6.14. Oxidation with dimethyldioxirane followed by ring opening of the intermediate α-keto lactone and immediate reclosure to the corresponding lactol gave, upon acidic workup, the final target triol 6.4 in good overall yield.

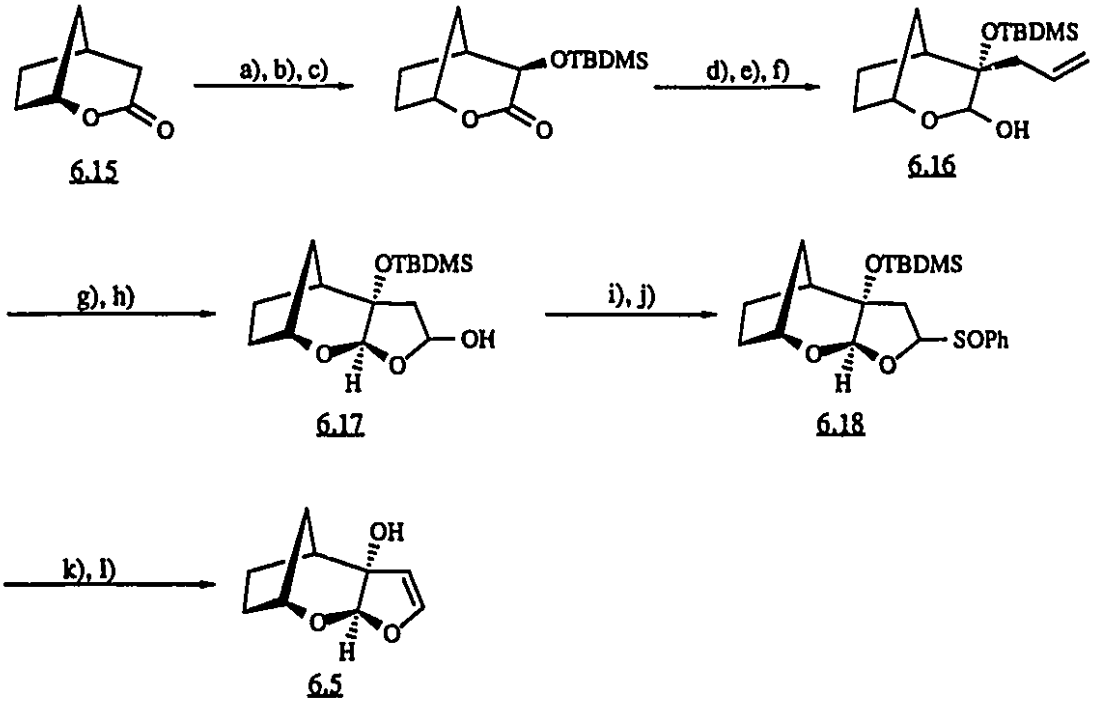


Reagents: a) i) L-Selectride, THF, -78°C, ii) TBDMSOTf, 2,6-lutidine, 0°C, iii) LiOH, EtOH-H_2O, 60°C, iv) CH_2N_2, 79% over 4 steps; b) i) periodinane, pyridine, ii) TBDMSOTf, Et_3N, -10°C, iii) O_3/O_2, -78oC, iv) PPh_3, -78°C to r.t., 74% over 4 steps; c) i) $ZnBH_4$, -10°C, ii) $NCCH_2COOH$, pTosCl, pyridine, 95% over 2 steps; d) i) TBAF, 4A sieves, ii) PDC, 4A sieves, iii) DBU, MeCN, 85% over 3 steps.; e) i) dimethyldioxirane, 0°C, 30 min., ii) MeOH, Et_3N, iii) CH_2N_2; iv) HCl MeCN, 45% over 4 steps.

Scheme 6.4

The cyclic acetal fragment of the parent structure 6.1 was prepared in a twelve step sequence from the known bicyclic lactone 6.15 as outlined in Scheme 6.5. Enolate oxidation of 6.15 followed by silylation and alkylation with allyl bromide and DIBAL reduction gave the lactol 6.16 in good yield. Ozonolysis of 6.16 to the aldehyde followed by cyclization provided the tricyclic lactol 6.17, which was converted to the sulphoxide 6.18 in a two step sequence. Pyrolytic elimination of the sulphoxide followed by silyl

deprotection afforded the tricyclic dihydrofuran acetal fragment 6.5. Later, the cyclic acetal fragment was prepared in optically pure form for eventual coupling to the left hand portion.



Reagents: a) LDA, THF, -78°C; b) MoOPH, -78 to 0°C; c) TBDMS chloride, imidazole, DMF; d) KDA,-78°C; e) allylbromide, -78°C; f) DIBALH, toluene, -78°C; g) O_3, CH_2Cl_2, -78°C; h) PPh_3, r.t.; i) PhSH, CH_3CN, Amberlyst 15, 4A sieves; j) MCPBA, CH_2Cl_2, r.t.; k) Toluene, heat; l) TBAF, THF, r.t.

Scheme 6.5

Bioassays on final instar larvae of the lepidopteran Spodoptera littoralis (Boisd) revealed that the tricyclic dihydrofuran acetal fragment 6.5 was a potent antifeedant, nearly as potent as azadirachtin 6.1 itself at the 10 ppm level.

Due to the complexity of the structures of the known antifeedants 6.1-6.3 and 1.12, chemical synthesis of any of these compounds is considered a major challenge and is not

likely to be used in any large scale application. Indeed, a more practical approach is to prepare simpler analogs of these compounds to determine any structure-activity relationship with respect to antifeedant activity. Since many of the known antifeedant compounds such as clerodin 1.12, azadirachtin 6.1 and Nic-1 6.2 contain a functionalized (oxygenated) decalin ring system, it may well be possible that it is partially responsible for antifeedant activity. We suspected that simple functionalized decalin analogs of these compounds may also be active, and for this reason, a number of the functionalized decalin compounds described in Chapters 2-5 (as well as others) were tested for antifeedant activity against the spruce budworm (*Chorisotoneura fumiferana).* Moderate but definate activity was observed for some of these compounds suggesting that the functionalized decalin fragment of the parent structure 6.1 may well be important for antifeedant activity.

6.2 Methods

Biological assays

Each set of biological assays involved feeding laboratory colony spruce budworm larvae on artificial diet [13], containing unless otherwise noted, 0.2% or 2000ppm (wet weight) of the test compounds. In the assays, newly-emerged 2nd instar larvae were reared individually at 26°C for a 17h photoperiod with 50 replicates per test compound. At the point at which approximately 50% of the controls had reached the 6th instar stage, the larvae were sacrificed. The mean development stage (instar) of the larvae on each treatment diet was then determined (mean instar in Tables 6.1 - 6.6) as well as the proportion of 6th instars. For the purposes of non-parametric statistical analysis, the rank transformation approach [14] was used. In each set of biological assays, all the observations (ie: the instar of each of the larvae) were ranked from the largest to the smallest, with average ranks assigned in the cases of ties. The compounds were then listed in descending order

according to their mean rank values (Tables 6.1 - 6.6). A one way analysis of variance applied to the rank values allows for nonparametric testing for intercompound differences [15,16]. When significant differences were detected in each set of biological assays (Tables 6.1 - 6.6), a Tukey type multiple comparison test, using rank sums instead of means was performed to locate the intercompound differences [15,16]. Compounds followed by the same letter were not significantly different ($p>0.05$) in their effect on the development rate of the budworm larvae.

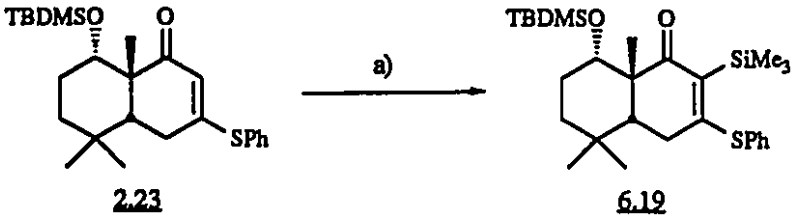
Biological testing was performed by A.W. Thomas, G.M. Strunz, M. Chiasson and A. Salonius at Forestry Canada - Maritimes Region, Fredericton, N.B.

Diet Preparation

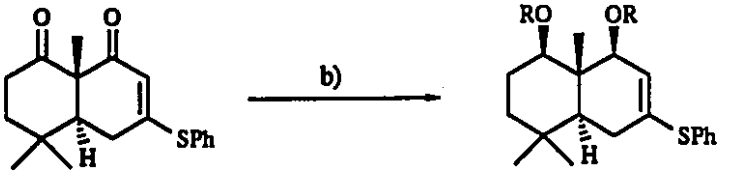
Diet containing (unless otherwise noted) 0.2% or 2000ppm (wet weight) of the test compounds was prepared by treating lyphilized McMorran diet with a solution of the test compound in methylene chloride and then removing the solvent completely at 30°C on a vacuum evaporator. The residual powder was rehydrated to 80% water content with 0.4% aqueous potassium sorbate solution (fungicide). Control diets were treated as above with methylene chloride.

Synthesis of the Test Compounds.

The compounds appearing in Table 6.3 as well as 6.19 were prepared by standard methods as outlined in Scheme 6.6 below. Compound 2.9 was prepared according to the litterature procedure [17]. The acyclic ketoesters 6.25, 6.26 and 6.27 were obtained from

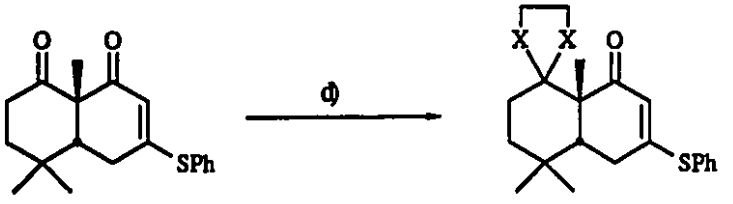


2.23 6.19



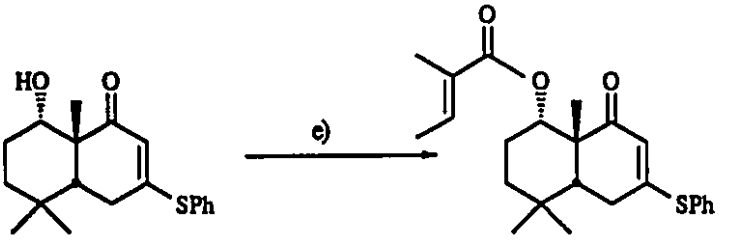
2.7

c) 6.20 R = H; 6.21 R = Ac



2.6

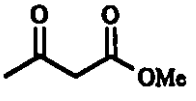
6.22 X = O (90%)
6.23 X = S (61% + 33% rec. 2.6)



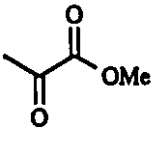
2.22 6.24

Reagents: a) LDA, TMSCl, THF, -78°C to r.t., 97%; b) $NaBH_4$, MeOH, 0°C, 18h, 79%; c) Ac_2O, pyridine, DMAP, CH_2Cl_2, r.t., 49.5h, 85%; d) $HXCH_2CH_2XH$, H^+; e) tigloyl chloride, pyridine, DMAP, CH_2Cl_2, reflux, 141h, 61%.

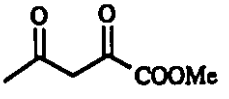
Scheme 6.6



6.25



6.26



6.27

Table 6.1 : Biological Assays

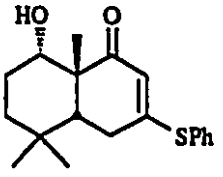
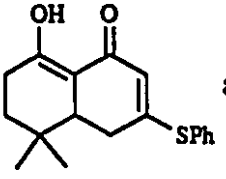
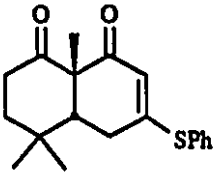
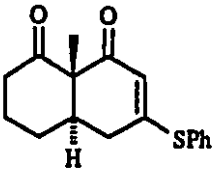
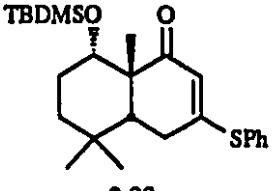
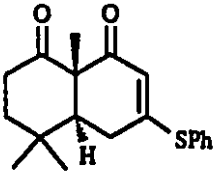
Compound		Mean Instar	% of 6 th Instars
Control	a	5.20	46
 2.22	a	5.20	24
 2.5	ab	4.98	26
 2.6	bc	4.60	8
 2.10	c	4.42	8
 2.23	c	4.30	10
 2.7	c	4.34	4

Table 6.2 : Biological Assays

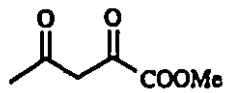
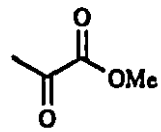
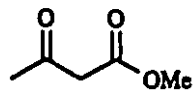
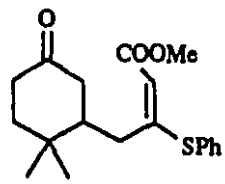
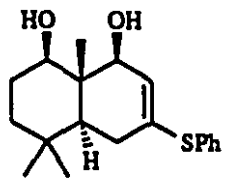
Compound		Mean Instar	% of 6 th Instars
Control	a	5.12	42
 6.27	a	4.98	43
 6.26	a	5.10	35
 6.25	a	5.04	38
 2.4a	a	5.08	30
 6.20	a	5.02	18

Table 6.3 : Biological Assays

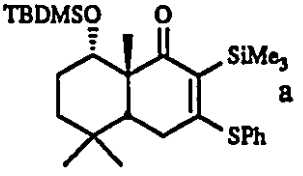
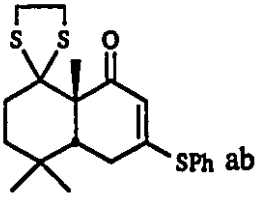
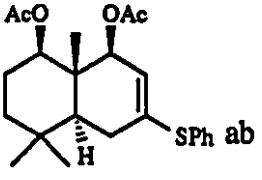
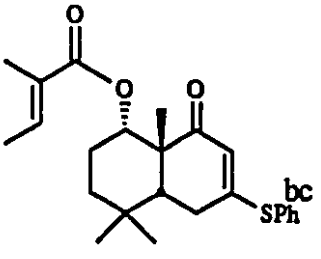
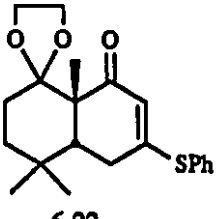
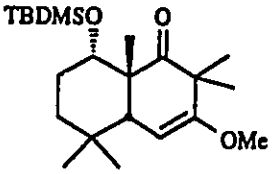
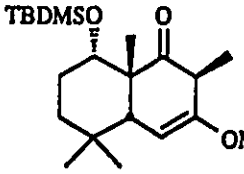
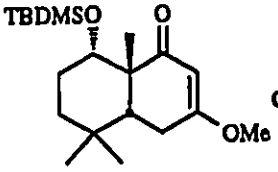
Compound		Mean Instar	% of 6 th Instars
Control	a	5.5	55
 6.19	a	5.6	59
 6.23	ab	5.4	48
 6.21	ab	5.4	46
 6.24	bc	5.1	19
 6.22	c	4.9	10

Table 6.4 : Biological Assays

Compound		Mean Instar [a]	% of 6 [th] Instars
Control	a	5.54	56
 3.3	a	5.54	56
 3.1	bcd	5.08	30
 2.25	cd	4.94	16

[a] Larvae already at the third instar development stage were used for this assay.

Table 6.5 : Biological Assays

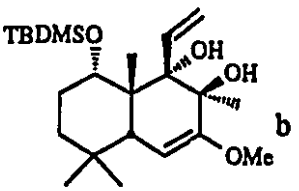
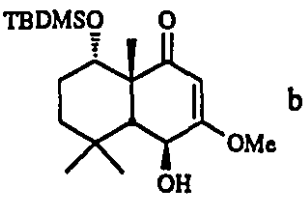
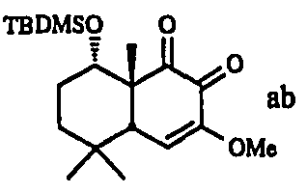
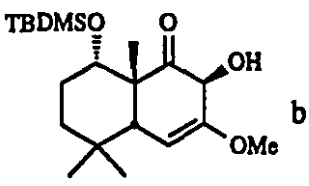
Compound		Mean Instar	% of 6 th Instars
Control	a	5.58	58
 3.5	b	5.16	36
 4.2	b	5.10	36

Table 6.6 : Biological Assays

Compound[a]		Mean Instar	% of 6 th Instars
Control	a	5.34	42
 4.3	ab	5.10	32
 4.1	b	4.82	12

[a] biological assays of compounds 4.3 and 4.1 were carried out at 1000ppm (0.1%) wet weight concentration.

Aldrich Chemical Co. and used without further purification. The preparation of the remaining compounds appearing in Tables 6.1, 6.2, 6.4, 6.5 and 6.6 are outlined in Chapters 2-5 of this thesis.

Deprotonation of 2.23 with LDA followed by quenching with TMS chloride gave 6.19 in almost quantitative yield (Scheme 6.6). Reduction of the trans diketone 2.7 with sodium borohydride in methanol gave the diol 6.20 stereoselectively (79%) which was acetylated with acetic anhydride / pyridine / DMAP to give the diacetate 6.21 in 85% yield. Reaction of the *cis* decalone 2.6 with ethylene glycol under acidic conditions delivered the dioxolane 6.22 in good yield. In a similar manner, the thioketal 6.23 was formed upon reaction with ethanedithiol in 61% yield. Acylation of 2.22 with tigloyl chloride / pyridine / DMAP gave the ester 6.24 in 61% yield.

6.3 Results and Discussion

The biological assays showed that the development of larvae reared from second or third instar on the test diets was significantly retarded by compounds (listed here in chronological order), 2.6, 2.10, 2.23, 2.7, 6.24, 6.22, 2.25, 3.1, 3.5, 4.2 and 4.1, but not by the other compounds. The results reveal a number of interesting aspects and several conclusions can be drawn concerning structure-activity relationships with respect to antifeedant activity.

The *cis* and *trans* methylated diketones 2.6 and 2.7 showed moderate activity whereas the diketone 2.5, lacking the angular methyl substituent, showed little or no antifeedant activity. The *trans* diketone 2.7 appeared to be slightly more active than its *cis* counterpart 2.6. These observations would suggest that both angular substitution and to a lesser extent, ring junction stereochemistry, are important for antifeedant activity. In comparing

compounds 2.7 and 2.10 it is clear that gem-dimethyl substitution at the C_5 (naphthalene numbering) position does not influence the biological activity.

The absence of activity of the three commercially available acyclic keto-esters 6.25, 6.26 and 6.27 as well as the monocyclic Michael adduct 2.4a (Table 6.2), suggests that the oxygen functionalities must be fixed in their relative positions. Presumably, the decalin ring system provides the rigid framework which is necessary for antifeedant activity.

The nature of the oxygen (or hetero-atom) substituents at both the C_1 and C_8 (naphthalene numbering) positions are of critical importance with the hydroxyl group generally giving inactive compounds. For example, the diol 6.20 and corresponding diacetate 6.21 were found to be inactive wheras the parent diketone 2.7 showed moderate but definate activity. Similarly, both the silyl ether 2.23 and ester 6.24 were found to be active, wheras the free alcohol 2.22 was not. In comparing compounds 6.22 and 6.23, oxygen (rather than sulphur) substitution at C_8 appears to be necessary for antifeedant activity. On the other hand, the β-methoxy enone 2.25 and its thiophenyl analog 2.23 showed comparable activity, suggesting that the nature of the C_3 substituent is not of great importance.

Interestingly, the siloxy compound 2.23 was found to be active, however the analogous 2-trimethylsilyl substituted compound 6.19 was not.

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CHAPTER 7

CONCLUSION

The (2C + 4C) annulation reaction based on tandem Michael-Claisen condensation developed earlier in our laboratory, has been used successfully as a key step in the stereoselective construction of a highly oxygenated decalin intermediate, 1,2,5,6,7,8,8a-heptahydro-1α,2α,4-trihydroxy-8α-(*tert*-butyldimethylsiloxy)-1β(1'-hexynyl)-2,5,5,8a-tetramethyl-naphthalen-3-one 5.9, for the synthesis of forskolin. The overall sequence leading to 5.9 proceeded with good stereoselectivity for the introduction of the C_1, C_2 and C_8 (naphthalene numbering) hydroxyl groups.

A novel method for the direct oxidation of enolates with dimethyldioxirane was developed which permitted smooth regio-selective introduction of a hydroxyl function α to the carbonyl group of *cis*- 3-Methoxy-4,4a,5,6,7,8,8a-heptahydro-8α(*tert*-butyldimethylsiloxy)-5,5,8a-trimethyl-(4H)-naphthalen-1-one 2.25, an intermediate in the synthesis of 5.9. The nature of this reaction was examined and it was found to offer a number of advantages over existing methods of enolate oxidation.

A number of the intermediate decalin compounds leading to the final target diketone 5.9 were found to exhibit moderate but definate antifeedant activity against the spruce budworm (*Choristoneura fumiferana*). Although these synthetic intermediates bear only a vague resemblance to the known antifeedants (ie: azadirachtin, clerodin and Nic-3), the decalin ring system provides a rigid framework to explore structure-activity relationships. Furthermore, the observation of definate activity in this series of readily accessible decalin compounds, gives hope that much more active compounds can be designed.

CHAPTER 8

EXPERIMENTAL

General Methods

Melting points were determined on a Gallencamp block and are uncorrected. The ^{1}H NMR spectra were recorded on either Varian XL-200 or XL-300 instruments and the data are reported in ppm relative to the $CHCl_3$ reference line with the multiplicity, coupling constants and number of protons given in parentheses. ^{13}C NMR spectra were recorded on either Varian XL-200, XL-300 or JEOL 270-CF instruments. The IR spectra were recorded on an Analect AQS-18 FT-IR instrument. Electron impact (EI) mass spectra were recorded at 70eV on either a Dupont 21-492B or Kratos MS25RFA instrument and are reported as m/z (% relative intensity). Low and high resolution ammonia chemical ionization (CI) mass spectra were recorded on Hewlett-Packard 5980A and ZAB 2F HS instruments respectively. All chemicals used were reagent grade and were distilled before using. All moisture sensitive reactions were carried out under dry argon or nitrogen atmosphere using oven dried (ca. 200°C) and desicator cooled glassware. Standard syringe / septum techniques were used to introduce the reagents and solvents into the reaction flask. In general, synthetic intermediates were pumped dry under high vacuo over P_2O_5 before carrying out the subsequent reaction. All solvents were dried and distilled prior to use: methylene chloride, hexanes and acetonitrile were dried over calcium hydride. THF and ether were dried over sodium metal / benzophenone. Methanol was dried over magnesium metal. Amine reagents such as diisopropylamine, hexamethyldisilazane (HMDS), diethylamine, triethylamine (TEA), tetramethyl ethylenediamine (TMEDA) and hexamethylphosphoric triamide (HMPA) were dried over calcium hydride and stored over molecular sieves. Flash chromatography was performed on Merck silica gel 60 (230-240 mesh). Thin layer chromatography (tlc) was performed using plastic-backed precoated

silica gel plates 60 F_{254} supplied by E. Merck Co. Visualization was effected by ultraviolet fluorescence (UV), iodine or by dipping the plate into ceric acid solution followed by heating.

Methyl (E)-3-phenylthio-crotonate 2.1

To a stirred solution of methyl acetoacetate (40.0 mL; 0.37 mol) and thiophenol (76.1 mL; 0.74 mol) in dry CH_2Cl_2 (400 mL) under argon at room temperature was added P_2O_5 (105.24 g; 0.741 mmol) in slowly over about 10 min.. After 26.5h, the methylene chloride was decanted away and the residue washed with several small portions of CH_2Cl_2. The combined washings were washed with 100 mL of 10% NaOH solution, dried ($MgSO_4$) and concentrated *in vacuo*. The thioketal 2.2 was easily removed from the crude oily residue at this stage by crystallization from hexanes (yield = 45.5g; 39%). The remaining filtrate was concentrated and then distilled *in vacuo* to give 19.3g (25%) of the vinyl sulfide 2.1 (bp. 168°C at 7 mm Hg) as a 4 : 1 mixture of E and Z isomers respectively. The spectroscopic data for the major isomer were in complete agreement with the reported values (see ref. 46 in Chapter 1).

The thioketal 2.2 had IR ($CHCl_3$, cm^{-1}): 2998, 1749, 1476, 1440, 1336, 1200, 1076; ^1H NMR ($CDCl_3$, ppm): 7.63 - 7.67 (m, 5H), 7.35 - 7.41 (m, 5H), 3.68 (s, 3H), 2.76 (s, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 169.7, 137.3, 131.2, 129.5, 128.7, 59.7, 51.7, 46.1, 28.0.

Conversion of the thioketal 2.2 to the vinyl sulfide 2.1 (DBU method)

To a stirring solution of the thioketal (200 mg; 0.628 mmol) in dry CH_2Cl_2 (5.0 mL) under argon at r.t. was added DBU (0.22 mL; 1.51 mmol) dropwise. The mixture was then warmed to reflux for 67h and then cooled to r.t., diluted with 10 mL of CH_2Cl_2 and

washed with 10 mL of water. The aqueous phase was further extracted with 5 mL of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated to give 199 mg of crude residue. Flash chromatography on silica gel (eluent : 5% ethyl acetate / hexanes) gave 130 mg (75%) of the vinyl sulfide 2.1.

1-Trimethylsiloxy-1-methoxy-3-phenylthio-1,3-butadiene (2.3)

To a stirred solution of diisopropylamine (6.80 mL; 48.0 mmol) in dry THF (120mL) under argon at 0°C was added n -butyllithium solution (22.0 mL of 2.2 M sol. in hexanes) dropwise. At the end of the addition the mixture was cooled to -78°C and trimethylsilyl chloride (8.00 mL; 63.0 mmol) was added dropwise. A solution of the thioketal 2.2 (8.391 g; 40.3 mmol) in 40 mL dry THF was added via cannula washing the transfer flask twice with 5 mL of dry THF. After 5 min. the mixture was allowed to warm up to room temperature for 15 min. and the solvent removed *in vacuo*. The oily residue was washed and filtered under argon with cold, dry hexanes and the filtrate concentrated *in vacuo* to give 11.310 g (100%) of the oily siloxydiene 2.3. The spectroscopic data for 2.3 were in complete agreement with the reported values (see ref. 46 in Chapter 1).

Methyl-3-phenylthio-4-(3'-oxo-6',6'-dimethylcyclohexyl)-but-2-enoate (2.4a, 2.4b)

To a stirred solution of 4,4-dimethyl-2-cyclohexen-1-one (0.50 g; 0.53 mL; 4.0 mmol) and the siloxydiene 2.3 (1.80 g; 6.4 mmol; 1.6 equiv.) in dry methylene chloride (20 mL) under argon at -78°C was added titanium tetrachloride (0.49 mL; 4.4 mmol; 1.1 equiv.) dropwise. The mixture immediately became deep red in color. After 2h 15 min. the mixture was allowed to warm to room temperature and poured into 10% aqueous sodium bicarbonate solution and extracted twice with 20 mL portions of methylene chloride. The

combined organic extracts were dried (Na_2SO_4) and concentrated to give 1.84 g of yellow semisolid residue. Flash chromatography on silica gel (eluent: 25% ethyl acetate / hexanes) provided the E (mp. 146-148°C) and Z (mp. 134-136°C) isomers of 2.4 in a ratio of 4 : 1 in 60% yield. In several large scale runs, the E isomer could be conveniently crystallized from the crude residue after workup using 10% ethyl acetate / hexanes.

The E isomer 2.4a had IR ($CHCl_3$, cm^{-1}): 3013, 2965, 1709, 1697, 1599, 1341, 1176; ^1H NMR ($CDCl_3$, ppm): 7.42-7.58 (m, 5H), 5.28 (s, 1H), 3.58 (s, 3H), 3.42-1.48 (m, 9H), 1.12 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 211.5, 165.3, 163.1, 135.5, 129.9, 129.8, 129.1, 112.1, 50.8, 45.9, 41.8, 40.3, 38.1, 33.0, 32.9, 28.6, 19.1; MS: 332 ($M^{+\cdot}$, 39), 301 (16), 219 (26), 176 (29), 134 (29), 55 (100). Exact mass calcd. for $C_{19}H_{24}O_3S$: 332.145; found: 332.148.

The Z isomer 2.4b had IR ($CHCl_3$, cm^{-1}): 3013, 2965, 1707, 1581, 1436, 1177; ^1H NMR ($CDCl_3$, ppm): 7.67-7.10 (m, 5H), 5.82 (s, 1H), 3.77 (s, 3H), 2.87-1.23 (m, 9H), 0.73 (s, 3H), 0.40 (s, 3H); MS: 332 ($M^{+\cdot}$, 56), 300 (16), 258 (39), 223 (41), 205 (60), 149 (49), 110 (60), 28 (100). Exact mass calcd. for $C_{19}H_{24}O_3S$: 332.145; found (EI): 332.141.

3-Phenylthio-4a,5,6,8a-tetrahydro-5,5-dimethyl-(4H,7H)-naphthalen-1,8-dione (2.5)

To a stirring solution of the E Michael adduct 2.4a (332 mg; 1.00 mmol) in dry *tert*-butanol (10 mL) under argon at 40°C was added potassium *tert*-butoxide (225 mg; 2.00 mmol; 2.0 equiv.) in one portion. After 4.5h, the mixture was quenched with 3.0 mL of water and the solvent removed *in vacuo*. The residue was taken into 15 mL of methylene chloride (CH_2CL_2) and washed once with 10 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the resulting semisolid

residue (eluent: 20% ethyl acetate / hexanes) afforded 254 mg (85%) of 2.5 as a bright canary yellow colored solid mp. 122-124°C.

2.5 had IR ($CHCl_3$,cm^{-1}): 2934, 1617, 1594, 1558, 1270, 1249; ^1H NMR ($CDCl_3$, ppm): 7.50-7.40 (m, 5H), 5.41 (s, 1H), 2.73-2.13 (m, 5H), 1.65-1.47 (m, 2H), 1.04 (s, 3H), 0.88 (s, 3H), 15.15 (s, exch. D_2O, 1H); ^{13}C NMR ($CDCl_3$, ppm): 187.5, 177.7, 162.6, 135.3, 130.1, 129.9, 128.1, 118.5, 104.1, 42.7, 36.0, 31.5, 30.6, 28.8, 27.4, 20.1; MS: 300 ($M^{+\cdot}$, 78), 298 (100), 283 (37), 255 (35), 244 (60), 191 (50), 135 (96), 110 (52). Exact mass calcd. for $C_{18}H_{20}O_2S$: 300.118; found (EI): 300.121.

