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THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF ANGULARLY FUNCTIONALIZED DECALIN COMPOUNDS AGAINST THE SPRUCE BUDWORM, *CHORISTONEURA FUMIFERANA*

by

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

Doctor of Philosophy

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THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF ANGULARLY FUNCTIONALIZED DECALIN COMPOUNDS AGAINST THE SPRUCE BUDWORM, *CHORISTONEURA FUMIFERANA*

by ANNETTE EJ.ISABETH SCHWERDTFEGER

ABSTRACT

A tandem Michael-Claisen (4C+2C) annelation reaction based on the propensity of siloxy diene, 1-(*tert*-butyldimethylsiloxy)-1-methoxy-3-(phenylthio)-5-(methoxycarbonyl)-penta-1,3-dienoate, to undergo Michael reaction with 2-cyclohexen-1-one under Lewis acid catalyzed conditions was developed to give 3-(phenylthio)-4-methoxycarbonyl-4a,5,6,8a-tetrahydronaphthalene-1,8(4*H*,7*H*)-dione.

Two functionalized 1,8-β-dicarbonyl decalin compounds, prepared via the tandem Michael-Claisen condensation, were hydroxymethylated at the angular position as the benzyloxymethoxy derivatives with diisopropylethylamine and benzyl chloromethyl ether in the presence of paraformaldehyde. The nature of this reaction was examined. The stereochemistry of *cis*-8a-[[(benzyloxy)methoxy]methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4*H*,7*H*)-dione was confirmed by X-ray analysis of its ethylene ketal derivative.

The [(benzyloxy)methoxy]methyl derivative mentioned above was employed as the intermediate in the preparation of a variety of angularly functionalized decalin compounds leading to the synthesis of three key keto diacetates. The methylenation of these keto diacetates was not successful, due to the steric hindrance experienced by the ketone functionality in these *cis*-fused decalin systems.

When the angularly functionalized decalin compounds were tested for their biological activity against the spruce budworm, *Choristoneura fumiferana*, seven compounds were found to exhibit moderate activity similar to a specionin analog prepared earlier in this laboratory.

LA SYNTHESE ET L'ACTIVITE BIOLOGIQUE DE SYSTEMES DECALINIQUES FONCTIONNALISES CONTRE LA TORDEUSE DES BOURGEONS DE L'EPINETTE, *CHORISTONEURA FUMIFERANA*

par ANNETTE ELISABETH SCHWERDTFEGER

RESUME

Une méthode d'annélation basée sur l'addition conjuguée du diène 1-(*tert*-butyldiméthylsiloxy)-1-méthoxy-3-phénylthio-pent-1,3-diènoate de méthyle sur la cylohex-2-ène-1-one, suivie de la cyclisation des adduits de Michaél par une condensation de Claisen a été mise au point afin d'accéder au 3-(phénylthio)-4-méthoxycarbonyl-4a,5,6,8a-tétrahydronaphtalène-1,8(4*H*,7*H*)-dione.

Deux décalines 1,8-β-dicarbonylées fonctionnalisées, obtenues par cette méthode d'annélation, ont été traitées avec la diisopropyléthylamine et le benzyl chlorométhyl éther en présence de paraformaldéhyde afin d'introduire un groupement hydroxyméthylène protégé sous forme d'éther benzylique. La stéréochimie du *cis*-8a-[[(benzyloxy)méthoxy]-méthyl]-3-(phénylthio)-4a,5,6,8a-tétrahydronaphtalène-1,8(4*H*,7*H*)-dione en jonction de cycle a été confirmée par l'analyse structurale du dérivé cétal éthylène par diffraction des rayons X.

Un des dérivés benzyloxyméthoxy a servi comme intermédiaire dans la préparation de piusieurs composés décaliniques fonctionnalisés à la position angulaire au cours de la synthèse de trois cétones diacétates clés. La méthylenation de ces trois cétones diacetates n'a pas été possible, à cause de l'encombrement stérique près de la fonctionnalité.

La plupart des composés décaliniques fonctionnalisés à la position angulaire ont été testés afin de vérifier leur activité biologique contre la tordeuse des bourgeons de l'épinette, *Choristoneura fumiferana*. Sept des composés ont montré une activité comparable à celle déjà mesurée pour un analogue de la spécionine préparé dans notre laboratoire.

ACKNOWLEDGEMENTS

I would like to express my deep appreciation to all who have made this thesis possible.

My interest in Organic Synthesis was first sparked by the following three people: Mr. Selwood, my high school Chemistry teacher, Dr. E. Piers, my undergraduate Organic Chemistry professor and Dr. Debbie Nicoll-Griffiths, for whom I worked in the summer of 1985 while she was completing her doctorate under the direction of Dr. L. Weiler. I am grateful to them for having shared their words of wisdom with me.

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My family has offered me moral support throughout the trials and tribulations - and successes - of my Ph. D. I would like to thank my father, who has graduate students of his own, for all of his advice; my sister, who is also a graduate student in Organic Chemistry, for her suggestions; my two brothers for their ever present sense of humor; and my mother for her understanding. The friendship and encouragement of Dr. Clément Gosselin, to whom I am now happily married, have accompanied me throughout my work at McGill.

A heartfelt thank you to all of you.

für meine Eltern
und meinen Mann, Clément

TABLE OF CONTENTS

List of Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
bp	boiling point
Bu	butyl
cat	catalyst
c.d.	circular dichroism
COSY	2D-homocorrelation (nmr experiment)
CSA	10-camphorsulfonic acid
d	doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DHP	3,4-dihydro-2*H*-pyran
DIBAL	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide or methyl sulfoxide
Et	ethyl
ether	diethyl ether
eV	electron volts
gem	geminal
h	hour(s)
HETCOR	2D-heterocorrelation (nmr experiment)

HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOAc	acetic acid
Hz	hertz
imid	imidazole
IPE	diisopropylether
IR	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
L-Selectride	lithium tri-*sec*-butylborohydride
m	multiplet
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM-Cl	2-methoxyethoxymethyl chloride
min	minute(s)
MHz	megahertz
mp	melting point
MS	mass spectrometry
NMO	*N*-methylmorpholine *N*-oxide monohydrate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
NPSP	*N*-(phenylseleno)phthalimide
Ph	phenyl
ppm	parts per million
iPr	isopropyl
PTSA	*para*-toluenesulphonic acid monohydrate

pyr	pyridine
q	quartet
s	singlet
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TosMIC	(*para*-tolylsulfonyl)methylisocyanide
Ts	tosyl or *para*-toluenesulfonyl

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

The siloxy diene, 1-(*tert*-butyldimethylsiloxy)-1-methoxy-3-(phenylthio)-5-(methoxycarbonyl)-penta-1,3-dienoate was found to undergo a tandem Michael-Claisen (4C+2C) annelation reaction with 2-cyclohexen-1-one to give 3-(phenylthio)-4-methoxycarbonyl-4a,5,6,8a-tetrahydronaphthalene-1,8(7*H*)-dione.

Two 1,8-β-dicarbonyl decalin compounds, 3 and 48 (p. 90 and 97), prepared via the tandem Michael-Claisen condensation, were treated with diisopropylethylamine and benzyl chloromethyl ether in the presence of paraformaldehyde in order to introduce a hydroxymethylene moiety, protected as a benzyloxymethoxy ether, at the angular position. The hydroxymethylation proceeds through a *cis*-oxymethylene aldol adduct which reacts with benzyl chloromethyl ether to form the observed products. This aldol adduct was isolated in the form of ethyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate when the procedure was applied to the monocyclic keto ester ethyl 2-oxocyclohexanecarboxylate. The aldol adduct could also be reacted with acetic anhydride so as to incorporate an acetoxymethoxymethylene moiety at the angular position. The stereochemistry of *cis*-8a-[[(benzyloxy)-methoxy]methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4*H*, 7*H*)-dione was confirmed by X-ray analysis of its ethylene ketal derivative.

The benzyloxymethoxy derivative mentioned above served as an intermediate in the preparation of a variety of angularly functionalized decalin compounds during the synthesis of three key keto diacetates. Examination of ^{1}H NMR coupling constants, NOE experiments and X-ray analysis confirmed that reagents approached the *cis*-fused decalin compounds from the β-face. Three of the angularly functionalized decalin compounds featuring a ketone moiety were subjected to a variety of methylenation conditions without success. Meanwhile the olefination of the benzyloxymethoxy derivative of the monocyclic keto ester mentioned above proceeded smoothly.

Most of the angularly functionalized decalin compounds prepared during the course of this work were tested for biological activity against the spruce budworm, *Choristoneura fumiferana*. Seven of the compounds were found to be active when incorporated into artificial diet at a concentration of 0.2% wet weight (2000 ppm). Four of these compounds exhibited moderate activity similar to the specionin analog tested earlier by our laboratory. However, two of the decalin compounds featuring a benzyloxymethoxymethyl moiety at the angular position were found to be more active than the specionin analog. One decalin compound, featuring a cyano moiety, was found to have an activity superior to all of the other compounds.

CHAPTER 1

INTRODUCTION

1.1 Clerodin and the Clerodanes

Clerodendron infortunatum Linn (from the Verbenaceae Family) is a small tree found throughout India. All parts of this Indian bhat tree have a bitter pungent taste. The leaves have been used in the treatment of certain tumors and skin diseases.[1]

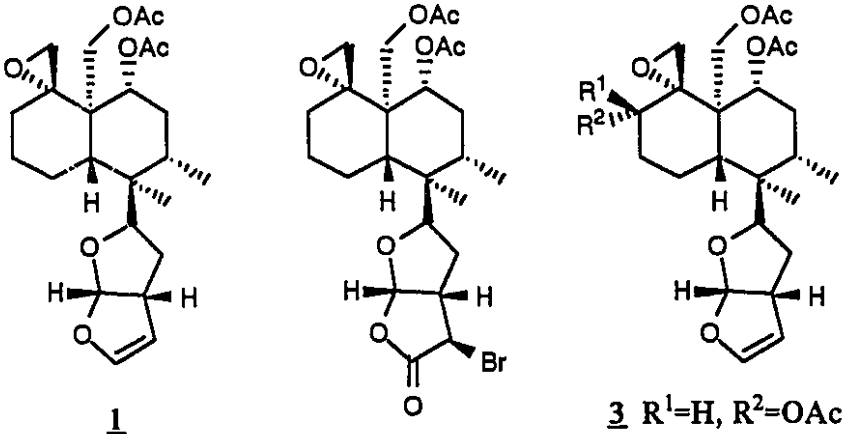
The bitter principle clerodin 10 was first isolated from the roots of the bhat tree in 1936 by Banerjee.[2,3] Clerodin was later found to be the major constituent isolated from the extraction of the ground leaves and twigs[4] of *Clerodendron infortunatum*, as well as from the extraction of the air-dried flowers.[5] Clerodin has also been isolated from the roots of *Clerodendron colebrookium* and *Clerodendron phlamoides* (both from the Verbenaceae Family).[6]

Banerjee[2,3] made a preliminary investigation of the compound clerodin and favoured the molecular formula $C_{13}H_{18}O_3$. Chaudhury and Dutta[7], as a result of further preliminary work, supported a larger molecular formula $C_{28}H_{40}O_8$.

The structure, stereochemistry and absolute configuration of clerodin were assigned in 1961/2 by Robertson *et al.*[8,9] from an X-ray study of the heavy-atom derivative clerodin bromolactone 2. The X-ray study led to an unfortunate error in the assignment of the absolute configuration of clerodin as 1. Barton *et al.*[4] confirmed the structure suggested by the X-ray study with optical rotatory dispersion measurements and nuclear magnetic resonance studies.

In 1973 Munakata and coworkers isolated both clerodin and another natural product, caryoptin, from *Caryopteris divaricata* Maxim[10a)] and they later isolated the natural product 3-epicaryoptin from *Clerodendron calamitosum.*[10b)] These plants both belong to

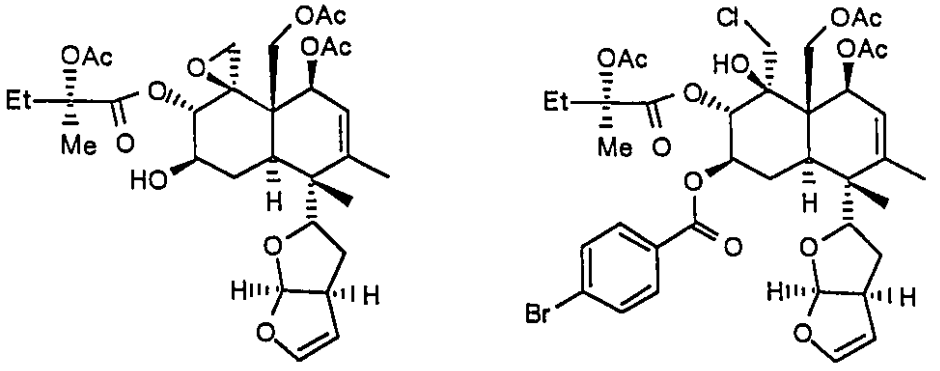
the Verbenaceae Family. Caryoptin and clerodin were shown physico-chemically to share a common chirality. Also, 3-epicaryoptin and clerodin had been isolated from plants of the same genus. They thus assigned the absolute stereochemistries 3 and 4 respectively to caryoptin and 3-epicaryoptin, based on the results of the clerodin X-ray study by Robertson *et al.*[8,9] However, the absolute structures of caryoptin and 3-epicaryoptin, as determined by the c.d. exciton method[11] , were antipodal to the supposed absolute structure of clerodin determined by the X-ray method. Thus caryoptin and 3-epicaryoptin were reported as exceptions to the exciton chirality theory[12] and attempts were made to explain away the contradiction.



Scheme 1.1 Previously accepted absolute configurations of clerodin 1, caryoptin 3, and 3-epicaryoptin 4.

At about the same time Munakata's group found that the natural product clerodendrin A 5 could be isolated from *Clerodendron tricotomum* Thumb[13] and *Clerodendron cryptollum*[14], both from the Verbenaceae Family. They determined the absolute configuration of clerodendrin A[15] by an X-ray study[16] of its heavy atom derivative 6. They found that this natural product was antipodal to the accepted structures of clerodin 1, caryoptin 3

and 3-epicaryoptin 4 in all corresponding chiral centres, in spite of their isolation from plants of the same genus.



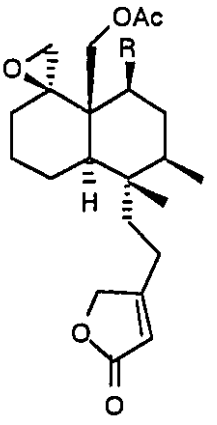
5 6

Scheme 1.2 clerodendrin 5 and its heavy-atom derivative 6

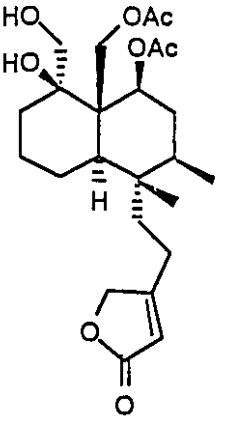
In 1976, Kubo, Nakanishi and coworkers[17] extracted the three natural products, ajugarin-I, -II and -III from the leaves of *Ajuga remota* (Labiatae) in Nairobi, Kenya. After careful spectral investigations of the three compounds, they put forward the clerodane structures 7, 8 and 9 for these compounds. The c.d. spectra of derivatives of the ajugarins agreed with the proposed structures, thus leading to the conclusion that the ajugarin configuration was antipodal to the then accepted absolute stereochemistry of clerodin 1, caryoptin 3, and 3-epicaryoptin 4.

A few years later Harada and Uda[18] compared the c.d. spectra of derivatives of clerodin, caryoptin and clerodendrin A and concluded that the absolute configurations for 1, 3 and 4 were antipodal to the stereochemistry originally assigned.

Both the results of the clerodendrin X-ray study and the comparison of the c.d. curves gave rise to some doubt about the earlier proposed absolute configuration of clerodin, caryoptin and 3-epicaryoptin. A few years later new X-ray studies of both clerodin and 3-epicaryoptin were carried out by Rogers, Ley and coworkers.[19] They yielded an



7 R = OAc
8 R = OH



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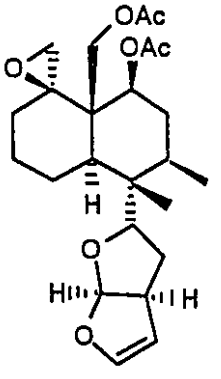
Scheme 1.3 Proposed and later accepted absolute configurations of ajugarin-I 7, ajugarin-II 8, and ajugarin-III 9

absolute stereochemistry opposite to the previously accepted absolute configuration. Thus the absolute stereochemistries of clerodin 1, caryoptin 3, and 3-epicaryoptin 4 were revised to 10, 11, and 12, identical to that of clerodendrin A 5.



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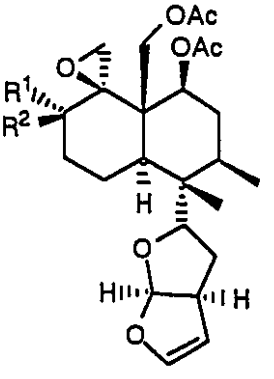
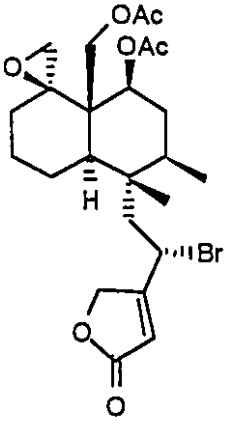


11 R^1=H, R^2=OAc
12 R^1=OAc, R^2=H

Scheme 1.4 Revised absolute configurations of clerodin 10, caryoptin 11, and 3-epicaryoptin 12.

This discovery led to some doubt about the absolute stereochemistry of the ajugarins. Should their absolute configuration also be revised?

One year later, Kubo and coworkers[20] isolated clerodin 10 from *Ajuga remota*, the same plant from which they had earlier isolated the three ajugarin diterpenes 7, 8, and 9. The fact that the ajugarins and clerodin, which had originally been considered antipodal, were present in the same plant, led this research group to seek a confirmation of the ajugarin absolute configuration by carrying out an X-ray analysis of 12-(R)-bromoajugarin-I 13. This derivative was prepared via the allylic bromination of the parent material. The absolute configuration of the molecule matched that of clerodin 10. Thus, the ajugarins 7-9 and clerodin 10 are not antipodal.



13

So, in 1980, forty-four years after the original isolation of clerodin 10, the structures of this natural product, the ajugarins 7-9, and other members of the clerodane family (3-5, 11, 12) were finally settled. Compounds with the same absolute stereochemistry as clerodin are now termed neo-clerodanes, with those structures enantiomeric to clerodin being termed ent-neo-clerodanes.[19] Clerodin is considered the parent compound of the over six hundred and fifty clerodane diterpenoids[21,22], which all possess the clerodane carbon skeleton.

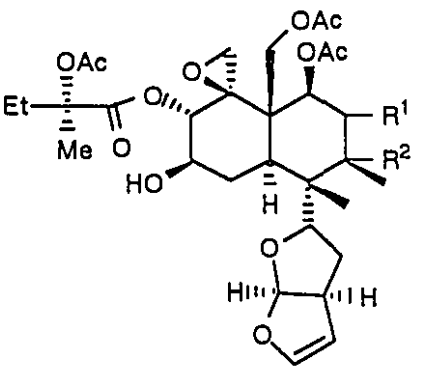
1.2 Antifeedant Activity of the Clerodanes

For many years insecticides have been used to exterminate insects. However, many synthetic broad spectrum insecticides are quite toxic to vertebrates, fish or beneficial lower life forms. Some are extremely persistent in the environment and may accumulate in animals.[23] With the growing concern for the environment, there has been a search for alternative methods of pest control which are non-toxic and will avoid pollution. In addition to looking at insect predators and pheromones as possible solutions to this problem, there is a growing interest in insect antifeedants.[24]

In 1972, Munakata and coworkers first described the natural product, clerodin, as an insect antifeedant.[13] According to Munakata, the term antifeedant is defined as a chemical that inhibits feeding but does not kill the insect directly, the insect remaining near the treated leaves and dying through starvation.[25] Many of the clerodanes from the Verbenaceae and Labiatae families possess marked antifeedant properties. **Scheme 1.5** and **Table 1.1** provide information on several of these diterpenes, listing the name of each compound, the source, the antifeedant activity and the corresponding reference. As a comparison, triphenyltinhydroxide (TPTH), the antifeeding agent presently used against the cotton worm, has been included in the table.[13] Note that most of the clerodanes would be at least 10 times more effective than TPTH, with the clerodin derivatives (10, 16, 17) and dihydro-caryoptin (14) being almost 100 times more effective.

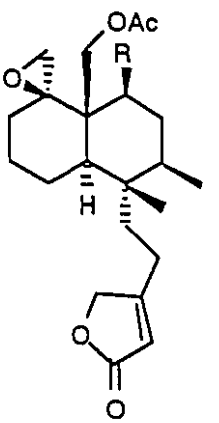
The screening procedure used for these antifeedants was of the "choice" type. In "choice" experiments,[22] the test insect is placed inside an observation cage with food with and without plant extracts. If the extract contains substances which deter the test insect from feeding, the insect will preferably eat the non-treated food. The ratio between the amounts eaten is a measure of the antifeedant activity. In a "no-choice" experiment,[22] the insect is given only treated food. The amount eaten or the weight of the dried excreta relative to a control after a particular time is a measure of the antifeedant activity. If the

insect does not eat at all and eventually dies, one speaks of an absolute antifeedant.[26] If the insect eventually rather prefers to eat than to die, one speaks of a relative antifeedant.[26] One advantage of the no-choice experiment is that it more closely resembles the actual operational situation in the field. A choice experiment has the advantage that it is more sensitive.[27]



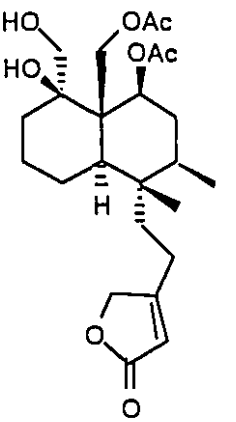
5 R^1+ R^2= bond

18 R^1= R^2= H



7 R = OAc

8 R = OH



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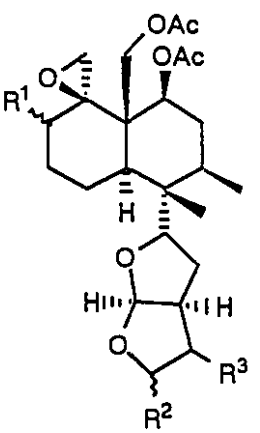


10 R^1= H, R^2+ R^3= bond

11 R^1= α-OAc, R^2+ R^3= bond

12 R^1= β-OAc, R^2+ R^3= bond

14 R^1= α-OAc, R^2= R^3= H

15 R^1= α-OAc, R^2= OH, R^3= H

16 R^1= R^2= R^3= H

17 R^1= R^3= H, R^2= OH

Scheme 1.5

Table 1.1 Antifeedant activity of clerodane diterpenes

Name	Species	Activity	Ref.
clerodendrin A 5	*Clerodendron tricotomum*	300 ppm	13
clerodendrin B 18	*Clerodendron tricotomum*	200 ppm	13
ajugarin-I 7	*Ajuga remota*	100 ppm	17
ajugarin-II 8	*Ajuga remota*	100 ppm	17
ajugarin-III 9	*Ajuga remota*	100 ppm	28
clerodin 10	*Clerodendron infortunatum*	80 ppm	13
caryoptin 11	*Caryopteris divaricata*	200 ppm	10a), 29
3-epi-caryoptin 12	*Clerodendron calamitosum*	200 ppm	10b), 29
dihydro-caryoptin 14	*Caryopteris divaricata*	80 ppm	10a), 29
caryoptin hemiacetal 15	*Caryopteris divaricata*	200 ppm	10a), 29
dihydro-clerodin 16	*Caryopteris divaricata*	50 ppm	10a), 29
clerodin hemiacetal 17	*Caryopteris divaricata*	50 ppm	10a), 29
triphenyltinhydroxide		5000 ppm	10a)

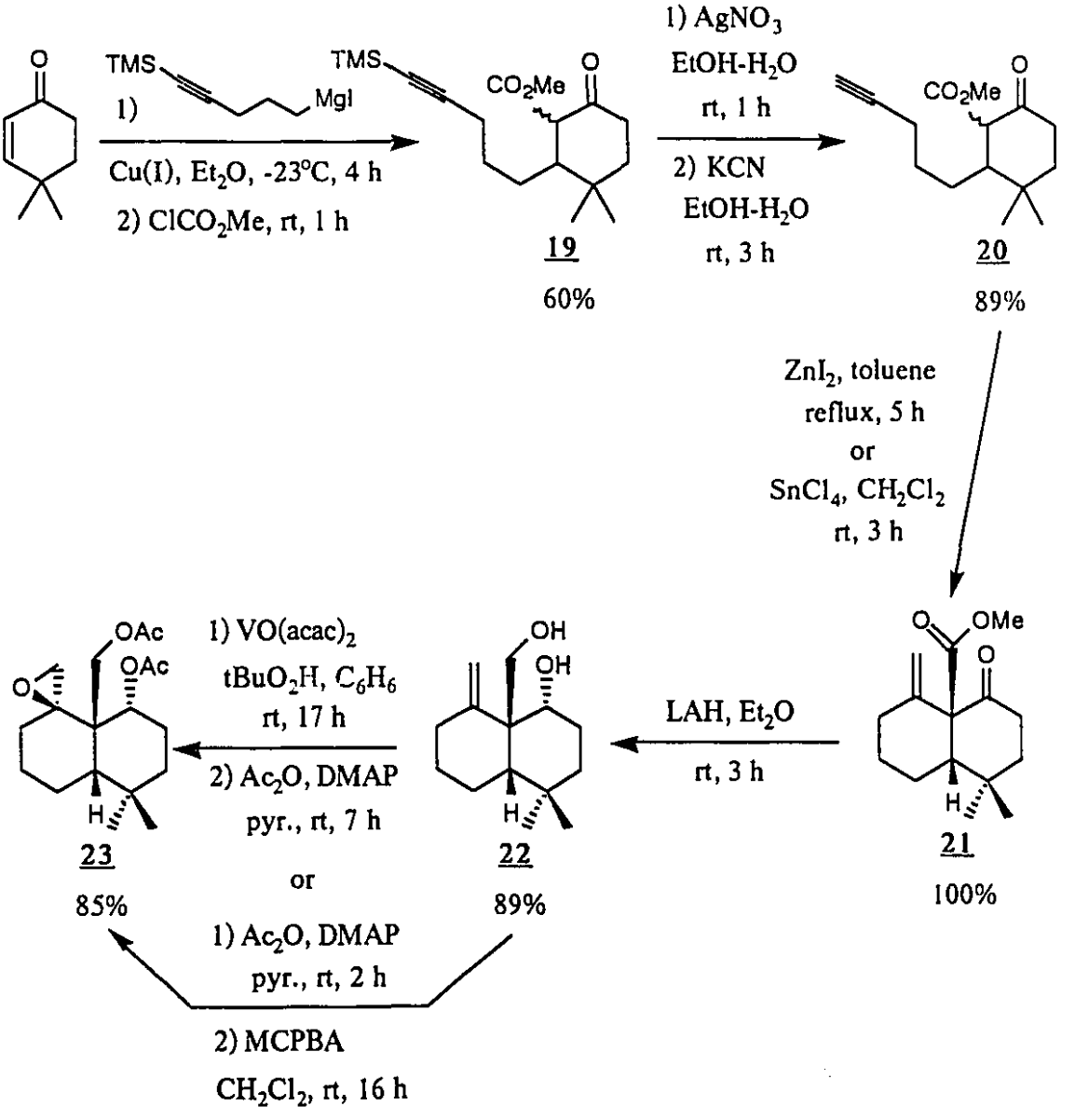
Note: All natural products were tested in a choice test against the tobacco cut worm, *Spodoptera litura*, except ajugarins I-III (7-9), which were tested in a choice test against the African army worm, *Spodoptera exempta*.

The useful biological properties demonstrated by these clerodane diterpene natural products has sparked an interest among the organic synthetic community in determining the functional group requirement for biological activity and has led to the total and partial synthesis of several members of this class of compounds.

1.3 Syntheses of Clerodanes and Clerodane Model Compounds

In the early 1980's three research groups, located in England, Japan, and the Netherlands, published the first syntheses of clerodane model compounds.

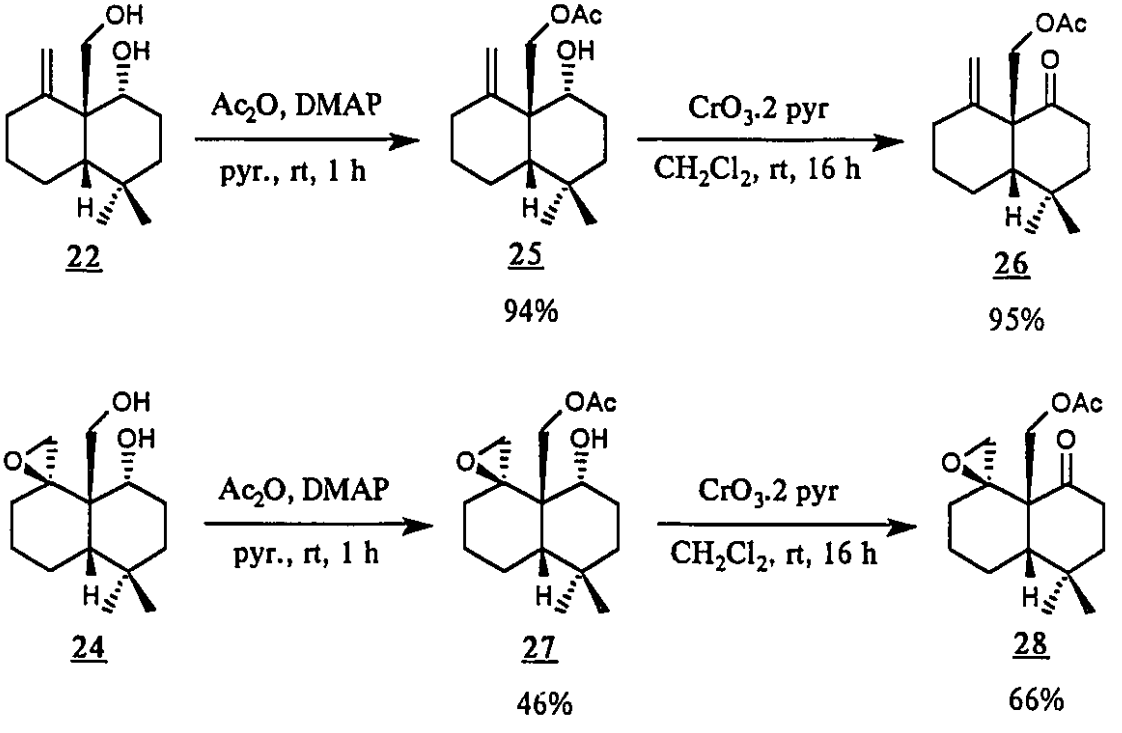
In 1979 Jackson and Ley[30] reported the synthesis of a *cis*-decalin 23 containing epoxydiacetate functions (see **Scheme 1.6**). They selected 4,4-dimethylcyclohex-2-enone



Scheme 1.6

as a starting material. The copper(I)-catalyzed conjugate addition of an appropriate Grignard reagent and subsequent trapping of the resulting enolate with methyl chloroformate afforded the adduct 19 in 60% yield. Deprotection, followed by cyclization gave the *cis*-fused decalin 21 in 89% overall yield. The angular ester moiety was then reduced to the primary alcohol 22 in 89% yield. Epoxidation of the terminal double bond, followed by acetylation of the epoxydiol provided the *cis*-decalin epoxydiacetate 23 in 85% yield. X-ray crystallographic determination[31] of compound 23 helped to unambiguously assign the structure.

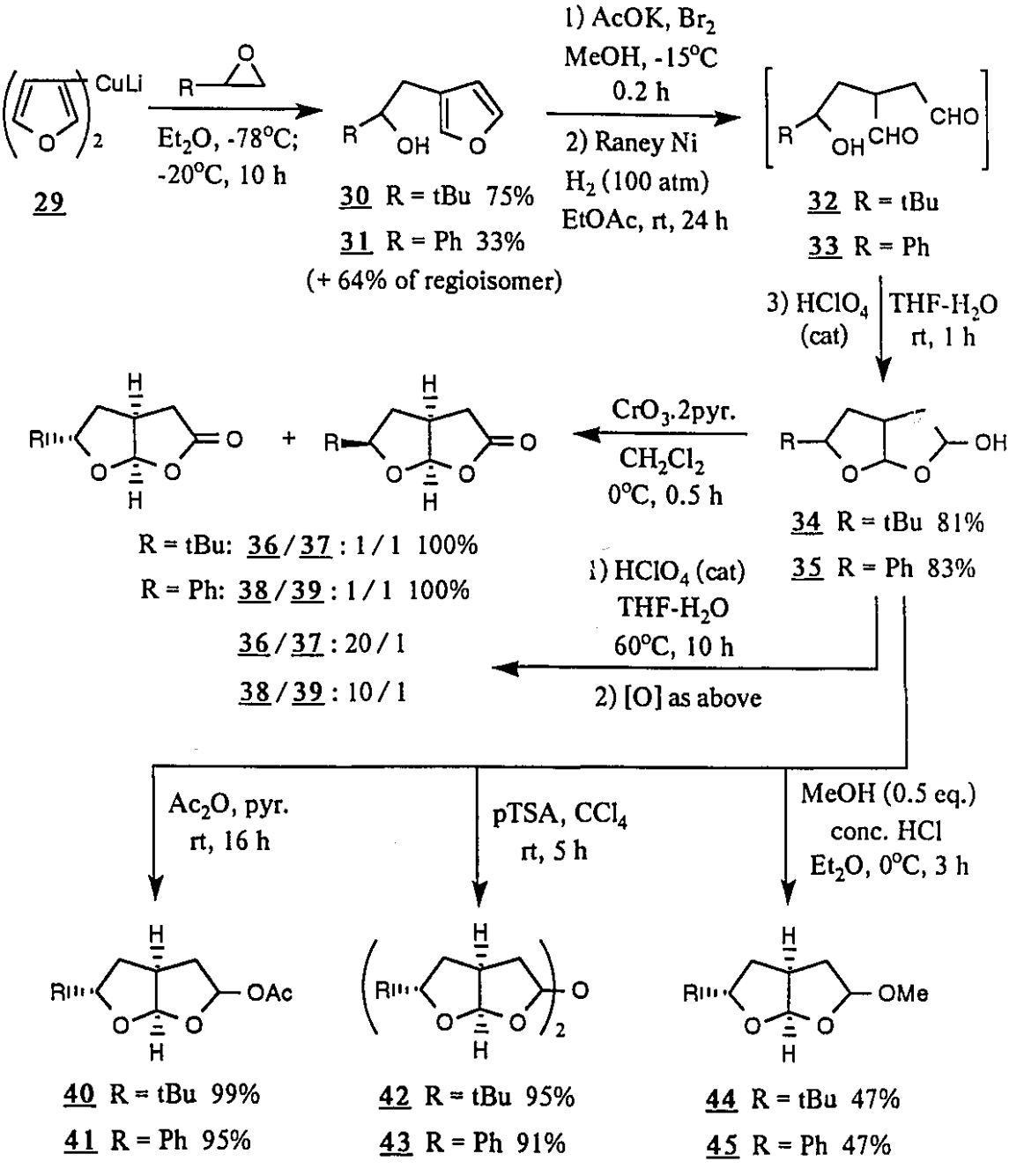
Jackson and Ley[31] also prepared various other *cis*-decalins (25-28) from 22 and 24 by conventional methods (see **Scheme 1.7**; also see **Table 1.4** for biological activity of *cis*-decalins 23 and 28).



22 → 25 (94%) → 26 (95%)

24 → 27 (46%) → 28 (66%)

Scheme 1.7



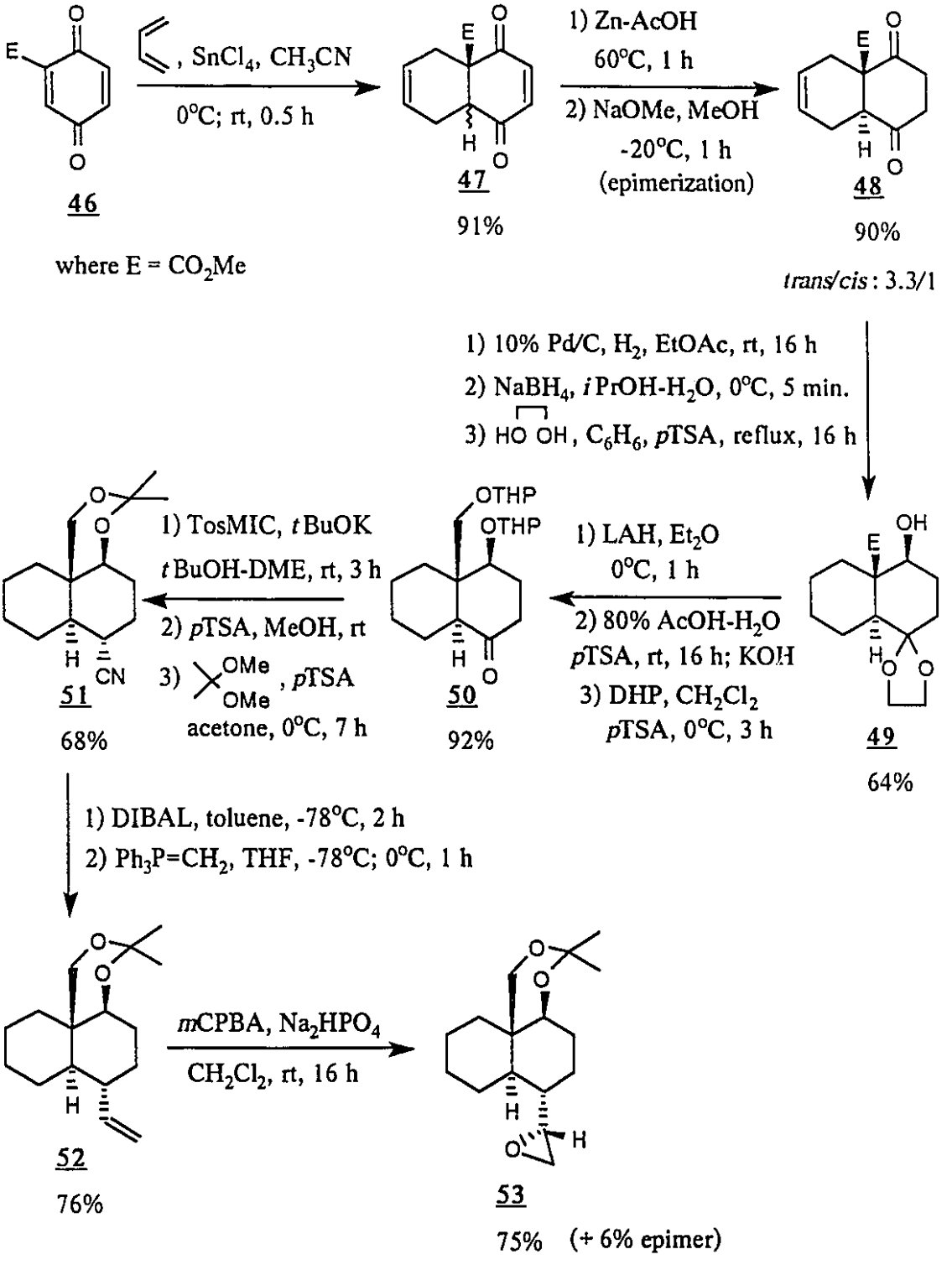
Scheme 1.8

Based on his earlier collaboration with Munakata, Kato[13] believed that the anti-feeding activity exhibited by clerodin 10, clerodendrin A 5, and caryoptin 11 was due to the perhydrofuro[2,3-*b*]furan ring in their structure. Thus, in 1980 Kojima and Kato[32] set out to prepare a variety of perhydrofuro[2,3-*b*]furans in order to study the structure-activity

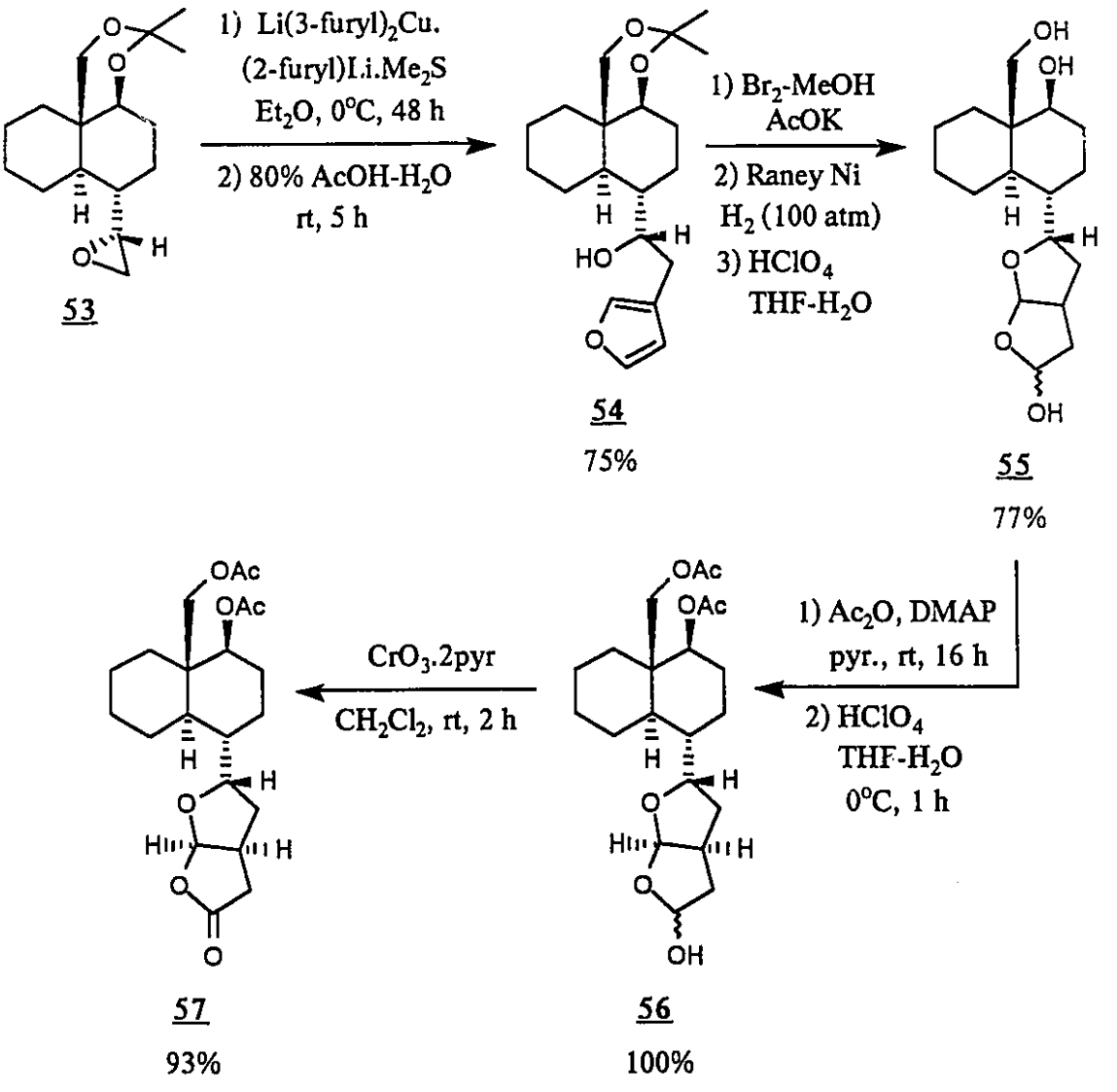
relationships of these compounds. Their synthetic route, outlined in **Scheme 1.8**, was based on the acid-catalyzed intramolecular cyclization of hydroxydialdehydes 32 and 33. These in turn were derived from the 3-substituted (R = *t* butyl or phenyl) furanalcohols 30 and 31, which were prepared from the coupling reaction of lithium di(3-furyl)cuprate 29 with the appropriate epoxide, a reaction developed by the same authors.[33]

Kojima and Kato[34] then prepared several other perhydrofuro[2,3-*b*]furan derivatives via the oxidation, acetylation, methylation and dehydration of hemiacetal compounds 34 and 35 as indicated in **Scheme 1.8** (see **Table 1.2** and **Table 1.3** for the biological activity of these compounds).

Somewhat disappointed with the results of the biological activity tests carried out on compounds 34-45 (*vide post*), Kojima and Kato[32,35] embarked on the synthesis of the clerodin homolog 56 (see **Scheme 1.9** and **Scheme 1.10**). In line with their recently developed methodology involving the coupling of epoxides with lithium di(3-furyl)cuprates such as 29 (see **Scheme 1.8**), they proceeded to prepare epoxy acetonide 53 from which they could prepare 54. This furan alcohol could then be transformed into the desired clerodin homolog using a procedure similar to that outlined in **Scheme 1.8**. They commenced their synthesis with the Diels-Alder reaction of *p*-quinone 46 and butadiene which gave 90% of a 4:1 mixture of the *cis*- and *trans*-adducts 47 (see **Scheme 1.9**). After reduction to the dihydro derivative, the mixture was epimerized to improve the ratio of the *cis*- and *trans*-decalin derivatives to 1:3.3. Catalytic hydrogenation of 48, followed by partial reduction with sodium borohydride to provide only the desired β-alcohol and protection of the remaining ketone functionality with ethylene glycol afforded 49 in 64% overall yield. Reduction of the ester moiety of 49 with lithium aluminum hydride, followed by deketalization and protection of the diol as tetrahydropyranyl ethers gave 50 in almost quantitative yield. At this point the construction of the 2,8-dioxabicyclo[3.3.0] octane ring functionality was addressed by the treatment of 50 with TosMIC, the hydrolysis of the tetrahydropyranyl ethers and the reprotection of the diol as its acetonide to provide nitrile


E
O
O
46
, SnCl4, CH3CN
0°C; rt, 0.5 h
47
91%
1) Zn-AcOH
60°C, 1 h
2) NaOMe, MeOH
-20°C, 1 h
(epimerization)
48
90%
trans/cis : 3.3/1
where E = CO2Me
1) 10% Pd/C, H2, EtOAc, rt, 16 h
2) NaBH4, iPrOH-H2O, 0°C, 5 min.
3) HO OH, C6H6, pTSA, reflux, 16 h
OH
49
64%
1) LAH, Et2O
0°C, 1 h
2) 80% AcOH-H2O
pTSA, rt, 16 h; KOH
3) DHP, CH2Cl2
pTSA, 0°C, 3 h
OTHP
OTHP
50
92%
1) TosMIC, tBuOK
tBuOH-DME, rt, 3 h
2) pTSA, MeOH, rt
3) OMe OMe, pTSA
acetone, 0°C, 7 h
CN
51
68%
1) DIBAL, toluene, -78°C, 2 h
2) Ph3P=CH2, THF, -78°C; 0°C, 1 h
52
76%
mCPBA, Na2HPO4
CH2Cl2, rt, 16 h
53
75% (+ 6% epimer)

Scheme 1.9



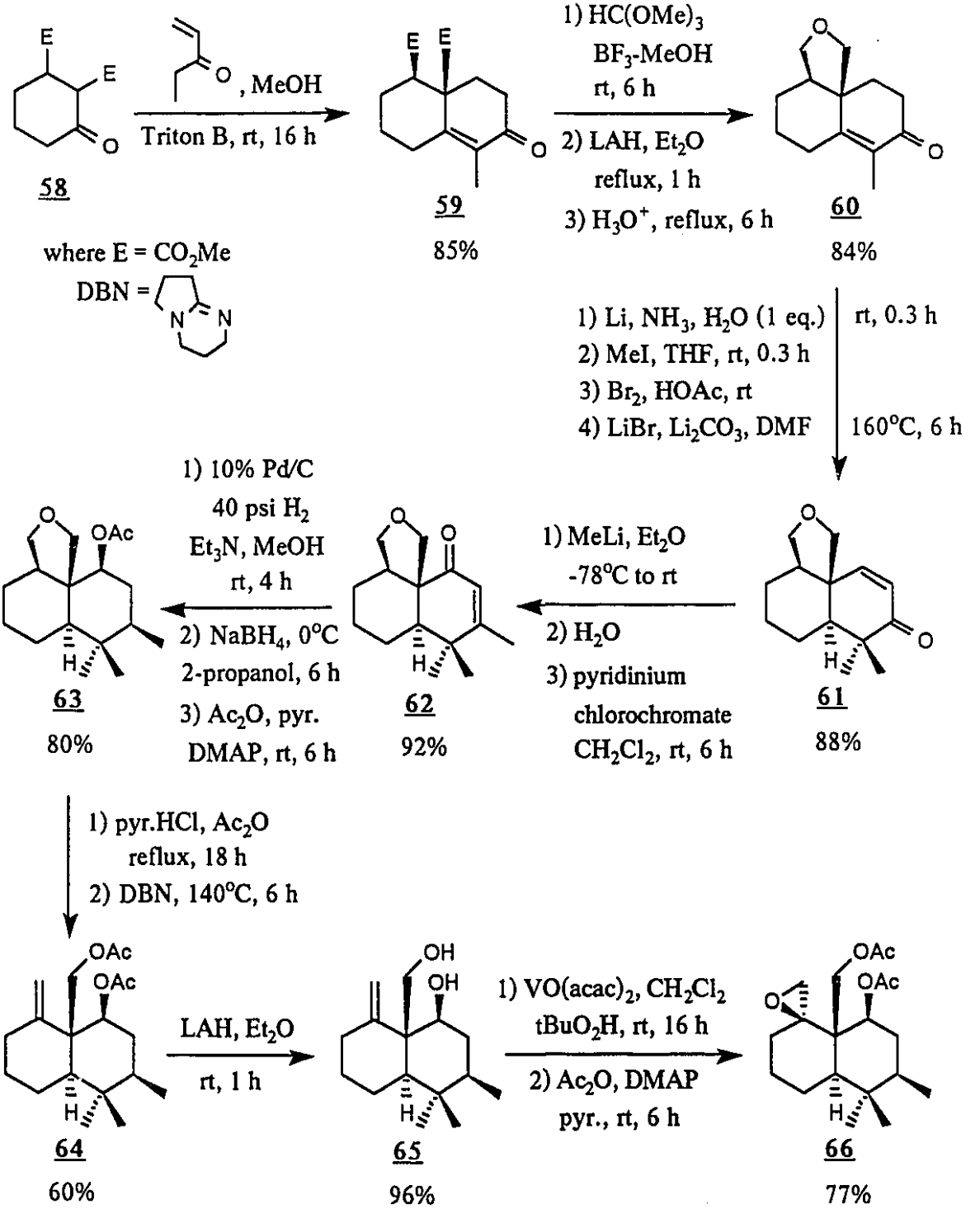
Scheme 1.10

acetonide 51 in 68% overall yield. Reduction of the nitrile functionality with DIBAL, followed by transformation of the resulting aldehyde into the terminal olefin and epoxidation gave a 12:1 mixture of epoxides 53 in 62% overall yield. The major product, the key intermediate 53, bearing the desired configuration, was then elaborated into the perhydrofuro[2,3-*b*]furan derivative 55 following the procedure described previously (see **Scheme 1.8**). Finally acetylation, followed by acid work-up gave the clerodin homolog

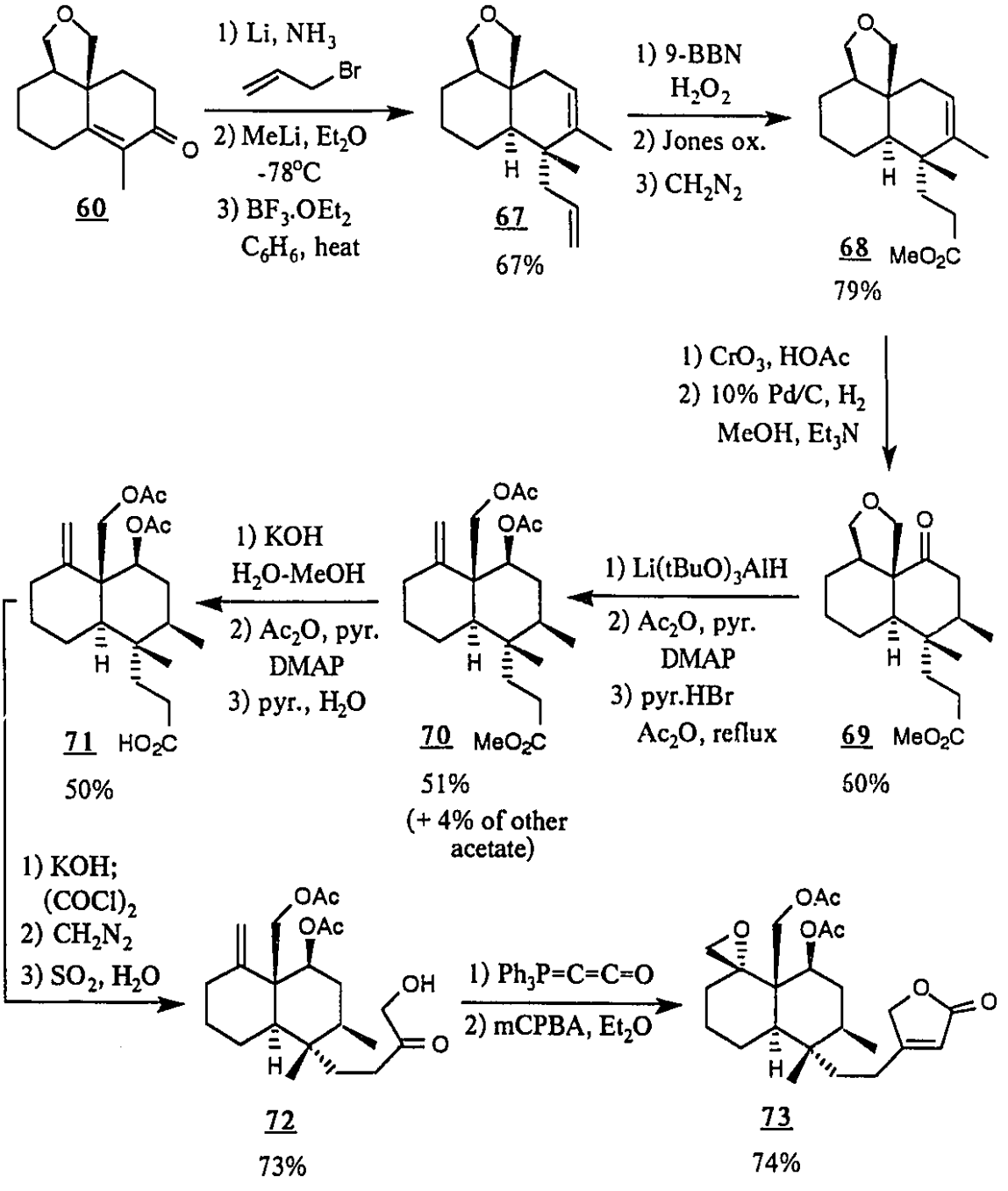
56 in quantitative yield. Oxidation of 56 gave compound 57 in 93% yield (see **Table 1.2** for the biological activity of 56, 57 and other clerodin analogs).

In 1981 Luteijn and de Groot[36] reported their synthesis of *trans*-decalin 66, the decalin unit present in both clerodin 10 and ajugarin-I 7 (see **Scheme 1.11**). They commenced by constructing an octalone 59 with suitably functionalized carbon atoms in 85% yield via a Robinson annulation of keto diester 58 with ethyl vinyl ketone. The two esters were then protected by transforming them in three steps into a cyclic ether moiety to give 60 in 84% overall yield. Reductive alkylation of enone 60 with methyl iodide served to prepare the *gem*-dimethyl functionality. At this point the alkylative carbonyl transposition process was started by treatment with bromine in acetic acid, followed by dehydrobromation to give 61 in 88% overall yield. The α,β-unsaturated ketone 61 was then treated with methyllithium and the resulting allylic alcohol oxidized with pyridinium chlorochromate which afforded the transposed α,β-unsaturated ketone 62 in 92% overall yield. Catalytic hydrogenation, followed by reduction of the ketone with sodium borohydride and acetylation of the resulting alcohol gave the acetate 63 in 80% yield along with 9% of the epimeric acetate. At this point the cyclic ether moiety was cleaved by refluxing 63 in acetic anhydride in the presence of pyridine hydrochloride. Elimination of hydrogen chloride from this molecule by treatment with 1,5-diazabicyclo[4.3.0]non-5-ene produced 64 in 60% yield. Since the direct epoxidation of diacetate 64 with *m*-CPBA gave a 1:1 mixture of epoxides, the diacetate was hydrolyzed to the diol 65, which was then epoxidized and reacetylated to give 66 as the sole product in 77% overall yield.

One year later the same researchers[37] published the synthesis of 4-*epi*-ajugarin-I 73, using once again octalone 60 as the starting material (see **Scheme 1.12**). Reductive alkylation of 60 with allyl bromide served to introduce the allyl group α to the resulting saturated ketone. The addition of methyllithium to the ketone, followed by dehydration provided compound 67 in 67% overall yield. Reaction of 67 with 9-BBN, followed by oxidation with hydrogen peroxide served to elaborate the terminal olefin into an alcohol.


E
E
O
58
, MeOH
Triton B, rt, 16 h
E E
O
59
85%
1) HC(OMe)3
BF3-MeOH
rt, 6 h
2) LAH, Et2O
reflux, 1 h
3) H3O+, reflux, 6 h
O
O
60
84%
where E = CO2Me
DBN =
N
N
1) Li, NH3, H2O (1 eq.)
2) MeI, THF, rt, 0.3 h
3) Br2, HOAc, rt
4) LiBr, Li2CO3, DMF
rt, 0.3 h
160°C, 6 h
O
H
61
88%
1) MeLi, Et2O
-78°C to rt
2) H2O
3) pyridinium
chlorochromate
CH2Cl2, rt, 6 h
O
O
H
62
92%
1) 10% Pd/C
40 psi H2
Et3N, MeOH
rt, 4 h
2) NaBH4, 0°C
2-propanol, 6 h
3) Ac2O, pyr.
DMAP, rt, 6 h
O
OAc
H
63
80%
1) pyr.HCl, Ac2O
reflux, 18 h
2) DBN, 140°C, 6 h
OAc
OAc
H
64
60%
LAH, Et2O
rt, 1 h
OH
OH
H
65
96%
1) VO(acac)2, CH2Cl2
tBuO2H, rt, 16 h
2) Ac2O, DMAP
pyr., rt, 6 h
O
OAc
OAc
H
66
77%

Scheme 1.11



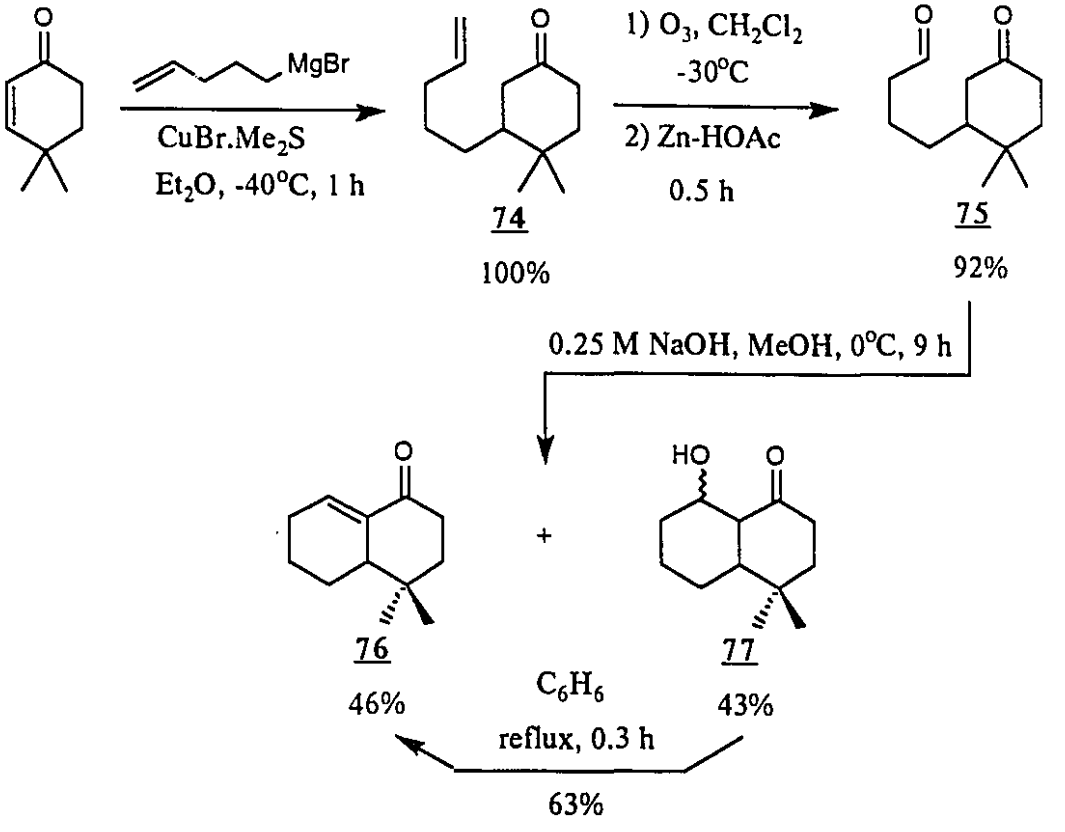
Scheme 1.12

Jones oxidation of the alcohol afforded the carboxylic acid which was converted into the methyl ester 68 in 79% overall yield on treatment with diazomethane. Allylic oxidation of

68, followed by hydrogenation of the resulting enone gave ketone 69 in 60% overall yield. Reduction of this compound with lithium tri-*t*-butoxy aluminum hydride gave a mixture of the equatorial and axial alcohols in a 4:1 ratio. Acetylation and treatment with pyridine hydrobromide provided the desired olefin diacetate 70 in 51% overall yield, along with 4% of the other isomer featuring an axial secondary acetate. Hydrolysis followed by reacetylation gave 71 in 50% overall yield. This carboxylic acid was converted into the corresponding acid chloride. Reaction of the acid chloride with diazomethane followed by hydrolysis of the intermediate diazoketone gave the hydroxy ketone 72 in 73% overall yield. Treatment of 72 with triphenylphosphoranylidene ketene gave a butenolide which the authors then treated with *m*-chloroperoxybenzoic acid in the hope that this would provide a 1:1 mixture of epoxides. In their synthesis of a functionalized *trans*-decalin clerodane model compound this had been an undesired result (see discussion accompanying **Scheme 1.11**), but in this case it would have allowed them to prepare 4-*epi*-ajugarin-I 73 as well as the natural product ajugarin-I 7. However, the epoxidation reaction gave 4-*epi*-ajugarin 73 as the sole product in 74% overall yield. Attempts to synthesize the natural product ajugarin-I were unsuccessful.

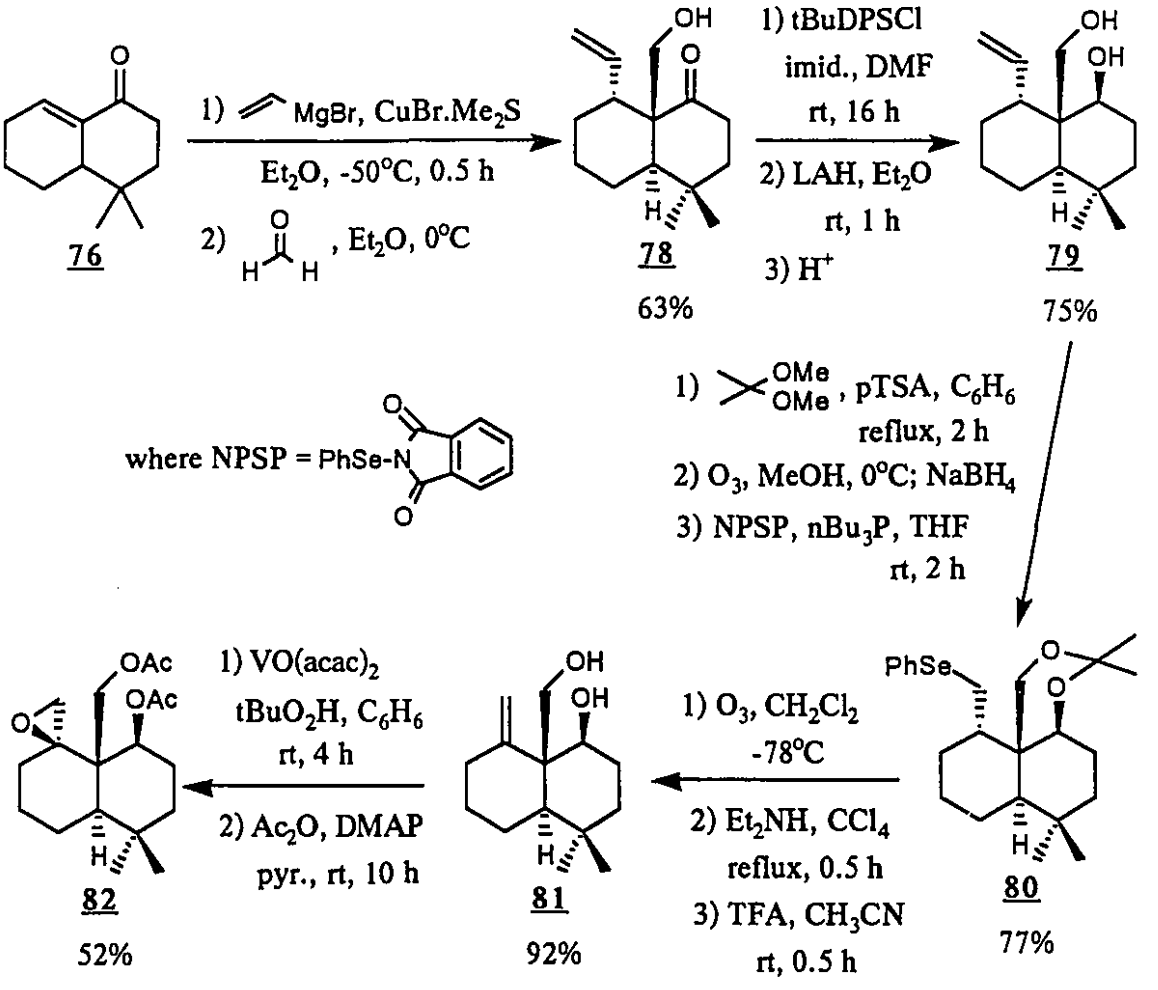
Also in 1982, Ley *et al.*[38] reported the synthesis of polyoxygenated *trans*-decalins, as outlined in **Scheme 1.14** and **Scheme 1.15**. As in their synthesis of the epoxydiacetate *cis*-decalin 23 (see **Scheme 1.6**), they chose 4,4-dimethylcyclohex-2-enone as the starting material (see **Scheme 1.13**). The CuBr.Me_2S catalyzed conjugate addition of pent-4-enylmagnesium bromide gave 74 in quantitative yield. Compound 74 was converted to ketoaldehyde 75 in 92% overall yield by ozonolysis and reductive work-up. Subsequent intramolecular aldol condensation provided the enone 76 in 46% along with 43% of ketoalcohol 77. Compound 77, however, could be readily dehydrated in benzene under Dean-Stark conditions to afford more 76 in 63% yield.

The conjugate addition of the appropriate cuprate to the enone 76 from the least hindered side followed by trapping of the resulting enolate from the opposite face by form-



Scheme 1.13

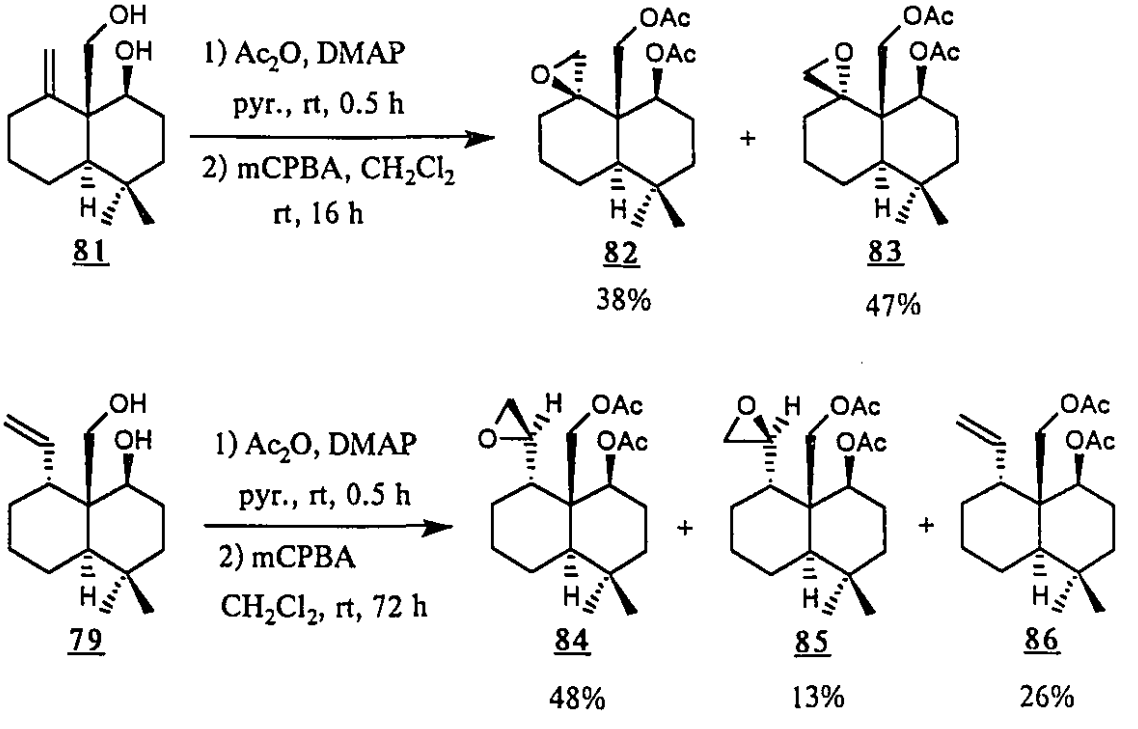
aldehyde gave the desired *trans*-fused product 78 in 63% yield (see **Scheme 1.14**). After protection of the primary alcohol, the ketone was reduced, providing after acidic work-up, the diol 79 in 75% overall yield. The diol was then protected by forming an acetonide. Then the terminal double bond was subjected to ozonolysis, followed by reductive work-up and conversion of the resulting primary alcohol into the phenyl selenide 80 in 77% overall yield using N-phenylselenophthalimide-tri-*n*-butylphosphine. Subsequent oxidation of 80 to the selenoxide, followed by *syn*-elimination and deprotection of the acetonide, afforded the diol 81 in 92% overall yield. Hydroxy-group-directed epoxidation, followed by diacetylation completed the synthesis of the model *trans*-fused compound 82 in 52% overall yield.



Scheme 1.14

Ley *et al.*[38] then prepared three other *trans*-epoxy-decalin diacetate analogs, as indicated in **Scheme 1.15**. The isomeric epoxide 83 was obtained in 47% together with 38% of 82 by epoxidation of the diacetate (obtained from the diol 81) by *m*-chloroperoxybenzoic acid. Acetylation of 79 followed by epoxidation gave the two epoxides 84 and 85 in a 1.3 : 1.0 ratio in 61% combined yield (see **Table 1.4** for the biological activity of *trans*-decalin analogs 82-85).

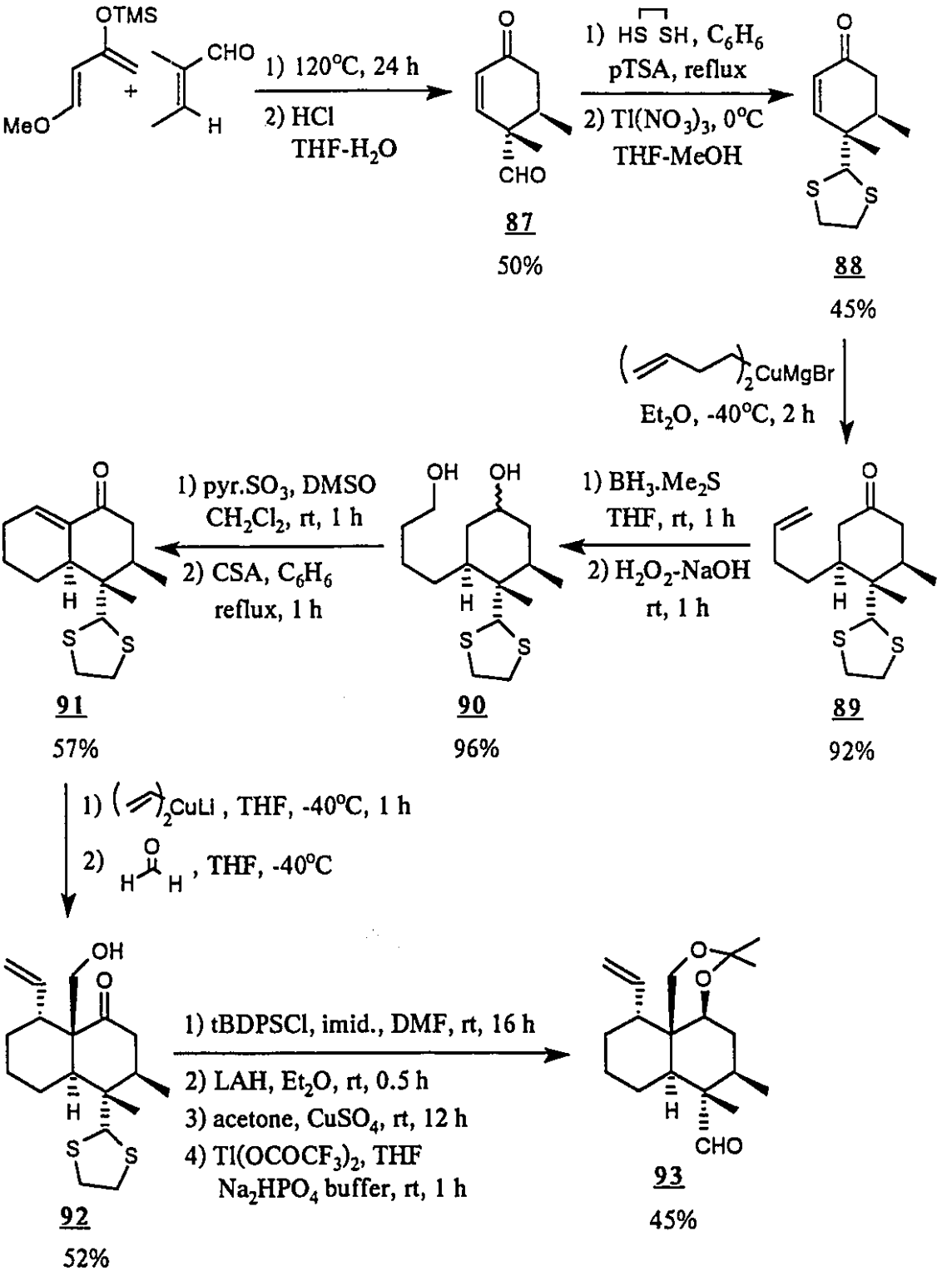
In 1983 Ley and coworkers[39,40] reported their total synthesis of ajugarin-I 7, using a strategy closely related to the one just described (see **Scheme 1.16** and **Scheme 1.17**) The starting enone 87 was prepared in 50% yield by the Diels-Alder reaction between



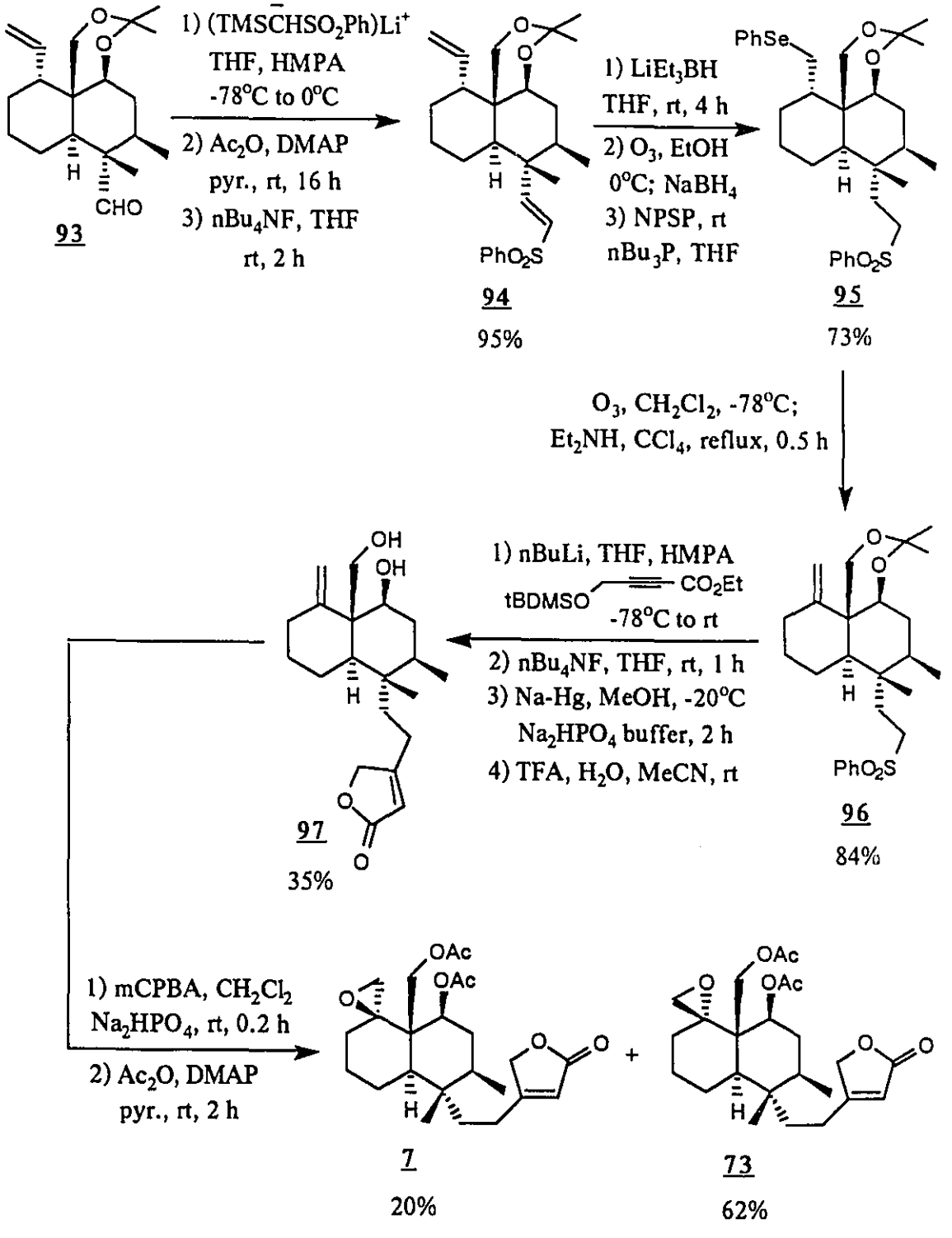
Scheme 1.15

Danishefsky's diene and E-2-methylbut-2-enal. Conversion of 87 into the monodithiolane 88 was achieved in 45% yield by a sequence of reactions which involved initial diprotection followed by specific removal of the more labile enone dithiolane group. Compound 88 was then transformed into decalin 92 by a series of reactions similar to those seen in **Scheme 1.14**. Transformation of the ketoalcohol 92 into the diol, followed by protection of the diol as an acetonide (as in **Scheme 1.14**) and regeneration of the aldehyde group from the dithiolane by treatment with thallium(III) trifluoroacetate afforded 93 in 45% overall yield.

At this point a homologated sulphone moiety was incorporated by reacting the aldehyde 93 with the anion from phenylsulphonyl(trimethylsilyl)methane to give an addition product from which the E-vinyl sulphone 94 was obtained in 95% yield by elimination. The vinyl side chain in 94 was then converted, via the selenide 95 (in 73% yield), in-


OTMS
CHO
MeO
H
1) 120°C, 24 h
2) HCl
THF-H2O
87
50%
1) HS SH, C6H6
pTSA, reflux
2) Tl(NO3)3, 0°C
THF-MeOH
88
45%
2CuMgBr
Et2O, -40°C, 2 h
89
92%
1) BH3.Me2S
THF, rt, 1 h
2) H2O2-NaOH
rt, 1 h
90
96%
1) pyr.SO3, DMSO
CH2Cl2, rt, 1 h
2) CSA, C6H6
reflux, 1 h
91
57%
1) 2CuLi , THF, -40°C, 1 h
2) , THF, -40°C
92
52%
1) tBDPSCl, imid., DMF, rt, 16 h
2) LAH, Et2O, rt, 0.5 h
3) acetone, CuSO4, rt, 12 h
4) Tl(OCOCF3)2, THF
Na2HPO4 buffer, rt, 1 h
93
45%

Scheme 1.16

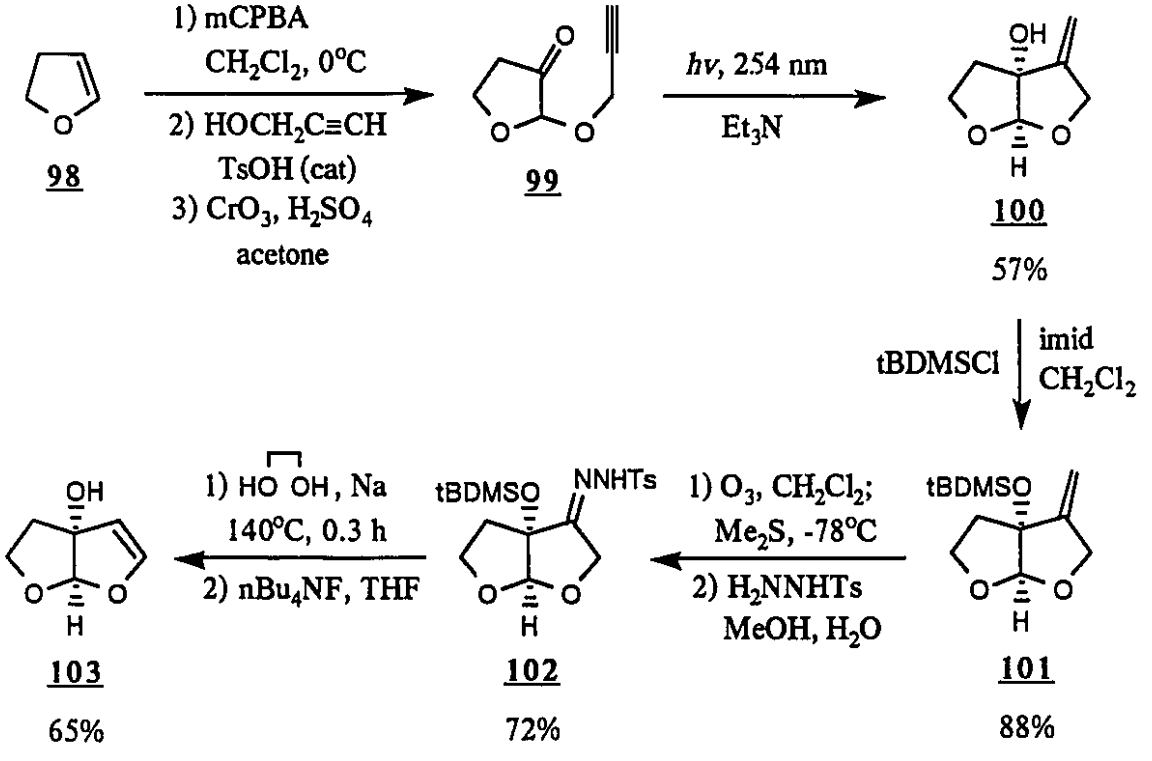

1) (TMSCHSO2Ph)Li+
THF, HMPA
-78°C to 0°C
2) Ac2O, DMAP
pyr., rt, 16 h
3) nBu4NF, THF
rt, 2 h
93
94
95%
1) LiEt3BH
THF, rt, 4 h
2) O3, EtOH
0°C; NaBH4
3) NPSP, rt
nBu3P, THF
95
73%
O3, CH2Cl2, -78°C;
Et2NH, CCl4, reflux, 0.5 h
96
84%
1) nBuLi, THF, HMPA
tBDMSO
CO2Et
-78°C to rt
2) nBu4NF, THF, rt, 1 h
3) Na-Hg, MeOH, -20°C
Na2HPO4 buffer, 2 h
4) TFA, H2O, MeCN, rt
97
35%
1) mCPBA, CH2Cl2
Na2HPO4, rt, 0.2 h
2) Ac2O, DMAP
pyr., rt, 2 h
7
20%
73
62%

Scheme 1.17

to the desired *exo*-methylene group which gave 96 in 84% yield (see also **Scheme 1.14**). The anion of 96 was then treated with a novel butenolide synthon providing an adduct which was immediately treated with tetra-*n*-butylammonium fluoride to effect deprotection and concomitant cyclization to the butenolide. Reductive removal of the phenylsulphone group and deprotection of the acetonide afforded the *exo*-methylene diol 97 in 35% overall yield. Final elaboration to the natural product required epoxidation followed by diacetylation which gave ajugarin-I 7 in 20% yield together with 62% yield of 4-*epi*-ajugarin-I 73.

At the end of the decade, in 1989 and 1990, Lallemand *et al.*[41,43] reported their syntheses of a furofuranic model and the *trans*-decalin epoxy-diacetate model 82 of the clerodanes.

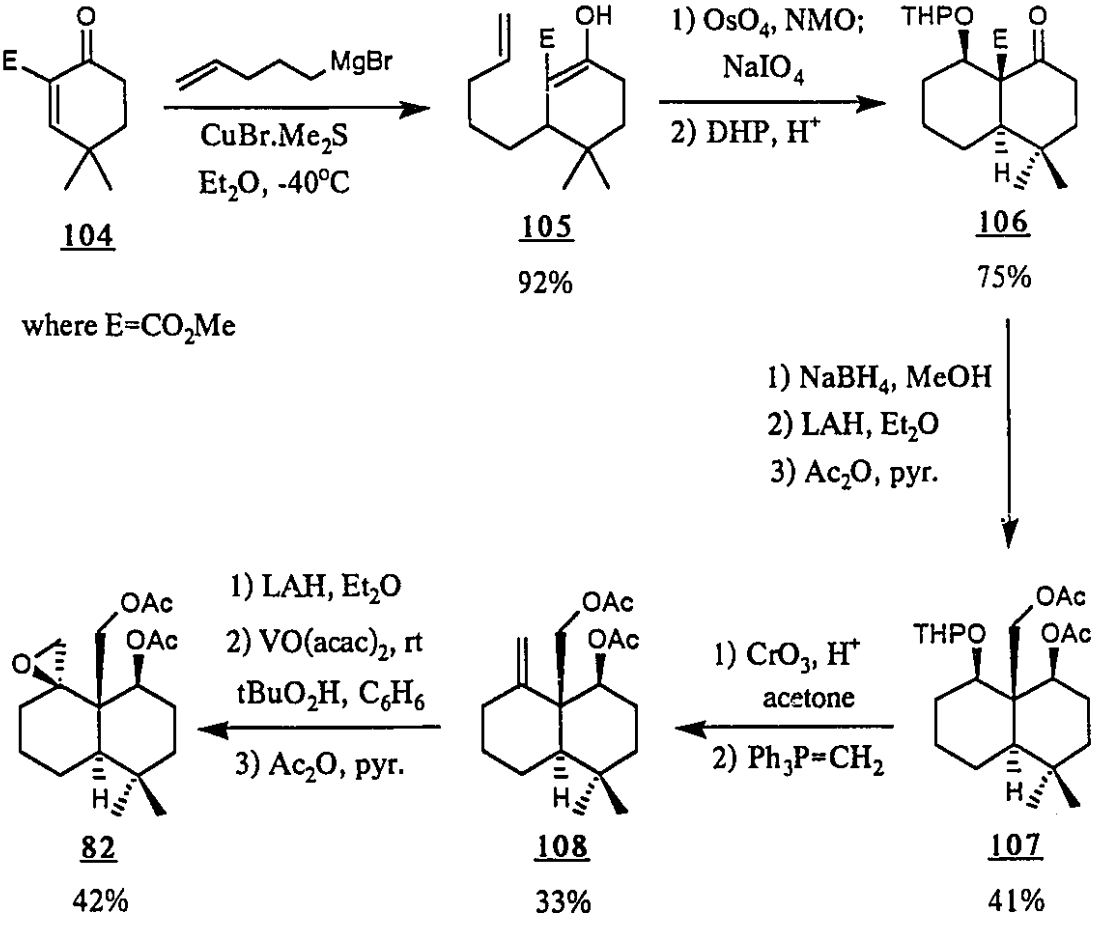
They began their preparation of the furofuranic model 103[41] (see **Scheme 1.18**)



Scheme 1.18

with ketone 99 which was readily derived from 98 in three steps.[42] Acetylenic ketone 99 was photochemically activated in the presence of triethylamine (as an electron source) to effect a single electron transfer cyclization affording alcohol 100 in 57% yield. The alcohol was then protected to give 101 in 88% yield. Subsequently the *exo*-methylene moiety was subjected to ozonolysis and the resulting ketone was transformed into 102 in 72% overall yield. Compound 102 was then converted to the desired furofanic model compound 103 in 65% yield using the Bamford-Stevens reaction.

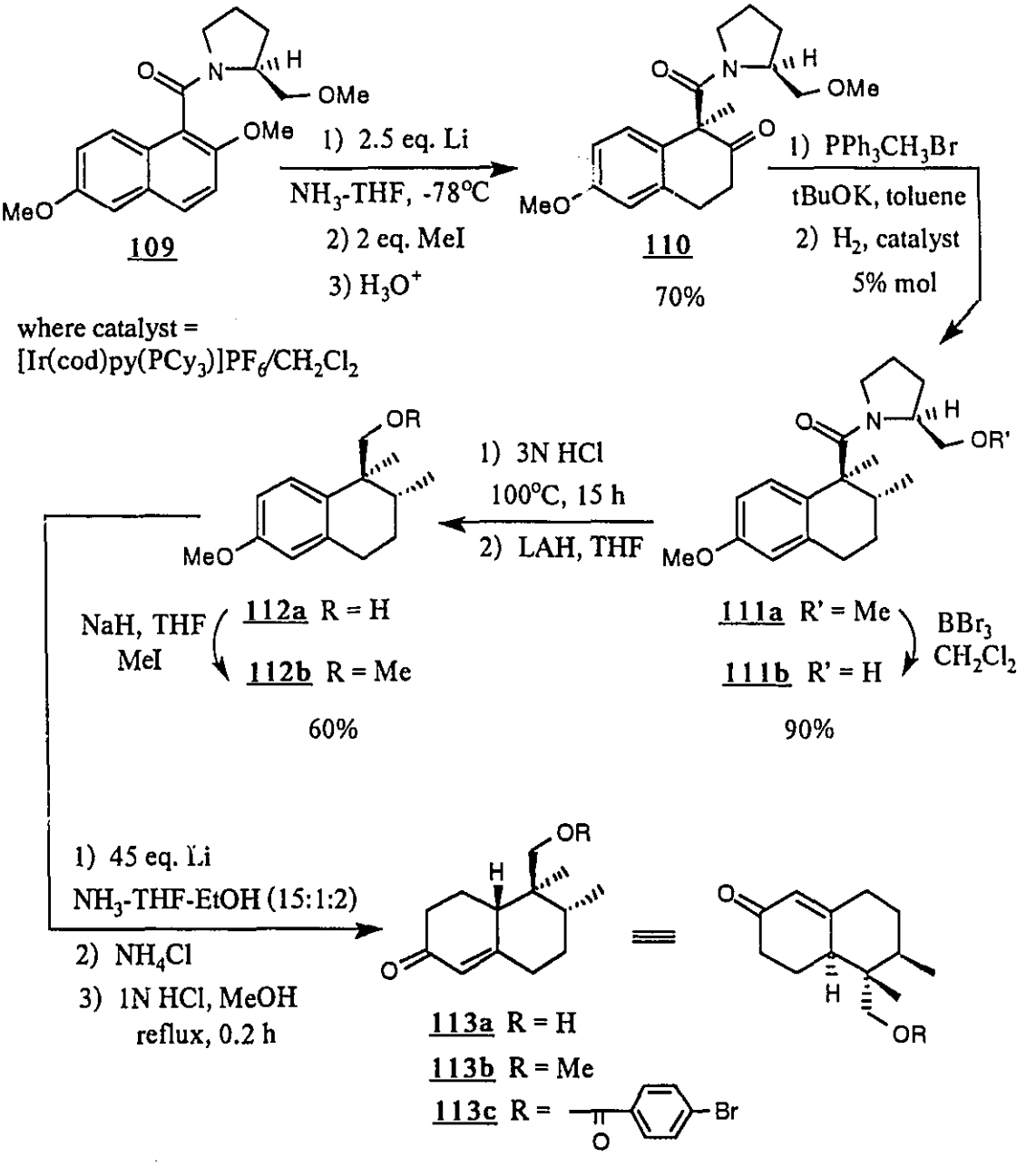
Bouchard and Lallemand[43] started their preparation of the polyoxygenated *trans*-decalin 82, already synthesized by Ley *et al.*[38] (see **Scheme 1.14**), with the unsaturated keto-ester 104, which was readily available from 4,4-dimethylcyclohex-2-enone (see



Scheme 1.19

Scheme 1.19). Similarly to Ley and coworkers, Bouchard and Lallemand then prepared 105 by a copper-catalyzed conjugate addition of the appropriate Grignard reagent to 104. Treatment of the terminal olefin with osmium tetroxide, followed by sodium periodate, spontaneously provided the *trans*-decalin via an intramolecular aldol condensation. The secondary alcohol was then protected as its tetrahydropyranyl ether to give 106 in 75% overall yield. Keto-ester 106 was stereo- and regio-specifically reduced with sodium borohydride followed by lithium aluminum hydride. The resulting diol was then acetylated into diacetate 107 in 41% overall yield from 106. The THP derivative 107 was then efficiently oxidized into a ketone which was converted, by a Wittig reaction, into the *exo*-methylene derivative 108 already described by Ley *et al.*[38]. Final transformation of 108 into 82 was then completed by reduction of the diacetate into the corresponding diol, followed by hydroxy-group directed epoxidation and diacetylation which afforded 82 in 42% overall yield (see **Table 1.4** and **Table 1.5** for the biological activity of *trans*-decalin 82).

In 1991, Lallemand *et al.*[44] reported their preliminary results on an approach to the chiral Δ^4-3-octalone 113 , a versatile intermediate for the enantioselective route towards clerodane diterpenoids (see **Scheme 1.20**). Reductive alkylation of the chiral L-prolinol naphthalene derivative 109, followed by acidic treatment gave ketone 110 in 70% yield. Sequential Wittig reaction and hydrogenation served to introduce the methyl group, providing 111a in 90% yield. Removal of the chiral auxiliary was then accomplished under acidic conditions. The crude mixture was promptly reduced with LAH in THF to afford 112a in 60% yield, which could be protected by methylation (112b). Further Birch reduction of 112, followed by acid hydrolysis of the resulting enol-ether, gave the desired enone 113. The absolute stereochemistry of 113 was established by X-ray single crystal analysis of the *p*-bromobenzoate derivative 113c. Further functionalization of this decalin structure will allow for the asymmetric synthesis of clerodane diterpenoids.


1) 2.5 eq. Li
NH3-THF, -78°C
2) 2 eq. MeI
3) H3O+
109
110
70%
1) PPh3CH3Br
tBuOK, toluene
2) H2, catalyst
5% mol
where catalyst =
[Ir(cod)py(PCy3)]PF6/CH2Cl2
1) 3N HCl
100°C, 15 h
2) LAH, THF
NaH, THF
MeI
112a R = H
112b R = Me
60%
111a R' = Me
111b R' = H
BBr3
CH2Cl2
90%
1) 45 eq. Li
NH3-THF-EtOH (15:1:2)
2) NH4Cl
3) 1N HCl, MeOH
reflux, 0.2 h
113a R = H
113b R = Me
113c R =
Br

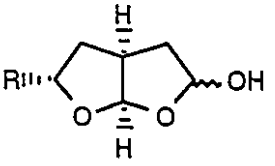
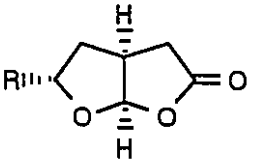
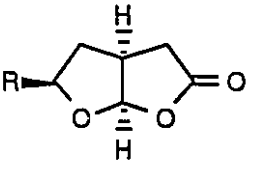
Scheme 1.20

1.4 Biological Activity of Synthetically Prepared Clerodane Analogs

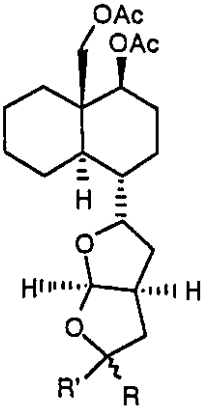
The antifeedant activity of several of the synthetically prepared clerodane analogs is given in **Tables 1.2 - 1.5**. The results of Kojima and Kato[32,35] are presented in **Tables 1.2** and **1.3**. Note that these compounds were all tested against the tobacco cut worm *Spodoptera litura*, as were the natural products presented in **Table 1.1**. It can be seen that the perhydrofuro[2,3-*b*]furan derivatives featuring the phenyl system are much more active than those of the *tert*-butyl system. Most of the *tert*-butyl derivatives are not active at all. Interestingly, when the rigidity and stability of the perhydrofuro[2,3-*b*]furan ring system is increased, by the addition of methyl groups on the phenyl ring, the activity of the derivatives increases. The activity of the 2,6-dimethylphenyl derivatives 115 and 117 is the same as the activity of the clerodin homologs 56 and 57 at 500 ppm and 250 ppm, respectively. As a comparison, the natural product clerodin hemiacetal 17 is active at 50 ppm when tested against the same insects (see **Table 1.1**). Thus Kojima and Kato believe that the perhydrofuro[2,3-*b*]furan ring system might be the responsible site for the activity in the clerodane structure.

On the other hand, Ley *et al.*[31,38] and de Groot *et al.*[36,37] believe that the epoxydiacetate decalin ring system is responsible for the activity of the clerodane structure. This statement would seem reasonable in light of the high feeding inhibition against *Spodoptera exempta* elicited by the ajugarins 7-9 (see **Table 1.1**). The results of the biological testing carried out by Ley and coworkers[31,38,45] are outlined in **Tables 1.4** and **1.5**. The *cis*- and *trans*-decalin clerodane analogs 23 and 82 showed significant activity against *Locusta migratoria* locusts, with the *trans*-decalin 82 exhibiting 10 times the activity of the *cis*-decalin 23. However the antifeedant activity index at 100 ppm of 23 and 82 is much lower than that of the natural product clerodin hemiacetal 17, when tested against the African army worm *Spodoptera exempta*. Thus Ley *et al.*[45] now believe that the antifeeding activi-

Table 1.2 Antifeedant Acivity of Clerodin Analogs prepared by Kojima and Kato[35]

Compound	Activity
	
34 R = tBu	not active
35 R = Ph	not active
114 R = 2-Me-phenyl	500 ppm : 60%
115 R = 2,6-diMe-phenyl	500 ppm : 80%
56 R = clerodin homolog	500 ppm : 80%
	
36 R = tBu	not active
38 R = Ph	1000 ppm : 35%
116 R = 2-Me-phenyl	250 ppm : 35%
117 R = 2,6-diMe-phenyl	250 ppm : 60%
57 R = clerodin homolog	250 ppm : 60%
	
37 R = tBu	not active
39 R = Ph	not active

clerodin homologs



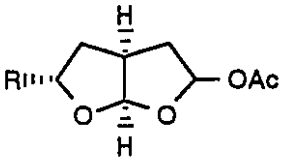
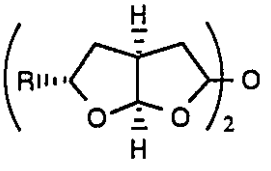
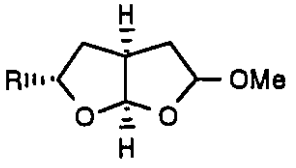
56 R = OH, R'= H

57 R, R'= O

Note: All compounds were tested in a choice test against the tobacco cut worm, *Spodoptera litura*

* clerodin hemiacetal 17 is active at 50 ppm against *Spodoptera litura* (see **Table 1.1**).

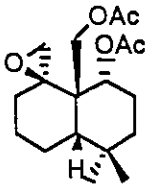
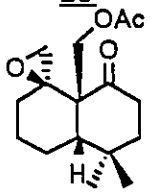
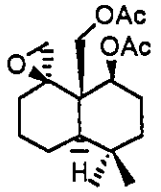
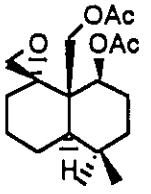
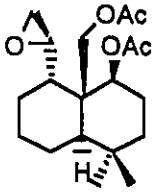
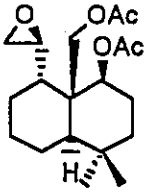
Table 1.3 Antifeedant Activity of Clerodin Analogs prepared by Kojima and Kato[32]

Compound	Activity
	
40 R = tBu	500 ppm : 35%
41 R = Ph	1000 ppm : 100%
	
42 R = tBu	1000 ppm : 35%
43 R = Ph	500 ppm : 60%
	
44 R = tBu	not active
45 R = Ph	500 ppm : 35%

Note: All compounds were tested in a choice test against the tobacco cut worm, *Spodoptera litura*

ty of the clerodane diterpenes lies in the configuration of both the furofuran unit and its decalin moiety.

Table 1.4 Antifeedant Activity of Clerodin Analogs prepared by Ley *et al.*[31,38] *

Compound	Activity
 **23**	1000 ppm : 72%
 **28**	1000 ppm : 30%
 **82**	100 ppm : 70%
The following analogs exhibited negligible activity:	
 **83**	
 **84**	
 **85**	

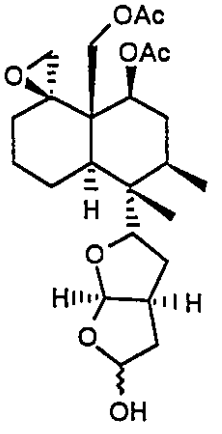
Note: All compounds were tested in a choice test against *Locusta migratoria* insects

* *trans*-decalin **82** was also prepared by Lallemand *et al.*[43]

Table 1.5 Antifeedant Index (C-T)/(C+T)% as measured at 100 ppm by Ley *et al.*.[45] C = Control and T = Treatment

Compound	Antifeedant Index
cis-decalin 23	15
trans-decalin 82	20
clerodin hemiacetal 17	84

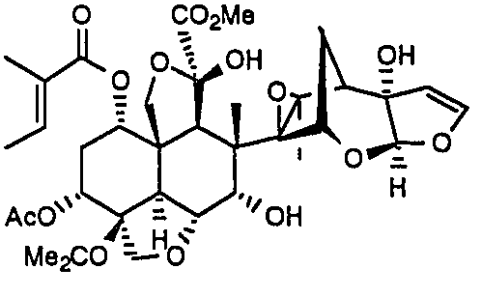
Note: compounds were tested in a choice test against African army worms, *Spodoptera exempta*



17

1.5 The Powerful Antifeedant Azadirachtin, 118

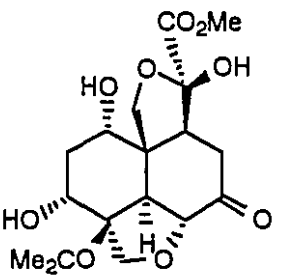
The extraction of the leaves, fruits and seeds of the Indian neem tree, *Azadirachta indica* has yielded the most promising antifeedant isolated to date, namely azadirachtin 118. Morgan's group[46] first isolated azadirachtin from the neem tree in 1968. The structure elucidation of this extremely complex triterpene took no less than 18 years. Two other structures were first proposed by Nakanishi *et al.*[47] in 1975 and Ley and Morgan *et al.*[48] in 1985, based on ^{1}H NMR and ^{13}C NMR spectroscopy, before structure 118, proposed by Kraus *et al.*[49], was proven to be correct by X-ray crystallography (carried out by Ley *et al.*[50]).



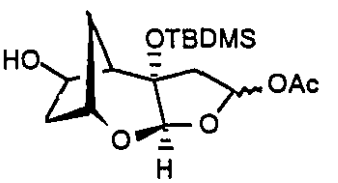
118

Azadirachtin is active at a concentration of 1 ppm and has shown feeding inhibition against some 40 different insect pests,[51] yet does not harm beneficial insects,[52] nor is it toxic to mammals or to birds.[53]

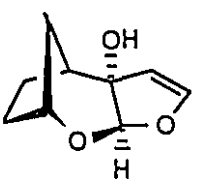
Synthetic efforts are now in course to prepare simpler analogs of azadirachtin and eventually the natural product itself. Ley and coworkers[54] have prepared the hydroxy dihydrofuran acetal 121, which represents a fragment of azadirachtin, and found this compound to be nearly as potent an insect antifeedant as azadirachtin itself when tested against larvae of the lepidopteran Egyptian cotton leafworm *Spodoptera littoralis* (see **Table 1.6**).



119



120



121

Table 1.6 Antifeedant Index (C-T)/(C+T)% as measured by Ley *et al.*[51]

Compound	Activity at 1 ppm
121	66
azadirachtin 118	99

Ley's group has since prepared the optically pure acetal intermediate 120[55] as well as the highly functionalized decalin fragment of azadirachtin 119.[56] A detailed description of these synthetic efforts towards azadirachtin is beyond the scope of this thesis and the reader is referred to the references mentioned.

1.6 The Spruce Budworm

The spruce budworm, *Choristoneura fumiferana*, is the most widely distributed and destructive defoliator of spruce-fir forests in eastern North America.[57] In eastern Canada the larvae of the budworm begin to feed on the buds or the newly opened shoots of the host tree in mid-May, while they consume the greatest amount of foliage during their sixth life stage, or 6th-instar in late June. A budworm outbreak can have devastating consequences for the pulp and paper industry. It has been estimated that for the Gaspé region of Québec alone, the damage due to timber lost can be as high as 5 billion dollars.[58] A budworm outbreak is followed by a dramatic decline of the insect population, and there is evidence indicating that during the last two centuries these oscillations have occurred quite regularly with a frequency of 30-40 years.[59]

The spruce budworm's life cycle is outlined in **Figure 1.1** (taken from reference 57). The adult insect is a small moth about 1.5 cm long. It emerges from the pupa during July and August. Female budworms lay about 180 eggs in clusters of about 20 eggs each on the host tree needles. Hatching occurs about 10 days later. The tiny larvae are then in their first stage or 1st-instar and retreat into their hibernacula, where they remain until Spring. In the Spring the larvae emerge from their hibernacula. The voracious budworms consume more and more foliage as they develop from the 2nd- to 6th-instar. At this point pupation occurs and the cycle begins again.

Efforts to control the spruce budwom up to now have relied on the spraying of chemical insecticides such as Fenotrothion or the microbial insecticide *Bacillus thuringiensis* (BT).[60] Chemical insecticides are considered environmentally undesirable. The efficacy of BT under field conditions is subject to a number of external factors. In addition, insect resistance to BT has recently been reported.[61]

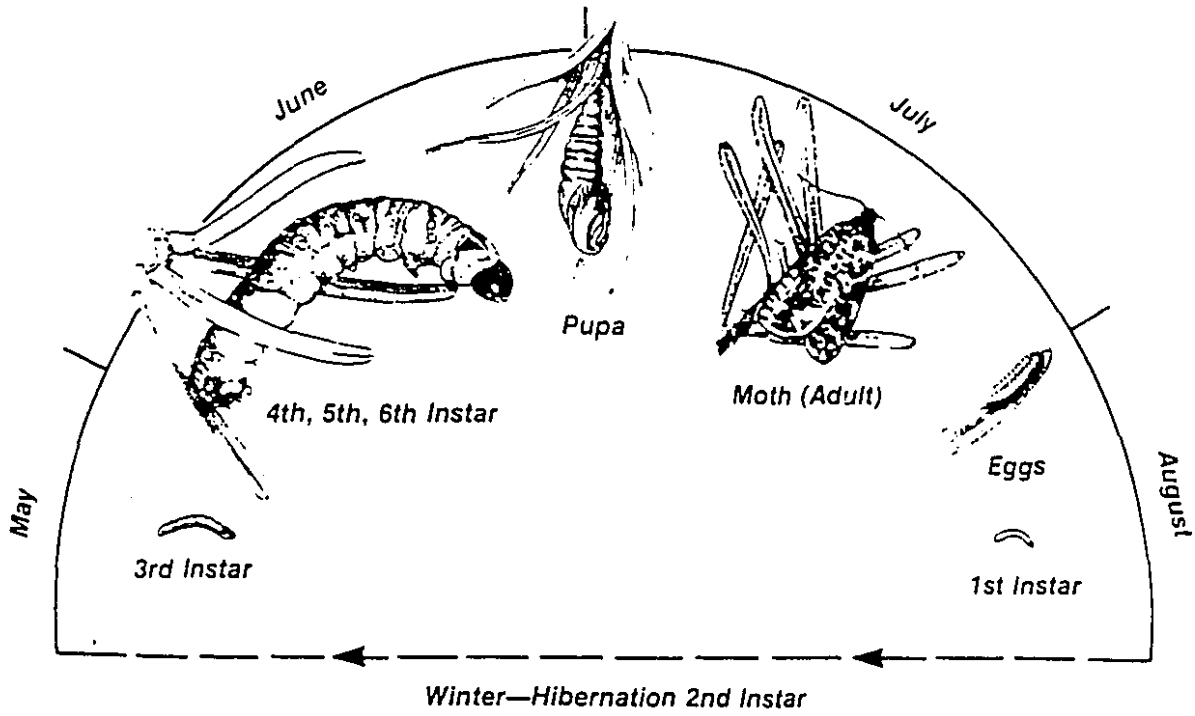
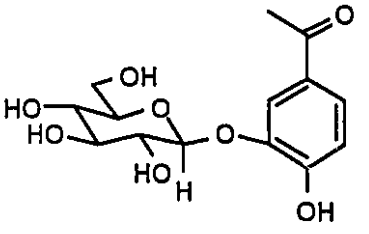


Figure 1.1

A pest control strategy involving the use of antifeedants may offer advantages over conventional pest control methods since the antifeedant could protect the current year foliage while leading indirectly to budworm mortality without being generally toxic.[62]

Whereas detailed information on the feeding behaviour of spruce budworm larvae has been available since the 1950's,[63,64] the first approach to a systematic examination of chemical aspects of the spruce budworm-host tree interaction can be attributed to Heron in 1965.[65] Heron studied the feeding response of 5th-instar larvae towards extracts of new vegetative shoots and mature needles of white spruce *Picea glauca*. He found that sucrose and amino acid L-proline showed pronounced phagostimulant effects in the bioassays. The phenolic glucoside pungenin, 122, is present at high concentrations in mature foliage of various *Picea* species, but is virtually absent in the new shoots. Heron reported that 5th-

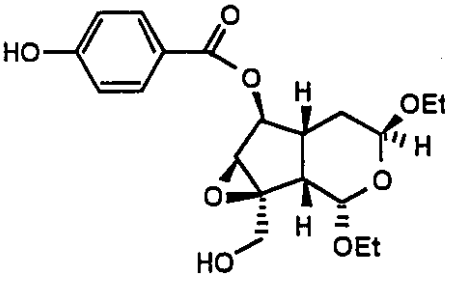
instar spruce budworm larvae, offered a choice between disks of Japanese elder pith impregnated with the phagostimulant sucrose, and identical disks also treated with a 1% solution of pungenin, showed a marked preference for the former. This finding appeared to provide a partial explanation for the fact that new vegetative shoots, devoid of pungenin, are much more acceptable to the larvae than mature foliage in which the glucoside is abundant.



122

However, in 1986 Strunz and coworkers[66] reported a synthesis of pungenin from commercially available acetovanillone. They found that spruce budworm larvae developed successfully from 2nd- to 6th-instar on synthetic McMorran diet[67] containing pungenin at a concentration of 5%, a level higher than that normally present in mature foliage of white spruce at the time the insects are feeding. They concluded that although pungenin exhibits deterrency in a choice situation, it cannot be considered a potent antifeedant.

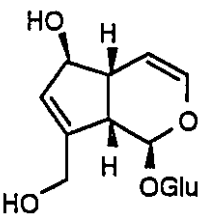
In 1983 Chang and Nakanishi[68] reported on the screening of extracts from foliage of 40 non-host trees for antifeedant activity against the spruce budworm. When incorpo-



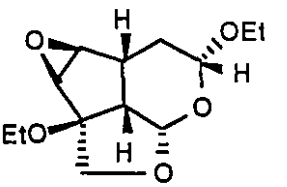
123

rated into diet at 50-100 ppm, antifeedant properties were attributed to an iridoid, designated specionin 123, from the leaves of *Catalpa speciosa.* Specionin has recently been synthesized by Van der Eycken *et al.*[69]

Because of the complexity of structures of known antifeedants, such as specionin 123, clerodin 10, and azadirachtin 118, our laboratory, like others in this field, has turned to the more practical approach of preparing simpler analogs of these compounds. In 1987 our laboratory[70] reported the synthesis and biological activity of seven analogs of specionin prepared from the natural iridoid aucubin 124, isolated from *Aucuba japonica.* When tested, at 0.2% wet weight in McMorran diet, for their effects on spruce budworm only compound 125 showed significant activity.



124



125

This thesis describes our continued efforts in the quest for antifeedants for the spruce budworm, focussing on the synthesis and biological activity of angularly functionalized decalin compounds.

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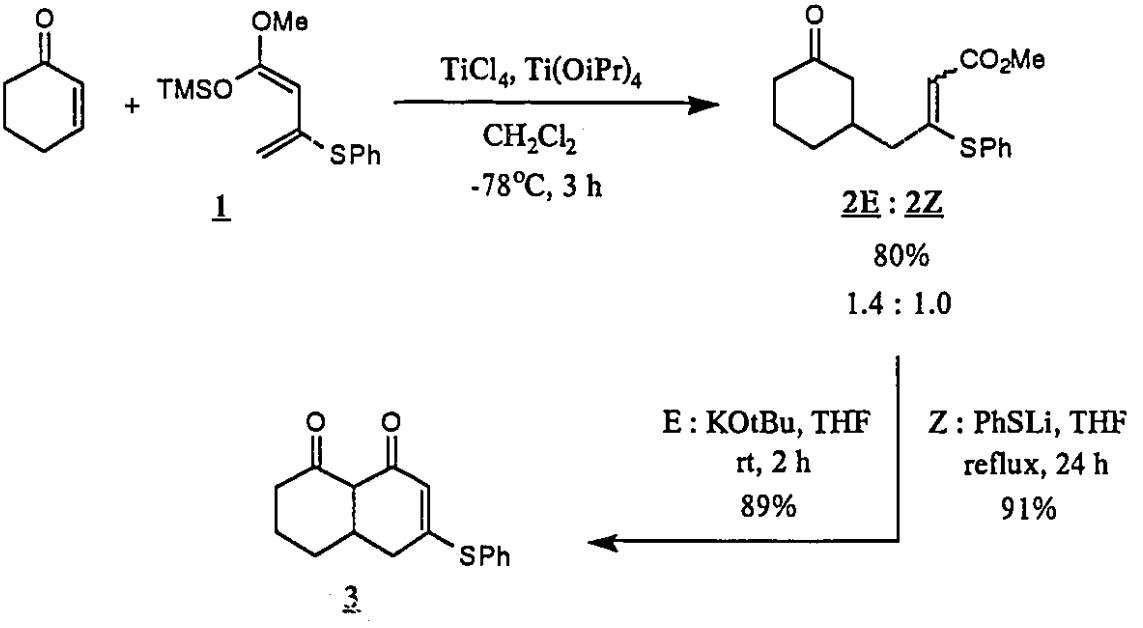
CHAPTER 2

CONSTRUCTION OF FUNCTIONALIZED DECALINS

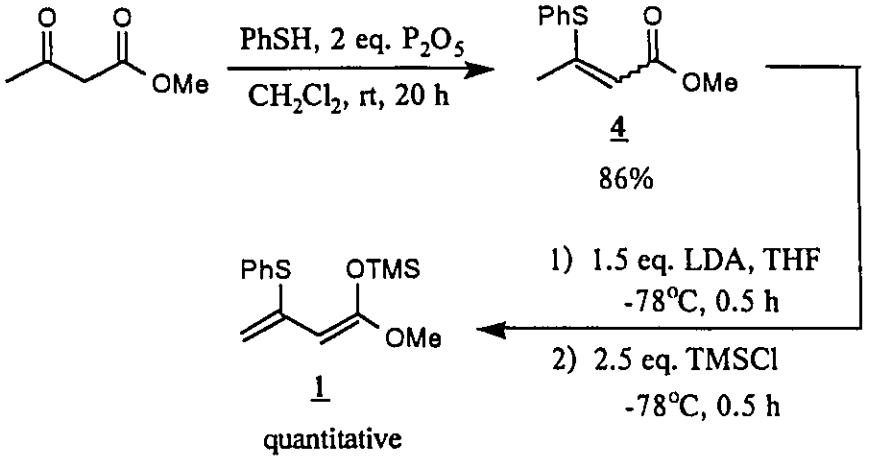
2.1 Introduction

Previously in our laboratory[1] it was found that the decalin 3 could be prepared by a tandem Michael-Claisen annelation reaction (see **Scheme 2.1**). The conjugate addition of siloxy diene 1 onto 2-cyclohexen-1-one provided the isomeric Michael adducts 2 which were cyclized by a Claisen condensation. The Michael addition was carried out using a mixture of titanium tetrachloride and titanium tetra-*iso*-propoxide as Lewis acid catalyst since 2-cyclohexen-1-one is highly sensitive to titanium tetrachloride.[2]



Scheme 2.1

The siloxy diene 1 was prepared in two steps from methyl acetoacetate as shown in **Scheme 2.2**.[3] Reaction of the latter with thiophenol and phosphorus pentoxide[4] gave a mixture of (E)- and (Z)-vinyl sulfide 4. Treatment of this mixture with LDA in THF at

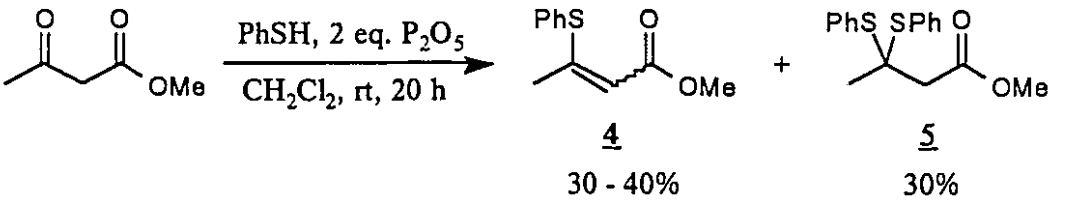


Scheme 2.2

-78°C, followed by quenching of the resulting anion with chlorotrimethylsilane afforded the enol silyl ether 1 in quantitative yield. It is important to note that in actual fact, as outlined in the experimental section,[1] the TMS-Cl is combined with LDA immediately *before* the addition of vinyl sulfide 4. This is essential for the success of this particular reaction. NOE experiments established the stereochemistry of 1 as Z.[3]

2.2 The Vinyl Sulfide Methyl 3-(Phenylthio)crotonate (4)

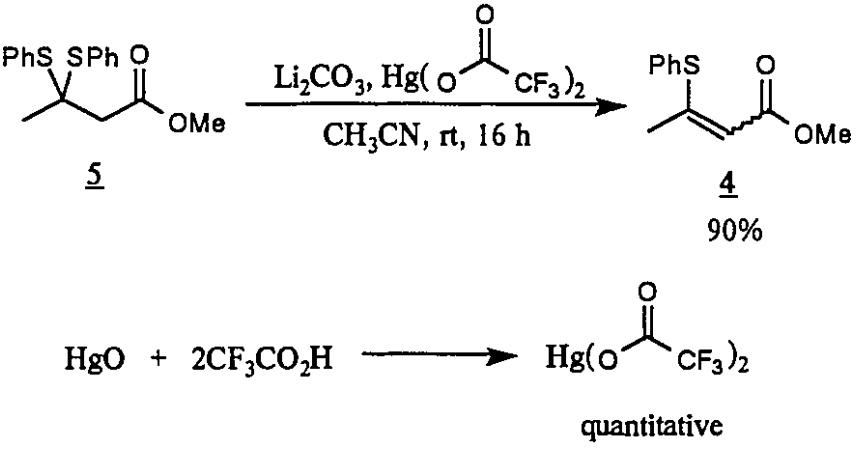
We found that the preparation of vinyl sulfide 4 was not as straightforward as reported. The reaction conditions[4] consistently provided a mixture of the liquid vinyl sulfide 4 together with an equal amount of thioketal 5, a white solid (see **Scheme 2.3**). This byproduct presumably arises from the addition of a second equivalent of thiophenol to vinyl sulfide 4. Reducing either the amount of thiophenol or the amount of phosphorus



Scheme 2.3

pentoxide present or reducing the reaction time did not reduce the amount of thioketal produced.

It was found that the thioketal could be transformed into the desired vinyl sulfide in 90% by treatment with mercuric trifluoroacetate in acetonitrile in the presence of lithium carbonate (see **Scheme 2.4**).[3,5] The mercuric trifluoroacetate was easily prepared according to literature[5] procedure (care must be taken to remove all excess trifluoroacetic acid

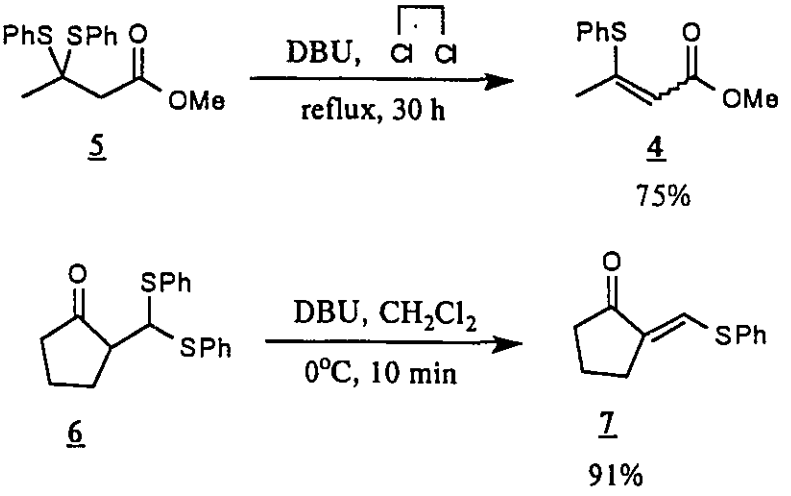


Scheme 2.4

from the final product). However, this method of preparing vinyl sulfide 4 was tedious, requiring the separation of the desired product from messy mercury salts.

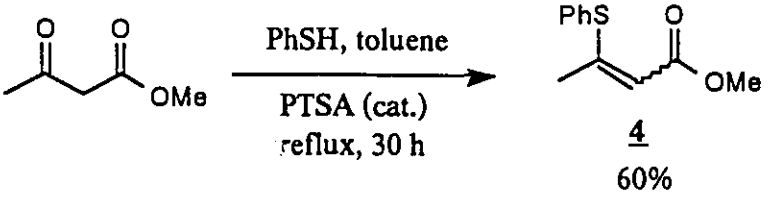
An alternative procedure[6] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 1,2-dichloroethane smoothly effected the transformation in 77% yield (see **Scheme 2.5**). The reaction mixture required refluxing in order to complete the elimination of thiophenol. In

contrast, Trost[6] was able to successfully carry out the conversion of 6 at 0°C in dichloromethane to produce the phenylthiomethylenated ketone 7 in 91% yield. This difference in reactivity between thioketals 5 and 6 is presumably due to the difference in acidity of the proton α to the thioketal which is eliminated in the process. Since in thioketal 5 this proton is α to an ester (as opposed to a ketone in 6), it has a higher pK_a and is less reactive, thus necessitating a higher temperature to complete the elimination.



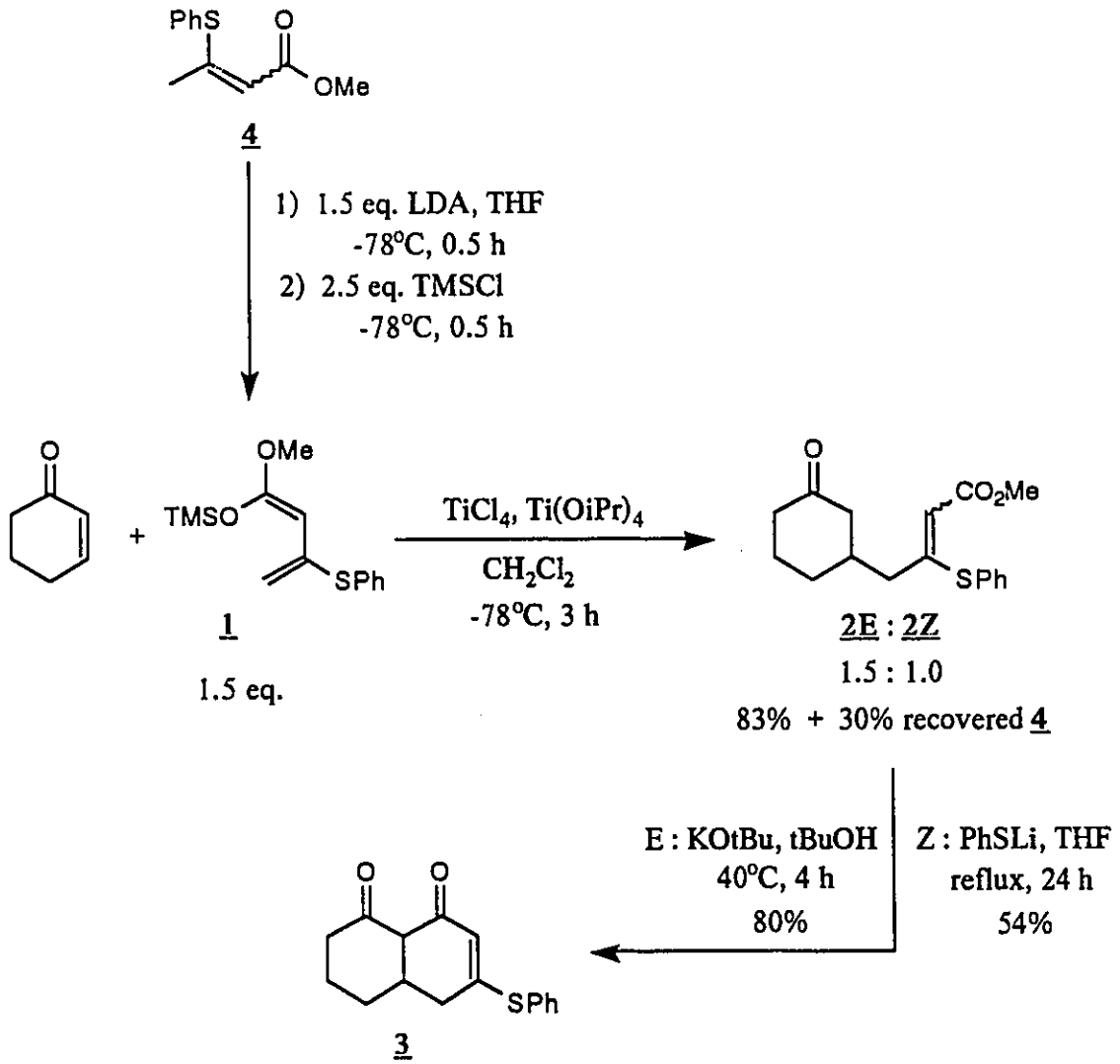
Scheme 2.5

The problems resulting from the thioketal byproduct could be avoided altogether when methyl acetoacetate and thiophenol were combined in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene (see **Scheme 2.6**).[6] When this mixture was refluxed on a Dean-Stark apparatus for 30 h, the desired vinyl sulfide was obtained as the sole product in 60% yield (unoptimized yield).