Representative angular methylation of the dione 2.5

To a stirred solurion of the dione 2.5 (100 mg; 0.33 mmol) and dried potassium carbonate (69 mg; 0.50 mmol; 1.5 equiv.) in dry acetonitrile (5.0 mL) under argon at room temperature was added methyl iodide (0.21 mL; 3.3 mmol; 10 equiv.). The reaction flask was then fitted with a condenser and warmed to reflux. After 26h, the mixture was allowed to cool down to room temperature. The solvent was removed *in vacuo* and the residue taken into 20 mL of CH_2Cl_2 and washed with 10 mL of water. The aqueous phase was further extracted with 10 mL of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated to give a crude yellow oily residue. Flash chromatography on silica gel (eluent: 30% ethyl acetate / hexanes) provided the *cis* compound 2.6 (mp. 116-117°C) and the *trans* compound 2.7 (mp. 132-134°C) in a ratio of 1.2 : 1 in 63% yield. Further elution of the column with 80% ethyl acetate / hexanes afforded the O-methyl product 2.8 in 28% yield.

cis-2.6 had IR ($CHCl_3$, cm^{-1}): 2966, 1717, 1646, 1591, 1230, 1097; ^1H NMR ($CDCl_3$, ppm): 7.44-7.56 (m, 5H), 5.44 (d, J = 2.2 Hz, 1H), 2.89 (ddd, J = 2.2, 6.3, 19 Hz, 1H), 2.57 (d, J = 19 Hz, 1H), 2.29 (dt, J = 3.4, 14 Hz, 1H), 2.06 (d, J = 6.3 Hz, 1H), 2.50-2.70 (m, 1H), 1.52-1.83 (m, 2H), 1.36 (s, 3H), 1.02 (s, 6H); ^{13}C NMR

($CDCl_3$, ppm): 208.7, 196.1, 164.2, 135.5, 130.3, 129.9, 127.3, 118.9, 58.4, 54.0, 41.2, 36.9, 34.7, 30.4, 28.7, 22.5, 20.8; MS: 314 ($M^{+\cdot}$, 9), 217 (17), 176 (63), 148 (39), 110 (32), 85 (24), 77 (56), 67 (100). Exact mass calcd. for $C_{19}H_{22}O_2S$: 314.134; found (EI): 314.135.

trans-2.7 had IR (KBr, cm^{-1}): 2950, 1718, 1648, 1590, 1250; ^1H NMR ($CDCl_3$, ppm): 7.40-7.55 (m, 5H), 5.35 (d, J = 1.8 Hz, 1H), 2.70 (ddd, J = 1.8, 12.2, 17.7 Hz, 1H), 2.40-2.63 (m, 4H), 1.58-1.90 (m, 2H), 1.41 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 208.8, 193.2, 163.9, 135.4, 130.3, 129.9, 127.7, 118.9, 57.1, 48.1, 37.6, 36.6, 32.2, 30.6, 28.8, 25.3, 18.2; MS: 314 ($M^{+\cdot}$, 8), 258 (3), 217 (7), 200 (9), 176 (78), 148 (70), 110 (41), 85 (47), 77 (70), 67 (100), 39 (68).

2.8 had ^1H NMR ($CDCl_3$, ppm): 7.34-7.58 (m, 5H), 5.44 (d, J = 1.6 Hz, 1H), 3.73 (s, 3H), 2.12-2.65 (m, 5H, 1.58 (s, 3H), 1.22-1.56 (m, 2H), 0.88 (s, 3H).

Cyclization / alkylation (one pot reaction) of the E adduct 2.4a

To a stirring suspension of 2.4a (10.870 g; 32.72 mmol) in 200 mL of dry t-butanol under argon at 40°C was added potassium t-butoxide (5.510 g; 49.08 mmol; 1.5 equiv.). After 1h, cyclization of 2.4a appeared to be complete by tlc (eluent: 20% ethyl acetate / hexanes) and so the mixture was quenched with methyl iodide (20.4 mL; 327.2 mmol; 10.0 equiv.) and then allowed to stir for 48h at 40°C. At this point, the mixture was allowed to cool down to room temperature and the solvent removed *in vacuo*. The residue was taken into 200 mL of CH_2Cl_2 and washed with 75 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a brown viscous oil. Flash chromatography on silica gel (eluent: 20% ethyl acetate / hexanes) provided the C-alkyl products 2.6 and 2.7 in a ratio of 2 : 1 in 70% yield. Further elution of the column with 80% ethyl acetate / hexanes provided the O-alkyl product 2.8 in 3% yield.

Cyclization / alkylation (one pot reaction) of the E and Z isomers of 2.4

To a stirred solution of thiophenol (0.25 mL; 4.0 equiv.) in 5.0 mL of dry THF under argon at 0°C was added n-butyllithium solution (1.00 mL of 2.3 M solution in hexanes; 2.3 mmol; 3.8 equiv.). A solution of 2.4a (200 mg; 0.60 mmol) in 2.0 mL of dry THF was added dropwise and the mixture warmed to room temperature and then to reflux. After 4h at reflux, the mixture was cooled to 40°C and methyl iodide (0.56 mL; 9.0 mmol; 15.0 equiv) was added. After 43h, another 10 equivalents of methyl iodide was added and the mixture warmed to 50°C for approximately 5 days. At this point, the mixture was allowed to cool down to room temperature and the solvent removed *in vacuo*. The residue was taken into 10 mL of CH_2Cl_2 and washed with 10 mL of water. The aqueous phase was further extracted with 10 mL of CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was chromatographed (eluent: 20% ethyl acetate / hexanes to give the C-alkyl products 2.6 and 2.7 in 34% and 25% yields respectively. A considerable amount of unreacted diketone 2.5 (34%) was also recovered. Further elution of the column with 80% ethyl acetate / hexanes provided the O-alkyl product 2.8 in 2% yield.

Representative reaction of the enone 2.16 with the diene 2.3

To a stirring solution of the enol silyl ether 2.3 (1.794 g; 6.40 mmol; 1.5 equiv.) and the enone 2.16 (0.561 g; 4.06 mmol) in 20 mL of dry CH_2Cl_2 under argon at -78°C was added titanium tetrachloride (0.44 mL; 4.0 mmol; 1.0 equiv.) dropwise. After 3h, the mixture was allowed to warm up to room temperature and poured into 10% $NaHCO_3$ solution and extracted twice with 30 mL portions of CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a crude brown oil. Flash chromatography on

silica gel (eluent: 20% ethyl acetate / hexanes) afforded the spirolactone 2.21 mp. 83-85°C (EtOH / H_2O) in 86% yield.

2.21 had IR ($CHCl_3$, cm^{-1}): 1689, 1603, 1288, 1050; ^1H NMR ($CDCl_3$, ppm): 7.40-7.57 (m, 5H), 5.34-5.29 (m, 2H), 2.92 (dd, J = 17.5, 2.2 Hz, 1H), 2.32 (d, J = 17.5 Hz, 1H), 1.92-2.07 (m, 2H), 1.74 (d, J = 1.5 Hz, 3H), 1.28-1.70 (m, 2H), 0.98 (s, 3H), 0.96 (s, 3H); MS: 314 ($M^{+\cdot}$, 32), 270 (51), 193 (81), 177 (60), 176 (100), 161 (60), 147 (63), 145 (88), 119 (61), 105 (60), 91 (91), 69 (65), 67 (90), 44 (74), 43 (60).

trans-6'-Phenylthio-3',4',4a',8a'-tetrahydro-4',4',8a'-trimethyl-spiro[1,3-dithiolane-2,1'(2'H)-naphthalen]-8'(5'H)-one 2.13

To a stirred solution of the dione 2.7 (1.26 g; 4.0 mmol) in benzene (70mL) was added a catalytic amount of p-toluenesulfonic acid and 1,2-ethanedithiol (1.0 mL; 12.0 mmol). The mixture was then refluxed (Dean-Stark) and the reaction followed by tlc (eluent: 20% ethyl acetate / hexane). At the end, the reaction mixture was diluted with 50 mL of ether and washed with 10% sodium bicarbonate solution. The solvent was evaporated _in vacuo_ and the compound purified by column chromatography (eluent: 20% ethyl acetate / hexanes) to give 2.13 in almost quantitative yield.

2.13 had ^1H NMR ($CDCl_3$, ppm): 7.43 (s, 5H), 5.32 (s, 1H), 3.00-3.80 (m, 4H), 1.43-2.73 (m, 7H), 1.38 (s, 3H), 0.93 (s, 6H); MS: 390 ($M^{+\cdot}$, 6), 331 (28), 298 (40), 283 (20), 255 (18), 244 (24), 229 (29), 191 (25), 176 (29), 155 (19), 135 (46), 131 (46), 118 (33), 110 (57), 107 (33), 77 (28), 55 (39), 41 (45), 28 (100). Exact mass calcd. for $C_{21}H_{26}OS_3$: 390.115; found (EI): 390.111.

trans-6'-Methoxy-3',4',4a',8a'-tetrahydro-4',4',8a'-trimethyl-spiro[1,3-dithiolane-2,1'(2'H)-naphthalen]-8'(5'H)-one (2.14)

To a well stirred solution of the 2.13 (0.78 g; 2.0 mmol) in dry methanol (40 mL) under nitrogen was added sodium methoxide (0.55 g; 10.0 mmol) and the mixture refluxed for 24h. The solvent was then removed *in vacuo* and the residue extracted with 100 mL of ether and the ether layer washed with 10 mL of water and then dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product purified by column chromatography (eluent: 30% ethyl acetate / hexane) to give 2.14 in 60% yield. The starting compound 2.13 was also recovered in 30% yield.

2.14 had ^1H NMR ($CDCl_3$, ppm): 5.13 (s, 1H), 3.30 (s, 3H), 3.10-3.80 (m, 4H), 1.50-2.53 (m, 7H), 1.20 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H); MS: 312 ($M^{+\cdot}$, 44), 253 (53), 155 (68), 139 (42), 131 (100), 122 (20), 118 (47), 98 (38), 69 (48), 55 (45). Exact mass calcd. for $C_{16}H_{24}O_2S_2$: 312.122; found (EI): 312.125.

trans-3-Methoxy-4,4a,5,6,7,8,8a-heptahydro-5,5,8a-trimethyl-(4H)-naphthalen-1-one (2.15)

To a stirred solution of 2.14 (0.62 g; 2.0 mmol) in 50 mL of ethanol was added 3.0 g of Raney nickel and the mixture was stirred for 6h. At this point the reaction mixture was refluxed for another 6h, the catalyst removed by filtration, and the solvent removed *in vacuo*. The crude product was purified by column chromatography (eluent: 20% ethyl acetate / hexanes). The product was further purified by crystallization from hexanes to give 2.15, mp. 55-57°C, in 85% yield. The spectral properties of 2.15 are identical in all respects to the reported values [1].

2.15 had ^1H NMR ($CDCl_3$, ppm): 5.18 (s, 1H), 3.78 (s, 3H), 1.18-2.55 (m, 9H), 1.08 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H); MS: 222 ($M^{+\cdot}$, 37), 207 (23), 151 (17), 139

(32), 109 (24), 98 (100), 68 (35), 41 (26), 28 (47). Exact mass calcd. for $C_{14}H_{22}O_2$: 222.162; found (EI): 222.160.

cis-3-Phenylthio-4,4a,5,6,7,8,8a-heptahydro-8α–hydroxy-5,5,8a-trimethyl-(4H)-naphthalen-1-one (2.22)

To a stirring solution of the *cis* dione 2.6 (5.152 g 16.41 mmol) in dry THF (225 mL) under argon at -20°C was added lithium tri-*t*-butoxyalumino hydride (8.345g; 32.82 mmol; 2.0 equiv.) in one portion. After 21.5h, the mixture was quenched with 3.0 mL of pH 7 buffer solution and the mixture allowed to come to room temperature. The solvent was removed *in vacuo* and the residue taken into 100 mL of CH_2Cl_2 and washed with 20 mL of water. The aqueous layer was further extracted several times with 10 mL of CH_2Cl_2 and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo* to give 5.185 g (100%) of the alcohol 2.22 as a single diastereomer. The crude product appeared to be very clean by NMR and tlc (one spot). The product could be further purified by recrystallization from absolute ethanol as white needles, mp. 180 - 182°C. Crystals suitable for X-ray analysis were obtained by slow evaporation (at 23°C) of a solution of 2.22 in methylene chloride.

2.22 had IR ($CHCl_3$, cm^{-1}): 3460, 3005, 2961, 1629, 1593, 1139, 1026; ^1H NMR ($CDCl_3$, ppm): 7.42-7.53 (m, 5H), 5.35 (d, J = 2.8 Hz, 1H), 4.81 (d, J = 10.6 Hz, exch. D_2O, 1H), 3.16 (dt, J = 10.6, 4.6 Hz, 1H), 2.92 (ddd, J = 19.1, 4.6, 2.8 Hz, 1H), 2.50 (dd, J = 19.1, 1.0 Hz, 1H), 1.21-1.89 (m, 5H), 1.47 (s, 3H), 0.96 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 203.7, 164.3, 135.6, 130.3, 129.9, 127.8, 120.4, 78.6, 52.5, 47.3, 40.2, 34.7, 31.1, 29.0, 28.8, 24.3, 23.4; MS: 316 ($M^{+\cdot}$, 10), 217 (100), 176 (54), 148 (54), 139 (71), 108 (80), 67 (67), 43 (91), 39 (85). Exact mass calcd. for $C_{19}H_{24}O_2S$: 316.150; found (EI): 316.144.

cis-3-Phenylthio-4,4a,5,6,7,8,8a-heptahydro-8α(_tert_-butyldimethylsiloxy)-5,5,8a-trimethyl-(4H)-naphthalen-1-one (2.23)

To a stirring solution of the alcohol 2.22 (320 mg; 1.01 mmol) and 2,6-lutidine (0.30 mL; 0.27 g; 2.5 mmol; 2.5 equiv.) in dry CH_2Cl_2 (1.0 mL; conc. = 1.0 mmol / mL) under argon at room temperature was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.35 mL; 0.40 g; 1.5 mmol; 1.5 equiv.) dropwise. After 5h, the mixture was diluted with 20 mL of CH_2Cl_2 and washed with 10 mL of 10% sodium bisulfate solution (to remove remaining lutidine). The aqueous layer was further extracted with 10 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oily residue. Flash chromatography on silica gel (eluent: 5% ethyl acetate / hexanes) afforded the silyl ether 2.23 in 77% yield as fine white crystals, mp. 64-67°C. As outlined in Chapter 2, in several larger scale runs, the enol silyl ether 2.24 was frequently a significant side product of this reaction. Conversion of 2.24 back to 2.23 was easily accomplished by the following simple procedure: To 4.293 g (7.88 mmol) of 2.24 at r.t was added 30 mL of 1 : 9 5% aq. HCl : THF in one portion and the mixture allowed to stir for 10 min. and then quenched with 10 mL of 10% Na_2CO_3 solution. The solvent was removed *in vacuo* and the residue taken into CH_2Cl_2 and washed once with water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel as described above gave 2.646 g (78%) of 2.23. Further elution of the column with 30% ethyl acetate / hexanes gave 343 mg (14%) of the alcohol 2.22.

2.23 had IR (Nujol, cm^{-1}) 1646, 1606, 1289, 1250, 1073, 1042; ^1H NMR ($CDCl_3$, ppm): 7.38-7.54 (m, 5H), 5.38 (d, J = 1.4 Hz, 1H), 2.81-3.00 (bm, 1H), 2.42 (dd, J = 17.0, 5.2 Hz, 1H), 1.72 - 1.90 (m, 3H), 1.49-1.67 (m, 1H), 1.28 (s, 3H), 1.19 (s, 3H), 0.98 (s, 3H), 0.84 (s, 9H), 0.01 (s, 3H), -0.12 (s, 3H); MS: 415 ($M^{+\cdot}$-15, 3), 373 (100), 249 (38), 217 (35), 75 (58), 57 (21), 41 (37). Exact mass calcd. for $C_{25}H_{39}O_2SSi$ (M+1): 431.244; found (CI, NH_3): 431.244.

2.24 had IR ($CHCl_3$, cm^{-1}): 2956, 1609, 1569, 1473, 1464, 1255, 1097, 922; ^1H NMR ($CDCl_3$, ppm): 7.35 - 7.15 (m, 5H), 5.64 (dd, J = 6.4, 1.0 Hz, 1H), 4.64 (d, J = 1.0 Hz, 1H), 3.32 (dd, J = 11.4, 2.8 Hz, 1H), 1.75 - 1.95 (m, 1H), 1.66 (d, J = 6.4 Hz, 1H), 1.58 - 1.20 (m, 3H), 1.25 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.83 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.00 (s, 3H).

cis-3-Methoxy-4,4a,5,6,7,8,8a-heptahydro-8α(_tert_-butyldimethylsiloxy)-5,5,8a-trimethyl-(4H)-naphthalen-1-one (2.25)

To a stirred solution of freshly prepared sodium methoxide (41.80 mmol; prepared by slow dropwise addition of dry methanol (140 mL) to sodium hydride (1.004 g) with external ice bath cooling) under argon at room temperature was added 2.23 (3.000 g; 7.00 mmol) in one portion. The reaction flask was then fitted with a condenser and warmed to reflux. After 72h, the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was taken into 100 mL of CH_2Cl_2 and washed once with 20 ml of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* and subjected to flash chromatography on silica gel (eluent: 8% ethyl acetate / hexanes) to give 2.256 g (92%) of the methoxy enone 2.25 as fine waxy crystals, mp. 68-70°C.

2.25 had IR ($CHCl_3$, cm^{-1}): 2929, 2856, 1627, 1381, 1079, 841; ^1H NMR ($CDCl_3$, ppm): 5.36 (d, J = 0.8 Hz, 1H), 3.82 (bm, 1H), 3.64 (s, 3H), 2.78 (m, 1H), 2.28 (dd, J = 17.8, 5.7 Hz, 1H), 1.50-1.90 (m, 5H), .1.31 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H), 0.79 (s, 9H), 0.02 (s, 3H), -0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 203.6, 177.2, 102.4, 75.4, 55.3, 49.8, 47.3, 33.1, 31.2, 30.8, 30.1, 29.9, 26.1, 25.7, 25.1, 17.8, -4.6, -5.6; MS: 337 (6), 297 (23), 296 (43), 295 (100), 171 (40), 139 (35), 101 (24), 89 (46), 75 (43), 73 (45), 41 (40). Exact mass calcd. for $C_{20}H_{37}O_3Si$ (M+1): 353.251; found (CI, NH_3): 353.251.

cis-3-Methoxy-4a,5,6,7,8,8a-hexahydro-8α(_tert_-butyldimethylsiloxy)-2,5,5,8a-tetramethyl-(4H)-naphthalen-1-one (3.1)

To a stirring solution of dry diisopropylamine (0.91 mL; 6.5 mmol; 2.3 equiv.) in dry THF (20 mL) under argon at -78°C was added n-butyllithium solution (3.16 mL of 1.8 M solution in pentane; 2.0 equiv.) dropwise. Hexamethylphosphoramide (HMPA, 2.50 mL; 14.2 mmol; 5.0 equiv.) was then added in one portion and the reaction mixture allowed to warm slightly by removal of the cooling bath until the HMPA completely dissolved (about 2 min.). The mixture was then cooled back to -78°C and a solution of the enone 2.25 (1.000 g; 2.83 mmol in 15 mL THF) was added dropwise (cannula) washing the transfer flask twice with 2 mL portions of dry THF. After 1h, methyl iodide (0.35 mL; 5.7 mmol; 2.0 equiv.) was added and the mixture warmed to -60°C (the temperature is important for acheiving clean monomethylation!) for 30 min. At this point, the mixture was quenched with 0.5 mL of pH 7 buffer solution, allowed to warm to room temperature and the solvent removed *in vacuo*. The residue was taken into 30 mL of CH_2Cl_2 and washed with 10 mL of water. The aqueous layer was further extracted with 10 mL of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (eluent: 4% ether / hexanes) to give 778 mg (75%) of 3.1 as a waxy solid mp. 85-87°C. Further elution of the column with 30% ether / hexanes gave 151.0 mg (15%) of recovered enone 2.25.

3.1 had IR ($CHCl_3$, cm^{-1}): 2949, 2854, 1716, 1664, 1463, 1257, 1117, 1045; ^1H NMR ($CDCl_3$, ppm): 4.76 (dd, J = 1.3, 6.9 Hz, 1H), 3.59 (s, 3H), 3.26 (dd, J = 4.0, 11.8 Hz, 1H), 2.74 (dq, J = 1.3, 6.9 Hz, 1H), 1.91-2.15 (m, 1H), 1.83 (d, J = 6.9 Hz, 1H), 1.40-1.63 (m, 2H), 1.20-1.38 (m, 1H), 1.29 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 3H), 0.59 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H); MS: 366 ($M^{+\cdot}$, 9), 351 (6), 309 (100), 169 (27), 152 (45), 101 (48), 75 (63), 73 (55), 59 (28). Exact mass calcd. for $C_{21}H_{39}O_3Si$ (M+1): 367.2668; found (CI, NH_3): 367.2669.

Preparation of the enone 3.2 and the dialkyl product 3.3

The reaction was carried out as above for the preparation of 3.1 (using 3.0 equiv. of LDA) however after the addition of methyl iodide (3.0 equiv.), the reaction mixture was allowed to warm to room temperature for 1h and then quenched with buffer solution and worked up. Chromatography on silica gel (eluent: 3% ether / hexanes) gave 3.1 in 23% yield as well as the dialkyl product 3.3 in 29% yield. Further elution of the column with 15% ether / hexanes provided the enone 3.2 in 36% yield.

3.2 had IR ($CHCl_3$, cm^{-1}): 2958, 2944, 1634, 1627, 1377, 1250, 1139, 1005; ^1H NMR ($CDCl_3$, ppm): 3.76 (bm, 1H), 3.75 (s, 3H), 2.43-2.76 (m, 2H), 1.43-1.98 (m, 5H), 1.65 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 0.99 (s, 3H), 0.77 (s, 9H), -0.03 (s, 3H), -0.15 (s, 3H); MS: 366 ($M^{+\cdot}$, 5), 351 (3), 309 (63), 153 (73), 135 (33), 112 (56), 101 (34), 75 (65), 73 (67), 57 (64), 55 (66), 43 (100), 41 (64). Exact mass calcd. for $C_{21}H_{38}O_3Si$: 366.259; found (EI): 366.255.

3.3 had IR ($CHCl_3$, cm^{-1}): 2951, 2856, 1717, 1661, 1464, 1243, 1150; ^1H NMR ($CDCl_3$, ppm): 4.70 (d, J = 6.7 Hz, 1H), 3.58 (s, 3H), 3.25 (dd, J = 11.8, 4.0 Hz, 1H), 1.90-2.20 (m, 1H), 1.85 (d, J = 6.7 Hz, 1H), 1.24-1.56 (m, 3H), 1.39 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.88 (s, 12H), 0.60 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H).

Preparation of 3.2 by isomerization of 3.1

To a stirring solution of sodium methoxide (38.2 mmol; prepared by careful dropwise addition of 70 mL of dry methanol to 617 mg of sodium hydride under argon with external ice bath cooling) was added the ketone 3.1 (1.350 g; 3.74 mmol) and the mixture warmed to reflux for 2h and then allowed to cool down to room temperature. The solvent was removed *in vacuo* and the residue taken into 50 mL of CH_2Cl_2 and washed with 10 mL of water. The organic layer was further extracted with 10 mL of CH_2Cl_2 and the combined

extracts dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 4% ethyl acetate / hexanes) gave 1.228 g (95%) of the conjugated enone 3.2.

cis-3-Methoxy-1,4,4a,5,6,7,8,8a-octahydro-8α(*tert*-butyldimethylsiloxy)-1β(vinyl)-2,5,5,8aβ-tetramethyl-naphthalen-1-ol (3.4)

To a stirring solution of the enone 3.2 (266 mg; 0.73 mmol) in dry diethyl ether (1.0 mL) under argon at 0°C was added vinyllithium solution in ether (10.89 mL of 0.20 mol / l solution*; 3.0 equiv.) dropwise. At the end of the addition, the reaction mixture was allowed to warm to room temperature for 30 min. and then quenched with 0.3 mL of pH 7 buffer solution and diluted with 10 mL of ether. The ether phase was washed with 10 mL of 10% sodium carbonate solution followed by 10 ml of brine and then dried (Na_2SO_4). Concentration *in vacuo* gave a crude oily residue which was chromatographed (eluent: 3% ethyl acetate / hexanes to give 226 mg (79%) of the labile allylic alcohol 3.4 as a single isomer. As expected, This compound appeared to be very sensitive to acid and precautions had to be taken to remove traces of HCl from the $CDCl_3$ prior to examination of the ^1H NMR spectrum.

3.4 had IR ($CHCl_3$, cm^{-1}): 3513, 2957, 2931, 2859, 1471, 1230, 1074, 1005, 836; 1H NMR ($CDCl_3$, ppm): 5.73 (dd, J = 17.2, 10.8 Hz, 1H), 5.02 (dd, J = 10.8, 1.6 Hz, 1H), 4.95 (m, 1H), 3.59 (dd, J = 8.6, 4.2 Hz, 1H), 3.54 (s, 3H), 2.94 (bs, exch. D_2O, 1H), 2.27 (m, 2H), 2.00-2.17 (m, 1H), 1.10-1.85 (m, 4H), 1.48 (t, J = 1.6 Hz, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); Exact mass calcd. for $C_{22}H_{39}O_2Si$ ($M+H^+$-MeOH): 363.2719; found (CI, NH_3): 363.2719.

* The vinylithium solutions in ether were generally standardized according to the following simple procedure: To a stirring solution of 2,5-dimethoxybenzyl alcohol (169 mg) in 5.0 mL of dry THF was added vinyllithium solution dropwise. Since 2.69 mL of vinyllithium

was required to reach the deep brown/red colored end point, the concentration is calculated to be 0.37 M.

cis-3-Methoxy-1,2,4a,5,6,7,8,8a-octahydro-1α,2β–hydroxy-8α(_tert_-butyldimethylsiloxy)-1-vinyl-2,5,5,8a-tetramethyl-naphthalene (3.5)

To a stirring solution of the allylic alcohol 3.4 (14.8 mg; 0.038 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was added 10% sodium carbonate solution (0.5 mL) followed by MCPBA (7.8 mg; 0.045 mmol; 1.2 equiv.) in one portion. After 21h, the mixture was allowed to come to room temperature and stirred for 2h 15 min. at which point another 0.2 equiv. of MCPBA was added and the mixture allowed to stir for an additional 45 min. At this point it was diluted with 10 mL of CH_2Cl_2 and washed with 3mL of water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 20% ether / hexanes) gave 5.8 mg (38%) of the diol 3.5 as well as 6.4 mg (30%) of the cleavage product 3.6.

the diol 3.5 had IR ($CHCl_3$, cm^{-1}): 3593, 3416, 3016, 2957, 1471, 1255, 1095, 833; ^1H NMR ($CDCl_3$, ppm): 6.45 (dd, J = 17.4, 10.8 Hz, 1H), 5.32 (dd, J = 10.8, 1.9 Hz, 2H), 4.76 (d, J = 5.4 Hz, 1H), 3.69 (dd, J = 7.9, 2.5 Hz, 1H), 3.58 (s, 3H), 3.48 (s, exch. D_2O, 1H), 1.91 (d, J = 5.4 Hz, 1H), 1.56 - 1.88 (m, 4H), 1.25 - 1.40 (m, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); MS: 395 (2), 351 (10), 335 (39), 235 (19), 123 (35), 101 (42), 81 (47), 75 (100), 73 (92), 55 (41), 44 (48). Exact mass calcd. for $C_{23}H_{41}O_3Si$ ($M+H^+-H_2O$): 393.2825; Found (CI, NH_3): 393.2826.

3.6 had 1H NMR ($CDCl_3$, ppm): 6.75 (dd, J = 17.0, 10.6 Hz, 1H), 5.44 (dd, J = 10.6, 2.0 Hz, 1H), 5.16 (dd, J = 17.0, 2.0 Hz, 1H), 4.66 (s, exch. D_2O, 1H), 3.63 (s, 3H), 3.60 (obstructed dd, 1H), 2.87 (d, AB system, J_{ab} = 17.6 Hz, 1H), 2.33 (s, 3H), 2.05 (m, 1H), 1.88 (dd, J = 17.6, 7.8 Hz, 1H), 1.10-1.70 (m, 3H), 1.13 (s, 3H), 0.95

(s, 9H), 0.88 (s, 3H), 0.81 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H); MS: 383 (13), 351 (9), 337 (9), 219 (31), 195 (19), 171 (23), 157 (24), 121 (47), 75 (100), 73 (76), 55 (57), 43 (48). Exact mass calcd. for $C_{23}H_{43}O_5Si$ (M+1): 427.2880; found (CI, NH_3): 427.2879.

cis-3-Methoxy-1,2,4a,5,6,7,8,8a-octahydro-1α,2β,8α-trihydroxy-1(vinyl)-5,5,2,8aβ-tetramethyl-(4H)-naphthalene (3.7)

To a stirring solution of the diol 3.5 (20.0 mg; 0.049 mmol) in 0.2 mL of THF at room temperature, was added tetrabutylammonium fluoride solution (0.073 mL of 1.0 mmol/mL solution in THF; 1.5 equiv.) dropwise. After allowing to stir for 3h at r.t., the solvent was removed *in vacuo* and the residue taken into 10 mL of CH_2Cl_2 and washed once with 3 mL of water. The organic layer was dried (Na_2SO_4) and evaporated to give a crude oily residue. Flash chromatography on silica gel (eluent: 50% ether / hexanes) afforded 13.1 mg (91%) of the crystalline triol 3.7 mp. 142 - 145°C. Crystals suitable for X-ray analysis were obtained by slow evaporation (at -20°C) of a solution of 3.7 in acetone.

3.7 had IR ($CHCl_3$, cm^{-1}): 3604, 3442, 2956, 2939, 1465, 1086, 928; ^1H NMR ($CDCl_3$, ppm): 6.72 (dd, J = 17.6, 10.8 Hz, 1H), 5.54 (dd, J = 17.6, 1.9 Hz, 1H), 5.42 (dd, J = 10.8, 1.9 Hz, 1H), 4.75 (d, J = 5.4 Hz, 1H), 3.63 (partially obstructed dt, J = 7.2, 2.4 Hz, 1H), 3.59 (s, 3H), 3.19 (s, exch. D_2O, 1H), 2.49 (d, J = 7.2 Hz, exch. D_2O, 1H), 1.91 (d, J = 5.4 Hz, 1H), 1.87-1.32 (m, 5H), 1.33 (s, 3H), 1.23 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H); MS: 296 ($M^{+\cdot}$, 3), 264 (5), 162 (29), 147 (33), 123 (44), 109 (33), 99 (30), 81 (46), 55 (71), 43 (100). Exact mass calcd. for $C_{17}H_{27}O_3$ ($M+H^+-H_2O$): 279.1960; found (CI, NH_3): 279.1961.

3-Methoxy-5,6,7,8,8a-pentahydro-8α(*tert*-butyldimethylsiloxy)-5,5,8aβ-trimethyl-(2H,4H)-naphthalen-1-one (4.5)

To a stirring solution of the deconjugated enone 4.4 (9.2 mg; 0.026 mmol) in dry dioxane (0.5 mL) under argon at room temperature was added selenium dioxide (3.5 mg; 0.031 mmol; 1.2 equiv.) in one portion and the mixture warmed to reflux. After 30 min., the mixture was allowed to cool and the solvent removed *in vacuo*. The residue was taken into 8 mL of CH_2Cl_2 and washed with 3 mL of 10% Na_2CO_3 solution. The organic phase was further extracted twice with 2 mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography on silica gel (eluent: 8% ethyl acetate / hexanes) gave 8.0 mg (88%) of the dienone 4.5.

4.5 had IR ($CHCl_3$, cm^{-1}): 2951, 2856, 1646, 1582, 1388, 1086, 838; ^1H NMR ($CDCl_3$, ppm): 6.08 (d, J = 1.8 Hz, 1H), 5.29 (d, J = 1.8 Hz, 1H), 4.37 (d, J = 2.9 Hz, 1H), 3.72 (s, 3H), 1.89-2.15 (m, 2H), 1.53-1.60 (m, 1H), 1.21-1.35 (m, 1H), 1.29 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H), 0.73 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H); MS: 335 (3), 293 (100), 275 (28), 223 (27), 81 (26), 75 (26), 73 (17). Exact mass calcd. for $C_{20}H_{35}O_3Si$ (M+1): 351.2355; found (CI, NH_3): 351.2354.