Scheme 2.6

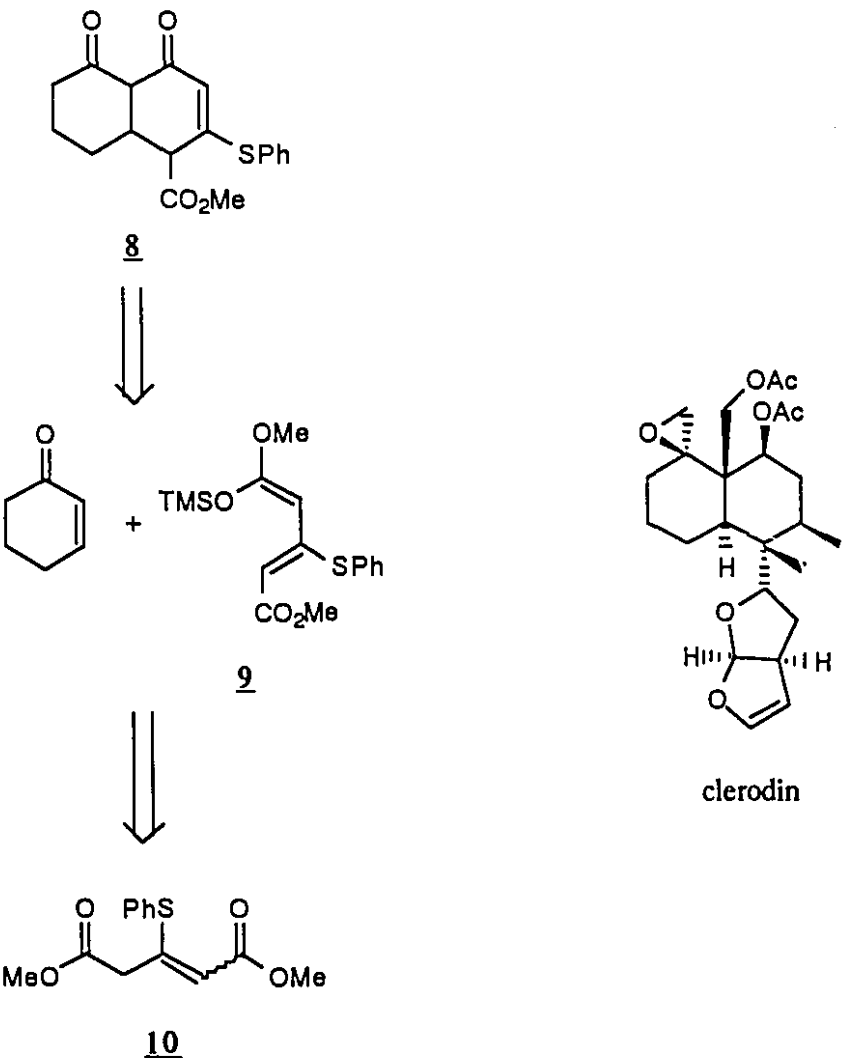
From vinyl sulfide 4, the enol silyl ether 1 was prepared as previously described.[1] The next step involved the Michael addition of siloxy diene 1 onto 2-cyclohexene-1-one. We found that for optimum results, it was best to allow a mixture of the enone, titanium tetrachloride and titanium tetra-*iso*-propoxide to stir in methylene chloride at -78°C for 30 min before adding the enol silyl ether. An excess of 1.5 equivalents of 1 then provided 83% product with 30% recovery of the vinyl sulfide 4, resulting from the hydrolysis of the excess siloxy diene 1 (see **Scheme 2.7**).



Scheme 2.7

In our case Michael adduct 2E was then cyclized with potassium *tert*-butoxide in *tert*-butanol which consistently gave 80% yield of product 3. We found that yields varied between 65-85% for the same cyclization in THF. Unfortunately we were never able to obtain more than 55% yield of decalin 3 via the treatment of Michael adduct 2Z with lithium thiophenoxide in refluxing THF. We found that 5 equivalents of lithium thiophenoxide gave better results than 10 equivalents of the same reagent for this cyclization.

2.3 Extending the Methodology

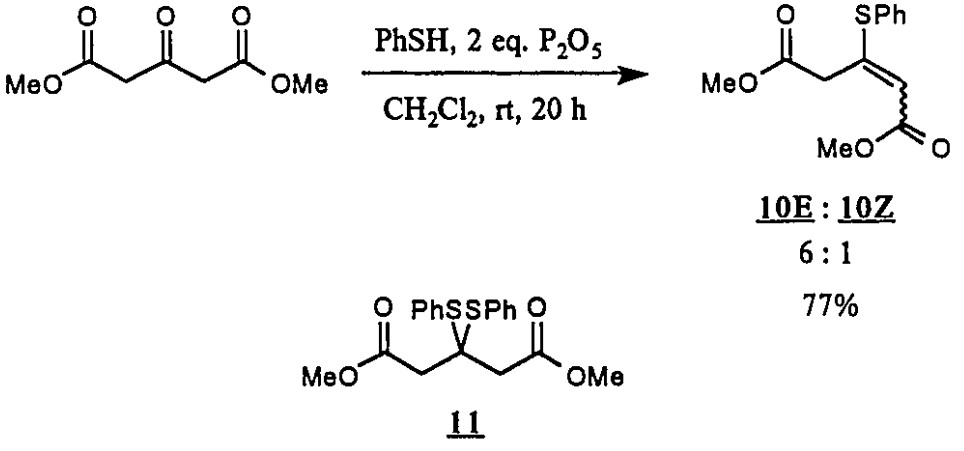


Scheme 2.8

With the target molecule clerodin in mind, it was thought that the tandem Michael-Claisen condensation could be extended towards the preparation of an intermediate such as 8 bearing an ester functionality α to the α,β-unsaturated ketone (see **Scheme 2.8**). This ester group would facilitate the eventual preparation of the bottom half of the natural product. This plan necessitated the preparation of siloxy diene 9 which in turn could be derived from vinyl sulfide 10.

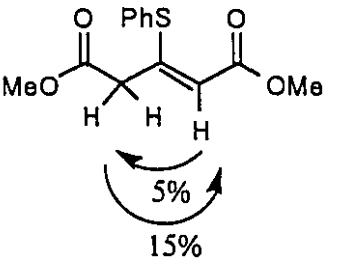
2.4 Preparation the Siloxy Diene (9)

The vinyl sulfide 10 was prepared using the procedure by Trost[4] which was described earlier. Thus dimethyl 1,3-acetonedicarboxylate was reacted with thiophenol in the presence of phosphorus pentoxide to give vinyl sulfide 10 as a 6:1 mixture of isomers



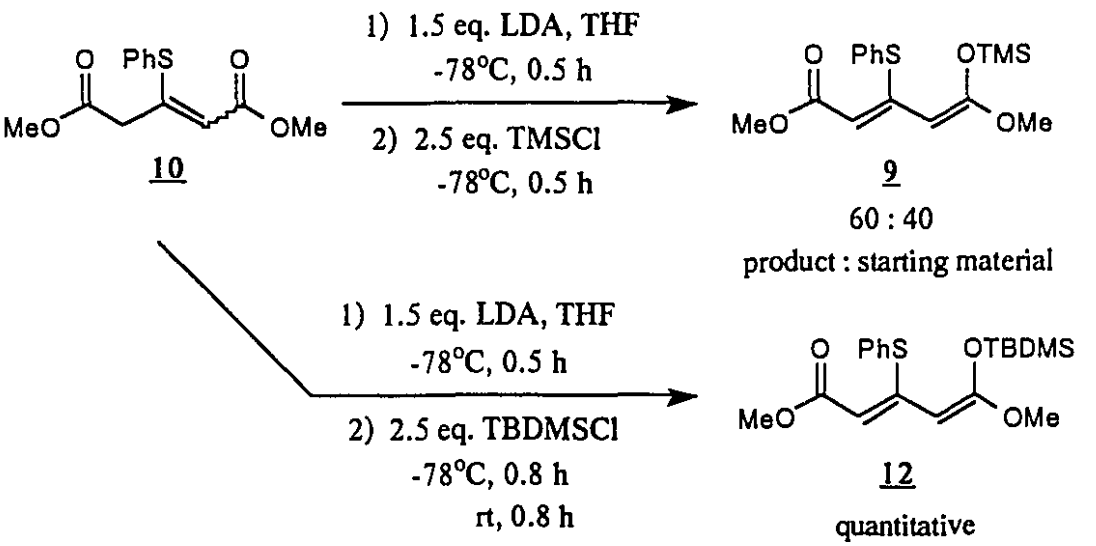
Scheme 2.9

in 77% yield (see **Scheme 2.9**). In this case the thioketal 11 was not formed, presumably because it would be too sterically hindered. The stereochemistry of the major isomer formed was established as E (10E). The minor isomer, 10Z, showed NOE enhancement between the methylene protons and the vinyl proton, whereas the major isomer exhibited no NOE enhancement.



10Z

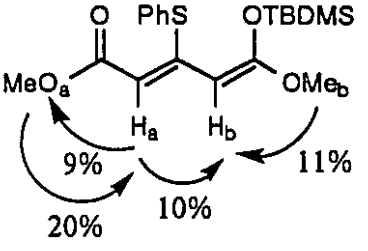
Several attempts were made to prepare the TMS enol silyl ether 9 from vinyl sulfide 10, but at best a 1:1 mixture of product and starting material was obtained. When the "reverse addition"[1] was carried out, ie. adding TMS-Cl to the LDA solution immediately *before* the addition of vinyl sulfide 10, the ratio of product to starting material was only improved to 3:2. However, the respective TBDMS siloxy diene 12 could be prepared in quantitative yield by quenching the anion with TBDMS-Cl and leaving the reaction for an additional 0.8 h at room temperature before the removal of the THF solvent (see **Scheme 2.10**). At this point a final attempt was made to prepare the TMS siloxy diene 9 by leaving the reaction mixture for 0.8 h at room temperature before the removal of the THF solvent.



Scheme 2.10

However, only starting material was recovered. It seems that compound 9 is extremely sensitive to hydrolysis, whereas compound 12 can be stored in the fridge for three weeks without appreciable hydrolysis taking place.

The stereochemistry of 12 could not be determined unambiguously. NOE enhancement was observed between MeO_a and H_a. However the results for H_b and MeO_b were not conclusive, as NOE enhancement was not reciprocal in these two cases. The results indi-



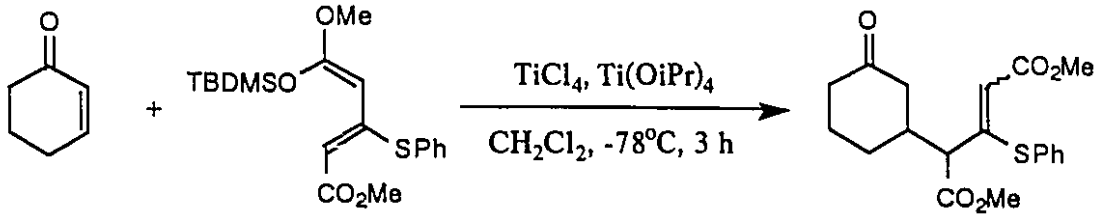
12

cate that the enhancement of the H_a signal by the irradiation of the MeO_a signal is more than double (20%) the reciprocal enhancement (9%). Hence given that the irradiation of the MeO_b signal produces itself only an 11% enhancement of the H_b signal, it is possible that the reciprocal enhancement (of the MeO_b signal by the irradiaiton of the H_b signal) is too small to be significant (An NOE enhancement of less than 5% is considered insignificant). However, what is more surprising is that the enhancement of the H_b signal by the irradiation of H_a signal (10%) is not reciprocated. Nevertheless the stereochemistry of the enol silyl ether 12 was tentatively assigned as Z,Z.

2.5 Michael Addition of the Siloxy Diene (12) to cyclohexenone

With siloxy diene 12 in hand, the Michael reaction was carried out under the previously described conditions to give the E- and Z- Michael adducts 13E and 13Z in a

1.5 to 1.0 ratio in 60% yield along with 45% recovered vinyl sulfide **10Z** (due to the hydrolysis of **12**, which was used in excess) as shown in **Scheme 2.11.**



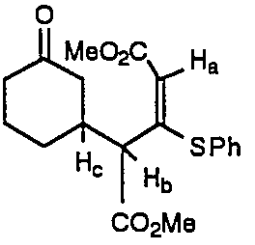
12
2.0 eq.

13E : 13Z
1.5 : 1.0
60%
(45% recovery of vinyl sulfide **10Z**)

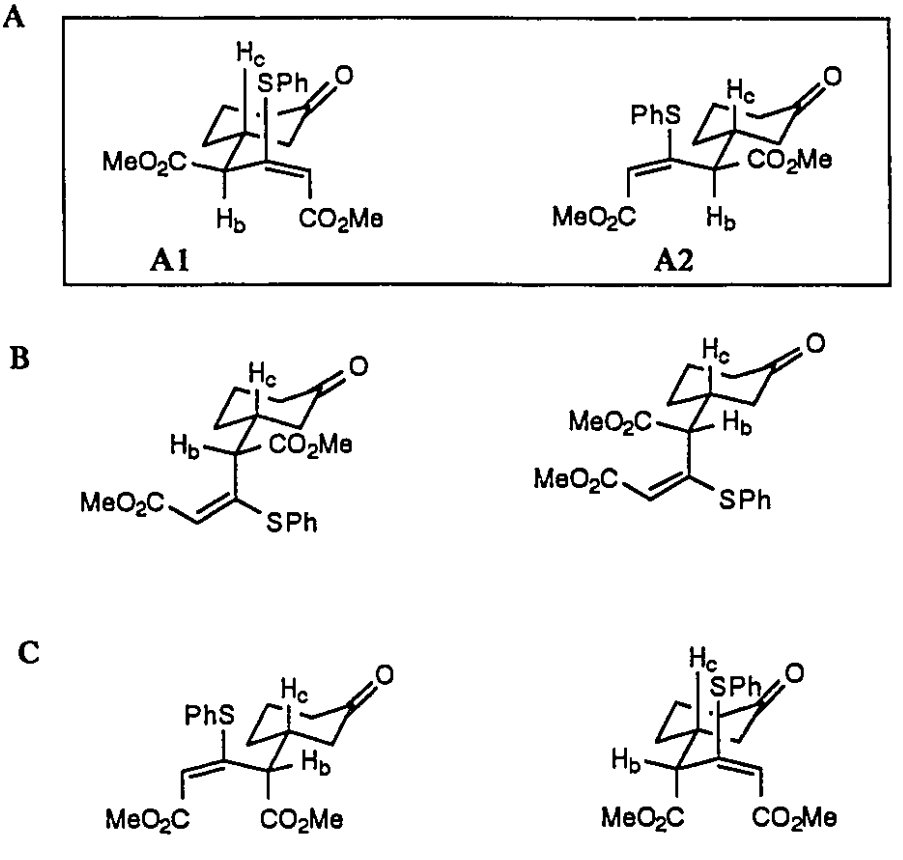
Scheme 2.11

COSY ^{1}H NMR and ^{13}C NMR spectra provided some information about the stereochemistry of the two Michael adduct isomers. Let us consider first the E isomer **13E**. There are two possible diastereomers due to the *threo-* or *erythro-* stereochemistry. Three possible rotamers of each of these two diastereomers are depicted in **Scheme 2.12** below. The ^{1}H COSY NMR indicates that the doublet (J = 0.8 Hz) at 5.2 ppm (H_a) is coupled to the double doublet at 5.4 ppm (H_b). This proton is markedly deshielded, presumably as a result of the influence of the α,β-unsaturated ester moiety. The double doublet (J = 0.8 Hz and J = 10.4 Hz) at 5.4 ppm (H_b) is coupled to the multiplet at 2.5 ppm (H_c). The assignment of H_b at 5.4 ppm was confirmed by a HETCOR experiment which indicated that the methoxy carbon of the saturated ester, at 52.4 ppm in the ^{13}C NMR, couples both to its own methoxy protons, at 3.59 ppm in the ^{1}H NMR, as well as to proton H_b, at 5.4 ppm in the ^{1}H NMR. The large H-H coupling constant of H_b (J = 10.4 Hz) with H_c suggests that there is a *trans* relationship between protons H_b and H_c (as seen in rotamers A). The ^{13}C NMR shows only one signal for each carbon. Thus, the E isomer

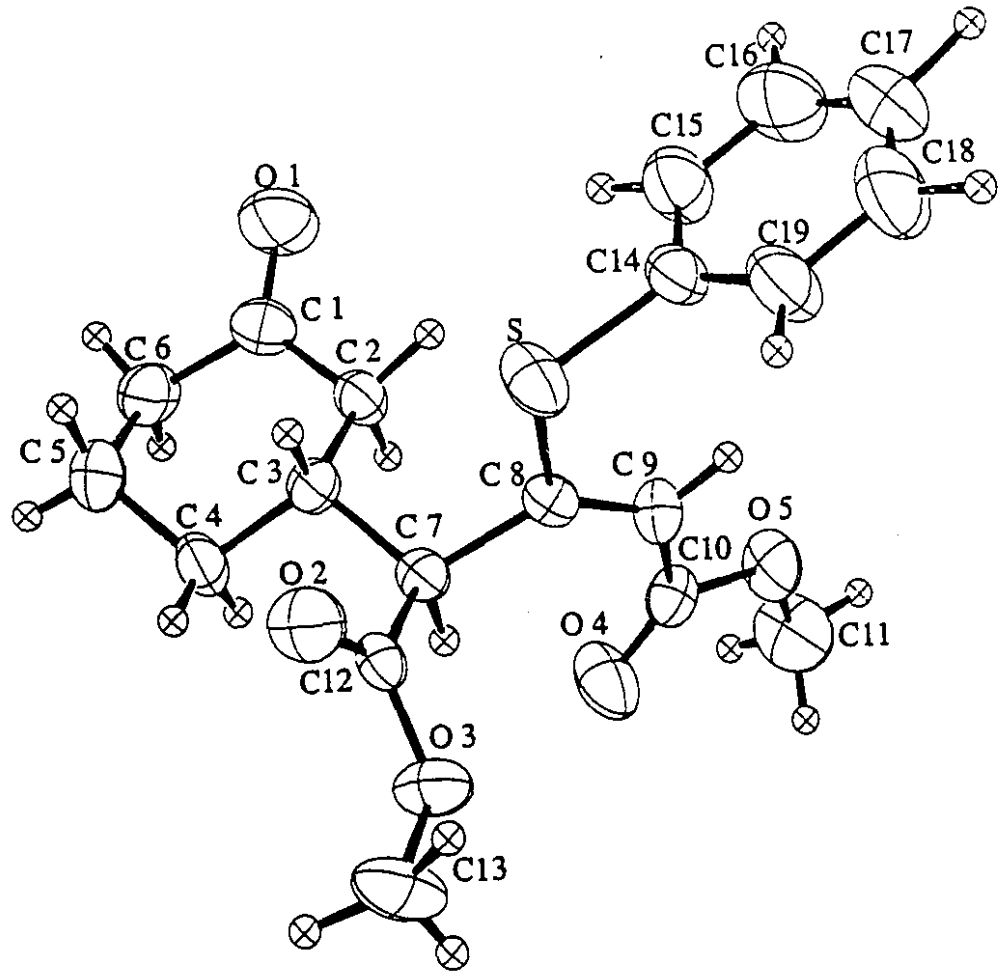
exists as one rotamer, ie. one of the two diastereomers shown in box A in **Scheme 2.12.** Recrystallization of the solid E isomer permitted us to distinguish between these two possibilities by carrying out an X-ray[7] diffraction study on the crystalline compound (see **Appendix A** for the X-ray Structure Report). The ORTEP diagram shown in **Figure 2.1** clearly indicates that the E isomer <u>13E</u> is diastereomer **A1**.

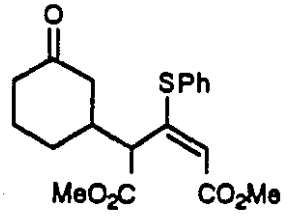


<u>13E</u>



Scheme 2.12

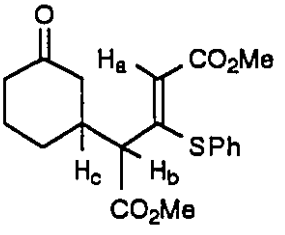




13E

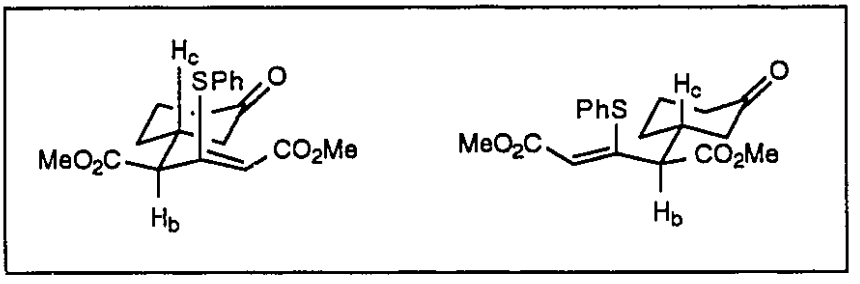
Figure 2.1

Similarly for the Z isomer, 13Z, the situation can be illustrated in **Scheme 2.13**. The ^{1}H COSY NMR spectrum indicates that the two doublets (H_a) at 6.06 ppm and 6.09 ppm (J = 0.8 Hz each) are coupled to the double doublet at 3.0 ppm (H_b). In the Z isomer, proton H_b is not as severely affected by the α,β-unsaturated ester as in the E isomer. The double doublet (J = 0.8 Hz and J = 10.6 Hz) at 3.0 ppm (H_b) is coupled to the multiplet at 2.0 ppm (H_c). The large coupling constant (J = 10.6 Hz) of H_b with H_c suggests that H_b



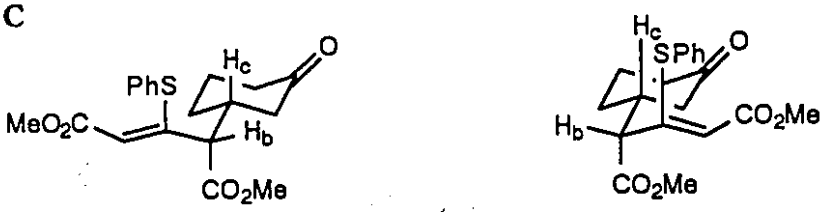
13Z

A



B

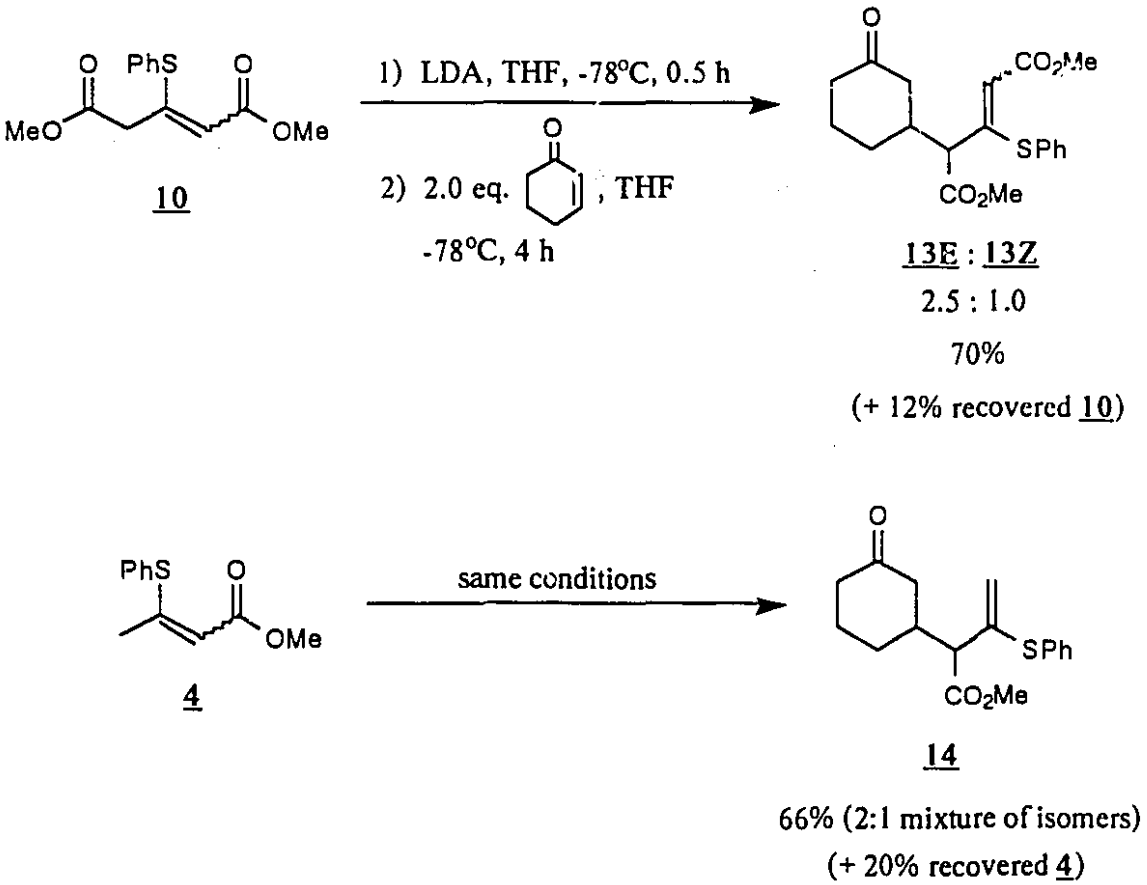
C



Scheme 2.13

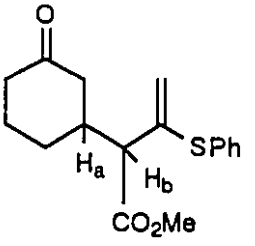
and H_c are oriented *trans* to each other (as seen in rotamers A). In the ^1H NMR the signals for H_a and the two OMe moieties are doubled in a 1:1 ratio. The ^{13}C NMR shows a doubling of each carbon signal. Thus the Z isomer 13Z exists as a 1:1 ratio of two diastereomers, ie. the two diastereomers shown in box A.

The Michael adducts 13E and 13Z can also be prepared in 70% yield directly from vinyl sulfide 10 by treatment of the latter with LDA, followed by quenching of the resulting anion with 2-cyclohexen-1-one (see **Scheme 2.14**). In this case the ratio of isomers E:Z is increased from 1.5:1.0 to 2.5:1.0 with the E isomer crystallizing out directly from the crude reaction product mixture, thus facilitating purification.

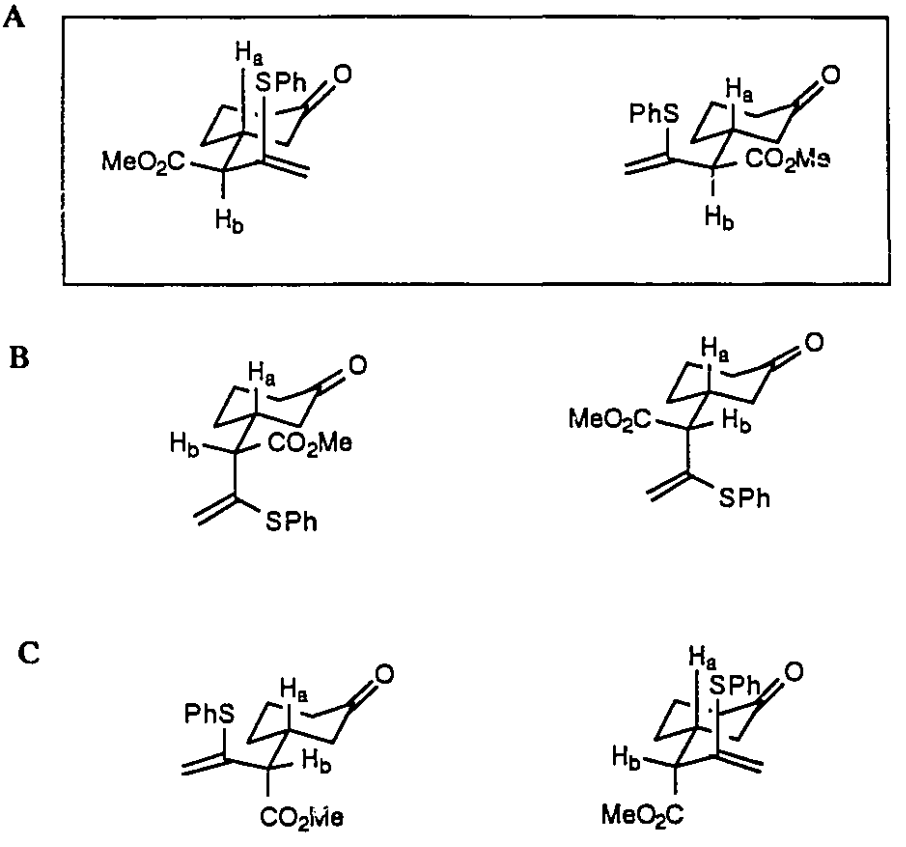


Scheme 2.14

When this same procedure was carried out with vinyl sulfide 4, compound 14 was formed in 66% as a 2:1 mixture of diastereomers. These were separable by chromatogra-



14



Scheme 2.15

phy with a benzene-acetone solvent system. The ^1H NMR spectra of both diastereomers indicates that the coupling constant of H_b ($J > 9$ Hz) with H_a is large, thus suggesting that there is a *trans* relationship between these two protons. Following an argument similar to

the one described for the Michael adducts 13E and 13Z, this leads to the conclusion that compound 14 consists of a mixture of the two diastereomers depicted as rotamers A in **Scheme 2.15.**

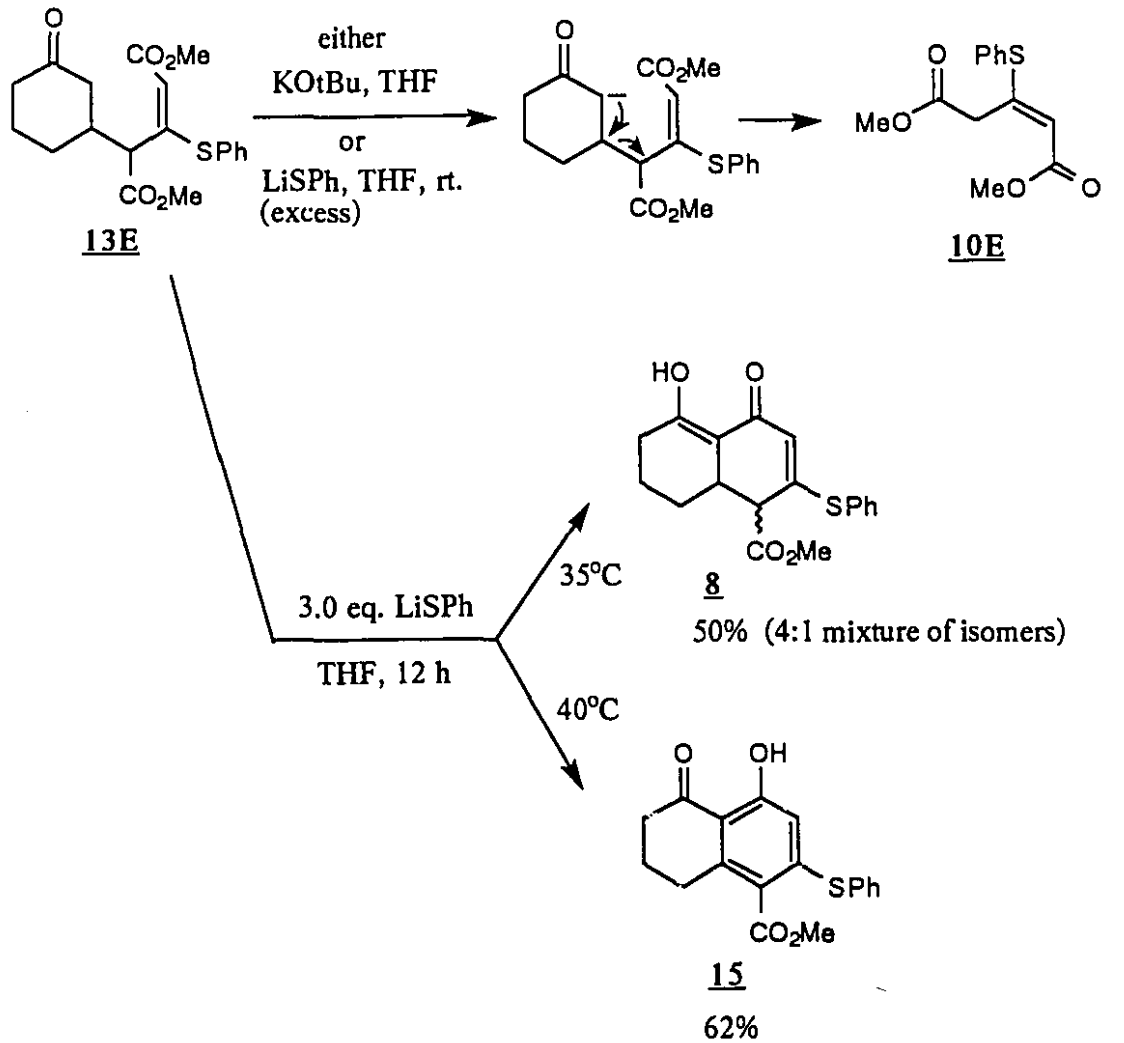
Scheme 2.14 illustrates that treatment of the vinyl sulfide with base, followed by alkylation results in alkylation α to the ester. On the other hand, Michael adduct 2 described at the beginning of this Chapter was formed by reaction with siloxy diene 1 which undergoes reaction selectively at the γ position.[3] Vinyl sulfide 10 is symmetrical and thus treatment with base followed by alkylation at the α position provides the same product 13 as alkylation at the γ position of the siloxy diene 12 in the Lewis acid catalyzed Michael addition reaction.

2.6 Cyclization of the Michael Adduct (13)

In order to complete the preparation of intermediate 8, Michael adduct 13E was then treated with potassium *tert*-butoxide in THF in an attempt to effect cyclization. However, the desired anion at the position α to the ketone is less favourable than an anion formed α to the methyl ester, which would in fact be stablizied by both methyl ester functionalities. Thus, instead of cyclization, a retro Michael occurred, resulting in the recovery of vinyl sulfide 10E (see **Scheme 2.16**). Even reducing the reaction temperature to -78°C and varying the reaction time did not result in any improvement.

When the conditions previously used to cyclize the Z-Michael adduct, ie. 10 equivalents of lithium thiophenoxide in refluxing THF, were applied to Michael adduct 13E, the reaction mixture soon turned black and only the vinyl sulfide 10E was isolated. Reducing the temperature to 25°C resulted in no improvement. However, when the amount of lithium thiophenoxide reagent was reduced to 3 equivalents and the mixture was gently warmed at 35°C, the desired product, 8, was obtained in 50% yield in a 4:1 mixture of isomers. In the ^{1}H NMR spectra of the two isomers there appears a sharp singlet

downfield of 14.90 ppm, indicating that both isomers exist predominantly in their enol forms. A slight increase in reaction temperature (40°C) led to the production of an undesired aromatic compound 15, possibly arising from the oxidation of compound 8 by a



Scheme 2.16

small quantity of air. The ^1H NMR of this compound features a sharp singlet at 12.83 ppm, due to the phenolic proton, and vinyl (singlet at 6.26 ppm) and methoxy (singlet at 3.94 ppm) protons which are markedly deshielded. The signals of the remaining protons include two triplets (centered at 2.92 and 2.64 ppm) and a quintet (centered at 2.06 ppm),

all three signals being clearly defined as a result of the rigidity of the structure. Finally, the ^{13}C NMR signal at 204.1 ppm confirms the presence of the saturated ketone. Reducing the reaction temperature (25°C) resulted in the production of a mixture of the desired product 8 (35%) and the vinyl sulfide 10E (20%). Thus it seems that careful monitoring of the reaction temperature and the amount of lithium thiophenoxide reagent used are critical to the success of this cyclization.

Experimental

General Methods

For all moisture sensitive reactions, glassware was oven-dried at @ 200°C and cooled in a dessicator. Such reactions were carried out under nitrogen or argon, which were dried by being passed through a column of indicating drierite and potassium hydroxide. Materials were obtained from commercial suppliers unless noted otherwise. Organolithium reagents were titrated periodically according to literature procedure.[8] **Table 2.1** indicates the drying and purification of the solvents and reagents used.

Solvents were evaporated under reduced pressure using a Buchi rotary evaporator followed by vacuum evaporation (0.05 - 0.1 Torr) for at least 30 min. Melting points (mp), determined on a Gallenkamp block, and boiling points (bp) are uncorrected. Analytical thin layer chromatography (TLC) was carried out using commercial, pre-coated plastic-backed silica gel plates (silica gel 60 F_{254}) supplied by E. Merck Co. Visualization was effected by ultraviolet fluorescence (UV) or by spraying the plates with an anisaldehyde-sulphuric acid spray[9], followed by heating. Flash chromatography[10] was performed on Merck silica gel 60 (230-400 mesh ASTM). Proton nuclear magnetic resonance (^{1}H NMR) spectra were taken on Varian XL-200 and XL-300 instruments. All spectra were taken with $CDCl_3$ as the solvent and internal standard. The data are reported in parts per million (ppm) relative to the $CHCl_3$ reference line with the multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), coupling constants (in Hertz) and the number of protons given in parentheses. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian XL-300 (75.4 MHz) spectrometer. Infrared (IR) spectra were obtained on an Analect AQS-18 FT-IR instrument and are reported in reciprocal centimeters (cm^{-1}). Solution spectra were obtained using sodium chloride solution cells of 0.2 mm thickness. Low resonance mass spectra were recorded on a Du Pont 21-492B (operating at

Table 2.1 Drying and Purification of Solvents and Reagents

Solvent or Reagent	Method of Purification
diethyl ether (ether)	distilled from Na (benzophenone as indicator)
tetrahydrofuran (THF)	" "
methanol	distilled from magnesium methoxide
acetonitrile	distilled from calcium hydride
dichloromethane (CH_2Cl_2)	" "
hexanes	" "
benzene	distilled from calcium hydride and stored over 3A sieves
tert-butanol	" "
chlorobenzene	" "
chlorotrimethylsilane (TMSCl)	" "
1,2-dichloroethane	" "
dimethylsulfoxide	" "
diisopropylamine	" "
N-ethyldiisopropylamine	" "
hexamethylphosphoramide (HMPA)	" "
hexamethyldisilazane (HMDS)	" "
pyridine	" "
methyl acetoacetate	distilled and stored over 3A sieves
methyl chloroformate	" "
methyl cyanoformate	" "
trimethylsilyltriflate	" "
potassium *tert*-butoxide	dried over P_2O_5 under high vacuum
Ph_3PCH_3Br	azeotroped (3x) with toluene

an ionization potential of 70 eV) or a Hewlett-Packard 5980A (using ammonia chemical ionization) mass spectrometer and are reported as *m/z* (relative intensity %). All high resolution mass spectra were recorded on a ZAB 2F HS instrument using ammonia chemical ionization.

Methyl 3-(phenylthio)crotonate (4) and Methyl 3,3-bis(phenylthio)butanoate (5)

Methyl acetoacetate (7.50 mL, 0.070 mol) and thiophenol (7.15 mL, 0.070 mol) were combined in 100 mL of CH_2Cl_2 at room temperature under argon together with P_2O_5 (19.50 g, 0.138 mol). The yellow reaction mixture was stirred for 20 h. The then orange slurry was poured into a separatory funnel along with 100 mL of CH_2Cl_2 rinsings. The organic layer was carefully washed with 10% sodium hydroxide (2 x 100 mL) and 100 mL brine. The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed. Vacuum distillation afforded a mixture of the E- and Z- vinyl sulfide 4 (115-120°C / 0.25 mm) as a pale yellow oil (4.517 g, 31%) and the thioketal 5 (135-140°C / 0.25 mm) as white crystals (6.690 g, 30%).

The vinyl sulfide 4 exhibited: ^{1}H NMR(200 MHz, $CDCl_3$): 7.38-7.55(m, 5H), 5.22(s, 1H), 3.58(s, 3H), 2.42(s, 3H). IR(film): 2930, 1721, 1611, 1593, 1442, 1182 cm^{-1}. MS: 208(71, M^+), 177(81), 149(100), 134(55), 109(60), 99(36), 65(44), 59(79), 51(29), 39(50), 32(44), 28(88). ^{13}C NMR(75.4 MHz, $CDCl_3$): (166.4, 165.5), (160.1, 158.4), (135.9, 135.3), (129.7, 129.6), (129.3, 128.9), (11.3, 110.1), (50.9, 50.6), (24.9, 19.8).

The thioketal 5 exhibited: ^{1}H NMR(200 MHz, $CDCl_3$): 7.63-7.67(m, 5H), 7.35-7.41(m, 5H), 3.68(s, 3H), 2.76(s, 2H), 1.61(s, 3H). IR($CHCl_3$ solution): 2998, 1749, 1476, 1440, 1336, 1200, 1076, 702 cm^{-1}. MS: 319(.2, $M+H^+$), 226(6), 210(13), 209(100). Exact mass calcd for $C_{17}H_{18}O_2S_2+H^+$: 319.0825, found: 319.0826. ^{13}C NMR(75.4 MHz, $CDCl_3$): 169.7, 137.3, 131.2, 129.5, 128.7, 59.7, 51.7, 46.1, 28.0.

Conversion of (5) into (4)

To a solution of the thioketal 5 (0.312 g, 0.98 mmol) in 7.5 mL acetonitrile under argon at room temperature was added lithium carbonate (0.441 g, 5.97 mmol). This white suspension was treated with mercuric trifluoroacetate, which was prepared according to literature procedure.[3] The pale yellow mixture was stirred for 16 h at room temperature, whereupon saturated ammonium chloride solution and ether were added. The aqueous layer was extracted with ether. At this point the mixture has to be filtered to remove a messy solid. The combined ether extracts were then dried over magnesium sulfate, filtered and the solvent removed to provide 0.315 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the vinyl sulfide (0.183 g, 90%), which was identical with compound 4 prepared above.

Alternative method for the conversion of (5) into (4)

To a solution of the thioketal 5 (0.502 g, 1.58 mmol) in 15 mL 1,2-dichloroethane at 0°C under argon was added DBU (0.30 mL, 2.05 mmol). The mixture was then stirred at 70°C for 24 h. After allowing the mixture to cool down, CH_2Cl_2 and 2% aqueous HCl were added and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over magnesium sulfate, filtered and the solvent removed. Vacuum distillation provided the vinyl sulfide 4 (0.260 g, 79%). See above for spectral details.

Alternative preparation of (4)

Methyl acetoacetate (1.50 mL, 0.014 mol) and thiophenol (1.35 mL, 0.014 mol) were combined in 25 mL dry toluene at room temperature under argon together with a catalytic amount of *p*-toluenesulfonic acid. The colourless reaction mixture was then refluxed for 30 h on a Dean-Stark apparatus. The then pale yellow solution was cooled down, diluted with 10 mL ether, and washed with 10% sodium hydroxide solution (2 x 25 mL), followed by saturated ammonium chloride solution (2 x 30 mL). The organic layer

was dried over magnesium sulfate, filtered and the solvent removed to provide pure vinyl sulfide (1.784 g, 60%), whose properties are identical with those described for the vinyl sulfide 4 above.

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

To a solution of dry diisopropylamine (21.1 mL, 0.150 mol) in 500 mL THF at 0°C under argon was added 2.5 M nBuLi (60.3 mL, 0.150 mol). The pale yellow solution was stirred for 20 min and then cooled to -78°C, at which point chlorotrimethylsilane (32.0 mL, 0.250 mol) was added, followed immediately by the addition of a solution of the vinyl sulfide 4 (26.0 g, 0.125 mol) in 20 mL THF. The orange solution was stirred for 30 min and then allowed to warm to room temperature (45 min). The solvent was removed. Under argon, the orange residue was washed with dry hexane and filtered. The hexane was removed from the orange filtrate under reduced pressure to give the product 1 (37.19 g) in quantitative yield. ^{1}H NMR(200 MHz, $CDCl_3$): 7.25-7.45(m, 5H), 5.50(s, 1H), 5.00(s, 1H), 4.10 (s, 1H), 3.47(s, 3H), 0.25(s, 9H). IR(film): 3080, 2960, 1650, 1581, 1442, 1236, 880 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 159.0, 137.4, 135.0, 131.8, 129.0, 128.8, 126.8, 111.2, 78.4, 55.1, 0.4.

Methyl 3-(phenylthio)-4-(3-oxocyclohexyl)but-2-enoate (2)

To a mixture of titanium tetrachloride (8.57 mL, 0.078 mol) and titanium isopropoxide (18.5 mL, 0.062 mol) in 500 mL CH_2Cl_2 at -78°C under argon was added a solution of 2-cyclohexen-1-one (7.55 mL, 0.078 mol) in 35 mL CH_2Cl_2. After stirring for 20 min a solution of the enol silyl ether 1 (37.19 g, 0.132 mol) in 65 mL CH_2Cl_2 was added. The dark red solution was stirred for 3 h at -78°C. The reaction mixture was then diluted with 300 mL of ether, carefully quenched with 300 mL saturated sodium bicarbonate at -78°C and allowed to warm slowly to room temperature. The aqueous layer was extracted with ether (4 x 300 mL). The combined organic extracts were dried over

magnesium sulfate, filtered and the solvent removed to provide 38.63 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the cream-coloured crystal 2E- (11.75 g, 50%) and 2Z- (7.868 g, 33%) Michael adducts in a 1.5 : 1.0 ratio along with some recovered vinyl sulfide 4 (4.819 g, 30%).

(E-) isomer (2E) (mp 74-76°C): ^{1}H NMR(200 MHz, $CDCl_3$): 7.40-7.52(m, 5H), 5.19(s, 1H), 3.57(s, 3H), 2.96(d, J=6.8 Hz, 2H), 1.40-2.60(m, 9H). IR($CHCl_3$ solution): 2949, 1709, 1696, 1599, 1434, 1194, 1168 cm^{-1}. MS: 304(4, M^+), 218(24), 208(51), 206(22), 177(42), 149(100), 134(21), 110(65), 109(51), 99(24), 97(27), 69(35), 65(33), 59(38), 41(33), 39(38), 28(33). ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.9, 165.0, 162.4, 135.3, 129.8, 129.7, 128.9, 111.0, 50.6, 47.1, 41.0, 38.9, 38.8, 30.9, 24.9.

(Z-) isomer (2Z) (mp 73-75°C): ^{1}H NMR(200 MHz, $CDCl_3$): 7.35-7.55(m, 5H), 5.81(s, 1H), 3.75(s, 3H), 1.05-2.38(m, 11H). IR($CHCl_3$ solution): 2952, 1713, 1694, 1581, 1438, 1212, 1204 cm^{-1}. MS: 304(52, M^+), 273(16), 208(47), 195(22), 175(26), 163(42), 149(29), 147(20), 135(53), 134(60), 110(80), 97(79), 77(23), 69(46), 55(52), 43(43), 41(100), 39(38), 28(59). ^{13}C NMR(75.4 MHz, $CDCl_3$): 209.9, 165.6, 158.2, 135.3, 130.0, 129.1, 128.8, 112.8, 50.8, 46.6, 42.7, 40.7, 37.4, 29.9, 24.3.

3-(Phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8-(4H,7H)-dione (3) prepared from 2E

To a solution of the E- Michael adduct 2E (0.297 g, 0.975 mmol) in 12 mL THF at 0°C under argon was added dry KOtBu (0.137 g, 1.17 mmol). After stirring for 30 min the light brown mixture was diluted with 10 mL ether and quenched with dilute ammonium chloride solution. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.214 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 3 (0.193 g, 72%) as a yellow solid (mp 123-125°C). ^{1}H NMR(200 MHz, $CDCl_3$): 7.41-7.51(m, 5H), 5.45(s, 1H), 1.20-2.88(m, 9H). IR($CHCl_3$ solution): 2936,

1619, 1614, 1598, 1442, 1250 cm^{-1}. MS: 272(50, M^+), 163(42), 135(56), 110(43), 107(33), 97(22), 91(29), 79(30), 77(41), 69(49), 67(22), 65(39), 57(51), 55(100), 51(32), 43(90), 39(50), 29(31). ^{13}C NMR(75.4 MHz, $CDCl_3$): 187.7, 177.7, 162.2, 135.8, 130.5, 130.1, 119.3, 106.0, 37.0, 33.4, 29.8, 29.7, 20.9.

Alternative procedure

To a solution of the E- Michael adduct 2E (10.220 g, 0.034 mol) in 550 mL *tert*-butanol at 30°C under argon was added dry KOtBu (4.37 g, 0.039 mol). The mixture was warmed to 40°C and stirred for 3 h. The light brown reaction mixture was then cooled to room temperature, diluted with 450 mL ether and washed with water (2 x 400 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent removed to provide 11.347 g crude material. Column chromatorgaphy (1:4 EtOAc:hexane) afforded the pure decalin 3 (7.287 g, 80%), whose properties were identical with those described above.

Preparation of (3) from Michael adduct (2Z)

To a solution of thiophenol (0.50 mL, 4.87 mmol) in 4 mL THF at 0°C under argon was added 2.5 M nBuLi (1.95 mL, 4.87 mmol). After stirring for 20 min a solution of the Z- Michael adduct 2Z (0.142 g, 0.467 mmol) in 2 mL THF was added. The pale yellow reaction mixture was then refluxed for 24 h. The mixture was then cooled to room temperature, diluted with 10 mL ether and quenched with 10 mL of 10% sodium hydroxide. The aqueous layer was extracted with ether (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.175 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 3 (0.069 g, 54%) as a yellow solid. See above for spectral data.

Methyl 3-(phenylthio)-4-(methoxycarbonyl)but-2-enoate (10)

Dimethyl 1,3-acetonedicarboxylate (4.50 mL, 0.031 mol) and thiophenol (3.14 mL, 0.031 mol) were combined in 50 mL CH_2Cl_2 at room temperature under argon together with P_2O_5 (8.752 g, 0.062 mol). The yellow reaction mixture was stirred for 22 h. The then orange slurry was poured into a separatory funnel along with 25 mL CH_2Cl_2 rinsings. The organic layer was carefully washed with 10% sodium hydroxide (2 x 40 mL) and 60 mL brine. The combined organic extracts were then dried over magnesium sulfate, filtered and the solvent removed. Vacuum distillation (138-142°C / 0.15 mm) provided a pale yellow viscous oil (6.268 g, 77%), the vinyl sulfide **10**, as a mixture of the E and Z isomers in a 6:1 ratio, separable by chromatography.

10E: ^{1}H NMR(200 MHz, $CDCl_3$): 7.23-7.57 (m, 5H), 5.41(s, 1H), 3.81(s, 2H), 3.69(s, 3H), 3.54(s, 3H). ^{13}C NMR(75.4 MHz, $CDCl_3$): 169.5, 165.3, 155.2, 135.5, 130.2, 129.9, 129.0, 113.4, 52.2, 51.1, 38.3.

10Z: ^{1}H NMR(200 MHz, $CDCl_3$): 7.29-7.52(m, 5H), 5.89(s, 1H), 3.71(s, 3H), 3.48(s, 3H), 3.11(s, 2H). ^{13}C NMR(75.4 MHz, $CDCl_3$): 169.1, 166.2, 153.5, 136.5, 130.0, 129.9, 129.8, 114.6, 52.2, 51.4, 42.1.

Mixture of **10E** and **10Z**: IR(film): 2952, 1742, 1706, 1613, 1599, 1432, 1347, 1321, 1202, 1165 cm^{-1}. MS: 267(32, M+H$^+$), 266(60, M$^+$), 235(41), 206(39), 203(48), 192(62), 174(36), 161(35), 157(20), 149(23), 147(100), 125(68), 110(90), 69(70), 67(46), 45(51), 39(55), 28(57). Exact mass calcd for $C_{13}H_{14}O_4S$ (M$^+$): 266.0612, found: 266.0544.

1-(Trimethylsiloxy)-1-methoxy-3-(phenylthio)-4-(methoxycarbonyl)-but-1, 3-dienoate (9)

To a solution of dry diisopropylamine (0.63 mL, 4.50 mmol) in 7.5 mL THF at 0°C under argon was added 2.5 M nBuLi (2.25 mL, 5.62 mmol). After stirring for 30 min at 0°C, the pale yellow solution was cooled to -78°C and chlorotrimethylsilane (0.95 mL,

7.48 mmol) was added, followed immediately by a solution of vinyl sulfide 10 (0.802 g, 3.01 mmol) in 5.0 mL THF. The orange solution was stirred at -78°C for another 30 min and then allowed to warm to room temperature. The solvent was removed. Under argon the orange residue was washed with dry hexane and filtered. The hexane was removed, providing an orange oil consisting of a 60:40 mixture of product and starting material. ^{1}H NMR(200 MHz, $CDCl_3$) showed signals corresponding to the product 9 (cf data given in the procedure below): 7.20-7.65(m), 6.58(s), 4.75(s), 3.78(s), 3.56(s), 0.26(s); and the starting material 10 (cf data given in procedure above): 7.20-7.65(m), 5.49(s), 3.86(s), 3.75(s), 3.61(s).

1-(*tert*-Butyldimethylsiloxy)-1-methoxy-3-(phenylthio)-4-(methoxycarbonyl)-but-1,3-dienoate (12)

To a solution of dry diisopropylamine (3.60 mL, 0.026 mol) in 50 mL THF at 0°C under argon was added 2.5 M nBuLi (10.0 mL, 0.025 mol). The pale yellow solution was stirred at 0°C for 30 min and then cooled to -78°C. A solution of vinyl sulfide 10 (4.640 g, 0.017 mol) in 25 mL THF was added. After another 30 min at -78°C, *tert*-butyldimethylsilylchloride (7.184g, 0.048 mol) was added and stirring was continued for another 45 min. The orange solution was then slowly warmed to room temperature while stirring for another 45 min. The solvent was removed under reduced pressure. Under argon the red residue was washed with dry hexane and filtered. The hexane was removed providing the product 12 in quantitative yield as a viscous red oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.31-7.57(m, 5H), 6.55(s, 1H), 4.67(s, 1H), 3.76(s, 3H), 3.53(s, 3H), 1.00(s, 9H), 0.28(s, 6H). IR(film): 2952, 1691, 1611, 1442, 1254, 1232, 1165, 1068, 840 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 166.9, 162.0, 158.9, 136.2, 135.5, 129.9, 128.7, 102.3, 55.9, 50.4, 38.4, 26.5, 25.9, 18.3.

Methyl 3-(phenylthio)-4-(3-oxocyclohexyl)-4-(methoxycarbonyl)but-2-enoate (13)

To a mixture of titanium tetrachloride (0.080 mL, 0.73 mmol) and titanium isopropoxide (0.17 mL, 0.58 mmol) in 5 mL CH_2Cl_2 at -78°C under argon was added a solution of 2-cyclohexen-1-one (0.07 mL, 0.72 mmol) in 2 mL CH_2Cl_2. The pale yellow mixture was stirred for 30 min at which time a solution of enol silyl ether 12 (0.605 g, 1.59 mmol) in 3 mL CH_2Cl_2 was added. After stirring for 3 h at -78°C the red solution was diluted with 10 mL ether and carefully quenched with 10 mL saturated sodium bicarbonate. The aqueous layer was extracted with ether (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.469 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the white crystal E- Michael adduct 13E (0.097 g, 37%) and Z- Michael adduct 13Z (0.060 g, 23%) along with some recovered vinyl sulfide 10Z (0.191 g, 45%). The E-isomer was recrystallized from a 3:2:2 solution of ether : methylene chloride : hexane.

E- isomer 13E (mp 162-163°C): ^{1}H NMR(200 MHz, $CDCl_3$): 7.46(s, 5H), 5.39(dd, J=0.8 Hz and J=10.4 Hz, 1H), 5.23(d, J=0.8 Hz, 1H), 3.78(s, 3H), 3.59(s, 3H), 1.38-2.77(m, 9H). IR($CHCl_3$ solution): 2952, 1739, 1733, 1701, 1598, 1436, 1204, 1181 cm^{-1}. MS: 362(60, M^+), 266(18), 221(84), 206(53), 193(94), 161(26), 147(41), 125(54), 110(99), 109(57), 105(22), 97(71), 91(25), 77(56), 69(70), 65(62), 59(55), 55(72), 51(76), 41(100), 39(66), 28(24). Exact mass calcd for $C_{19}H_{22}O_5S$ (M^+): 362.118, found: 362.123. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.4, 170.9, 165.3, 159.2, 135.8, 130.2, 130.0, 127.9, 113.5, 52.4, 51.0, 43.9, 41.1, 38.9, 30.1, 24.5.

Z- isomer 13Z (mp 96-98°C): ^{1}H NMR(200 MHz, $CDCl_3$): 7.40-7.60(m, 5H), 6.06 and 6.10(two d in a 1:1 ratio, J=0.8 Hz each, together 1H), 3.74 and 3.75(two s in a 1:1 ratio, together 3H), 3.65 and 3.67(two s in a 1:1 ratio, together 3H), 3.03(dd, J=0.8 Hz and J=10 Hz, 1H), 0.88- 2.50(m, 9H). IR($CHCl_3$ solution): 2952, 1739, 1711, 1690, 1587, 1434, 1223, 1204, 1189, 1158 cm^{-1}. MS: 362(42, M^+), 266(17), 221(45), 206(62),

193(57), 147(67), 125(41), 110(54), 109(46), 97(52), 77(42), 69(74), 65(53), 59(82), 55(99), 43(69), 41(100), 39(60), 27(40). Exact mass calcd for $C_{19}H_{22}O_5S$ (M^+): 362.118, found: 362.128. ^{13}C NMR(75.4 MHz $CDCl_3$): 209.5, 170.7, 166.1, 155.4, 136.3, 130.0, 129.5, 113.0, 53.2, 52.3, 44.9, 42.0, 40.1, 28.7, 24.4. All the signals in the ^{13}C NMR are doubled.

Alternative procedure

To a solution of dry diisopropylamine (0.30 mL, 2.14 mmol) in 10 mL THF at 0°C under argon was added 2.5 M nBuLi (0.90 mL, 2.25 mmol). The pale yellow solution was stirred for 20 min at 0°C and then cooled to -78°C. A solution of the vinyl sulfide 10 (0.542 g, 2.03 mmol) in 2 mL THF was added and stirring was continued at -78°C for another 20 min. Then a solution of 2-cyclohexen-1-one (0.35 mL, 3.62 mmol) in 2 mL THF was added. After stirring for 4 h at -78°C, the orange mixture was diluted with 10 mL ether and quenched with 20 mL dilute ammonium chloride solution. The aqueous layer was extracted with ether (3 x 20 mL) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to afford 0.594 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the E-Michael adduct 13E (0.303g, 49%) and Z-Michael adduct 13Z (0.117 g, 19%) in a 2.6:1.0 ratio along with recovered vinyl sulfide 10Z (0.066 g, 12%). See above for spectral data.

Methyl 3-(phenylthio)-2-(3-oxocyclohexyl)but-3-enoate (14)

To a solution of dry diisopropylamine (0.20 mL, 1.43 mmol) in 7 mL THF at 0°C under argon was added 2.5 M nBuLi (0.56 mL, 1.43 mmol). The pale yellow solution was stirred for 20 min and then cooled to -78°C. A solution of vinyl sulfide 4 (0.288 g, 1.38 mmol) in 1 mL THF was added and stirring was continued for another 20 min at -78°C. Then a solution of 2-cyclohexen-1-one (0.25 mL, 2.50 mmol) in 1 mL THF was added. After stirring for 4 h at -78°C, the orange mixture was diluted with 10 mL ether and

quenched with 15 mL dilute aqueous ammonium chloride solution. The aqueous layer was extracted with ether (3 x 15 mL) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to give 0.389 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the pale yellow oil product 14 (0.278 g, 66%) as a 2:1 mixture of two diastereomers, along with recovered vinyl sulfide 4 (0.054 g, 19%). The two diastereomers could be separated by column chromatography using 10:1 benzene:acetone as eluant with the major isomer being the more polar one.

Minor isomer: ^{1}H NMR(200 MHz, $CDCl_3$): 7.33-7.51(m, 5H), 5.27(s, 1H), 4.77(s, 1H), 3.69(s, 3H), 3.01(d, J=9.8 Hz, 1H), 1.25-2.68 (m, 9H). IR($CHCl_3$ solution): 2949, 1746, 1711, 1686, 1436, 1325, 1233, 1199, 1024 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.5, 171.9, 141.6, 134.7, 131.2, 129.5, 129.4 128.9, 114.5, 58.0, 52.3, 45.0, 41.2, 40.0, 29.7, 24.7.

Major isomer: ^{1}H NMR(200 MHz, $CDCl_3$): 7.34(s, 5H), 5.33(s, 1H), 4.87(s, 1H), 3.67(s, 3H), 3.05(d, J=9.0 Hz, 1H), 1.25-2.55(m, 9H). IR($CHCl_3$ solution): 2949, 1746, 1711, 1696, 1448, 1328, 1236, 1197, 1023 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.1, 171.5, 141.7, 134.3, 131.5, 129.4, 128.7, 114.1, 57.4, 52.1, 45.6, 41.1, 39.9, 28.4, 24.6

Mixture of the two isomers: MS: 304(2, M^+), 208(29), 204(31), 149(53), 147(26), 110(35), 109(34), 97(56), 96(56), 91(70), 77(43), 69(33), 68(100), 67(48), 65(25), 59(26), 55(54), 51(34), 43(41), 39(70), 28(47).

3-(Phenylthio)-4-methoxycarbonyl-4a,5,6,8a-tetrahydronaphthalene-1,8-(7H)-dione (8) and 1-Hydroxy-3-phenylthio-4-methoxycarbonyl-5,6,7-trihydronaphthalene-8-one (15)

To a solution of thiophenol (0.12 ml, 1.17 mmol) in 10 ml THF at 0°C under argon was added 2.5 M nBuLi (0.50 ml, 1.25 mmol). After stirring for 20 min a solution of the E-Michael adduct 13E (0.144g, 0.40 mmol) in 5 ml THF was added. The reaction mixture

was stirred at 35°C for 12 h, at which time 20 ml ether was added and the reaction was quenched with 20 ml 10% sodium hydroxide. The organic layer was washed with 10% sodium hydroxide (3 x 20 ml), followed by water (20 ml). The combined aqueous layer was then extracted with ether (2 x 20 ml). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:4 EtOAc:hexane) of the crude material provided a thick yellow oil 8 (0.070g, 50%) as a 4:1 mixture of two isomers.

When the reaction was carried out in the same way except that the mixture was stirred at 40°C for 12 h, then an aromatic product 15 is obtained in 62% yield.

Major isomer of 8: ^{1}H NMR(200 MHz, $CDCl_3$): 14.96(s, 1H), 7.41-7.54(m, 5H), 5.60(d, J=1.8 Hz, 1H), 3.71(d, J=1.8 Hz, 3H), 3.33(dd, J=1.8 Hz and 6 Hz, 1H), 3.11-3.20(m, 1H), 2.26-2.40(m, 2H), 1.84-2.03(m, 2H), 1.18-1.73(m, 2H). IR($CHCl_3$ solution): 2948, 1731, 1629, 1616, 1582, 1442, 1331, 1245, 1165, 754 cm^{-1}. MS: 330(9, M^+), 328(39), 295(50), 107(59), 92(76), 91(100), 86(88), 84(77), 79(38), 77(55), 65(39), 59(23), 55(30), 51(65), 47(28), 43(44), 41(39), 39(48). Exact mass calcd for $C_{18}H_{18}O_4S$ (M^+): 330.0925, found: 330.1038. ^{13}C NMR(75.4 MHz, $CDCl_3$): 187.1, 177.0, 169.4, 157.6, 135.3, 130.3, 130.0, 127.7, 121.8, 113.3, 103.6, 52.4, 50.5, 36.2, 29.6, 26.8, 20.8.

Minor isomer of 8: ^{1}H NMR(200 MHz, $CDCl_3$): 15.28(s, 1H), 7.39-7.56(m, 5H), 5.55(d, J=2 Hz, 1H), 3.86(s, 3H), 3.40(dd, J=2 Hz and 13 Hz, 1H), 3.15(dt, J=4.8 Hz and 12.8 Hz, 1H), 2.33-2.43(m, 2H), 1.82-1.98(m, 2H), 1.25-1.70(m, 2H). IR: same as above. MS: 330(15, M^+), 271(54), 270(44), 221(85), 206(50), 204(39), 147(34), 110(40), 109(45), 97(25), 86(67), 84(88), 77(42), 69(67), 65(43), 59(64), 55(85), 41(47), 39(54), 28(100). Exact mass calcd for $C_{18}H_{18}O_4S$ (M^+): 330.0925, found: 330.1004. ^{13}C NMR(75.4 MHz, $CDCl_3$): 185.0, 179.4, 171.9, 158.9, 135.7, 130.5, 130.1, 129.7, 120.8, 104.3, 53.9, 52.4, 36.7, 30.2, 28.0, 20.5.

Aromatic compound, 15: ^{1}H NMR(200 MHz, $CDCl_3$): 12.83(s, 1H), 7.40-7.60(m, 5H), 6.26(s, 1H), 3.94(s, 3H), 2.92(t, J=6 Hz, 2H), 2.64(t, J=6 Hz, 2H), 2.06(quintet, J=6 Hz, 2). IR($CHCl_3$ solution): 2948, 1717, 1630, 1582, 1437, 1359, 1260, 1187 cm^{-1}. MS: 328(7, M^+), 327(36), 296(55), 291(58), 123(36), 111(42), 110(100), 109(35), 106(55), 97(25), 79(47), 77(45), 65(36), 39(37), 28(61). ^{13}C NMR(75.4 MHz, $CDCl_3$): 204.1, 167.8, 163.7, 148.6, 144.1, 135.2, 130.5, 129.9, 129.7, 122.2, 114.1, 52.3, 38.4, 27.8, 22.4.

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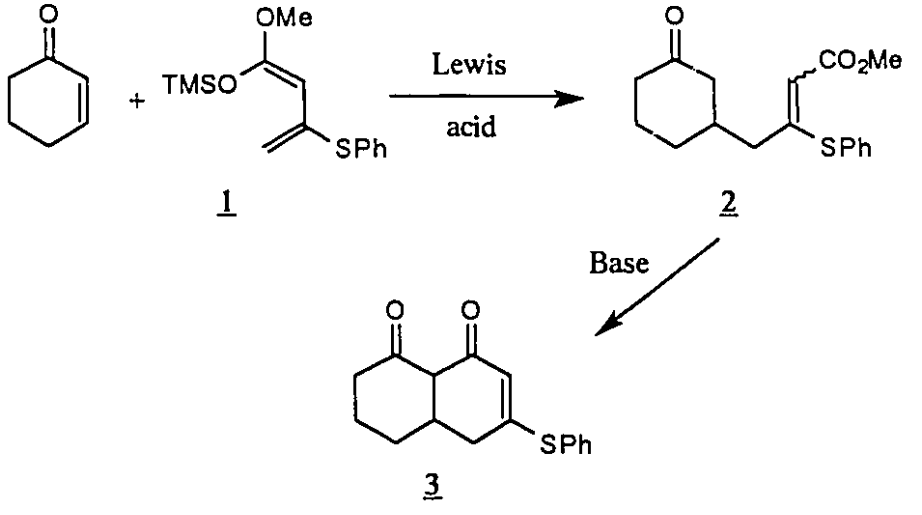
CHAPTER 3

INTRODUCTION OF ANGULAR FUNCTIONAL GROUPS[1]

3.1 Introduction

As seen in the first part of **Chapter 2**, decalin 3 is easily prepared according to the procedure developed in our laboratory by Prasad and Chan[2] (see **Scheme 3.1**). Func-



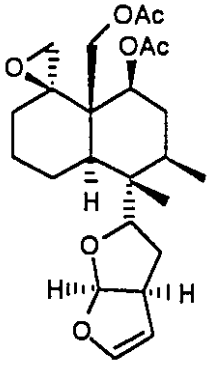
1 2 3

Scheme 3.1

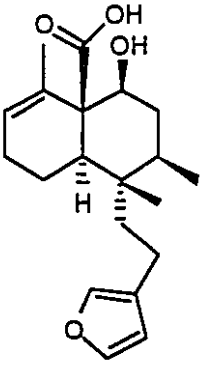
tionalization of diketone 3 at the angular position in order to prepare intermediates of type 16 and 17 could provide an entry into the decalinic skeletons of natural products such as kerlinic acid[3] and clerodin[4] (see **Scheme 3.2**). Our goal was to then use intermediate 17 to prepare the angularly functionalized decalin compounds 18 - 20, which will be described in **Chapter 4.**

Recently Burke[5] and coworkers have demonstrated that unactivated methyl groups, such as the C_{10a} methyl group in compound 21, which enjoy a favourable 1,3-diaxial relationship with a hydroxy group (in this case at C_6) can be functionalized via an alkoxy

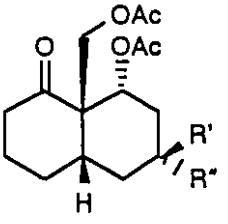
radical intermediate using the Barton[6] photochemical reaction to provide 22 in 89% yield (see **Scheme 3.3**).



clerodin



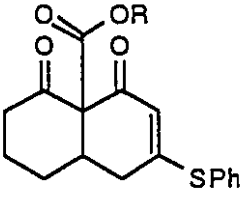
kerlinic acid



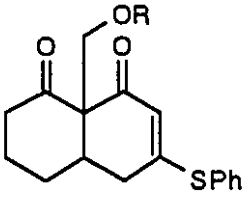
18 R"= R'= H

19 R"= H, R'= Me

20 R"= R'= Me



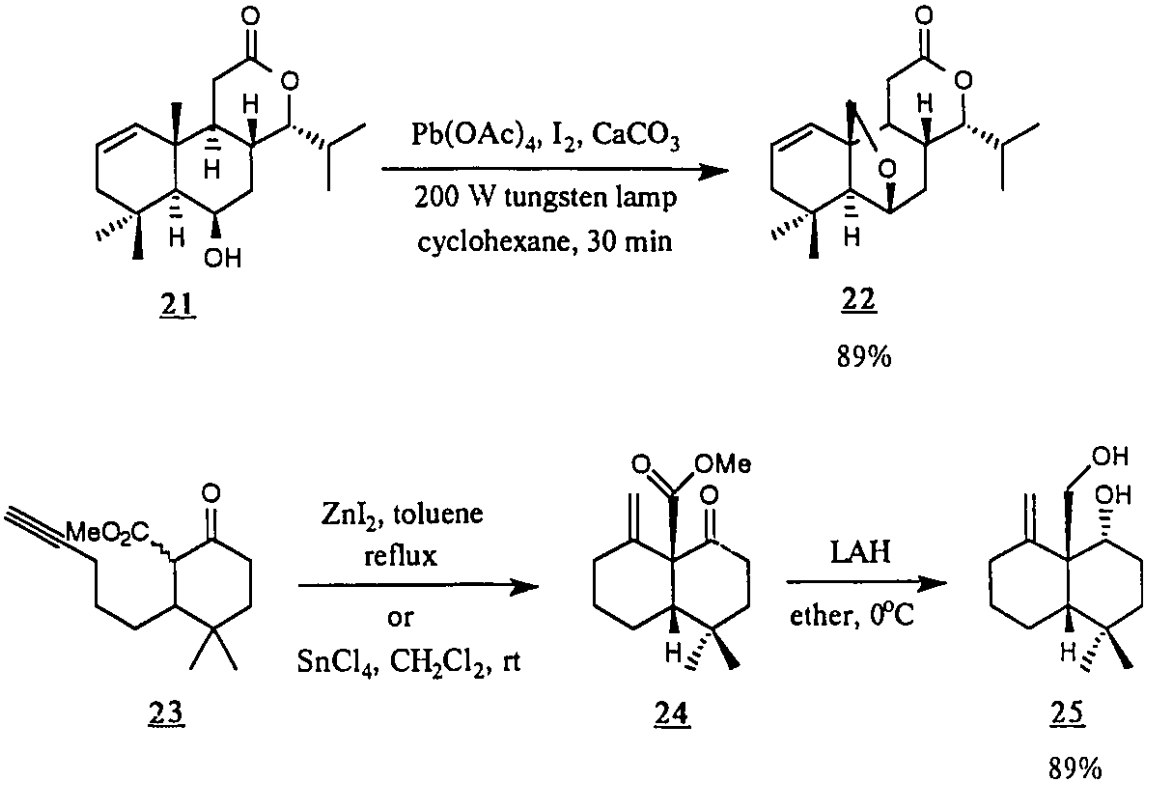
16



17

Scheme 3.2

For their part Jackson and Ley[7] have introduced an angular ester moiety via the cyclization of compound 23 as shown in **Scheme 3.3**. Reduction of the ester functionality in compound 24 then provided compound 25 bearing an angular hydroxymethylene moiety, as already outlined in the Introduction (see **Chapter 1: Scheme 1.6** and accompanying text).

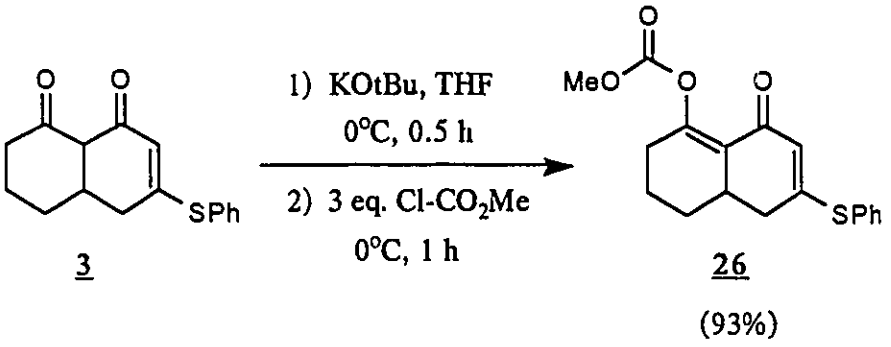


Scheme 3.3

This Chapter describes our efforts to introduce ester and hydroxymethylene functionalities at the angular position of a decalin system.

3.2 Efforts Towards the Introduction of an Angular Ester Moiety

In the hope of preparing intermediate 16 (see **Scheme 3.2**), decalin 3 was treated with potassium *tert*-butoxide in THF and the resulting anion was quenched with 3 equivalents of methyl chloroformate. However, this provided the O-alkylated product 26 in 93% yield (see **Scheme 3.4**). This is not surprising since it is known that ethyl chloroformate gives predominantly O-alkylation.[8,9] The O-alkylation was confirmed by the presence of only one carbonyl carbon (an unsaturated carbonyl) in the ^{13}C NMR (at 183.8 ppm), as well as the presence of the carbonate signal (at 163.6 ppm). If C-alkylation had taken place, an ester signal around 170 ppm and two carbonyl signals would have been expected in the ^{13}C NMR spectrum.

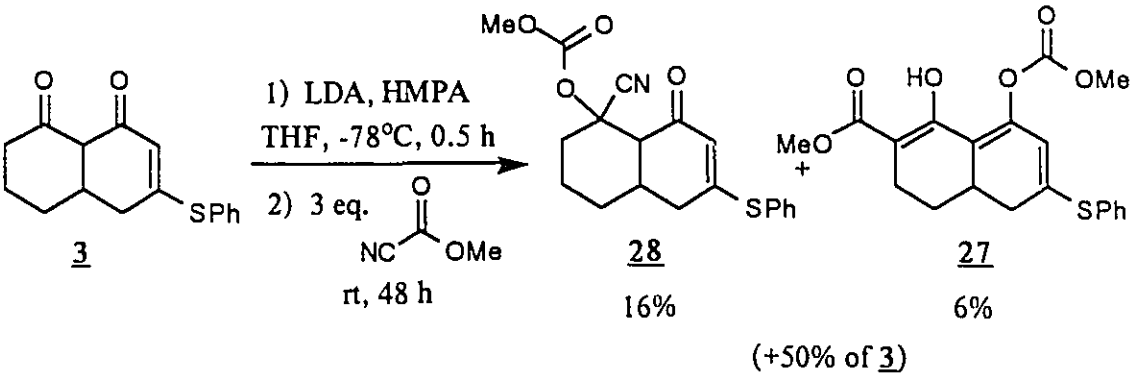


3 → 26 (93%)

Scheme 3.4

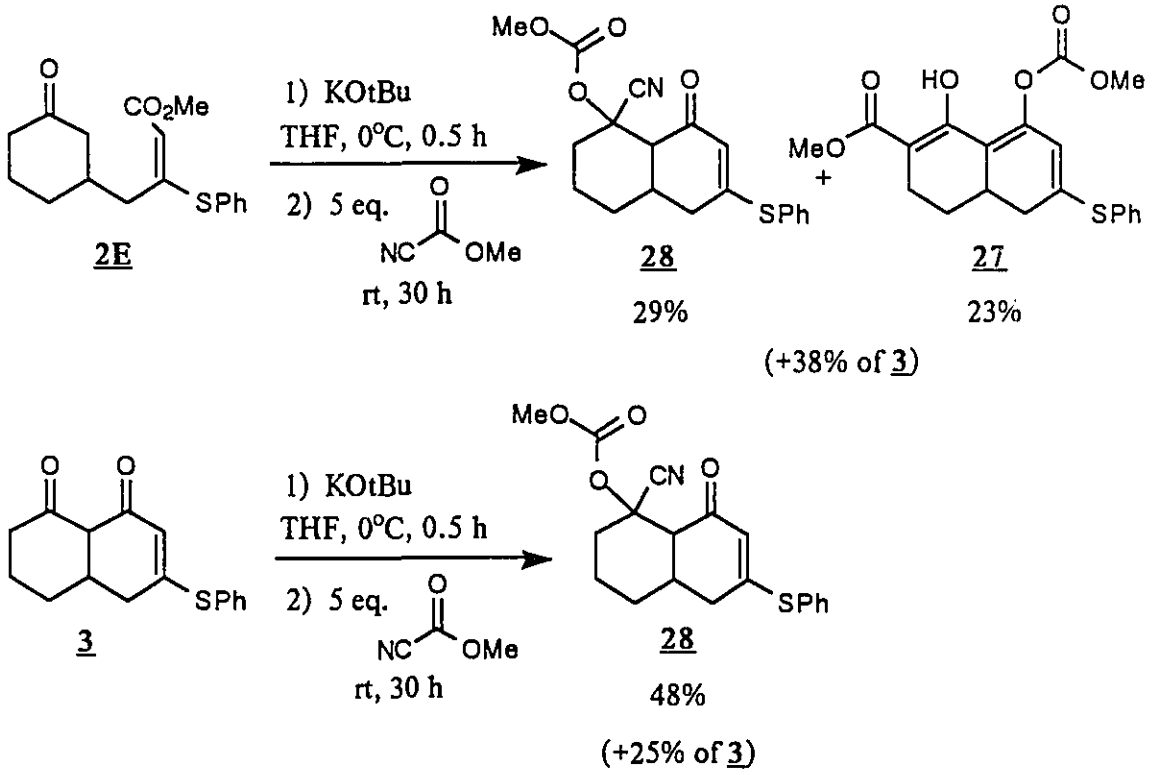
Recently Mander and Sethi[10] described a C-acylation of lithium enolates by methyl cyanoformate[11] which provided high yields of β-keto esters. When these reaction conditions were applied to decalin 3, a diacylated product 27 and compound 28 were formed in 6% and 16% respectively, together with 50% recovered decalin 3 (see **Scheme 3.5**). Note that the reaction mixture required stirring for 48 h at room temperature, whereas Man-

der and Sethi were able to cause ketones to react in 15 min at -78°C. This suggests that di-



Scheme 3.5

ketone 3 is much less reactive than an ordinary ketone. The reaction conditions described by Mander and Sethi were thus modified in the following way.



Scheme 3.6

The Michael adduct 2E was treated with potassium *tert*-butoxide in THF, thus promoting the Claisen condensation, and the resulting anion quenched with methyl cyanoformate, providing after 30 h at room temperature the dialkylated product 27 in 23% yield together with 29% of compound 28 and 38% decalin 3 (see **Scheme 3.6**). Interestingly Mander and Sethi had observed that no reaction took place when potassium enolates were reacted with methyl cyanoformate, even at 20°C.

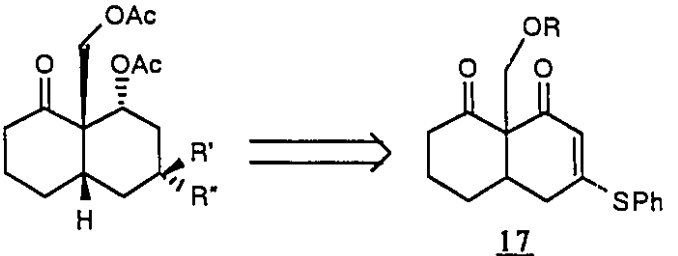
Subjecting decalin 3 to the same conditions provided 28 as the sole product in 48% yield together with 25% starting material. For compound 27, O-acylation and the presence of an α,β-unsaturated ester moiety was confirmed by the presence of the two carbonate signals at 165.4 and 162.4 ppm in the ^{13}C NMR. The structure of compound 28 was confirmed by the presence of an unsaturated carbonyl signal at 189.2 ppm and a carbonate signal at 165.1 ppm in the ^{13}C NMR. The presence of the CN functionality was evident from the weak peak at 2361 cm^{-1} in the IR spectrum and from the even numbered (358) $M+H^+$ peak in the mass spectrum. An even numbered $M+H^+$ peak occurs when a N is present in the molecule.

ANGULAR HYDROXYMETHYLENE FUNCTIONALITY

3.3 Preliminary Results

As mentioned previously, the angularly functionalized decalin compounds 18 - 20 which we wish to prepare, could be derived from an intermediate of type 17 (see **Scheme 3.7**).

It was thought that such an intermediate could be prepared using a procedure similar to that followed by Ley and coworkers.[12] As described in the Introduction (see **Chapter 1 : Scheme 1.14** and accompanying text), the key step in their approach was the conjuga-



17

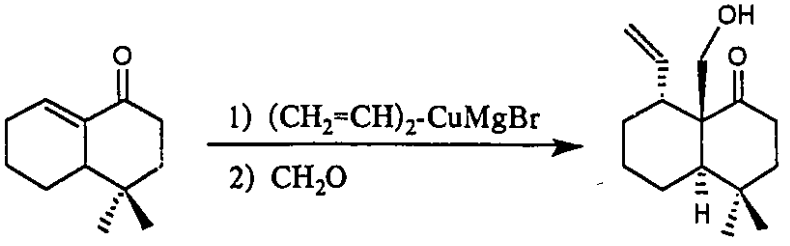
18 R"= R'= H

19 R"= H, R'= Me

20 R"= R'= Me

Scheme 3.7

te addition of vinylcuprate to the enone 29 followed by trapping of the resulting enolate with formaldehyde to give the *trans*-decalin 30 (see **Scheme 3.8**). In our case, the Michael adduct 2E was treated with potassium *tert*-butoxide in THF to form the decalin 3

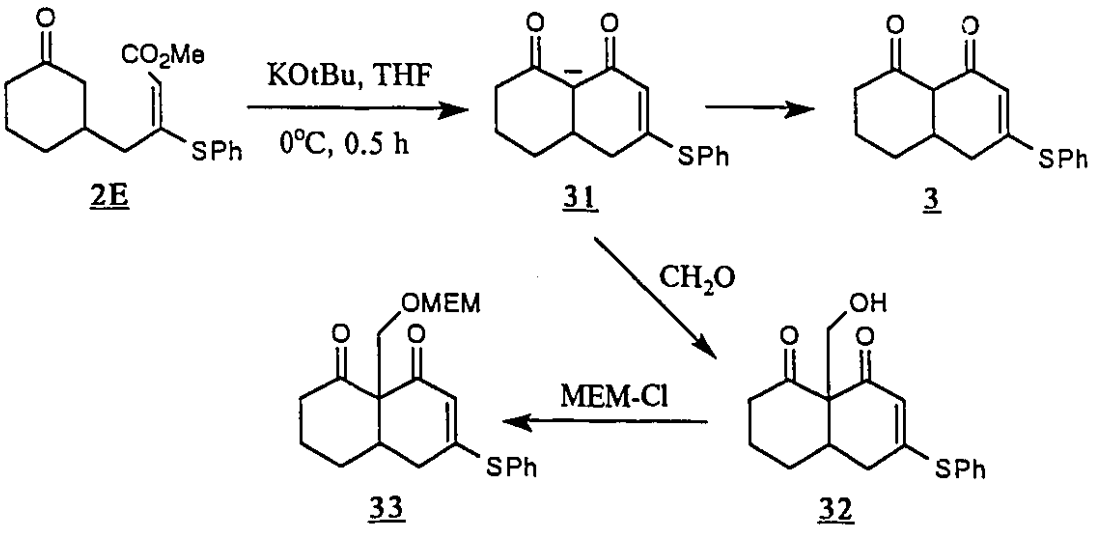


29 30

63%

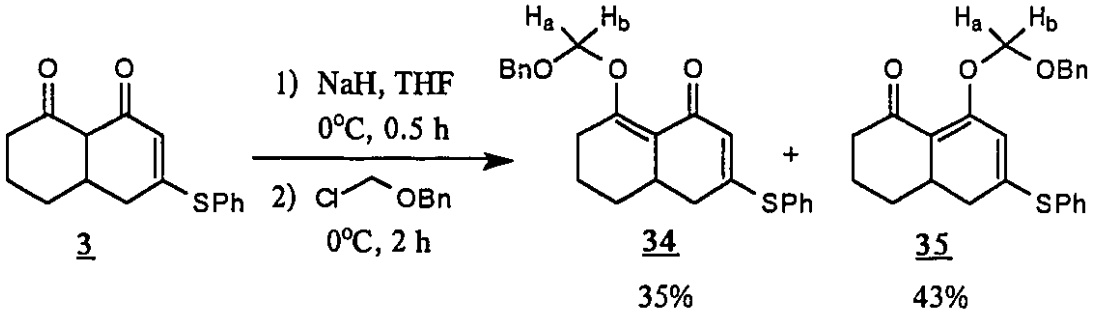
Scheme 3.8

and the resulting anion 31 was quenched by bubbling formaldehyde gas into the reaction mixture in the hope of preparing 32 featuring the hydroxymethylene unit (see **Scheme 3.9**). However, even after repeated column chromatography the product, if it were formed, could not be separated from the formaldehyde polymer. One attempt was made to treat the crude product with MEM-Cl[13], in the hope that the protected 33 would be more easily separated from the formaldehyde polymer, but no reaction took place.



Scheme 3.9

When the decalin 3 was treated with sodium hydride in THF at 0°C and the resulting anion 31 was reacted with benzyl chloromethyl ether, the O-alkylated products 34 and 35 were obtained in 35% and 43% yield, respectively (see **Scheme 3.10**). From the ^{1}H NMR spectra, it was quite clear that 34 and 35 were isomeric, and that both were



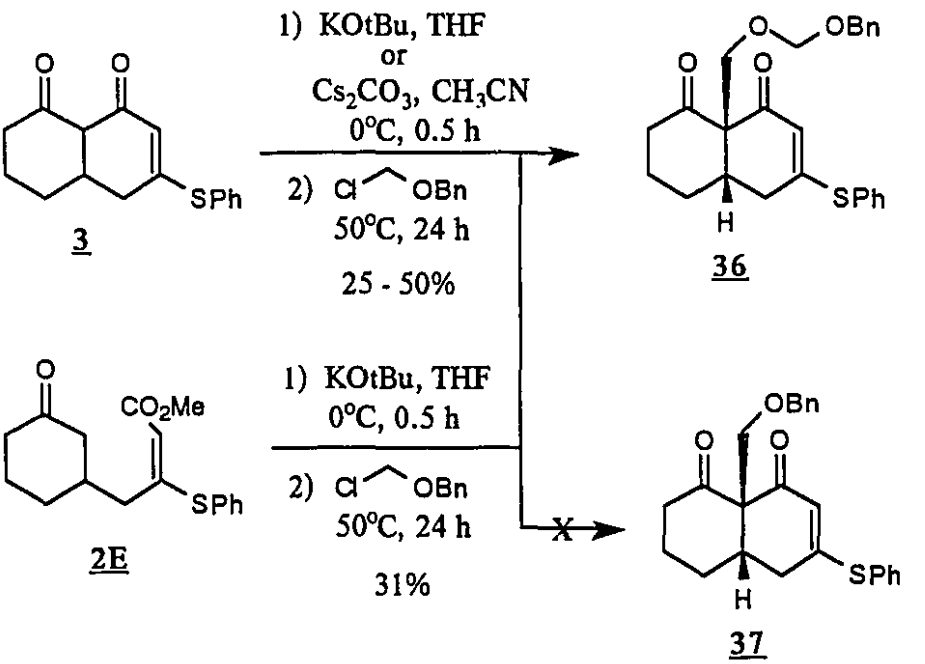
Scheme 3.10

O-alkylated products. The ^{1}H NMR of 35 showed that protons H_a and H_b, represented by an AB system at 4.97 ppm and 5.21 ppm (J = 6.9 Hz), are unequivalent. In contrast, the ^{1}H NMR of 34 indicated that protons H_a and H_b, represented by one singlet at 4.89 ppm,

are equivalent. We tentatively assigned the structures of 34 and 35 as indicated in **Scheme 3.10.** Replacing sodium hydride with sodium ethoxide[14] again resulted in O-alkylation. The use of zinc triflate[14] in methylene chloride, tetrabutylammonium hydroxide in benzene[2] or potassium carbonate in refluxing acetone[15] proved to be too mild, resulting only in recovery of unreacted decalin 3.

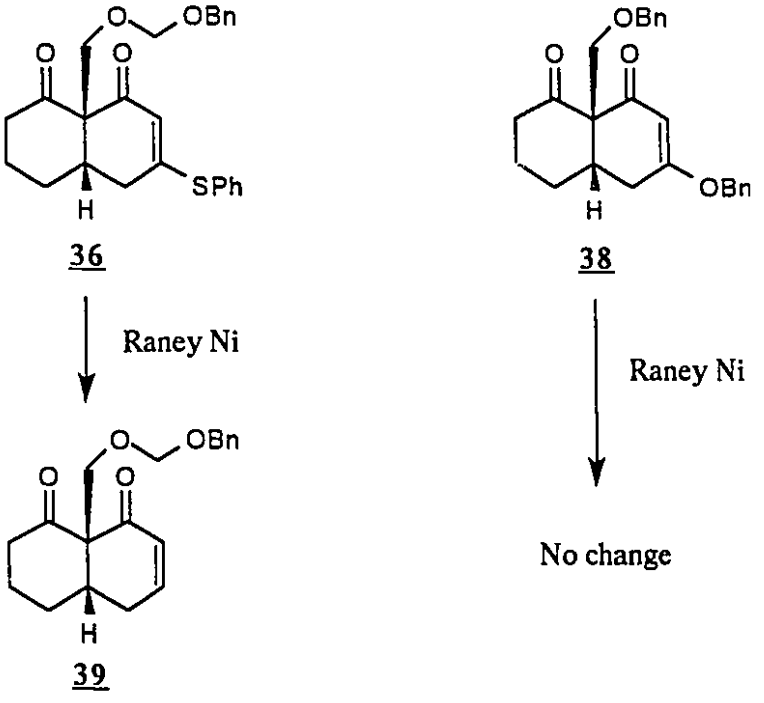
3.4 A Surprising Result

When decalin 3 was treated with potassium *tert*-butoxide in THF or cesium carbonate in acetonitrile and the resulting anion was quenched with benzyl chloromethyl ether, a C-alkylated compound was obtained in modest yields of 25-50%. The same pro-



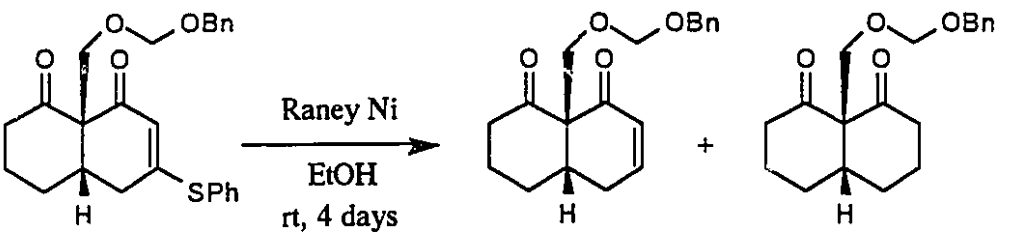
Scheme 3.11

duct could be obtained in 31% yield by treating the E-Michael adduct 2E first with potassium *tert*-butoxide in THF to effect cyclization and then with benzyl chloromethyl ether (see **Scheme 3.11**).



Scheme 3.12

Surprisingly, the product was not the expected 37. Both NMR and mass spectral data indicated the presence of an extra "CH_2O" moiety. Originally structures 36 and 38 (both consistent with the ^1H NMR data) were proposed as possible reaction products (see **Scheme 3.12**). Chemical correlation would help determine the correct structure of the compound by way of treatment with Raney nickel. If the reaction product was 36, reaction with Raney nickel would reduce the SPh moiety, providing enone 39. On the other hand if the reaction product were 38, treatment with Raney nickel would not effect any change. Thus, the compound was treated with Raney nickel in absolute ethanol at room temperature for four days, providing two products, 39 and 40 (see **Scheme 3.13**). This result suggested that the C-alkylation product (see **Scheme 3.11**) was compound 36 and



36 39 40

30% 60%

Scheme 3.13

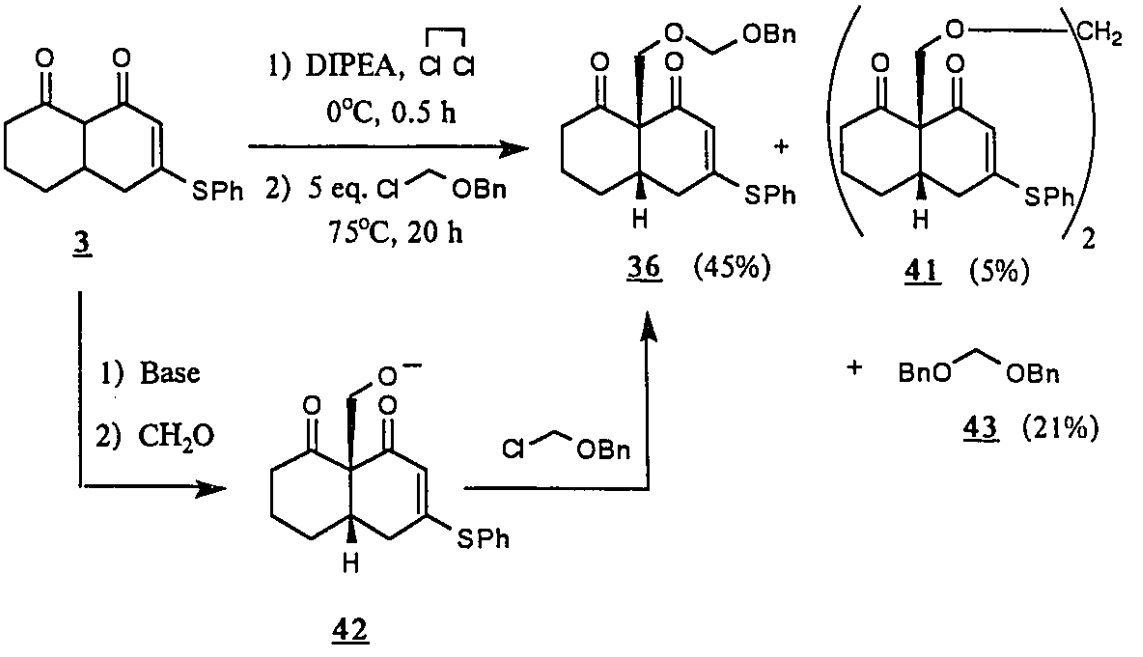
not 38. The C-alkylation leading to compound 36 was confirmed by the presence of two carbonyl carbons (a saturated carbonyl at 205.6 ppm and an unsaturated carbonyl at 192.0 ppm) in the ^{13}C NMR of 36. A COSY NMR helped to confirm that the signals at 4.82 and 4.75 ppm do couple together and form an AB system representing the *methylene* protons of the benzyloxymethoxy*methylene* functionality of 36.

3.5 Improving the C-alkylation Procedure

The yield of 36 from 3 could be improved somewhat by the use of diisopropylethylamine (DIPEA) in 1,2-dichloroethane[16,17] and excess benzyl chloromethyl ether (5 equivalents). Under such conditions 36 could be obtained in 45% yield together with 5% of dimer 41, 20% of recovered 3 and 21% of compound 43 (see **Scheme 3.14**). When chlorobenzene was used as a solvent instead of 1,2-dichloroethane, so as to permit an increase in reflux temperature in an attempt to further improve the yield, the desired product 36 was only formed in 27% even after 24 h at 100°C.

The formation of product 36 and dimer 41 with the extra "CH_2O" can be rationalized if one accepts the presence of formaldehyde in the reaction mixture.[18] In fact, reaction of the enolate of diketone 3 with formaldehyde produces an intermediate 42, which is more

reactive than the enolate of 3, and reacts directly with benzyl chloromethyl ether to give compound 36 (see **Scheme 3.14**). It is also possible that the anion 42 can react with

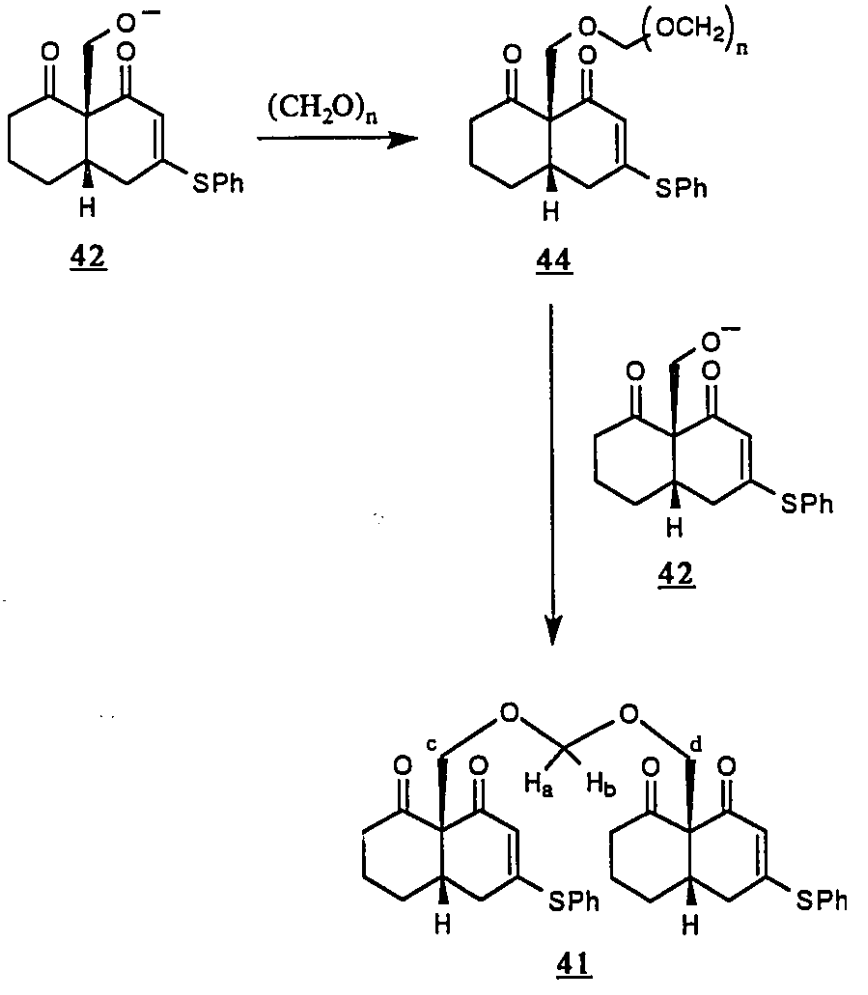


Scheme 3.14

paraformaldehyde to form 44 (see **Scheme 3.15**). The dimer 41 then presumably arises from the reaction of another molecule of 42 with 44.

Decoupling experiments helped to clearly establish the structure of the dimer. The two signals in the ^1H NMR at 4.6 and 4.8 ppm were indeed found to be part of the same AB pattern, that representing protons H_a and H_b (see **Scheme 3.15**). Interestingly there were two other signals which appeared to be part of a second AB pattern, at 3.6 and 4.0 ppm, but their integration was double that of the first AB pattern. When decoupling experiments showed that they indeed coupled together and were in fact one AB pattern (or two superimposable AB patterns), it was surmised that they represented *two* methylene units, c and d. It then followed that the compound which had been formed was a dimer with

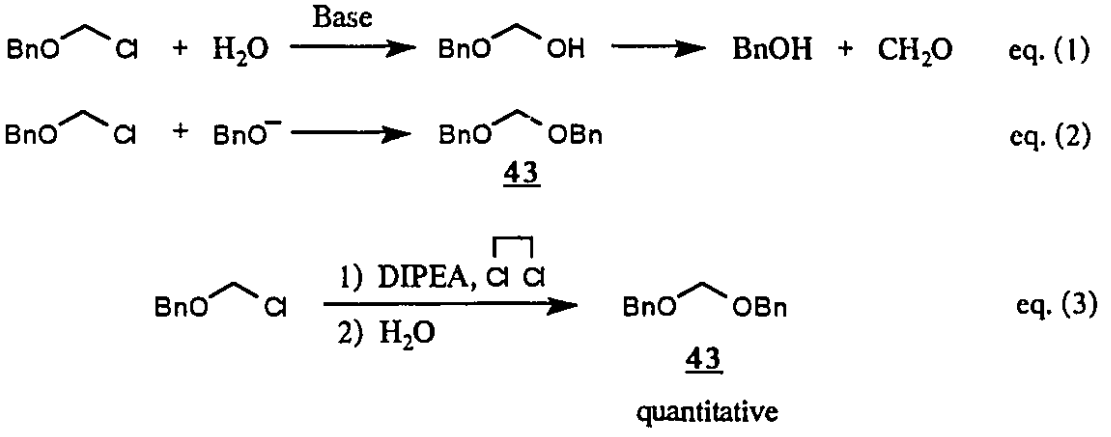
structure 41. This conclusion was supported by the ^{13}C NMR data and was confirmed by the low and high resolution mass spectra.



Scheme 3.15

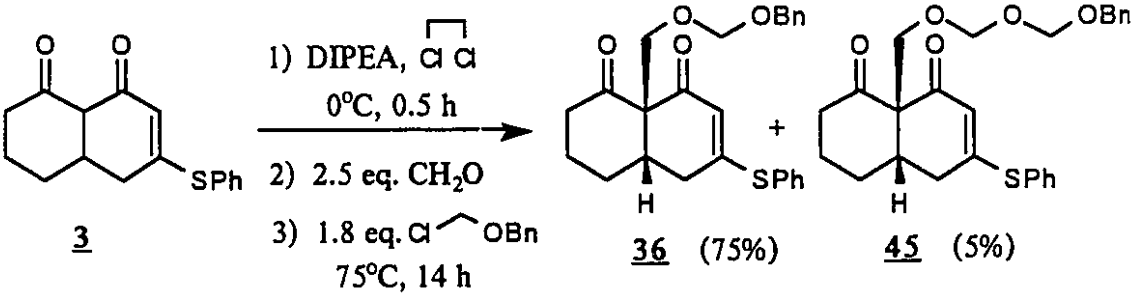
The presence of formaldehyde in the reaction mixture is probably due to the partial decomposition of the alkylating agent benzyl chloromethyl ether by a small quantity of water according to **Scheme 3.16**. The anion of benzyl alcohol, formed by the action of the basic media (DIPEA) on the alcohol, can then react with another molecule of the reagent to form 43 (see eq. 2). In fact compound 43 can be formed in quantitative yield from the combination of the alkylating agent and base in 1,2-dichloroethane in the presence of 1.0

equivalent of water (see eq. 3). When the alkylating agent was carefully distilled and then used in the reaction, the yield of product 36 decreased to 35%. The fact that not even a trace of the expected product 37 was ever detected indicates that the enolate of 3 is not reactive enough to react directly with benzyl chloromethyl ether. Instead the enolate of 3 reacts with smaller electrophiles, such as formaldehyde, thus forming a more reactive nucleophile, 42, which can then react with benzyl chloromethyl ether.



Scheme 3.16

We decided to try and take advantage of this situation and increase the yield of product 36 by adding formaldehyde directly to the reaction mixture. In this way, compound 36 was prepared in 75% yield by adding 2.5 equivalents of paraformaldehyde to the reaction mixture (see **Scheme 3.17**). Now 1.8 equivalents of benzyl chloromethyl ether

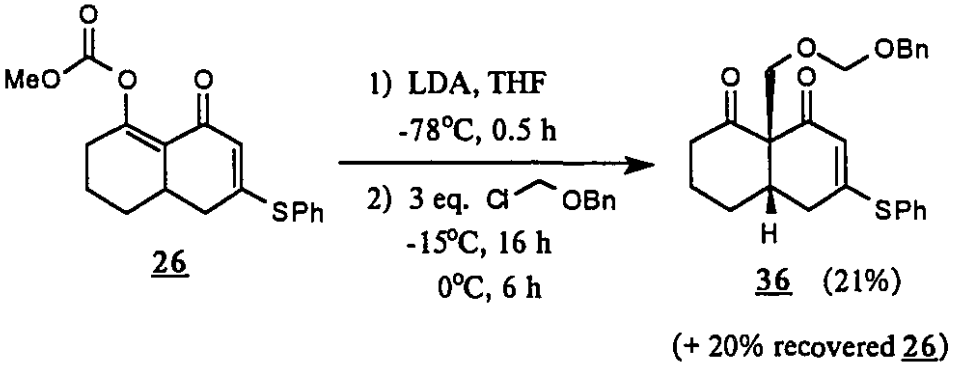


Scheme 3.17

was sufficient to complete the alkylation, as opposed to the 5.0 equivalent excess previously required. In addition the reaction time was reduced to half (14 h) the previously required time (30 h).

The same reaction also produced 5% of compound 45 resulting from the addition of two formaldehyde units to the diketone anion, followed by trapping of this intermediate by benzyl chloromethyl ether. An attempt to avoid the formation of this byproduct by reducing the amount of paraformaldehyde to 1.0 equivalent resulted in a lower yield (45%) of the desired product.

It was later found that compound 36 could also be prepared from the O-carbome-



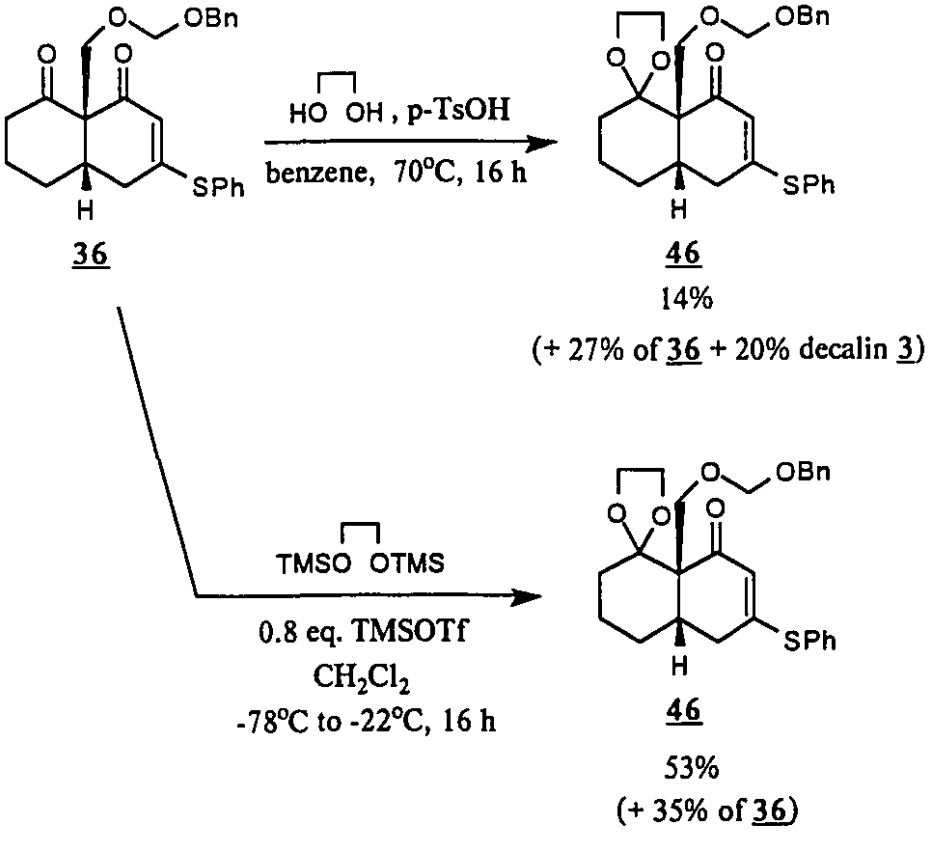
Scheme 3.18

thoxy alkylated compound 26. Treatment of the latter with LDA, followed by the addition of 3 equivalents of benzyl chloromethyl ether provided 36 in 21% together with 20% recovered 26 (see **Scheme 3.18**).

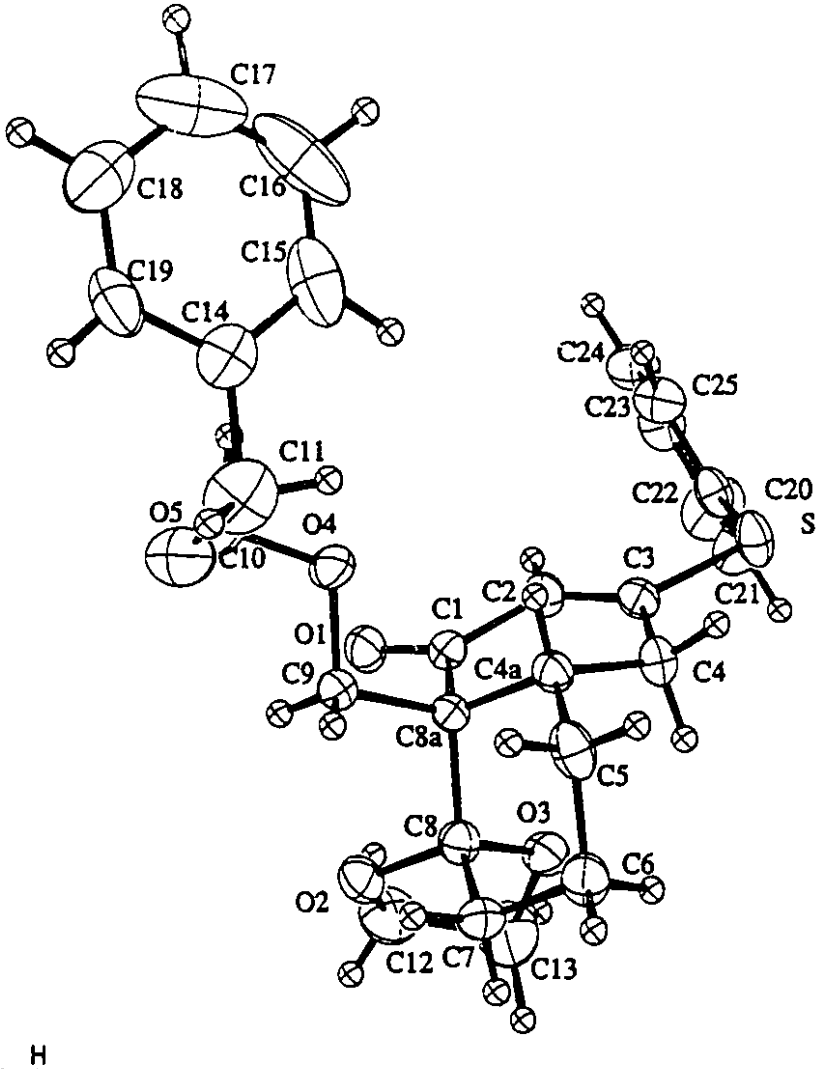
3.6 Stereochemistry

The angular hydroxymethylation described in the previous section was highly stereoselective in giving one major isomer. The stereochemistry of 36 could not be assigned on the basis of spectroscopic information. Refluxing 36 with ethylene glycol in

benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid on a Dean-Stark apparatus[19] provided the ethylene ketal 46 in only 14% yield, together with 27% starting material and 20% decalin 3 (see **Scheme 3.19**). Evidently, under acidic conditions, 36 can undergo acid deacetalization followed by reverse aldol reaction. However, by using a variation of the Noyori conditions[20], ie. treatment of 36 with 1,2-bis(trimethylsiloxy)-ethane in methylene chloride at -78°C in the presence of trimethylsilyl triflate, followed by warming to -22°C and stirring at this temperature overnight, ketal 46 could be obtained in 53% yield together with 35% starting material, but without formation of 3. Ketal 46 was crystalline and X-ray structure determination[21] confirmed the *cis* stereochemistry at the ring junction (see **Appendix B** for X-ray Structure Report). The ORTEP diagram of 46 in **Figure 3.1** clearly shows the *cis* relationship between proton C_{4a} and the protected hydroxy-methylene moiety.



Scheme 3.19


C17
C18
C16
C15
C19
C14
C24
C25
C23
C11
C22
C20
S
O5
O4
C10
C3
C2
C21
C1
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C9
C4a
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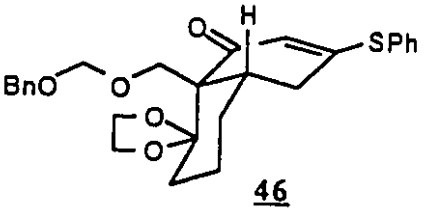
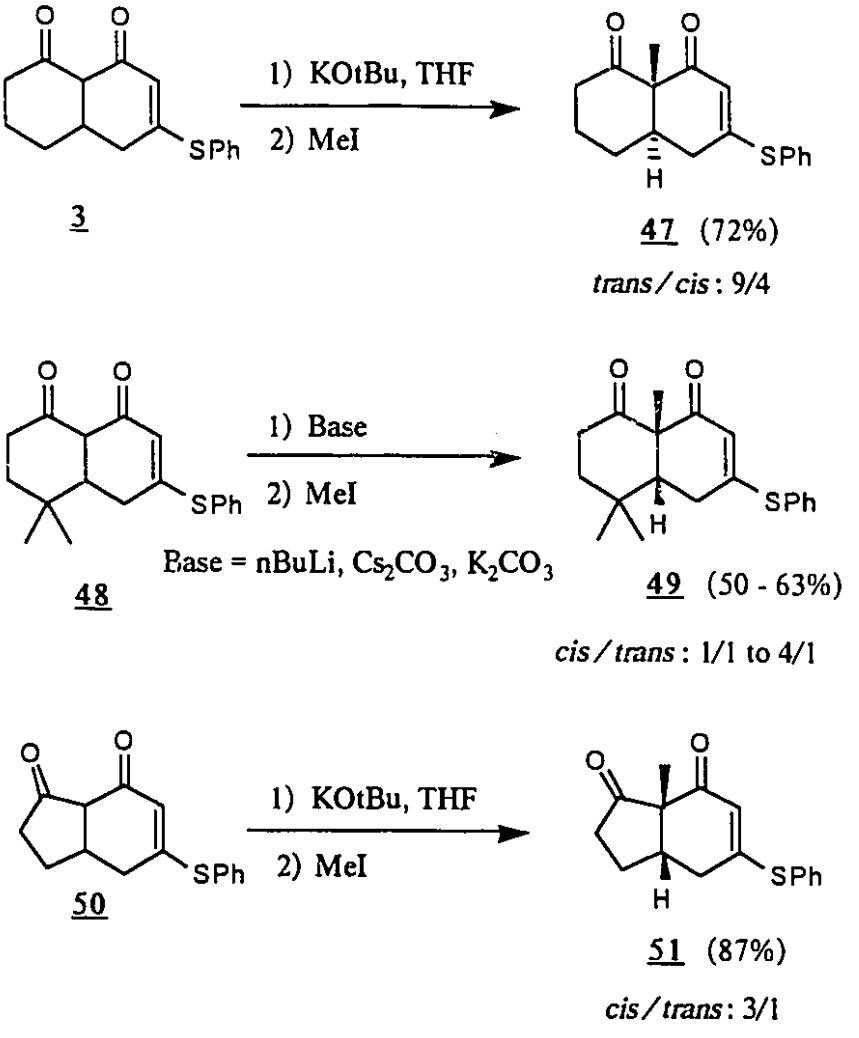
C8a
C5
C8
O3
C6
O2
C12
C7
C13


O
H
SPh
BnO
O
O
O

46

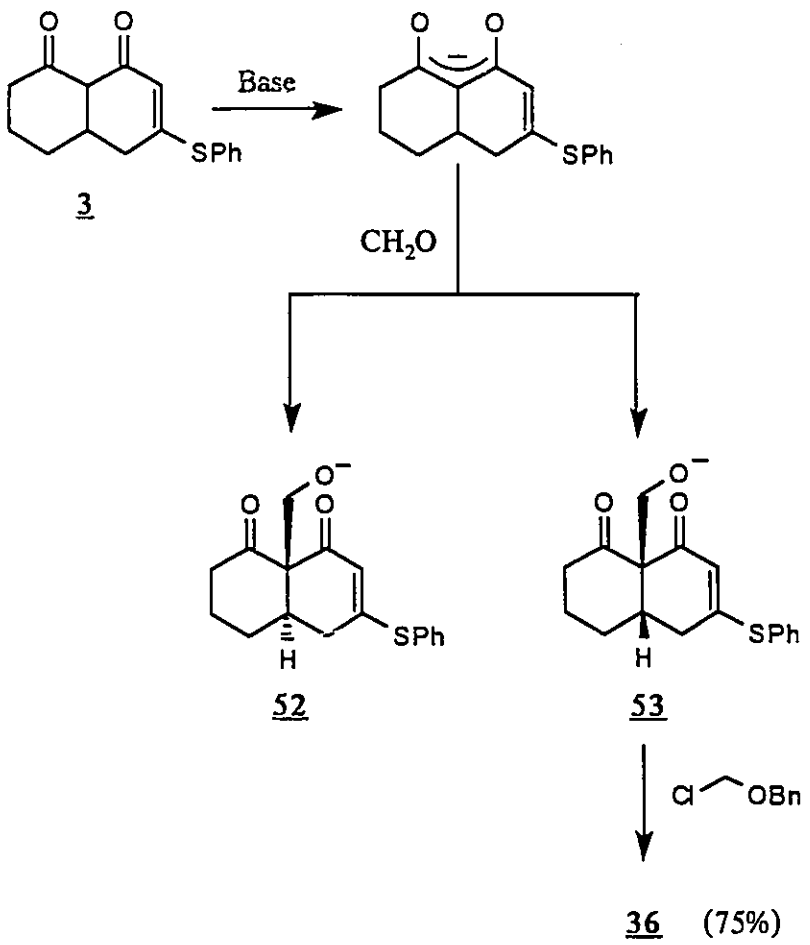
Figure 3.1



Scheme 3.20

Previously in our laboratory Prasad and Chan[2] had observed that methylation of 3 was stereoselective in giving mainly the *trans* isomer 47 (see **Scheme 3.20**). On the other hand, Chan, Guertin and Prasad[22] found that methylation of the corresponding *gem*-dimethyl-substituted decalin 48 gave preferentially the *cis* isomer 49. Similarly methylation of the hydrindan 50[23] gave preferentially the *cis* isomer 51.

The stereochemistry of the angular alkylation is thus quite sensitive to structural variations. In the present hydroxymethylation, the *cis* aldol adduct 53 may well be kineti-



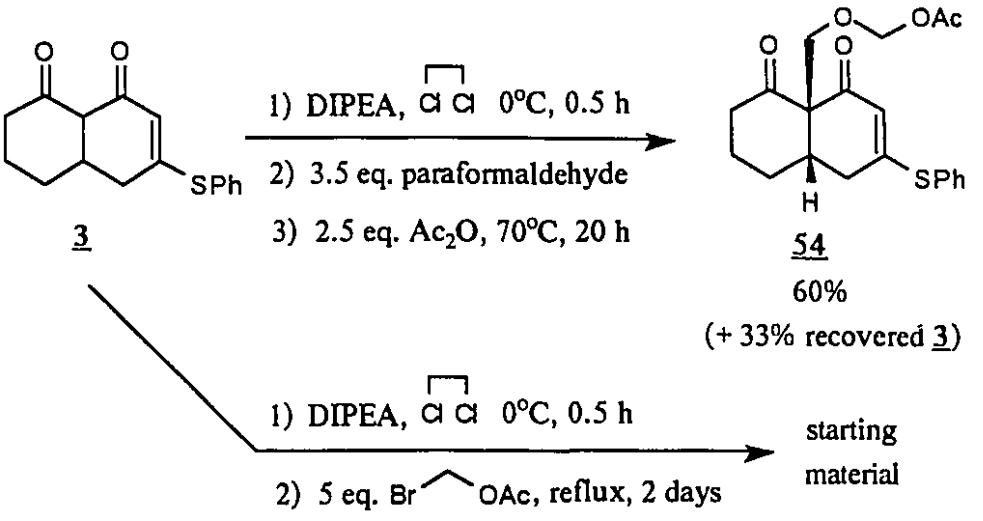
Scheme 3.21

cally favoured over the corresponding *trans* adduct 52 (see **Scheme 3.21**). Trapping of 53 by benzylchloromethyl ether then gave 36.

3.7 Other Hydroxymethylations

The trapping of the intermediate aldol 53 can also be accomplished with acetic anhydride. Thus treatment of 3 with DIPEA, paraformaldehyde, and acetic anhydride in 1,2-dichloroethane gave the angular (acetoxymethoxy)methyl compound 54 in 60% yield, together with 33% recovered 3 (see **Scheme 3.22**). Interestingly in this case, 2 mol of "CH_2O" have been incorporated.

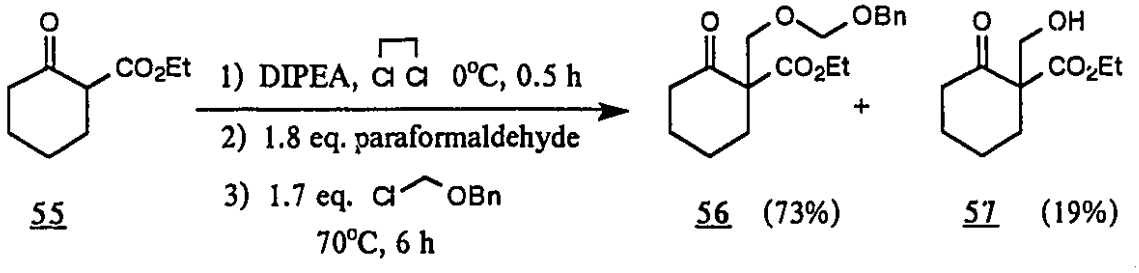
An attempt made previously to prepare the decalin 54 featuring an acetoxymethylene unit at the angular position by treating decalin 3 with DIPEA in 1,2-dichloroethane,



Scheme 3.22

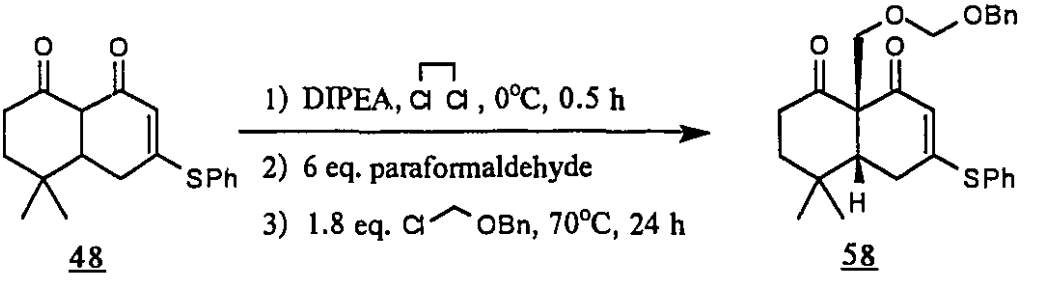
followed by quenching of the anion with bromomethyl acetate had failed. Even after the addition of 5 equivalents of bromomethyl acetate and refluxing the reaction mixture for 2 days only starting material was recovered, thus again demonstrating that the anion of diketone 3 is not reactive enough to be directly alkylated with reagents such as bromomethyl acetate and benzyl chloromethyl ether.

While the intermediacy of 53 was inferred from these products, 53 itself was too unstable to be isolated, presumably due to the ease of the reverse aldol reaction. However,



Scheme 3.23

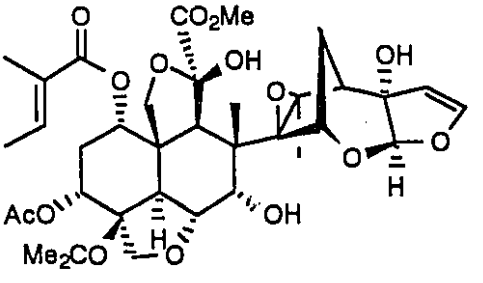
with keto ester 55 it was possible to isolate the intermediate aldol adduct 57 as shown in **Scheme 3.23**). When 55 was treated under identical reaction conditions, 57 was isolated in 19% yield together with 73% of the [(benzyloxy)methoxy]methyl product 56. It is remarkable that in none of these reactions was the (benzyloxy)methyl adduct ever observed.



48 58

30%

(+ 70% recovered 48)



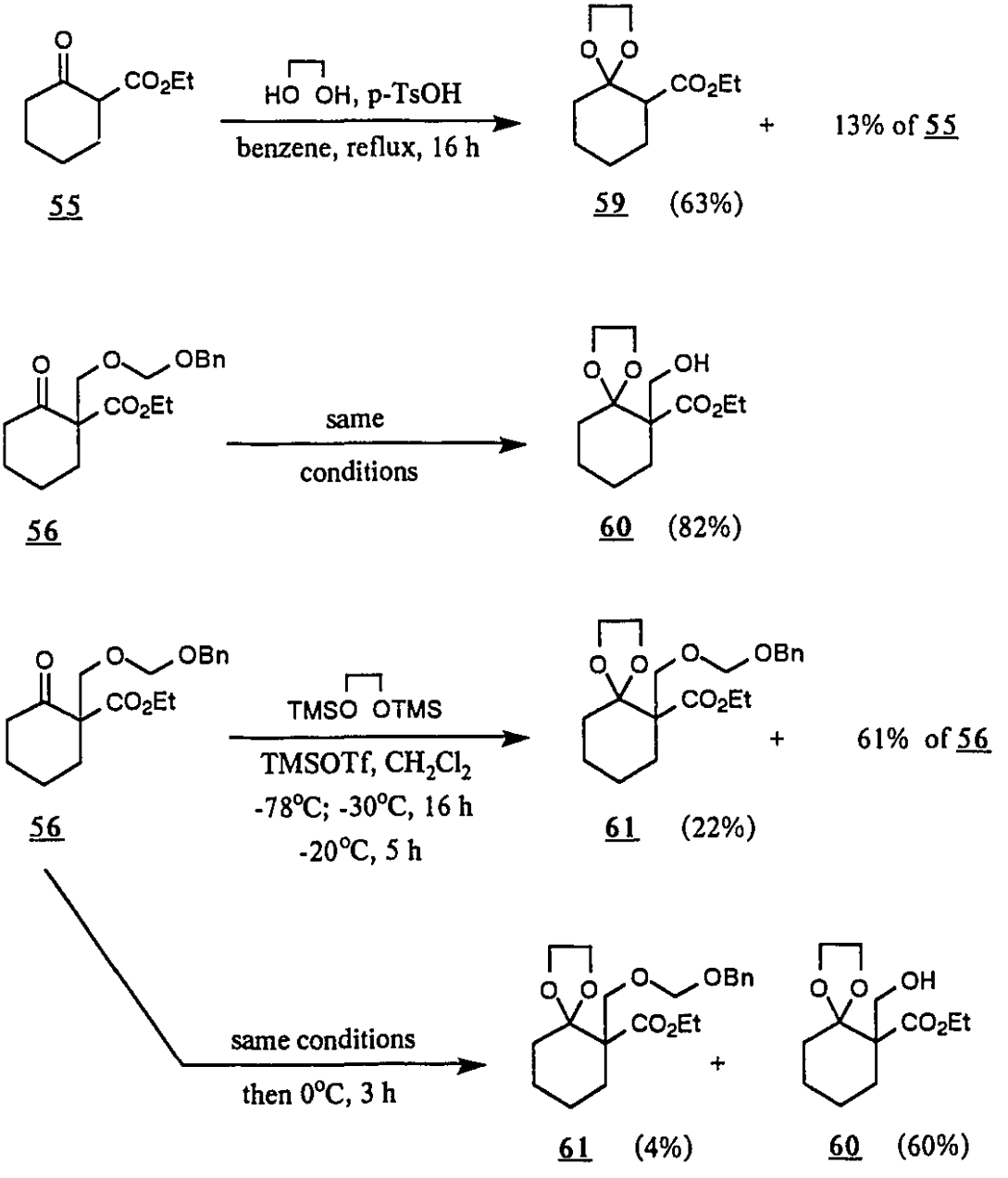
azadirachtin

Scheme 3.24

Finally, reaction of the *gem*-dimethyl-substituted decalin 48 under similar reaction conditions gave the [(benzyloxy)methoxy]methyl compound 58 as indicated in **Scheme 3.24**. In this case the yield was not optimized. The reaction may therefore provide an entry into the azadirachtin skeleton as well. The stereochemistry of 58 was tentatively assigned to be *cis* on the basis of the similarity of its proton NMR spectrum with that of 36.