***cis*-3-Methoxy-2,4a,5,6,7,8,8a-heptahydro-2-hydroxy-8α(*tert*-butyldimethylsiloxy)-5,5,8a-trimethyl-(2H,4H)-naphthalen-1-one (4.1)**

To a stirring solution of hexamethyldisilazane (0.90 mL; 4.3 mmol; 1.5 equiv.) in 15 mL of dry THF under argon at -78°C was added n-butyllithium (1.70 mL of 2.0 mmol/mL solution of pentane; 1.2 equiv.) dropwise. HMPA (2.47 mL; 14.2 mmol; 5.0 equiv.) was then added and the mixture allowed to warm slightly by removal of the cooling bath until all the HMPA had dissolved (approx. 2 min.). The mixture was cooled back to -78°C and a solution of the enone 2.25 (1.000 g; 2.84 mmol) in 20 mL of dry THF was added

dropwise (cannula) washing the transfer flask twice with 5 mL portions of dry THF. After 1h, the enolate solution was transferred dropwise (over about a 15 min. period) to a second flask containing anhydrous dimethyldioxirane solution in acetone (60.8 mL of 0.070 mmol/mL solution; 1.5 equiv.) also at -78°C, again washing the transfer flask twice with 5 mL portions of dry THF. After 15 min. the mixture was quenched with 4.0 mL of pH 7 buffer solution and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue taken into 100 mL of CH_2Cl_2 and washed with 20 mL of water. The aqueous layer was further extracted twice with 10 mL portions of CH_2Cl_2 and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oily residue. Flash chromatography on silica gel (eluent: 16% ethyl acetate / hexanes) afforded 836 mg (80%) of the α-hydroxy product 4.1 as a gum. Further elution of the column with 30% ethyl acetate / hexanes gave 128 mg (12%) of the γ-hydroxy product 4.2 (mp. 146-148°C).

4.1 had IR ($CHCl_3$, cm^{-1}): 3585, 2960, 1722, 1669, 1463, 1117, 838; ^1H NMR ($CDCl_3$, ppm): 4.94 (d, J = 6.9 Hz, 1H), 4.10 (d, J = 2.3 Hz, 1H), 3.67 (s, 3H), 3.35 (dd, J = 11.5, 3.7 Hz, 1H), 2.75 (d, J = 2.8 Hz, exch. D_2O, 1H), 2.05-1.83 (m, 1H), 1.95 (d, J = 6.9 Hz, 1H), 1.65-1.24 (m, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.56 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 208.9, 153.6, 96.0, 78.2, 71.0, 55.0, 53.1, 50.7, 38.7, 36.1, 31.1, 28.0, 26.8, 24.4, 21.4, 18.0, -2.9, -4.9; MS: 368 ($M^{+\cdot}$, 2), 311 (30), 295 (10), 159 (7), 101 (8), 81 (9), 75 (100). Exact mass calcd. for $C_{20}H_{37}O_4Si$ (M+1): 369.2461; found (CI, NH_3): 369.2461.

4.2 had IR ($CHCl_3$, cm^{-1}): 3585, 2961, 2929, 1667, 1463, 1257, 1119, 841; ^1H NMR ($CDCl_3$, ppm): 5.26 (s, 1H), 4,27 (d, J = 2.9 Hz, 1H), 3.70 (s, 3H), 3.41 (dd, J = 8.5, 2.9 Hz, 1H), 2.45 (s, exch. D_2O, 1H), 1.90-1.11 (m, 5H), 1.43 (s, 3H), 1.06 (s, 3H), 0.87 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), -0.02 (s, 3H); MS: 368 ($M^{+\cdot}$, 1), 353 (4), 311 (100), 279 (40), 251 (21), 159 (14), 101 (9), 81 (12), 75 (39). Exact mass calcd. for $C_{20}H_{37}O_4Si$ (M+1): 369.2461; found (CI, NH_3): 369.2461.

cis-3-Methoxy-4a,5,6,7,8,8a-hexahydro-8α(_tert_-butyldimethylsiloxy)-5,5,8a-trimethyl-(4H)-naphthalen-1,2-dione (4.3)

To a stirring solution of the α-hydroxy enone 4.1 (1.490 g; 4.04 mmol) in pentane (97 mL) at room temperature was added manganese dioxide (1.295 g; 14.90 mmol; 3.7 equiv.) in one portion. After 2h, the solvent was removed *in vacuo* and the solid residue taken into 30 mL of CH_2Cl_2 and filtered through a bed of celite and the yellow filtrate concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 25% ethyl acetate / hexanes) gave 1.400 g (95%) of the diketone 4.3 as a pale yellow solid (mp. 191-193°C).

4.3 had IR ($CHCl_3$, cm^{-1}): 2958, 2931, 1734, 1693, 1459, 1366, 1119, 836; ^1H NMR ($CDCl_3$, ppm): 6.04 (d, J = 7.1 Hz, 1H), 3.71 (s, 3H), 3.39 (dd, J = 11.7, 4.0 Hz, 1H), 2.29 (d, J = 7.1 Hz, 1H), 2.03 (m, 1H), 1.75-1.20 (m, 3H), 1.37 (s, 3H), 1.00 (s, 3H), 0.87 (s, 9H), 0.64 (s., 3H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm): 194.9, 181.2, 153.3, 118.1, 77.7, 55.4, 54.7, 54.2, 39.2, 36.7, 31.3, 28.0, 25.7, 23.6, 21.7, 18.0, -3.7, -4.9; MS: 309 ($M^{+\cdot}$-57, 19), 281 (4), 265 (8), 167 (11), 149 (35), 129 (16), 75 (100), 57 (28). Exact mass calcd. for $C_{20}H_{35}O_4Si$ (M+1): 367.2305; found (CI, NH_3): 367.2306.

Preparation and Standardization of the Dimethyldioxirane Solutions

Dimethyldioxirane solutions in acetone were prepared according to the small scale litterature procedure [2] with only a slight modification. In general, the preparation was done using a 1L flask and all of the reagents were scaled up four fold. In addition to a receiving flask (100 mL) cooled to -78°C, a dry ice-acetone trap was attached to the end of the vacuum outlet of the receiving adapter and the vacuum line attached to the outlet of the cold trap. In this way, relatively large volumes (ie: 30-40 mL) of dimethyldioxirane

solution (ca. 0.06-0.10 mmol / mL) could be conveniently obtained for large scale enolate oxidations.

Dimethyldioxirane solutions prepared as mentioned above were standardized using a slight modification of the thioanisole procedure [2]. The dimethyldioxirane solution (1.00 mL) was mixed with a stirred solution of phenyl methyl sulfide (0.4 mL of 0.55M solution in acetone). After 15 min., the solvent was removed carefully at 0°C *in vacuo*, and the residue redissolved in acetone-d6 and the ^{1}H NMR spectrum examined.

General procedure for enolate oxidation with dimethyldioxirane (LDA used as base)

To a stirring solution of diisopropylamine (0.087 mL; 0.62 mmol; 1.5 equiv.) in 2.0 mL of dry THF under argon at -78°C was added n-butyllithium solution (0.32 mL of 1.7 M solution in pentane; 1.3 equiv.) dropwise. After 10 min., a solution of α-tetralone 4.10a (40.0 mg; 0.27 mmol) in 0.5 mL of dry THF was added dropwise (cannula), washing the transfer flask twice with 1.0 mL portions of dry THF to ensure complete transfer. After allowing the enolate to generate (1h), the mixture was transferred dropwise (cannula) to a second flask containing anhydrous dimethyldioxirane solution in acetone (5.80 mL of 0.062 M solution; 1.4 equiv.) also cooled to -78°C. After allowing to stir for 10 min., the reaction mixture was quenched with 0.3 mL of pH 7 buffer solution and then allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue taken into CH_2Cl_2 (10 mL) and washed with 5 mL of water. The aqueous phase was further extracted twice with 5 mL portions of CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a clear oily residue. Flash chromatography on silica gel (eluent: 35% ether / hexanes) gave 36.4 mg (82%) of 2-hydroxy-α-tetralone 4.10b as a slightly yellow colored oil which darkens on exposure to air. A small amount (3.2 mg, 8%) of α-tetralone 4.10a was also recovered.

4.10b had IR (film, cm^{-1}): 3407, 1686; ^1H NMR ($CDCl_3$, ppm): 8.06-7.24 (m, 4H), 4.38 (dd, J = 13.6, 5.4 Hz, 1H), 3.91 (s, exch. D_2O, 1H), 3.24-3.95 (m, 2H), 2.59-2.46 (m, 1H), 2.14-1.92 (m, 1H); MS: 162 ($M^{+\cdot}$, 50), 144 (16), 130 (26), 118 (100), 90 (48), 77 (10). Exact mass calcd. for $C_{10}H_{11}O_2$ (M+1): 163.0759; found (CI, NH_3): 163.0759.

α-hydroxycamphor (4.11b)

The reaction was carried out as mentioned above using camphor 4.11a (60 mg; 0.394 mg) and dimethyldioxirane (9.70 mL of 0.053 M solution; 1.3 equiv.). Flash chromatography on silica gel (eluent: 40% ether / hexanes) gave 49 mg (74%) of the volatile α-hydroxy derivative 4.11b as a mixture of diastereomers (exo : endo = 2.2:1). A significant quantity of camphor 4.11a (11 mg, 18%) was also recovered. IR and ^1H NMR data were in agreement with the reported values [3].

α-hydroxyacetophenone (4.12b)

The reaction was carried out as above using acetophenone 4.12a (50 mg; 0.42 mmol). The crude residue was chromatographed (eluent : 50% ether / hexanes) to give 44 mg (77%) of α-hydroxyacetophenone 4.12b as well as 2.0 mg (4%) of recovered 4.12a. The identity of 4.12b was confirmed by comparison of spectral data with the literature values in Sadtler standard spectra (1H NMR 17161M, IR grating 24179K).

(+)-2-hydroxy-4-cholesten-3-one (4.13b)

The reaction was carried out as above using (+)-4-cholesten-3-one 4.13a (80 mg; 0.21 mmol). The product was isolated by flash chromatography (eluent: 35% ether / hexanes) to

give 50 mg (60%) of 4.13b as a 2 : 1 mixture of diastereomers. The starting enone 4.13a was also recovered (20.5 mg; 26%).

4.13b had ^{1}H NMR ($CDCl_3$, ppm): 5.77 (s, 1H, isomers A,B), 4.29-4.12 (m, 1H, isomers A,B), 3.53 (s, exch. D_2O, 1H, isomer A), 3.47 (s, exch. D_2O, 1H, isomer B), 2.15-2.60 (m, 2H), 0.90-2.10 (m, 27 H), 1.27 (s, 3H, isomer A), 1.16 (s, 3H, isomer B) 0.89 (d, J = 6.6 Hz, 3H, isomers A,B), 0.85 (d, J = 6.6 Hz, 3H isomers A,B), 0.69 (s, 3H, isomers A,B); MS: 400 ($M^{+\cdot}$, 59), 384 (27), 356 (83), 261 (25), 229 (25), 149 (75), 129 (100), 124 (53), 95 (55), 71 (53), 57 (68), 43 (49). Exact mass calcd. for $C_{27}H_{45}O_2$ (M+1): 401.3420; found (CI, NH_3): 401.3421.

cis-3-Methoxy-2,4a,5,6,7,8,8a-heptahydro-2α-hydroxy-8α(_tert_-butyldimethylsiloxy)-2,5,5,8a-tetramethyl-naphthalen-1-one (4.15)

To a stirring solution of the α-diketone 4.3 (295 mg; 0.080 mmol) in dry CH_2Cl_2 (21 mL) under argon at -78°C was added trimethylaluminum solution (1.41 mL of 2.0 M sol. in toluene; 3.5 equiv.) dropwise over a 5 min period. At the end of the addition, the mixture was allowed to stir for 20 min. and then quenched with 1.0 mL of pH 7 buffer solution and allowed to warm up to room temperature. The mixture was diluted with CH_2Cl_2 and washed once with water. The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (eluent: 14% ethyl acetate / hexanes) afforded 286 mg (93%) of the addition products 4.15 and 4.16 in a ratio of 2 : 1. After two chromatographic separations, a relatively clean sample of 4.15 could be obtained (contaminated with only about 5 - 10% of 4.16).

The major product 4.15 had IR ($CHCl_3$, cm^{-1}): 3526, 2931, 2854, 1715, 1664, 1473, 1368, 1117; ^{1}H NMR ($CDCl_3$, ppm): 4.79 (d, J = 6.7 Hz, 1H), 3.64 (s, 3H), 3.56 (s, exch. D_2O, 1H), 3.29 (dd, J = 11.7, 4.1 Hz, 1H), 2.07 (m, 1H), 1.94 (d, J = 6.7 Hz, 1H), 1.18-1.62 (m, H), 1.41 (s, 3H), 0.87 (s, 12H), 0.59 (s, 3H), 0.08 (s, 3H), 0.02 (s,

3H); MS: 367 (1), 325 (13), 307 (9), 293 (100), 233 (23), 81 (60), 75 (75), 73(51), 55 (42). Exact mass calcd. for $C_{21}H_{39}O_4Si$ (M+1): 383.2618; found (CI, NH_3): 383.2619.

The minor isomer 4.16 had ^1H NMR ($CDCl_3$, ppm): 5.69 (d, J = 2.9 Hz, 1H), 3.90 (t, J = 2.2 Hz, 1H), 3.65 (s, exch. D_2O, 1H), 3.57 (s, 3H), 2.18 (s, 1H), 2.10 (m, 1H), 1.05-1.95 (m,3 H), 1.24 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 0.79 (s, 9H) -0.02 (s, 6H).

trans-3-Methoxy-1,2,4a,5,6,7,8,8a-octahydro-2,8α-dihydroxy-1β(1'-hexynyl)-2,5,5,8aα-tetramethyl-naphthalen-1-ol (4.17)

To a stirring solution of 1-hexyne (1.05 mL; 9.1 mmol; 13 equiv.) in 16 mL of dry THF under argon at -78°C was added n-butyllithium solution (4.94 mL of 1.7M sol. in pentane; 8.4 mmol; 12 equiv.) dropwise. After 30 min., a solution of the ketone 4.15 (264 mg; 0.69 mmol) in 4.0 mL of dry THF was added dropwise (cannula), washing the transfer flask twice with 2mL portions of dry THF. The mixture was then allowed to warm up to room temperature for about 30 min. and then warmed to reflux temperature. After 4h at reflux, the mixture was allowed to cool down for 30 min. and then quenched with 1.5 mL of pH 7 buffer solution and the solvent removed *in vacuo*. The residue was taken into CH_2Cl_2 and washed once with 10% Na_2CO_3 solution. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 50% ether / hexanes) gave 194 mg (80%) of the triol 4.17 as a single isomer (mp. 99-101°C).

4.17 had IR ($CHCl_3$, cm^{-1}): 3588, 2961, 2215, 1672, 1100, 1011; ^1H NMR ($CDCl_3$, ppm): 4.80 (s, 1H), 4.49 (ddd, J = 11.1, 4.8, 2 2 Hz, 1H), 3.57 (s, 3H), 2.76 (d, J = 2.2 Hz, exch. D_2O, 1H), 2.29 (t, J = 7.0 Hz, 2H), 2.23 (s, 1H), 2.13 (s, exch. D_2O, 1H), 2.00 (s, exch. D_2O, 1H), 1.19-1.80 (m, 10H), 1.55 (s, 3H), 1.51 (s, 3H), 1.19 (s, 3H), 1.07 (s, 3H), 0.91 (t, J = Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm): 153.1, 96.6, 90.5, 81.1,

80.5, 73.3, 69.6, 54.3, 47.7, 46.7, 34.8, 34.7, 32.2, 30.4, 30.1, 26.7, 23.2, 22.0, 19.0, 18.4, 13.4; MS: 350 ($M^{+\cdot}$,10), 332 (7), 289 (11), 233 (49), 216 (45), 195 (46), 165 (46), 152 (100), 126 (55), 109 (43), 99 (72), 81 (83), 55 (39), 43 (69). Exact mass calcd. for $C_{21}H_{33}O_3$ ($M+H^+-H_2O$): 333.2430; found (CI, NH_3): 333.2428.

trans-3-Methoxy-1,2,4a,5,6,7,8,8a-octahydro-2-hydroxy-8α-acetoxy-1-β(1'-hexynyl)-2,5,5,8aα-tetramethyl-naphthalen-1-ol (4.21)

To a stirring solution of the triol 4.17 (100 mg; 0.28 mmol) in 5.0 mL of dry CH_2Cl_2 under argon at room temperature was added pyridine (0.069 mL; 0.86 mmol; 3.0 equiv) followed by acetic anhydride (0.081ml; 0.86 mmol; 3.0 equiv.). A catalytic amount of 4-dimethylamino pyridine (DMAP, approx. 0.25 equiv.). The reaction mixture was then warmed to reflux and after 24h, another 3 equiv. of pyridine and acetic anhydride were added and reflux continued for a further 6 days. At this point, the reaction mixture was allowed to cool down to room temperature, diluted with 10 mL of CH_2Cl_2 and washed with 5 mL of 10% Na_2CO_3 solution. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 52% ether / hexanes) afforded 99 mg (89%) of the acetate 4.21 (mp. 102-104°C).

4.21 had IR ($CHCl_3$, cm^{-1}): 3611, 3008, 2937, 2226, 1717, 1674, 1371, 1257, 1216, 1000; ^1H NMR ($CDCl_3$, ppm): 5.55 (dd, J = 10.8, 5.7 Hz, 1H), 4.76 (d, J = 1.6 Hz, 1H), 3.55 (s, 3H), 2.31 (d, J = 1.6 Hz, 1H), 2.28 (t, J = 6.7 Hz, 2H), 2.19 (s, exch. D_2O, 1H), 1.98 (s, 3H), 1.83 - 1.22 (m, 9H), 1.58 (s, 3H), 1.50 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); MS: 392 ($M^{+\cdot}$, 2), 374 (6), 332 (4), 289 (27), 205 (23), 109 (29), 81 (31), 69 (22), 55 (22), 43 (100). Exact mass calcd. for $C_{23}H_{35}O_5$ ($M+H^+-H_2O$): 375.2535; found (CI, NH_3): 375.2534.

trans-3-Methoxy-1,2,3,4,4a,5,6,7,8,8a-decahydro-1α,8α-dihydroxy-2,3-epoxy-1β(1'-hexynyl)-2,5,5,8aα-tetramethyl-naphthalen-4-ol (4.25)

To a stirring solution of the acetate 4.21 (336 mg; 0.86 mmol) in 65 mL of dry CH_2Cl_2 under argon at room temperature was added chilled (ie: to approx. -20°C) dimethyldioxirane solution (14.8 mL of 0.087 M solution; 1.5 equiv.) rapidly. After 1h, the solvent was removed *in vacuo* affording 353 mg (100%) of the oily epoxy ether 4.25 which appeared to be quite pure by ^1H NMR.

4.25 had IR ($CHCl_3$, cm^{-1}): 3579, 3453, 3003, 2960, 2236, 1707, 1458, 1376, 1263, 1003; ^1H NMR ($CDCl_3$, ppm): 6.02 (t, J = 9.0 Hz, 1H), 4.22 (d, J = 5.7 Hz, 1H), 3.72 (s, exch. D_2O, 1H), 3.57 (s, 3H), 2.23 (t, J = 6.7 Hz, 2H), 2.01 (s, 3H), 1.85-1.30 (m, 10H), 1.55 (s, 3), 1.37 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 0.90 (t, J = 6.9 Hz, 3H); MS: 408 ($M^{+\cdot}$, 15), 348 (11), 331 (9), 259 (42), 217 (27), 203 (25), 189 (49), 165 (29), 123 (34), 109 (47), 81 (31), 43 (100).

trans-3-Methoxy-1,2,3,4a,5,6,7,8,8a-nonahydro-1-hydroxy-8α-acetoxy-2,3-epoxy-1β(1'-hexynyl)-2,5,5,8aα-tetramethyl-naphthalen-4-one (4.26)

To a stirring solution of the epoxy ether 4.25 (350 mg; 0.86 mmol) in dry CH_2Cl_2 (28 mL) under argon at room temperature was added sodium acetate (246 mg; 3.00 mmol; 3.5 equiv.) in one portion. Pyridinium chlorochromate (PCC, 554 mg; 2.57 mmol; 3.0 equiv.) was then added and the mixture stirred for 24h. Another 1.0 equiv. of PCC was then added and the mixture allowed to stir for a further 2h at r.t.. At this point, the reaction mixture was diluted with 100 mL of diethyl ether and the resulting suspension filtered through a bed of celite. Concentration of the filtrate gave a crude brown oily mass that was subjected to flash chromatography on silica gel (eluent: 23% ether / hexanes) to give 227

mg (65%) of the epoxy ketone 4.26 as a gum. Further elution of the column with 35% ether / hexanes afforded 26 mg (7%) of recovered 4.25 .

4.26 had IR ($CHCl_3$, cm^{-1}): 3618, 2949, 1737, 1711, 1270, 1260, 1003; ^1H NMR ($CDCl_3$, ppm): 6.09 (m, 1H), 3.82 (s, exch D_2O, 1H), 3.42 (s, 3H), 2.39 (s, 1H), 2.27 (t, J = 6.7 Hz, 2H), 2.03 (s, 3H), 1.98-1.19 (m, 8H), 1.50 (s, 3H), 1.49 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 0.91 (t, J = 7.0 Hz, 3H); MS: 406 ($M^{+\cdot}$, 7), 363 (25), 346 (89), 328 (28), 303 (25), 287 (38), 243 (43), 223 (73), 189 (100), 149 (71), 123 (52), 109 (49), 81 (38), 43 (61). Exact mass calcd. for $C_{23}H_{35}O_6$ (M+1): 407.2434; found (CI, NH_3): 407.2435.

1,2,5,6,7,8,8a-heptahydro-1,2,4-trihydroxy-8α-acetoxy-1β(1'-hexynyl)-2,5,5,8aα-tetramethyl-naphthalen-3-one (4.27)

To a stirring solution of the epoxy-ketone 4.26 (113 mg; 0.028 mmol) in dry CH_2Cl_2 (2.3 mL) under argon at -78°C was added triethylamine (0.12 mL; 0.83 mmol; 3.0 equiv.) followed by dimethylboron bromide (2.78 mL of 0.30 M sol. in CH_2Cl_2; 0.83 mmol; 3.0 equiv.) dropwise. The mixture was then allowed to warm to 0°C and another 4.0 equiv. of dimethylboron bromide (3.71 mL of 0.30 M solution in CH_2Cl_2) was added dropwise over a 10 min. period. At the end of the addition, the mixture was quenched with 2.0 mL of 10% $NaHCO_3$ solution, allowed to warm to room temperature for 10 min. and diluted with 10 mL of CH_2Cl_2. The phases were separated and the organic layer washed once with 5 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel (eluent: 60% ether / hexanes) afforded 90 mg (83%) of the α-diketone 4.27 (mp. 110-112°C).

4.27 had ^1H NMR ($CDCl_3$, ppm): 6.34 (s, exch. D_2O, 1H), 5.61 (t, J = 7.9 Hz, 1H), 3.24 (s, exch. D_2O, 1H), 3.06 (s, exch. D_2O, 1H), 2.56 - 2.12 (m, 2H), 2.11 (t, J = 6.4 Hz, 2H), 2.08 (s, 3H), 2.06-1.91 (m, 2H), 1.66-1.20 (m, 4H), 1.55 (s, 3H), 1.45 (s,

3H), 1.36 (s, 3H), 1.32 (s, 3H), 0.84 (t, J = 6.7 Hz, 3H); MS: 332 (8), 314 (2), 289 (11), 223 (29), 154 (34), 150 (72), 123 (41), 43 (100). Exact mass calcd. for $C_{22}H_{33}O_6$ (M+1): 393.2277; found (CI, NH_3): 393.2276.

2,5,6,7,8,8a-Hexahydro-4-hydroxy-8a(*tert*-butyldimethylsiloxy)-2,2,5,5,8a-pentamethyl-naphthalen-1,3-dione (4.23)

To a stirring solution of the enol ether 3.3 (35 mg; 0.092 mmol) in dry pyridine under nitrogen at room temperature was added osmium tetroxide (28 mg; 0.11 mmol; 1.2 equiv.) in one portion. The mixture was then warmed to reflux for 5h. At this point, the reaction mixture was allowed to cool down to room temperature and a suspension of 200 mg of magnesium silicate and 200 mg of sodium thiosulphate in 3 mL of water was added and the resulting suspension filtered and extracted four times with 5 mL portions of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 4% ether / hexanes) afforded 8.3 mg (24%) of the α-diketone 4.23 as an oil as well as 17.3 mg (49%) of unreacted enol ether 3.3.

4.23 had IR ($CHCl_3$, cm^{-1}): 3418, 2957, 2931, 1712, 1657, 1620, 1471, 1087, 838; ^1H NMR ($CDCl_3$, ppm): 6.60 (s, exch. D_2O, 1H), 4.46 (t, J = 3.2 Hz, 1H), 1.42-2.10 (m, 4H), 1,48 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 0.79 (s, 9H), 0.07 (s, 3H), -0.02 (s, 3H); MS: 380 (7), 337 (7), 323 (78), 295 (16), 253 (75), 231 (97), 203 (67), 171 (63), 161 (94), 133 (39), 75 (100), 73 (82). Exact mass calcd. for $C_{21}H_{37}O_4Si$ (M+1): 381.2461; found (CI, NH_3): 381.2462.

1,2,5,6,7,8,8a-heptahydro-1α,2,4-trihydroxy-1α-acetoxy-1(*cis*-1',2'-hexenyl)-2,5,5,8aα–tetramethyl-naphthalen-3-one (4.28)

To a stirred solution of the α-diketone 4.27 (22.5 mg ; 0.057 mmol) in 1.0 mL of absolute ethanol under hydrogen (1 atmosphere) at room temperature was added a catalytic amount of palladium on carbon (5.6 mg of 10% by weight Pd/C). After 1h, the mixture was diluted with 10 mL of CH_2Cl_2 and filtered through a bed of celite to remove the catalyst. The filtrate was concentrated *in vacuo* to give 23.4 mg of crude oily residue. Flash chromatography on silica gel (eluent: 25% ethyl acetate / hexanes) afforded the oily E and Z allylic alcohols 4.29 and 4.28 in a ratio of 1 : 12 in 98% yield.

The major Z isomer 4.28 had IR ($CHCl_3$, cm^{-1}): 3566, 3453, 2960, 1749, 1674, 1654, 1374, 1013; ^1H NMR ($CDCl_3$, ppm): 6.36 (s, exch. D_2O, 1H), 5.68 (m, 1H), 5.28 (d, J = 1.4 Hz, 1H), 5.24 (d, J = 7.3 Hz, 1H), 3.07 (s, exch. D_2O, 1H), 2.65 (s, exch. D_2O, 1H), 2.64-2.23 (m, 3H), 2.07 (s, 3H), 1.90-2.04 (m, 1H), 1.58 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.70-1.19 (m, 6H), 0.87 (m, 1H); MS: 334 (6), 291 (5), 223 (43), 156 (22), 150 (29), 123 (82), 111 (53), 101 (45), 55 (52), 43 (100). Exact mass calcd. for $C_{22}H_{35}O_6$ (M+1): 395.2434; found (CI, NH_3): 395.2435.

The minor E isomer 4.29 had ^1H NMR ($CDCl_3$, ppm): 6.38 (s, exch. D_2O, 1H), 5.95 (m, 1H), 5.49 (d, J = 15.3 Hz, 1H), 5.02 (t, J = 7.6 Hz, 1H), 2.93 (s, exch. D_2O, 1H), 2.47 (s, exch. D_2O, 1H), 2.40 (m, 1H), 2.05 (s, 3H), 2.00-2.08 (m, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.70 - 1.15 (m, 6H), 0.88 (m, 3H); MS: 334 (8), 291 (6), 223 (63), 156 (42), 150 (47), 123 (100), 111 (45), 101 (49), 95 (25), 55 (51), 43 (89). Exact mass calcd. for $C_{22}H_{35}O_6$ (M+1): 395.2434; found (CI, NH_3): 395.2435.

trans-1,2,3,4,4a,5,6,7,8,8a-decahydro-1β,2α,3β,4β-tetrahydroxy-8-acetoxy-1-(_cis_-1',2'-hexenyl)-2,5,5,8aβ-tetramethyl-naphthalene (4.30)

To a stirred solution of Z 4.28 (16.6 mg; 0.042 mmol) in 1.0 mL of dry THF under argon at room temperature was added t-butylamine borane complex (14.6 mg; 4.0 equiv.) and the mixture warmed to reflux. After 24h, the mixture was allowed to cool to r.t. and the solvent removed *in vacuo*. The residue was taken into 10 mL of CH_2Cl_2 and washed with 3 mL of 10% sodium bisulphate solution. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 75% ether / hexanes) afforded 8.7 mg (52%) of the tetrol 4.30. Recrystallization of a small sample from hexanes gave 4.30 as fine white plates (mp. 146-148°C). Crystals suitable for X-ray analysis were obtained by slow evaporation (at -20°C) of a solution of 4.30 in acetone / hexanes (1 : 4).

4.30 had IR ($CHCL_3$, cm^{-1}): 3585, 3010, 2960, 1743, 1366, 1234, 1105, 1029; ^1H NMR ($CDCl_3$, ppm): 5.77 (m, 1H), 5.52 (d, J = 12.4 Hz, 1H), 4.92 (dd, J = 10.5, 5.1 Hz, 1H), 4.37 (m, 1H), 3.40 (d, J = 3.6 Hz, 1H), 2.62 (s, exch. D_2O, 1H), 2.60 - 2.27 (m, 2H), 2.25 (s, exch. D_2O, 1H), 2.11 (s, exch. D_2O, 1H), 2.02 (s, 3H), 1.90 - 1.20 (m, 9H), 1.63 (bs, exch. D_2O, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.28 (s, 3H), 1.02 (s, 3H), 0.88 (m, 3H); MS: 380 ($M^{+\cdot}$, 6), 323 (9), 215 (35), 155 (34), 152 (31), 123 (31), 111 (100), 95 (33), 81 (29), 69 (26), 55 (49), 43 (7). Exact mass calcd. for $C_{22}H_{37}O_5$ (M+1): 381.2641; found (CI, NH_3): 381.2641.

Acetylide addition on the diketone 4.3

To a stirring solution of 1-hexyne (1.70 mL; 14.8 mmol) in dry toluene (50 mL) under argon at -78°C was added n-butyllithium solution (6.2 mL of 2.0 mmol/mL solution in pentane) dropwise. The reaction mixture gradually thickened to a gelatinous consistancy and consequently stirring became difficult. The cooling bath was removed and the mixture

allowed to warm gradually to room temperature. After approximately 1/2h most of the acetylide had dissolved although the solution remained relatively viscuous. This solution was added dropwise (cannula) to a stirring solution of the diketone 4.3 (300 mg; 0.82 mmol) in 30 mL of dry toluene under argon at -78°C. At the end of the addition (about 20 min.), the cooling bath was replaced with an ice bath (0°C) and the mixture stirred at this temperature for an additional 15 min. and then quenched by dropwise addition of 5.0 mL of pH 7 buffer solution. The solvent was removed *in vacuo* and the residue taken into 10 mL of CH_2Cl_2 and washed once with 3 mL of water followed by 3 mL of brine solution. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. ^1H NMR of the crude reaction mixture revealed a 1:1 mixture of the two regioisomers as determined from integration of their enol ether proton signals. Flash chromatography of the crude residue on silica gel (eluent: 8% ethyl acetate / hexanes) provided 154 mg (42%) of the adduct 5.1 as a gum. Further elution of the column with 25% ethyl acetate / hexanes provided 168 mg (46%) of 5.2 as an oil.

5.2 had IR ($CHCl_3$, cm^{-1}): 2960, 2936, 1729, 1662, 1463, 1116, 1048, 838; ^1H NMR ($CDCl_3$, ppm): 4.85 (d, J = 6.6 Hz, 1H), 4.06 (s, exch. D_2O, 1H), 3.69 (s. 3H), 3.31 (dd, J = 11.4, 3.8 Hz, 1H), 2.18 (t, J = 6.8 Hz, 2H), 2.02 - 2.20 (m, 1H), 1.99 (d, J = 6.6 Hz, 1H), 1.57 (s, 3H), 1.19 - 1.55 (m, 7H), 0.88 (s, 12H), 0.85 (obstructed t, J = 8.0 Hz, 3H), 0.55 (s, 3H), 0.09 (s, 3H), 0.04 (s, 3H); MS: 448 ($M^{+\cdot}$, 2), 391 (23), 359 (100), 299 (34), 109 (29), 81 (34), 75 (67), 73 (61). Exact mass calcd. for $C_{26}H_{45}O_4Si$ (M+1): 449.3087; found (CI, NH_3): 449.3087.