3.8 Ketal Formation With Keto-ester (55)

The ketal of keto-ester 55 was easily formed by refluxing compound 55 with ethylene glycol in benzene on a Dean-Stark[19] apparatus in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the desired product 59 in 63% yield together with



Scheme 3.25

13% recovered keto-ester 55 as shown in **Scheme 3.25** (unoptimized yield). However, when the [(benzyloxy)methoxy]methyl product 56 was treated under the same conditions, compound 60 was produced in 82% yield. This demonstrates once again the acid sensitivity of the benzyloxymethoxymethyl moiety. However, since compound 56 was less prone to retro aldol reaction, the hydroxymethylene unit remained intact upon ketalization. If the same starting material was treated under a variation of the Noyori[20] conditions, 22% of the ketal 61 was formed together with 61% recovered 56, after stirring for 5 h at -20°C. If warming was continued to 0°C, then after only 3 h at this temperature only 4% of ketal 61 was produced together with 60% of ketal 60, featuring the deprotected hydroxymethylene moiety.

Experimental

General Methods: See **Chapter 2, Experimental.** For compounds 39 and 40 the MH^+ peak was observed on the ZAB 2F HS instrument even though only the $M+NH_4^+$ peak (and not the MH^+ peak) was observed on the Hewlett-Packard 5980A instrument.

3-Phenylthio-8-(methoxycarbonyl)oxy-2,4,4a,5,6,7-hexahydronaphthalene-1-one (26)

To a solution of decalin 3 (0.203 g, 0.744 mmol) in 15 mL THF at 0°C under argon was added KOtBu (0.086 g, 0.768 mmol). After 20 min methyl chloroformate (0.17 mL, 2.22 mmol) was added. The reaction mixture was stirred for 1 h and then quenched by the addition of saturated ammonium chloride solution. The mixture was extracted with ether (3 x 25 mL) and the combined extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.260 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the O-alkylated product 26 (0.228 g, 93%) as a beige oil which crystallized on standing (mp. 77-78°C). ^{1}H NMR(200 MHz, $CDCl_3$): 7.36-7.53(m, 5H), 5.42(s, 1H), 3.80(s, 3H), 2.80-3.03(m, 1H), 2.40-2.55(m, 2H), 2.26-2.39(m, 2H), 1.55-2.07(m, 4H). IR($CHCl_3$ solution): 3012, 1762, 1664, 1608, 1586, 1443, 1268, 1196, 784 cm^{-1}. MS: 330(19, M^+), 270(32), 77(23), 55(25), 44(100), 31(75), 28(34). ^{13}C NMR(75.4 MHz, $CDCl_3$): 183.8, 163.6, 153.8, 152.5, 135.3, 130.1, 129.8, 127.8, 122.2, 121.9, 55.1, 36.7, 35.7, 29.3, 29.0, 20.3.

1-(Methoxycarbonyl)oxy-3-phenylthio-7-methoxycarbonyl-8-hydroxy-4,4a,5,6-tetrahydronaphthalene (27) and 3-Phenylthio-8-(methoxycarbonyl)oxy-8-cyano-2,4,4a,5,6,7-hexahydronaphthalene-1-one (28)

To a solution of diisopropylamine (0.09 mL, 0.64 mmol) in 1.5 mL THF at 0°C under argon was added 2.5 M nBuLi (0.26 mL, 0.65 mmol). The mixture was stirred for

15 min at 0°C and was then cooled to -78°C. A solution of decalin 3 (0.136 g, 0.50 mmol) in 4 mL THF was added and the mixture was stirred for 10 min at -78°C, followed by 45 min at 0°C. The solution was then recooled to -78°C and HMPA (0.08 mL, 0.50 mmol) was added, followed by methyl cyanoformate (0.08 mL, 1.00 mmol). The mixture was stirred for 16 h at -30°C. More methyl cyanoformate (0.02 mL, 0.25 mmol) was added and the mixture was stirred for another 16 h at room temperature. The reaction was then quenched by the addition of saturated ammonium chloride solution and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.193 g crude material. Column chromatography (1:4 EtOAc:hexane) provided 27 (0.012 g, 6%) and 28 (0.026 g, 16%), together with recovered starting material 3 (0.076 g, 50%).

27: ^{1}H NMR(200 MHz, $CDCl_3$): 7.43-7.55(m, 5H), 5.24(s, 1H), 3.83(s, 3H), 3.58(s, 3H), 1.08-3.05(m, 7H). IR(neat): 2948, 1752, 1743, 1709, 1603, 1582, 1437, 1234, 1192, 1175, 1147 cm^{-1}. MS: 389(29, $M+H^+$), 272(86), 208(52), 172(26), 163(31), 147(55), 135(100), 134(71), 110(80), 109(43), 77(55), 59(23), 55(31), 41(25). ^{13}C NMR(75.4 MHz, $CDCl_3$): 165.4, 162.4, 152.9, 135.7, 130.1, 129.9, 129.1, 117.8, 111.8, 55.2, 50.9, 40.6, 35.0, 30.8, 22.3.

28: ^{1}H NMR(200 MHz, $CDCl_3$): 7.42(s, 5H), 5.45(s, 1H), 3.76(s, 3H), 1.25-3.10(m, 9H). IR($CHCl_3$ solution): 3028, 2950, 2361, 1757, 1666, 1577, 1442, 1285, 1245, 1181 cm^{-1}. MS: 375(19, $M+NH_4^+$), 358(100, $M+H^+$), 282(60). ^{13}C NMR(75.4 MHz, $CDCl_3$): 189.2, 165.1, 152.6, 135.5, 130.5, 130.0, 127.5, 120.6, 118.1, 70.6, 55.9, 55.2, 37.1, 34.9, 34.2, 31.5, 19.0.

Alternative procedure

Potassium *tert*-butoxide (0.050 g, 0.44 mmol) was added to a solution of E Michael adduct 2E (0.124 g, 0.41 mmol) in 5 mL THF at 0°C under argon. After stirring for 20 min, methyl cyanoformate (0.18 mL, 2.27 mmol) was added. The reaction mixture was

allowed to warm to room temperature and stirred for 8 h. The red mixture was then diluted with 5 mL ether and quenched with 10 mL water. The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.127 g crude material. Column chromatography (1:4 EtOAc:hexane) provided 27 (0.036 g, 23%) and 28 (0.038 g, 29%), along with some recovered decalin 3 (0.042 g, 38%). See procedure above for spectral data of compounds 27 and 28.

3-Phenylthio-8-(carbomethoxy)oxy-8-cyano-2,4,4a,5,6,7-hexahydronaphthalene-1-one (28)

Potassium *tert*-butoxide (0.195 g, 1.74 mmol) was added to a solution of decalin 3 (0.330 g, 1.20 mmol) in 15 mL THF at 0°C under argon. After stirring for 20 min at 0°C, methyl cyanoformate (0.80 mL, 10.1 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 30 h. The red mixture was then diluted with 200 mL ether and quenched with 200 mL saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 75 mL) and the combined extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.460 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product (0.192 g, 48%) along with some recovered decalin starting material (0.079 g, 25%). See procedure above for spectral data of 28.

8-[(Benzyloxy)methoxy]-3-(phenylthio)-4a,5,6,7-tetrahydronaphthalene-1(4H)-one (34) and 1-[(Benzyloxy)methoxy]-3-(phenylthio)-4a,5,6,7-tetrahydronaphthalene-8(4H)-one (35)

Sodium hydride (0.012 g, 0.50 mmol) was weighed into a dried flask under argon, 1 mL THF was added and the mixture cooled to -5°C. A solution of the decalin 3 (0.093 g, 0.36 mmol) in 1 mL THF was added and the pale yellow mixture was stirred for 30 min

at which time benzyl chloromethyl ether (0.050 mL, 0.36 mmol) was added. After stirring for 2 h at -5°C, the mixture was diluted with 3 mL ether and quenched with water. The aqueous layer was extracted with ether (3 x 10 mL). The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.136 g crude material. Column chromatography (1:4 EtOAc:hexane) provided 34 (0.050 g, 35%) as a lemon yellow oil and 35 (0.060 g, 43%) as a pale yellow oil.

34: ^{1}H NMR(200 MHz, $CDCl_3$): 7.23-7.54(m, 10H), 5.45(d, J=2 Hz, 1H), 4.89(s, 2H), 4.65(s, 2H), 2.69-2.90(m, 1H), 2.20-2.50(m, 4H), 1.82-2.01(m, 2H), 1.49-1.75(m, 1H), 1.20-1.41(m, 1H). IR($CHCl_3$ solution): 2952, 1614, 1592, 1242 cm^{-1}. MS: 393(22, $M+H^+$), 363(14), 273(100). Exact mass calcd for $C_{24}H_{24}O_3S+H^+$: 393.1524, found: 393.1524. ^{13}C NMR(75.4 MHz, $CDCl_3$): 196.9, 159.1, 151.4, 137.2, 135.4, 134.6, 130.0, 129.8, 129.5, 128.4, 127.7, 119.1, 114.9, 93.5, 76.6, 70.3, 40.7, 36.6, 36.4, 30.5, 21.5.

35: ^{1}H NMR(200 MHz, $CDCl_3$): 7.35-7.52(m, 5H), 7.31(s, 5H), 5.45(d, J=1.8 Hz, 1H), 5.21 and 4.97(AB, J=6.9 Hz, 2H), 4.67(s, 2H), 2.73-2.95(m, 1H), 2.25-2.51(m, 4H), 1.19-2.00(m, 4H). IR($CHCl_3$ solution): 2937, 1648, 1590, 1270, 748 cm^{-1}. MS: 393(31, $M+H^+$), 363(19), 273(100). Exact mass calcd for $C_{24}H_{24}O_3S+H^+$: 393.1524, found: 393.1524. ^{13}C NMR(75.4 MHz, $CDCl_3$): 185.6, 161.8, 161.0, 137.3, 135.4, 129.9, 129.8, 128.3, 128.1, 127.7, 122.8, 116.4, 92.7, 70.4, 37.7, 36.3, 29.4, 28.1, 20.6

cis-8a-[[(Benzyloxy)methoxy]methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydro-naphthalene-1,8(4H,7H)-dione (36)

Cesium carbonate Procedure

Cesium carbonate (0.338 g, 1.04 mmol) was weighed into a dried flask. The flask was then flame dried. Once the flask had cooled to room temperature, a solution of decalin 3 (0.166 g, 0.61 mmol) in 10 mL acetonitrile was added, followed 15 min later by benzyl

chloromethyl ether (0.25 mL, 1.80 mmol). The pale yellow reaction mixture was heated to 50°C and stirred for 6 h. Then more benzyl chloromethyl ether (0.40 mL, 2.90 mmol) was added and the mixture was stirred for another 20 h at 50°C. The mixture was then cooled to room temperature and diluted with 10 mL ether and quenched with 15 mL water. The aqueous layer was extracted with ether (3 x 15 mL). The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.665 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the *cis*-fused alkylated decalin 36 (0.122 g, 52%) as a yellow oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.25-7.52(m, 10H), 5.47(d, J=1.8 Hz, 1H), 4.82 and 4.75 (AB, J=8 Hz, 2H), 4.67 and 4.57(AB, J=12 Hz, 2H), 4.10 and 3.66(AB, J=10 Hz, 2H), 2.75-3.05(m, 2H), 2.15-2.50(m, 3H), 1.57-2.09(m, 4H). IR(neat): 2936, 2860, 1717, 1646, 1576, 1442, 1331, 1208, 1106, 1045, 749 cm^{-1}. MS: 423(100, $M+H^+$), 393(74), 315(36). Exact mass calcd for $C_{25}H_{26}O_4S+H^+$: 423.1629, found: 423.1630. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.6, 192.0, 165.5, 135.5, 130.4, 130.0, 128.4, 127.9, 127.7, 118.6, 95.4, 69.8, 66.0, 65.3, 40.1, 39.2, 33.3, 27.6, 24.6.

Alternative procedure

To a solution of decalin 3 (0.690 g, 2.53 mmol) in 25 mL 1,2-dichloroethane at 0°C under argon was added diisopropylethylamine (0.45 mL, 2.53 mmol), followed 20 min later by benzyl chloromethyl ether (0.70 mL, 5.03 mmol). The reaction mixture was heated to 75°C and stirred for 16 h. At this time more benzyl chloromethyl ether (0.60 mL, 4.31 mmol) was added and stirring was continued for an additional 3 h. The mixture was then cooled down, diluted with 50 mL ether and washed with water (2 x 50 mL). The organic layer was separated, dried over magnesium sulfate, filtered and the solvent removed to provide 1.987 g crude material. Column chromatography (1:4 EtOAc:hexanes) provided the product 36 (0.425 g, 40%), in addition to a dimer 41 (0.075 g, 5%) and recovered starting material 3 (0.133 g, 20%). The spectral data for the product are identical

with those described above. The dimer was a cream-coloured solid with mp 194-195°C: ^{1}H NMR(200 MHz, $CDCl_3$): 7.46-7.57(m, 10 H), 5.50(s, 2H), 4.78 and 4.62(AB, J=6 Hz, 2H), 4.05 and 3.65(two superimposable AB, J=10 Hz, 4H), 3.10-3.26(m, 2H), 2.78-2.94(m, 2H), 2.13-2.50(m, 6H), 1.62-2.08 (m, 8H). IR($CHCl_3$ solution): 2944, 1717, 1641, 1577, 1333, 1220, 1038 cm^{-1}. MS(x 20): 617(3, $M+H^+$), 316(22), 315(100), 285(21), 273(23). Exact mass calcd for $C_{35}H_{36}O_6S_2+H^+$: 617.2032, found: 617.2031. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.4, 192.1, 166.3, 135.6, 130.3, 129.9, 127.6, 118.5, 96.4, 66.1, 65.3, 40.2, 39.0, 33.4, 27.7, 24.5.

Conversion of (26) into (36)

To a solution of diisopropylamine (0.02 mL, 0.15 mmol) in 1.8 mL THF at 0°C under argon was added 2.5 M nBuLi (0.08 mL, 0.19 mmol). After stirring for 25 min at 0°C, the mixture was cooled to -78°C and a solution of **26** (0.050 g, 0.15 mmol) in 1.3 mL THF was added. After stirring for 0.5 h at -78°C, benzyl chloromethyl ether (0.06 mL, 0.45 mmol) was added. The mixture was stirred for 16 h at -15°C, followed by 6 h at 0°C. The reaction was then quenched by the addition of saturated ammonium chloride solution and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.129 g crude material. Column chromatography (1:4 EtOAc:hexane) provided compound **36** (0.013 g, 21%) along with some recovered **26** (0.010 g, 20%). The spectral data for **36** were identical with those described above.

Benzyloxymethyl benzyl ether (43)

To a solution of diisopropylethylamine (0.040 mL, 0.23 mmol) in 2.5 mL 1,2-dichloroethane at room temperature under argon was added benzyl chloromethyl ether (0.10 mL, 0.72 mmol). The mixture was heated to 75°C for 30 min at which time water (0.0050 mL, 0.28 mmol) was added. After allowing the mixture to stir for 16 h at 75°C, it was

cooled down and water and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide pure 43 (0.095 g, 100%) as a pale beige oil.

^{1}H NMR(200 MHz, $CDCl_3$): 7.32-7.38(m, 10H), 4.86(s, 2H), 4.66(s, 4H). IR($CHCl_3$ solution): 3015, 1498, 1455, 1229, 1205, 1052, 1038 cm^{-1}. MS: 246(100, $M+NH_4^+$), 229(5, $M+H^+$), 216(25), 198(11), 138(12), 108(10). Exact mass calcd for $C_{15}H_{16}O_2$ $+NH_4^+$: 246.14930, found: 246.14940. ^{13}C NMR(75.4 MHz, $CDCl_3$): 137.8, 128.4, 127.9, 127.7, 93.9, 69.4.

Paraformaldehyde procedure

for formation of ***cis*-8a-[[[(Benzyloxy)methoxy]methoxy]methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione (45)**

To a solution of decalin 3 (0.785 g, 2.88 mmol) in 30 mL 1,2-dichloroethane at 0°C under argon was added diisopropylethylamine (0.63 mL, 3.62 mmol). After stirring for 20 min at 0°C, the ice-bath was removed and paraformaldehyde (0.783 g, 8.69 mmol) was added. After stirring for 10 min at room temperature benzyl chloromethyl ether (0.72 mL, 5.18 mmol) was added and the mixture was heated to 70°C and stirred for 14 h at this temperature. The yellow mixture was then cooled to room temperature, diluted with 30 mL ether and quenched with 40 mL saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 40 mL). The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 1.664 g crude material. Column chromatography (1:4 EtOAc:hexane) afforded the *cis*-alkylated product 36 (0.916 g, 75%), compound 45 (0.058 g, 5%), some dimer 41 (0.087 g, 5%), compound 43 (0.279 g, 42%) and some starting material (0.0398 g, 5%). Spectral data for the *cis*-alkylated product 36, dimer 41 and compound 43 are given above.

Compound 45 exhibited: ^{1}H NMR(200 MHz, $CDCl_3$): 7.30-7.54(m, 10H), 5.47(d, J=2 Hz, 1H), 4.92(s, 2H), 4.86(s, 2H), 4.63(s, 2H), 4.06 and 3.67(AB, J=10 Hz, 2H), 2.75-

3.10(m, 2H), 2.15-2.45(m, 3H), 1.60-2.10(m, 4H). IR($CHCl_3$ solution): 2936, 1733, 1709, 1656, 1632, 1574, 1476, 1333, 1250, 1236, 1124, 1081, 1024 cm^{-1}. MS: 424(25, $M+2H^+$), 423(100, $M+H^+$), 393(23), 345(12), 316(19), 315(78). Exact mass calcd for $C_{25}H_{26}O_4S+H^+$: 423.1631, found: 423.1630. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.5, 191.9, 165.7, 137.5, 135.5, 130.5, 130.0, 128.4, 127.9, 127.8, 127.3, 118.5, 92.8, 88.6, 69.9, 66.4, 65.3, 40.1, 39.1, 33.3, 27.6, 24.5.

8a-[[(Benzyloxy)methoxy]methyl]-4a,5,6,8a-tetrahydronaphthalene-1,8-(4H,7H)-dione (39) and 8a-[[(Benzyloxy)methoxy]methyl]-3,4,4a,5,6,8a-hexahydronaphthalene-1,8(2H,7H)-dione (40)

To a solution of the alkylated decalin 36 (0.380 g, 0.90 mmol) in 25 mL absolute ethanol under argon was added a slurry of Raney nickel (2.204 g) in 5 mL absolute ethanol. The reaction mixture was stirred at room temperature for 4 days. The Raney nickel catalyst was then filtered off through a Celite pad and washed with ethanol. The solvent was removed to provide 0.064 g crude material. Column chromatography (1:4 EtOAc:hexane) provided 39 (0.085 g, 30%) and 40 (0.170 g, 60%).

39: ^1H NMR(200 MHz, $CDCl_3$): 7.25-7.40(m, 5H), 6.89-7.00(m, 1H), 6.06(d, J=12 Hz, 1H), 4.80 and 4.75(AB, J=8 Hz, 2H), 4.65 and 4.57(AB, J=12 Hz, 2H), 4.09 and 3.73 (AB, J=10 Hz, 2H), 1.60-2.81(m, 9H). IR($CHCl_3$ solution): 2936, 1717, 1669, 1026 cm^{-1}. MS: 332(80, $M+NH_4^+$), 285(24), 256(14), 255(55), 208(23), 207(100). Exact mass calcd for $C_{19}H_{22}O_4+H^+$: 315.1596, found: 315.1596. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.8, 196.2, 148.4, 137.9, 128.4, 128.0, 127.8, 127.6, 95.4, 69.7, 66.1, 65.9, 40.1, 39.0, 29.4, 27.8, 24.9.

40: ^1H NMR(200 MHz, $CDCl_3$): 7.25-7.40(m, 5H), 4.78(s, 2H), 4.63(s, 2H), 4.03(s, 2H), 2.45(t, J=7 Hz, 4H), 1.60-2.14(m, 9H). IR($CHCl_3$ solution): 2941, 1718, 1044 cm^{-1}. MS: 334(100, $M+NH_4^+$), 258(15), 257(53), 210(18), 209(82), 192(11). Exact mass calcd for $C_{19}H_{24}O_4+H^+$: 317.1752, found: 317.1753. ^{13}C NMR(75.4 MHz,

$CDCl_3$): 208.7, 137.9, 128.4, 127.9, 127.7, 95.3, 69.8, 68.9, 66.5, 42.4, 40.1, 26.9, 23.5.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-3-(phenylthio)-4a, 5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione (46)

To a solution of trimethylsilyltriflate (0.080 mL, 0.41 mmol) in 0.50 mL CH_2Cl_2 at -78°C under argon was added 1,2-bis(trimethylsiloxy)ethane (8.80 mL, 35.8 mmol) followed by compound 36 (0.233 g, 0.550 mmol) in 2.0 mL CH_2Cl_2. Stirring was continued at -78°C for 1 h. The solution was then warmed to -20°C and stirred for 18 h. The reaction was then quenched by the addition of pyridine (0.040 mL, 0.49 mmol) at -78°C, and poured into saturated sodium bicarbonate. The mixture was extracted with ether (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.218 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 46 (0.135 g, 53%) as a clear oil, in addition to recovered starting material 36 (0.073 g, 31%). Dissolving the product in some ether resulted in the formation of clear crystal needles (mp 97-98°C) which were submitted for X-Ray diffraction analysis. ^1H NMR(200 MHz, $CDCl_3$): 7.26-7.51(m, 10 H), 5.55(d, J=1.8 Hz, 1H), 4.69(s, 2H), 4.54(s, 2H), 4.36(AB, J=10 Hz, 1H), 3.69-3.88(m, 5H), 3.15-3.33(m, 1H), 2.81-2.97(m, 1H), 1.58-2.30(m, 7H). IR($CHCl_3$ solution): 2946, 1649, 1638, 1593, 1292, 1212, 1104, 1079, 1039, 689 cm^{-1}. MS: 467(100, $M+H^+$), 327(76), 133(38). Exact mass calcd for $C_{27}H_{30}O_5S+H^+$: 467.1891, found: 467.1892. ^{13}C NMR(75.4 MHz, $CDCl_3$): 195.5, 165.9, 137.9, 135.4, 130.0, 129.7, 128.3, 127.8, 127.5, 121.9, 110.7, 95.1, 69.5, 67.1, 65.1, 64.6, 55.7, 34.0, 33.0, 32.8, 25.4, 18.6.

8a-[(Acetoxymethoxy)methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione (54)

To a solution of decalin 3 (0.093 g, 0.34 mmol) in 3.5 mL 1,2-dichloroethane at 0°C was added diisopropylethylamine (0.070 mL, 0.40 mmol). After stirring the solution at 0°C for 20 min, the ice-bath was removed and paraformaldehyde (0.095 g, 1.10 mmol) was added, followed 10 min later by acetic anhydride (0.080 mL, 0.84 mmol). The mixture was heated to 70°C overnight and was then allowed to cool to room temperature at which point it was diluted with 5 mL ether and quenched with 5 mL saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 5 mL) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.135 g crude material. Column chromatography (eluting first with 1:4 EtOAc:hexane and then with 1:2 EtOAc:hexane) afforded the product 54 (0.071 g, 60%) as a yellow oil, along with recovered decalin 3 (0.031 g, 33%). ^{1}H NMR(200 MHz, $CDCl_3$): 7.42-7.58(m, 5H), 5.45(d, J=2 Hz, 1H), 5.30 and 5.22(AB, J=6 Hz, 2H), 4.14 and 3.74(AB, J=10 Hz, 2H), 2.10(s, 3H), 1.51-3.09(m, 9H). IR($CHCl_3$ solution): 3013, 1741, 1717, 1646, 1577, 1230, 1013 cm^{-1}. MS: 375(9, M+H$^+$), 345(16), 315(100), 176(17). Exact mass calcd for $C_{20}H_{22}O_5S$+H$^+$: 375.1267, found: 375.1266. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.4, 191.6, 170.5, 166.0, 135.5, 130.5, 130.0, 127.3, 118.4, 89.4, 68.0, 65.2, 40.0, 38.9, 33.2, 27.6, 24.5, 21.0.

Ethyl 1-[[(benzyloxy)methoxy]methyl]-2-oxocyclohexanecarboxylate (56) and Ethyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate (57)

To a solution of ethyl-2-oxocyclohexanecarboxylate 55 (0.68 mL, 4.30 mmol) in 40 mL 1,2-dichloroethane at 0°C under argon was added diisopropylethylamine (0.85 mL, 4.89 mmol). After stirring the solution at 0°C for 20 min, the ice-bath was removed and paraformaldehyde (0.730 g, 8.08 mmol) was added, followed 10 min later by benzyl chloromethyl ether (1.18 mL, 8.50 mmol). The mixture was heated to 70°C for 6 h and

then allowed to cool down to room temperature, at which point it was diluted with 40 mL ether and quenched with 50 mL saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 50 mL and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 1.985 g crude material. Column chromatography (1:5 EtOAc:hexane) afforded 56 (0.998 g, 73%) and 57 (0.238 g, 19%) both as clear oils.

56: ^{1}H NMR(200 MHz, $CDCl_3$): .7.29-7.37(m, 5H), 4.73(s, 2H), 4.57(s, 2H), 4.20(dq, J=7.2 Hz and J=2 Hz, 2H), 3.96 and 3.75(AB, J=9.6 Hz, 2H), 2.42-2.65(m, 3H), 1.96-2.12(m, 1H), 1.58-1.87(m, 5H), 1.25(t, J=7.2 Hz, 3H). IR(neat): 2898, 1717, 1702, 1454, 1236, 1024 cm^{-1}. MS: 338(100, $M+NH_4^+$), 321(8, $M+H^+$), 308(19), 213(44). Exact mass calcd for $C_{18}H_{24}O_5+H^+$: 321.1703, found: 321.1702. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.9, 169.9, 137.5, 128.0, 127.5, 127.3, 94.5, 69.7, 68.9, 61.2, 61.1, 40.7, 33.3, 26.9, 21.7, 13.8.

57: ^{1}H NMR(200 MHz, $CDCl_3$): 4.24(q, J=7.1 Hz, 2H), 3.82 and 3.69(AB, J=11.4 Hz, 2H), 2.23-2.93(m, 4H), 1.95-2.12(m, 1H), 1.40-1.84(m, 4H), 1.28(t, J=7.0 Hz, 3H). IR(neat): 3553, 2986, 2938, 1739, 1694, 1458, 1311, 1199, 1064 cm^{-1}. MS: 218(100, $M+NH_4^+$), 201(41, $M+H^+$). Exact mass calcd for $C_{10}H_{16}O_4+H^+$: 201.1128, found: 201.1127. ^{13}C NMR(75.4 MHz, $CDCl_3$): 211.3, 171.5, 66.5, 62.5, 61.7, 40.9, 32.7, 26.8, 21.8, 14.0.

8a-[[(Benzyloxy)methoxy]methyl]-5,5-dimethyl-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione (58)

To a solution of decalin 48 (0.077 g, 0.26 mmol) in 2.7 mL 1,2-dichloroethane at 0°C under argon was added diisopropylethylamine (0.060 mL, 0.34 mmol). After stirring the solution for 20 min at 0°C, the ice-bath was removed and paraformaldehyde (0.074 g, 0.82 mmol) was added, followed 10 min later by benzyl chloromethyl ether (0.060 mL, 0.43 mmol). The mixture was heated to 85°C and stirred overnight. At this time more

paraformaldehyde (0.045 g, 0.50 mmol) and benzyl chloromethyl ether (0.08 mL, 0.58 mmol) were added and the mixture was stirred at 70°C for 18 h, at which time it was allowed to cool to room temperature, diluted with 3 mL ether and quenched with 5 mL saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 10 mL) and the combined ether extracts were dried over magnesium sulfate, filtered, and the solvent removed to provide 0.212 g crude material. Column chromatography (1:4 EtOAc:hexane) afforded the product 58 (0.033 g, 28%) as a yellow oil along with recovered decalin 48 (0.054 g, 70%). ^{1}H NMR(200 MHz, $CDCl_3$): 7.32-7.48(m, 5H), 5.44(d, J=2 Hz, 1H), 4.82 and 4.76(AB, J=6.6 Hz, 2H), 4.67 and 4.58(AB, J=10 Hz, 2H), 4.12 and 3.54(AB, J=9.8 Hz, 2H), 2.25-2.89(m, 5H), 1.60-1.71(m, 2H), 1.07(s, 3H), 1.02(s, 3H). IR($CHCl_3$ solution): 2963, 1717, 1646, 1587, 1230, 1042 cm^{-1}. MS: 451(100, $M+H^+$), 421(65), 359(24), 343(96), 200(47), 148(37), 108(52). Exact mass calcd for $C_{27}H_{30}O_4S+H^+$: 451.1941, found: 451.1943. ^{13}C NMR(75.4 MHz, $CDCl_3$): 205.6, 192.5, 166.2, 137.8, 135.5, 130.5, 130.0, 128.0, 127.9, 119.5, 95.5, 69.9, 67.1, 63.7, 46.8, 40.1, 36.9, 34.3, 30.5, 28.6, 23.0.

Ethylene ketal of Ethyl 2-Oxocyclohexanecarboxylate (59)

A mixture of ethyl 2-oxocyclohexanecarboxylate 55 (0.32 mL, 2.0 mmol), ethylene glycol (0.34 mL, 6.0 mmol) and a catalytic amount of *para*-toluenesulfonic acid in 10 mL benzene were refluxed on a Dean Stark apparatus for 9 h. The mixture was then cooled down to room temperature and 10% sodium bicarbonate solution and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:5 EtOAc:hexane) of the crude material provided the ketal 59 (0.257 g, 63%) along with recovered starting material 55 (0.046 g, 13%). ^{1}H NMR(200 MHz, $CDCl_3$): 4.00(q, J=7.1 Hz, 2H), 3.75-3.90(m, 4H), 2.52(t, J=7.2 Hz, 1H), 1.69-1.88(m, 3H), 1.27-1.69(m, 5H), 1.12(t, J=7.0 Hz, 3H).

Ethylene ketal of ethyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate (60)

A mixture of 56 (0.225 g, 0.70 mmol), ethylene glycol (0.22 mL, 4.2 mmol) and a catalytic amount of *para*-toluenesulfonic acid in 6 mL of benzene were refluxed on a Dean Stark apparatus for 16 h. The mixture was then allowed to cool to room temperature and 10% sodium bicarbonate solution and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:4 EtOAc:hexane) of the crude material provided the ketal 60 (0.139 g, 82%). ^{1}H NMR(200 MHz, $CDCl_3$): 4.20(q, J=7 Hz, 2H), 3.88-4.10(m, 5H), 3.63(AB, J=11 Hz, 1H), 2.10-2.90(broad s, 1H), 1.85-2.10(m, 2H), 1.38-1.80(m, 6H), 1.27(t, J=8.7 Hz, 3H). IR($CHCl_3$ solution): 3503, 2938, 1733, 1448, 1223, 1199, 1089, 1029 cm^{-1}. MS: 262(10, $M+NH_4^+$), 245(100, $M+H^+$), 215(4), 200(9), 169(15), 99(72). Exact mass calcd for $C_{12}H_{20}O_5+H^+$: 245.1388, found: 245.1389. ^{13}C NMR(75.4 MHz, $CDCl_3$): 172.8, 111.3, 65.3, 64.6, 64.3, 60.8, 56.1, 31.6, 30.0, 22.9, 21.4, 14.2.

Ethylene ketal of ethyl 1-[[(benzyloxy)methoxy]methyl]-2-oxocyclohexane-carboxylate (61)

To a solution of trimethylsilyltriflate (0.04 mL, 0.20 mmol) in 0.50 mL CH_2Cl_2 at -78°C under argon was added 1,2-bis(trimethylsiloxy)ethane (4.10 mL, 17.0 mmol) followed by a solution of 56 (0.078 g, 0.24 mmol) in 1.0 mL CH_2Cl_2. After stirring the mixture for 1 h at -78°C, 16 h at -30°C and 5 h at -25°C, the reaction was quenched by the addition of pyridine (0.04 mL, 0.21 mmol). Saturated sodium bicarbonate and ether were added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:4 EtOAc:hexane) of the crude material afforded the ketal 61 (0.020 g, 22%) together with recovered starting material 56 (0.048 g, 61%). Note that if warming is continued and

the reaction mixture is allowed to stir for 3 h at 0°C, one obtains the ketal **61** in only 4%, together with 60% ketal **60**. ^{1}H NMR(200 MHz, $CDCl_3$): 7.33(s, 5H), 4.72(s, 2H), 4.56(s, 2H), 4.10-4.22(m, 3H), 3.93(s, 4H), 3.79(AB, J=9.4 Hz, 1H), 1.84-2.15(m, 2H), 1.30-1.84(m, 6H), 1.26(t, J=7 Hz, 3H). IR(neat): 2864, 1734, 1654, 1448, 1226, 1132, 1026 cm^{-1}. MS: 382(18, $M+NH_4^+$), 365(9, $M+H^+$), 257(100). Exact mass calcd for $C_{20}H_{28}O_6+H^+$: 365.1964, found: 365.1963. ^{13}C NMR(75.4 MHz, $CDCl_3$): 172.8, 137.9, 128.4, 127.9, 127.8, 127.7, 109.8, 95.0, 69.3, 68.2, 64.8, 64.7, 60.6, 55.4, 33.0, 28.2, 23.1, 20.6, 14.2.

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CHAPTER 4

SYNTHESIS OF ANGULARLY FUNCTIONALIZED DECALIN COMPOUNDS

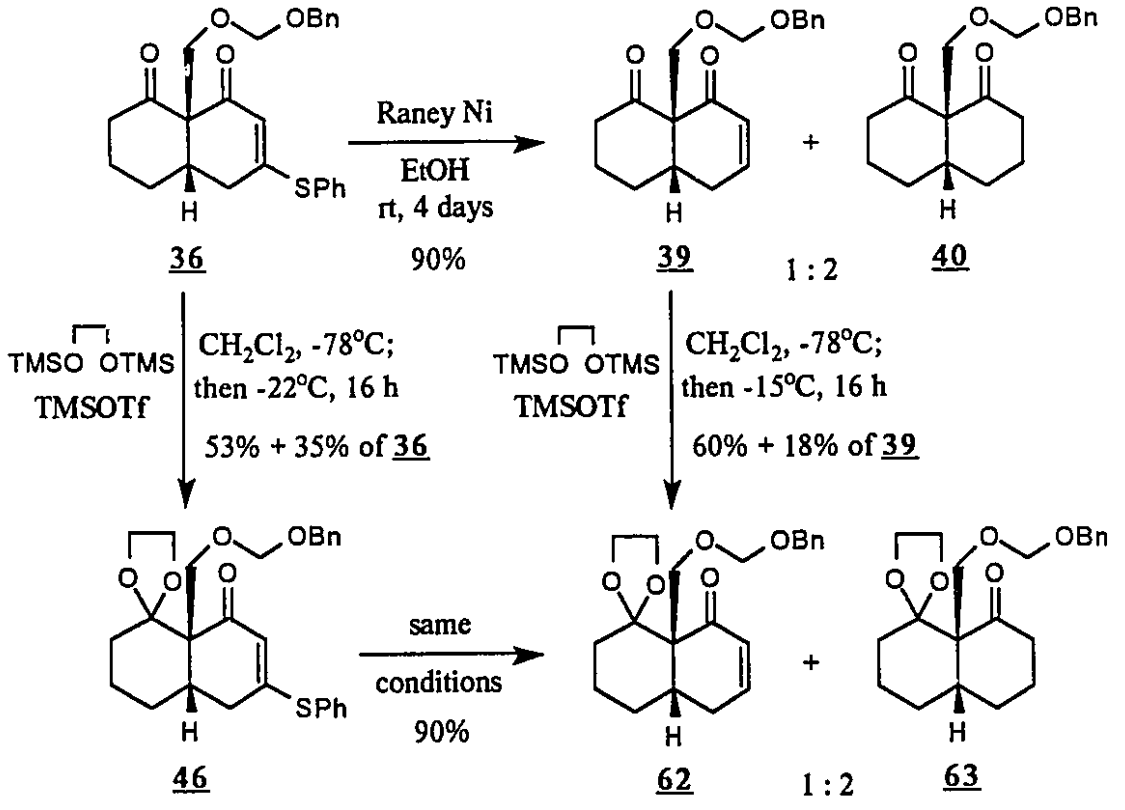
4.1 Introduction

Chapter 3, Section 3.4 detailed the utility of the following chemical transformation (equation 1 in **Scheme 4.1**) in establishing the structure of compound **36**. Treatment of **36** with Raney nickel provided both the desulfurized product **39** and the product resulting from excess reduction **40**. It was found that decreasing the reaction time or the Raney nickel : starting material ratio led to the recovery of as much as 20% starting material once the catalyst was removed. On the other hand as the Raney nickel : starting material ratio is increased, the production of the symmetric diketone is favoured with a ratio of 6.5 giving rise to the formation of almost solely **40** (see **Table 4.1**).

The Raney nickel : starting material (R. Ni : s. m.) Ratio

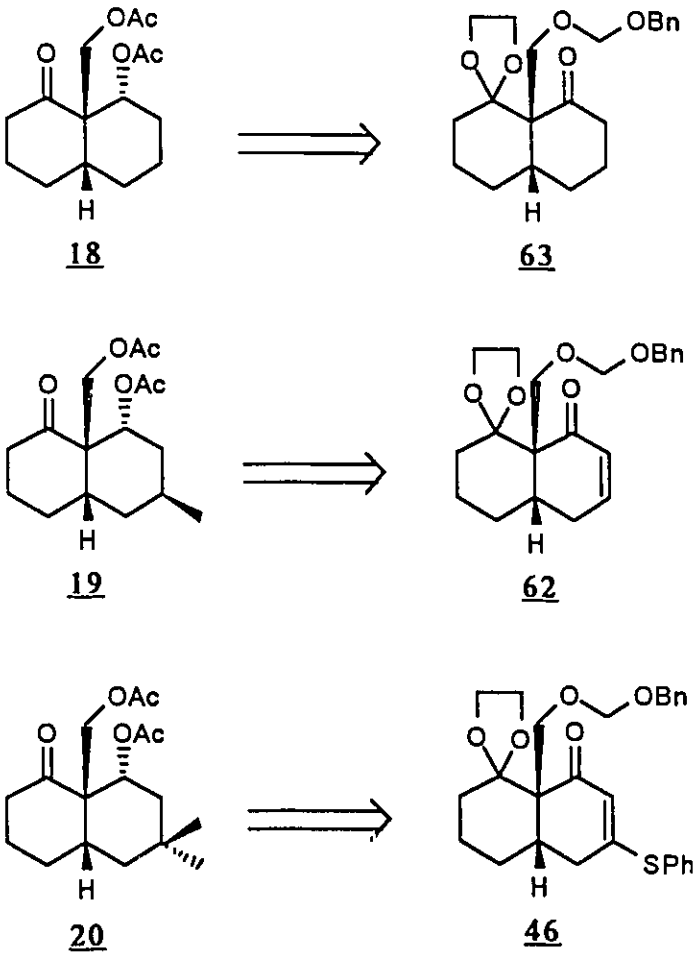
Ratio = $\frac{\text{R. Ni weight}}{\text{s. m. weight}}$	compound **39** (yield)	compound **40** (yield)
5.0	49%	51%
5.5	30%	60%
6.5	10%	90%

Table 4.1



Scheme 4.1

When ketal 46 was treated in a similar fashion, a mixture of enone 62 and 63 was produced in 90% yield, the ratio again varying from 1:1 to 1:25 depending on the Raney nickel : starting material ratio. As mentioned in **Chapter 3, Section 3.6**, ketal 46 can be prepared in 53% yield with 35% recovery of the starting material 36 using a variation of the Noyori[1] reaction conditions. Similarly enone 39 can be protected to provide 62 in 60% yield together with 18% recovered enone 39. This procedure was never actually used to protect the symmetrical diketone 40, as compound 63 was usually prepared by the Raney nickel reduction of ketal 46. The three ketals 46, 62, and 63 can serve as intermediates in the preparation of the target angularly functionalized decalin compounds 18 - 20 as illustrated in **Scheme 4.2.**

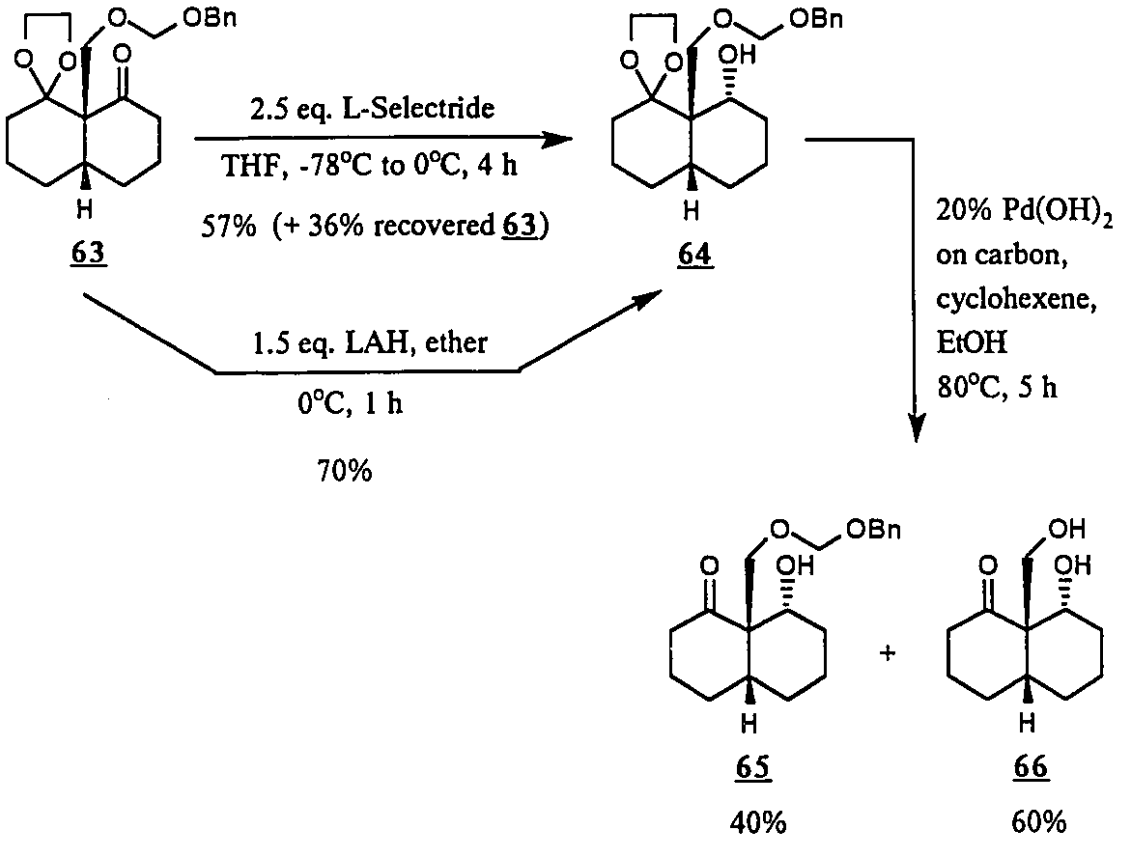


Scheme 4.2

4.2 Preparation of Keto Diacetate (18)

The synthesis of compound 18 began with the reduction of ketone 63 with excess lithium tri-*sec*-butylborohydride (L-Selectride)[2] in THF to provide alcohol 64 in 57% yield together with 36% recovered ketone 63 after stirring for 4 h at 0°C (see **Scheme 4.3**). The same product could be obtained in 70% yield by treatment of the ketone with 1.5 equivalents of lithium aluminum hydride in ether at 0°C for 1 h. No information about the relative stereochemistry of the newly formed secondary alcohol could be obtained from the

^{1}H NMR since the signal of the proton α to this alcohol was buried under the signals for the ethylene protons of the ketal protecting group.

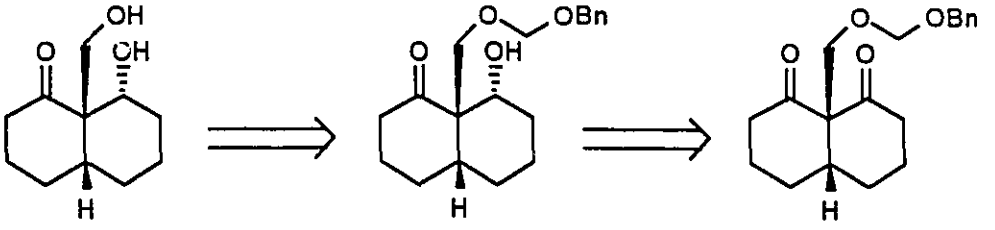


Scheme 4.3

Alcohol 64 was then treated with 10% palladium on carbon in ethanol under a hydrogen atmosphere (1 atm.) in order to remove the benzyloxymethylene protecting group, to liberate the primary alcohol. But after three days at room temperature no reaction had taken place and only starting material was recovered. However, when 20% palladium hydroxide on carbon was employed and the mixture was heated in ethanol at 80°C for 5 h with cyclohexene as a hydrogen source, catalyic hydrogenolysis took place with the simultaneous deprotection of the carbonyl moiety, providing a 2:3 mixture of keto-alcohol

65 and keto-diol 66 in quantitaive yield (see **Scheme 4.3**). The reaction conditions seem to have been slightly acidic, leading to the hydrolysis of the ethylene ketal functionality.

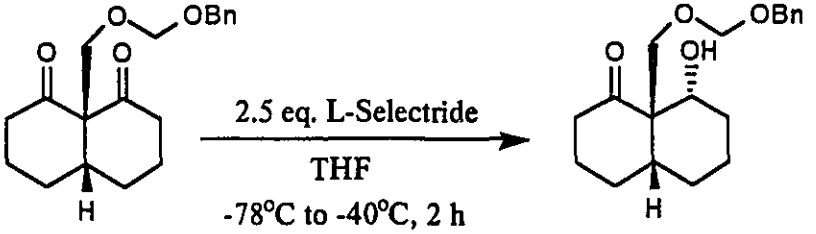
The fact that the catalytic hydrogenolysis of monoalcohol 64 provided a mixture of both the keto-monoalcohol 65 and the keto-diol 66 suggests that the keto-monoalcohol could be resubmitted to the reaction conditions in order to prepare additional keto-diol. This leads to the possibility that the keto-alcohol could be directly prepared from the symmetrical diketone 40, thus shortening the overall sequence by one step (see **Scheme 4.4**). The protection of one of the carbonyl moieties of compound 40 would no longer be required if the mono-reduction (40 to 65) was a success.



66 65 40

Scheme 4.4

Thus compound 40 was treated with L-Selectride[2] to reduce one of the two carbonyl moieties, providing keto-alcohol 65 in 88% yield (see **Scheme 4.5**). With this alcohol in hand, which features the unprotected carbonyl, the relative stereochemistry of the

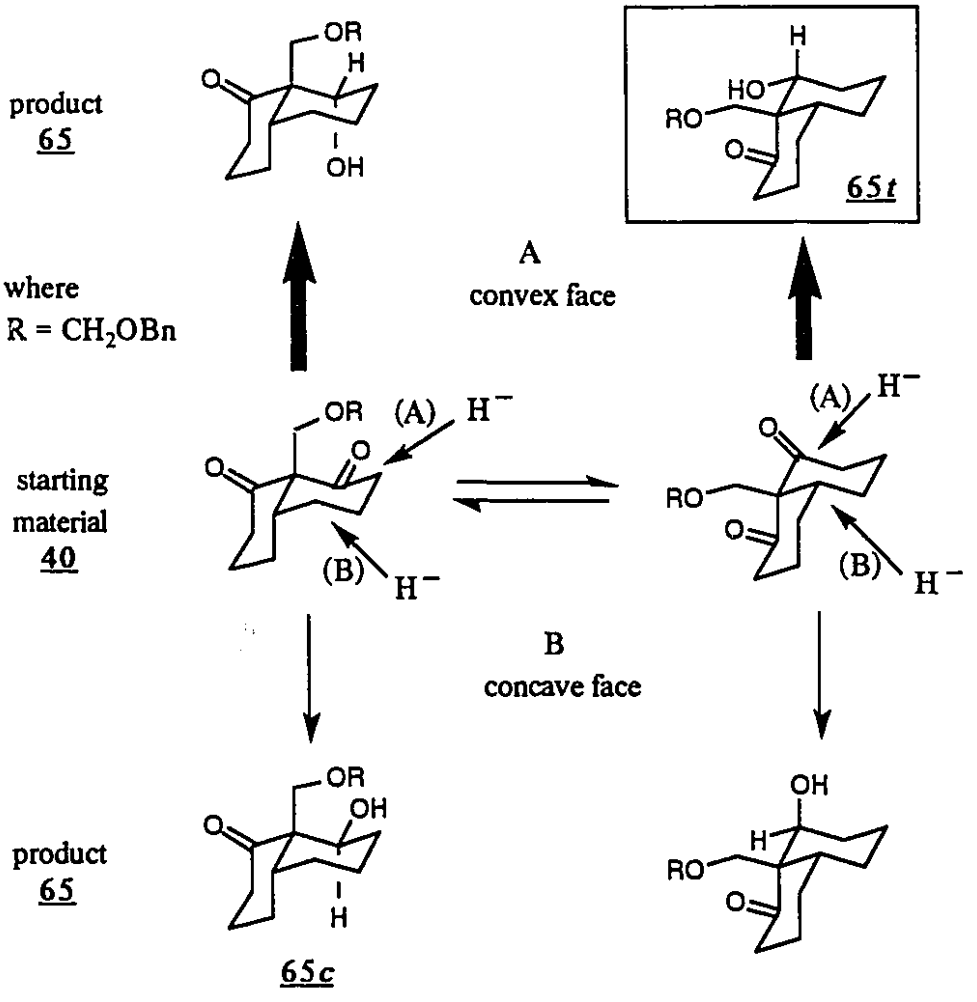


40 65

88%

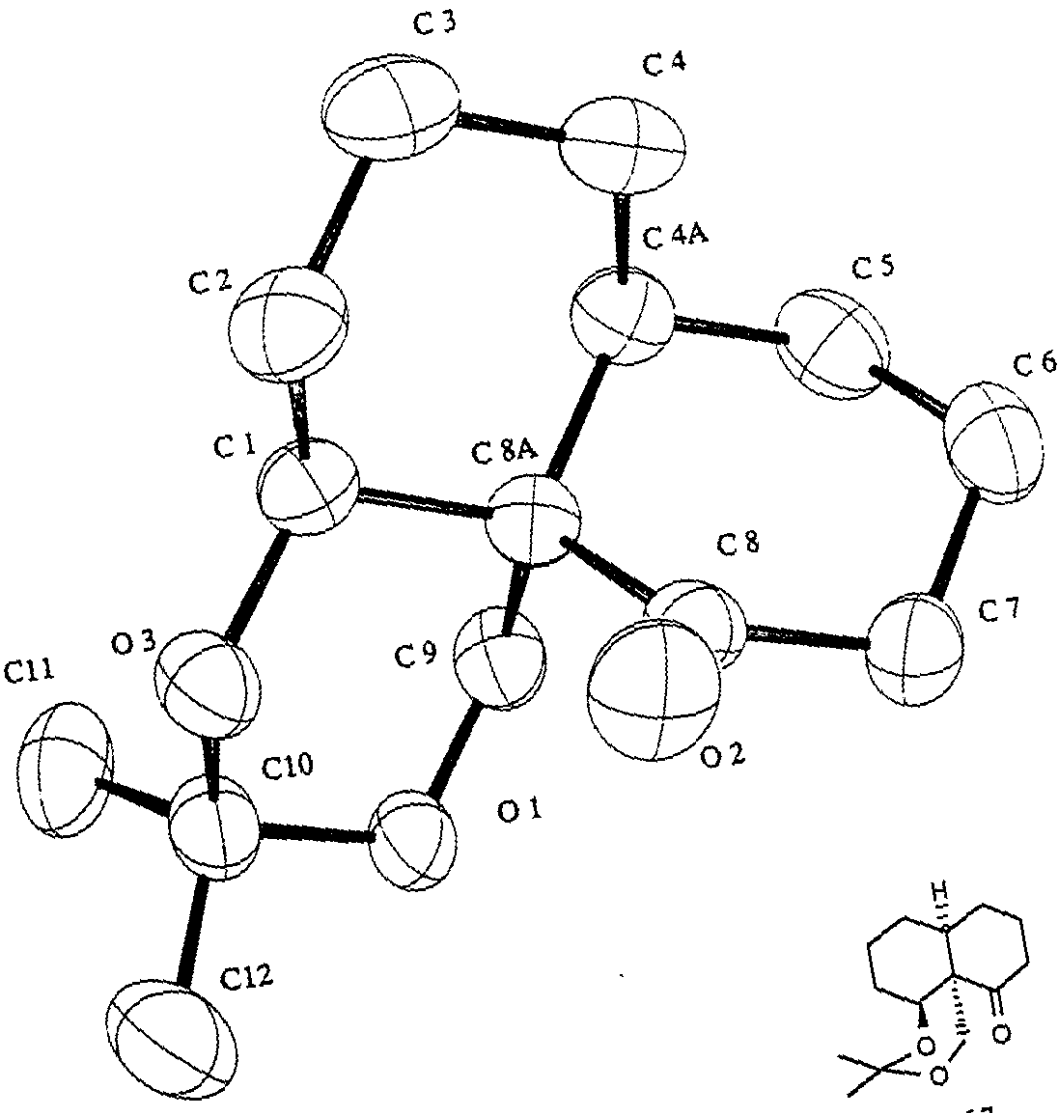
Scheme 4.5

secondary alcohol was now examined. D_2O exchange indicated that the proton α to the secondary alcohol just formed was axial (J = 11.1 Hz and J = 3.7 Hz). Since the substrate is a *cis*-fused decalin, there are two possible chair-chair conformers: one in which the secondary alcohol is *cis* to the protected hydroxymethylene unit (65*c* in **Scheme 4.6**) or one which the two moieties exist in a *trans* relationship (65*t* in **Scheme 4.6**). A sterical-



Scheme 4.6

ly hindered base such as L-Selectride would be expected to approach the *cis*-fused decalin from the convex face, thus leading to the formation of 65*t*, where the secondary alcohol and the protected hydroxymethylene moiety are oriented *trans* to each other. The relative

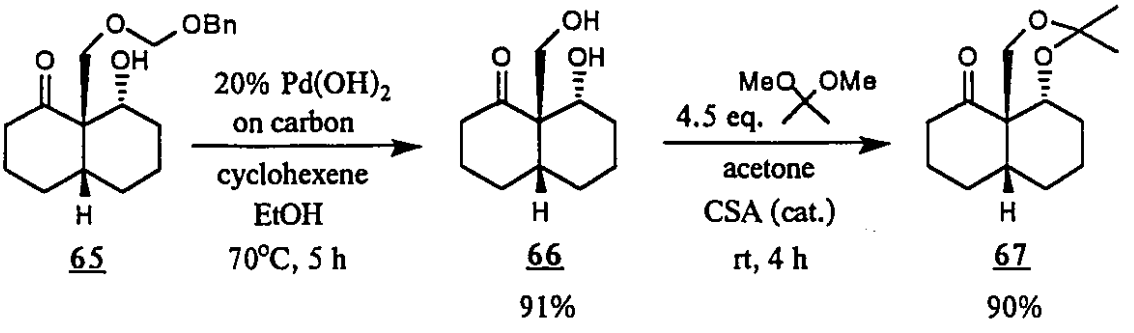


67

Figure 4.1

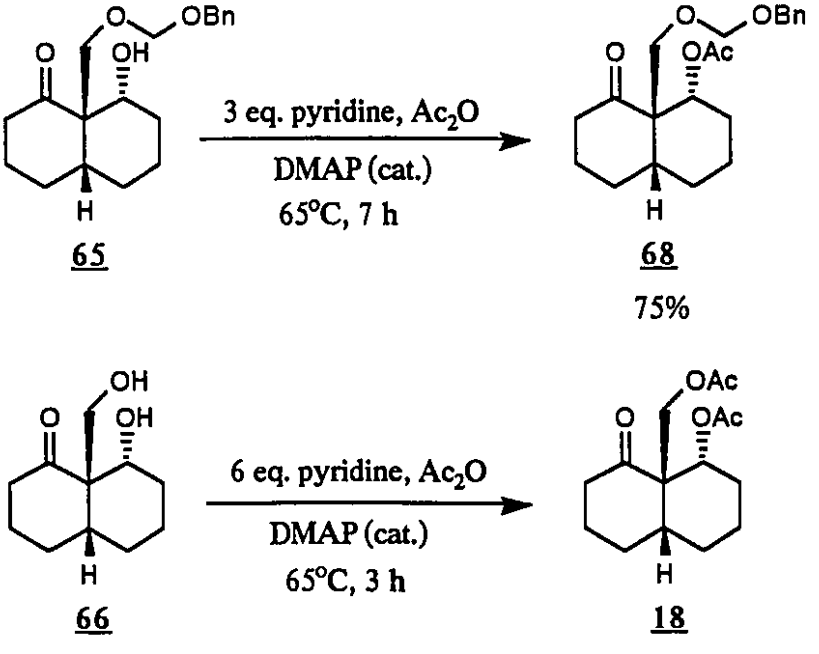
stereochemistry was later established as *trans* through the X-ray structure determination[5] of 67 thus confirming that indeed α alcohol 65 was formed in the L-Selectride reduction. By extention this then established the stereochemistry of the secondary alcohol in compounds 64 and 66 as α as well.

Subsequent catalytic hydrogenolysis[4] of keto-alcohol 65 then provided keto-diol



Scheme 4.7

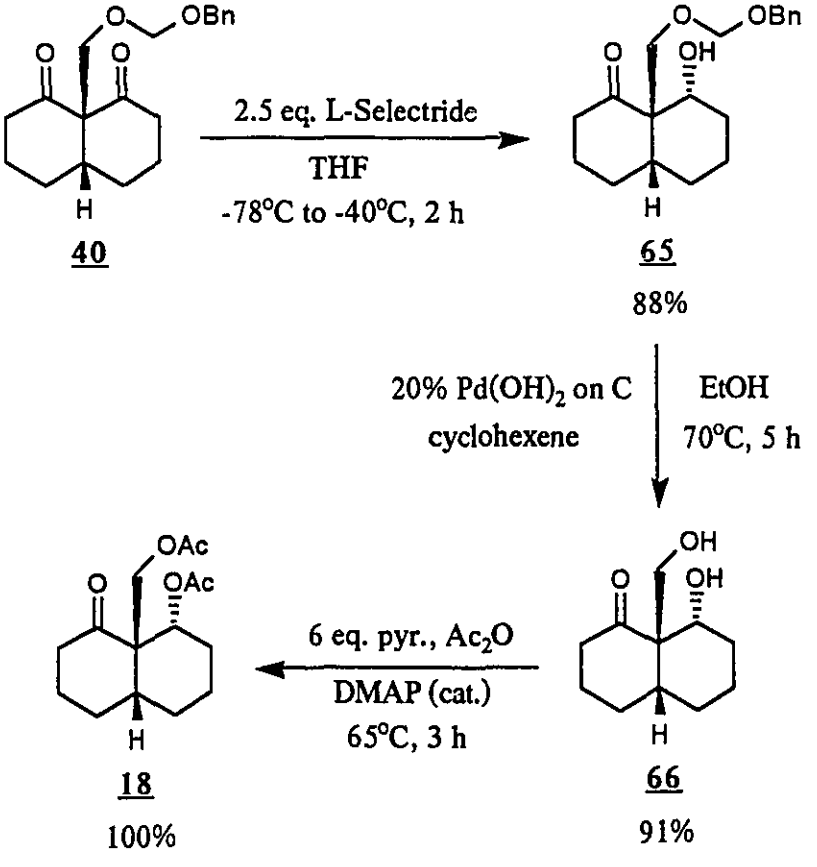
66 in 91% yield. The diol unit was then converted to its isopropylidene derivative by treat-



Scheme 4.8

ment with 2,2'-dimethoxypropane in dry acetone[6] in the presence of 10-camphor sulfonic acid at room temperature to provide the crystalline ketal 67 in 90% yield (see **Scheme 4.7**). X-ray structure determination[5] of this compound (see **Appendix C** for X-ray Structure Report) confirmed that the primary and the secondary alcohols in keto-diol 66 indeed exist in a *trans* relationship (see **Figure 4.1**).

Both keto-diol 66 and the keto alcohol 65 prepared earlier were each in turn treated with pyridine in acetic anhydride[7] in the presence of a catalytic amount of DMAP to provide the corresponding target diacetate 18 in quantitative yield and the monoacetate 68 in 75% yield (see **Scheme 4.8**). Compound 65 featuring the more sterically hindered secondary alcohol required a longer reaction time (7 h) than the diol (3 h) in order to effect acetylation.

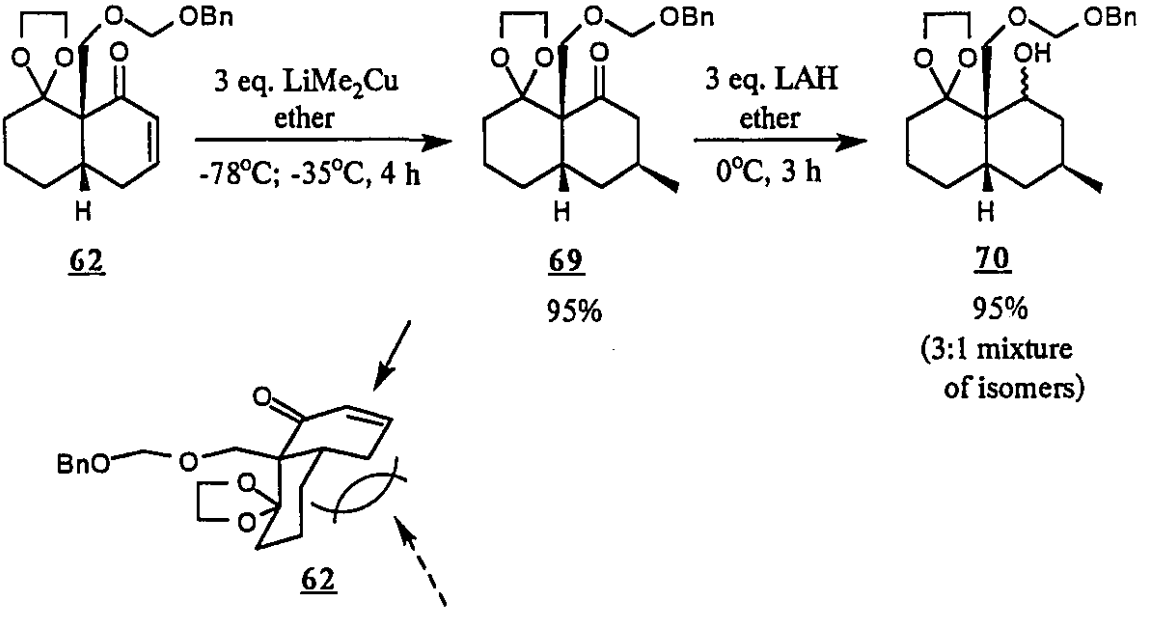


Scheme 4.9

Scheme 4.9 illustrates the final sequence for the preparation of angularly functionalized decalin 18.

4.3 Preparation of Monomethyl Keto Diacetate (19)

The monomethyl keto diacetate 19 was prepared starting from intermediate 62. The conjugate addition of an excess of lithium dimethylcuprate to enone 62 gave after 4 h at -35°C, the β-alkylated ketone 69 as a single isomer in 95% yield after purification (see **Scheme 4.10**). The approach of the lithium dimethyl cuprate reagent from the α face would have been sterically hindered due to the concave nature of the *cis*-fused decalin. The ketone was then treated with L-Selectride[2] in an attempt to prepare the corresponding alco-



62 69 70

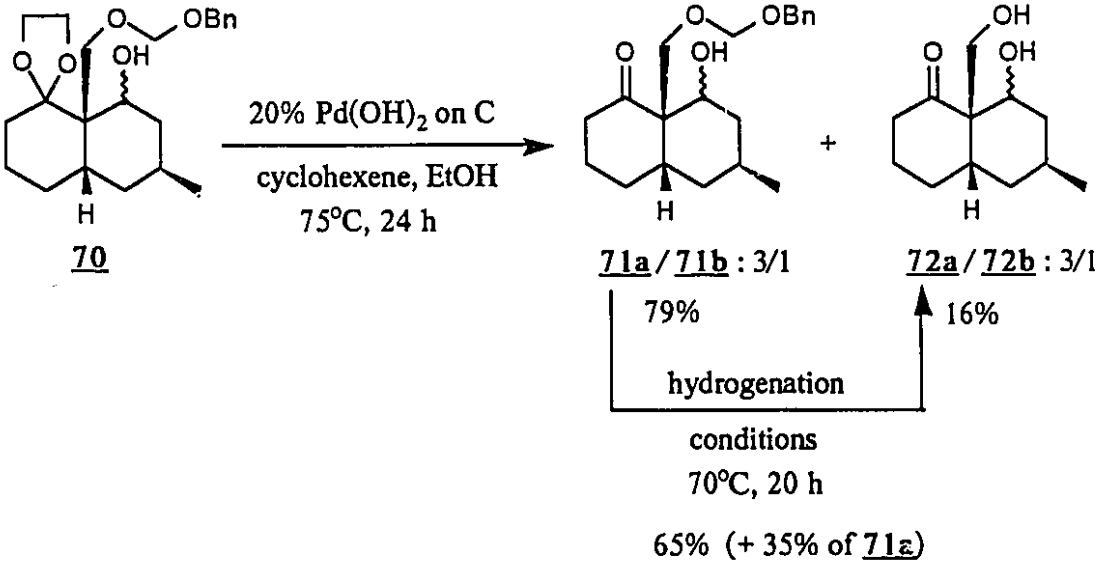
95% 95% (3:1 mixture of isomers)

62

Scheme 4.10

hol. However, only starting material was recovered even after allowing the reaction mixture to stir at 0°C for 8 h. Presumably the ketone is too sterically crowded by the presence of both the protected hydroxymethylene moiety and the β methyl group, thus hindering the approach of the bulky reducing agent. On the other hand, the crude ketone 69 could be directly treated with lithium aluminum hydride in ether at 0°C for 3 hours to provide the alcohol 70 in 89% overall yield for the two steps after purification. The alcohol is a 3:1 mixture of isomers.

Catalytic hydrogenolysis[4] of the alcohol mixture 70 once again effected simultaneous deprotection of the carbonyl moiety to afford after 24 h at 75°C, a mixture of four compounds: the keto alcohols 71a and 71b in a 3:1 ratio in 79% combined yield and the keto diols 72a and 72b in a 3:1 ratio in 16% yield (see **Scheme 4.11**). If the reaction was left for 48 h at 75°C, 54% of 71a and 71b were formed together with 34% of 72a and 72b. When the major keto alcohol isomer 71a was resubjected to the hydrogenolysis



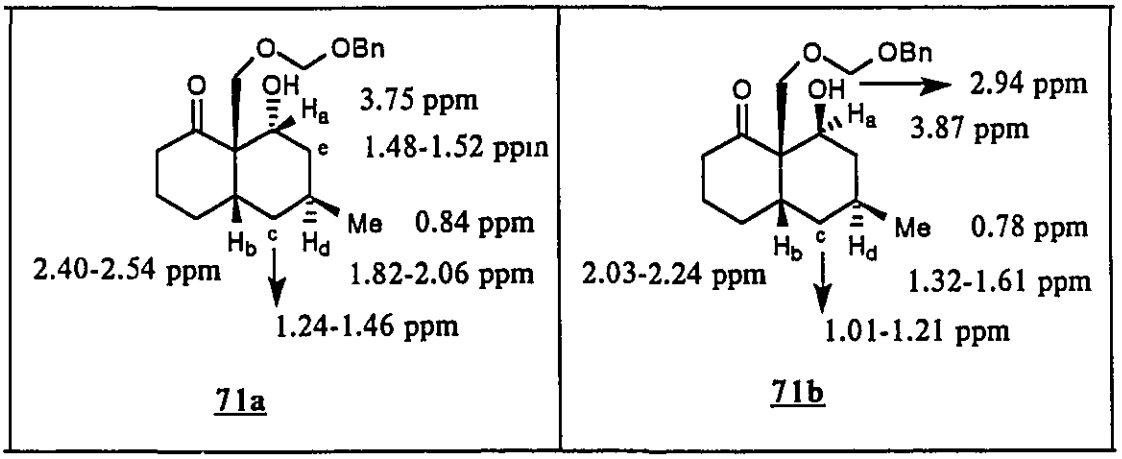
70

Scheme 4.11

conditions, keto diol 72a was formed in 65% together with 35% recovered 71a. The keto alcohols 71a and 71b were also obtained in a 3:1 ratio in 80% combined yield when the

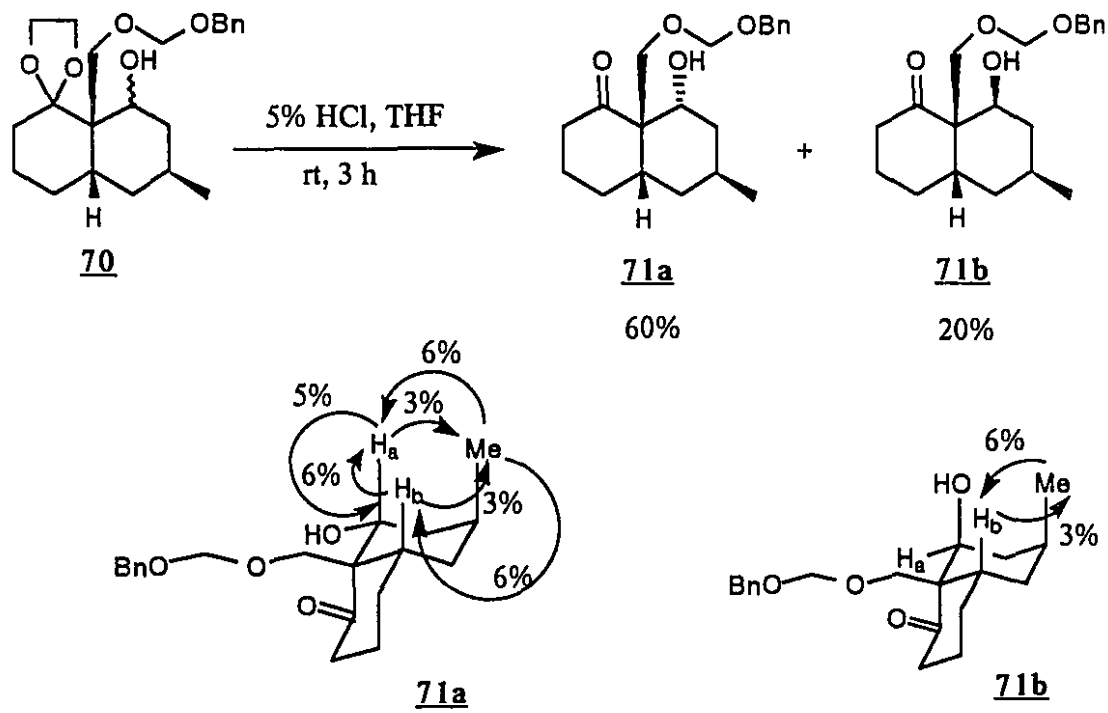
alcohol mixture 70 was subjected to mildly acidic treatment (5% HCl) for 3 h at room temperature (see **Scheme 4.12**).

The keto alcohols 71a and 71b proved to be suitable candidates for NOE experiments which would serve to establish the stereochemistry of the secondary alcohol. Now, the ^1H NMR spectrum of the major isomer 71a in $CDCl_3$ solvent is rather complex with most of the proton signals appearing together in selected narrow regions of the spectrum. However, when the $CDCl_3$ solvent was replaced by C_6D_6, the ^1H NMR spectrum of the same compound was simplified, allowing the individual proton signals to be more easily distinguished. For example, the multiplet representing H_a α to the secondary alcohol was no longer hidden under the AB pattern of the benzyloxymethoxy*methylene* protons; it was now clearly visible, centered at 3.75 ppm. A COSY NMR showed that the signal for H_a at



3.75 ppm was coupled to the methylene -CH_{2e}- protons, represented by a multiplet at 1.48-1.52 ppm. These methylene protons were in turn coupled to the multiplet at 1.82-2.06 ppm, representing H_d. Proton H_d was also coupled to the methyl group, represented by a doublet at 0.84 ppm. In addition, proton H_d also coupled with the methylene -CH_{2c}- protons, represented by a multiplet at 1.24-1.46. The methylene -CH_{2c}- protons permitted us to locate the ring junction proton H_b, at 2.40-2.54 ppm. Having confirmed the chemical

shifts of protons H_a, H_b and the methyl group, an NOE experiment was carried out, which confirmed the structure of 71a to be as shown in **Scheme 4.12.** The signal of H_a was enhanced both by irradiating the signal of the methyl group (6% enhancement) and by irradiating the signal of H_b (6% enhancement). The irradiation of H_a in turn effected a 5% enhancement of the signal of H_b. Irradiation of the H_a signal only effected a 3% enhancement of the methyl signal. The signal of H_b was enhanced by 6% when the methyl group signal was irradiated. Irradiation of the H_b signal in turn effected only a 3% enhancement of the methyl group signal. Thus, similarly to the NOE experiments carried out on the siloxy diene 12 (see **Chapter 2, Section 2.4**), the irradiation of protons H_a and H_b each provided only a 3% enhancement of the methyl signal (an enhancement of less than 5% is



Scheme 4.12

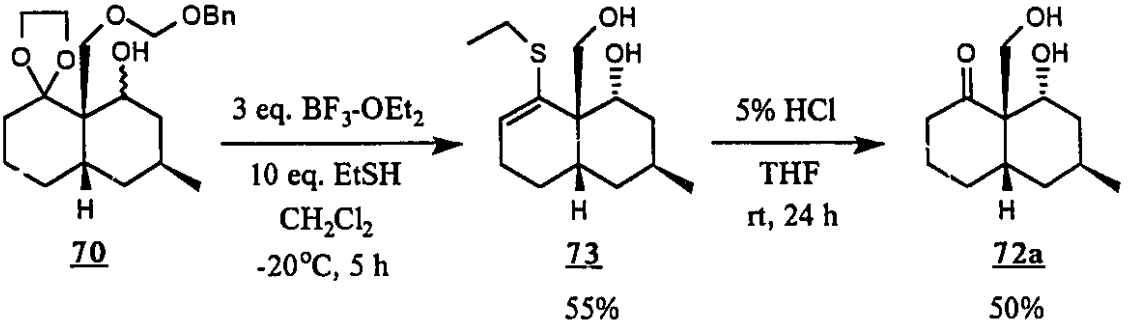
usually not considered significant), whereas irradiation of the methyl signal was able to effect a definite 6% enhancement of each of the two proton signals. As stated already in **Section 2.4**, this suggests that it is difficult for the irradiation of a single proton signal to

cause a significant enhancement of a methyl (or as in **Section 2.4**: a methoxy) group signal. Nevertheless, the mutual enhancement of the signals of protons H_a and H_b suggests that these protons are both axial, thus indicating that the secondary alcohol and the benzyloxymethoxymethylene moiety exist in a *trans* relationship in the major keto alcohol isomer **71a**. The β orientation of the methyl group, already alluded to in **Scheme 4.10**, is further confirmed by the fact that irradiation of this signal enhances the signals of both the H_a and H_b protons.

Similarly for the minor isomer of the keto alcohol **71b**, the ^1H NMR spectrum of the compound in C_6D_6 solvent proved to be less complex than the ^1H NMR spectrum of the same compound in $CDCl_3$. A COSY NMR then showed that the signal for proton H_a, α to the secondary alcohol, at 3.87 ppm, was coupled to the doublet at 2.94 ppm, representing the alcohol proton. The signal for the methyl group at 0.78 ppm was coupled to the multiplet at 1.32-1.61 ppm, representing proton H_d. Proton H_d in turn was coupled to the methylene protons $-CH_{2c}-$, which in turn permitted us to locate the chemical shift of the ring junction proton H_b at 2.03-2.24 ppm. Having confirmed the chemical shifts of protons H_a, H_b and the methyl group, an NOE experiment was carried out to establish the stereochemistry of compound **71b**. In this case there was no mutual enhancement of protons H_a and H_b or of proton H_a and the methyl group. Irradiation of the methyl group signal did effect a 6% enhancement of the signal of proton H_b. Irradiation of the proton H_b signal effected only a 3% enhancement of the methyl group signal. It was thus concluded that the structure of keto alcohol isomer **71b** is as shown in **Scheme 4.12** and that in this case the secondary alcohol and the benzyloxymethylene functionality exist in a *cis* relationship.

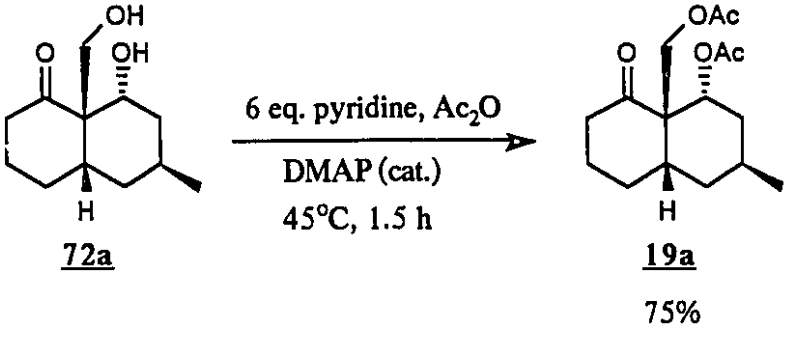
Following the report that Nicolaou *et al.*[8,9] had deprotected a hydroxymethylene functionality, protected as its benzyloxymethyl ether, with boron-trifluoride etherate and ethanethiol in dichloromethane at -20°C, this same procedure was applied to the alcohol mixture **70** (see **Scheme 4.13**) as an alternative to catalytic hydrogenolysis. However,

not surprisingly under the acidic conditions, the vinyl sulfide diol 73 was formed after only 5 h. These same reaction conditions have been used to form dithio acetals and ketals.[10] The other isomer of vinyl sulfide diol 73 was not detected, perhaps because the yield of the reaction was rather moderate. The vinyl sulfide could nevertheless be smoothly transformed into the desired keto diol 72a under aqueous mildly acidic (5% HCl) conditions.



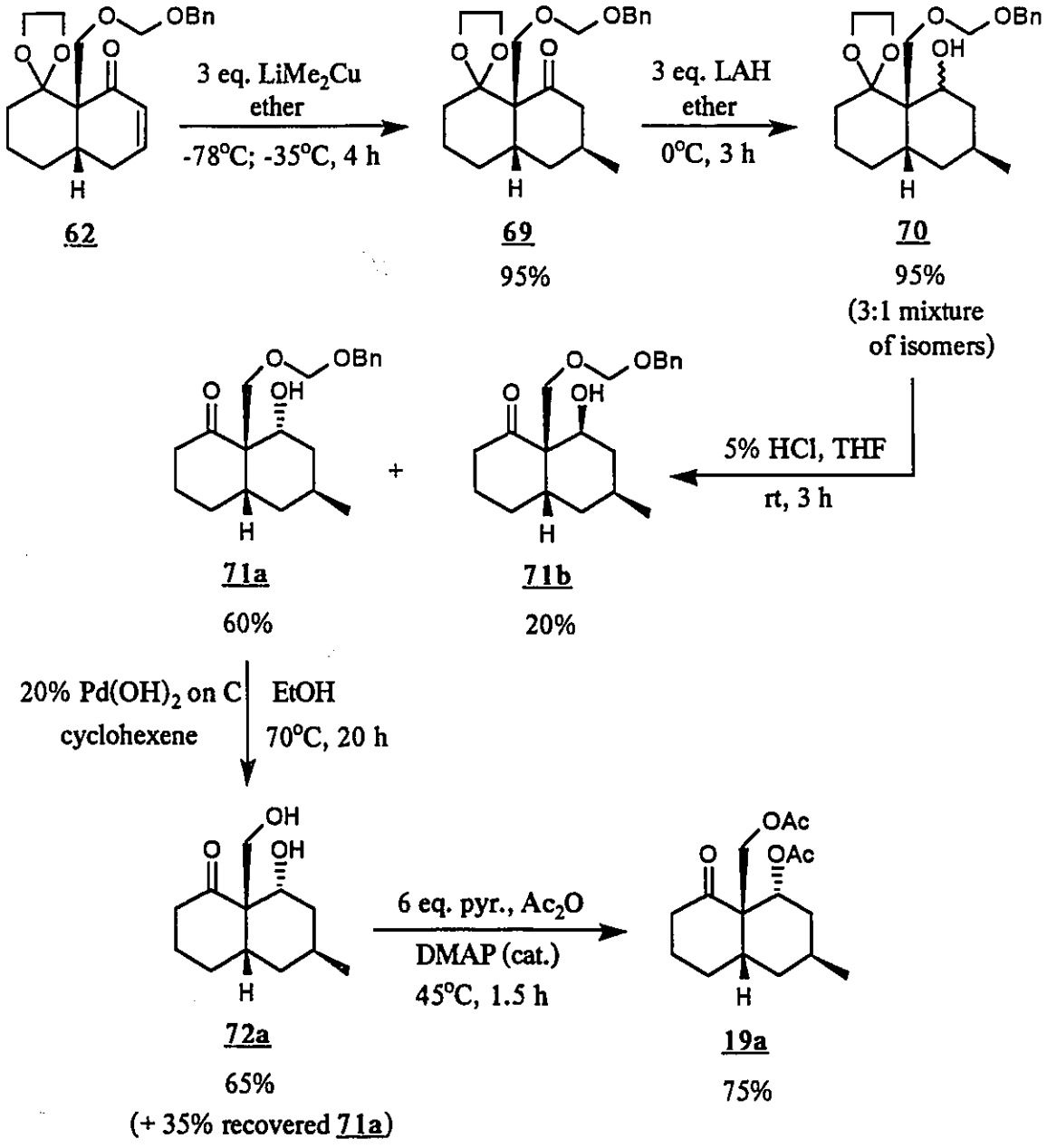
Scheme 4.13

The keto diol major isomer 72a was then treated with pyridine in acetic anhydride[7] in the presence of a catalytic amount of dimethylaminopyridine to afford the monomethyl keto diacetate 19.(see **Scheme 4.14**).



Scheme 4.14

Scheme 4.15 illustrates the final sequence for the preparation of keto diacetate 19.

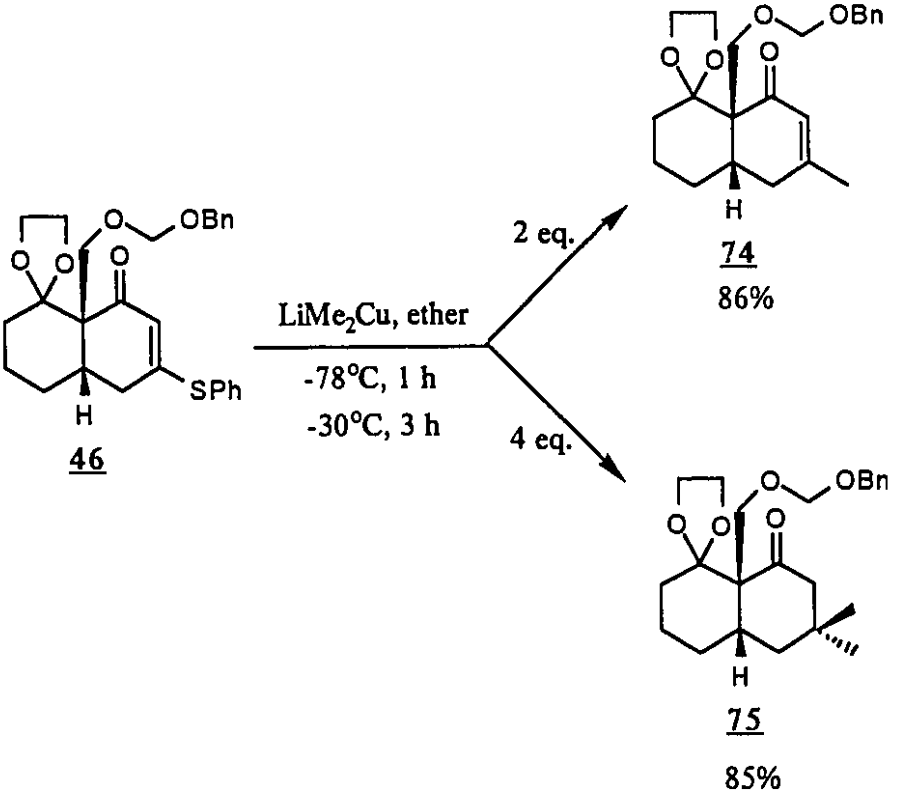

OBn
3 eq. LiMe2Cu
ether
-78°C; -35°C, 4 h
3 eq. LAH
ether
0°C, 3 h
OH
62
69
95%
70
95%
(3:1 mixture
of isomers)
5% HCl, THF
rt, 3 h
71a
60%
71b
20%
20% Pd(OH)2 on C
cyclohexene
EtOH
70°C, 20 h
6 eq. pyr., Ac2O
DMAP (cat.)
45°C, 1.5 h
OAc
72a
65%
(+ 35% recovered 71a)
19a
75%

Scheme 4.15

4.4 Preparation of Dimethyl Keto Diacetate (20)

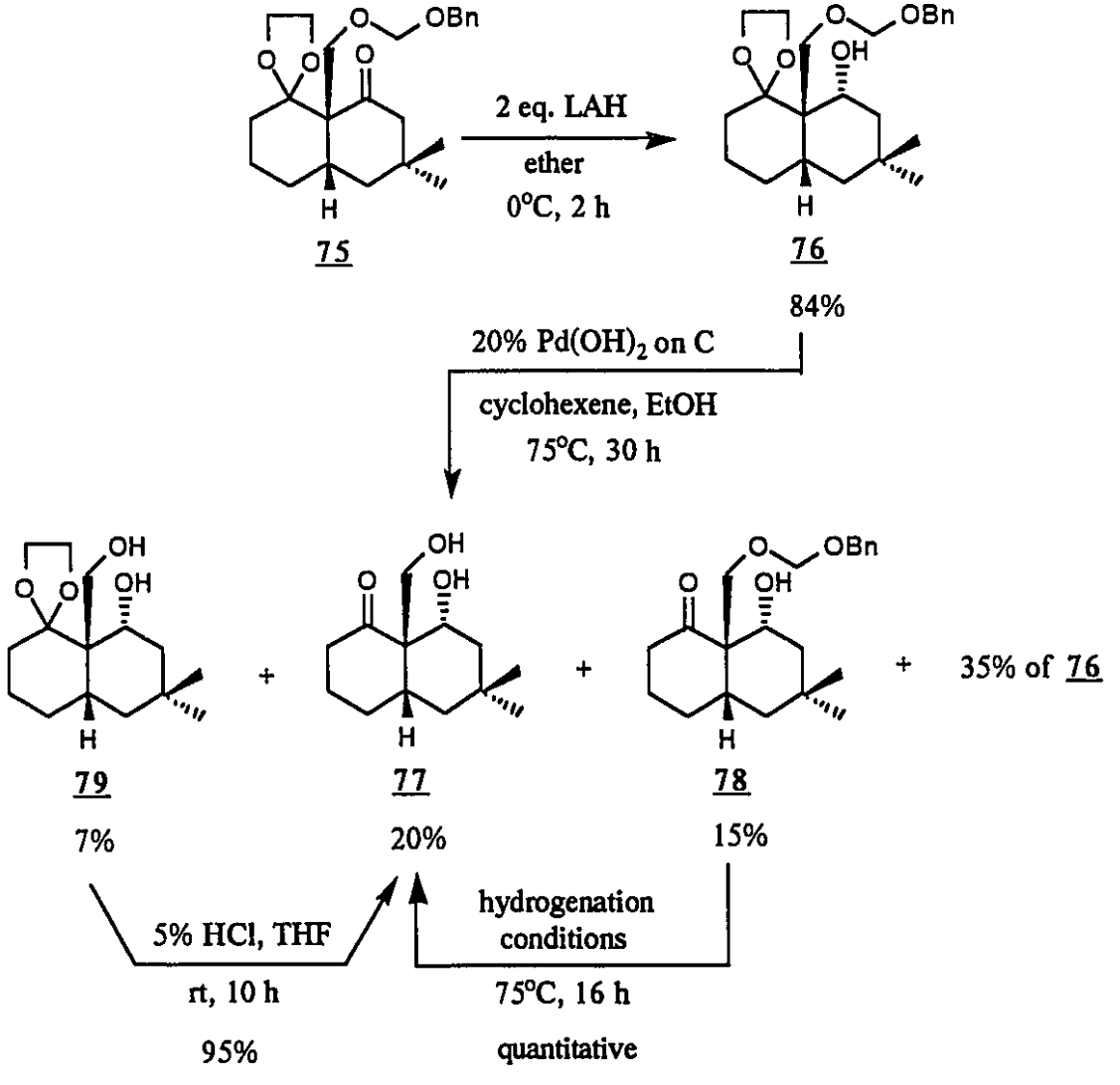
The ketal 46 served a precursor to the *gem*-dimethyl compound 20. When the ketal was treated with 2 equivalents of lithium dimethylcuprate the β-alkylated enone 74 was produced in 86% yield after stirring for 3 h at -30°C. When a larger excess of lithium dimethylcuprate was employed, the desired β,β-dialkylated ketone 75 was formed in 85% yield after purification (see **Scheme 4.16**). The crude product could be directly treated with lithium aluminum hydride to provide alcohol 76 in 78% overall yield for the two steps after purification (see **Scheme 4.17**).

The alcohol was then subjected to the catalytic hydrogenolysis conditions[4] which produced a mixture of three products together with 35% recovered starting material (see **Scheme 4.17**). The desired keto diol 77 was formed in 20% yield along with 15% keto



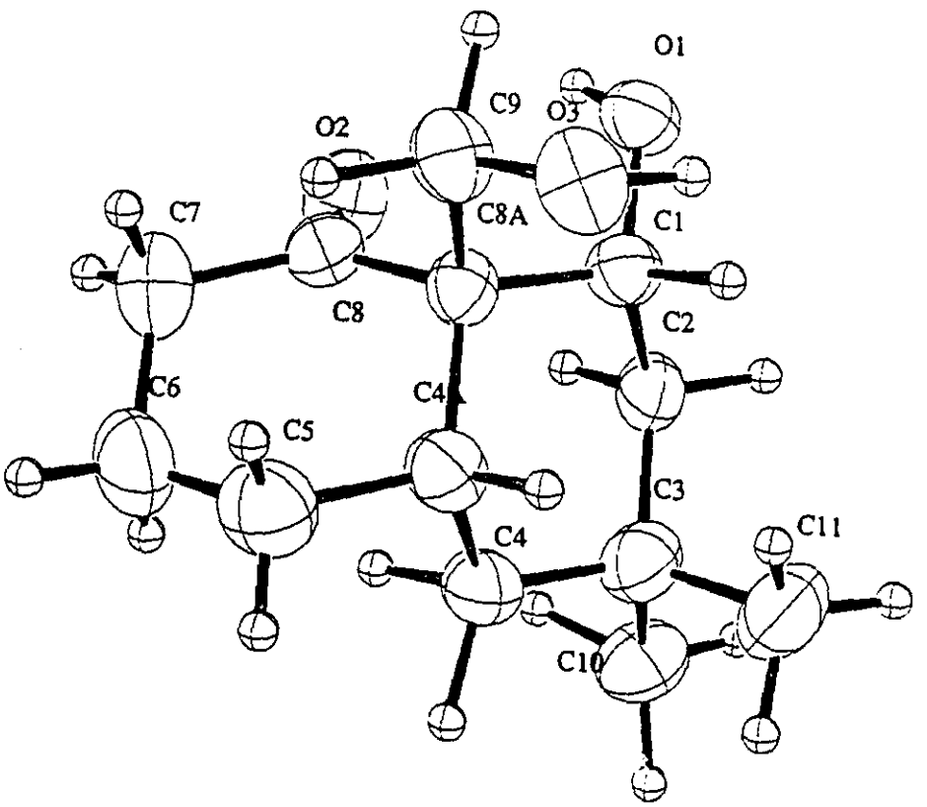
Scheme 4.16

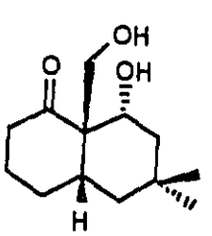
alcohol 78 and 7% of the diol 79 with the protected carbonyl. Compound 79 could be deprotected under mildly acidic conditions (5% HCl)[11] to provide 95% of the desired keto diol 77. Keto alcohol 78 could be resubjected to the reaction conditions to provide the keto



Scheme 4.17

diol 77 in quantitative yield. The stereochemistry of keto diol 77 was confirmed by an X-ray structure determination (see **Figure 4.2** and the X-ray Structure Report in **Appendix D**).[12]

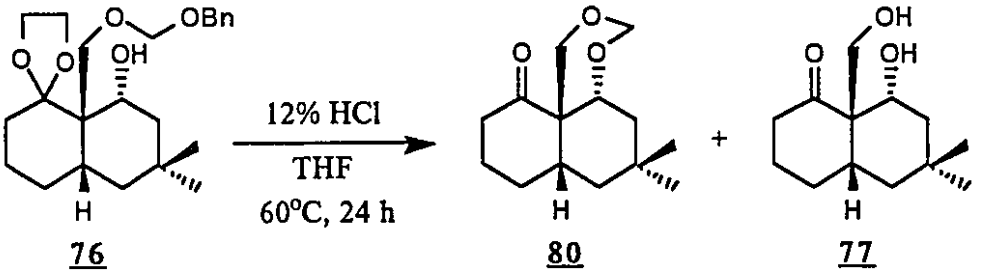




77

Figure 4.2

An attempt to improve the deprotection of the hydroxymethylene moiety by treating alcohol 76 directly with 12% HCl provided a mixture of the desired keto diol 77 and a tri-

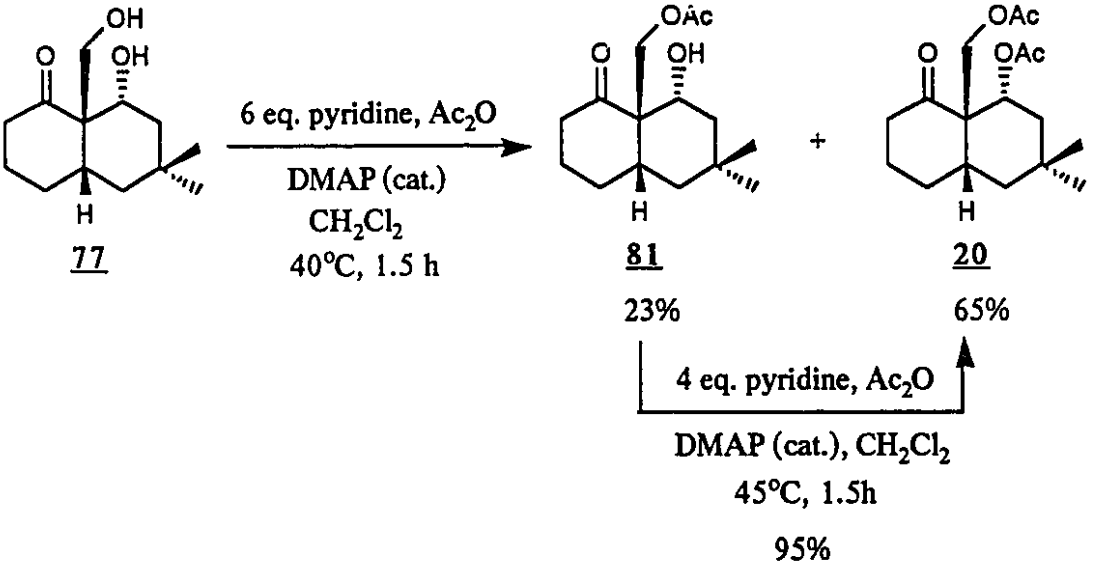


76 → 80 (32%) + 77 (51%)

Scheme 4.18

cyclic compound 80 (see **Scheme 4.18**). Thus, under these reaction conditions, the secondary alcohol in compound 76 competes with water in reacting intramolecularly with the benzyloxymethylene moiety to liberate benzyl alcohol, giving the observed tricyclic compound 80.

Keto diol 77 was then treated with pyridine in 2:1 acetic anhydride[7] : dichloromethane (since 77 would not dissolve in acetic anhydride alone) to provide after 1.5 h at 40°C



77 → 81 (23%) + 20 (65%)

Scheme 4.19

a mixture of the mono acetate 81 and the desired diacetate 20 (see **Scheme 4.19**). When the mono acetate 81 was resubjected to the reaction conditions at 45°C for 1.5 h it was smoothly transformed into the diacetate 20 in 95% yield. This completes the preparation of the dimethyl keto diacetate 20.

Experimental

General Methods: See **Chapter 2, Experimental.** Selected NMR spectra were taken in C_6D_6 as the solvent and internal standard and the data are reported relative to the C_6H_6 reference line.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-4a,5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione (62) and Ethylene ketal of *cis*-8a-[[(Benzyloxy)-methoxy]methyl]-3,4,4a,5,6,8a-hexahydronaphthalene-1,8-(2H,7H)-dione (63)

To a solution of the ethylene ketal 46 (0.224 g, 0.48 mmol) in 17 mL absolute ethanol at room temperature under argon was added Raney nickel (1.421 g). The mixture was stirred for 4 days at room temperature at which time the catalyst was removed by filtration and the solvent removed to provide 0.198 g crude material. Column chromatography (1:4 EtOAc:hexane) provided 62 (0.100 g, 58%) and 63 (0.065 g, 37%).

62: ^{1}H NMR(200 MHz, $CDCl_3$): 7.28-7.35(m, 5H), 6.92-7.06(m, 1H), 6.06(d, J=10 Hz, 1H), 4.73 and 4.70(AB, J=6 Hz, 2H), 4.55(s, 2H), 4.39(AB, J=10 Hz, 1H), 3.65-3.89(m, 5H), 2.78-2.98(m, 2H), 2.05-2.30(m, 1H), 1.39-1.99(m, 6H). IR($CHCl_3$ solution): 3012, 2949, 1662, 1217, 1078 cm^{-1}. MS: 359(25, M+H$^+$), 329(19), 251(93), 189(100). Exact mass calcd for $C_{21}H_{26}O_5$+H$^+$: 359.1857, found: 359.1858. ^{13}C NMR(75.4 MHz, $CDCl_3$): 200.3, 150.3, 138.0, 130.6, 128.4, 127.9, 127.6, 110.8, 95.2, 69.5, 67.1, 65.1, 64.6, 56.5, 33.7, 32.7, 29.2, 25.5, 18.8.

63: ^{1}H NMR(200 MHz, $CDCl_3$): 7.27-7.45(m, 5H), 4.75 and 4.70(AB, J=6 Hz, 2H), 4.57(s, 2H), 4.34(AB, J=9.5 Hz, 1H), 3.65-3.90(m, 5H), 1.39-2.59(m, 13H). IR($CHCl_3$ solution): 2958, 1734, 1699, 1457, 1232, 1077 cm^{-1}. MS: 361(10, M+H$^+$), 331(24), 329(13), 254(17), 253(100), 223(10). Exact mass calcd for $C_{21}H_{28}O_5$+H$^+$: 361.20167, found: 361.20150. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.5, 138.0, 128.5,

128.3, 127.8, 127.6, 110.1, 95.2, 69.5, 67.1, 66.2, 64.1, 59.6, 42.1, 37.0, 32.8, 26.9, 26.8, 23.8, 19.2.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-4a,5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione (62)

To a solution of trimethylsilyltriflate (0.01 mL, 0.052 mmol) in 0.10 mL CH_2Cl_2 at -78°C under argon was added 1,2-bis(trimethylsiloxy)ethane (1.70 mL, 6.93 mmol), followed by the starting material 39 (0.075 g, 0.24 mmol) in 0.40 mL CH_2Cl_2. The reaction mixture was then slowly warmed to -45°C and stirred at this temperature for 20 h. The mixture was then further warmed to -15°C and stirred for an additional 20 h. The reaction was then quenched by the addition of pyridine (0.02 mL, 0.25 mmol) at -15°C, and poured into saturated sodium bicarbonate. The aqueous layer was extracted with ether (3 x 10 mL) and the combined extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.090 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 62 (0.050 g, 60%) as a clear oil. For spectral data: see the preceding experiment.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-1α-hydroxy-1,3,4,4a,5,6,8a-septahydronaphthalene-8(2H,7H)-one (64)

To a solution of protected mono-ketone 63 (0.081 g, 0.22 mmol) in 7.0 mL THF at -78°C under argon was added 1M L-Selectride (0.90 mL, 0.90 mmol). After stirring for 1 h at -78°C, the mixture was warmed to 0°C for 4 h and then to room temperature for 2 h. The mixture was then diluted with ether (10 mL) and quenched with saturated ammonuim chloride solution (10 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.161 g crude material. Column chromatography (1:4 EtOAc:hexane) afforded the protected mono-alcohol 64 (0.046 g, 57%), along with some starting material

63 (0.029 g, 36%). ^{1}H NMR(200 MHz, $CDCl_3$): 7.26-7.38(m, 5H), 4.81(s, 2H), 4.62(s, 2H), 3.79-4.13(m, 8H), 1.14-2.20(m, 13H). IR($CHCl_3$ solution): 3564, 3010, 2938, 1453, 1229, 1170, 1039, 909 cm^{-1}. MS: 363(11, $M+H^+$), 333(10), 301(16), 289(6), 271(34), 256(15), 255(100), 241(23), 225(62), 211(36), 209(46), 207(14), 195(13), 193(26), 165(13), 147(15). ^{13}C NMR(75.4 MHz, $CDCl_3$): 137.9, 128.4, 128.0, 127.7, 114.3, 95.1, 76.6, 73.4, 69.5, 67.9, 63.4, 62.3, 47.1, 36.5, 31.5, 27.2, 26.7, 23.6, 18.7.

cis-8a-[[(Benzyloxy)methoxy]methyl]-1α-hydroxy-1,3,4,4a,5,6,8a-septahydronaphthalene-8(2H,7H)-one (65)

To a solution of the starting material 40 (0.222 g, 0.701 mmol) in 11.5 mL THF at -78°C under argon was added 1M L-Selectride (1.75 mL, 1.75 mmol). The solution was stirred for 1 h at -78°C, followed by 2 h at -40°C. The reaction mixture was then diluted with 10 mL ether and quenched with 10 mL saturated ammonium chloride solution at -40°C. The organic layer was separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.425 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the ketoalcohol 65 (0.197 g, 88%) as a clear oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.31-7.44(m, 5H), 4.79(s, 2H), 4.62(s, 2H), 3.98(s, 2H), 3.49-3.51(m, 2H), 1.25-2.50(m, 13H). D_2O exchange clarifies the multiplet at 3.49-3.51 to: 3.51(dd, J=11.8 Hz and J=4.4 Hz, 1H). IR($CHCl_3$ solution): 3500, 2939, 1694, 1453, 1288, 1028, 748, 697 cm^{-1}. MS: 319(37, M^+), 289(8), 212(18), 211(100). Exact mass calcd for $C_{19}H_{26}O_4$ (M^+): 319.1910, found: 319.1909. ^{13}C NMR(75.4 MHz, $CDCl_3$): 217.0, 137.7, 128.4, 128.0, 127.8, 95.0, 72.8, 69.7, 67.3, 58.3, 40.1, 39.2, 31.9, 28.3, 25.4, 23.8, 21.5.

cis-8a-(Hydroxymethyl)-1α-hydroxy-1,3,4,4a,5,6,8a-septahydronaphthalene-8(2H,7H)-one (66)

To a solution of the keto alcohol 65 (0.148 g, 0.46 mmol) in 6.5 mL absolute ethanol was added 20% palladium hydroxide on carbon (0.282 g), followed by cyclohexene (6.60 mL, 65.7 mmol). The mixture was heated to 70°C and stirred for 5 h. The catalyst was then removed by filtration and the solvent removed. Column chromatography (1:1 EtOAc:hexane) provided the keto-diol product 66 (0.085 g, 91%).

Note that when the ethylene ketal of 65 (ie. compound 63) is subjected to the same reaction conditions, but with four times less 20% palladium hydroxide on carbon present in the reaction mixture, then after 5 hours at 80°C, keto diol 66 is produced in 60% together with 40% keto alcohol 65.

^{1}H NMR(200 MHz, $CDCl_3$): depending on the concentration of the sample in $CDCl_3$, the spectrum is either: 4.43(t, J=11.5 Hz, 1H), 3.87(t, J=9.8 Hz, 2H), 3.80(d, J=10 Hz, 1H), 3.47(dt, J=4.4 Hz and J=11.5 Hz, 1H), 2.54-2.79(m, 1H), 1.16-2.38(m, 12H) or ^{1}H NMR(200 MHz, $CDCl_3$): 4.39(d, J=11 Hz, 1H), 3.85(d, J=11.5 Hz, 3H), 3.42(dd, J=11 Hz and J=2 Hz, 1H), 2.54-2.79(m, 1H), 1.16-2.38(m, 12H). D_2O exchange: 4.38(d, J=11.5 Hz, 1H), 3.77-3.97(m, 1H), 3.36-3.52(dd, J=3.8 Hz and J=11.2 Hz, 1H). IR($CHCl_3$ solution): 3505, 3015, 2947, 1693, 1226, 1066, 792 cm^{-1}. MS: 216(11, $M+NH_4^+$), 200(22, $M+2H^+$), 199(100, $M+H^+$). Exact mass calcd for $C_{11}H_{18}O_3+H^+$: 199.13339, found: 199.13342. ^{13}C NMR(75.4 MHz, $CDCl_3$): 217.2, 80.5, 71.5, 57.9, 40.8, 39.6, 32.3, 28.2, 25.8, 23.9, 22.1.

cis-8a-[[(Benzyloxy)methoxy]methyl]-1α-acetoxy-1,3,4,4a,5,6,8a-septahydronaphthalene-8(2H,7H)-one (68)

To a solution of the mono-alcohol 65 (0.060 g, 0.19 mmol) in 1.80 mL acetic anhydride at room temperature under argon was added pyridine (0.05 mL, 0.62 mmol), followed by dimethylaminopyridine (0.0210 g, 0.17 mmol). The mixture was heated to

70°C and stirred at this temperature for 48 h, by which time the yellow solution had turned brown. The mixture was allowed to cool to room temperature, was diluted with ether (2 mL), and quenched with saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide the mono acetate 68 (0.052 g, 75%) as a clear oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.24-7.38(m, 5H), 4.86(dd, J=3.8 Hz and 8.2 Hz, 1H), 4.71 and 4.67(AB, J=8 Hz, 2H), 4.55(s, 2H), 3.94 and 3.70(AB, J=9.4 Hz, 2H), 2.11-2.63(m, 3H), 2.00(s, 3H), 1.28-1.96(m, 8H). IR(neat): 2931, 2867, 1749, 1714, 1453, 1378, 1233, 1105, 1029, 738, 699 cm^{-1}. MS: 378(34, $M+NH_4^+$), 361(4, $M+H^+$), 348(8), 331(25), 281(6), 271(26), 254(16), 253(100), 223(26), 193(22), 179(6), 163(6), 151(7), 108(6). Exact mass calcd for $C_{21}H_{28}O_5+H^+$: 361.20167, found: 361.20150. ^{13}C NMR(75.4 MHz, $CDCl_3$): 211.2, 170.1, 137.6, 128.4, 127.8, 127.7, 95.1, 76.6, 74.0, 69.6, 68.3, 56.2, 46.4, 37.4, 27.2, 26.1, 22.5, 21.4, 19.9.

cis-8a-Oxymethyl-9,1α,O-isopropylidene-1,3,4,4a,5,6,8a-septahydronaphthalene-8(2H,7H)-one (67)

To a solution of the starting material 66 (0.062 g, 0.311 mmol) in 2.0 mL spectrograde acetone under argon at room temperature was added 2,2'-dimethoxypropane (0.17 mL, 1.40 mmol) and a catalytic amount of camphor sulphonic acid. The mixture was stirred at room temperature for 3 h, at which time a few drops of concentrated aqueous ammonium hydroxide were added and the solvent was evaporated. Ether and water were added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered, and the solvent evaporated to provide 0.068 g crude material. The crude material was purified by simply filtering it through a silica gel plug to provide the product 67 (0.068 g, 90%) as white crystals (mp 86-88°C).

^{1}H NMR(200 MHz, $CDCl_3$): 4.43 and 3.83(AB, J=12 Hz, 2H), 3.51(dd, J=4.2 Hz and 12 Hz, 1H), 2.69-2.87(m, 1H), 2.05-2.33(m, 2H), 1.54-2.05(m, 10H), 1.44(s, 3H), 1.36(s, 3H). IR($CHCl_3$ solution): 2944, 1711, 1453, 1384, 1234, 1197, 1102, 1059 cm^{-1}. MS: 256(7, $M+NH_4^+$), 239(100, $M+H^+$), 181(19), 151(9). Exact mass calcd for $C_{14}H_{22}O_3+H^+$: 239.1647; found: 239.1648. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.5, 99.5, 75.7, 69.4, 52.9, 41.4, 39.1, 29.7, 27.5, 27.1, 25.2, 24.1, 22.6, 18.6.

cis-8a-Acetoxymethyl-1α-acetoxy-1,3,4a,4,5,6,8a-septahydronaphthalene-8(2H,7H)-one (18)

To a solution of the diol 66 (0.028 g, 0.14 mmol) in 2.0 mL acetic anhydride at room temperature under argon was added pyridine (0.070 mL, 0.87 mmol), followed by a catalytic amount of dimethylaminopyridine. The mixture was heated to 50°C and stirred for 3 h at which time the reaction was complete. The mixture was allowed to cool down and was then diluted with ether (2 mL) and quenched with saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined ether extracts were dried over magnesium sulfate, filtered and the solvent was removed to provide 0.059 g crude material. Column chromatography (eluting first with 1:4 EtOAc:hexane and then with 1:1 EtOAc:hexane) provided the diacetate 18 as a pale orange oil (0.054 g, quantitative) which crystallized on standing (mp 83-85°C). ^{1}H NMR(200 MHz, $CDCl_3$): 4.76(dd, J=3.7 Hz and J=9.5 Hz, 1H), 4.36(s, 2H), 2.41-2.59(m, 2H), 2.04(s, 3H), 2.02(s, 3H), 1.37-2.39(m, 11H). IR($CHCl_3$ solution): 3029, 2947, 1741, 1736, 1374, 1233, 1212, 1042, 784 cm^{-1}. MS: 300(100, $M+NH_4^+$), 283(9, $M+H^+$), 223(33). Exact mass calcd for $C_{15}H_{22}O_5+H^+$: 283.1544, found: 283.1544. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.0, 170.6, 170.2, 73.7, 63.6, 55.5, 40.4, 38.2, 27.2, 27.1, 26.1, 22.6, 21.4, 20.8, 20.3.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-3β-methyl-4,4a,5,6,8a-pentahydronaphthalene-1,8(2H,7H)-dione (69)

To a suspension of cuprous iodide (0.1224 g, 0.62 mmol) in 1.3 mL dry ether at -35°C under argon was added 1.4M MeLi (0.89 mL, 1.25 mmol). The mixture was then cooled to -78°C and the starting enone 62 (0.075 g, 0.21 mmol) in 3.3 mL dry ether was added. After stirring at -78°C for 15 min, the reaction mixture was warmed to -35°C and stirred for 4 h. The reaction was then quenched by the addition of saturated ammonium chloride solution (4.0 mL). The aqueous phase was extracted with ether (3 x 10 mL) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:4 EtOAc:hexane) provided the mono-methyl product 69 (0.077 g, 95%) as a clear oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.25-7.34(m, 5H), 4.72(s, 2H), 4.58(s, 2H), 4.19(AB, J=10 Hz, 1H), 3.78-3.95(m, 5H), 1.30-2.61(m, 12H), 0.98(d, J=6.5 Hz, 3H). IR($CHCl_3$ solution): 2958, 1711, 1456, 1229, 1170, 1041, 720 cm^{-1}. MS: 375(19, $M+H^+$), 345(13), 268(17), 267(100), 237(12). Exact mass calcd for $C_{22}H_{30}O_5+H^+$: 375.21718, found: 375.21715. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.8, 138.0, 128.4, 127.8, 127.7, 110.4, 95.3, 70.3, 69.6, 64.6, 63.9, 59.7, 48.9, 34.2, 32.2, 28.9, 27.5, 25.5, 21.4, 20.4.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-1α-hydroxy-3β-methyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (70)

To a solution of the crude starting material 69 (0.073 g, 0.20 mmol) in 9.0 mL ether at 0°C under argon was added lithium aluminum hydride (0.024 g, 0.62 mmol). After stirring for 3 h at 0°C, the reaction was quenched with 5 mL saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 10 mL ether) and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography of the crude material (1:4 EtOAc:hexane) provided the product 70 (0.080 g, 95%), a pale yellow oil, as a mixture of two isomers in a ratio of

3:1. These isomers could not be separated in an EtOAc:hexane or a benzene:acetone solvent system and were thus carried on to the next step as a mixture.

^{1}H NMR(200 MHz, $CDCl_3$): 7.30-7.41(m, 5H), 4.76 and 4.79(two s in a 3:1 ratio, 2H), 4.61 and 4.64(two s in a 3:1 ratio, 2H), 4.13-4.37(m, 1H), 3.83-4.08(m, 4H), 3.74-3.82(m, 2H), 1.10-2.80(m, 12H), 0.88 and 0.95(two d in a 1:3 ratio, J=6.2 Hz, 3H). D_2O exchange simplifies one of the multiplets to: 1.10-2.56(m, 11H). IR($CHCl_3$ solution): 3494, 2952, 1456, 1176, 1081, 1041 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 138.0, 128.4, 128.0, 127.7, 114.4, 95.4, 69.5, 69.0, 65.6, 64.9, 63.7, 47.6, 38.9, 38.3, 36.1, 33.7, 30.4, 27.3, 25.2, 22.5. All signals in the ^{13}C NMR spectrum are doubled.

cis-8a-[[(Benzyloxy)methoxy]methyl]-1α-hydroxy-3β-methyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (71a) and **_cis_-8a-[[(Benzyloxy)methoxy]methyl]-1β-hydroxy-3β-methyl-1,4,4a,5,6,8a-hexahydronaphthalene-8-(2H,7H)-one (71b)** and **_cis_-8a-Hydroxymethyl-1α-hydroxy-3β-methyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (72a)** and **_cis_-8a-Hydroxymethyl-1β-hydroxy--3β-methyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (72b)**

To a solution of the alcohol 70 (0.057 g, 0.15 mmol) in 2.5 mL absolute ethanol under argon was added 20% palladium hydroxide on carbon (0.170 g) and cyclohexene (3.40mL, 33.6 mmol). The mixture was stirred at 70°C for 24 h, whereupon the catalyst was removed by filtration through a Celite pad. Column chromatography (1:3 EtOAc: hexane) of the crude material provided the keto diols 72a and 72b (0.004 g, 16%) as a 3:1 mixture of isomers (the major isomer 72a being the less polar one) together with the keto-mono-alcohols 71a and 71b (0.016 g, 79%) as a 3:1 mixture of isomers (the major one 71a being the less polar one). Compound 71a was resubmitted to the reaction conditions to give after 24 h at 70°C 65% keto diol 72a and 35% recovered keto-mono-alcohol 71a.

72a: ^{1}H NMR(200 MHz, $CDCl_3$): 4.38(t, J=11.7 Hz, 1H), 3.70-3.90(m, 3H), 3.34(d, J=11.7 Hz, 1H), 2.55-2.73(m, 1H), 2.26-2.43(m, 1H), 1.82-2.22(m, 5H), 1.45-1.74(m, 3H), 1.14-1.34(m, 2H), 0.98(d, J=7.2 Hz, 3H). D_2O simplifies the region downfield of 3.5 ppm to: 4.27 and 3.84(AB, J=11.7 Hz, 2H), 3.82(dd, J=3 Hz and J=8 Hz, 1H). IR($CHCl_3$ solution): 3503, 2949, 1693, 1421, 1230, 1073 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 218.0, 75.0, 70.5, 57.9, 40.0, 37.9, 35.3, 34.0, 26.3, 26.1, 22.4, 18.7.

72b: ^{1}H NMR(200 MHz, $CDCl_3$): 4.36(dd, J=4 Hz and J=12 Hz, 1H), 4.19 and 3.92(AB, J=12 Hz, 2H), 2.76(dt, J=6 Hz and J=14 Hz, 1H), 2.23-2.37(m, 1H), 1.06-2.04(m, H), 0.96(d, J=6.4 Hz, 3H). IR: same as above. ^{13}C NMR(75.4 MHz, $CDCl_3$): 217.5, 74.8, 69.9, 56.4, 40.9, 40.2, 38.3, 36.0, 27.3, 27.1, 24.9, 21.3.

71a: ^{1}H NMR(200 MHz, $CDCl_3$): 7.25-7.42(m, 5H), 4.78(s, 2H), 4.60(s, 2H), 3.93 and 3.78(AB, J=9.2 Hz, 2H), 3.69-3.85(m, 1H), 1.35-2.90(m, 12H), 1.20-1.35(m, 1H), 0.97(d, J=7 Hz, 3H). ^{1}H NMR(200 MHz, C_6D_6): 7.10-7.50(m, 5H, hidden under C_6D_6 solvent), 4.69 and 4.64(AB, J=6 Hz, 2H), 4.61 and 4.55(AB, J=11.2 Hz, 2H), 3.93 and 3.69(AB, J=9 Hz, 2H), 3.75(dt, J=3 Hz and J=8 Hz, 1H), 2.40-2.54(m, 1H), 2.33(t, J=6 Hz, 2H), 2.10-2.25(m, 1H), 1.82-2.06(m, 1H), 1.48-1.82(m, 4H), 1.24-1.46(m, 2H), 1.01-1.17(m, 1H), 0.84(d, J=6.8 Hz, 3H). IR($CHCl_3$ solution): 2949, 1691, 1457, 1111, 1039 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 216.6, 137.7, 128.4, 128.0, 127.7, 95.0, 69.7, 69.6, 67.8, 57.3, 40.6, 38.3, 34.7, 33.8, 26.2, 24.7, 21.9, 19.7.

71b: ^{1}H NMR(200 MHz, $CDCl_3$): 7.26-7.44(m, 5H), 4.77(s, 2H), 4.62(s, 2H), 4.15-4.18(dd, J=4 Hz and J=10 Hz, 1H), 4.11 and 3.85(AB, J=10 Hz, 2H), 3.09(d, J=4 Hz, 1H), 2.34-2.72(m, 2H), 2.16-2.34(m, 1H), 1.65-2.09(m, 5H), 1.16-1.65(m, 4H), 0.94(d, J=6.6 Hz, 3H). ^{1}H NMR(200 MHz, C_6D_6): 7.06-7.46(m, 5H, hidden under C_6D_6 solvent), 4.68(s, 2H), 4.60(s, 2H), 4.32 and 3.88(AB, J=10 Hz, 2H), 3.88-3.99(m, 1H), 2.94(d, J=5.2 Hz, 1H), 2.25-2.37(m, 1H), 2.03-2.24(m, 1H), 1.74(dt, J=4 Hz and J=12 Hz, 1H), 1.32-1.61(m, 4H), 1.01-1.21(m, 4H), 0.78(d, J=6 Hz, 3H). IR:

same as above. ^{13}C NMR(75.4 MHz, $CDCl_3$): 215.2, 137.9, 128.5, 128.1, 127.8, 95.2, 70.1, 69.8, 66.5, 56.9, 39.3, 38.5, 38.3, 35.5, 27.0, 26.6, 24.4, 22.2.

Alternative Procedure for the formation of compounds (71a)and (71b)

To a solution of the alcohol mixture 70 (0.065 g, 0.17 mmol) in 1.20 mL THF at room temperature was added 5% HCl (0.39 mL, 0.54 mmol). After stirring for 4 h at room temperature, sodium bicarbonate solution and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:3 EtOAc:hexane) of the crude material provided the keto alcohols 71a (0.034 g, 60%) and 71b (0.011 g, 20%). The spectral data for the keto alcohols are given at the end of the preceding experimental procedure.

cis-8a-Hydroxymethyl-1α-hydroxy-3β-methyl-8-ethanesulfuryl-1,2,4,4a, 5,6-hexahydronaphthalene (73)

To a solution of the ketal-mono-alcohol 70 (0.077 g, 0.20 mmol) in 2.9 mL CH_2Cl_2 at -25°C was added ethanethiol (0.15 mL, 2.04 mmol) followed by boron trifluoride etherate (0.08 mL, 0.65 mmol). The pale yellow mixture was stirred at -20°C for 5 h at which time ether and sodium bicarbonate solution were added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:3 EtOAc:hexane) provided the vinyl sulfide 73 (0.029 g, 55%) as a clear oil.

^1H NMR(200 MHz, $CDCl_3$): 5.93(broad s, 1H), 3.86(s, 1H), 3.65(s, 2H), 2.77(q, J=5 Hz, 2H), 2.13-2.27(m, 2H), 1.92-2.12(m, 2H), 1.66-1.93(m, 4H), 1.39-1.56(m, 3H), 1.33(t, J=5Hz, 3H), 1.03-1.16(m, 1H), 0.90(d, J=4.2 Hz, 3H). IR($CHCl_3$ solution): 3545, 3028, 2926, 1691, 1458, 1379, 1230, 1021 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 133.7, 127.1, 69.6, 63.8, 49.8, 37.2, 33.8, 26.8, 25.6, 25.2, 22.3, 20.9, 13.4.

Conversion of (73) into (72a)

To a solution of compound 73 (0.014 g, 0.055 mmol) in 0.3 mL THF at room temperature was added 5% HCl (0.12 mL, 0.16 mmol). After stirring at room temperature for 16 h, saturated sodium bicarbonate solution was added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide the crude product. Column chromatography (1:3 EtOAc:hexane) provided the keto diol (0.006 g, 51%), which was identical to compound 72a described above.

cis-8a-Acetoxymethyl-1α-acetoxy-3β-methyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (19a)

To a solution of the methyl keto diol 72a (0.016 g, 0.075 mmol) in 1.50 mL acetic anhydride under argon was added pyridine (0.04 mL, 0.50 mmol) and a catalytic amount of DMAP. The mixture was stirred at 45°C for 1.5 h, whereupon saturated ammonium chloride solution and ether were added. The aqueous layer was extracted with ether and the ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:3 EtOAc:hexane) of the crude material afforded the diacetate 19a (0.016 g, 72%). ^{1}H NMR(200 MHz, $CDCl_3$): 4.86(broad t, J=3 Hz, 1H), 4.27 and 4.22(AB, J=10.6 Hz, 2H), 2.45-2.63(m, 1H), 2.10(s, 6H), 1.07-2.37(m, 11H), 0.88(d, J=6.1 Hz, 3H). IR($CHCl_3$ solution): 2949, 1731, 1702, 1458, 1378, 1248, 1035 cm^{-1}. MS: 314(100, $M+NH_4^+$), 237(40). Exact mass calcd for $C_{16}H_{24}O_5+H^+$: 297.1703, found: 297.1702. ^{13}C NMR(75.4 MHz, $CDCl_3$): 211.7, 170.6, 169.0, 74.2, 64.4, 53.1, 40.9, 35.9, 35.6, 35.0, 27.4, 22.5, 21.8, 21.4, 20.9.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-3-methyl-4a,5,6,-8a-tetrahydronaphthalene-1,8(4H,7H)-dione (74)

To a suspension of copper iodide (0.030 g, 0.16 mmol) in 0.50 mL dry ether at -30°C under argon was added 1.4 M MeLi (0.23 mL, 0.32 mmol). The first few drops cause the appearance of a bright yellow precipitate, due to the presence of excess copper iodide. As one approaches the "end-point", this precipitate disappears. Enough MeLi is added so that there is only a slight excess of copper iodide. The mixture was then cooled down to -78°C and the protected enone 46 (0.041 g, 0.088 mmol) in 1.5 mL dry ether was added, causing the mixture to turn orange and thicken. The mixture was stirred for 1 h at -78°C and then quenched by the addition of saturated ammonium chloride solution at -30°C and extracted with ether (3 x 10 mL). The organic extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.031 g crude material. Column chromatography (1:4 EtOAc:hexanes) provided the product 74 (0.027 g, 86%) as a clear oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.29-7.40(m, 5H), 5.91(s, 1H), 4.73 and 4.68(AB, J=8 Hz, 2H), 4.55(s, 2H), 4.38(AB, J=10 Hz, 1H), 3.67-3.86(m, 5H), 2.78-2.95(m, 2H), 1.94(s, 3H), 1.50-2.05(m, 7H). IR($CHCl_3$ solution): 3016, 1654, 1205, 1026, 774, 738, 675 cm^{-1}. MS: 373(55, $M+H^+$), 265(100), 203(50). Exact mass calcd for $C_{22}H_{28}O_5+H^+$: 373.2014, found: 373.2015. ^{13}C NMR(75.4 MHz, $CDCl_3$): 198.8, 162.1, 138.0, 128.4, 127.9, 127.6, 127.5, 110.8, 95.2, 69.5, 67.2, 65.1, 64.6, 55.1, 34.3, 33.5, 32.9, 25.5, 24.5, 18.7.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-3,3-dimethyl-2,4a,5,6,8a-pentahydronaphthalene-1,8(4H,7H)-dione (75)

To a suspension of copper iodide (0.206 g, 1.09 mmol) in 4 mL dry ether at -30°C under argon was added 1.4 M MeLi (1.5 mL, 2.13 mmol). The mixture was cooled down to -78°C and a solution of the ketal 46 (0.130 g, 0.278 mmol) in 2.0 mL dry ether was added. The thick orange mixture was stirred for 15 min at -78°C, followed by 4 h at -30°C.