5.1 had IR ($CHCl_3$, cm-1): 3481, 2950, 2930, 2856, 2226, 1702, 1642, 1144, 1076, 1064, 1005, 842; ^1H NMR ($CDCl_3$, ppm): 5.75 (d, J = 2.8 Hz, 1H), 4.06 (s, exch. D_2O, 1H), 3.90 (t, J = 2.5 Hz, 1H), 3.58 (s, 3H), 2.44 (s, 3H), 2.16 (t, J = 6.6 Hz, 2H), 1.00 - 1.90 (m, 8H), 1.39 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 0.86 (t, J = 6.9 Hz, 3H), 0.77 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); MS: 448 ($M^{+\cdot}$, 1), 391 (19), 359 (100), 299 (50),

109 (28), 99 (33), 81 (66), 75 (90), 73 (52). Exact mass calcd. for $C_{26}H_{45}O_4Si$ (M+1): 449.3087; found (CI, NH_3): 449.3087.

Cis-1,2,4a,5,6,7,8,8a-octahydro-1a,2a-dihydroxy-3-methoxy-8a-(_tert_-butyldimethylsiloxy)-2-(1',2'-hexynyl)-1,5,5,8a-tetramethyl-[4H]-naphthalene (5.4)

To a stirring solution of the of the ketone 5.2 (20 mg; 0.045 mmol) in dry hexanes (2.0 mL) under argon at -15°C, was added methyllithium solution (0.69 mL of 1.3 mmol / mL solution in diethyl ether; 20 equiv.) dropwise over a 10 min. period. After 3h, the mixture was quenched with 1.0 mL of pH 7 buffer solution and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue taken into CH_2Cl_2 (10 mL) and washed with 2 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 20% ether / hexanes) afforded 11 mg (52%) of the diol 5.4 along with 4 mg (20%) of recovered 5.2.

5.4 had IR ($CHCl_3$, cm^{-1}): 3483, 2960, 2228, 1682, 1464, 1257, 1097, 1051; ^1H NMR ($CDCl_3$, ppm): 4.73 (d, J = 4.8 Hz, 1H), 4.00 (s, exch. D_2O, 1H), 3.64 (obstructed dd, 1H), 3.63 (s, 3H), 3.44 (s, exch. D_2O, 1H), 2.20 (t, J = 6.6 Hz, 2H), 2.23 - 2.02 (m, 1H), 1.83 (d, J = 4.8 Hz, 1H), 1.67 - 1.16 (m, H), 1.59 (s, 3H), 1.23 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.91 (s, 9H), 0.87 (t, J = 7.4 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); MS: 464 ($M^{+\cdot}$, 17), 389 (13), 359 (10), 332 (64), 271 (41), 225 (51), 215 (60), 180 (100), 101 (47), 81 (53), 75 (84), 73 (95).

Cis-1,2,4a,5,6,7,8,8a-octahydro-1α,2α-dihydroxy-3-methoxy-8α-(_tert_-butyldimethylsiloxy)-1-(1',2',-hexynyl)-2,5,5,8a-tetramethyl-[4H]-naphthalene (5.3)

To a stirring solution of the enone 5.1 (315 mg; 0.70 mmol) in 20 mL of dry hexanes under argon at -15°C (CO_2 / ethylene glycol bath) was added methyllithium solution (10.8 mL of 1.3 mmol / mL solution; 20 Equiv.) dropwise over a 15 min. period. After 90 min., the reaction mixture was quenched with 2 mL of pH 7 buffer solution and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue taken into 15 mL of CH_2Cl_2 and washed with 5 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 10% ethyl acetate / hexanes) provided 250 mg (77%) of the diol 5.3 as a viscous oil.

5.3 had IR ($CHCl_3$, cm^{-1}): 3371, 3018, 2931, 2231, 1670, 1466, 1391, 1363, 1260, 1074, 1049; ^1H NMR ($CDCl_3$, ppm): 5.86 (bs, exch. D_2O, 1H), 4.62 (d, J = 4.1 Hz, 1H), 4.10 (bs, exch. D_2O, 1H), 4.04 (d, J = 3.5 Hz, 1H), 3.56 (s, 3H), 2.22 (m, 2H), 1.96 (d, J = 4.0 Hz, 1H), 1.10 - 1.90 (m, 8H), 1.13 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H), 0.93 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H), 0.20 (s, 3H), 0.14 (s, 3H); MS: 464 ($M^{+\cdot}$, 5), 449 (8), 433 (22), 389 (33), 332 (17), 301 (21), 289 (62), 271 (24), 258(25), 217 (43), 81(54), 75(100), 73 (78). Exact mass calcd. for $C_{27}H_{47}O_3Si$ ($M+H^+-H_2O$): 447.3294; found (CI, NH_3): 447.3295.

Cis-1,2,4a,5,6,7,8,8a-octahydro-1α,2α,8α-trihydroxy-3-methoxy-1-(1',2',-hexynyl)-2,5,5,8a-tetramethyl-[4H]-naphthalene (4.18)

To a stirring solution of the diol 5.3 (26 mg; 0.06 mmol) in 1.0 mL of THF at r.t was added TBAF solution (0.17 mL of 1.0 mmol / mL solution; 3 equiv.) dropwise. After 15 min., the solvent was removed *in vacuo* and the residue taken into 15 mL of CH_2Cl_2 and

washed with 5 mL of water. The aqueous layer was further extracted with 5 mL of CH_2Cl_2 and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 35% ethyl acetate / hexanes) provided 19 mg (96%) of the crystalline triol 4.18 mp. 120 - 122°C. Crystals suitable for X-ray analysis were obtained by slow evaporation (at -20°C) of a solution of 4.18 in acetone : hexanes (1 : 4).

4.18 had IR ($CHCl_3$, cm-1): 3490, 3227, 2961, 2936, 2231, 1654, 1456, 1389, 1099, 1026; ^1H NMR ($CDCl_3$, ppm): 6.43 (bs, exch. D_2O, 1H), 4.86 (d, J = 1.8 Hz, 1H), 3.94 (s, exch D_2O, 1H), 3.83 (bm, 1H), 3.56 (s, 3H), 2.40 (bs, exch. D_2O, 1H), 2.29 (s, 1H), 2.20 (t, J = 6.8 Hz, 2H), 2.02 - 2.13 (m, 1H), 1.25 - 1.70 (m, 7H), 1.53 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm): 157.2, 97.2, 86.0, 81.4, 78.0, 71.5, 70.6, 54.6, 46.4, 46.1, 34.2, 32.3, 30.5, 29.4, 27.2, 25.5, 23.2, 22.0, 18.4, 13.5; MS: 350 ($M^{+\cdot}$, 1), 332 (11), 209 (21), 167 (24), 149 (100), 123 (29), 81 (32), 55 (28), 43 (64). Exact mass calcd. for $C_{21}H_{33}O_3$ ($M+H^+-H_2O$): 333.2430; found (CI, NH_3): 333.2428.

Cis-1,2,3,4,4a,5,6,7,8,8a-decahydro-1α,2α-dihydroxy-3,4-(β-epoxy)-3-methoxy-8α-(_tert_-butyldimethylsiloxy)-1-(1',2',-hexynyl)-2,5,5,8a-tetramethyl-naphthalene (5.7)

To a stirred solution of the enol ether 5.3 (240 mg; 0.52 mmol) in 12 mL of dry CH_2Cl_2 under argon at room temperature was added a chilled* (to approximately -20°C) solution of dimethyldioxirane in acetone (12.9 mL of 0.06M solution; 1.5 equiv.) rapidly. After 1h, the solvent was simply evaporated *in vacuo* to provide 250 mg (100%) of oily epoxy ether 5.7 which appeared to be quite pure by ^1H NMR (>90%), although two well separated spots were observed on tlc. We believe that one of these spots correspond to the Payne rearrangement product of 5.7 which is formed due to the slightly acidic nature of the silica gel. The product was used without further purification for the subsequent oxidation step.

* Dimethyldioxirane (DD) solutions in acetone are unstable at r.t. and therefore were stored at approximately -20°C. In general, the chilled DD solutions were handled rapidly to avoid decomposition.

5.7 had ^{1}H NMR ($CDCl_3$, ppm): 5.81 (s, exch. D_2O, 1H), 4.47 (s, exch. D_2O, 1H), 3.94 (d, J = 3.8 Hz, 1H), 3.51 (s, 1H), 3.42 (s, 3H), 2.28 - 2.15 (m, 2H), 1.90 - 1.34 (m, 9H), 1.56 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 0.94 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H), 0.20 (s, 3H), 0.16 (s, 3H); MS: 480 ($M^{+\cdot}$, 2), 419 (13), 405 (24), 391 (15), 387 (16), 373 (14), 287 (14), 281 (16), 123 (46), 109 (38), 81 (42), 75 (100), 73 (89), 43 (43). Exact mass calcd. for $C_{27}H_{49}O_5Si$ (M+1): 481.3349; found (CI, NH_3): 481.3347.

Cis-1,2,3,4a,5,6,7,8,8a-nonahydro-1α-hydroxy-2,3-(α-epoxy)-8α-(_tert_-butyldimethylsiloxy)-1-(1',2'-hexynyl)-2,5,5,8a-tetramethyl-naphthalen-4-one (5.8)

To a stirred solution of dry DMSO (0.024 mL; 0.33 mmol) in dry CH_2Cl_2 (1.0 mL) under argon at -78°C was added oxalyl chloride (0.022 mL; 0.25 mmol) dropwise. After 15 min. a solution of the epoxy ether 5.7 (40 mg; 0.083 mmol) in 0.5 mL of dry CH_2Cl_2 was added dropwise (cannula), washing the transfer flask twice with 0.25 mL portions of dry CH_2Cl_2. After 45 min., triethylamine (0.069 mL; 0.50 mmol) was added dropwise, the cooling bath removed and the mixture allowed to warm up to room temperature over a 30 min period. At this point, the solvent was removed *in vacuo* and the solid residue washed and filtered with 10 mL of distilled hexanes. The filtrate was washed once with 5 mL of water to remove remaining DMSO, dried ($MgSO_4$) and concentrated *in vacuo* to give 40 mg (100%) of crude epoxy ketone (judged to be >60% pure by ^{1}H NMR) 5.8 which was used for subsequent reactions without further purification.

Crude 5.8 had IR (film, cm^{-1}): 3569, 2938, 1728, 1465, 1389, 1247, 1095; ^1H NMR ($CDCl_3$, ppm): 4.10 (dd, J = 6.8, 1.4 Hz, 1H), 3.44 (s, 3H), 3.43 (s, exch. D_2O, 1H), 2.37 (s, 1H), 2.30 (t, J = 6.7 Hz, 2H), 2.20 - 1.70 (m, 2H), 1.57 - 1.10 (m, 6H), 1.35 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); MS: 478 ($M^{+\cdot}$, 6), 421 (34), 389 (11), 361 (14), 329 (21), 287 (30), 247 (23), 189 (44), 123 (23), 81 (34), 75 (83), 73 (100), 43 (41).

1,2,5,6,7,8,8a-heptahydro-1α,2α,4-trihydroxy-8α-(*tert*-butyldimethylsiloxy)-1β(1'-hexynyl)-2,5,5,8aβ-tetramethyl-naphthalen-3-one (5.9)

To a stirred solution of the epoxyketone (10 mg; 0.0221 mmol) 5.8 in 0.8 mL of dry diisopropyl ether under argon at -84°C was added triethylamine (0.028 mL of 0.75M solution in dry CH_2Cl_2; 1.0 equiv.) dropwise followed by dimethylboron bromide (0.084 mL of 0.75M solution in dry CH_2Cl_2; 3.0 equiv.). At the end of the addition, the cooling bath was replaced with an ice bath (0°C) and the mixture allowed to stir at this temperature for 20 min.. At this point, the resulting lemon yellow colored solution was quenched with 0.2 mL of saturated $NaHCO_3$ solution, allowed to warm to room temperature for 10 min., diluted with 10 mL of diethyl ether and washed with 3.0 mL of 10% $NaHSO_4$ solution (to remove the triethylamine). If the triethylamine is not removed at this stage, a considerable quantity of the presumed tautomeric product 5.10 may be observed in the crude ^1H NMR spectrum. The ether layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oily residue. Tlc of the crude residue revealed only 5.9 and none of the presumed keto tautomer 5.10 could be detected at this stage. Flash chromatography on silica gel (eluent = 25% Et_2O / hexanes) provided 3.3 mg of impure 5.10 followed by 3.4 mg (35%) of the enol tautomer 5.9.

5.9 had ^{1}H NMR ($CDCl_3$, ppm): 6.77 (s, slow exch. D_2O, 1H), 6.61 (s, exch. D_2O, 1H), 4.36 (t, J = 3.2 Hz, 1H), 3.86 (s, exch. D_2O, 1H), 2.35 - 2.10 (m, 3H), 1.51 (d, J = 1.1 Hz, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.27 (s, 3H), 1.93 - 1.20 (m, 7H), 0.91 (t, J = 8.1 Hz, 3H), 0.91 (s, 9H), 0.24 (s, 3H), 0.91 (s, 3H); MS: 464 ($M^{+\cdot}$, 3), 446 (2), 407 (11), 389 (20), 347 (16), 315 (34), 271 (47), 217 (32), 171 (100), 75 (73), 73 (72); Exact mass calcd. for $C_{26}H_{45}O_5Si$ (M+1): 465.3036, found (CI, NH_3): 465.3037.

Formation of the cyclic orthoformates 5.11

To a stirred solution of the diol 5.9 (3.2 mg; 0.0069 mmol) in dry trimethylorthoformate (0.5 mL) under argon at room temperature was added a trace of para-toluenesulfonic acid (TsOH). After 30 min. the mixture was quenched with 0.1 mL of saturated $NaHCO_3$ solution and the solvent removed *in vacuo*. The residue was taken into 5 mL of CH_2Cl_2 and washed with 1 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give 3.0 mg (90%) of the oily orthoformates 5.11 as a 9 : 1 ratio of diastereomers.

the major isomer of 5.11 had ^{1}H NMR ($CDCl_3$, ppm): 6.37 (s, exch. D_2O, 1H), 5.56 (s, 1H), 4.16 (dd, J = 4.2, 1.3 Hz, 1H), 3.38 (s, 3H), 2.30 (t, J = 6.9 Hz, 2H), 2.27 - 1.91 (m, 2H), 1.74 (s, 3H), 1.63 - 1.20 (m, 6H), 1.42 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 0.91 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H).

***cis*-3-phenylthio-4a,5,6,7,8,8a-hexahydro-8α(*ert*-butyldimethylsiloxy)-2-trimethylsilyl-5,5,8a-trimethyl-(4H)-naphthalen-1-one (6.19)**

To a stirring solution of LDA (0.66 mL of 1.50M solution in THF; 0.99 mmol; 3.0 equiv.) in dry THF (3.0 mL) under argon at -78°C was added trimethylsilyl chloride (0.13 mL; 3.0 equiv.) dropwise followed by a solution of the enone 2.23 (142 mg; 0.33 mmol) dissolved in 1.0 mL of dry THF (cannula), rincing the transfer flask several times with

small portions of dry THF. After 30 min., the mixture was allowed to warm to room temperature and the solvent removed *in vacuo*. The residue was washed with cold dry hexanes and filtered *in vacuo*. The filtrate was concentrated *in vacuo* to give 185 mg of oily residue. Flash chromatography on silica gel (eluent: 2% ethyl acetate / hexanes) afforded 158 mg (97%) of the vinyl silane 6.19 as an oil.

6.19 had IR ($CHCl_3$, cm^{-1}): 2952, 2929, 1636, 1539, 1253, 1078; ^1H NMR ($CDCl_3$, ppm): 7.32-7.47 (m, 5H), 3.91 (bm, 1H), 2.45-2.55 (m, 1H), 2.23 (dd, J = 17.6, 4.7 Hz, 1H), 1.45-1.87 (m, 5H), 1.19 (s, 3H), 0.82 (s, 12H), 0.57 (s, 3H), 0.29 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H); MS: 502 ($M^{+\cdot}$,1), 487 (1), 445 (40), 105 (43), 93 (61), 91 (64), 85 (67), 73 (100), 43 (82). Exact mass calcd. for $C_{28}H_{33}OSSi$ ($M^{+\cdot}$-TBDMS): 445.202; found (EI): 445.204.

Trans-3-phenylthio-4a,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-8β-hydroxy-naphthalen-1β[1H, 4H]-ol 6.20.

To a well stirred solution of 2.7 (250.0 mg; 0.796 mmol) in 10 mL of dry methanol under argon at 0°C was added sodium borohydride (39 mg; 1.03 mmol; 1.3 equiv.) in one portion. After 18h, the mixture was quenched with 1.0 mL of water and the solvent removed *in vacuo*. The residue was taken into 10 mL of CH_2Cl_2 and washed with 5 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a clear semisolid residue. Flash chromatography on silica gel (eluent: 23% ethyl acetate / hexanes) afforded 199 mg (79%) of the diol 6.20.

6.20 had IR ($CHCl_3$, cm^{-1}): 3200-3550 (B), 3007, 2931, 1476, 1086, 1019; ^1H NMR ($CDCl_3$, ppm): 7.26-7.42 (m, 5H), 5.43 (d, J = 1.5 Hz, 1H), 4.20 (bm, 1H), 3.58-3.63 (ddd, J = 10.5, 5.2, 3.2 Hz, 1H), 2.95 (d, J = 3.9 Hz, exch. D_2O, 1H), 2.63 (d, J = 3.2 Hz, exch D_2O, 1H), 2.11-2.18 (m, 2H), 1.25-1.70 (m, 5H), 0.94 (s, 3H), 0.88 (s, 3H),

0.81 (s, 3H); MS: 318 ($M^{+\cdot}$, 3), 300 (5), 209 (71), 191 (58), 109 (96), 69 (89), 43 (100); Exact mass calcd. for $C_{19}H_{26}O_2S$ ($M^{+\cdot}$): 318.165; found (EI): 318.169.

Trans-3-phenylthio-4a,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1β,8β-diacetoxy-[1H, 4H] naphthalene 6.21

To a stirred solution of the diol 6.20 (218 mg; 0.68 mmol) in dry CH_2Cl_2 (8.0 mL) under argon at room temperature was added pyridine (0.33 mL; 4.1 mmol; 6.0 equiv.) followed by acetic anhydride (0.39 mL; 4.1 mmol; 6.0 equiv.). A trace of DMAP was then added and the mixture allowed to stir at room temperature for 49.5h. At this point, the mixture was diluted with 20 mL of CH_2Cl_2 and washed with 10 mL of water. The organic phase was then dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was chromatographed (eluent: 20% ethyl acetate / hexanes) to give the diacetate 6.21 (mp. 104-107°C) in 85% yield.

6.21 had IR ($CHCl_3$, cm^{-1}): 2933, 1736, 1373, 1260, 1026; ^1H NMR ($CDCl_3$, ppm): 7.27-7.38 (m, 5H), 5.32-5.39 (m, 2H), 4.73 (dd, J = 10.7, 5.2 Hz, 1H), 2.13-2.20 (m, 2H), 2.00 (s, 3H), 1.99 (s, 3H), 1.54-1.71 (m, 2H), 1.35-1.53 (m, 3H), 1.08 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H); MS: 402 ($M^{+\cdot}$, 3), 359 (4), 342 (25), 191 (17), 173 (25), 105 (21), 91 (31), 43 (100). Exact mass calcd. for $C_{23}H_{31}O_4S$ (M+1): 403.194; found CI, NH_3): 403.194.

cis-3',4',4a',8a'-Tetrahydro-4',4',8a'-trimethyl-6'-(phenylthio)-spiro[1,3-dioxolane-2.1'(2'H)-naphthalen]-8'(5'H)-one (6.22)

To a stirring solution of 2.6 (1.269g; 4.0 mmol) in 60 mL of benzene were added a catalytic amount of p-toluenesulfonic acid and ethylene glycol (0.50 g; 8.0 mmol). The reaction mixture was refluxed on a Dean-Stark apparatus. After 4h, once again ethylene

glycol (0.50 g; 8.0 mmol) was added and reflux continued for another 4h. At this point, the solvent was removed *in vacuo* and the residue dissolved in 100 mL of ether. The ether extract was washed once with 10 mL of saturated $NaHCO_3$ and the extract dried (Na_2SO_4). The crude viscous mass after evaporation was column chromatographed (eluent: 30% ethyl acetate / hexanes) to give 6.22 in almost quantitative yield.

6.22 had IR (KBr, cm^{-1}): 2950, 1655, 1598; ^1H NMR ($CDCl_3$, ppm): 7.45-7.53 (m, 5H), 5.38 (d, J = 2.1 Hz, 1H), 2.79 (ddd, J = 19.0, 6.3, 2.1 Hz, 1H), 2.42 (dd, J = 19.0, 1.5 Hz, 1H), 2.15 (dd, J = 6.3, 1.5 Hz, 1H), 1.30-1.95 (m, 4H), 1.25 (s, 3H), 0.94 (s, 3H), 0.77 (3, 3H); MS: 358 (4), 176 (11), 99 (100), 86 (48), 77 (18), 67 (32), 55 (26), 41 (41).

cis-3',4',4a',8a'-Tetrahydro-4',4',8a'-trimethyl-6'-(phenylthio)-spiro[1,3-dithiolane-2.1'(2'H)-naphthalen]-8'(5'H)-one 6.23

To a stirring solution of 2.6 (100 mg; 0.32 mmol) and ethanedithiol (0.03 mL; 1.6 mmol; 5 equiv.) in 15 mL of benzene at room temperature was added a catalytic amount of p-toluenesulfonic acid. The mixture was then warmed to reflux (Dean-Stark). After 6 days 18h, the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was taken into 20 mL of CH_2Cl_2 and washed with 5 mL of 10% Na_2CO_3 solution. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 15% ethyl acetate / hexanes) gave 7[illegible] mg (61%) of the thioketal 6.23 as well as 33 mg (33%) of unreacted 2.6.

6.23 had ^1H NMR ($CDCl_3$, ppm): 7.39 - 7.50 (m, 5H), 5.36 (d, J = 1.6 Hz, 1H), 2.81 - 3.26 (m, 2H), 2.36 - 2.52 (m, 2H), 2.19 (d, J = 6.0 Hz, 1H), 1.66 - 1.93 (m, 2H), 1.58 (s, 3H), 1.56 (s, 3H), 1.25 - 1.41 (m, 1H), 0.94 (s, 3H), 0.76 (s, 3H); MS: 390 (15), 362 (6), 331 (6), 253 (12), 217 (17), 131 (100), 118 (53), 91 (12), 77 (14), 67 (23). Exact mass calcd. for $C_{21}H_{27}OS_3$ (M+1): 391.1224; found: 391.1225.

cis-3-Phenylthio-4,4a,5,6,7,8,8a-heptahydro-8α-(2',3'-dimethyl-2'-propen-1-oxy)-5,5,8a-trimethyl-(4H)-naphthalen-1-one (6.24)

To a stirring solution of the alcohol 2.22 (54 mg; 0.17 mmol) in 2.0 mL of CH_2Cl_2 was added pyridine (0.07 mL; 0.8 mmol; 4.0 equiv.) followed by tigloyl chloride (95 mg; 0.81 mmol; 4.0 equiv.). A trace of DMAP was then added and the mixture warmed to reflux. After 5 days 21h, the mixture was allowed to cool to room temperature and diluted with 15 mL of CH_2Cl_2 and washed with 10 mL of 10% Na_2CO_3. The aqueous phase was further extracted three times with 5 mL of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluent: 18% ether / hexanes) afforded 41 mg (61%) of the tiglic ester 6.24 as a viscous oil.

6.24 had IR ($CHCl_3$, cm^{-1}): 2965, 1698, 1654, 1596, 1213, 1137, 1008; ^1H NMR ($CDCl_3$, ppm): 7.39-7.51 (m, 5H), 6.92-7.01 (m, 1H), 5.38 (d, J = 2.2 Hz, 1H), 4.59 (dd, J = 10.6, 4.0 Hz, 1H), 2.77-2.91 (ddd, J = 18.8, 6.2, 2.2 Hz, 1H), 2.50 (dd, J = 18.8, 2.2 Hz, 1H), 1.67-1.90 (m, 3H), 1.43-1.50 (m, 2H), 1.26 (s, 3H), 0.97 (s, 3H), 0.79 (s, 3H); MS: 398 ($M^{+\cdot}$, 12), 315 (6), 299 (8), 176 (100), 148 (23), 123 (26), 83 (67), 67 (58), 55 (70). Exact mass calcd. for $C_{24}H_{31}O_3S$ (M+1): 399.1994; found (CI, NH_3): 399.1992

References

1. Wenkert, E.; Strike, D.P. *J. Am. Chem. Soc.* **1964**, *86*, 2044.
2. Adam, W.; Chan, Y.Y.; Cremer, D.; Gauss, J.; Schentzow, O.; Schindler, M.J. *J. Org. Chem.* **1987**, *52*, 2800.
3. Thoren, S. *Acta Chem. Scand.* **1970**, *No.1*, 24.

Appendices 1 - 4: X-ray Structure Reports

Appendix 1

X-ray Structure Report

For

Compound 2.22 *

* I would like to thank Dr. Jim Britten of the McGill X-ray Facility for this determination.

TABLE OF CONTENTS

INTRODUCTION

The structure of KEV1 was determined and it was in agreement with the proposed structure. The stereochemistry was confirmed. The only surprise was that a single enantiomer was obtained from a racemic sample. The absolute configuration of the molecule in the chosen crystal was determined. R = .049 with no correction for anomolous dispersion. After correction, the two enantiomers gave R values of .054 and .046. The latter was chosen as the final model.

EXPERIMENTAL

DATA COLLECTION

A colorless needle crystal of $C_{19}H_{24}O_2S$ having approximate dimensions of 0.100 X 0.150 X 0.400 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation and a 12KW rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 0 carefully centered reflections in the range $0.00 < 2\theta < 0.00°$ corresponded to an orthorhombic cell with dimensions:

a = 13.522 (2)Å
b = 19.592 (1)Å
c = 6.314 (2)Å
V = 1672.7 (5)Å^3

For Z = 4 and F.W. = 316.46, the calculated density is 1.257 g/cm^3. Based on the systematic absences of:

h00: h ≠ 2n
0k0: k ≠ 2n
00l: l ≠ 2n

and the successful solution and refinement of the structure, the space group was determined to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of 19 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.28° with a take-off angle of 6.0°. Scans of (1.00 + 0.30 tan θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 280.0 mm.

DATA REDUCTION

Of the 2690 reflections which were collected, 1486 were unique (R_{int} = .052). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for Cu Kα is 17.0 cm^{-1}. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.94 to 1.00. The data were corrected for Lorentz and polarization effects.

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods[2]. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement[3] was based on 1937 observed reflections ($I > 2.50\sigma(I)$) and 224 variable parameters and converged (largest parameter shift was 0.06 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \; ||Fo| - |Fc|| \; / \; \Sigma \; |Fo| = 0.047$$

$$R_w = [(\Sigma \; w \; (|Fo| - |Fc|)^2 \; / \; \Sigma \; w \; Fo^2)]^{1/2} = 0.041$$

The standard deviation of an observation of unit weight[4] was 1.67. The weighting scheme was based on counting statistics and included a factor (p = 0.01) to downweight the intense reflections. Plots of $\Sigma \; w \; (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.20 and -0.26 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5]. Anomalous dispersion effects were included in Fcalc[6]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer[7]. All calculations were performed using the TEXSAN[8] crystallographic software package of Molecular Structure Corporation.

References

(1) ORTEP:
Johnson,C.K.; ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee (1976).

(2) Structure Solution Methods:
PHASE
Calbrese,J.C.; PHASE - Patterson Heavy Atom Solution Extractor. Univ. of Wisconsin-Madison, Ph.D. Thesis (1972).
DIRDIF
Beurskens,P.T.; DIRDIF: Direct Methods for Difference Structures - an automatic procedure for phase extension and refinement of difference structure factors. Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

(3) Least-Squares:
Function minimized: $\Sigma\ w\ (|Fo| - |Fc|)^2$
where: $w = 4Fo^2/\sigma^2(Fo^2)$
$\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$
S = Scan rate
C = Total Integrated Peak Count
R = Ratio of Scan Time to background counting time.
B = Total Background Count
Lp = Lorentz-polarization factor
p = p-factor

(4) Standard deviation of an observation of unit weight:

$$[\Sigma\ w(|Fo| - |Fc|)^2/(No - Nv)]^{1/2}$$

where: No = number of observations
Nv = number of variables

(5) Cromer,D.T. & Waber,J.T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers,J.A. & Hamilton,W.C.; Acta Crystallogr., 17, 781 (1964).

(7) D.T. Cromer, "International Tables for X-ray Crystallography", Vol/ IV, The Kynoch Press, Birmingham, England, Table 2.3.1 (1974).