The reaction was then quenched by the addition of saturated ammonium chloride solution at -30°C and extracted with ether (3 x 10 mL). The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.099 g crude material. Column chromatography provided the ββ-dialkylated product 75 (0.091 g, 85%) as a clear oil, which crystallized (mp 79-80°C) upon standing. ^{1}H NMR(200 MHz, $CDCl_3$): 7.22-7.43(m, 5H), 4.72(q, J=6 Hz, 2H), 4.57(s, 2H), 4.38(AB, J=10 Hz, 1H), 3.67-3.84(m, 5H), 2.74-2.88(m, 1H), 2.11-2.50(m, 4H), 1.34-1.90(m, 5H), 1.13-1.28(m, 1H), 1.01(s, 3H), 0.93(s, 3H). IR($CHCl_3$ solution): 2958, 1696, 1229, 1049, 759 cm^{-1}. MS: 388(7, M^+), 297(32), 267(47), 112(70), 99(99), 91(100), 86(86), 55(48), 41(30), 28(39). Exact mass calcd for $C_{23}H_{32}O_5+H^+$: 389.2329, found: 389.2328. ^{13}C NMR(75.4 MHz, $CDCl_3$): 211.0, 138.1, 128.4, 128.0, 127.6, 110.0, 95.2, 69.5, 67.0, 64.1, 64.0, 58.0, 55.7, 40.5, 33.1, 32.6, 32.3, 31.4, 26.8, 26.5, 18.8.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-1α-hydroxy-3,3-dimethyl-1,4,4a,5,6,8a-hexahydronaphthalene-1,8(2H,7H)-dione (76)

To a solution of the crude starting material 75 (0.114 g, 0.294 mmol) in 8.0 mL ether at 0°C under argon was added lithium aluminum hydride (0.024 g, 0.63 mmol). The mixture was stirred for 2.5 h at 0°C and then diluted with more ether (5 mL) and quenched with saturated ammonium chloride solution (7 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the ether extracts were dried over magnesium sulfate, filtered and the solvent evaporated to provide 0.099 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the alcohol 76 (0.085 g, 78% from ketal 46) as a pale yellow oil. ^{1}H NMR(200 MHz, $CDCl_3$): 7.22-7.41(m, 5H), 4.82(s, 2H), 4.63(s, 2H), 3.65-4.18(m, 8H), 2.12-2.31(m, 1H), 1.99(t, J=17 Hz, 2H), 1.40-1.80(m, 6H), 1.10-1.31(m, 1H), 0.95(s, 3H), 0.94(s, 3H). IR($CHCl_3$ solution): 3493, 3009, 2965, 1455, 1208, 1168, 1107, 1034, 1006, 924 cm^{-1}. MS: 391(22, $M+H^+$), 373(23), 329(18), 299(57), 284(18), 283(100), 269(42), 265(31), 253(20), 251(8), 238(10), 237(64), 235(23), 222(15),

221(77), 191(11), 175(41), 99(20). Exact mass calcd for $C_{23}H_{34}O_5+H^+$: 391.24830, found: 391.24845. ^{13}C NMR(75.4 MHz, $CDCl_3$): 138.0, 128.4, 128.0, 127.7, 114.3, 95.2, 70.6, 69.6, 67.9, 63.5, 62.2, 46.8, 44.1, 40.3, 33.2, 31.8, 31.3, 30.8, 26.4, 26.0, 18.5..

cis-8a-(Hydroxymethyl)-1α-hydroxy-3,3-dimethyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (77)

To a solution of the protected dimethyl mono-alcohol 76 (0.089 g, 0.228 mmol) in 2.2 mL absolute ethanol was added 20% palladium hydroxide on carbon (0.151 g), followed by cyclohexene (4.70 mL, 46.5 mmol). After stirring the mixture overnight at 70°C, the catalyst was removed by filtration and the solvent removed providing 0.035 g crude material. Column chromatography (1:1 EtOAc:hexane) provided the dimethyl keto diol 77 (0.011 g, 20%) as a white solid (m.p. 149-151°C), the protected dimethyl diol 79 (0.005 g, 7%) as a white solid (mp. 120-121°C), the deprotected dimethyl keto-alcohol 78 (0.011 g, 14%) and some recovered starting material 76 (0.031 g, 35%). Resubjecting 78 to the reaction conditions provided 77 in quantitative yield.

77: ^1H NMR(200 MHz, $CDCl_3$): 4.38-4.52(d broad, J=11 Hz, 1H), 3.88(d, J=11 Hz, 1H), 3.60-4.09(m, 3H), 2.57-2.79(m, 1H), 2.07-2.36(m, 2H), 1.88-2.07(m, 2H), 1.61(d, J=9.2 Hz, 2H), 1.21-1.50(m, 3H), 0.90-1.12(m, 1H), 0.93(s, 3H), 0.90(s, 3H). D_2O exchange: 4.40(d, J=11.5 Hz, 1H), 3.87(d, J=11.5 Hz, 1H), 3.66(broad t, J=8 Hz, 1H). IR($CHCl_3$ solution): 3511, 1691, 1223, 1074, 785 cm^{-1}. MS: 244(7, $M+NH_4^+$), 228(26, $M+2H^+$), 227(100, $M+H^+$), 209(5). Exact mass calcd for $C_{13}H_{22}O_3+H^+$: 227.16471, found: 227.16472. ^{13}C NMR(75.4 MHz, $CDCl_3$): 217.3, 77.4, 71.5, 57.5, 44.7, 41.1, 39.4, 36.5, 32.9, 31.4, 25.6, 24.7, 22.1.

78: ^1H NMR(200 MHz, $CDCl_3$): 7.35(s, 5H), 4.82(s, 2H), 4.64(s, 2H), 4.00(s, 2H), 3.49-3.81(m, 2H), 1.05-2.55(m, 11H), 0.95(s, 3H), 0.93(s, 3H).

79: ^{1}H NMR(200 MHz, $CDCl_3$): 4.40 and 3.57(AX, J=11.8 Hz, 2H), 3.80-4.18(m, 7H), 1.88-2.06(m, 2H), 1.35-1.83(m, 7H), 1.18-1.30(m, 1H), 0.93(s, 6H), 0.75-0.88(m, 1H). IR($CHCl_3$ solution): 3510, 2959, 1418, 1199, 1118, 1016 cm^{-1}.

Preparation of dimethylketodiol (77) from the ketal (79)

To a solution of the ketal 79 (0.023 g, 0.082 mmol) in 0.40 mL THF at room temperature was added 5% HCl (0.18 mL, 0.25 mmol). After stirring for 10 h at room temperature, sodium bicarbonate solution and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:2 EtOAc:hexane) of the crude material provided the ketodiol 77 (0.022 g, 94%). The spectral data for the ketodiol are given at the end of the preceding experimental procedure.

Alternative procedure leading to the formation of

cis-8a-(Oxymethylene)-9,1α,O-methylene-3,3-dimethyl-1,4,4a,5,6,8a-hexahydronaphthalene-8(2H,7H)-one (80)

To a solution of the ketal 76 (0.071 g, 0.18 mmol) in 1.6 mL THF at room temperature was added 12% HCl (0.50 mL, 1.65 mmol). The mixture was heated to 60°C and stirred at this temperature overnight. The mixture was then allowed to cool to room temperature and sodium bicarbonate solution and ether were added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography (1:2 EtOAc:hexane) of the crude material gave the dimethyl ketodiol 77 (0.021 g, 51%) and 80 (0.014 g, 32%) as a white solid (mp. 125-126°C).

^{1}H NMR(200 MHz, $CDCl_3$): 5.13 and 4.75(AX, J=5.7 Hz, 2H), 4.73 and 3.59(AX, J=11.5 Hz, 2H), 3.41(dd, J=4.4 Hz and 12.6 Hz, 1H), 2.60-2.82(m, 1H), 2.21-2.34(m, 1H), 1.80-2.12(m, 5H), 1.31-1.52(m, 3H), 1.00-1.08(m, 1H), 0.97(s, 3H), 0.95(s, 3H),

0.78-0.91(m, 1H). IR($CHCl_3$ solution): 2956, 1709, 1448, 1157, 1024 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.6, 95.1, 80.0, 75.5, 53.5, 40.3, 39.1, 39.0, 37.3, 33.1, 31.3, 25.7, 24.7, 22.5.

***cis*-8a-(Acetoxymethyl)-1α-acetoxy-3,3-dimethyl-1,4,4a,5,6,8a-hexahydro-naphthalene-8(2H,7H)-one (20)**

To a solution of the dimethyl-keto-diol 77 (0.021 g, 0.095 mmol) in 3 mL of 2:1 acetic anhydride:methylene chloride (as the starting material would not dissolve in acetic anhydride alone) under argon at room temperature was added pyridine (0.050 mL, 0.58 mmol) and a catalytic amount of DMAP. The mixture was then stirred at 50°C for 1.5 h, at which time the solvent was removed. To the residue was added ether and saturated ammonium chloride solution. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to give 0.032 g crude material. Column chromatography (1:10 spectrograde acetone:benzene) provided both the monoacetate 81 (0.008 g, 31%) and the diacetate 20 (0.020 g, 69%). These two compounds were inseparable in an EtOAc:hexane solvent system. Resubjecting the monoacetate to the reaction conditions for 1.5 h at 45°C with 4 equivalents rather than 6 equivalents of pyridine, smoothly transformed it into the diacetate.

81: ^1H NMR(200 MHz, $CDCl_3$): 4.71 and 4.37(AB, J=11 Hz, 2H), 3.69(dt, J= 5.1 Hz and 11.7 Hz, 1H), 3.43(d, J=11.7 Hz, 1H), 2.09(s, 3H), 1.01-2.55(m, 11H), 0.93(s, 6H). IR($CHCl_3$ solution): 3545, 2958, 1736, 1694, 1419, 1248, 1039 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 216.2, 170.7, 69.7, 63.1, 60.0, 44.2, 41.0, 40.0, 35.1, 32.9, 31.2, 25.2, 24.7, 21.2, 20.9.

20: ^1H NMR(200 MHz, $CDCl_3$): 4.98(dd, J=4.7 Hz and 12.4 Hz, 1H), 4.48 and 4.37(AB, J=11.4 Hz, 2H), 2.05(s, 3H), 2.00(s, 3H), 1.00-2.58(m, 11H), 0.98(s, 3H), 0.91(s, 3H). IR($CHCl_3$ solution): 2960, 1736, 1728, 1250, 1037 cm^{-1}. MS: 328(100, $M+NH_4^+$), 311(25, $M+H^+$), 251(54), 191(21). Exact mass calcd for $C_{17}H_{26}O_5+H^+$:

311.1858, found: 311.1858. ^{13}C NMR(75.4 MHz, $CDCl_3$): 209.0, 170.9, 170.7, 71.1, 63.4, 56.6, 40.4, 40.1, 38.2, 36.4, 32.7, 31.3, 25.5, 25.1, 22.9, 21.3, 20.9.

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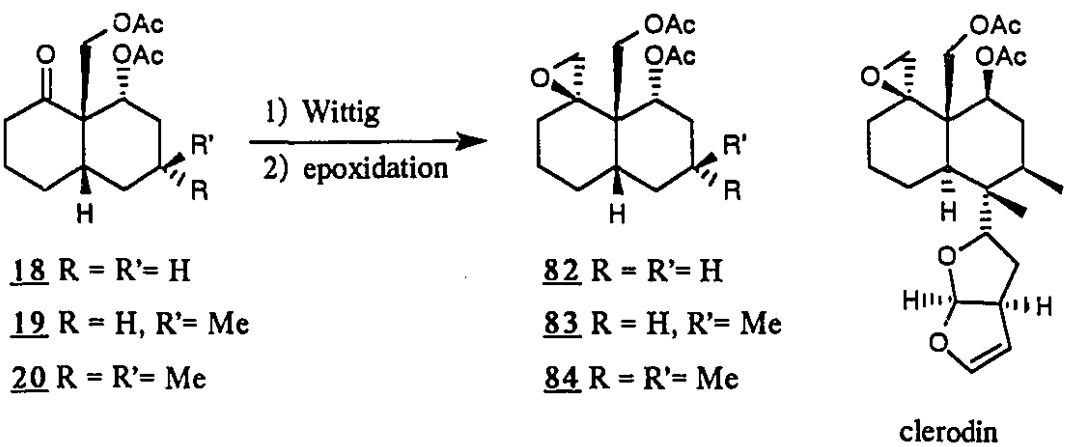
12. We thank Dr. J. Britten from the McGill X-ray Facility for the X-ray structure determination.

CHAPTER 5

EFFORTS TOWARDS THE METHYLENATION OF KETO DIACETATES (18) - (20)

5.1 Introduction

Having prepared the diacetates 18 - 20, we hoped to now transform these into the epoxides 82 - 84 via a Wittig-epoxidation sequence, in this way preparing *cis*-fused decalin compounds featuring oxygen functionalities very similar to clerodin itself (see **Scheme**



18 R = R'= H
19 R = H, R'= Me
20 R = R'= Me

82 R = R'= H
83 R = H, R'= Me
84 R = R'= Me

clerodin

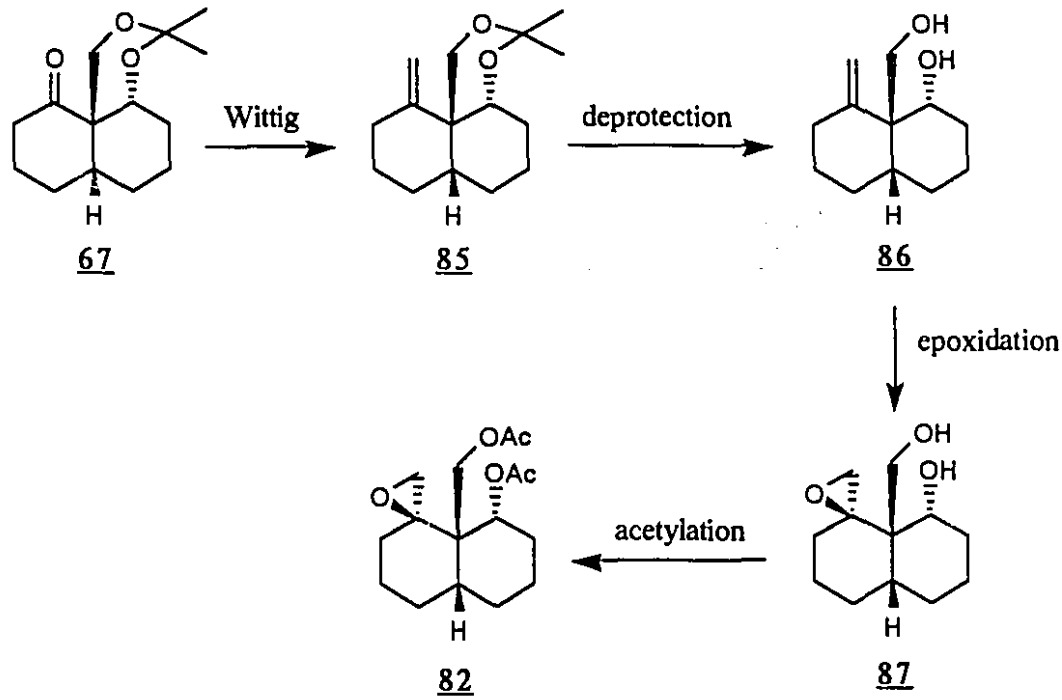
Scheme 5.1

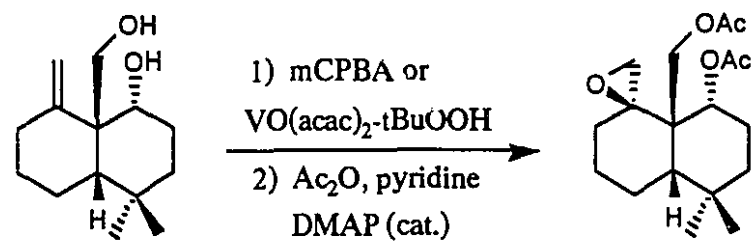
5.1). However, the Wittig reaction turned out to be not as straightforward as expected. Our efforts to effect the transformation are described here.

5.2 Wittig Reaction Conditions Applied to Keto-ester (56) and Ketal (67)

For the preparation of epoxydiacetate 82 we planned to follow the route outlined in **Scheme 5.2.** It was envisaged that the ketal 67 would be a suitable candidate for the

Wittig reaction, since the isopropylidene moiety of 85 could then be removed to provide the diol 86. Ley and coworkers[1] have described the epoxidation-acetylation sequence of 88 to give 89 in 79% overall yield (see **Chapter 1, Scheme 1.5** and accompanying text). This epoxidation-acetylaion sequence could be applied to diol 86 to complete the preparation of epoxydiacetate 82.

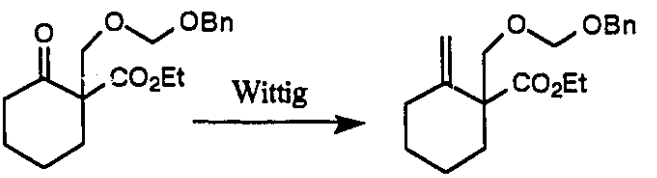




Scheme 5.2

Before carrying out the Wittig reaction on ketal 67, a model study was performed using ketoester 56. As indicated in **Table 5.1**, the use of trimethylsilylmethylmagnesium-chloride, followed by treatment with acetyl chloride[3,4] did not suitably effect the trans-formation, giving at best a mixture of compounds from which only 10% of the desired product could be isolated. On the other hand, methylenetriphenylphosphorane[5], prepared from methyltriphenylphosphonium bromide and n-butyllithium in THF, gave after 2 h at -20°C, 60% of the desired product 90. The formation of compound 90 was confirmed by the two vinyl proton signals at 6.14 ppm and 5.53 ppm in the ^1H NMR spectrum, as well as the disappearance of the carbonyl carbon signal in the ^{13}C NMR and the appearance of two new signals at 147.7 ppm and 109.2 ppm , characteristic of an exocyclic double bond.

Table 5.1



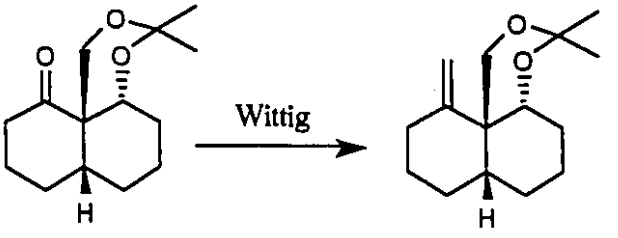
56 90

Conditions	Result
1.3 eq. $TMSCH_2MgCl$, Et_2O, -40°C to 0°C 0°C to 25°C reflux (40°C)	Starting Material 10% of 90 Decomposition
1.5 eq. $Ph_3P{=}CH_2$, THF, -78°C to -20°C	60% of 90

Next the ketal 67 was subjected to the Wittig reaction. However, exposure of this compound to a variety of conditions never provided any of the desired product 85 (see **Table 5.2**).

Since methylenetriphenylphosphorane, either in THF[5] or in DMSO[6], remains the most generally useful Wittig reagent and was successful in converting ketone 56 into a teminal olefin, this was the first method employed in order to effect the methylenation of ketone 67. However, even with 4.6 equivalents of this reagent and heating to 60°C, only starting material was recovered.

Table 5.2



67 85

Conditions	Result
1.5 eq. $Ph_3P{=}CH_2$, THF, -78°C to 50°C	Starting Material 67
4.6 eq. $PH_3P{=}CH_2$, THF, 60°C	"
1.6 eq. $TMSCH_2Li$, Et_2O, 25°C	"
same conditions with $CeCl_3$	"
4.6 eq. $TMSCH_2Li$, IPE*, 60°C	"
2.5 eq. $Ph_3P{=}CH_2$, DMSO, 60°C	"
2.0 eq. Cp_2TiMe_2, THF, 60°C	"
2.0 eq. $Ph_3P{=}CHLi$, HMPA, Et_2O, 0°C, 10 h	"
2.0 eq. CH_2I_2, SmI_2; SmI_2, DMAE,* HMPA rt, 16 h; 50°C, 2 h	"
1.3 eq. $Zn\text{-}CH_2Br_2\text{-}TiCl_4$, CH_2Cl_2, 25°C	Ketodiol 66

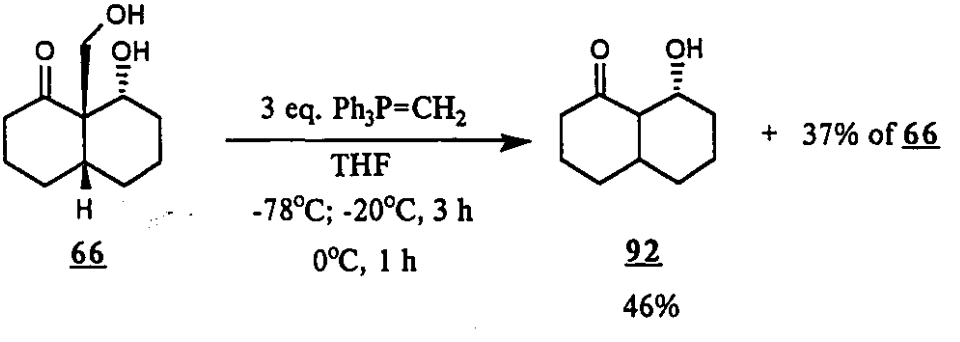
* where IPE = diisopropylether
DMAE = N,N-dimethylaminoethanol

Treatment of compound 67 with trimethylsilylmethyllithium[3], followed by reaction with acetyl chloride to decompose the β-silylcarbinol into a terminal olefin, was also unsuccessful. Even when Imamato's[10,7] cerium(III) chloride methodology was employed, involving what has been described as a remarkably nucleophilic "$RCeCl_2$" species, the situation did not improve.

Suspecting that compound 67 bears an enolizable ketone, the compound was treated with dimethyltitanocene[8], an aluminum-free alternative to the Tebbe reagent[11] or the Grubb's titanacyclobutane.[12] This reagent was readily prepared according to the procedure described by Claus *et al.*[13] and can be exposed to air during weighing and handling. However, even after 16 h at 60°C, this reagent was not successful in transforming the ketone moiety of 67 into a terminal olefin.

Compound 67 was also treated with Corey's "α-lithiomethylenetriphenylphosphorane" in the hope of effecting methylenation. This reactive species is formed by treating methylenetriphenylphosphorane with *tert*-butyllithium, before the addition of the ketone starting material. With this reagent, Corey *et al.*[14] observed olefination of ketones after only a few hours at 0°C, however compound 67 did not react even after 10 h at 0°C.

At this point a carbonyl methylenation method described by Inanaga *et al.*[15] was applied to compound 67. This procedure involves the SmI_2-induced iodomethylation of a carbonyl, followed by the SmI_2-induced deoxygenation by an efficient electron transfer system of SmI_2-THF-HMPA in the presence of N,N-dimethylaminoethanol. Again, this



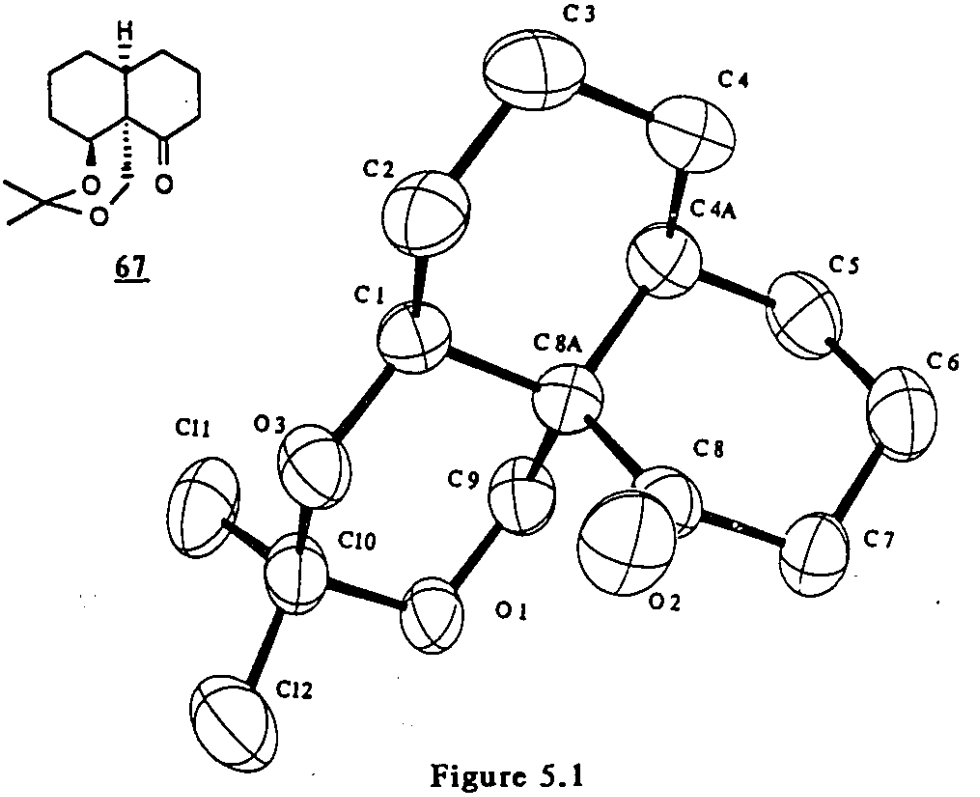
66

Scheme 5.3

procedure was unsuccessful in convincing compound 67 to react.

A reagent which has allowed the methylenation of a ketone present in a base-sensitive compound is the highly active species prepared from Zn-CH_2Br_2-$TiCl_4$[9], a variation of the procedure developed by Oshima *et al.*.[16] However, this resulted in the hydrolysis of the isopropylidene protecting group to give the ketodiol 66. The ketodiol itself was then treated with an excess of methylenetriphenylphosphorane, however this resulted in a retro-aldol reaction, giving compound 92 (see **Scheme 5.3**).

The unwillingness of compound 67 to undergo methylenation suggests that the ketone functionality in this molecule is severely hindered. The ORTEP diagram of compound 67, which is also shown in **Figure 4.1** of **Chapter 4**, has been reproduced here (see **Figure 5.1**) to show the crowded environment surrounding the ketone moiety in this molecule. This may explain why the Wittig reaction conditions, which were able to effect methylenation of the less sterically hindered ketone present in compound 56, were unable to effect olefination of compound 67.

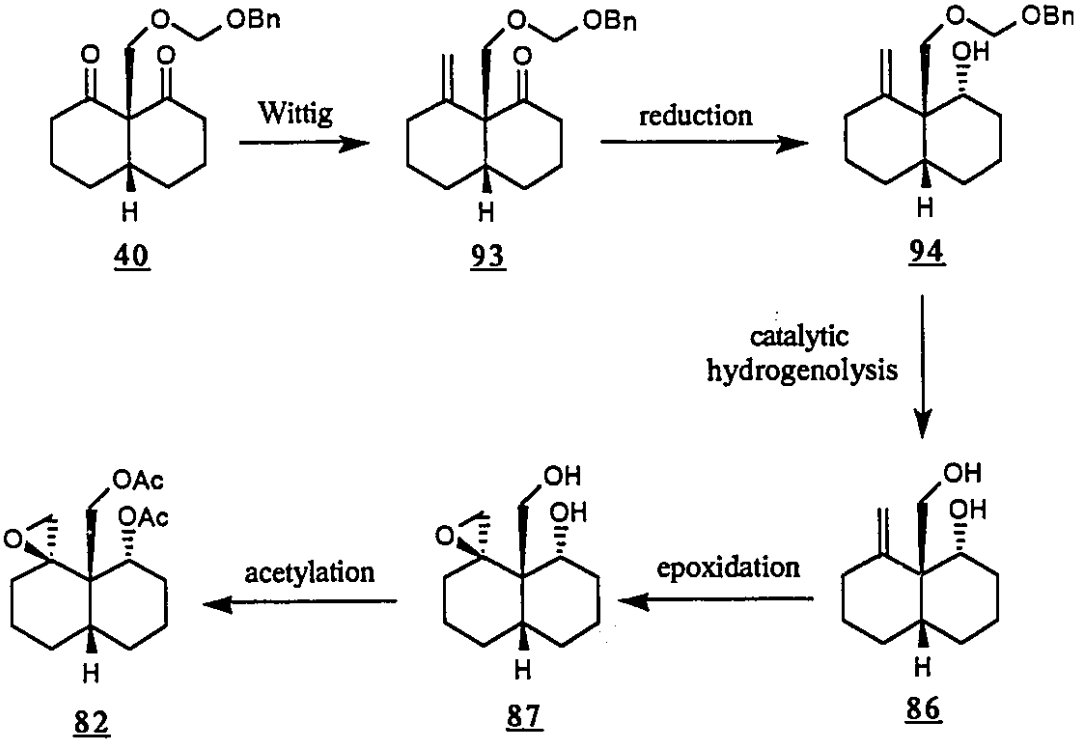


67

Figure 5.1

5.3 Wittig Reaction Conditions Applied to Diketone (40)

Another possible candidate for the Wittig reaction required to prepare epoxydiacetate 82 was the symmetric diketone 40. A successful methylenation of this compound would produce 93 which could be carried through the sequence shown in **Scheme 5.4** to provide the diacetate epoxide 82.

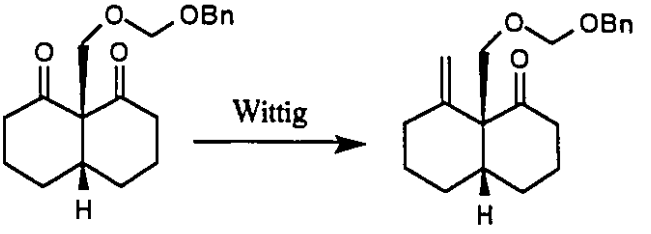


Scheme 5.4

However, exposure of diketone 40 to a variety of conditions (see **Table 5.3**) provided either starting material or, if forcing conditions were employed, resulted in decomposition of the starting material.

An alternative way to effect methylenation of a ketone would be to treat the ketone with methyllithium to produce a tertiary alcohol. Treatment of this alcohol with a dehydrating agent should then produce a mixture of the exocyclic and endocyclic olefin. Thus dike-

Table 5.3

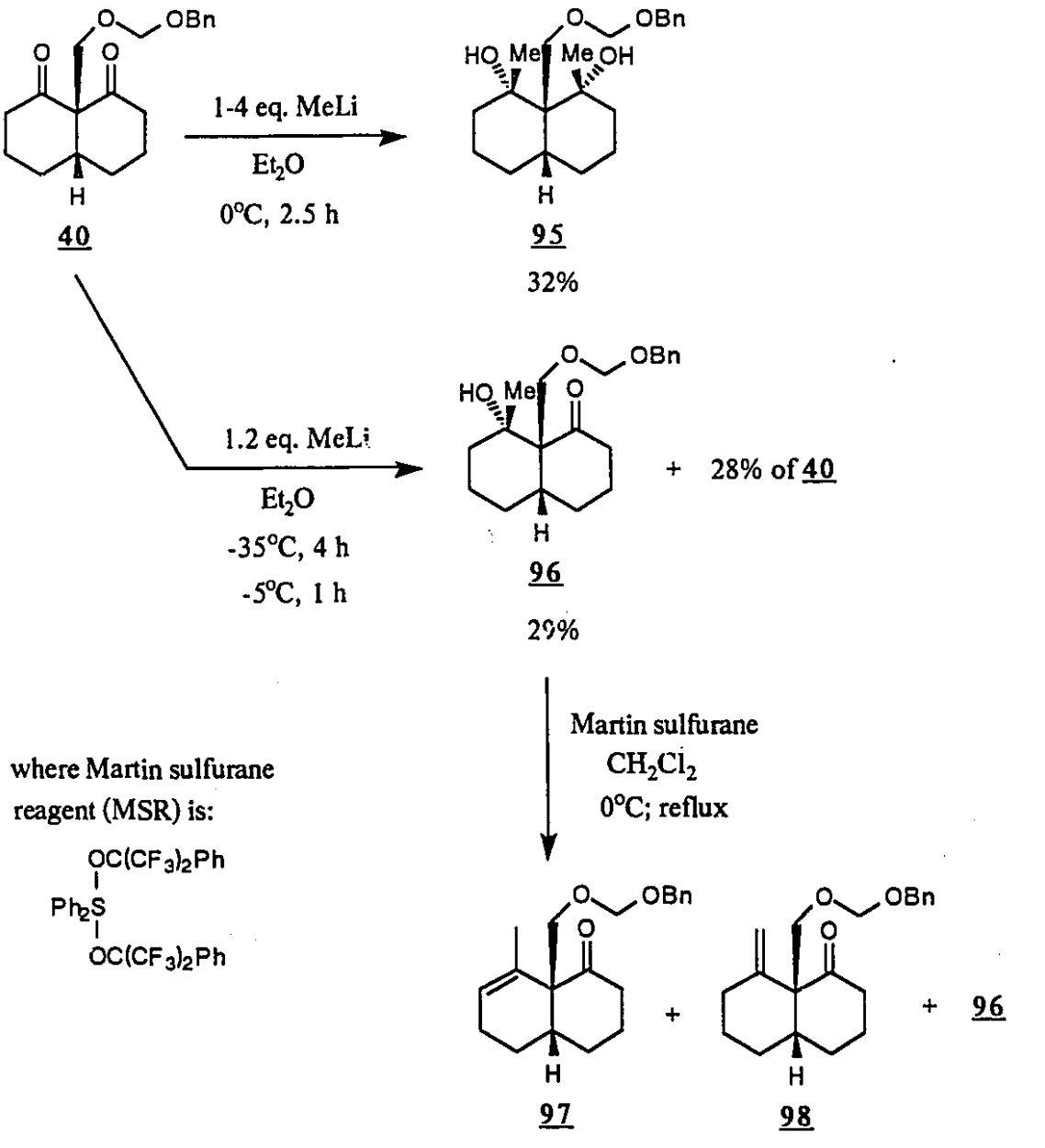


40 93

Conditions	Result
1.5 eq. $Ph_3P{=}CH_2$, THF, -78°C to 0°C	Decomposition
1.3 eq. $TMSCH_2MgCl$, Et_2O, -78°C to 0°C	Starting Material
same conditions with $CeCl_3$	Starting Material
3.0 eq. $TMSCH_2MgCl$, Et_2O, 40°C	Decomposition
1.6 eq. $Zn\text{-}CH_2Br_2\text{-}TiCl_4$, CH_2Cl_2, 25°C	Decomposition

tone 40 was treated with methyllithium. The use of an excess of methyllithium and a temperature of 0°C resulted in a di-addition of methyllithium, providing compound 95. However, when the amount of methyllithium was decreased to 1.2 equivalents and the temperature was not allowed to increase above -5°C, a single addition of methyllithium occurred giving compound 96. The yield could not be improved above 29% (with 28% recovered 40), since increasing the amount of methyllithium or the temperature would cause the formation of the dimethyl compound 95 as well as compound 96 (see **Scheme** 5.5).

Compound 96 was then treated with the Martin sulfurane reagent[18-20], known to give preferentially the exocyclic double bond upon dehydration. However, the reaction temperature had to be increased to reflux (40°C, as the solvent was dichloromethane) to



2.8 eq. MSR, reflux, 8 h:	37%	26%	39%
3.5 eq. MSR, reflux, 4 h:	78%	–	10%

Scheme 5.5

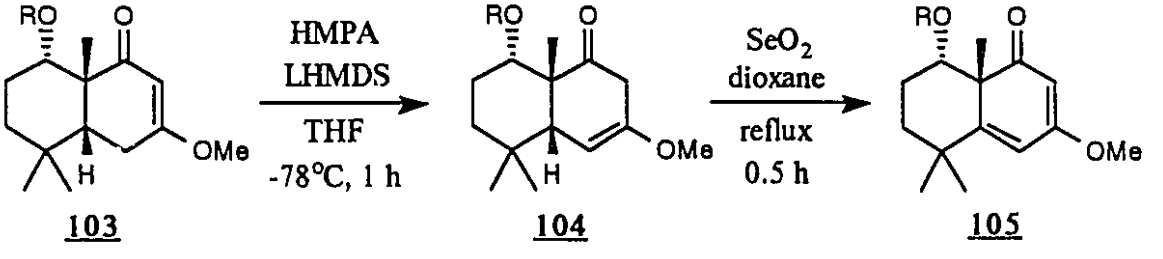
effect a reaction and at best only 26% of the exocyclic olefin 98 was formed, together with 37% of the endocyclic olefin 97 and 39% recovered starting material 96. Compound 98

featured the signals characteristic for an exocyclic double bond, at 145.1 ppm and 106.1 ppm in the ^{13}C NMR; whereas the ^{13}C NMR spectrum of compound 97 indicated the presence of an endocyclic double bond with signals at 125.9 ppm and 113.6 ppm. Increasing the amount of Martin sulfurane reagent only encouraged the formation of more of the endocyclic olefin 97, now produced in 78% together with 10% recovered 96.

Compound 67 was also treated with methyllithium with the aim of then subjecting the resulting tertiary alcohol to dehydration. However, even with 20 equivalents of methyllithium and heating to 60°C in diisopropylether solvent, no reaction took place. This demonstrates once again that the ketone functionality in compound 67 is unreative.

5.4 Examining the Possibility of Changing the *cis* Ring Junction

At this point the possibility of converting the *cis* ring junction of the Wittig substrate to a *trans* ring junction was studied. It was reasoned that a *trans* decalin would be less sterically hindered than the *cis* decalin substrate, thus facilitating the approach of the Wittig reagent and increasing the chances of a successful reaction. To this end a series of suitable enones were treated under strongly basic conditions to isomerize the conjugated double bond and provide compounds 99 - 102 (see **Table** 5.4). It was recently found in our laboratory[17] that compound 104, featuring a deconjugated double bond, could be treated with selenium dioxide to provide 105 (see **Scheme** 5.6). The addition of hydrogen to



103 104 105

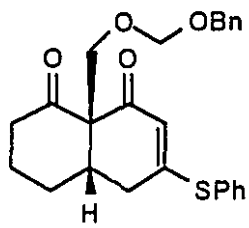
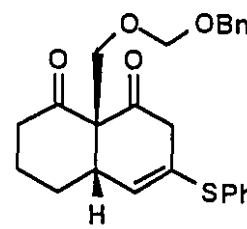
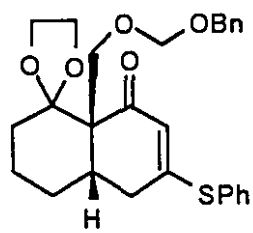
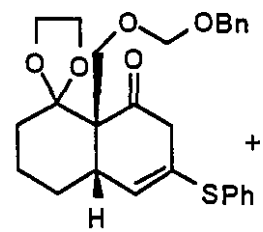
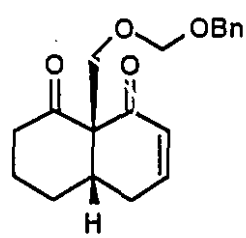
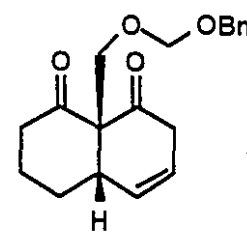
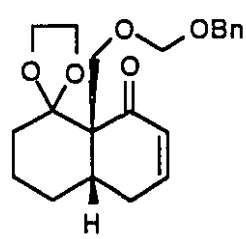
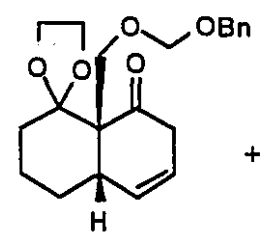
where R = TBDMS

Scheme 5.6

Table 5.4

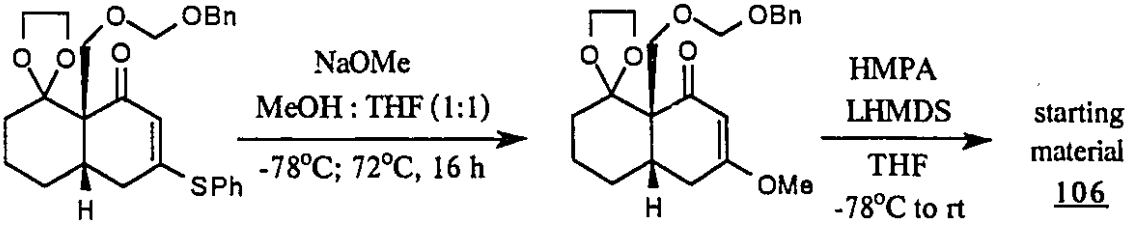
Deconjugation of the Enone Double Bond

conditions: 1.5 eq. LHMDS, 5.0 eq. HMPA, THF, -78°C

Starting Material	Product
 **36**	 + 60% of **36** **99** (40%)
 **46**	 + 30% of **46** **100** (70%)
 **39**	 + 12% of **39** **101** (36%)
 **62**	 + 15% of **62** **102** (50%)

such a compound may provide a decalin with a *trans* ring junction. It was hoped that compounds 99 to 102 would react in a similar way with selenium dioxide, and that subsequent hydrogenolysis would then provide a series of *trans* decalins. However, compounds 99 to 102 all decomposed upon exposure to selenium dioxide, even when a small amount of pyridine was added to reduce the acidity of the reaction mixture.

In the hope that the selenium dioxide reaction would provide a successful result in the presence of an OMe moiety (as in compound 104), compound 106 was prepared from compound 46 and exposed to the strongly basic conditons (see **Scheme 5.7**). However,

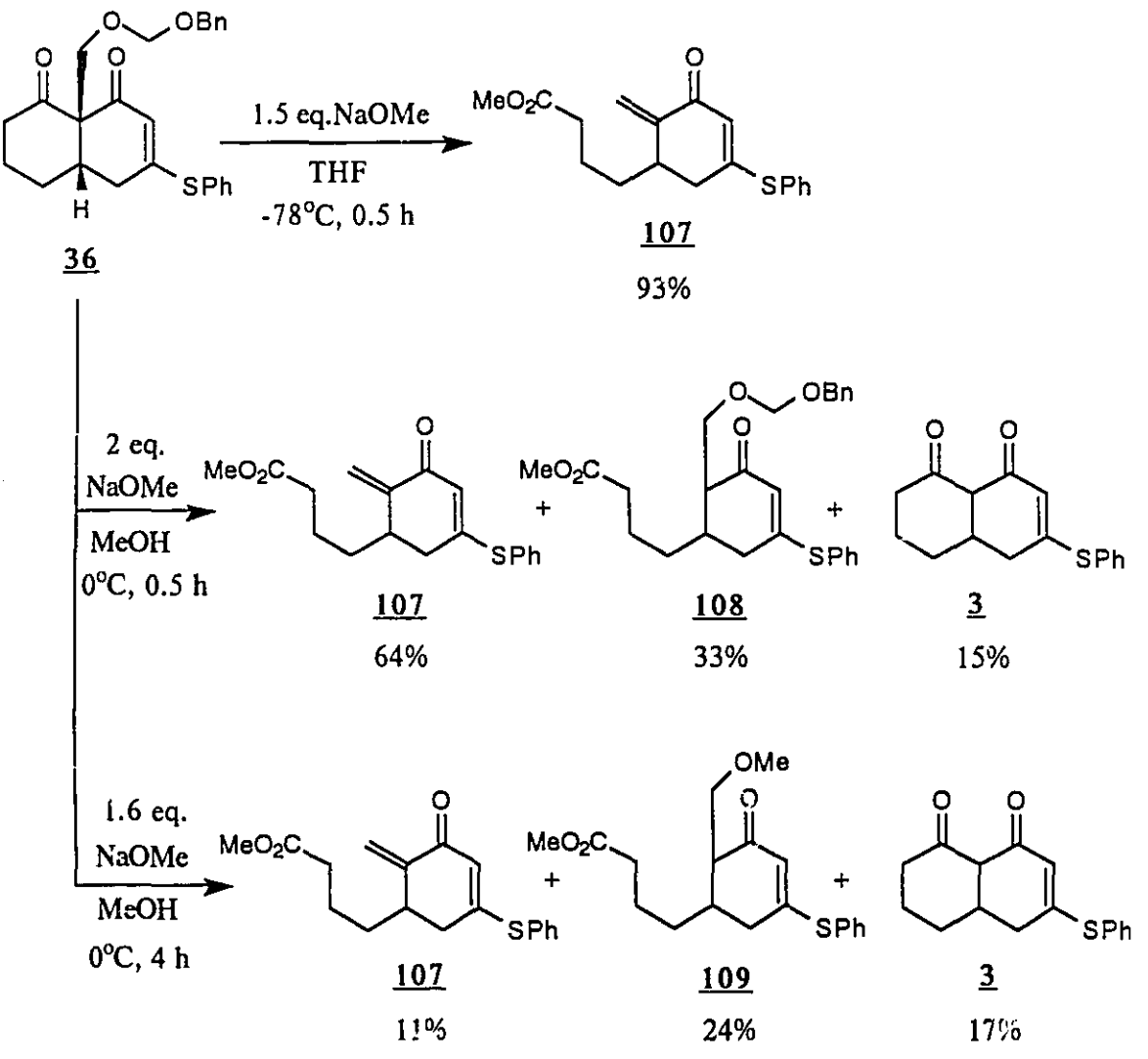


46 106 63%

Scheme 5.7

the conjugated double bond could not be convinced to isomerize even at room temperature. Thus an attempt was made to prepare the OMe derivative of compound 36. However, treatment of 36 with sodium methoxide resulted in an attack on the unprotected saturated carbonyl moiety to provide a series of substituted cylohexenone derivatives 107, 108 and 109 as illustrated in **Scheme 5.8**.

Upon closer examination of **Scheme 5.8**, it becomes evident that the methoxide anion first attacks the saturated ketone, opening the ring to provide compound 108.[21] The benzyloxymethoxy moiety present in compound 108 can easily be eliminated to give compound 107, featuring an exocyclic double bond. This compound is the major product at low temperature (-78°C) or at 0°C when the reaction time is minimized to 0.5 h. When the reaction is allowed to proceed for 4 h at 0°C, an important quantity of compound 109 is

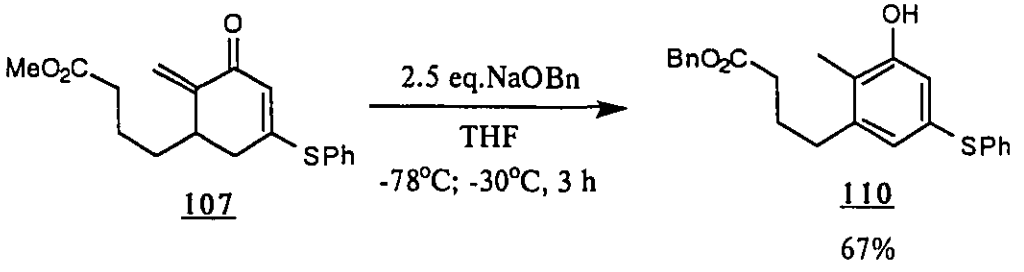


Scheme 5.8

produced. In this case a second methoxide anion has added to the exocyclic methylene moiety. At 0°C, the strongly basic reaction conditions also encourage retro aldol reaction to give rise to the formation of decalin 3.

It was then reasoned that treatment of compound 36 with a catalytic amount of sodium methoxide or potassium *tert*-butoxide might induce ring opening followed by ring closure, perhaps providing a *trans*-fused decalin. However, a catalytic amount of these bases was not able to induce any reaction, leading simply to the recovery of compound 36.

On the other hand, it was thought that perhaps compound 107 could be treated with either an equal or a catalytic amount of base, such as sodium benzyloxide, to induce recyclization to possibly provide a *trans* decalin compound featuring a benzyloxymethylene moiety at the angular position. However, treatment of this compound with 2.5 equivalents of benzyl alcohol in the presence of sodium hydride provided, after 3 h at -30°C, 67% of compound 110 (see **Scheme 5.9**). Compound 110 featured two singlets at 6.78 ppm and 6.61 ppm in the ^{1}H NMR. Only an ester carbonyl signal was present in the ^{13}C NMR (at 173.2 ppm) and in the IR spectrum (at 1733 cm^{-1}), indicating that aromatization had taken place.



107 110

67%

The tendency of compound 107 towards aromatization under basic conditions suggests that this procedure would not be recommendable for the formation of a bicyclic compound. At this point, the idea of transforming the *cis* ring junction into a *trans* ring junction, in order to provide a more favourable substrate for the Wittig reaction, was abandoned.

Experimental

General Methods: See Chapter 2, Experimental.

Ethyl 1-[[(benzyloxy)methoxy]methyl]-2-exomethylenecyclohexanecarboxylate (90)

To a suspension of methyltriphenylphosphonium bromide (0.139 g, 0.39 mmol) in 2.4 mL THF under argon at -78°C was added 2.5 M n-BuLi (0.16 mL, 0.38 mmol), causing the white mixture to turn lemon-yellow immediately. Afer 10 min, a solution of the starting material 56 (0.089 g, 0.28 mmol) in 2.4 mL THF was added. After stirring for 1 h at -78°C, the mixture was slowly warmed to -20°C and stirred at this temperature for 0.50 h, causing the mixture to turn cream in colour. The mixture was then stirred at 0°C for 1 h, at which time it was quenched with saturated ammonium chloride solution and ether was added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.108 g crude material. Column chromatography (1:5 EtOAc:hexane) provided the product 90 (0.052 g, 58%) as a pale yellow oil.

^{1}H NMR(200 MHz, $CDCl_3$): 7.34(s, 5H), 6.14 (s, 1H), 5.53(s, 1H), 4.91 and 4.83(AB, J=7 Hz, 2H), 4.55-4.75(m, 2H), 4.19(q, J=7 Hz, 2H), 3.96 and 3.75(AB, J=9.2 Hz, 2H), 2.05-2.41(m, 3H), 1.38-1.82(m, 5H), 1.26(t, J=7 Hz, 3H). IR($CHCl_3$ solution): 3012, 1722, 1649, 1448, 1223, 1162, 1045 cm^{-1}. MS: 336(100, $M+NH_4^+$), 319($M+H^+$), 289(9), 211(49). Exact mass calcd for $C_{19}H_{26}O_4+H^+$: 319.1909; found: 319.1908. ^{13}C NMR(75.4 MHz, $CDCl_3$): 173.6, 147.7, 137.7, 128.4, 127.9, 127.7, 109.2, 94.9, 72.5, 69.4, 60.7, 53.7, 34.7, 33.2, 27.9, 22.6, 14.2.

cis-1α-Hydroxy-2,3,4,4a,5,6,7,8a-oxahydronaphthalene-8-one (92)

To a suspension of methyltriphenylphosphonium bromide (0.247 g, 0.692 mmol) in 1.5 mL THF under argon at -78°C was added 2.5 M nBuLi (0.28 mL, 0.668 mmol). After 0.5 h at -78°C, a solution of keto diol 66 (0.043 g, 0.217 mmol) in 1.5 mL THF was added, causing the yellow mixture to turn creamy in colour. After stirring for 15 min at -78°C, the mixture was slowly warmed to -20°C and stirred at this temperature for 3 h. At this point the reaction was quenched by the addition of saturated ammonium chloride solution. The aqueous layer was extracted with ether and the ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.046 g crude material. Column chromatography (1:3 EtOAc:hexane) provided compound 92 (0.017 g, 46%) along with recovered keto diol 66 (0.016 g, 37%).

^{1}H NMR(200 MHz, $CDCl_3$): 3.81(dt, J=9.6 Hz and 4.4 Hz, 1H), 3.61(s, 1H), 2.21-2.47(m, 2H), 1.05-2.16(m, 12H). ^{13}C NMR(75.4 MHz, $CDCl_3$): 215.6, 69.5, 62.1, 43.1, 42.2, 33.8, 32.9, 32.3, 26.3, 23.6.

cis-8a-[[(Benzyloxy)methoxy]methyl]-8β-methyl-8α-hydroxy-2,3,4,4a,5,6-hexahydronaphthalene-1-one (96)

To a solution of the symmetric diketone 40 (0.055 g, 0.18 mmol) in 2.4 mL dry ether under argon at -78°C was added MeLi (0.16 mL, 0.22 mmol) dropwise. After stirring the solution for 1 h at -78°C, it was allowed to warm up to -30°C and stirred at this temperature for 14 h. The mixture was then stirred at -5°C for an additional 2 h, at which time the reaction was quenched with saturated ammonium chloride solution and the aqueous layer extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.043 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 96 (0.017 g, 29%) as a clear oil as well as recovered starting material 40 (0.017 g, 31%).

^{1}H NMR(200 MHz, $CDCl_3$): 7.30-7.37(m, 5H), 4.75(s, 2H), 4.60(s, 2H), 3.98(q, J=10 Hz, 2H), 3.98(m, hidden under quartet, 1H), 2.54-2.71(m, 1H), 2.23-2.47(m, 3H), 1.23-2.11(m, 10H), 1.15(s, 3H). IR($CHCl_3$ solution): 3493, 2944, 1691, 1454, 1236, 1026 cm^{-1}. MS: 333(62, $M+H^+$), 225(19), 207(100), 195(11). Exact mass calcd for $C_{20}H_{29}O_4+H^+$: 333.2066, found: 333.2067. ^{13}C NMR(75.4 MHz, $CDCl_3$): 217.1, 137.8, 132.7, 128.5, 127.9, 126.2, 95.2, 74.2, 69.9, 68.4, 59.3, 40.6, 39.1, 38.5, 29.7, 28.4, 26.4, 24.3, 21.7.

cis-8a-[[(Benzyloxy)methoxy]methyl]-1β-methyl-1α-hydroxy-8β-methyl-8α-hydroxy-2,3,4,4a,5,6-hexahydronaphthalene (95)

To a solution of the diketone 40 (0.091 g, 0.29 mmol) in 3.20 mL ether at -40°C under argon was added 1.4M MeLi (0.22 mL, 0.31 mmol), causing the solution to turn cloudy orange. The solution was stirred for 2 h at -40°C and 1 h at 0°C , at which time saturated ammonium chloride solution was added. The aqueous layer was extracted with ether and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide the crude product. Column chromatography (1:4 EtOAc: hexane) provided the product 95 (0.037 g, 32%) as a yellow oil.

^{1}H NMR(200 MHz, $CDCl_3$): 7.35(s, 5H), 4.77(s, 2H), 4.64(s, 2H), 3.73(s, 2H), 2.20-2.50(broad singlet, 2H), 1.20-2.05(m, 10H), 1.50(s, 6H). IR($CHCl_3$ solution): 3544, 2930, 1445, 1232, 1118, 1089 cm^{-1}. MS: 349(4, $M+H^+$), 334(11), 313(7), 223(7), 210(19), 205(15), 193(100), 175(23). ^{13}C NMR(75.4 MHz, $CDCl_3$): 137.4, 128.6, 127.9, 127.8, 95.4, 77.6, 75.4, 70.6, 49.0, 40.3, 39.1, 28.3.

***cis*-8a-[[(Benzyloxy)methoxy]methyl]-8-methyl-2,3,4,4a,5,6-hexahydro-naphthalene-1-one (97) and *cis*-8a-[[(Benzyloxy)methoxy]methyl]-8-exo-methylene-2,3,4,4a,5,6,7-heptahydronaphthalene-1-one (98)**

To a solution of compound 96 (0.028 g, 0.085 mmol) in 2 mL dichloromethane at 0°C under argon was added a solution of the Martin sulfurane (0.161 g, 0.24 mmol) in 0.8 mL dichloromethane. The mixture was then slowly heated to reflux (40°C) and refluxed for 7 h.. At this point, the mixture was allowed to cool, the solvent evaporated. The crude mixture was directly subjected to column chromatography (1:6 EtOAc:hexane) providing compound 97 (0.010 g, 37%) and compound 98 (0.007 g, 26%) along with recovered starting material 96 (0.011 g, 39%).

When the amount of Martin sulfurane reagent was increased to 3.5 equivalents and the reaction mixture refluxed for 4 h, compound 97 was formed in 78% together with 10% recovered starting material 96.

97: ^{1}H NMR(200 MHz, $CDCl_3$): 7.25-7.47(m, 5H), 5.62(broad s, 1H), 4.82 and 4.74(AB, J=7.2 Hz, 2H), 4.64 and 4.58(AB, J=10 Hz, 2H), 4.15 and 3.47(AB, J=10 Hz, 2H), 1.58-2.61(m, 11H), 1.49(s, 3H). IR($CHCl_3$ solution): 2938, 1701, 1454, 1233, 1176, 1104, 1026 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 212.1, 138.3, 128.5, 128.1, 127.8, 125.9, 113.6, 95.2, 69.5, 68.7, 58.1, 40.8, 35.6, 26.6, 24.7, 22.7, 21.7, 20.2.

98: ^{1}H NMR(200 MHz, $CDCl_3$): 7.05-7.42(m, 7H), 4.75(s, 2H), 4.62(s, 2H), 4.07 and 3.59(AB, J=10 Hz, 2H), 2.66(broad s, 2H), 1.21-2.22(m, 11H). ^{13}C NMR(75.4 MHz, $CDCl_3$): 210.4, 145.1, 135.1, 128.9, 128.6, 127.8, 127.4, 125.7, 106.1, 95.2, 69.4, 67.6, 58.9, 38.9, 35.9, 32.3, 28.2, 27.9, 27.0, 17.1.

cis-8a-[[(Benzyloxy)methoxy]methyl]-3-phenylthio-2,4a,5,6,7-pentahydro-naphthalene-1,8-dione (99)

To a solution of hexamethyldisilazane (0.050 mL, 0.23 mmol) in 1.0 mL of dry THF under argon at -78°C was added 2.5 M nBuLi (0.080 mL, 0.20 mmol) dropwise. After stirring the solution for 10 min at -78°C, HMPA (0.13 mL, 0.76 mmol) was added. The mixture was then warmed slightly above -78°C for about 5 min to dissolve the frozen crystals of HMPA. After recooling the solution to -78°C, a solution of compound 36 (0.064 g, 0.15 mmol) in 1.0 mL dry THF was added dropwise. After stirring the solution for 2 h at -78°C, the reaction was quenched with saturated ammonium chloride solution at -78°C and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.071 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 99 (0.026 g, 41%) as a clear oil, along with recovered starting material 36 (0.038 g, 59%).
^{1}H NMR(200 MHz, $CDCl_3$): 7.22-7.39(m, 10H), 5.97-6.00(m, 1H), 4.74(s, 2H), 4.59(s, 2H), 4.00 and 3.93(two diastereotopic protons, AB, J=9.5 Hz, 2H), 3.12 and 2.93(AB, J=22 Hz, 2H), 3.03(m, hidden under AB system, 1H), 2.47(t, J=6 Hz, 2H), 1.55-2.14(m, 5H). IR($CHCl_3$ solution): 3012, 1722, 1636, 1577, 1474, 1229, 1114, 1041 cm^{-1}. MS: 440(100, $M+NH_4^+$), 423(29, $M+H^+$), 410(10), 393(48), 315(17). Exact mass calcd for $C_{25}H_{26}O_4S+H^+$: 423.1630; found: 423.1631. ^{13}C NMR(75.4 MHz, $CDCl_3$): 207.7, 204.7, 137.7, 132.2, 131.9, 130.8, 129.3, 128.5, 128.0, 127.8, 95.1, 69.8, 66.4, 65.8, 43.0, 42.9, 40.2, 28.8, 23.8.

Ethylene ketal of _cis_-8a-[[(Benzyloxy)methoxy]methyl]-3-phenylthio-2,4a,-5,6, 7-pentahydronaphthalene-1,8-dione (100)

The reaction was performed as above with ketal 46 (0.036 g, 0.077 mmol). Column chromatography (1:3.5 EtOAc:hexane) of the crude material provided the product 100 (0.026 g, 70%) as a clear oil, along with some recovered 46 (0.010 g, 30%).

^{1}H NMR(200 MHz, $CDCl_3$): 7.24-7.43(m, 10H), 6.18(s, 1H), 4.71 and 4.67(AB, J=4.5 Hz, 2H), 4.29(part of AB, J=10 Hz, 1H), 3.76-3.94(m, 5H), 3.13(broad s, 1H), 2.98(s, 2H), 1.43-1.83(m, 6H). IR($CHCl_3$ solution): 2949, 1712, 1641, 1593, 1442, 1229, 1212, 1105, 1041 cm^{-1}. MS: 484(6, $M+NH_4^+$), 467(100, $M+H^+$), 329(14), 297(8). Exact mass calcd for $C_{27}H_{30}O_5S+H^+$: 467.1892, found: 467.1891. ^{13}C NMR(75.4 MHz, $CDCl_3$): 207.2, 137.8, 135.6, 133.6, 130.9, 128.9, 128.4, 128.1, 127.8, 127.7, 127.0, 110.3, 95.1, 69.6, 67.0, 64.9, 64.1, 57.7, 44.7, 38.6, 32.3, 28.1, 20.6.

cis-8a-[[(Benzyloxy)methoxy]methyl]-2,4a,5,6,7-pentahydronaphthalene-1,8-dione (101)

The reaction was performed as above with enone **39** (0.047 g, 0.15 mmol). After stirring at -78°C for 6 h, saturated ammonium chloride solution was added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide the crude product. Column chromatography (1:4 EtOAc:hexane) provided the product **101** (0.017 g, 36%) as a clear oil along with recovered **39** (0.012 g, 24%).

^{1}H NMR(200 MHz, $CDCl_3$): 7.23-7.42(m, 5H), 5.76(s, 2H), 4.77(s, 2H), 4.61(s, 2H), 3.99(q, J=9.6 Hz, 2H), 3.06 and 2.88(AB, J=22 Hz, plus an extra proton, 3H), 2.43-2.56(m, 2H), 1.49-2.15(m, 4H). IR($CHCl_3$ solution): 2944, 1722, 1717, 1455, 1229, 1042 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 207.6, 206.4, 137.8, 129.7, 128.4, 128.0, 127.7, 124.5, 95.2, 69.7, 67.1, 65.9, 43.0, 40.4, 39.2, 28.8, 23.9.

Ethylene ketal of _cis_-8a-[[(Benzyloxy)methoxy]methyl]-2,4a,5,6,7-pentahydronaphthalene-1,8-dione (102)

The reaction was performed as above with enone **62** (0.038 g, 0.11 mmol). After stirring at -78°C for 2 h, saturated ammonium chloride solution was added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium

sulfate, filtered and the solvent removed to provide 0.060 g crude material. Column chromatography (1:4 EtOAc:hexane) gave the product 102 (0.020 g, 50%) as a clear oil together with some recovered starting material 62 (0.005 g, 15%). ^{1}H NMR(200 MHz, $CDCl_3$): 7.23-7.41(m, 5H), 5.74-5.85(m, 2H), 4.70(s, 2H), 4.55(s, 2H), 4.18(AB, J=10 Hz, 1H), 3.71-4.04(m, 5H), 2.79-3.03(m, 3H), 1.17-1.95(m, 6H). IR($CHCl_3$ solution): 2938, 1716, 1669, 1232, 1215, 1199, 1045 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 208.1, 137.9, 130.8, 128.4, 127.8, 123.6, 110.3, 95.3, 95.2, 69.5, 67.5, 65.1, 63.9, 59.1, 40.9, 39.7, 32.0, 29.0, 21.2.

Ethylene ketal of *cis*-8a-[[(Benzyloxy)methoxy]methyl]-3-methoxy-4a,5,6,-8a-tetrahydronaphthalene-1,8(4H,7H)-dione (106)

Sodium hydride (0.010 g, 0.42 mmol) was added to 1.00 mL methanol at -78°C under argon , followed by the addition of a solution of the starting material 46 (0.053 g, 0.11 mmol) in 2.00 mL of 1:1 methanol:THF (since the compound did not dissolve in methanol alone). The mixture was then slowly warmed to 72°C and refluxed overnight. The methanol was then removed under reduced pressure and saturated ammonium chloride solution and ether were added. Extraction of the aqueous layer, followed by drying over magnesium sulfate, filtering and removing the solvent under vacuum provided the crude product. Column chromatography (1:1 EtOAc:hexane) provided the product 106 (0.028 g, 63%) as a pale yellow oil.

^{1}H NMR(200 MHz, $CDCl_3$): 7.29-7.36(m, 5H), 5.46(s, 1H), 4.76 and 4.72(AB, J=6.6 Hz, 2H), 4.60 and 4.53(AB, J=12 Hz, 2H), 4.42(part of AB, J=9.5 Hz, 1H), 3.75-3.89(m including other part of AB, 5H), 3.69(s, 3H), 2.79-3.13(m, 2H), 2.09(dd, J=4.5 Hz, J=16 Hz, 1H), 1.40-2.88(m, 6H). IR(neat): 2925, 1648, 1442, 1384, 1223, 1168, 1105, 1058 cm^{-1}. MS: 389(100, M+H$^+$), 281(7). Exact mass calcd for $C_{22}H_{29}O_6$+H$^+$: 389.1964, found: 389.1966. ^{13}C NMR(75.4 MHz, $CDCl_3$): 198.7, 178.3, 138.0, 128.3,

127.9, 127.6, 110.6, 103.6, 95.2, 69.5, 67.3, 65.1, 64.7, 55.4, 55.3, 33.0, 32.7, 31.6, 25.4, 18.6.