(8) TEXSAN - TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{19}H_{24}O_2S$
Formula Weight	316.46
Crystal Color, Habit	colorless, needle
Crystal Dimensions (mm)	0.100 X 0.150 X 0.400
Crystal System	orthorhombic
No. Reflections Used for Unit Cell Determination (2θ range)	0 (0.0 - 0.0°)
Omega Scan Peak Width at Half-height	0.28
Lattice Parameters:	a = 13.522 (2)Å b = 19.592 (1)Å c = 6.314 (2)Å V = 1672.7 (5)Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.257 g/cm^3
F_{000}	680
$\mu_{(CuK\alpha)}$	17.04 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	CuKα (λ = 1.54178 Å)
Temperature	19°C
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to Detector Distance	40 cm

Scan Type	ω-2θ
Scan Rate	16.0°/min (in omega) (2 rescans)
Scan Width	(1.00 + 0.30 tanθ)°
$2\theta_{max}$	120.2°
No. of Reflections Measured	Total: 2690 Unique: 1486 (R_{int} = .052)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.94 - 1.00)

C. Structure Solution and Refinement

Structure Solution	Patterson Method
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.01
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>2.50σ(I)) No. Variables Reflection/Parameter Ratio	1937 224 8.65
Residuals: R; R_w	0.047; 0.041
Goodness of Fit Indicator	1.67
Max Shift/Error in Final Cycle	0.06
Maximum Peak in Final Diff. Map Minimum Peak in Final Diff. Map	0.20 $e^-/Å^3$ -0.26 $e^-/Å^3$

Positional parameters and B(eq) for kev1

atom	x	y	z	B(eq)
S	0.4880(1)	0.01879(7)	0.5605(2)	3.94(6)
O(1)	0.5329(3)	-0.3020(2)	1.0142(6)	4.2(2)
O(2)	0.4626(2)	-0.1743(2)	1.0944(5)	3.6(2)
C(1)	0.6021(4)	-0.2620(2)	0.8981(8)	3.3(3)
C(2)	0.6876(4)	-0.2377(3)	1.035(1)	4.2(3)
C(3)	0.7653(4)	-0.2030(3)	0.8969(9)	4.2(3)
C(4)	0.7271(4)	-0.1405(2)	0.7779(8)	3.2(3)
C(5)	0.6320(3)	-0.1620(2)	0.6500(7)	2.7(2)
C(6)	0.5829(3)	-0.1021(2)	0.5303(7)	3.0(2)
C(7)	0.5090(4)	-0.0628(2)	0.6646(7)	2.8(2)
C(8)	0.4685(3)	-0.0882(2)	0.8406(7)	2.6(2)
C(9)	0.4930(3)	-0.1555(2)	0.9203(7)	2.7(2)
C(10)	0.5528(4)	-0.2028(2)	0.7752(7)	2.4(2)
C(11)	0.7084(4)	-0.0815(3)	0.934(1)	4.3(3)
C(12)	0.8076(4)	-0.1185(3)	0.624(1)	5.3(4)
C(13)	0.4773(4)	-0.2341(2)	0.6187(8)	3.6(3)
C(14)	0.3034(4)	0.0621(2)	0.6796(8)	3.1(2)
C(15)	0.2362(4)	0.0921(3)	0.816(1)	3.8(3)
C(16)	0.2679(4)	0.1131(3)	1.0131(9)	3.9(3)
C(17)	0.3654(4)	0.1054(3)	1.0772(9)	3.7(3)
C(18)	0.4310(4)	0.0765(2)	0.937(1)	3.6(3)
C(19)	0.4010(4)	0.0542(2)	0.7410(8)	2.9(2)
H(1)	0.6299	-0.2914	0.7944	3.9
H(2)	0.7166	-0.2758	1.1044	5.1
H(3)	0.6638	-0.2063	1.1371	5.1
H(4)	0.7886	-0.2352	0.7962	5.1
H(5)	0.8184	-0.1890	0.9853	5.1
H(6)	0.6549	-0.1922	0.5430	3.3
H(7)	0.5494	-0.1199	0.4101	3.6
H(8)	0.6332	-0.0716	0.4852	3.6
H(9)	0.4220	-0.0612	0.9161	3.2
H(10)	0.2826	0.0468	0.5439	3.7
H(11)	0.1693	0.0982	0.7742	4.5
H(12)	0.2217	0.1332	1.1075	4.7
H(13)	0.3862	0.1196	1.2140	4.4
H(14)	0.4986	0.0721	0.9762	4.3
H(24)	0.509(5)	-0.276(3)	1.10(1)	10(3)
H(15)	0.766(2)	-0.076(2)	1.019(7)	5.4(8)
H(16)	0.687(3)	-0.043(2)	0.874(6)	5.4(8)
H(17)	0.654(3)	-0.089(2)	1.060(6)	5.4(8)
H(18)	0.873(3)	-0.114(2)	0.713(7)	5.8(8)
H(19)	0.801(4)	-0.076(2)	0.563(8)	5.8(8)
H(20)	0.822(4)	-0.153(2)	0.529(7)	5.8(8)
H(21)	0.443(3)	-0.199(1)	0.528(6)	4.6(8)
H(22)	0.509(3)	-0.264(2)	0.510(6)	4.6(8)
H(23)	0.424(3)	-0.262(2)	0.674(6)	4.6(8)

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
S	C(7)	1.752(4)	C(5)	C(10)	1.553(6)
S	C(19)	1.779(5)	C(6)	C(7)	1.520(6)
O(1)	C(1)	1.424(6)	C(7)	C(8)	1.335(6)
O(2)	C(9)	1.230(6)	C(8)	C(9)	1.449(6)
C(1)	C(2)	1.518(7)	C(9)	C(10)	1.534(6)
C(1)	C(10)	1.546(7)	C(10)	C(13)	1.548(7)
C(2)	C(3)	1.524(8)	C(14)	C(15)	1.382(7)
C(3)	C(4)	1.526(7)	C(14)	C(19)	1.384(7)
C(4)	C(5)	1.575(7)	C(15)	C(16)	1.380(8)
C(4)	C(11)	1.542(8)	C(16)	C(17)	1.388(8)
C(4)	C(12)	1.522(8)	C(17)	C(18)	1.376(8)
C(5)	C(6)	1.545(7)	C(18)	C(19)	1.373(8)

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	S	C(19)	102.9(2)	C(7)	C(8)	C(9)	122.3(4)
O(1)	C(1)	C(2)	112.3(4)	O(2)	C(9)	C(8)	120.4(4)
O(1)	C(1)	C(10)	112.8(4)	O(2)	C(9)	C(10)	122.0(4)
C(2)	C(1)	C(10)	112.3(4)	C(8)	C(9)	C(10)	117.6(4)
C(1)	C(2)	C(3)	109.9(5)	C(1)	C(10)	C(5)	110.1(4)
C(2)	C(3)	C(4)	113.9(4)	C(1)	C(10)	C(9)	112.4(4)
C(3)	C(4)	C(5)	108.4(4)	C(1)	C(10)	C(13)	107.9(4)
C(3)	C(4)	C(11)	110.0(4)	C(5)	C(10)	C(9)	110.9(4)
C(3)	C(4)	C(12)	107.4(4)	C(5)	C(10)	C(13)	109.5(4)
C(5)	C(4)	C(11)	113.3(4)	C(9)	C(10)	C(13)	105.8(4)
C(5)	C(4)	C(12)	109.4(4)	C(15)	C(14)	C(19)	120.0(5)
C(11)	C(4)	C(12)	108.2(4)	C(14)	C(15)	C(16)	119.0(5)
C(4)	C(5)	C(6)	113.5(4)	C(15)	C(16)	C(17)	121.7(5)
C(4)	C(5)	C(10)	116.0(4)	C(16)	C(17)	C(18)	118.0(5)
C(6)	C(5)	C(10)	110.1(4)	C(17)	C(18)	C(19)	121.3(5)
C(5)	C(6)	C(7)	113.2(4)	S	C(19)	C(14)	119.6(4)
S	C(7)	C(6)	111.1(3)	S	C(19)	C(18)	120.3(4)
S	C(7)	C(8)	125.9(4)	C(14)	C(19)	C(18)	119.9(5)
C(6)	C(7)	C(8)	123.0(4)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Special Contacts Involving the Nonhydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(1)	O(2)	2.724(5)	1	O(2)	O(1)	2.724(5)	1

Contacts out to 3.20 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

(*) footnote

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one digit numbers and one two digit number: TA(1st digit) + TB(2nd digit) + TC(3rd digit) + SN(4th and 5th digit). TA, TB, & TC are the crystal lattice translation digits along cell edges a, b, and c. A translation digit of 5 indicates the origin unit cell. If TA=4, this indicates a translation of one unit cell length along the a axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus (+/-)4 lattice translations from the origin (TA=5,TB=5, TC=5) can be represented.

The SN or symmetry operator number refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of the symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell (TA=5,TB=5,TC=5) and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always ADC=55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of that atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (i.e.cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	+X	,	+Y	,	+Z	(2)	1/2-X	,	-Y	,1/2+Z
(3)	1/2+X	,1/2-Y	,	-Z		(4)	-X	,1/2+Y	,1/2-Z	

U[illegible]es for kevl

atom	U11	U22	U33	U12	U13	U23
S	0.053(1)	0.0417(7)	0.0550(8)	0.0142(8)	0.0132(8)	0.0146(7)
O(1)	0.053(3)	0.042(2)	0.065(3)	-0.003(2)	0.009(2)	0.016(2)
O(2)	0.053(2)	0.047(2)	0.038(2)	0.007(2)	0.017(2)	0.009(2)
C(1)	0.046(3)	0.033(3)	0.045(4)	0.008(3)	0.008(3)	0.004(3)
C(2)	0.040(3)	0.056(4)	0.064(4)	0.004(3)	-0.013(3)	0.020(3)
C(3)	0.038(3)	0.059(4)	0.064(4)	0.007(3)	-0.010(3)	0.001(3)
C(4)	0.024(3)	0.042(3)	0.057(4)	0.000(3)	0.007(3)	0.005(3)
C(5)	0.035(3)	0.033(3)	0.035(3)	0.005(2)	0.014(2)	0.000(2)
C(6)	0.040(3)	0.041(3)	0.033(3)	0.000(3)	0.006(3)	0.005(3)
C(7)	0.027(3)	0.037(3)	0.042(3)	0.009(3)	-0.00[illegible](3)	-0.001(2)
C(8)	0.029(3)	0.034(3)	0.038(3)	0.008(2)	0.010(2)	-0.003(2)
C(9)	0.025(3)	0.037(3)	0.043(3)	-0.001(2)	-0.005(3)	-0.005(2)
C(10)	0.032(3)	0.028(3)	0.031(3)	-0.000(2)	0.001(2)	-0.004(2)
C(11)	0.038(3)	0.059(4)	0.065(4)	-0.001(3)	-0.011(3)	-0.020(4)
C(12)	0.037(3)	0.068(5)	0.096(6)	-0.004(4)	0.026(4)	0.019(4)
C(13)	0.048(4)	0.045(3)	0.044(3)	-0.011(3)	-0.004(3)	-0.004(3)
C(14)	0.043(3)	0.038(3)	0.037(3)	-0.001(3)	-0.009(3)	-0.002(3)
C(15)	0.031(3)	0.051(4)	0.061(4)	0.001(3)	-0.009(3)	0.005(3)
C(16)	0.049(3)	0.043(3)	0.058(4)	0.010(3)	0.014(3)	0.003(3)
C(17)	0.059(4)	0.041(3)	0.041(3)	0.001(3)	-0.005(3)	-0.001(3)
C(18)	0.033(3)	0.040(3)	0.064(4)	0.004(3)	-0.013(3)	-0.002(3)
C(19)	0.036(3)	0.027(3)	0.049(3)	0.008(3)	0.002(3)	0.005(2)

Table of Torsion Angles in Degrees for KEV1

C19	S	C7	C6	-180.0(4)	C19	S	C7	C8	-1.4(3)
[illegible]	S	C19	C14	-107.3(4)	C7	S	C19	C18	75.7(3)
O1	C1	C2	C3	173.0(6)	C10	C1	C2	C3	-58.6(4)
O1	C1	C10	C5	-179.2(6)	O1	C1	C10	C9	56.6(3)
O1	C1	C10	C13	-59.7(4)	C2	C1	C10	C5	52.6(3)
C2	C1	C10	C9	-71.6(4)	C2	C1	C10	C13	172.1(6)
C1	C2	C3	C4	60.3(4)	C2	C3	C4	C5	-53.5(4)
C2	C3	C4	C11	70.9(4)	C2	C3	C4	C12	-171.5(6)
C3	C4	C5	C6	177.2(6)	C3	C4	C5	C10	48.2(3)
C11	C4	C5	C6	54.9(4)	C11	C4	C5	C10	-74.1(4)
C12	C4	C5	C6	-66.0(4)	C12	C4	C5	C10	165.0(6)
C4	C5	C6	C7	-87.1(4)	C10	C5	C6	C7	44.8(3)
C4	C5	C10	C1	-48.4(3)	C4	C5	C10	C9	76.7(4)
C4	C5	C10	C13	-166.9(5)	C6	C5	C10	C1	-179.0(5)
C6	C5	C10	C9	-54.0(3)	C6	C5	C10	C13	62.4(4)
C5	C6	C7	S	159.7(5)	C5	C6	C7	C8	-19.0(3)
S	C7	C8	C9	-177.5(5)	C6	C7	C8	C9	0.9(2)
C7	C8	C9	O2	172.1(6)	C7	C8	C9	C10	-11.0(3)
O2	C9	C10	C1	-21.4(3)	O2	C9	C10	C5	-145.2(5)
O2	C9	C10	C13	96.2(5)	C8	C9	C10	C1	161.8(5)
C8	C9	C10	C5	38.0(3)	C8	C9	C10	C13	-80.7(4)
C19	C14	C15	C16	-0.8(3)	C15	C14	C19	S	-177.3(6)
C15	C14	C19	C18	-0.3(3)	C14	C15	C16	C17	0.6(3)
C15	C16	C17	C18	0.6(3)	C16	C17	C18	C19	-1.8(3)
C17	C18	C19	S	178.6(6)	C17	C18	C19	C14	1.6(3)

Table of Distances(A) to the Least-squares Planes.

Plane no. 1

Equation of the plane : 10.248(21)X + 7.210(23)Y + 3.401(11)Z = 7.041(5)

Distances(A) to the plane from the atoms in the plane.

S	0.0014(19)	C6	-0.001(7)
C7	-0.018(5)	C8	-0.018(5)
C9	0.019(6)		

Chi squared for this plane 33.448

Distances(A) to the plane from the atoms out of the plane.

O2	0.165(6)	C5	0.478(7)
C10	-0.202(7)		

Plane no. 2

Equation of the plane : 2.763(23)X + 17.769(8)Y - 2.326(10)Z = 0.377(17)

Distances(A) to the plane from the atoms in the plane.

S	0.0018(19)	C14	-0.017(6)
C15	0.015(7)	C16	0.016(6)
C17	-0.001(7)	C18	-0.005(7)
C19	-0.030(5)		

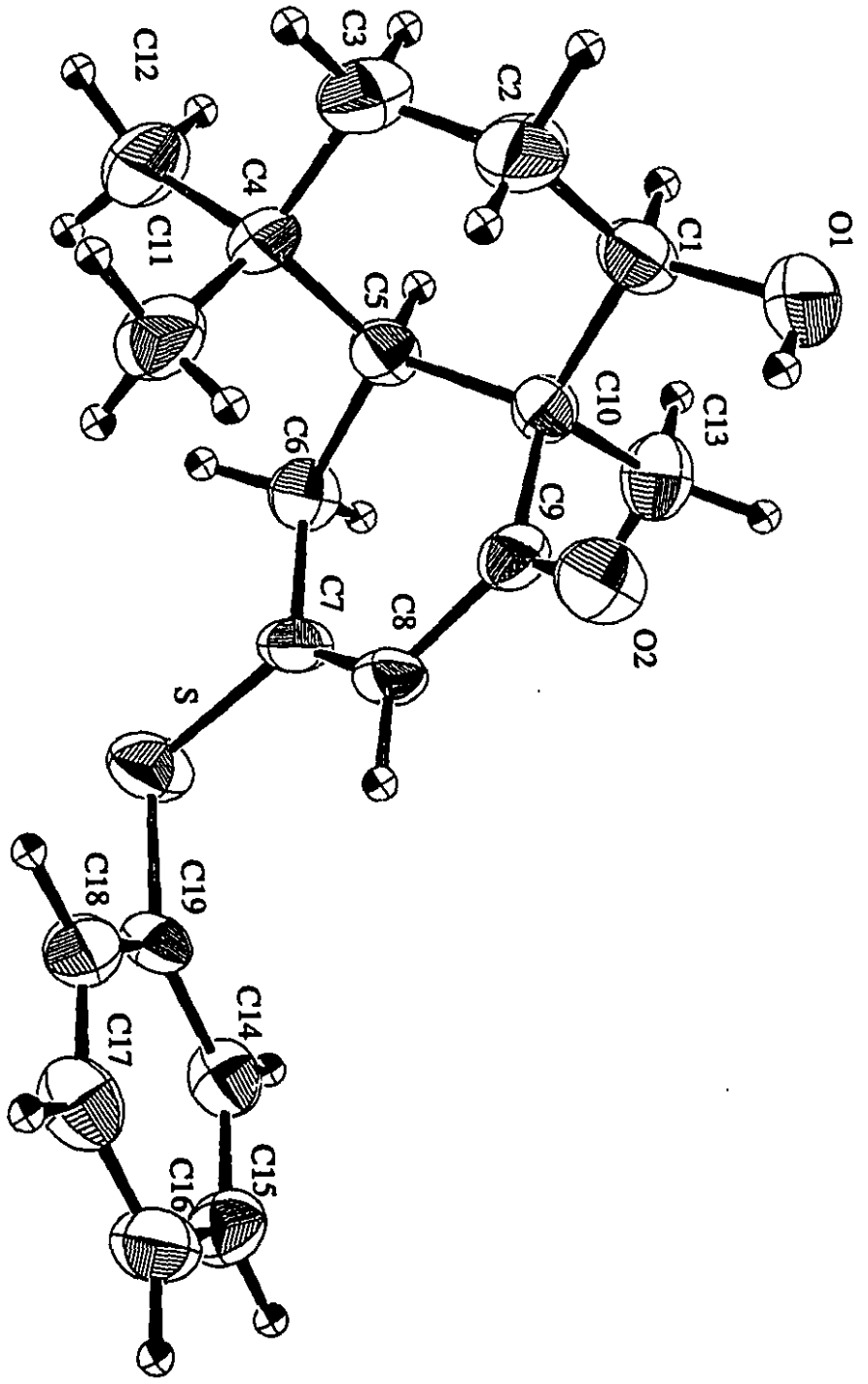
Chi squared for this plane 50.381

Distances(A) to the plane from the atoms out of the plane.

C7	-1.633(5)

Dihedral angle between planes A and B

A	B	Angle(deg)
1	2	73.13(14)


C3
C2
C12
C4
C1
O1
C11
C5
C10
C13
C6
C9
C7
C8
O2
S
C19
C18
C14
C17
C15
C16

Appendix 2

X-ray Structure Report

For

Compound 3.7 *

* I would like to thank Dr. Jim Britten of the McGill X-ray Facility for this determination.

EXPERIMENTAL

DATA COLLECTION

A colorless chunk crystal of $C_{17}H_{28}O_4$ having approximate dimensions of 0.200 X 0.180 X 0.400 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation at 1.75kW.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $65.61 < 2\theta < 90.72°$ corresponded to an orthorhombic cell with dimensions:

$a = 23.147\ (2)\text{Å}$
$b = 19.888\ (3)\text{Å}$
$c = 14.168\ (2)\text{Å}$
$V = 6522\ (2)\text{Å}^3$

For $Z = 16$ and F.W. = 296.41, the calculated density is 1.207 g/cm^3. Based on the systematic absences of:

0kl: $k \neq 2n$
h0l: $l \neq 2n$
hk0: $h \neq 2n$

and the successful solution and refinement of the structure, the space group was determined to be:

Pbca (#61)

The data were collected at a temperature of 20 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.38° with a take-off angle of 6.0°. Scans of (1.52 + 0.30 tan θ)° were made at a speed of 32.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 9 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 280.0 mm.

DATA REDUCTION

A total of 5389 reflections was collected. The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for Cu Kα is 6.4 cm^{-1}. An empirical absorption correction, using the program DIFABS[2], was applied which resulted in transmission factors ranging from 0.87 to 1.11. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.15154E-06).

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods[3]. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement[4] was based on 2244 observed reflections ($I > 3.00\sigma(I)$) and 380 variable parameters and converged (largest parameter shift was 0.13 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \; ||Fo| - |Fc|| \; / \; \Sigma \; |Fo| = 0.068$$

$$R_w = [(\Sigma \; w \; (|Fo| - |Fc|)^2 \; / \; \Sigma \; w \; Fo^2)]^{1/2} = 0.059$$

The standard deviation of an observation of unit weight[5] was 2.57. The weighting scheme was based on counting statistics and included a factor (p = 0.01) to downweight the intense reflections. Plots of $\Sigma \; w \; (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.51 and -0.34 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion effects were included in Fcalc[7]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer[8]. All calculations were performed using the TEXSAN[9] crystallographic software package of Molecular Structure Corporation.

References

(1) ORTEP:
Johnson,C.K.; ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee (1976).

(2) DIFABS:
Walker & Stuart, Acta Cryst. A39, 158-166, (1983).

(3) Structure Solution Methods:
MITHRIL
Gilmore,C.J.; MITHRIL - an integrated direct methods computer program. J. Appl. Cryst. 17, 42-46, Univ. of Glasgow, Scotland, (1984).
DIRDIF
Beurskens,P.T.; DIRDIF: Direct Methods for Difference Structures - an automatic procedure for phase extension and refinement of difference structure factors. Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

(4) Least-Squares:
Function minimized: $\Sigma\, w\, (|Fo| - |Fc|)^2$
where: $w = 4Fo^2/\sigma^2(Fo^2)$
$\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$
S = Scan rate
C = Total Integrated Peak Count
R = Ratio of Scan Time to background counting time.
B = Total Background Count
Lp = Lorentz-polarization factor
p = p-factor

(5) Standard deviation of an observation of unit weight:

$$[\Sigma\, w(|Fo| - |Fc|)^2/(No - Nv)]^{1/2}$$

where: No = number of observations
Nv = number of variables

(6) Cromer,D.T. & Waber,J.T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers,J.A. & Hamilton,W.C.; Acta Crystallogr., 17, 781 (1964).

(8) D.T. Cromer, "International Tables for X-ray Crystallography", Vol/ IV, The Kynoch Press, Birmingham, England, Table 2.3.1 (1974).

(9) TEXSAN - TEXRAY Structure Analysis Package,

Molecular Structure Corporation (1985).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{17}H_{28}O_4$
Formula Weight	296.41
Crystal Color, Habit	colorless, chunk
Crystal Dimensions (mm)	0.200 X 0.180 X 0.400
Crystal System	orthorhombic
No. Reflections Used for Unit Cell Determination (2θ range)	25 (65.6 - 90.7°)
Omega Scan Peak Width at Half-height	0.38
Lattice Parameters:	a = 23.147 (2)Å b = 19.888 (3)Å c = 14.168 (2)Å V = 6522 (2)Å^3
Space Group	Pbca (#61)
Z value	16
D_{calc}	1.207 g/cm^3
F_{000}	2592
$\mu_{(CuK\alpha)}$	6.43 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	CuKα (λ = 1.54178 Å)
Temperature	20°C
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to Detector Distance	40 cm

Scan Type	ω-2θ
Scan Rate	32.0°/min (in omega) (9 rescans)
Scan Width	(1.52 + 0.30 tanθ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 5389
Corrections	Lorentz-polarization Absorption (trans. factors: 0.87 - 1.11) Secondary Extinction (coefficient: 0.15154E-06)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w $(\|Fo\| - \|Fc\|)^2$
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.01
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2244
No. Variables	380
Reflection/Parameter Ratio	5.91
Residuals: R; R_w	0.068; 0.059
Goodness of Fit Indicator	2.57
Max Shift/Error in Final Cycle	0.13
Maximum Peak in Final Diff. Map	0.51 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-0.34 $e^-/Å^3$

Positional parameters for KEV3

atom	x	y	z
O(1A)	0.1829(3)	0.1281(3)	0.9587(4)
O(2A)	0.1660(2)	0.1868(2)	0.7474(3)
O(3A)	0.3155(2)	0.2455(2)	0.7379(3)
O(4A)	0.3060(2)	0.1938(2)	0.5523(3)
C(1A)	0.1992(3)	0.0863(4)	0.8864(5)
C(2A)	0.1443(4)	0.0543(5)	0.8462(7)
C(3A)	0.1586(3)	-0.0013(4)	0.7771(7)
C(4A)	0.1907(3)	0.0257(4)	0.6945(5)
C(5A)	0.2445(3)	0.0683(3)	0.7251(4)
C(6A)	0.2727(3)	0.0994(3)	0.6424(5)
C(7A)	0.2795(3)	0.1640(4)	0.6286(5)
C(8A)	0.2626(3)	0.2191(3)	0.6976(5)
C(9A)	0.2241(3)	0.1913(3)	0.7804(4)
C(10A)	0.2405(3)	0.1188(3)	0.8109(4)
C(11A)	0.2149(3)	-0.0357(4)	0.6419(6)
C(12A)	0.1490(3)	0.0609(4)	0.6262(6)
C(13A)	0.3008(3)	0.1193(3)	0.8569(5)
C(14A)	0.2282(3)	0.2421(4)	0.8602(5)
C(15A)	0.1855(3)	0.2812(4)	0.8896(5)
C(16A)	0.2331(3)	0.2772(3)	0.6466(5)
C(17A)	0.3298(4)	0.1496(4)	0.4849(6)
H(1)	0.3468	0.2507	0.6730
H(2)	0.1096	0.0300	0.6002
H(3)	0.2685	0.2402	0.8982
H(4)	0.1860	-0.0625	0.6249
H(5)	0.2635	0.3022	0.5978
H(6)	0.1887	-0.0481	0.8147
H(7)	0.2202	0.3075	0.6939
H(8)	0.2605	-0.0647	0.6683
H(9)	0.1247	0.0930	0.6612
H(10)	0.1661	0.0844	0.5608
H(11)	0.1189	-0.0083	0.7980
H(12)	0.1408	0.2755	0.8754
H(13)	0.2017	0.2641	0.5997
H(14)	0.1928	0.3133	0.9404
H(15)	0.2206	-0.0208	0.5543
H(16)	0.2725	0.0339	0.7575
H(17)	0.2900	0.0600	0.5935
H(18)	0.3036	0.1390	0.9149
H(19)	0.3317	0.1370	0.8266
H(20)	0.3064	0.0632	0.8820
H(21)	0.1427	0.2304	0.7296
H(22)	0.2203	0.0481	0.9158
H(23)	0.1190	0.0399	0.8976
H(24)	0.1223	0.0907	0.8147
H(25)	0.3487	0.1775	0.4334
H(26)	0.3632	0.1150	0.5229
H(27)	0.3034	0.1117	0.4605
H(28)	0.1860	0.1795	0.9478
O(1B)	0.8763(2)	0.6064(2)	0.3819(3)

Positional parameters for KEV3

atom	x	y	z
O(2B)	0.9185(2)	0.6994(2)	0.2772(3)
O(3B)	1.0699(2)	0.7319(3)	0.3231(3)
C(4B)	1.0690(2)	0.7122(2)	0.1198(3)
C(1B)	0.9334(3)	0.5792(3)	0.4030(5)
C(2B)	0.9302(3)	0.5045(4)	0.3847(5)
C(3B)	0.9087(3)	0.4886(4)	0.2856(5)
C(4B)	0.9379(3)	0.5291(3)	0.2066(5)
C(5B)	0.9890(3)	0.5720(3)	0.2464(5)
C(6B)	1.0203(3)	0.6127(3)	0.1731(5)
C(7B)	1.0351(3)	0.6764(3)	0.1826(5)
C(8B)	1.0193(3)	0.7220(3)	0.2638(5)
C(9B)	0.9719(3)	0.6891(3)	0.3268(4)
C(10B)	0.9811(3)	0.6120(3)	0.3412(4)
C(11B)	0.9634(4)	0.4790(4)	0.1353(6)
C(12B)	0.8938(3)	0.5707(4)	0.1533(5)
C(13B)	1.0375(3)	0.5985(4)	0.3963(5)
C(14B)	0.9698(3)	0.7254(4)	0.4215(5)
C(15B)	0.9301(3)	0.7671(4)	0.4515(5)
C(16B)	0.9984(4)	0.7911(3)	0.2271(6)
C(17B)	1.0879(3)	0.6771(4)	0.0374(5)
H(29)	1.1112	0.7174	-0.0051
H(30)	1.0712	0.6088	0.3699
H(31)	1.0362	0.6142	0.4541
H(32)	1.0418	0.5875	0.1117
H(33)	0.9444	0.5952	0.4728
H(34)	0.9042	0.4862	0.4299
H(35)	1.0545	0.6664	-0.0001
H(36)	0.8688	0.5405	0.1242
H(37)	1.0031	0.7186	0.4555
H(38)	1.0193	0.5417	0.2682
H(39)	0.9865	0.8156	0.2832
H(40)	0.8665	0.6247	0.4365
H(41)	0.9147	0.4255	0.2743
H(42)	0.9571	0.7839	0.1838
H(43)	1.1133	0.6467	0.0439
H(44)	0.9889	0.4495	0.1576
H(45)	0.9810	0.5012	0.0842
H(46)	0.9669	0.4863	0.4089
H(47)	0.9420	0.7998	0.5180
H(48)	0.8924	0.7729	0.4127
H(49)	1.0424	0.5435	0.4354
H(50)	0.8873	0.6814	0.3315
H(51)	1.0323	0.8133	0.1990
H(52)	0.9353	0.4443	0.1221
H(53)	0.8655	0.6040	0.1918
H(54)	0.8687	0.4984	0.2797
H(55)	0.9084	0.6008	0.1084
H(56)	1.0870	0.7564	0.2529

Positional parameters and B(eq) for KEV3

atom	x	y	z	B(eq)
O(1A)	0.1829(3)	0.1281(3)	0.9587(4)	7.7(4)
O(2A)	0.1660(2)	0.1868(2)	0.7474(3)	2.9(2)
O(3A)	0.3155(2)	0.2455(2)	0.7379(3)	4.2(3)
O(4A)	0.3060(2)	0.1938(2)	0.5523(3)	4.2(3)
C(1A)	0.1992(3)	0.0863(4)	0.8864(5)	4.3(4)
C(2A)	0.1443(4)	0.0543(5)	0.8462(7)	7.4(6)
C(3A)	0.1586(3)	-0.0013(4)	0.7771(7)	5.8(5)
C(4A)	0.1907(3)	0.0257(4)	0.6945(5)	4.2(4)
C(5A)	0.2445(3)	0.0683(3)	0.7251(4)	2.8(3)
C(6A)	0.2727(3)	0.0994(3)	0.6424(5)	3.2(3)
C(7A)	0.2795(3)	0.1640(4)	0.6286(5)	3.0(3)
C(8A)	0.2626(3)	0.2191(3)	0.6976(5)	2.9(3)
C(9A)	0.2241(3)	0.1913(3)	0.7804(4)	2.6(3)
C(10A)	0.2405(3)	0.1188(3)	0.8109(4)	2.5(3)
C(11A)	0.2149(3)	-0.0357(4)	0.6419(6)	5.8(5)
C(12A)	0.1490(3)	0.0609(4)	0.6262(6)	5.4(5)
C(13A)	0.3008(3)	0.1193(3)	0.8569(5)	4.0(4)
C(14A)	0.2282(3)	0.2421(4)	0.8602(5)	3.4(4)
C(15A)	0.1855(3)	0.2812(4)	0.8896(5)	4.2(4)
C(16A)	0.2331(3)	0.2772(3)	0.6466(5)	3.7(4)
C(17A)	0.3298(4)	0.1496(4)	0.4849(6)	6.9(6)
H(1)	0.3468	0.2507	0.6730	4.6
H(2)	0.1096	0.0300	0.6002	5.8
H(3)	0.2685	0.2402	0.8982	3.9
H(4)	0.1860	-0.0625	0.6249	4.8
H(5)	0.2635	0.3022	0.5978	4.4
H(6)	0.1887	-0.0481	0.8147	7.4
H(7)	0.2202	0.3075	0.6939	4.4
H(8)	0.2605	-0.0647	0.6683	4.0
H(9)	0.1247	0.0930	0.6612	5.8
H(10)	0.1661	0.0844	0.5608	5.8
H(11)	0.1189	-0.0083	0.7980	4.0
H(12)	0.1408	0.2755	0.8754	7.0
H(13)	0.2017	0.2641	0.5997	4.4
H(14)	0.1928	0.3133	0.9404	3.5
H(15)	0.2206	-0.0208	0.5543	7.5
H(16)	0.2725	0.0339	0.7575	2.3
H(17)	0.2900	0.0600	0.5935	3.8
H(18)	0.3036	0.1390	0.9149	4.1
H(19)	0.3317	0.1370	0.8266	3.9
H(20)	0.3064	0.0632	0.8820	6.5
H(21)	0.1427	0.2304	0.7296	3.5
H(22)	0.2203	0.0481	0.9158	5.4
H(23)	0.1190	0.0399	0.8976	8.0
H(24)	0.1223	0.0907	0.8147	8.0
H(25)	0.3487	0.1775	0.4334	7.7
H(26)	0.3632	0.1150	0.5229	7.7
H(27)	0.3034	0.1117	0.4605	7.7
H(28)	0.1860	0.1795	0.9478	4.0
O(1B)	0.8763(2)	0.6064(2)	0.3819(3)	4.2(3)

Positional parameters and B(eq) for KEV3

atom	x	y	z	B(eq)
O(2B)	0.9185(2)	0.6994(2)	0.2772(3)	3.0(2)
O(3B)	1.0699(2)	0.7319(3)	0.3231(3)	4.9(3)
C(4B)	1.0690(2)	0.7122(2)	0.1198(3)	4.4(3)
C(1B)	0.9334(3)	0.5792(3)	0.4030(5)	3.2(4)
C(2B)	0.9302(3)	0.5045(4)	0.3847(5)	4.0(4)
C(3B)	0.9087(3)	0.4886(4)	0.2856(5)	4.5(4)
C(4B)	0.9379(3)	0.5291(3)	0.2066(5)	3.2(3)
C(5B)	0.9890(3)	0.5720(3)	0.2464(5)	2.9(3)
C(6B)	1.0203(3)	0.6127(3)	0.1731(5)	3.1(3)
C(7B)	1.0351(3)	0.6764(3)	0.1826(5)	3.3(3)
C(8B)	1.0193(3)	0.7220(3)	0.2638(5)	3.3(3)
C(9B)	0.9719(3)	0.6891(3)	0.3268(4)	2.7(3)
C(10B)	0.9811(3)	0.6120(3)	0.3412(4)	2.8(3)
C(11B)	0.9634(4)	0.4790(4)	0.1353(6)	5.7(5)
C(12B)	0.8938(3)	0.5707(4)	0.1533(5)	5.0(4)
C(13B)	1.0375(3)	0.5985(4)	0.3963(5)	3.9(4)
C(14B)	0.9698(3)	0.7254(4)	0.4215(5)	3.7(4)
C(15B)	0.9301(3)	0.7671(4)	0.4515(5)	4.9(5)
C(16B)	0.9984(4)	0.7911(3)	0.2271(6)	5.0(4)
C(17B)	1.0879(3)	0.6771(4)	0.0374(5)	4.4(4)
H(29)	1.1112	0.7174	-0.0051	4.2
H(30)	1.0712	0.6088	0.3699	3.1
H(31)	1.0362	0.6142	0.4541	2.5
H(32)	1.0418	0.5875	0.1117	5.8
H(33)	0.9444	0.5952	0.4728	3.2
H(34)	0.9042	0.4862	0.4299	4.1
H(35)	1.0545	0.6664	-0.0001	4.0
H(36)	0.8688	0.5405	0.1242	2.7
H(37)	1.0031	0.7186	0.4555	4.0
H(38)	1.0193	0.5417	0.2682	4.0
H(39)	0.9865	0.8156	0.2832	6.0
H(40)	0.8665	0.6247	0.4365	4.6
H(41)	0.9147	0.4255	0.2743	5.3
H(42)	0.9571	0.7839	0.1838	6.0
H(43)	1.1133	0.6467	0.0439	2.6
H(44)	0.9889	0.4495	0.1576	5.5
H(45)	0.9810	0.5012	0.0842	5.7
H(46)	0.9669	0.4863	0.4089	4.6
H(47)	0.9420	0.7998	0.5180	5.4
H(48)	0.8924	0.7729	0.4127	5.4
H(49)	1.0424	0.5435	0.4354	4.4
H(50)	0.8873	0.6814	0.3315	3.4
H(51)	1.0323	0.8133	0.1990	6.0
H(52)	0.9353	0.4443	0.1221	8.9
H(53)	0.8655	0.6040	0.1918	6.0
H(54)	0.8687	0.4984	0.2797	3.7
H(55)	0.9084	0.6008	0.1084	6.8
H(56)	1.0870	0.7564	0.2529	5.8

U values for KEV3

atom	U11	U22	U33	U12	U13	U23
O(1A)	0.154(6)	0.059(4)	0.078(4)	-0.017(4)	0.061(5)	-0.007(4)
O(2A)	0.034(3)	0.037(3)	0.041(3)	0.004(2)	-0.004(2)	0.001(3)
O(3A)	0.036(3)	0.061(3)	0.064(4)	-0.017(3)	-0.006(3)	0.001(3)
O(4A)	0.055(3)	0.052(3)	0.053(3)	0.009(3)	0.015(3)	0.009(3)
C(1A)	0.067(6)	0.074(6)	0.024(4)	0.002(5)	0.013(4)	-0.008(4)
C(2A)	0.101(8)	0.103(8)	0.077(7)	-0.045(7)	0.033(6)	0.010(6)
C(3A)	0.066(6)	0.048(5)	0.104(8)	-0.012(5)	0.048(6)	-0.007(5)
C(4A)	0.054(5)	0.039(5)	0.066(5)	-0.002(4)	0.006(5)	-0.008(4)
C(5A)	0.035(4)	0.032(4)	0.041(4)	0.000(3)	0.003(4)	0.005(3)
C(6A)	0.041(4)	0.036(4)	0.043(4)	-0.003(4)	0.004(4)	0.000(4)
C(7A)	0.031(4)	0.050(5)	0.033(4)	-0.001(4)	0.010(3)	0.008(4)
C(8A)	0.028(4)	0.038(4)	0.046(4)	-0.002(3)	-0.008(4)	0.008(4)
C(9A)	0.032(4)	0.029(4)	0.038(4)	0.003(3)	-0.011(3)	-0.006(3)
C(10A)	0.031(4)	0.034(4)	0.030(4)	0.004(3)	-0.003(3)	0.003(3)
C(11A)	0.069(6)	0.051(5)	0.100(7)	-0.012(5)	-0.001(5)	-0.037(5)
C(12A)	0.046(5)	0.096(7)	0.063(6)	-0.006(5)	-0.012(5)	-0.003(6)
C(13A)	0.056(5)	0.046(5)	0.049(5)	0.007(4)	-0.015(4)	-0.001(4)
C(14A)	0.055(5)	0.044(5)	0.031(4)	-0.002(4)	-0.003(4)	0.002(4)
C(15A)	0.067(5)	0.050(5)	0.043(5)	0.010(4)	0.001(4)	-0.007(4)
C(16A)	0.057(5)	0.038(4)	0.047(5)	0.007(4)	0.003(4)	0.009(4)
C(17A)	0.109(8)	0.070(7)	0.082(7)	0.033(6)	0.069(6)	0.030(6)
H(1)	0.0587					
H(2)	0.0740					
H(3)	0.0494					
H(4)	0.0606					
H(5)	0.0556					
H(6)	0.0935					
H(7)	0.0556					
H(8)	0.0507					
H(9)	0.0740					
H(10)	0.0740					
H(11)	0.0507					
H(12)	0.0890					
H(13)	0.0556					
H(14)	0.0449					
H(15)	0.0954					

U values for KEV3

atom	U11	U22	U33	U12	U13	U23
H(16)	0.0287					
H(17)	0.0477					
H(18)	0.0522					
H(19)	0.0488					
H(20)	0.0828					
H(21)	0.0440					
H(22)	0.0690					
H(23)	0.1009					
H(24)	0.1009					
H(25)	0.0978					
H(26)	0.0978					
H(27)	0.0978					
H(28)	0.0507					
O(1B)	0.035(3)	0.057(3)	0.067(3)	0.004(3)	0.011(3)	0.001(3)
O(2B)	0.036(3)	0.036(3)	0.043(3)	0.003(2)	0.001(2)	0.002(2)
O(3B)	0.050(3)	0.085(4)	0.051(3)	-0.033(3)	0.005(3)	-0.009(3)
O(4B)	0.068(4)	0.050(3)	0.048(3)	-0.022(3)	0.025(3)	-0.003(3)
C(1B)	0.032(4)	0.048(5)	0.043(5)	-0.001(4)	0.004(3)	0.003(4)
C(2B)	0.056(5)	0.046(5)	0.051(5)	-0.009(4)	0.005(4)	0.021(4)
C(3B)	0.064(5)	0.049(5)	0.057(5)	-0.020(4)	-0.003(4)	0.008(4)
C(4B)	0.047(5)	0.030(4)	0.045(4)	-0.002(4)	-0.005(4)	-0.001(4)
C(5B)	0.036(4)	0.033(4)	0.039(4)	0.003(3)	-0.000(4)	0.004(4)
C(6B)	0.037(4)	0.042(5)	0.038(4)	-0.005(4)	0.011(4)	-0.003(4)
C(7B)	0.047(4)	0.036(4)	0.041(4)	-0.007(4)	0.008(4)	0.001(4)
C(8B)	0.045(5)	0.038(4)	0.042(4)	-0.012(4)	0.002(4)	0.000(4)
C(9B)	0.038(4)	0.033(4)	0.031(4)	0.004(3)	-0.005(3)	-0.005(3)
C(10B)	0.037(4)	0.038(4)	0.030(4)	-0.005(3)	0.001(3)	0.005(3)
C(11B)	0.084(6)	0.047(5)	0.084(6)	-0.011(5)	0.027(6)	-0.022(5)
C(12B)	0.063(5)	0.054(5)	0.071(6)	-0.012(4)	-0.030(5)	0.008(5)
C(13B)	0.038(4)	0.077(6)	0.035(4)	0.012(4)	-0.003(4)	0.004(4)
C(14B)	0.046(5)	0.054(5)	0.041(5)	-0.011(4)	-0.000(4)	-0.008(4)
C(15B)	0.046(5)	0.070(6)	0.071(6)	0.003(5)	-0.001(5)	-0.036(5)
C(16B)	0.086(6)	0.033(4)	0.072(6)	-0.010(5)	0.024(5)	-0.004(4)
C(17B)	0.067(6)	0.056(5)	0.047(5)	0.004(5)	0.019(4)	0.010(4)
H(29)	0.0527					
H(30)	0.0390					

U values for KEV3

atom	U11	U22	U33	U12	U13	U23
H(31)	0.0320					
H(32)	0.0737					
H(33)	0.0405					
H(34)	0.0525					
H(35)	0.0507					
H(36)	0.0343					
H(37)	0.0507					
H(38)	0.0507					
H(39)	0.0754					
H(40)	0.0578					
H(41)	0.0672					
H(42)	0.0754					
H(43)	0.0325					
H(44)	0.0694					
H(45)	0.0726					
H(46)	0.0584					
H(47)	0.0686					
H(48)	0.0686					
H(49)	0.0561					
H(50)	0.0432					
H(51)	0.0754					
H(52)	0.1130					
H(53)	0.0760					
H(54)	0.0466					
H(55)	0.0863					
H(56)	0.0740					

Torsion or Conformation Angles (cont)

(1)	(2)	(3)	(4)	angle
C(10AC	(5A)C	(4A)C	(12A	85.7(8)
C(10AC	(9A)C	(8A)C	(16A	159.6(5)
C(10AC	(9A)C	(14AC	(15A	-123.3(8)
C(13AC	(10AC	(9A)C	(14A	-54.0(7)
C(14AC	(9A)C	(8A)C	(16A	-75.2(6)
O(1B)C	(1B)C	(2B)C	(3B)	54.5(8)
O(1B)C	(1B)C	(10BC	(5B)	-89.2(6)
O(1B)C	(1B)C	(10BC	(9B)	39.5(8)
O(1B)C	(1B)C	(10BC	(13B	159.5(6)
O(2B)C	(9B)C	(8B)O	(3B)	162.3(5)
O(2B)C	(9B)C	(8B)C	(7B)	-79.0(6)
O(2B)C	(9B)C	(8B)C	(16B	43.9(7)
O(2B)C	(9B)C	(10BC	(1B)	-62.7(7)
O(2B)C	(9B)C	(10BC	(5B)	64.5(7)
O(2B)C	(9B)C	(10BC	(13B	-178.8(5)
O(2B)C	(9B)C	(14BC	(15B	-8(1)
O(3B)C	(8B)C	(7B)O	(4B)	-73.3(7)
O(3B)C	(8B)C	(7B)C	(6B)	105.7(8)
O(3B)C	(8B)C	(9B)C	(10B	-79.1(7)
O(3B)C	(8B)C	(9B)C	(14B	44.7(7)
O(4B)C	(7B)C	(6B)C	(5B)	172.9(6)
O(4B)C	(7B)C	(8B)C	(9B)	169.2(5)
O(4B)C	(7B)C	(8B)C	(16B	46.6(8)
C(1B)C	(2B)C	(3B)C	(4B)	47.1(9)
C(1B)C	(10BC	(5B)C	(4B)	24.8(8)
C(1B)C	(10BC	(5B)C	(6B)	162.2(5)

(1)	(2)	(3)	(4)	angle
C(1B)C	(10BC	(9B)C	(8B)	-179.3(5)
C(1B)C	(10BC	(9B)C	(14B	57.9(7)
C(2B)C	(1B)C	(10BC	(5B)	29.4(8)
C(2B)C	(1B)C	(10BC	(9B)	158.1(6)
C(2B)C	(1B)C	(10BC	(13B	-82.0(7)
C(2B)C	(3B)C	(4B)C	(5B)	6.9(9)
C(2B)C	(3B)C	(4B)C	(11B	124.3(7)
C(2B)C	(3B)C	(4B)C	(12B	-119.5(7)
C(3B)C	(2B)C	(1B)C	(10B	-67.3(8)
C(3B)C	(4B)C	(5B)C	(6B)	179.5(6)
C(3B)C	(4B)C	(5B)C	(10B	-43.9(8)
C(4B)C	(5B)C	(6B)C	(7B)	134.4(7)
C(4B)C	(5B)C	(10BC	(9B)	-103.5(6)
C(4B)C	(5B)C	(10BC	(13B	136.1(6)
C(5B)C	(6B)C	(7B)C	(8B)	-6(1)
C(5B)C	(10BC	(9B)C	(8B)	-52.2(7)
C(5B)C	(10BC	(9B)C	(14B	-175.0(5)
C(6B)C	(5B)C	(4B)C	(11B	61.8(7)
C(6B)C	(5B)C	(4B)C	(12B	-55.5(8)
C(6B)C	(5B)C	(10BC	(9B)	34.0(8)
C(6B)C	(5B)C	(10BC	(13B	-86.5(6)
C(6B)C	(7B)O	(4B)C	(17B	2(1)
C(6B)C	(7B)C	(8B)C	(9B)	-12(1)
C(6B)C	(7B)C	(8B)C	(16B	-134.4(8)
C(7B)C	(6B)C	(5B)C	(10B	-6(1)
C(7B)C	(8B)C	(9B)C	(10B	39.6(8)

The sign is positive if when looking from atom to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	angle
O(1A)	C(1A)	C(2A)	C(3A)	-170.5(7)
O(1A)	C(1A)	C(10AC	(5A)	-169.4(6)
O(1A)	C(1A)	C(10AC	(9A)	-42.9(9)
O(1A)	C(1A)	C(10AC	(13A	77.8(8)
O(2A)	C(9A)	C(8A)	O(3A)	160.5(5)
O(2A)	C(9A)	C(8A)	C(7A)	-81.7(6)
O(2A)	C(9A)	C(8A)	C(16A	43.1(7)
O(2A)	C(9A)	C(10AC	(1A)	-56.1(7)
O(2A)	C(9A)	C(10AC	(5A)	67.5(6)
O(2A)	C(9A)	C(10AC	(13A	-174.5(5)
O(2A)	C(9A)	C(14AC	(15A	-6(1)
O(3A)	C(8A)	C(7A)	O(4A)	-69.8(6)
O(3A)	C(8A)	C(7A)	C(6A)	107.0(8)
O(3A)	C(8A)	C(9A)	C(10A	-83.1(6)
O(3A)	C(8A)	C(9A)	C(14A	42.1(7)
O(4A)	C(7A)	C(6A)	C(5A)	179.5(6)
O(4A)	C(7A)	C(8A)	C(9A)	171.8(5)
O(4A)	C(7A)	C(8A)	C(16A	46.6(7)
C(1A)	C(2A)	C(3A)	C(4A)	-63(1)
C(1A)	C(10AC	(5A)	C(4A)	35.5(8)
C(1A)	C(10AC	(5A)	C(6A)	168.6(5)
C(1A)	C(10AC	(9A)	C(8A)	-174.1(5)
C(1A)	C(10AC	(9A)	C(14A	64.4(7)
C(2A)	C(1A)	C(10AC	(5A)	-43.5(9)
C(2A)	C(1A)	C(10AC	(9A)	83.1(8)
C(2A)	C(1A)	C(10AC	(13A	-156.2(7)
C(2A)	C(3A)	C(4A)	C(5A)	52(1)
C(2A)	C(3A)	C(4A)	C(11A	167.1(7)
C(2A)	C(3A)	C(4A)	C(12A	-77.8(9)
C(3A)	C(2A)	C(1A)	C(10A	60(1)
C(3A)	C(4A)	C(5A)	C(6A)	-175.1(6)
C(3A)	C(4A)	C(5A)	C(10A	-41.6(9)
C(4A)	C(5A)	C(6A)	C(7A)	119.8(8)
C(4A)	C(5A)	C(10AC	(9A)	-92.2(7)
C(4A)	C(5A)	C(10AC	(13A	147.8(6)
C(5A)	C(6A)	C(7A)	C(8A)	3(1)
C(5A)	C(10AC	(9A)	C(8A)	-50.5(7)
C(5A)	C(10AC	(9A)	C(14A	-172.0(5)
C(6A)	C(5A)	C(4A)	C(11A	69.9(7)
C(6A)	C(5A)	C(4A)	C(12A	-47.7(8)
C(6A)	C(5A)	C(10AC	(9A)	40.9(7)
C(6A)	C(5A)	C(10AC	(13A	-79.1(7)
C(6A)	C(7A)	O(4A)	C(17A	-3(1)
C(6A)	C(7A)	C(8A)	C(9A)	-11(1)
C(6A)	C(7A)	C(8A)	C(16A	-136.6(7)
C(7A)	C(6A)	C(5A)	C(10A	-18(1)
C(7A)	C(8A)	C(9A)	C(10A	34.7(7)
C(7A)	C(8A)	C(9A)	C(14A	160.0(5)
C(8A)	C(7A)	O(4A)	C(17A	174.0(6)
C(8A)	C(9A)	C(10AC	(13A	67.4(7)
C(8A)	C(9A)	C(14AC	(15A	111.5(8)
C(10AC	(5A)	C(4A)	C(11A	-156.7(6)

The sign is positive if when looking from atom to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Intramolecular Bond Angles Involving the Hydrogen Atoms (cont)

atom	atom	atom	angle	atom	atom	atom	angle
O(4A)	C(17A)	H(27)	116.95	C(4B)	C(11B)	H(45)	111.49
H(25)	C(17A)	H(26)	111.58	C(4B)	C(11B)	H(52)	109.41
H(25)	C(17A)	H(27)	114.38	H(44)	C(11B)	H(45)	107.24
H(26)	C(17A)	H(27)	96.65	H(44)	C(11B)	H(52)	92.57
C(1B)	O(1B)	H(40)	101.93	H(45)	C(11B)	H(52)	118.48
C(9B)	O(2B)	H(50)	100.05	C(4B)	C(12B)	H(36)	106.77
C(8B)	O(3B)	H(56)	80.66	C(4B)	C(12B)	H(53)	119.51
O(1B)	C(1B)	H(33)	107.08	C(4B)	C(12B)	H(55)	116.43
C(2B)	C(1B)	H(33)	117.54	H(36)	C(12B)	H(53)	103.89
C(10B)	C(1B)	H(33)	103.26	H(36)	C(12B)	H(55)	109.59
C(1B)	C(2B)	H(34)	107.00	H(53)	C(12B)	H(55)	99.78
C(1B)	C(2B)	H(46)	104.98	C(10B)	C(13B)	H(30)	119.32
C(3B)	C(2B)	H(34)	109.57	C(10B)	C(13B)	H(31)	112.44
C(3B)	C(2B)	H(46)	121.76	C(10B)	C(13B)	H(49)	117.32
H(34)	C(2B)	H(46)	99.76	H(30)	C(13B)	H(31)	109.99
C(2B)	C(3B)	H(41)	106.57	H(30)	C(13B)	H(49)	108.19
C(2B)	C(3B)	H(54)	110.94	H(31)	C(13B)	H(49)	84.14
C(4B)	C(3B)	H(41)	112.22	C(9B)	C(14B)	H(37)	111.43
C(4B)	C(3B)	H(54)	104.90	C(15B)	C(14B)	H(37)	120.77
H(41)	C(3B)	H(54)	107.36	C(14B)	C(15B)	H(47)	116.46
C(4B)	C(5B)	H(38)	108.72	C(14B)	C(15B)	H(48)	119.26
C(6B)	C(5B)	H(38)	101.95	H(47)	C(15B)	H(48)	123.98
C(10B)	C(5B)	H(38)	97.33	C(8B)	C(16B)	H(39)	105.02
C(5B)	C(6B)	H(32)	120.53	C(8B)	C(16B)	H(42)	109.28
C(7B)	C(6B)	H(32)	113.17	C(8B)	C(16B)	H(51)	106.63
C(4B)	C(11B)	H(44)	116.70	H(39)	C(16B)	H(42)	105.30

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Hydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C(1A)	O(1A)	H(28)	117.87	H(8)	C(11A)	H(15)	107.92
C(9A)	O(2A)	H(21)	120.64	C(4A)	C(12A)	H(2)	116.97
C(8A)	O(3A)	H(1)	104.20	C(4A)	C(12A)	H(9)	109.66
O(1A)	C(1A)	H(22)	106.50	C(4A)	C(12A)	H(10)	119.49
C(2A)	C(1A)	H(22)	104.29	H(2)	C(12A)	H(9)	93.21
C(10A)	C(1A)	H(22)	107.43	H(2)	C(12A)	H(10)	103.85
C(1A)	C(2A)	H(23)	110.04	H(9)	C(12A)	H(10)	110.51
C(1A)	C(2A)	H(24)	106.89	C(10A)	C(13A)	H(18)	116.56
C(3A)	C(2A)	H(23)	113.51	C(10A)	C(13A)	H(19)	121.18
C(3A)	C(2A)	H(24)	110.79	C(10A)	C(13A)	H(20)	102.77
H(23)	C(2A)	H(24)	103.84	H(18)	C(13A)	H(19)	101.81
C(2A)	C(3A)	H(6)	112.45	H(18)	C(13A)	H(20)	97.28
C(2A)	C(3A)	H(11)	72.69	H(19)	C(13A)	H(20)	115.15
C(4A)	C(3A)	H(6)	108.61	C(9A)	C(14A)	H(3)	113.74
C(4A)	C(3A)	H(11)	139.56	C(15A)	C(14A)	H(3)	120.61
H(6)	C(3A)	H(11)	106.38	C(14A)	C(15A)	H(12)	127.33
C(4A)	C(5A)	H(16)	105.07	C(14A)	C(15A)	H(14)	119.19
C(6A)	C(5A)	H(16)	110.47	H(12)	C(15A)	H(14)	112.12
C(10A)	C(5A)	H(16)	96.51	C(8A)	C(16A)	H(5)	110.67
C(5A)	C(6A)	H(17)	110.81	C(8A)	C(16A)	H(7)	106.61
C(7A)	C(6A)	H(17)	123.43	C(8A)	C(16A)	H(13)	115.86
C(4A)	C(11A)	H(4)	109.36	H(5)	C(16A)	H(7)	110.81
C(4A)	C(11A)	H(8)	121.72	H(5)	C(16A)	H(13)	99.34
C(4A)	C(11A)	H(15)	108.72	H(7)	C(16A)	H(13)	113.48
H(4)	C(11A)	H(8)	116.04	O(4A)	C(17A)	H(25)	108.32
H(4)	C(11A)	H(15)	87.39	O(4A)	C(17A)	H(26)	108.35

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms (cont)

atom	atom	atom	angle	atom	atom	atom	angle
C(6B)	C(5B)	C(10B)	111.9(5)				
C(5B)	C(6B)	C(7B)	125.0(6)				
O(4B)	C(7B)	C(6B)	125.2(6)				
O(4B)	C(7B)	C(8B)	108.5(6)				
C(6B)	C(7B)	C(8B)	126.2(6)				
O(3B)	C(8B)	C(7B)	109.0(6)				
O(3B)	C(8B)	C(9B)	107.0(5)				
O(3B)	C(8B)	C(16B)	109.0(6)				
C(7B)	C(8B)	C(9B)	110.8(5)				
C(7B)	C(8B)	C(16B)	110.7(6)				
C(9B)	C(8B)	C(16B)	110.2(6)				
O(2B)	C(9B)	C(8B)	105.4(5)				
O(2B)	C(9B)	C(10B)	108.7(5)				
O(2B)	C(9B)	C(14B)	109.6(5)				
C(8B)	C(9B)	C(10B)	113.0(5)				
C(8B)	C(9B)	C(14B)	109.1(5)				
C(10B)	C(9B)	C(14B)	110.8(5)				
C(1B)	C(10B)	C(5B)	110.6(5)				
C(1B)	C(10B)	C(9B)	112.9(5)				
C(1B)	C(10B)	C(13B)	104.1(5)				
C(5B)	C(10B)	C(9B)	113.7(5)				
C(5B)	C(10B)	C(13B)	104.2(5)				
C(9B)	C(10B)	C(13B)	110.6(6)				
C(9B)	C(14B)	C(15B)	127.5(7)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C(7A)	O(4A)	C(17A)	115.9(6)	O(2A)	C(9A)	C(10A)	105.4(5)
O(1A)	C(1A)	C(2A)	107.6(7)	O(2A)	C(9A)	C(14A)	110.2(5)
O(1A)	C(1A)	C(10A)	115.1(7)	C(8A)	C(9A)	C(10A)	113.3(5)
C(2A)	C(1A)	C(10A)	115.0(6)	C(8A)	C(9A)	C(14A)	106.5(5)
C(1A)	C(2A)	C(3A)	111.3(8)	C(10A)	C(9A)	C(14A)	113.3(5)
C(2A)	C(3A)	C(4A)	110.8(7)	C(1A)	C(10A)	C(5A)	107.3(5)
C(3A)	C(4A)	C(5A)	112.0(6)	C(1A)	C(10A)	C(9A)	114.9(5)
C(3A)	C(4A)	C(11A)	106.0(6)	C(1A)	C(10A)	C(13A)	105.5(5)
C(3A)	C(4A)	C(12A)	110.3(7)	C(5A)	C(10A)	C(9A)	113.0(5)
C(5A)	C(4A)	C(11A)	105.8(6)	C(5A)	C(10A)	C(13A)	106.1(5)
C(5A)	C(4A)	C(12A)	115.4(6)	C(9A)	C(10A)	C(13A)	109.5(5)
C(11A)	C(4A)	C(12A)	106.6(7)	C(9A)	C(14A)	C(15A)	125.3(7)
C(4A)	C(5A)	C(6A)	111.0(6)	C(7B)	O(4B)	C(17B)	116.5(5)
C(4A)	C(5A)	C(10A)	120.6(6)	O(1B)	C(1B)	C(2B)	106.5(6)
C(6A)	C(5A)	C(10A)	111.8(5)	O(1B)	C(1B)	C(10B)	111.9(5)
C(5A)	C(6A)	C(7A)	125.7(6)	C(2B)	C(1B)	C(10B)	110.6(6)
O(4A)	C(7A)	C(6A)	126.4(7)	C(1B)	C(2B)	C(3B)	112.3(6)
O(4A)	C(7A)	C(8A)	108.0(6)	C(2B)	C(3B)	C(4B)	114.7(6)
C(6A)	C(7A)	C(8A)	125.5(6)	C(3B)	C(4B)	C(5B)	110.9(6)
O(3A)	C(8A)	C(7A)	107.2(5)	C(3B)	C(4B)	C(11B)	107.9(6)
O(3A)	C(8A)	C(9A)	108.2(5)	C(3B)	C(4B)	C(12B)	110.7(6)
O(3A)	C(8A)	C(16A)	106.9(5)	C(5B)	C(4B)	C(11B)	107.4(6)
C(7A)	C(8A)	C(9A)	111.8(5)	C(5B)	C(4B)	C(12B)	113.1(5)
C(7A)	C(8A)	C(16A)	110.9(6)	C(11B)	C(4B)	C(12B)	106.6(6)
C(9A)	C(8A)	C(16A)	111.5(5)	C(4B)	C(5B)	C(6B)	114.1(6)
O(2A)	C(9A)	C(8A)	108.1(5)	C(4B)	C(5B)	C(10B)	119.7(6)

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	atom	atom	distance
C(16B)	H(51)	0.985			
C(17B)	H(29)	1.139			
C(17B)	H(35)	0.961			
C(17B)	H(43)	0.848			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	atom	atom	distance
O(1A)	H(28)	1.037	C(17A)	H(26)	1.167
O(2A)	H(21)	1.052	C(17A)	H(27)	1.030
O(3A)	H(1)	1.175	O(1B)	H(40)	0.884
C(1A)	H(22)	0.994	O(2B)	H(50)	1.114
C(2A)	H(23)	0.979	O(3B)	H(56)	1.176
C(2A)	H(24)	0.992	C(1B)	H(33)	1.070
C(3A)	H(6)	1.280	C(2B)	H(34)	0.951
C(3A)	H(11)	0.976	C(2B)	H(46)	0.986
C(5A)	H(16)	1.049	C(3B)	H(41)	1.271
C(6A)	H(17)	1.119	C(3B)	H(54)	0.950
C(11A)	H(4)	0.889	C(5B)	H(38)	0.973
C(11A)	H(8)	1.259	C(6B)	H(32)	1.121
C(11A)	H(15)	1.283	C(11B)	H(44)	0.890
C(12A)	H(2)	1.158	C(11B)	H(45)	0.941
C(12A)	H(9)	0.986	C(11B)	H(52)	0.967
C(12A)	H(10)	1.112	C(12B)	H(36)	0.932
C(13A)	H(18)	0.913	C(12B)	H(53)	1.080
C(13A)	H(19)	0.906	C(12B)	H(55)	0.937
C(13A)	H(20)	1.178	C(13B)	H(30)	0.888
C(14A)	H(3)	1.077	C(13B)	H(31)	0.877
C(15A)	H(12)	1.062	C(13B)	H(49)	1.231
C(15A)	H(14)	0.977	C(14B)	H(37)	0.918
C(16A)	H(5)	1.105	C(15B)	H(47)	1.177
C(16A)	H(7)	0.949	C(15B)	H(48)	1.039
C(16A)	H(13)	1.018	C(16B)	H(39)	0.973
C(17A)	H(25)	1.016	C(16B)	H(42)	1.145

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
O(1A)	C(1A)	1.372(8)	O(1B)	C(1B)	1.460(7)
O(2A)	C(9A)	1.427(7)	O(2B)	C(9B)	1.437(7)
O(3A)	C(8A)	1.450(7)	O(3B)	C(8B)	1.456(7)
O(4A)	C(7A)	1.377(7)	O(4B)	C(7B)	1.385(7)
O(4A)	C(17A)	1.410(9)	O(4B)	C(17B)	1.429(8)
C(1A)	C(2A)	1.53(1)	C(1B)	C(2B)	1.511(9)
C(1A)	C(10A)	1.574(9)	C(1B)	C(10B)	1.551(8)
C(2A)	C(3A)	1.51(1)	C(2B)	C(3B)	1.52(1)
C(3A)	C(4A)	1.49(1)	C(3B)	C(4B)	1.536(9)
C(4A)	C(5A)	1.569(9)	C(4B)	C(5B)	1.564(9)
C(4A)	C(11A)	1.538(9)	C(4B)	C(11B)	1.537(9)
C(4A)	C(12A)	1.53(1)	C(4B)	C(12B)	1.515(9)
C(5A)	C(6A)	1.476(8)	C(5B)	C(6B)	1.503(8)
C(5A)	C(10A)	1.580(8)	C(5B)	C(10B)	1.572(9)
C(6A)	C(7A)	1.308(8)	C(6B)	C(7B)	1.318(9)
C(7A)	C(8A)	1.521(9)	C(7B)	C(8B)	1.510(9)
C(8A)	C(9A)	1.574(8)	C(8B)	C(9B)	1.558(9)
C(8A)	C(16A)	1.524(8)	C(8B)	C(16B)	1.546(9)
C(9A)	C(10A)	1.552(8)	C(9B)	C(10B)	1.561(8)
C(9A)	C(14A)	1.520(9)	C(9B)	C(14B)	1.524(9)
C(10A)	C(13A)	1.540(9)	C(10B)	C(13B)	1.545(9)
C(14A)	C(15A)	1.324(9)	C(14B)	C(15B)	1.309(9)

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(1A)	O(1B)	2.676(7)	64603	O(4A)	O(4B)	3.574(7)	66504
O(1A)	C(16A)	3.462(9)	7	C(15A)	O(2B)	3.397(8)	66605
O(1A)	C(1B)	3.470(9)	64603	C(15A)	C(15B)	3.51(1)	64603
O(2A)	O(2B)	3.011(6)	66605	C(15A)	C(12B)	3.52(1)	66605
O(3A)	O(3B)	2.948(6)	66504	C(16A)	O(1B)	3.453(8)	66605
O(3A)	O(4B)	3.263(7)	66504	C(17A)	C(13B)	3.47(1)	64506
O(4A)	C(14A)	3.503(8)	55407	O(3B)	C(17B)	3.560(8)	56507
O(4A)	C(17B)	3.560(9)	66504				

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

(*) footnote

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one digit numbers and one two digit number: TA(1st digit) + TB(2nd digit) + TC(3rd digit) + SN(4th and 5th digit). TA, TB, & TC are the crystal lattice translation digits along cell edges a, b, and c. A translation digit of 5 indicates the origin unit cell. If TA=4, this indicates a translation of one unit cell length along the a axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus (+/-)4 lattice translations from the origin (TA=5,TB=5, TC=5) can be represented.

The SN or symmetry operator number refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of the symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell (TA=5,TB=5,TC=5) and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always ADC=55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of that atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (i.e.cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	+X	+Y	+Z	(2)	1/2+X	1/2-Y	-Z
(3)	-X	1/2+Y	1/2-Z	(4)	1/2-X	-Y	1/2+Z
(5)	-X	-Y	-Z	(6)	1/2-X	1/2+Y	+Z
(7)	+X	1/2-Y	1/2+Z	(8)	1/2+X	+Y	1/2-Z

Intermolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(1A)	H(40)	1.875	64603	C(6A)	H(41)	3.528	45602
O(1A)	H(13)	2.963	7	C(7A)	H(14)	3.369	55407
O(1A)	H(5)	3.047	7	C(11A)	H(5)	3.320	54506
O(1A)	H(33)	3.171	64603	C(11A)	H(43)	3.512	45507
O(1A)	H(15)	3.374	4	C(11A)	H(7)	3.537	54506
O(1A)	H(8)	3.482	4	C(11A)	H(22)	3.545	55404
O(1A)	H(50)	3.550	64603	C(12A)	H(48)	3.485	66605
O(2A)	H(48)	2.759	66605	C(12A)	H(36)	3.594	64503
O(2A)	H(42)	3.068	66605	C(13A)	H(41)	3.347	45602
O(2A)	H(50)	3.105	66605	C(13A)	H(43)	3.358	64606
O(2A)	H(39)	3.557	66605	C(13A)	H(52)	3.373	45602
O(3A)	H(56)	2.267	66504	C(13A)	H(54)	3.418	45602
O(3A)	H(25)	3.257	7	C(13A)	H(29)	3.431	64606
O(4A)	H(3)	2.691	55407	C(13A)	H(15)	3.451	4
O(4A)	H(29)	2.730	66504	C(13A)	H(36)	3.556	45602
O(4A)	H(14)	3.066	55407	C(14A)	H(25)	3.378	7
C(1A)	H(40)	3.031	64603	C(14A)	H(13)	3.451	7
C(1A)	H(15)	3.288	4	C(14A)	H(5)	3.574	7
C(2A)	H(49)	3.308	45507	C(15A)	H(53)	2.818	66605
C(2A)	H(33)	3.385	64603	C(15A)	H(13)	3.133	7
C(2A)	H(40)	3.392	64603	C(15A)	H(55)	3.200	66605
C(3A)	H(30)	3.225	45507	C(15A)	H(47)	3.250	64603
C(3A)	H(38)	3.327	45507	C(15A)	H(48)	3.335	64603
C(3A)	H(27)	3.513	4	C(16A)	H(50)	2.921	66605
C(5A)	H(54)	3.165	45602	C(16A)	H(28)	3.141	55407
C(6A)	H(54)	3.153	45602	C(16A)	H(8)	3.163	6

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
C(16A)	H(48)	3.183	66605	H(2)	H(38)	3.474	45507
C(16A)	H(40)	3.240	66605	H(3)	H(25)	2.526	7
C(16A)	H(14)	3.556	55407	H(3)	H(5)	2.953	7
C(17A)	H(3)	2.886	55407	H(3)	H(29)	3.136	64606
C(17A)	H(30)	2.927	64506	H(3)	H(27)	3.180	7
C(17A)	H(29)	2.981	66504	H(3)	H(13)	3.248	7
C(17A)	H(6)	3.174	55404	H(4)	H(43)	2.637	45507
C(17A)	H(31)	3.211	64506	H(4)	H(5)	2.959	54506
C(17A)	H(14)	3.316	55407	H(4)	H(18)	3.350	55404
C(17A)	H(34)	3.424	45602	H(4)	H(32)	3.380	45507
H(1)	H(56)	1.910	66504	H(4)	H(20)	3.446	55404
H(1)	O(4B)	2.215	66504	H(4)	C(17B)	3.447	45507
H(1)	H(29)	2.777	66504	H(4)	H(7)	3.515	54506
H(1)	C(17B)	2.835	66504	H(5)	H(28)	2.805	55407
H(1)	O(3B)	2.891	66504	H(5)	H(8)	2.883	6
H(1)	H(43)	2.892	66504	H(5)	H(18)	2.990	55407
H(1)	H(51)	3.095	66504	H(5)	H(43)	3.123	66504
H(1)	C(7B)	3.097	66504	H(5)	H(29)	3.269	66504
H(1)	C(8B)	3.399	66504	H(5)	H(40)	3.376	66605
H(2)	H(32)	2.820	45507	H(5)	C(17B)	3.569	66504
H(2)	H(44)	2.939	45507	H(5)	H(15)	3.593	6
H(2)	H(45)	3.051	45507	H(5)	H(14)	3.596	55407
H(2)	H(36)	3.225	64503	H(6)	H(27)	2.428	4
H(2)	H(55)	3.301	64503	H(6)	H(30)	3.077	45507
H(2)	H(45)	3.399	64503	H(6)	H(25)	3.193	4
H(2)	C(11B)	3.426	45507	H(6)	H(26)	3.452	4

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
H(7)	H(50)	2.524	66605	H(11)	C(5B)	3.343	45507
H(7)	H(8)	2.606	6	H(11)	H(32)	3.554	45507
H(7)	O(1B)	3.012	66605	H(11)	C(6B)	3.558	45507
H(7)	H(40)	3.043	66605	H(11)	H(27)	3.571	4
H(7)	H(53)	3.108	66605	H(12)	H(47)	2.486	64603
H(7)	O(2B)	3.240	66605	H(12)	H(53)	2.582	66605
H(7)	H(48)	3.410	66605	H(12)	O(2B)	2.609	66605
H(7)	H(28)	3.586	55407	H(12)	H(42)	2.690	66605
H(8)	O(1B)	2.894	45602	H(12)	H(55)	2.720	66605
H(8)	H(54)	2.924	45602	H(12)	C(15B)	2.954	64603
H(8)	H(40)	3.106	45602	H(12)	H(48)	3.099	64603
H(8)	H(53)	3.232	45602	H(12)	H(50)	3.123	66605
H(9)	H(48)	2.892	66605	H(12)	C(12B)	3.188	66605
H(9)	H(39)	3.247	66605	H(12)	H(13)	3.565	7
H(9)	H(44)	3.254	45507	H(13)	H(48)	2.304	66605
H(9)	C(15B)	3.450	66605	H(13)	H(28)	2.454	55407
H(10)	H(14)	2.725	55407	H(13)	H(50)	2.521	66605
H(10)	H(36)	2.878	64503	H(13)	H(14)	2.741	55407
H(10)	H(55)	2.972	64503	H(13)	H(40)	2.763	66605
H(10)	H(48)	3.166	66605	H(13)	O(1B)	3.154	66605
H(10)	C(12B)	3.347	64503	H(13)	C(15B)	3.195	66605
H(10)	H(47)	3.580	66605	H(13)	O(2B)	3.361	66605
H(11)	H(38)	2.437	45507	H(14)	H(53)	2.833	66605
H(11)	H(30)	2.500	45507	H(14)	H(48)	2.978	64603
H(11)	H(49)	2.723	45507	H(14)	H(27)	2.978	7
H(11)	C(13B)	2.951	45507	H(14)	H(55)	2.980	66605

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
H(14)	H(47)	3.186	64603	H(19)	H(52)	2.982	45602
H(14)	C(12B)	3.332	66605	H(19)	H(56)	3.021	66504
H(14)	C(15B)	3.358	64603	H(19)	H(29)	3.160	64606
H(14)	H(36)	3.364	66605	H(19)	H(54)	3.201	45602
H(15)	H(22)	2.453	55404	H(19)	H(43)	3.338	64606
H(15)	H(20)	2.657	55404	H(19)	C(3B)	3.455	45602
H(15)	H(18)	3.121	55404	H(19)	O(3B)	3.462	66504
H(15)	H(36)	3.487	64503	H(20)	H(36)	2.519	45602
H(15)	H(43)	3.531	45507	H(20)	H(54)	2.971	45602
H(16)	H(54)	2.375	45602	H(20)	H(52)	2.988	45602
H(16)	H(36)	3.155	45602	H(20)	H(41)	3.353	45602
H(16)	C(3B)	3.241	45602	H(20)	C(12B)	3.382	45602
H(16)	H(41)	3.418	45602	H(20)	H(43)	3.388	64606
H(16)	H(53)	3.559	45602	H(20)	C(3B)	3.508	45602
H(17)	H(54)	2.810	45602	H(21)	O(2B)	1.991	66605
H(17)	H(34)	2.820	45602	H(21)	H(50)	2.075	66605
H(17)	H(22)	3.320	55404	H(21)	H(48)	2.175	66605
H(17)	C(3B)	3.379	45602	H(21)	H(42)	2.632	66605
H(17)	H(41)	3.453	45602	H(21)	C(15B)	3.071	66605
H(17)	C(2B)	3.504	45602	H(21)	H(39)	3.133	66605
H(18)	H(43)	2.659	64606	H(21)	C(9B)	3.200	66605
H(18)	H(29)	2.757	64606	H(21)	C(16B)	3.351	66605
H(18)	C(17B)	3.146	64606	H(21)	H(53)	3.481	66605
H(18)	H(52)	3.509	45602	H(21)	C(14B)	3.484	66605
H(18)	H(35)	3.541	64606	H(22)	H(40)	3.275	64603
H(19)	H(41)	2.698	45602	H(22)	H(27)	3.286	4

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
H(23)	H(49)	2.485	45507	H(26)	H(31)	2.524	64506
H(23)	H(33)	2.595	64603	H(26)	H(30)	2.650	64506
H(23)	H(34)	2.721	64603	H(26)	H(49)	2.886	64506
H(23)	H(40)	2.914	64603	H(26)	C(13B)	2.934	64506
H(23)	C(1B)	3.174	64603	H(26)	C(2B)	3.125	45602
H(23)	H(30)	3.181	45507	H(26)	H(41)	3.213	45602
H(23)	C(13B)	3.336	45507	H(26)	H(46)	3.280	45602
H(23)	C(2B)	3.363	64603	H(26)	H(29)	3.409	66504
H(23)	H(38)	3.364	45507	H(26)	C(3B)	3.565	45602
H(23)	O(1B)	3.395	64603	H(26)	H(54)	3.594	45602
H(23)	H(46)	3.551	64603	H(27)	H(30)	3.173	64506
H(23)	H(46)	3.561	45507	H(27)	H(34)	3.413	45602
H(23)	H(26)	3.579	4	H(28)	H(40)	2.313	64603
H(24)	H(42)	3.099	66605	H(28)	O(1B)	3.164	64603
H(24)	H(33)	3.384	64603	H(28)	H(48)	3.264	64603
H(24)	H(39)	3.426	66605	H(28)	C(15B)	3.505	64603
H(24)	H(40)	3.599	64603	H(28)	H(50)	3.558	64603
H(25)	H(29)	2.448	66504	O(3B)	H(29)	2.803	56507
H(25)	H(30)	2.472	64506	O(3B)	H(35)	3.240	56507
H(25)	O(3B)	2.676	64506	O(4B)	H(37)	3.105	56407
H(25)	H(31)	2.961	64506	O(4B)	H(47)	3.284	56407
H(25)	C(13B)	3.111	64506	C(1B)	H(49)	3.394	76605
H(25)	H(56)	3.350	64506	C(2B)	H(49)	2.796	76605
H(25)	H(37)	3.541	64506	C(2B)	H(31)	3.375	76605
H(25)	C(17B)	3.563	66504	C(6B)	H(47)	3.338	56407
H(26)	H(34)	2.324	45602	C(7B)	H(47)	3.211	56407

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
C(11B)	H(45)	3.390	76505	H(35)	H(47)	2.702	56407
C(11B)	H(35)	3.493	76505	H(35)	H(52)	2.809	76505
C(12B)	H(47)	3.399	56407	H(35)	H(44)	3.362	76505
C(13B)	H(46)	3.237	76605	H(35)	H(39)	3.469	56407
C(13B)	H(34)	3.275	76605	H(37)	H(42)	3.406	56507
C(14B)	H(35)	3.116	56507	H(37)	H(51)	3.573	56507
C(15B)	H(35)	3.243	56507	H(39)	H(44)	2.849	75503
C(15B)	H(55)	3.478	56507	H(39)	H(41)	3.267	75503
C(15B)	H(42)	3.499	56507	H(39)	H(52)	3.410	75503
C(16B)	H(41)	3.346	75503	H(41)	H(51)	2.575	74503
C(16B)	H(44)	3.561	75503	H(41)	H(56)	3.386	74503
C(17B)	H(37)	3.083	56407	H(42)	H(47)	2.900	56407
C(17B)	H(52)	3.350	76505	H(43)	H(52)	3.173	76505
C(17B)	H(47)	3.419	56407	H(44)	H(51)	3.421	74503
H(29)	H(37)	2.864	56407	H(45)	H(45)	2.545	76505
H(29)	H(56)	3.514	56407	H(46)	H(49)	2.295	76605
H(30)	H(34)	3.455	76605	H(46)	H(46)	3.051	76605
H(31)	H(46)	2.787	76605	H(47)	H(55)	2.481	56507
H(31)	H(34)	2.930	76605	H(47)	H(53)	3.586	56507
H(32)	H(45)	3.332	76505	H(49)	H(49)	3.195	76605
H(32)	H(52)	3.414	76505				
H(32)	H(47)	3.482	56407				
H(33)	H(49)	3.065	76605				
H(33)	H(46)	3.106	76605				
H(34)	H(49)	2.349	76605				
H(35)	H(37)	2.655	56407				

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

(*) footnote

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one digit numbers and one two digit number: TA(1st digit) + TB(2nd digit) + TC(3rd digit) + SN(4th and 5th digit). TA, TB, & TC are the crystal lattice translation digits along cell edges a, b, and c. A translation digit of 5 indicates the origin unit cell. If TA=4, this indicates a translation of one unit cell length along the a axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus (+/-)4 lattice translations from the origin (TA=5,TB=5, TC=5) can be represented.

The SN or symmetry operator number refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of the symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell (TA=5,TB=5,TC=5) and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always ADC=55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of that atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (i.e.cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	+X	+Y	+Z	(2)	1/2+X	1/2-Y	-Z
(3)	-X	1/2+Y	1/2-Z	(4)	1/2-X	-Y	1/2+Z
(5)	-X	-Y	-Z	(6)	1/2-X	1/2+Y	+Z
(7)	+X	1/2-Y	1/2+Z	(8)	1/2+X	+Y	1/2-Z

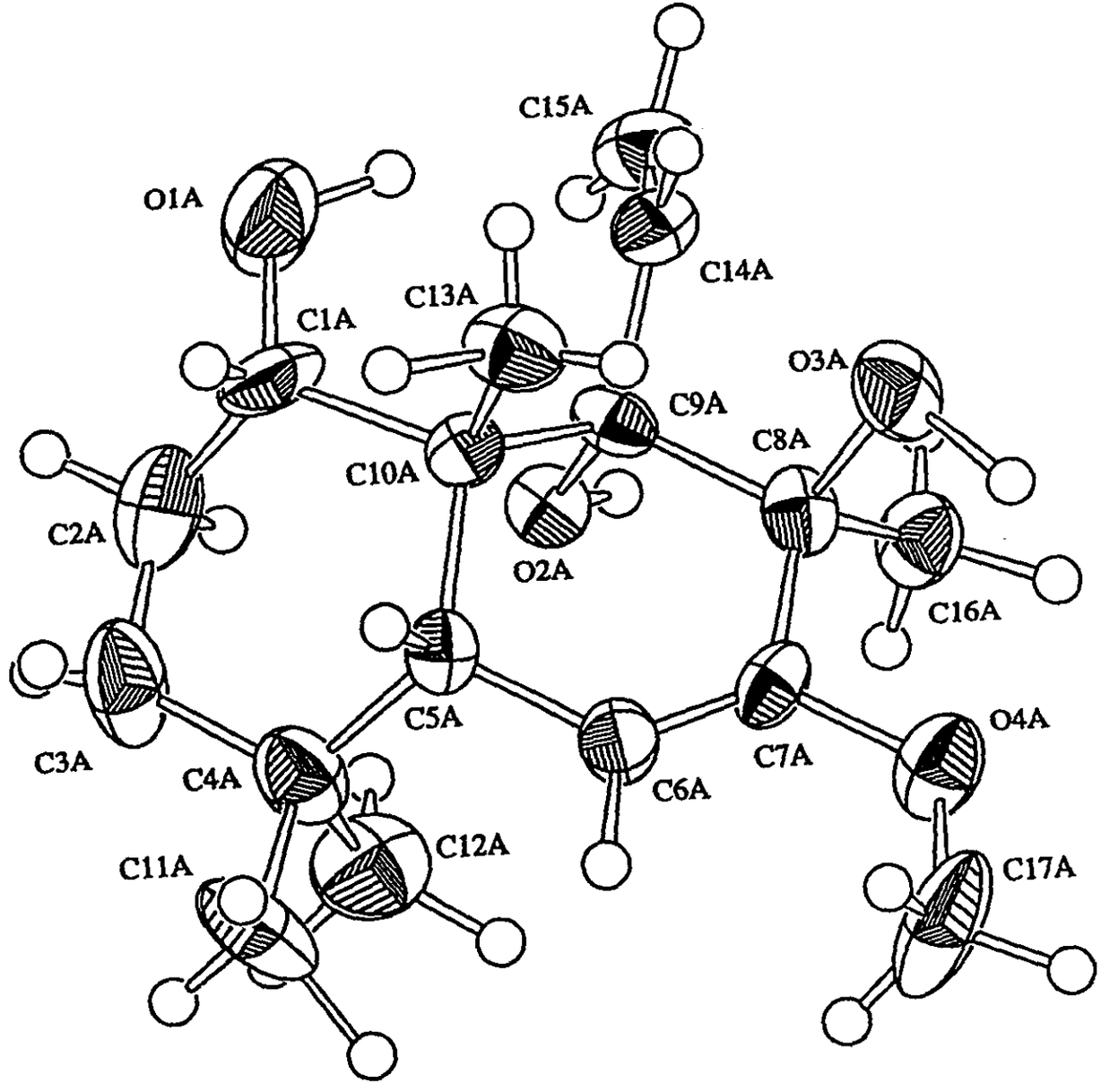
Cartesian coordinates

atom	x	y	z
O1A	4.2337	2.5471	13.5826
O2A	3.8417	3.7146	10.5892
O3A	7.3035	4.8822	10.4543
O4A	7.0824	3.8541	7.8250
C1A	4.6101	1.7157	12.5584
C2A	3.3410	1.0792	11.9884
C3A	3.6714	-0.0250	11.0099
C4A	4.4130	0.5121	9.8394
C5A	5.6606	1.3585	10.2725
C6A	6.3110	1.9772	9.1010
C7A	6.4703	3.2610	8.9062
C8A	6.0775	4.3580	9.8842
C9A	5.1866	3.8036	11.0569
C10A	5.5678	2.3625	11.4891
C11A	4.9747	-0.7109	9.0945
C12A	3.4479	1.2102	8.8718
C13A	6.9630	2.3725	12.1406
C14A	5.2824	4.8155	12.1876
C15A	4.2947	5.5920	12.6043
C16A	5.3950	5.5128	9.1605
C17A	7.6333	2.9748	6.8707
H1	8.0280	4.9854	9.5349
H2	2.5378	0.5960	8.5033
H3	6.2140	4.7767	12.7263
H4	4.3043	-1.2430	8.8541
H5	6.0989	6.0105	8.4694
H6	4.3682	-0.9575	11.5422
H7	5.0978	6.1155	9.8309
H8	6.0304	-1.2864	9.4684
H9	2.8853	1.8498	9.3683

H10	3.8455	1.6790	7.9451
H11	2.7522	-0.1651	11.3063
H12	3.2584	5.4794	12.4029
H13	4.6677	5.2533	8.4970
H14	4.4623	6.2316	13.3232
H15	5.1057	-0.4129	7.8534
H16	6.3084	0.6736	10.7327
H17	6.7121	1.1942	8.4091
H18	7.0269	2.7646	12.9630
H19	7.6786	2.7249	11.7112
H20	7.0921	1.2568	12.4966
H21	3.3033	4.5823	10.3377
H22	5.1021	1.0090	12.9597
H23	2.8290	0.7173	12.7021
H24	2.8338	1.7469	11.5418
H25	8.0711	3.5295	6.1403
H26	8.4066	2.2865	7.4087
H27	7.0236	2.2208	6.5239
H28	4.3053	3.5699	13.4277
O1B	20.2828	12.0605	5.4114
O2B	21.2601	13.9094	3.9279
O3B	24.7658	14.5552	4.5778
O4B	24.7447	14.1649	1.6969
C1B	21.6064	11.5199	5.7093
C2B	21.5309	10.0336	5.4498
C3B	21.0328	9.7162	4.0462
C4B	21.7092	10.5230	2.9272
C5B	22.8931	11.3748	3.4912
C6B	23.6158	12.1857	2.4529
C7B	23.9597	13.4513	2.5875
C8B	23.5930	14.3586	3.7373
C9B	22.4962	13.7043	4.6304
C10B	22.7089	12.1712	4.8340

C11B	22.2997	9.5259	1.9174
C12B	20.6896	11.3501	2.1725
C13B	24.0153	11.9037	5.6147
C14B	22.4484	14.4266	5.9711
C15B	21.5283	15.2549	6.3975
C16B	23.1104	15.7322	3.2172
C17B	25.1809	13.4656	0.5300
H29	25.7215	14.2673	-0.0724
H30	24.7949	12.1077	5.2410
H31	23.9852	12.2145	6.4340
H32	24.1135	11.6836	1.5831
H33	21.8598	11.8371	6.6992
H34	20.9303	9.6697	6.0907
H35	24.4084	13.2528	-0.0008
H36	20.1089	10.7497	1.7596
H37	23.2180	14.2910	6.4528
H38	23.5924	10.7724	3.7992
H39	22.8348	16.2202	4.0122
H40	20.0559	12.4247	6.1847
H41	21.1723	8.4628	3.8867
H42	22.1547	15.5894	2.6040
H43	25.7682	12.8612	0.6223
H44	22.8901	8.9391	2.2332
H45	22.7065	9.9686	1.1934
H46	22.3812	9.6714	5.7930
H47	21.8041	15.9056	7.3392
H48	20.6554	15.3714	5.8469
H49	24.1289	10.8097	6.1684
H50	20.5377	13.5523	4.6971
H51	23.8953	16.1746	2.8192
H52	21.6492	8.8359	1.7293
H53	20.0332	12.0125	2.7175
H54	20.1067	9.9113	3.9623

	H55	21.0270	11.9487	1.5361
	H56	25.1604	15.0426	3.5825


C15A
O1A
C14A
C13A
C1A
O3A
C9A
C8A
C10A
C2A
O2A
C16A
C5A
O4A
C3A
C7A
C4A
C6A
C12A
C11A
C17A

Appendix 3

X-ray Structure Report

For

Compound 4.30 *

* I would like to thank Dr. Rosi Hynes of the McGill X-ray Facility for this determination.

KEV5 - KG/CHAN - AUG 8/91

Space Group and Cell Dimensions Monoclinic, C 2/c
a 17.242(3) b 21.796(3) c 12.628(3)
beta 107.717(14)
Volume 4520.7(13)A**3

Empirical formula : C22 H34 O6 .1/2 H2O

Cell dimensions were obtained from 19 reflections with 2Theta angle in the range 20.00 - 30.00 degrees.

Crystal dimensions : 0.20 X 0.20 X 0.02 mm

FW = 402.50 Z = 8 F(000) = 1749.44

Dcalc 1.183Mg.m-3, mu 0.64mm-1, lambda 1.54056A, 2Theta(max) 90.0

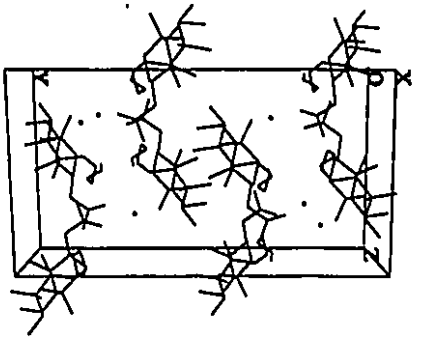
The intensity data were collected on a Rigaku diffractometer, using the theta/2theta scan mode.
The h,k,l ranges are :-- -12 12, 0 19, 0 11
No. of reflections measured 1802
No. of unique reflections 1723
No. of reflections with Inet > 2.0sigma(Inet) 970
No correction was made for absorption

The last least squares cycle was calculated with
63 atoms, 225 parameters and 970 out of 1723 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000500

The residuals are as follows :--
For significant reflections, RF 0.118, Rw 0.135 GoF 3.21
For all reflections, RF 0.232, Rw 0.138.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.076.

In the last D-map, the deepest hole was -0.550e/A**3,
and the highest peak 0.500e/A**3.

Solved by direct methods (SOLVER). Hydrogens calculated. Non-hydrogens anisotropic, except those in the hexenyl chain which were left isotropic. There is solvent water present (about 2:1 molecule:solvent) Standards moved 1.5 % over course of collection. Merging R was 3.4% fo 79 pairs of symmetry equivalent pairs of relections. Diffractometer controlled by TEXRAY software. Solution and refinement with NRCVAX system of crystal structure solving programs.



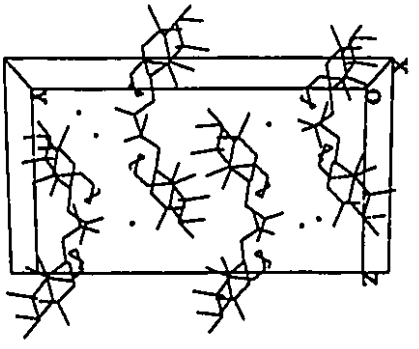


Table 2. Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
O 1	0.6592 (7)	0.8802(5)	0.8282 (9)	3.1(7)
O 2	0.6391 (8)	0.7796(6)	0.7908 (10)	5.6(8)
O 3	0.8105 (6)	0.9401(5)	0.9187 (8)	2.2(6)
O 4	0.9454 (6)	0.9344(5)	1.1246 (9)	2.8(6)
O 5	0.8987 (6)	0.9783(5)	1.3180 (8)	2.7(6)
O 6	0.7364 (6)	1.0115(5)	1.2152 (8)	2.7(6)
C 1	0.6614 (10)	0.8715(8)	0.9448 (12)	2.6(10)
C 2	0.5723 (10)	0.8675(8)	0.9454 (13)	3.2(9)
C 3	0.5712 (10)	0.8540(8)	1.0630 (13)	2.8(10)
C 4	0.6178 (10)	0.8998(7)	1.1503 (13)	2.4(9)
C 5	0.7039 (9)	0.9093(7)	1.1397 (12)	1.7(8)
C 6	0.7612 (10)	0.9486(8)	1.2285 (14)	3.1(10)
C 7	0.8488 (10)	0.9389(8)	1.2292 (13)	2.6(10)
C 8	0.8650 (10)	0.9556(8)	1.1192 (13)	2.5(9)
C 9	0.8029 (10)	0.9158(7)	1.0234 (13)	2.3(9)
C10	0.7087 (11)	0.9233(7)	1.0190 (13)	2.8(10)
C11	0.5646 (10)	0.9572(8)	1.1437 (13)	2.7(9)
C12	0.6250 (11)	0.8706(8)	1.2638 (14)	3.5(10)
C13	0.6746 (10)	0.9853(7)	0.9715 (13)	2.3(9)
C14	0.8309 (10)	0.8492(7)	1.0388 (13)	2.1(4)
C15	0.8673 (11)	0.8149(8)	0.9816 (15)	4.0(5)
C16	0.8962 (15)	0.8293(11)	0.8836 (20)	7.9(7)
C17	1.0364 (18)	0.8051(13)	0.9474 (24)	11.0(9)
C18	0.9757 (20)	0.8464(15)	0.905 (3)	13.0(11)
C19	1.1326 (19)	0.8124(13)	0.980 (3)	11.8(10)
C20	0.8672 (10)	1.0245(8)	1.0981 (13)	2.9(10)
C21	0.6520 (12)	0.8286(8)	0.7628 (14)	4.1(11)
C22	0.6600 (12)	0.8479(9)	0.6548 (14)	4.5(12)
OW	1/2	0.6908(8)	0.75000	4.9(5)

Beq is the mean of the principal axes of the thermal ellipsoid for atoms refined anisotropically. For carbons C14-C19, Beq = Biso.

Table 3. Bond Distances (A) and Angles (Degrees)

O(1)-C(1)	1.475(17)	C(5)-C(10)	1.581(20)
O(1)-C(21)	1.377(19)	C(6)-C(7)	1.523(21)
O(2)-C(21)	1.170(20)	C(7)-C(8)	1.541(21)
O(3)-C(9)	1.468(17)	C(8)-C(9)	1.605(21)
O(4)-C(8)	1.444(18)	C(8)-C(20)	1.529(22)
O(5)-C(7)	1.466(17)	C(9)-C(10)	1.616(23)
O(6)-C(6)	1.432(18)	C(9)-C(14)	1.522(20)
C(1)-C(2)	1.542(22)	C(10)-C(13)	1.522(21)
C(1)-C(10)	1.535(22)	C(14)-C(15)	1.323(22)
C(2)-C(3)	1.520(21)	C(15)-C(16)	1.50(3)
C(3)-C(4)	1.523(21)	C(16)-C(18)	1.37(4)
C(4)-C(5)	1.544(21)	C(17)-C(18)	1.36(4)
C(4)-C(11)	1.541(22)	C(17)-C(19)	1.59(4)
C(4)-C(12)	1.538(21)	C(21)-C(22)	1.475(23)
C(5)-C(6)	1.514(21)		

C(1)-O(1)-C(21)	117.6(12)	C(7)-C(8)-C(9)	106.8(12)
O(1)-C(1)-C(2)	106.8(11)	C(7)-C(8)-C(20)	114.3(12)
O(1)-C(1)-C(10)	111.2(12)	C(9)-C(8)-C(20)	116.6(12)
C(2)-C(1)-C(10)	112.6(13)	O(3)-C(9)-C(8)	105.1(11)
C(1)-C(2)-C(3)	109.0(12)	O(3)-C(9)-C(10)	107.3(11)
C(2)-C(3)-C(4)	114.7(12)	O(3)-C(9)-C(14)	110.4(12)
C(3)-C(4)-C(5)	109.7(12)	C(8)-C(9)-C(10)	113.8(12)
C(3)-C(4)-C(11)	108.6(12)	C(8)-C(9)-C(14)	107.8(12)
C(3)-C(4)-C(12)	106.1(12)	C(10)-C(9)-C(14)	112.2(12)
C(5)-C(4)-C(11)	117.3(12)	C(1)-C(10)-C(5)	105.8(12)
C(5)-C(4)-C(12)	109.2(12)	C(1)-C(10)-C(9)	106.7(12)
C(11)-C(4)-C(12)	105.3(12)	C(1)-C(10)-C(13)	110.0(12)
C(4)-C(5)-C(6)	116.1(12)	C(5)-C(10)-C(9)	107.1(12)
C(4)-C(5)-C(10)	116.3(12)	C(5)-C(10)-C(13)	115.1(12)
C(6)-C(5)-C(10)	113.0(12)	C(9)-C(10)-C(13)	111.6(12)
O(6)-C(6)-C(5)	110.6(12)	C(9)-C(14)-C(15)	130.9(14)
O(6)-C(6)-C(7)	113.2(12)	C(14)-C(15)-C(16)	131.4(16)
C(5)-C(6)-C(7)	110.4(13)	C(15)-C(16)-C(18)	117.5(21)
O(5)-C(7)-C(6)	105.9(11)	C(18)-C(17)-C(19)	130.4(25)
O(5)-C(7)-C(8)	109.0(12)	C(16)-C(18)-C(17)	120(3)
C(6)-C(7)-C(8)	114.4(12)	O(1)-C(21)-O(2)	123.8(15)
O(4)-C(8)-C(7)	108.4(11)	O(1)-C(21)-C(22)	107.8(13)
O(4)-C(8)-C(9)	105.9(11)	O(2)-C(21)-C(22)	128.4(16)
O(4)-C(8)-C(20)	104.3(12)		

Table S-2. Calculated Hydrogen Atom Parameters

	x	y	z	Biso
H 1	0.688	0.828	0.977	3.5
H 2A	0.538	0.834	0.887	3.6
H 2B	0.542	0.910	0.916	3.6
H 3A	0.510	0.851	1.067	3.6
H 3B	0.595	0.809	1.089	3.6
H 5	0.730	0.864	1.157	2.5
H 6	0.756	0.935	1.309	3.7
H 7	0.866	0.892	1.249	3.3
H11A	0.505	0.951	1.155	3.4
H11B	0.553	0.978	1.063	3.4
H11C	0.596	0.993	1.199	3.4
H12A	0.663	0.897	1.333	4.3
H12B	0.652	0.826	1.267	4.3
H12C	0.566	0.863	1.275	4.3
H13A	0.705	1.024	1.020	2.8
H13B	0.611	0.991	0.964	2.8
H13C	0.677	0.993	0.888	2.8
H14	0.817	0.824	1.104	2.9
H15	0.889	0.770	1.014	4.8
H16A	0.862	0.869	0.844	8.6
H16B	0.881	0.791	0.827	8.6
H17A	0.996	0.849	0.832	13.8
H17B	1.001	0.886	0.955	13.8
H18A	1.024	0.758	0.919	11.8
H18B	1.034	0.798	1.031	11.8
H19A	1.152	0.856	1.021	12.6
H19B	1.142	0.815	0.899	12.6
H19C	1.170	0.775	1.023	12.6
H20A	0.808	1.046	1.085	3.8
H20B	0.882	1.035	1.023	3.8
H20C	0.909	1.050	1.165	3.8
H22A	0.606	0.839	0.586	5.1
H22B	0.708	0.825	0.631	5.1
H22C	0.669	0.896	0.643	5.1

Hydrogen positions calculated assuming C/O-H distance of 1.08A. Biso(H) is from U(H) = Ueq(C) + 0.01.

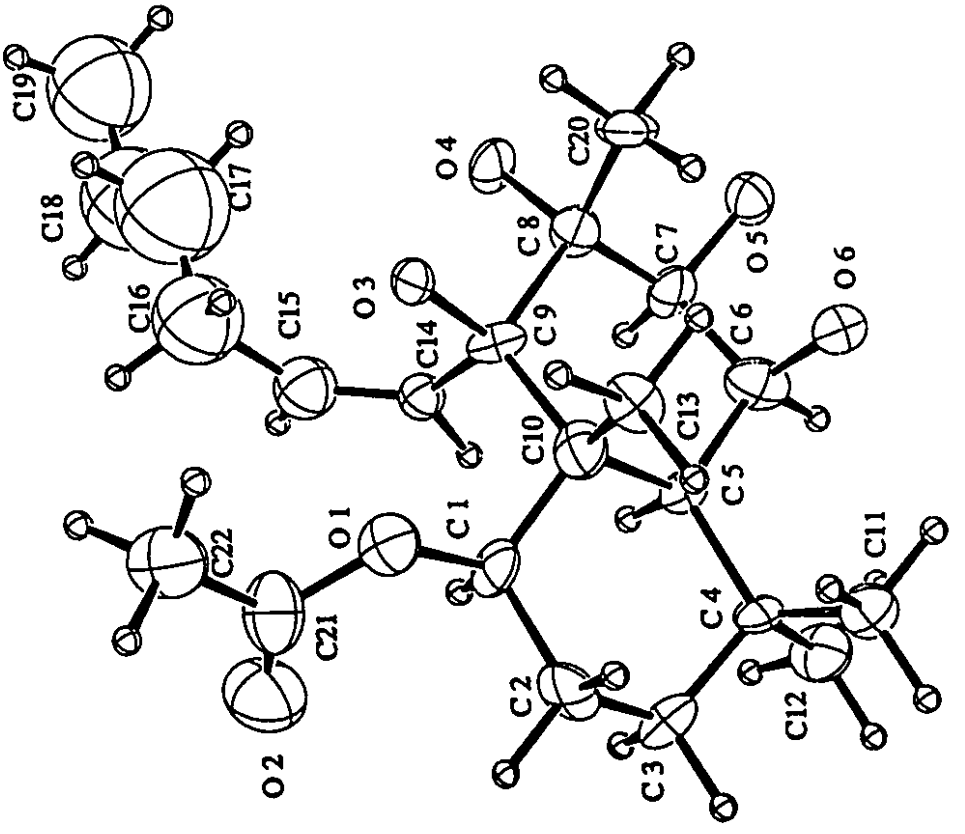
Table S-3. Anisotropic u(i,j) values *100.
E.S.Ds. refer to the last digit printed

	u11	u22	u33	u12	u13	u23
O 1	3.9(9)	4.3(8)	3.5(7)	0.0(7)	1.0(6)	0.3(6)
O 2	8.9(12)	6.0(10)	6.5(10)	-1.8(9)	2.6(9)	0.3(8)
O 3	4.0(8)	3.0(7)	1.9(7)	-1.1(6)	1.5(6)	-0.5(6)
O 4	1.7(8)	5.1(8)	3.9(8)	0.3(7)	0.9(6)	-1.0(7)
O 5	3.0(8)	3.8(8)	3.5(7)	0.0(7)	0.8(6)	-0.7(6)
O 6	3.1(8)	3.6(7)	3.7(8)	-0.5(6)	1.4(6)	-0.2(6)
C 1	3.6(13)	4.8(13)	2.0(10)	-0.1(11)	1.5(9)	0.4(9)
C 2	2.9(13)	4.9(13)	3.1(11)	-0.3(11)	-0.9(10)	-1.1(10)
C 3	2.3(13)	4.7(13)	3.9(12)	0.4(11)	1.5(10)	0.9(10)
C 4	3.3(13)	3.1(11)	3.2(11)	-1.6(10)	2.0(10)	-0.3(9)
C 5	1.8(12)	2.5(11)	2.2(10)	0.1(9)	0.6(9)	0.6(9)
C 6	2.6(13)	3.9(12)	4.4(13)	0.0(10)	-0.2(11)	0.2(10)
C 7	1.6(13)	5.1(13)	2.9(11)	0.2(10)	0.4(10)	-0.6(10)
C 8	2.1(12)	4.4(12)	2.5(11)	-0.2(10)	0.1(9)	-0.5(9)
C 9	2.1(12)	3.4(12)	3.3(11)	-0.5(10)	0.7(10)	1.0(10)
C10	4.3(13)	3.5(12)	3.1(12)	0.0(10)	1.5(10)	0.3(10)
C11	2.7(13)	3.8(12)	3.3(12)	0.2(10)	0.5(10)	0.2(9)
C12	5.1(14)	5.2(13)	3.1(12)	-0.9(12)	1.7(10)	0.6(11)
C13	1.8(12)	2.9(11)	3.0(11)	1.1(10)	-0.8(9)	0.2(9)
C20	4.1(14)	3.4(13)	3.9(13)	-2.2(10)	1.5(11)	-0.2(10)
C21	6.6(17)	5.9(14)	3.0(12)	1.1(12)	1.4(12)	0.3(11)
C22	5.5(15)	7.4(16)	3.4(13)	-1.1(13)	0.3(11)	0.7(12)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table S-4. Torsion Angles in Degrees

C21	O 1	C 1	C 2	-84.3(12)	C21	O 1	C 1	C10	152.5(15)
C 1	O 1	C21	O 2	8.3(8)	C 1	O 1	C21	C22	-173.9(16)
O 1	C 1	C 2	C 3	176.1(17)	C10	C 1	C 2	C 3	-61.6(11)
O 1	C 1	C10	C 5	178.3(16)	O 1	C 1	C10	C 9	-67.9(10)
O 1	C 1	C10	C13	53.4(9)	C 2	C 1	C10	C 5	58.5(10)
C 2	C 1	C10	C 9	172.3(16)	C 2	C 1	C10	C13	-66.4(11)
C 1	C 2	C 3	C 4	56.2(10)	C 2	C 3	C 4	C 5	-50.0(9)
C 2	C 3	C 4	C11	79.4(12)	C 2	C 3	C 4	C12	-167.8(16)
C 3	C 4	C 5	C 6	-173.8(16)	C 3	C 4	C 5	C10	49.5(9)
C11	C 4	C 5	C 6	61.7(10)	C11	C 4	C 5	C10	-75.0(11)
C12	C 4	C 5	C 6	-57.9(10)	C12	C 4	C 5	C10	165.4(15)
C 4	C 5	C 6	O 6	-70.8(10)	C 4	C 5	C 6	C 7	163.2(16)
C10	C 5	C 6	O 6	67.2(10)	C10	C 5	C 6	C 7	-58.8(10)
C 4	C 5	C10	C 1	-53.5(10)	C 4	C 5	C10	C 9	-167.0(15)
C 4	C 5	C10	C13	68.2(11)	C 6	C 5	C10	C 1	168.5(16)
C 6	C 5	C10	C 9	55.0(10)	C 6	C 5	C10	C13	-69.8(11)
O 6	C 6	C 7	O 5	56.0(9)	O 6	C 6	C 7	C 8	-64.1(10)
C 5	C 6	C 7	O 5	-179.5(16)	C 5	C 6	C 7	C 8	60.4(10)
O 5	C 7	C 8	O 4	71.5(10)	O 5	C 7	C 8	C 9	-174.8(16)
O 5	C 7	C 8	C20	-44.3(8)	C 6	C 7	C 8	O 4	-170.1(16)
C 6	C 7	C 8	C 9	-56.5(10)	C 6	C 7	C 8	C20	74.0(11)
O 4	C 8	C 9	O 3	-73.7(10)	O 4	C 8	C 9	C10	169.3(16)
O 4	C 8	C 9	C14	44.1(8)	C 7	C 8	C 9	O 3	170.9(16)
C 7	C 8	C 9	C10	53.9(9)	C 7	C 8	C 9	C14	-71.3(11)
C20	C 8	C 9	O 3	41.8(8)	C20	C 8	C 9	C10	-75.3(11)
C20	C 8	C 9	C14	159.5(16)	O 3	C 9	C10	C 1	77.9(11)
O 3	C 9	C10	C 5	-169.2(16)	O 3	C 9	C10	C13	-42.4(8)
C 8	C 9	C10	C 1	-166.3(16)	C 8	C 9	C10	C 5	-53.4(9)
C 8	C 9	C10	C13	73.4(11)	C14	C 9	C10	C 1	-43.5(9)
C14	C 9	C10	C 5	69.4(11)	C14	C 9	C10	C13	-163.8(16)
O 3	C 9	C14	C15	8.2(8)	C 8	C 9	C14	C15	-106.1(14)
C10	C 9	C14	C15	127.8(16)	C 9	C14	C15	C16	2.2(9)
C14	C15	C16	C18	94.1(20)	C15	C16	C18	C17	67.8(19)
C19	C17	C18	C16	179.9(31)					


C19
C18
C17
C16
C15
O3
C14
C9
O4
C20
C8
C7
O5
O6
C6
C13
C10
C5
C11
C4
C12
C2
C3
O1
C1
C22
C21
O2

Appendix 4

X-ray Structure Report

For

Compound 4.18 *

* I would like to thank Dr. Rosi Hynes of the McGill X-ray Facility for this determination.

KEV6 - KG/CHAN - DEC 9 91

Space Group and Cell Dimensions Monoclinic, P 21/c
a 9.7056(23) b 10.375(4) c 20.489(5)
beta 92.950(19)
Volume 2060.4(11)A**3

Empirical formula : C21 H34 O4

Cell dimensions were obtained from 24 reflections with 2Theta angle in the range 35.00 - 40.00 degrees.

Crystal dimensions : 0.40 X 0.15 X 0.15 mm

FW = 350.50 Z = 4 F(000) = 767.92

Dcalc 1.130Mg.m-3, mu 0.07mm-1, lambda 0.70930A, 2Theta(max) 44.9

The intensity data were collected on a Rigaku diffractometer, using the theta/2theta scan mode.
The h,k,l ranges are :-- -10 10, 0 11, 0 22
No. of reflections measured 2881
No. of unique reflections 2695
No. of reflections with Inet > 2.5sigma(Inet) 1791
No correction was made for absorption

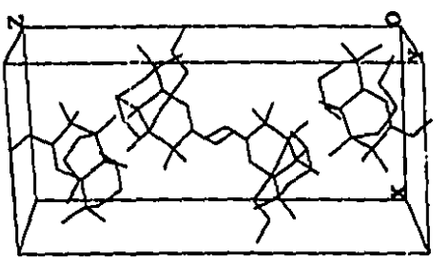
The last least squares cycle was calculated with
59 atoms, 227 parameters and 1791 out of 2695 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000100

The residuals are as follows :--
For significant reflections, RF 0.068, Rw 0.075 GoF 2.63
For all reflections, RF 0.104, Rw 0.076.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.022.

In the last D-map, the deepest hole was -0.370e/A**3,
and the highest peak 0.570e/A**3.

Secondary ext. coeff. = 0.747167 sigma = 0.199042

Standards intensities changed an average of .63 % over the course of collection. Merging R was 3.9 % for 186 pairs of symmetry equivalent reflections. Structure was solved by direct methods (SOLVER). Hydrogen atoms on carbon were included in calculated positions; hydroxyl hydrogens were located in a difference map. Hydrogens were not refined. All non-hydrogen atoms were refined anisotropically.



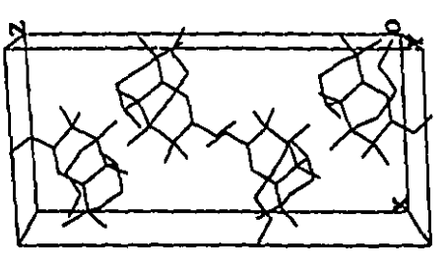


Table 2. Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
O 1	0.5964(3)	0.4732(3)	0.80877(15)	4.13(16)
O 2	0.4684(3)	0.1826(3)	0.76861(15)	4.13(15)
O 3	0.4014(3)	0.3441(3)	0.85761(15)	4.49(17)
O 4	0.5344(4)	0.3313(4)	0.98776(16)	5.69(20)
C 1	0.6772(5)	0.3885(4)	0.76946(22)	3.70(21)
C 2	0.8114(5)	0.4594(5)	0.75798(24)	4.62(25)
C 3	0.8989(5)	0.4752(5)	0.8215 (3)	5.1 (3)
C 4	0.9392(5)	0.3457(5)	0.85351(24)	4.2 (3)
C 5	0.8057(4)	0.2626(4)	0.86360(22)	3.32(21)
C 6	0.7322(5)	0.3043(5)	0.92320(22)	3.88(23)
C 7	0.5985(5)	0.2960(5)	0.93166(23)	4.03(23)
C 8	0.4919(5)	0.2445(5)	0.88217(23)	3.96(23)
C 9	0.5681(5)	0.1846(4)	0.82390(22)	3.54(21)
C10	0.7025(4)	0.2555(4)	0.80203(21)	3.27(21)
C11	1.0180(6)	0.3742(6)	0.9187 (3)	6.1 (3)
C12	1.0418(5)	0.2712(6)	0.8122 (3)	5.9 (3)
C13	0.7573(5)	0.1687(5)	0.74749(23)	4.40(24)
C14	0.6054(5)	0.0503(5)	0.84020(24)	4.26(21)
C15	0.6371(6)	-0.0553(5)	0.8559 (3)	5.6 (3)
C16	0.6802(8)	-0.1847(5)	0.8791 (4)	8.6 (4)
C17	0.8096(11)	-0.1815(9)	0.9244 (4)	11.9 (6)
C18	0.9255(13)	-0.1443(10)	0.8865 (5)	13.9 (7)
C19	1.0573(11)	-0.1433(14)	0.9222 (5)	17.9 (10)
C20	0.3946(5)	0.1475(6)	0.9126 (3)	5.8 (3)
C21	0.6165(6)	0.3877(6)	1.0388 (3)	7.0 (3)

Beq is the mean of the principal axes of the thermal ellipsoid.

Table 3. Bond Distances(A) and Angles(Degrees)

O(1)-C(1)	1.450(6)	C(5)-C(10)	1.571(6)
O(2)-C(9)	1.452(5)	C(6)-C(7)	1.321(7)
O(3)-C(8)	1.430(6)	C(7)-C(8)	1.509(7)
O(4)-C(7)	1.384(6)	C(8)-C(9)	1.565(7)
O(4)-C(21)	1.409(7)	C(8)-C(20)	1.534(7)
C(1)-C(2)	1.525(7)	C(9)-C(10)	1.582(6)
C(1)-C(10)	1.546(6)	C(9)-C(14)	1.474(7)
C(2)-C(3)	1.525(7)	C(10)-C(13)	1.550(6)
C(3)-C(4)	1.537(7)	C(14)-C(15)	1.177(8)
C(4)-C(5)	1.578(6)	C(15)-C(16)	1.478(8)
C(4)-C(11)	1.534(7)	C(16)-C(17)	1.523(13)
C(4)-C(12)	1.546(7)	C(17)-C(18)	1.452(16)
C(5)-C(6)	1.509(7)	C(18)-C(19)	1.441(17)

C(7)-O(4)-C(21)	117.7(4)	O(3)-C(8)-C(20)	103.7(4)
O(1)-C(1)-C(2)	106.5(4)	C(7)-C(8)-C(9)	108.6(4)
O(1)-C(1)-C(10)	112.3(4)	C(7)-C(8)-C(20)	112.0(4)
C(2)-C(1)-C(10)	112.3(4)	C(9)-C(8)-C(20)	112.0(4)
C(1)-C(2)-C(3)	111.3(4)	O(2)-C(9)-C(8)	106.2(3)
C(2)-C(3)-C(4)	112.8(4)	O(2)-C(9)-C(10)	108.2(3)
C(3)-C(4)-C(5)	110.0(4)	O(2)-C(9)-C(14)	108.0(3)
C(3)-C(4)-C(11)	107.9(4)	C(8)-C(9)-C(10)	117.4(4)
C(3)-C(4)-C(12)	111.1(4)	C(8)-C(9)-C(14)	108.8(4)
C(5)-C(4)-C(11)	111.5(4)	C(10)-C(9)-C(14)	107.9(4)
C(5)-C(4)-C(12)	110.8(4)	C(1)-C(10)-C(5)	112.7(4)
C(11)-C(4)-C(12)	105.4(4)	C(1)-C(10)-C(9)	115.0(4)
C(4)-C(5)-C(6)	112.0(4)	C(1)-C(10)-C(13)	105.1(4)
C(4)-C(5)-C(10)	114.4(4)	C(5)-C(10)-C(9)	107.2(3)
C(6)-C(5)-C(10)	110.8(4)	C(5)-C(10)-C(13)	112.2(4)
C(5)-C(6)-C(7)	126.6(4)	C(9)-C(10)-C(13)	104.6(4)
O(4)-C(7)-C(6)	125.3(4)	C(9)-C(14)-C(15)	177.1(5)
O(4)-C(7)-C(8)	109.3(4)	C(14)-C(15)-C(16)	176.8(6)
C(6)-C(7)-C(8)	125.4(4)	C(15)-C(16)-C(17)	112.7(6)
O(3)-C(8)-C(7)	111.6(4)	C(16)-C(17)-C(18)	108.5(7)
O(3)-C(8)-C(9)	108.9(4)	C(17)-C(18)-C(19)	115.0(8)

Table S-2. Calculated Hydrogen Atom Parameters

	x	y	z	Biso
HO1	0.572	0.553	0.779	3.2
HO2	0.400	0.259	0.778	3.2
HO3	0.468	0.422	0.838	3.2
H 1	0.621	0.372	0.722	4.7
H 2A	0.870	0.405	0.723	5.5
H 2B	0.788	0.554	0.736	5.5
H 3A	0.840	0.530	0.857	5.8
H 3B	0.992	0.530	0.814	5.8
H 5	0.842	0.164	0.872	4.3
H 6	0.795	0.346	0.964	4.6
H11A	1.049	0.284	0.943	6.9
H11B	1.110	0.430	0.912	6.9
H11C	0.953	0.426	0.952	6.9
H12A	0.993	0.248	0.764	6.6
H12B	1.133	0.328	0.804	6.6
H12C	1.073	0.182	0.836	6.6
H13A	0.780	0.072	0.765	5.2
H13B	0.682	0.161	0.706	5.2
H13C	0.852	0.209	0.729	5.2
H16A	0.595	-0.230	0.906	8.9
H16B	0.696	-0.249	0.838	8.9
H17A	0.828	-0.280	0.945	10.2
H17B	0.796	-0.116	0.963	10.2
H18A	0.938	-0.217	0.847	13.9
H18B	0.903	-0.053	0.864	13.9
H19A	1.142	-0.106	0.893	15.3
H19B	1.053	-0.064	0.962	15.3
H19C	1.088	-0.227	0.946	15.3
H20A	0.457	0.066	0.934	6.4
H20B	0.340	0.190	0.952	6.4
H20C	0.322	0.108	0.877	6.4
H21A	0.558	0.412	1.081	7.6
H21B	0.701	0.322	1.056	7.6
H21C	0.667	0.476	1.022	7.6

Hydrogen positions calculated assuming C-H of 1.08A. Biso is from Uiso(H) = Ueq(C) + .01. Hydroxy hydrogens were located in a difference map but not refined.

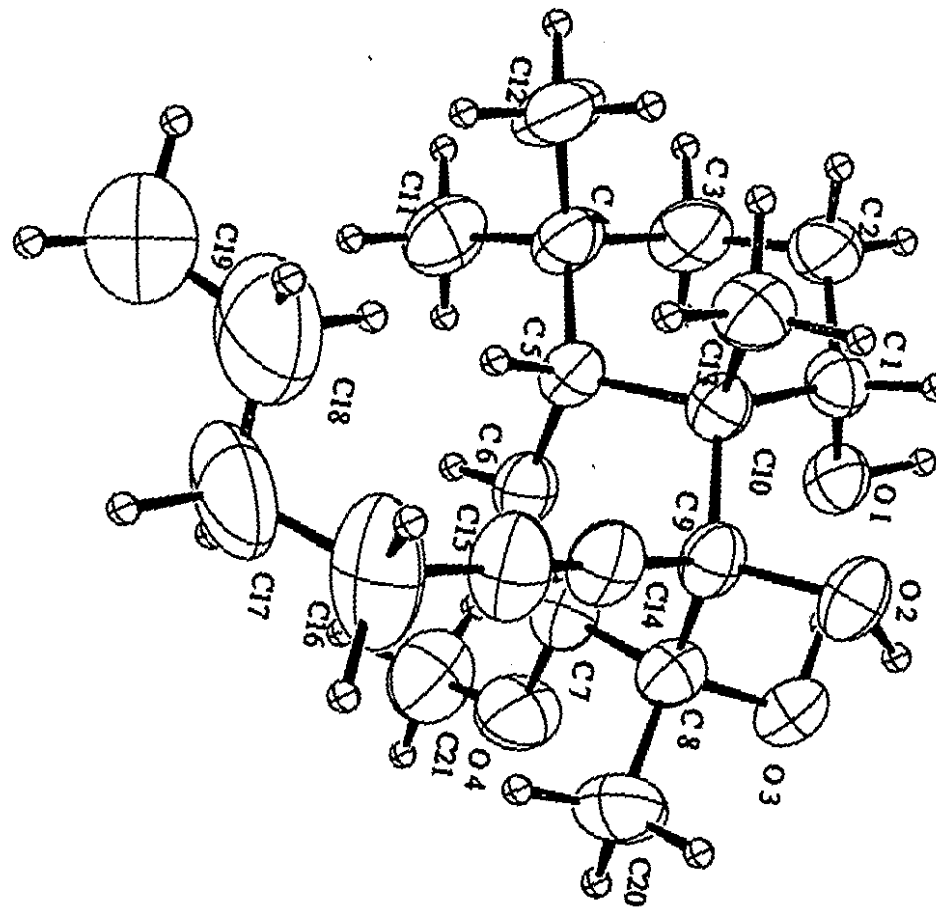
Table S-3. Anisotropic u(i,j) values *100.
E.S.Ds. refer to the last digit printed

	u11	u22	u33	u12	u13	u23
O 1	5.20(21)	4.05(19)	6.42(21)	0.61(17)	0.02(18)	1.05(17)
O 2	4.70(20)	4.86(21)	5.94(22)	0.05(16)	-1.50(17)	-0.89(17)
O 3	3.96(19)	6.17(23)	6.87(23)	0.60(18)	-0.05(17)	-0.10(19)
O 4	6.8 (3)	9.8 (3)	5.06(22)	0.10(23)	1.22(20)	-1.70(21)
C 1	5.1 (3)	4.5 (3)	4.4 (3)	0.5 (3)	0.3 (3)	0.38(24)
C 2	5.2 (3)	5.5 (3)	6.9 (4)	-0.2 (3)	0.9 (3)	1.7 (3)
C 3	5.0 (3)	4.8 (3)	9.4 (4)	-1.4 (3)	0.1 (3)	0.8 (3)
C 4	3.7 (3)	5.8 (3)	6.5 (4)	-0.3 (3)	-0.3 (3)	0.2 (3)
C 5	3.7 (3)	3.8 (3)	5.1 (3)	0.05(23)	-0.32(24)	0.05(24)
C 6	5.0 (3)	5.0 (3)	4.7 (3)	-0.2 (3)	-0.8 (3)	-0.3 (3)
C 7	5.1 (3)	5.2 (3)	5.0 (3)	0.3 (3)	-0.2 (3)	-0.2 (3)
C 8	4.2 (3)	5.5 (3)	5.3 (3)	-0.2 (3)	-0.2 (3)	0.0 (3)
C 9	4.2 (3)	3.8 (3)	5.3 (3)	-0.36(24)	-1.09(24)	-0.03(24)
C10	4.2 (3)	3.4 (3)	4.8 (3)	0.32(22)	-0.12(24)	0.06(22)
C11	5.0 (3)	9.4 (5)	8.7 (4)	-1.8 (3)	-1.5 (3)	0.0 (4)
C12	3.7 (3)	8.8 (4)	10.0 (5)	0.9 (3)	1.0 (3)	0.5 (4)
C13	5.7 (3)	5.6 (3)	5.5 (3)	0.6 (3)	0.5 (3)	-1.2 (3)
C14	5.2 (3)	4.1 (3)	6.7 (4)	-0.9 (3)	-1.3 (3)	0.0 (3)
C15	8.2 (4)	4.6 (3)	8.4 (4)	-1.0 (3)	-2.5 (3)	0.7 (3)
C16	15.6 (7)	3.6 (3)	12.8 (6)	-0.1 (4)	-5.0 (6)	1.5 (4)
C17	18.7 (9)	17.0 (9)	10.1 (6)	12.2 (8)	5.3 (7)	7.8 (6)
C18	20.3 (12)	17.6 (10)	15.2 (9)	10.6 (9)	2.7 (9)	6.8 (8)
C19	14.3 (9)	35.7 (18)	18.2 (11)	5.8 (11)	1.7 (8)	13.8 (11)
C20	5.7 (4)	8.6 (4)	7.7 (4)	-2.2 (3)	1.1 (3)	0.8 (3)
C21	9.1 (5)	11.5 (5)	5.7 (4)	1.4 (4)	-0.7 (4)	-3.1 (4)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table S-4. Torsion Angles in Degrees

C21	O 4	C 7	C 6	3.9(3)	C21	O 4	C 7	C 8	-177.0(6)
O 1	C 1	C 2	C 3	67.0(4)	C10	C 1	C 2	C 3	-56.3(3)
O 1	C 1	C10	C 5	-70.9(3)	O 1	C 1	C10	C 9	52.3(3)
O 1	C 1	C10	C13	166.7(5)	C 2	C 1	C10	C 5	49.1(3)
C 2	C 1	C10	C 9	172.3(5)	C 2	C 1	C10	C13	-73.3(4)
C 1	C 2	C 3	C 4	60.1(4)	C 2	C 3	C 4	C 5	-54.4(3)
C 2	C 3	C 4	C11	-176.3(6)	C 2	C 3	C 4	C12	68.6(4)
C 3	C 4	C 5	C 6	-79.9(4)	C 3	C 4	C 5	C10	47.3(3)
C11	C 4	C 5	C 6	39.8(3)	C11	C 4	C 5	C10	167.0(5)
C12	C 4	C 5	C 6	156.9(5)	C12	C 4	C 5	C10	-75.9(4)
C 4	C 5	C 6	C 7	150.5(6)	C10	C 5	C 6	C 7	21.4(3)
C 4	C 5	C10	C 1	-45.4(3)	C 4	C 5	C10	C 9	-172.8(5)
C 4	C 5	C10	C13	72.9(4)	C 6	C 5	C10	C 1	82.4(4)
C 6	C 5	C10	C 9	-45.0(3)	C 6	C 5	C10	C13	-159.3(5)
C 5	C 6	C 7	O 4	177.8(6)	C 5	C 6	C 7	C 8	-1.1(2)
O 4	C 7	C 8	O 3	69.0(4)	O 4	C 7	C 8	C 9	-170.9(6)
O 4	C 7	C 8	C20	-46.8(3)	C 6	C 7	C 8	O 3	-111.9(5)
C 6	C 7	C 8	C 9	8.1(3)	C 6	C 7	C 8	C20	132.3(6)
O 3	C 8	C 9	O 2	-36.9(2)	O 3	C 8	C 9	C10	84.2(4)
O 3	C 8	C 9	C14	-152.9(5)	C 7	C 8	C 9	O 2	-158.6(5)
C 7	C 8	C 9	C10	-37.5(3)	C 7	C 8	C 9	C14	85.4(4)
C20	C 8	C 9	O 2	77.3(4)	C20	C 8	C 9	C10	-161.6(5)
C20	C 8	C 9	C14	-38.8(3)	O 2	C 9	C10	C 1	51.1(3)
O 2	C 9	C10	C 5	177.2(5)	O 2	C 9	C10	C13	-63.5(3)
C 8	C 9	C10	C 1	-68.9(3)	C 8	C 9	C10	C 5	57.2(3)
C 8	C 9	C10	C13	176.5(5)	C14	C 9	C10	C 1	167.8(5)
C14	C 9	C10	C 5	-66.2(4)	C14	C 9	C10	C13	53.1(3)
O 2	C 9	C14	C15	-158.6(6)	C 8	C 9	C14	C15	-43.8(4)
C10	C 9	C14	C15	84.6(5)	C 9	C14	C15	C16	-6.9(3)
C14	C15	C16	C17	-30.1(5)	C15	C16	C17	C18	-68.4(7)
C16	C17	C18	C19	-177.0(12)					


C12
C11
C
C3
C2
C19
C18
C5
C4
C1
C9
C10
O1
C15
C9
O2
C17
C16
C14
C7
C8
O4
C21
O3
C20