3-Phenylthio-5-(4-carbomethoxy-butanyl)-6-exomethylene-2-cyclohexen-1-one (107)

To a THF solution containing sodium hydride (0.003 g, 0.14 mmol) and methanol (0.01 mL, 0.14 mmol) at -78°C under argon was added a solution of the alkylated decalin 36 (0.039 g, 0.093 mmol) in 1.00 mL THF. After stirring for 30 min at -78°C, saturated ammonium chloride solution was added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.030 g crude material. Column chromatography (1:4 EtOAc:hexane) provided the product 107 (0.029 g, 93%) as a pale yellow oil.

107: ^{1}H NMR(200 MHz, $CDCl_3$): 7.42-7.51(m, 5H), 6.00(s, 1H), 5.55(s, 1H), 5.27(s, 1H), 3.68(s, 3H), 2.76-2.89(m, 2H), 2.22-2.49(m, 3H), 1.49-1.72(m, 4H). IR(neat): 2946, 1741, 1659, 1609, 1577, 1440, 1305, 1276, 1195, 1024 cm^{-1}. MS: 317(100, $M+H^+$). Exact mass calcd for $C_{18}H_{20}O_3S+H^+$: 317.1211; found: 317.1213. ^{13}C NMR(75.4 MHz, $CDCl_3$): 185.6, 173.8, 165.4, 145.7, 135.5, 135.4, 130.3, 130.0, 128.0, 120.6, 119.7, 51.6, 41.1, 36.2, 33.9, 32.0, 22.5.

3-Phenylthio-5-(4-carbomethoxy-butanyl)-6-methoxymethyl-2-cyclohexen-1-one (109)

Sodium hydride (0.012 g, 0.51 mmol) was added to 2.00 mL methanol at -78°C under argon. After stirring for 20 min at -78°C, a solution of the alkylated decalin 36 (0.130 g, 0.31 mmol) in 2.50 mL methanol was added dropwise. After stirring for 30 min at -78°C, the mixture was warmed to 0°C. After stirring for 4.5 h at 0°C, saturated ammonium chloride solution was added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent

removed to provide 0.095 g crude material. Column chromatography (1:4 EtOAc:hexane) provided 107 (0.011 g, 11%), 109 (0.026 g, 24%) and some recovered decalin 3 (0.014 g, 17%). See previous procedure for spectral data of compound 107.

109: ^{1}H NMR(200 MHz, $CDCl_3$): 7.32-7.53(m, 5H), 5.45(s, 1H), 3.84 and 3.51(AB, each dd, J= 4.4 or 3.7 Hz, and J= 9.5 Hz, 2H), 3.67(s, 3H), 3.29(s, 3H), 2.56-2.77(m, 2H), 2.15-2.42(m, 4H), 1.29-1.83(m, 4H). IR($CHCl_3$ solution): 3028, 1733, 1646, 1577, 1442, 1221, 1202, 1177 cm^{-1}. MS: 349(100, $M+H^+$). Exact mass calcd for $C_{19}H_{24}O_4S+H^+$: 349.1474; found: 349.1474. ^{13}C NMR(75.4 MHz, $CDCl_3$): 195.2, 173.8, 165.0, 135.5, 130.2, 129.9, 128.0, 120.4, 69.7, 69.0, 59.1, 51.6, 50.1, 35.2, 34.0, 32.3, 22.0.

3-Phenylthio-5-(4-carbomethoxy-butanyl)-6-[[(benzyloxy)methoxy]-methyl]-2-cyclohexen-1-one (108)

Sodium hydride (0.010 g, 0.40 mmol) was added to 1.50 mL methanol at -78°C under argon. After stirring for 10 min at -78°C, a solution of the alkylated decalin 36 (0.085 g, 0.20 mmol) in 1.50 mL methanol was added dropwise. After stirring for 30 min at -78°C and 1 h at 0°C, saturated ammonium chloride solution was added and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide the crude material. Column chromatography (1:4 EtOAc:hexane) provided 107 (0.040 g, 64%), 108 (0.030 g, 33%), and some recovered decalin 3 (0.008 g, 15%). The spectral data for compound 107 was identical to that already described above.

108: ^{1}H NMR(200 MHz, $CDCl_3$): 7.21-7.54(m, 10H), 5.48(s, 1H), 4.74 and 4.69(AB, J=6.7 Hz, 2H), 4.60 and 4.52(AB, J=11.5 Hz, 2H), 4.15 and 3.72(ABX, J=9.7 Hz and 4.3Hz, 2H), 3.66(s, 3H), 2.56-2.87(m, 2H), 2.11-2.48(m, 4H), 1.01-1.83(m, 4H). ^{13}C NMR(75.4 MHz, $CDCl_3$): 165.1, 135.5, 130.2, 129.9, 128.4, 127.9, 127.7, 120.5, 107.5, 97.5, 94.9, 69.4, 64.1, 51.4, 35.3, 34.0, 32.2.

3-Phenylthio-5-(4-benzyloxycarbonyl-butanyl)-6-methyl-phenol (110)

To a solution of benzyl alcohol (0.02 mL, 0.29 mmol) in 0.8 mL THF at -78°C under argon was added sodium hydride (0.005 g, 0.20 mmol). After stirring the suspension for 20 min at -78°C, a solution of compound 107 (0.025 g, 0.08 mmol) in 0.8 mL THF was added. The mixture was allowed to warm up to -30°C and stirred at this temperature for 3 h, at which time the reaction was quenched by the addition of saturated ammonium chloride solution. The aqueous layer was extracted with ether; and the combined ether extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 0.028 g crude material. Column chromatography (1:4 EtOAc:hexane) provided compound 110 (0.0211 g, 67%).

^{1}H NMR(200 MHz, $CDCl_3$): 7.10-7.40(m, 10H), 6.78(s, 1H), 6.61(s, 1H), 5.11(s, 2H), 2.59(t, J=10 Hz, 2H), 2.37(t, J=10 Hz, 2H), 2.13(s, 3H), 1.87(dt, J=3 Hz and J=9 Hz, 2H). IR($CHCl_3$ solution): 3010, 1733, 1576, 1478, 1232, 1199, 1024 cm^{-1}. ^{13}C NMR(75.4 MHz, $CDCl_3$): 173.2, 154.4, 142.3, 132.5, 136.4, 130.5, 129.1, 128.5, 128.4, 127.6, 126.8, 125.1, 121.9, 115.9, 66.3, 33.8, 32.8, 25.4, 11.1.

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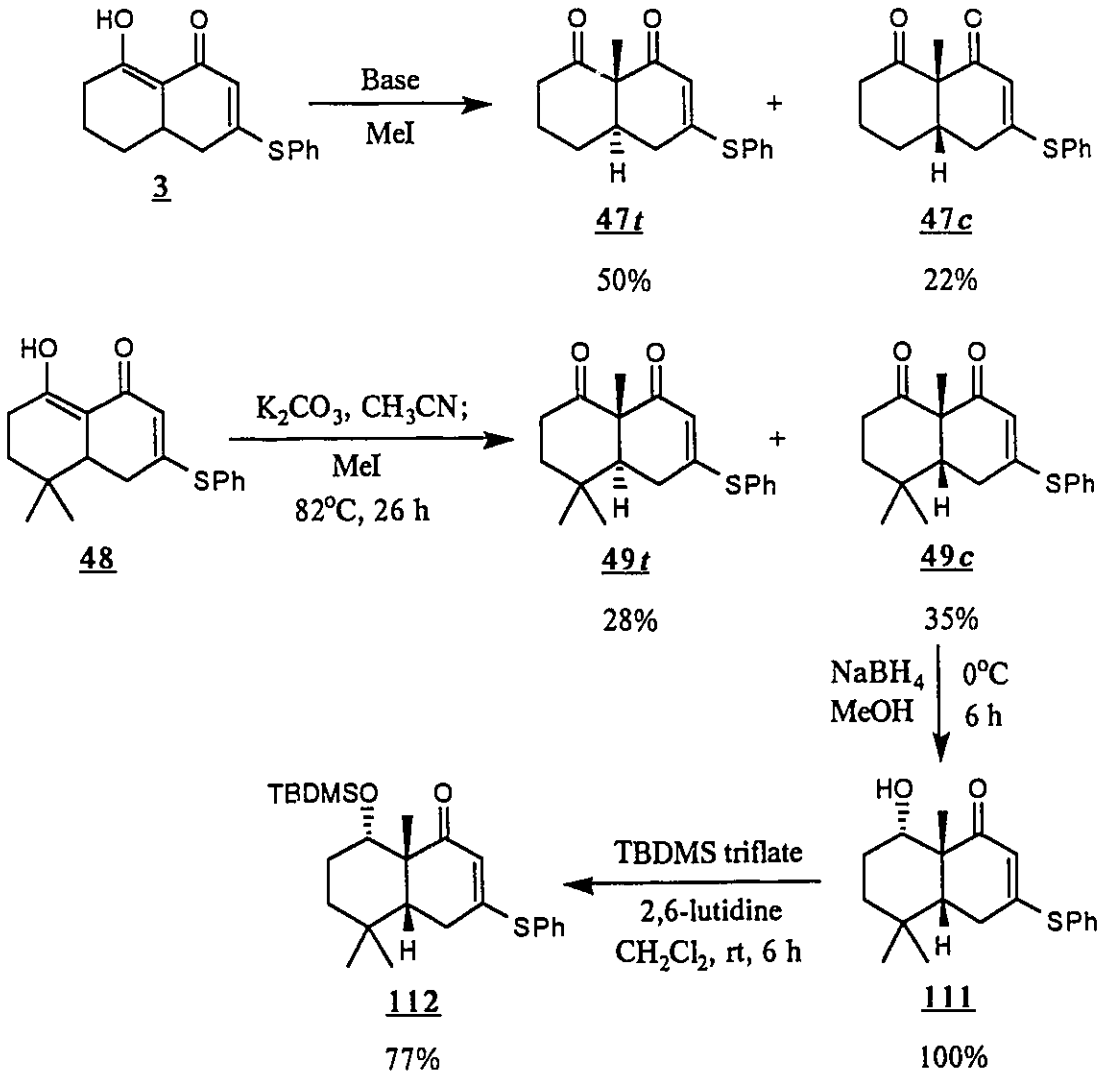
CHAPTER 6

BIOLOGICAL ACTIVITY OF THE ANGULARLY FUNCTIONALIZED DECALIN COMPOUNDS

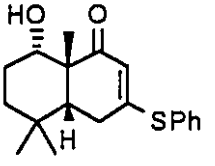
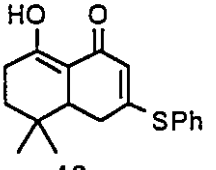
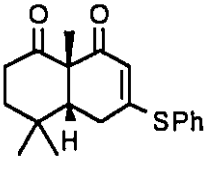
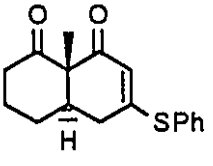
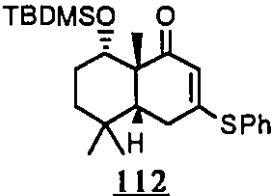
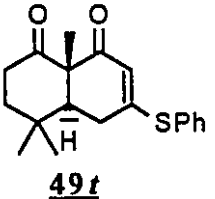
6.1 Introduction

Most of the angularly functionalized decalin compounds prepared during the course



Scheme 6.1

Table 6.1 Biological assays[1]

Compound	Code	Mean instar	% of 6th instars
Control	a	5.20	46
 **111**	a	5.20	24
 **48**	ab	4.98	26
 **49*c***	bc	4.60	8
 **47*t***	c	4.42	8
 **112**	c	4.30	10
 **49*t***	c	4.34	4

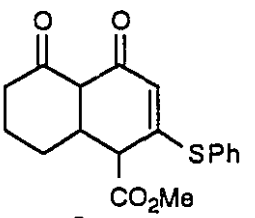
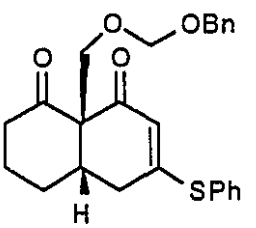
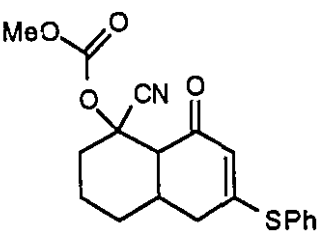
of this work have been tested for biological activity against the spruce budworm, *Choristoneura fumiferana.* The biological testing was carried out at the Fredericton Forestry Centre in New Brunswick by Annalise Salonius and Marilyn Chiasson under the direction of Dr. A. W. Thomas and Dr. G. M. Strunz. Recently our laboratory reported the synthesis and biological activity of some functionalized decalin compounds against the spruce budworm.[1] Some of these results have been included here in **Scheme 6.1** and **Table 6.1** for comparison purposes.

6.2 Biological Activity of the Angularly Functionalized Decalin Compounds

Tables 6.2 to **6.7** present the biological assay results of the angularly functionalized decalin compounds in the chronological order in which the compounds were tested. It is important not to combine all of the results into one Table, since it can be seen that the control in each experiment is significantly different from the controls in the other experiments. The results of each compound should be regarded with respect to the corresponding control of the respective biological assay concerned.

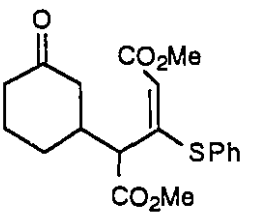
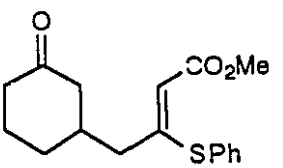
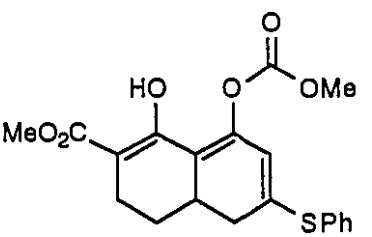
Each bioassay involved feeding laboratory-colony spruce budworm larvae on artificial McMorran[2] diet containing 0.2% wet weight (2000 ppm) of the test compounds. In the assay, newly emerged 2nd-instar larvae were reared individually at 26°C, 17 h photoperiod, 50 replicates per test compound. At the point at which approximately 50% of the controls had reached the final (6th) instar, the larvae were sacrificed and their developmental stage determined. The mean development stage (instar) of the larvae on each treatment diet was determined (mean instar in the Tables) as well as the proportion of 6th instars remaining. Because the data are clearly nonparametric, the rank transformation approach[3] was used for the purpose of statistical analysis. In each set of biological assays, all the ob-

Table 6.2 Biological assays

Compound	Code	Mean instar	% of 6th instars
Control	a	5.36	42
 **8**	bc	4.60	14
 **36**	c	4.28	0
 **28**	c	3.52	0

servations (the instar of each of the total number of larvae in a set, ex. the instar of each of the 200 larvae in set 1 in **Table 6.2**) were ranked from the largest to the smallest, with average ranks assigned in cases of ties. The compounds were then listed in descending order according to their mean rank values. A one-way analysis of variance applied to the rank values allowed us to test nonparametrically for intercompound differences.[4,5] Significant differences were detected between the compounds in the biological assays outlined in **Tables 6.2, 6.3, 6.5** and **6.6** and a Tukey-type multiple comparison test,

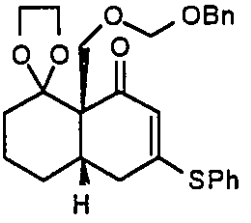
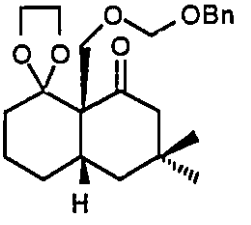
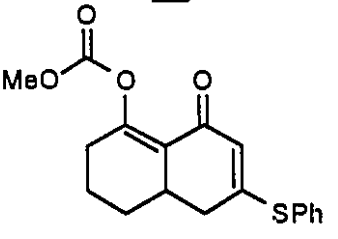
Table 6.3 Biological assays

Compound	Code	Mean instar	% of 6th instars
Control	a	5.12	42
 **13E**	a	5.16	35
 **2Z**	a	5.10	33
 **27**	ab	4.63	18

using rank sums instead of means, was performed to locate the differences.[4,5] Compounds followed by the same letter ("code" in the Tables) were not significantly different at the 5% level ($P > 0.05$) in their effect on the development rate of budworm larvae. No significant difference was found between the compounds in the biological assays outlined in **Tables 6.4** and **6.7.**

The biological assay showed that the development of larvae reared from second instar on artificial diets containing 0.2% wet weight (2000 ppm) of the test compounds was

Table 6.4 Biological assays

Compound	Code	Mean instar	% of 6th instars
Control	a	5.36	42
 **46**	a	5.32	42
 **75**	a	5.30	50
 **26**	ab	5.06	24

significantly retarded by compounds (listed here in chronological order of testing) **8**, **36**, **28**, **27**, **62**, **65**, **39**, and **58**, but not by the other compounds. The level of activity of compounds **27**, **62**, **65**, and **58** is comparable to that of the specionin analog reported previously by our laboratory[6] (see **Table 6.8**), as is the level of activity of compounds ***47t***, ***49c***, ***49t***, and **112** shown in **Table 6.1**, also reported previously.[1] However, the activity of compounds **36** and **39** is slightly better than the activity of the latter compounds and the activity of compound **28** is superior to all of the other compounds.

Table 6.5 Biological assays

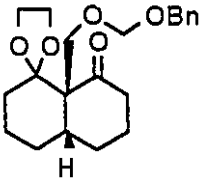
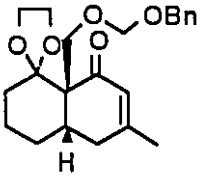
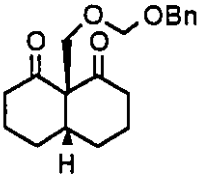
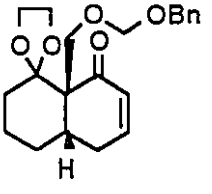
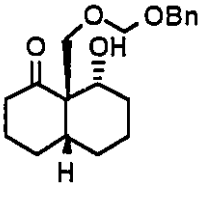
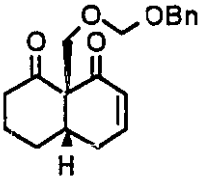
Compound	Code	Mean instar	% of 6th instars
Control	a	5.00	36
 **63**	ab	4.80	30
 **74**	ab	4.56	32
 **40**	ab	4.50	14
 **62**	b	4.42	10
 **65**	b	4.38	14
 **39**	bc	4.18	10

Table 6.6 Biological assays

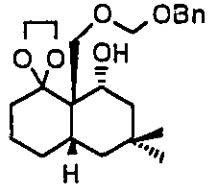
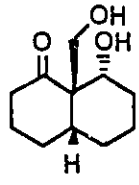
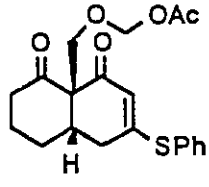
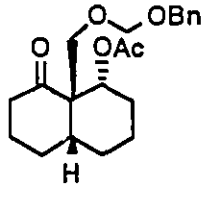
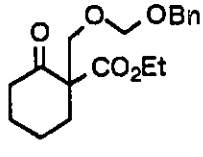
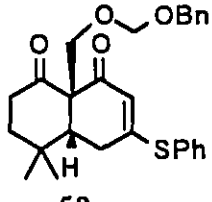
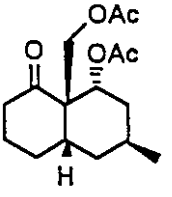
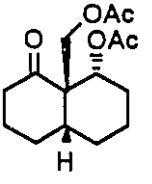
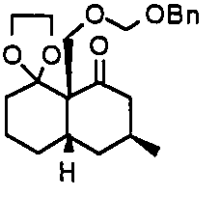
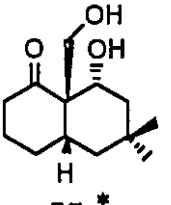
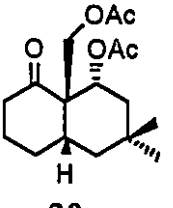
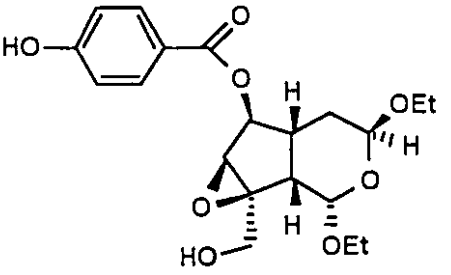
Compound	Code	Mean instar	% of 6th instars
Control	a	5.64	70
 **76**	ab	5.48	56
 **66**	ab	5.46	52
 **54**	ab	5.30	50
 **68**	ab	5.28	48
 **56**	ab	5.28	46
 **58**	b	5.22	34

Table 6.7 Biological assays

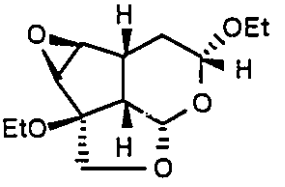
Compound	Code	Mean instar	% of 6th instars
Control	a	5.54	60
 **19** *	a	5.24	54
 **18**	a	5.12	48
 **69**	a	5.10	34
 **77** *	a	5.08	40
 **20**	a	4.96	38

* tested at 0.1% wet weight

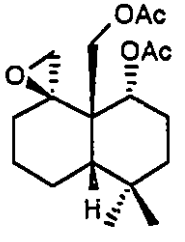


specionin

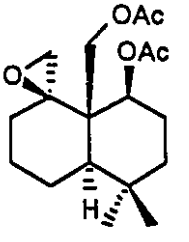
Table 6.8 Biological assays[6]

Compound	Mean instar
Control	5.28
 specionin analog	4.36

Several conclusions can be drawn from the structure-activity relationship observed. The absence of activity in the monocyclic compounds 2Z, 13E, and 56 suggests that the oxygen functionalities, generally considered responsible for biological activity, have to be fixed in their relative positions, a conclusion already reached earlier by our laboratory.[1] The nature of the oxygen function is of critical importance, with the hydroxy and ketal groups generally giving the inactive compounds, with the exception of the moderate activity demonstrated by compounds 62 and 65. Surprisingly the keto diacetates 18, 19 and 20 showed no significant activity. It was expected that since both the *cis*- and *trans*-fused decalin compounds synthesized by Ley *et al.*[7] showed definite activity against *Locusta mi-*



cis-decalin
active at 1000 ppm



trans-decalin
active at 100 ppm

gratoria (see **Table 1.4 in Chapter 1**), that the keto diacetates 18 - 20 would also show some activity against *Choristoneura fumiferana*. Interestingly, the simple decalins 36, 39

and 58, featuring the benzyloxymethoxymethyl moiety, are definitely active. The surprising activity of decalin 28, the most active compound submitted for testing against the spruce budworm by our laboratory thus far, may be due to the presence of the cyano functionality.

Experimental

Diet containing 0.2% wet weight of the test compounds was prepared by treating lyophilized McMorran[2] diet with a solution of the test compound in methylene chloride and then removing the solvent completely at 30°C on a rotary 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. In the biological assay, newly-emerged 2nd-instar larvae were reared individually at 26°C, 17 h photo-period, 50 replicates per test compound. Once 50% of the control larvae had reached the 6th instar, the larvae were sacrificed and their mean development stage determined.

References

1. Chan, T. H.; Guertin, K. R.; Prasad, C. V. C.; Thomas, A. W.; Strunz, G. M.; Salonius, A.; *Can. J. Chem.* **1990**, 68, 1170.

2. McMorran, A.; *Can. Entomol.* **1965**, 97, 58.

3. Conover, W. J. and Iman, R. L.; *Am. Stat.* **1981**, 35, 124.

4. SAS User's Guide: Statistics, Version 5; 1985 Edition, SAS Institute Inc., Cary, N. C., U. S. A.

5. Zar, J. H.; Biostatistical analysis; 2nd ed. Prentice-Hall, New York, 1984.

6. Chan, T. H.; Zhang, Y. J.; Sauriol, F.; Thomas, A. W.; Strunz, G. M.; *Can. J. Chem.* **1987**, 65, 1853.

7.a) Jackson, W. P. and Ley, S. V.; *J. Chem. Soc. Perkin Trans I* **1981**, 1516.

b) Ley, S. V.; Neuhaus, D.; Simpkins, N. S.; Whittle, A. J.; *J. Chem. Soc. Perkin Trans I* **1982**, 2157.

CONCLUSION

The (2C+4C) annelation reaction, based on a tandem Michael-Claisen condensation, developed earlier in our laboratory, has been extended to include siloxy diene 1-(*tert*-butyldimethylsiloxy)-1-methoxy-3-(phenylthio)-5-(methoxycarbonyl)-penta-1,3-dienoate, which acts as a remarkably facile Michael donor in its reaction with the α,β-unsaturated carbonyl compound 2-cyclohexen-1-one under Lewis acid catalyzed conditions.

A hydroxymethylation procedure was developed which permitted the incorporation of a hydroxymethylene moiety, protected as its benzyloxymethoxy ether, at the angular position of 1,8-β-dicarbonyl decalin compounds when these were treated with diisopropylethylamine and benzyl chloromethyl ether in the presence of paraformaldehyde. The stereochemistry of *cis*-8a-[[(benzyloxy)methoxy]methyl]-3-(phenylthio)-4a,5,6,8a-tetrahydronaphthalene-1,8(4H,7H)-dione was confirmed by X-ray analysis of its ethylene ketal derivative, thus indicating that this procedure produced mainly the *cis* isomer. The intermediacy of an aldol adduct featuring an oxymethylene moiety at the angular position was confirmed by the isolation of ethyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate when the hydroxymethylation procedure was applied to keto ester ethyl 2-oxocyclohexanecarboxylate.

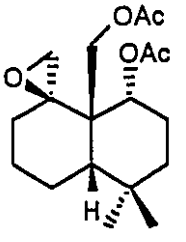
When the benzyl chloromethyl ether reagent was replaced by acetic anhydride, an acetoxymethoxymethylene moiety was incorporated at the angular position. This suggests that benzyl chloromethyl ether could be replaced by other reagents, such as trimethylsilyltriflate, to prepare a variety of angularly functionalized decalin compounds, presumably providing predominantly the *cis* isomer.

The β-dicarbonyl decalin compounds featuring a protected hydroxymethylene moiety at the angular position will undergo a retro aldol reaction under acidic or strongly basic conditions. They must therefore be treated only under mildly acidic or basic conditions.

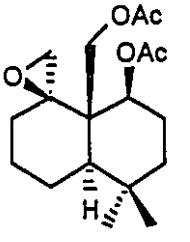
The *cis*-fused β-dicarbonyl benzyloxymethoxy decalin derivatives are mainly approached from the β-face by reagents, as evidenced by the α-alcohols produced upon reduction of the ketone moieties in these compounds. The stereochemistry of the α-alcohols was confirmed by ^{1}H NMR, NOE and X-ray analysis.

Once one of the ketone functionalities has been reduced, it becomes exceedingly difficult to effect a reaction on the other ketone moiety, due to the nature of the *cis*-fused decalin system. This was demonstrated by the numerous unsuccessful methylenation attempts on the protected keto diol *cis*-decalin. On the other hand, a monocyclic β-dicarbonyl benzyloxymethoxy derivative readily underwent a Wittig reaction to provide the exocyclic double bond.

Most of the angularly functionalized decalin compounds were tested for biological activity against the spruce budworm, *Choristoneura fumiferana*. Seven of the compounds were found to be as active, if not more active, than a specionin analog prepared and tested earlier by our laboratory. Interestingly, it was the simple decalin compounds which exhibited the most activity. The three keto diaceteates were not active.



cis-decalin
active at 1000 ppm



trans-decalin
active at 100 ppm

Ley *et al.*[1] found that when they tested a *cis*- and a *trans*-epoxydiacetate decalin for biological activity against *Locusta migratoria*, the *trans*-fused decalin exhibited ten times the activity of the *cis*-fused decalin. Thus, a *trans* decalin seems to mimic more closely the activity of the natural product clerodin, which has itself a *trans*-fused ring junction.

On the other hand, the surprisingly strong activity exhibited at 2000 ppm by the decalin compound featuring a cyano moiety points out that even simple compounds may serve as effective antifeedants against the spruce budworm.

References

1.a) Jackson, W. P. and Ley, S. V.; *J. Chem. Soc. Perkin Trans I* **1981**, 1516.

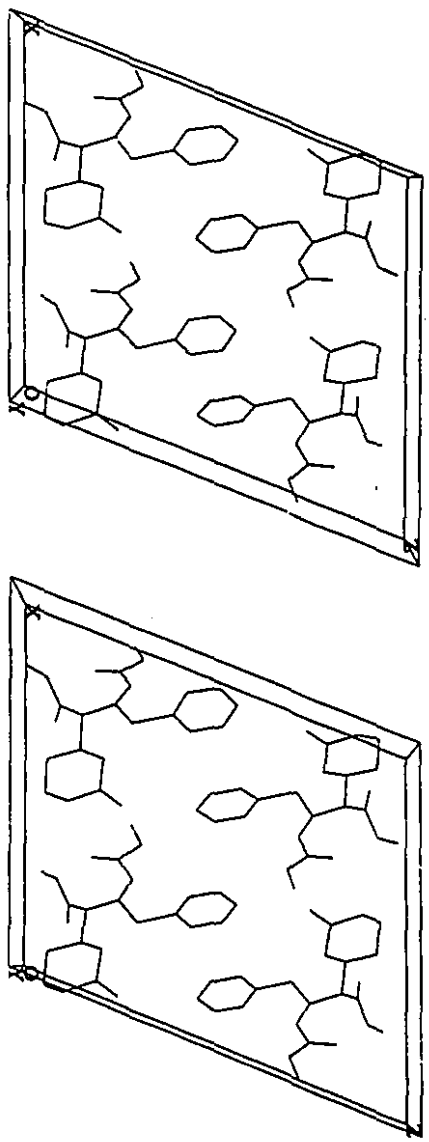
b) Ley, S. V.; Neuhaus, D.; Simpkins, N. S.; Whittle, A. J.; *J. Chem. Soc. Perkin Trans I* **1982**, 2157.

Appendix A

X-ray Structure Report

for

Compound (13E)



ANNET2 - CHAN - OCT 24/91

Space Group and Cell Dimensions Monoclinic, P 21/a
a 16.752(5) b 6.4150(11) c 19.031(4)
beta 111.841(17)
Volume 1898.4(8)A**3

Empirical formula : C19 H22 O5 S

Cell dimensions were obtained from 23 reflections with 2Theta angle in the range 38.00 - 45.00 degrees.

Crystal dimensions : 0.30 X 0.30 X 0.30 mm

FW = 362.44 Z = 4 F(000) = 768.75

Dcalc 1.268Mg.m-3, mu 0.19mm-1, lambda 0.70930A, 2Theta(max) 45.0

The intensity data were collected on a Rigaku diffractometer, using the theta/2theta scan mode.
The h,k,l ranges are :-- -18 16, 0 6, 0 20
No. of reflections measured 2583
No. of unique reflections 2475
No. of reflections with Inet > 2.5sigma(Inet) 1723
No correction was made for absorption

The last least squares cycle was calculated with
47 atoms, 315 parameters and 1723 out of 2475 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 0.043, Rw 0.051 GoF 2.39
For all reflections, RF 0.081, Rw 0.052.
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 0.071.

In the last D-map, the deepest hole was -0.190e/A**3,
and the highest peak 0.220e/A**3.

Secondary ext. coeff. = 0.228716 sigma = 0.101022

Standard intensities changed an average of 0.25% over the course of collection. Merging R was 5.4% for 108 pairs of symmetry equivalent reflections. Structure was solved by direct methods (SOLVER). Hydrogens were located in a difference map and refined isotropically.
All non-hydrogens were refined anisotropically. All computing for solution and refinement used NRCVAX. Diffractometer controlled by TEXRAY programs.

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

	x	y	z	Beq
S	0.24343(8)	0.33022(19)	0.29774(6)	3.84(6)
O 1	0.03501(23)	0.9729 (6)	0.26121(20)	5.74(21)
O 2	0.16514(21)	0.2317 (5)	0.11744(17)	4.30(17)
O 3	0.27467(19)	0.3721 (5)	0.09484(16)	3.82(17)
O 4	0.36216(20)	0.8700 (5)	0.19370(18)	5.05(18)
O 5	0.44578(19)	0.9165 (5)	0.31558(17)	4.00(16)
C 1	0.0524 (3)	0.9211 (7)	0.2078 (3)	3.47(24)
C 2	0.1369 (3)	0.8208 (8)	0.2184 (3)	3.00(23)
C 3	0.1306 (3)	0.6401 (7)	0.16441(23)	2.66(21)
C 4	0.0766 (3)	0.7035 (9)	0.08349(24)	3.33(25)
C 5	-0.0125 (3)	0.7735 (10)	0.0769 (3)	4.5 (3)
C 6	-0.0080 (4)	0.9586 (9)	0.1279 (3)	4.2 (3)
C 7	0.2208 (3)	0.5667 (7)	0.17184(22)	2.39(20)
C 8	0.2807 (3)	0.5314 (6)	0.25368(22)	2.49(21)
C 9	0.3509 (3)	0.6438 (7)	0.2907 (3)	2.96(23)
C10	0.3837 (3)	0.8180 (7)	0.2591 (3)	3.09(23)
C11	0.4839 (6)	1.0963 (12)	0.2947 (5)	6.0 (4)
C12	0.2157 (3)	0.3705 (7)	0.12593(21)	2.62(22)
C13	0.2750 (6)	0.1888 (10)	0.0496 (4)	5.1 (4)
C14	0.3056 (3)	0.3594 (7)	0.39560(23)	3.36(23)
C15	0.2880 (4)	0.5155 (9)	0.4366 (3)	4.8 (3)
C16	0.3351 (5)	0.5306 (11)	0.5144 (3)	6.4 (4)
C17	0.3977 (4)	0.3901 (12)	0.5499 (3)	6.3 (4)
C18	0.4144 (4)	0.2347 (12)	0.5083 (3)	6.9 (4)
C19	0.3693 (4)	0.2186 (9)	0.4305 (3)	5.1 (3)
H 2A	0.167 (3)	0.936 (7)	0.2024 (22)	4.4 (11)
H 2B	0.166 (3)	0.786 (7)	0.2750 (24)	5.0 (11)
H 3	0.1056 (21)	0.523 (6)	0.1790 (19)	2.4 (9)
H 4A	0.1082 (24)	0.821 (6)	0.0730 (21)	3.3 (10)
H 4B	0.075 (3)	0.584 (7)	0.0528 (22)	4.1 (11)
H 5A	-0.045 (3)	0.652 (7)	0.0966 (24)	6.0 (13)
H 5B	-0.048 (3)	0.807 (7)	0.0295 (24)	4.5 (12)
H 6A	0.009 (3)	1.079 (7)	0.1057 (24)	4.6 (12)
H 6B	-0.058 (3)	0.999 (6)	0.1311 (21)	3.4 (11)
H 7	0.2486 (22)	0.672 (6)	0.1500 (19)	2.5 (9)
H 9	0.3818 (22)	0.611 (5)	0.3425 (19)	2.1 (8)
H11A	0.513 (4)	1.054 (10)	0.261 (4)	10.1 (23)
H11B	0.446 (5)	1.174 (11)	0.259 (4)	11.7 (30)
H11C	0.523 (4)	1.166 (9)	0.343 (3)	8.4 (17)
H13A	0.320 (4)	0.206 (11)	0.044 (4)	10.5 (28)
H13B	0.229 (3)	0.203 (8)	-0.002 (3)	6.9 (15)
H13C	0.291 (3)	0.062 (9)	0.093 (3)	9.1 (17)
H15	0.241 (3)	0.619 (7)	0.4065 (24)	5.7 (13)
H16	0.315 (3)	0.637 (8)	0.542 (3)	7.4 (15)
H17	0.429 (4)	0.395 (9)	0.615 (3)	10.3 (18)
H18	0.460 (4)	0.134 (10)	0.539 (4)	12.0 (23)
H19	0.376 (3)	0.091 (8)	0.398 (3)	7.6 (15)

Beq is the mean of the principal axes of the thermal ellipsoid for non-hydrogen atoms. For hydrogens, Beq = Biso.

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

S-C(8)	1.775(4)	C(3)-C(7)	1.538(6)
S-C(14)	1.774(4)	C(4)-C(5)	1.519(7)
O(1)-C(1)	1.204(6)	C(5)-C(6)	1.517(8)
O(2)-C(12)	1.198(6)	C(7)-C(8)	1.523(5)
O(3)-C(12)	1.327(5)	C(7)-C(12)	1.516(6)
O(3)-C(13)	1.458(6)	C(8)-C(9)	1.335(6)
O(4)-C(10)	1.207(6)	C(9)-C(10)	1.469(6)
O(5)-C(10)	1.343(5)	C(14)-C(15)	1.368(7)
O(5)-C(11)	1.445(7)	C(14)-C(19)	1.366(7)
C(1)-C(2)	1.500(6)	C(15)-C(16)	1.398(8)
C(1)-C(6)	1.498(7)	C(16)-C(17)	1.356(11)
C(2)-C(3)	1.525(6)	C(17)-C(18)	1.365(11)
C(3)-C(4)	1.523(6)	C(18)-C(19)	1.393(8)

C(8)-S-C(14)	104.28(20)	S-C(8)-C(9)	122.6(3)
C(12)-O(3)-C(13)	115.1(4)	C(7)-C(8)-C(9)	125.1(4)
C(10)-O(5)-C(11)	116.5(4)	C(8)-C(9)-C(10)	125.8(4)
O(1)-C(1)-C(2)	121.2(4)	O(4)-C(10)-O(5)	122.7(4)
O(1)-C(1)-C(6)	121.9(4)	O(4)-C(10)-C(9)	128.2(4)
C(2)-C(1)-C(6)	116.9(4)	O(5)-C(10)-C(9)	109.1(4)
C(1)-C(2)-C(3)	114.2(4)	O(2)-C(12)-O(3)	123.5(4)
C(2)-C(3)-C(4)	110.1(4)	O(2)-C(12)-C(7)	125.5(4)
C(2)-C(3)-C(7)	110.5(3)	O(3)-C(12)-C(7)	111.0(4)
C(4)-C(3)-C(7)	111.6(3)	S-C(14)-C(15)	120.6(4)
C(3)-C(4)-C(5)	111.0(4)	S-C(14)-C(19)	119.2(4)
C(4)-C(5)-C(6)	111.4(4)	C(15)-C(14)-C(19)	120.1(4)
C(1)-C(6)-C(5)	112.2(4)	C(14)-C(15)-C(16)	120.0(6)
C(3)-C(7)-C(8)	113.0(3)	C(15)-C(16)-C(17)	120.5(6)
C(3)-C(7)-C(12)	111.0(3)	C(16)-C(17)-C(18)	119.0(6)
C(8)-C(7)-C(12)	109.9(3)	C(17)-C(18)-C(19)	121.5(6)
S-C(8)-C(7)	112.2(3)	C(14)-C(19)-C(18)	119.0(5)

Table S-2. Anisotropic u(i,j) values *100.
E.S.Ds. refer to the last digit printed

	u11	u22	u33	u12	u13	u23
S	5.65(8)	4.56(8)	3.54(7)	-1.74(7)	0.73(6)	0.68(6)
O 1	8.0 (3)	8.3 (3)	6.43(25)	1.94(22)	3.74(22)	-1.03(21)
O 2	6.16(22)	4.68(21)	5.94(22)	-1.93(19)	2.74(18)	-1.61(17)
O 3	5.81(21)	4.72(21)	5.16(20)	-0.48(17)	3.41(18)	-0.96(16)
O 4	6.45(24)	7.7 (3)	4.06(21)	-2.93(20)	0.79(18)	1.39(19)
O 5	4.77(20)	4.61(20)	5.20(21)	-2.12(17)	1.13(17)	-0.67(16)
C 1	5.6 (3)	3.7 (3)	4.3 (3)	0.10(24)	2.3 (3)	-0.34(23)
C 2	3.9 (3)	4.2 (3)	3.1 (3)	0.47(25)	1.08(23)	-0.23(24)
C 3	3.3 (3)	3.4 (3)	3.4 (3)	-0.53(22)	1.27(21)	-0.04(22)
C 4	4.0 (3)	4.9 (3)	3.0 (3)	0.4 (3)	0.45(23)	-0.25(25)
C 5	3.5 (3)	7.8 (4)	4.8 (3)	0.9 (3)	0.5 (3)	0.3 (3)
C 6	4.2 (3)	6.4 (4)	5.2 (3)	2.0 (3)	1.7 (3)	1.2 (3)
C 7	3.25(25)	3.0 (3)	2.72(24)	-0.33(21)	1.03(20)	-0.01(20)
C 8	3.55(25)	3.1 (3)	2.78(23)	0.07(22)	1.18(20)	0.15(20)
C 9	3.2 (3)	3.6 (3)	3.8 (3)	0.03(23)	0.54(23)	0.32(24)
C10	3.2 (3)	3.9 (3)	4.6 (3)	-0.25(23)	1.27(24)	0.2 (3)
C11	8.6 (5)	6.9 (5)	7.5 (5)	-4.3 (4)	3.3 (5)	-0.7 (4)
C12	3.4 (3)	3.9 (3)	2.33(23)	0.27(23)	0.68(21)	0.39(20)
C13	9.4 (5)	6.1 (4)	4.9 (4)	1.2 (4)	4.0 (4)	-1.1 (3)
C14	4.7 (3)	4.8 (3)	3.2 (3)	-0.2 (3)	1.46(23)	0.44(24)
C15	6.5 (4)	6.4 (4)	5.0 (4)	1.4 (3)	1.6 (3)	0.1 (3)
C16	10.0 (5)	8.7 (5)	6.2 (5)	0.2 (4)	3.7 (4)	-2.3 (4)
C17	8.2 (5)	11.2 (6)	4.0 (4)	0.5 (4)	1.8 (3)	0.3 (4)
C18	8.0 (5)	11.7 (6)	5.3 (4)	3.9 (4)	1.0 (4)	2.3 (4)
C19	7.4 (4)	7.6 (4)	3.8 (3)	2.2 (3)	1.6 (3)	0.8 (3)

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

Table S-3. Torsion Angles in Degreees

C14	S	C 8	C 7	-166.0(3)	C14	S	C 8	C 9	10.6(2)
C 8	S	C14	C15	76.2(3)	C 8	S	C14	C19	-106.6(3)
C13	O 3	C12	O 2	-0.9(3)	C13	O 3	C12	C 7	179.8(5)
C11	O 5	C10	O 4	2.6(3)	C11	O 5	C10	C 9	-178.5(5)
O 1	C 1	C 2	C 3	138.9(5)	C 6	C 1	C 2	C 3	-42.7(3)
O 1	C 1	C 6	C 5	-138.2(6)	C 2	C 1	C 6	C 5	43.4(3)
C 1	C 2	C 3	C 4	48.5(3)	C 1	C 2	C 3	C 7	172.3(5)
C 2	C 3	C 4	C 5	-57.4(3)	C 7	C 3	C 4	C 5	179.4(5)
C 2	C 3	C 7	C 8	48.9(3)	C 2	C 3	C 7	C12	172.9(4)
C 4	C 3	C 7	C 8	171.9(4)	C 4	C 3	C 7	C12	-64.2(3)
C 3	C 4	C 5	C 6	59.7(3)	C 4	C 5	C 6	C 1	-51.2(3)
C 3	C 7	C 8	S	63.0(2)	C 3	C 7	C 8	C 9	-113.5(4)
C12	C 7	C 8	S	-61.6(2)	C12	C 7	C 8	C 9	121.9(4)
C 3	C 7	C12	O 2	-36.2(2)	C 3	C 7	C12	O 3	143.1(4)
C 8	C 7	C12	O 2	89.5(4)	C 8	C 7	C12	O 3	-91.2(3)
S	C 8	C 9	C10	-177.3(4)	C 7	C 8	C 9	C10	-1.2(2)
C 8	C 9	C10	O 4	-12.0(2)	C 8	C 9	C10	O 5	169.2(5)
S	C14	C15	C16	177.1(5)	C19	C14	C15	C16	-0.1(3)
S	C14	C19	C18	-176.1(5)	C15	C14	C19	C18	1.2(3)
C14	C15	C16	C17	-0.7(3)	C15	C16	C17	C18	0.5(3)
C16	C17	C18	C19	0.5(3)	C17	C18	C19	C14	-1.4(3)

Table S-4. Bond Distances and Angles Involving Hydrogens

C(2)-H(2A)	1.01(4)	C(2)-H(2B)	1.03(4)
C(3)-H(3)	0.95(4)	C(4)-H(4A)	0.98(4)
C(4)-H(4B)	0.96(4)	C(5)-H(5A)	1.09(5)
C(5)-H(5B)	0.90(4)	C(6)-H(6A)	0.97(5)
C(6)-H(6B)	0.91(4)	C(7)-H(7)	0.99(4)
C(9)-H(9)	0.95(3)	C(11)-H(11A)	0.98(7)
C(11)-H(11B)	0.89(7)	C(11)-H(11C)	1.01(6)
C(13)-H(13A)	0.80(7)	C(13)-H(13B)	1.00(6)
C(13)-H(13C)	1.12(6)	C(15)-H(15)	1.02(5)
C(16)-H(16)	0.99(6)	C(17)-H(17)	1.15(6)
C(18)-H(18)	1.00(7)	C(19)-H(19)	1.05(5)

C(1)-C(2)-H(2A)	101.7(23)	C(1)-C(2)-H(2B)	106.8(23)
C(3)-C(2)-H(2A)	105.7(22)	C(3)-C(2)-H(2B)	115.5(24)
H(2A)-C(2)-H(2B)	112(3)	C(2)-C(3)-H(3)	109.4(21)
C(4)-C(3)-H(3)	110.2(20)	C(7)-C(3)-H(3)	104.8(20)
C(3)-C(4)-H(4A)	104.3(22)	C(3)-C(4)-H(4B)	105.7(24)
C(5)-C(4)-H(4A)	110.2(22)	C(5)-C(4)-H(4B)	112.9(24)
H(4A)-C(4)-H(4B)	112(3)	C(4)-C(5)-H(5A)	110.8(24)
C(4)-C(5)-H(5B)	114(3)	C(6)-C(5)-H(5A)	104.7(23)
C(6)-C(5)-H(5B)	108(3)	H(5A)-C(5)-H(5B)	106(4)
C(1)-C(6)-H(6A)	112(3)	C(1)-C(6)-H(6B)	105.8(24)
C(5)-C(6)-H(6A)	107(3)	C(5)-C(6)-H(6B)	116.2(25)
H(6A)-C(6)-H(6B)	103(4)	C(3)-C(7)-H(7)	110.6(20)
C(8)-C(7)-H(7)	107.2(19)	C(12)-C(7)-H(7)	104.8(19)
C(8)-C(9)-H(9)	117.4(20)	C(10)-C(9)-H(9)	116.7(20)
O(5)-C(11)-H(11A)	109(4)	O(5)-C(11)-H(11B)	113(5)
O(5)-C(11)-H(11C)	107(3)	H(11A)-C(11)-H(11B)	91(6)
H(11A)-C(11)-H(11C)	114(5)	H(11B)-C(11)-H(11C)	118(6)
O(3)-C(13)-H(13A)	100(5)	O(3)-C(13)-H(13B)	109(3)
O(3)-C(13)-H(13C)	101(3)	H(13A)-C(13)-H(13B)	104(5)
H(13A)-C(13)-H(13C)	102(6)	H(13B)-C(13)-H(13C)	132(4)
C(14)-C(15)-H(15)	115.9(25)	C(16)-C(15)-H(15)	124.1(25)
C(15)-C(16)-H(16)	116(3)	C(17)-C(16)-H(16)	122(3)
C(16)-C(17)-H(17)	118(3)	C(18)-C(17)-H(17)	122(3)
C(17)-C(18)-H(18)	114(4)	C(19)-C(18)-H(18)	124(4)
C(14)-C(19)-H(19)	117(3)	C(18)-C(19)-H(19)	123(3)

Appendix B

X-ray Structure Report

for

Compound (46)

MSC MOLECULAR STRUCTURE CORPORATION

3200A Research Forest Drive The Woodlands, Texas 77381
Tel 713/363-1033 Telex 55-9314 (MOLECULAR) FAX 713/292-2472 800 543-2379

20-SEP-89

X-ray Structure Report for
Dr. James F. Britten
McGill University

Ref. No.: AS131
MSC Code: MS-3870

EXPERIMENTAL

DATA COLLECTION

A colorless plate crystal of $C_{27}H_{30}O_5S$ having approximate dimensions of 0.300 X 0.100 X 0.100 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R 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 25 carefully centered reflections in the range $63.89 < 2\theta < 78.93°$ corresponded to a triclinic cell with dimensions:

a =	13.666 (1)Å	α =	101.603 (8)°
b =	13.950 (1)Å	β =	97.247 (8)°
c =	7.3178 (6)Å	γ =	115.527 (7)°
V =	1196.9 (2)Å^3		

For $Z = 2$ and F.W. = 466.59, the calculated density is 1.294 g/cm^3. Based on a statistical analysis of intensity distribution, the most probable space group is:

$P\bar{1}$ (#2)

The data were collected at a temperature of -120 ± 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 0.33° with a take-off angle of 6.0°. Scans of (1.26 + 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 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 40 cm.

DATA REDUCTION

Of the 3743 reflections which were collected, 3568 were unique (R_{int} = .026). 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 14.5 cm^{-1}. An empirical absorption correction, based on azimuthal scans of several reflections, resulted in transmission factors ranging from 0.91 to 1.00.

EXPERIMENTAL DETAILS

A. Crystal Data

Crystal Color, Habit	colorless, plate
Crystal Dimensions (mm)	0.300 X 0.100 X 0.100
Crystal System	triclinic
No. Reflections Used for Unit Cell Determination (2θ range)	25 (63.9 - 78.9°)
Omega Scan Peak Width at Half-height	0.33
Lattice Parameters:	a = 13.666 (1)Å b = 13.950 (1)Å c = 7.3178 (6)Å α = 101.603 (8)° β = 97.247 (8)° γ = 115.527 (7)° V = 1196.9 (2)Å^3
Space Group	$P\bar{1}$ (#2)
Z value	2
D_{calc}	1.294 g/cm^3
F_{000}	496
$\mu_{(CuK\alpha)}$	14.51 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC5R
Radiation	CuKα (λ = 1.54178 Å)
Temperature	-120°C
Attenuators	Zr foil (factors: 3.6, 12.2, 44.0)
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) (2 rescans)
Scan Width	(1.26 + 0.30 tanθ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 3743 Unique: 3568 (R_{int} = .026)
Corrections	Lorentz-polarization

AS131

```
   Space Group and Cell Dimensions    Triclinic,    P -1
a  13.6660(10)   b  13.9500(10)   c   7.3178(6)
alpha 101.603(8)   beta  97.247(8)   gamma 115.527(7)
        Volume  1196.89(16)A**3

Empirical formula : S O5 C27 H30


Cell dimensions were obtained from  25 reflections with 2Theta angle
in the range  63.89 -  78.93 degrees.

Crystal dimensions :   .30  X   .10  X   .10  mm

FW =    466.59     Z =    2     F(000) =     495.95

Dcalc  1.295Mg.m-3, mu   1.45mm-1, lambda 1.54056A, 2Theta(max) 120.0

The intensity data were collected on a Rigaku AFC5R diffractometer,
using the theta/2theta scan mode, at -120C.
The h,k,l ranges are :--     -15  13,     0  15,    -8   8
No. of reflections measured                    3743
No. of unique reflections                      3568
No. of reflections with Inet > 2.5sigma(Inet)  2855
A psi correction was made for absorption.


The last least squares cycle was calculated with
 63 atoms, 419 parameters and 2855 out of 3568 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is  .000100

The residuals are as follows :--
For significant reflections,  RF  .050, Rw  .066 GoF  1.81
For all reflections,          RF  .067, Rw  .068.
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 refIns - No. of params.)]
The maximum shift/sigma ratio was  1.170.

In the last D-map, the deepest hole was   -.300e/A**3,
and the highest peak    .660e/A**3.

Secondary ext. coeff. =    .237119      sigma =    .053279
```

non-H atom refined anisotropically. H found from difference map and refined isotropically.

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

	x	y	z	Beq
S	0.84476(7)	0.51582(7)	0.38229(13)	2.78(4)
O1	1.12910(19)	0.92226(18)	0.6511 (3)	2.68(12)
O2	1.19112(19)	0.98989(18)	0.3060 (3)	2.67(12)
O3	1.03400(18)	0.82488(19)	0.1650 (3)	2.68(12)
O4	1.31771(18)	0.84874(19)	0.6531 (3)	2.69(11)
O5	1.51223(21)	0.92930(25)	0.7285 (4)	4.05(16)
C1	1.1037 (3)	0.8333 (3)	0.5365 (4)	2.02(16)
C2	1.0030 (3)	0.7349 (3)	0.5326 (5)	2.25(16)
C3	0.9664 (3)	0.6375 (3)	0.4027 (5)	2.15(16)
C4	1.0267 (3)	0.6217 (3)	0.2516 (5)	2.29(17)
C4A	1.1512 (3)	0.7030 (3)	0.3129 (5)	2.02(15)
C5	1.2075 (3)	0.6900 (3)	0.1485 (5)	2.63(18)
C6	1.1782 (3)	0.7342 (3)	-0.0104 (5)	2.87(18)
C7	1.2064 (3)	0.8550 (3)	0.0688 (5)	2.49(18)
C8	1.1524 (3)	0.8738 (3)	0.2319 (5)	2.26(15)
C8A	1.17585(24)	0.82456(24)	0.3954 (4)	1.83(15)
C9	1.2986 (3)	0.8966 (3)	0.5053 (5)	2.22(16)
C10	1.4181 (3)	0.9177 (3)	0.7900 (5)	2.81(18)
C11	1.5251 (5)	0.8325 (4)	0.6915 (7)	4.7 (3)
C12	1.0997 (4)	1.0122 (4)	0.2773 (7)	4.1 (3)
C13	1.0117 (4)	0.9104 (4)	0.1261 (8)	4.5 (3)
C14	1.5379 (3)	0.7932 (3)	0.8699 (5)	3.20(20)
C15	1.4543 (4)	0.7047 (4)	0.9023 (9)	4.9 (3)
C16	1.4676 (6)	0.6733 (5)	1.0631 (13)	7.0 (5)
C17	1.5659 (8)	0.7335 (6)	1.2017 (9)	6.5 (5)
C18	1.6507 (5)	0.8222 (4)	1.1731 (7)	5.2 (3)
C19	1.6368 (4)	0.8519 (3)	1.0097 (7)	3.99(24)
C20	0.7801 (3)	0.5590 (3)	0.5540 (5)	2.56(17)
C21	0.6903 (4)	0.5744 (4)	0.4952 (6)	4.02(25)
C22	0.6376 (4)	0.6037 (4)	0.6301 (7)	4.9 (3)
C23	0.6755 (3)	0.6190 (3)	0.8206 (6)	3.77(22)
C24	0.7667 (3)	0.6046 (3)	0.8808 (6)	3.49(21)
C25	0.8180 (3)	0.5737 (3)	0.7476 (6)	3.17(21)

Table 2. (cont'd)

	x		y		z		Beq	
H2	0.965	(3)	0.748	(3)	0.628	(5)	3.2	(8)
H4A	1.015	(3)	0.546	(3)	0.219	(5)	2.8	(8)
H4B	0.993	(3)	0.6319	(25)	0.133	(5)	1.8	(7)
H(4A)	1.1799	(24)	0.6846	(24)	0.414	(4)	1.3	(6)
H5A	1.190	(3)	0.617	(3)	0.099	(5)	2.9	(8)
H5B	1.286	(3)	0.728	(3)	0.196	(4)	1.6	(6)
H6A	1.218	(3)	0.729	(3)	-0.105	(5)	2.8	(8)
H6B	1.098	(3)	0.692	(3)	-0.071	(5)	3.2	(8)
H7A	1.178	(3)	0.8766	(25)	-0.028	(5)	1.4	(6)
H7B	1.286	(3)	0.897	(3)	0.118	(5)	2.3	(7)
H9A	1.310	(3)	0.970	(3)	0.558	(5)	2.6	(7)
H9B	1.348	(3)	0.892	(3)	0.428	(5)	2.3	(7)
H10A	1.408	(3)	0.880	(3)	0.903	(5)	1.9	(7)
H10B	1.420	(3)	0.992	(3)	0.827	(6)	4.4	(10)
H11A	1.456	(3)	0.761	(3)	0.640	(5)	1.0	(7)
H11B	1.592	(4)	0.844	(4)	0.643	(7)	6.5	(13)
H12A	1.076	(4)	1.019	(4)	0.398	(7)	4.7	(11)
H12B	1.118	(4)	1.075	(4)	0.245	(6)	4.5	(10)
H13A	1.029	(4)	0.920	(4)	-0.020	(8)	7.7	(14)
H13B	0.940	(4)	0.891	(3)	0.151	(6)	4.3	(10)
H15	1.387	(4)	0.668	(4)	0.788	(7)	6.4	(13)
H16	1.406	(5)	0.610	(5)	1.082	(8)	8.8	(16)
H17	1.580	(5)	0.714	(5)	1.316	(9)	9.4	(18)
H18	1.721	(4)	0.862	(4)	1.274	(7)	4.8	(10)
H19	1.688	(4)	0.906	(4)	0.982	(6)	4.6	(11)
H21	0.664	(3)	0.562	(3)	0.355	(6)	4.5	(10)
H22	0.579	(4)	0.616	(3)	0.581	(6)	4.6	(10)
H23	0.638	(4)	0.638	(3)	0.914	(6)	4.5	(10)
H24	0.796	(3)	0.620	(3)	1.022	(6)	3.4	(8)
H25	0.881	(3)	0.557	(3)	0.794	(5)	3.5	(8)

Beq is the mean of the principal axes of the thermal ellipsoid for atoms refined anisotropically (i.e. all non-H). For hydrogens, Beq= Biso.

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

	u11	u22	u33	u12	u13	u23
S	2.69(5)	2.56(5)	4.32(6)	0.47(4)	1.50(4)	0.30(4)
O1	3.98(14)	2.72(13)	2.77(13)	1.01(11)	1.08(10)	0.44(10)
O2	3.77(14)	2.51(12)	3.87(14)	1.47(11)	0.75(11)	1.05(10)
O3	2.66(12)	3.80(13)	3.74(14)	1.42(11)	0.21(10)	1.67(11)
O4	2.30(12)	4.10(14)	3.05(13)	0.73(10)	0.09(10)	1.57(11)
O5	3.57(15)	7.13(20)	5.93(19)	2.85(14)	1.73(13)	3.28(15)
C1	2.86(17)	2.40(17)	2.19(17)	1.13(14)	0.39(13)	0.56(14)
C2	2.49(17)	2.96(18)	2.92(18)	1.04(15)	1.12(15)	0.80(15)
C3	2.66(17)	2.76(17)	3.05(18)	1.30(14)	1.04(14)	1.14(14)
C4	2.52(18)	2.47(18)	3.32(20)	0.96(15)	0.70(15)	0.50(15)
C4A	2.39(17)	2.53(17)	2.75(18)	1.07(14)	0.71(14)	0.90(14)
C5	2.59(19)	2.62(19)	4.52(22)	0.96(16)	1.54(16)	0.66(16)
C6	3.40(21)	3.59(20)	3.17(20)	0.92(17)	1.50(17)	0.66(16)
C7	3.38(21)	3.37(19)	2.58(19)	1.31(16)	0.83(15)	1.13(15)
C8	2.45(17)	2.81(17)	3.05(19)	1.02(14)	0.48(14)	0.92(14)
C8A	2.17(16)	2.28(16)	2.23(16)	0.71(13)	0.61(13)	0.81(13)
C9	2.47(17)	2.74(19)	2.73(18)	0.73(15)	0.38(15)	1.06(15)
C10	2.35(18)	3.97(21)	3.94(21)	1.53(16)	-0.17(15)	0.76(17)
C11	5.8 (3)	7.3 (3)	5.4 (3)	3.7 (3)	2.17(24)	1.21(24)
C12	5.8 (3)	4.8 (3)	6.5 (3)	3.47(23)	1.22(24)	2.21(23)
C13	4.5 (3)	5.7 (3)	7.5 (3)	3.18(23)	-0.18(24)	1.95(25)
C14	4.15(22)	4.48(22)	4.08(22)	2.80(19)	1.16(18)	0.42(17)
C15	3.58(25)	3.80(24)	10.5 (4)	1.68(20)	2.1 (3)	0.8 (3)
C16	8.9 (5)	6.3 (4)	17.2 (8)	5.1 (4)	10.0 (5)	7.1 (5)
C17	16.3 (7)	9.5 (5)	6.7 (4)	10.5 (5)	7.4 (4)	4.8 (4)
C18	9.3 (4)	5.3 (3)	5.4 (3)	5.1 (3)	-1.2 (3)	-0.46(24)
C19	4.18(24)	2.79(21)	7.7 (3)	1.27(19)	1.08(23)	1.59(21)
C20	2.39(17)	2.47(17)	4.52(22)	0.77(14)	1.26(15)	0.84(15)
C21	4.80(25)	6.5 (3)	4.5 (3)	3.63(22)	0.71(20)	0.61(21)
C22	5.4 (3)	8.6 (4)	6.6 (3)	5.3 (3)	1.28(24)	1.3 (3)
C23	4.73(24)	4.33(23)	5.4 (3)	2.29(20)	2.23(21)	0.68(19)
C24	4.53(23)	5.42(25)	4.21(24)	2.57(20)	2.01(19)	2.07(19)
C25	3.56(21)	4.74(22)	4.63(24)	2.28(18)	1.45(18)	2.08(18)

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

Table 3. Bond Distances in Angstroms

S-C(3)	1.752(3)	C(6)-C(7)	1.521(5)
S-C(20)	1.776(3)	C(7)-C(8)	1.517(5)
O(1)-C(1)	1.225(4)	C(8)-C(8A)	1.558(4)
O(2)-C(8)	1.426(4)	C(8A)-C(9)	1.534(4)
O(2)-C(12)	1.413(5)	C(11)-C(14)	1.533(6)
O(3)-C(8)	1.428(4)	C(12)-C(13)	1.499(7)
O(3)-C(13)	1.423(5)	C(14)-C(15)	1.362(6)
O(4)-C(9)	1.433(4)	C(14)-C(19)	1.381(6)
O(4)-C(10)	1.392(4)	C(15)-C(16)	1.353(11)
O(5)-C(10)	1.371(4)	C(16)-C(17)	1.371(13)
O(5)-C(11)	1.413(6)	C(17)-C(18)	1.359(10)
C(1)-C(2)	1.457(4)	C(18)-C(19)	1.359(7)
C(1)-C(8A)	1.537(4)	C(20)-C(21)	1.368(5)
C(2)-C(3)	1.332(5)	C(20)-C(25)	1.387(5)
C(3)-C(4)	1.496(5)	C(21)-C(22)	1.389(6)
C(4)-C(4A)	1.524(4)	C(22)-C(23)	1.364(7)
C(4A)-C(5)	1.529(5)	C(23)-C(24)	1.380(6)
C(4A)-C(8A)	1.549(4)	C(24)-C(25)	1.376(5)
C(5)-C(6)	1.509(5)		

Table 4. Bond Angles in Degrees

C(3)-S-C(20)	103.70(15)	C(1)-C(8A)-C(8)	108.20(25)
C(8)-O(2)-C(12)	109.3(3)	C(1)-C(8A)-C(9)	107.5(3)
C(8)-O(3)-C(13)	106.1(3)	C(4A)-C(8A)-C(8)	111.10(25)
C(9)-O(4)-C(10)	113.4(3)	C(4A)-C(8A)-C(9)	110.3(3)
C(10)-O(5)-C(11)	114.6(3)	C(8)-C(8A)-C(9)	108.30(24)
O(1)-C(1)-C(2)	119.5(3)	O(4)-C(9)-C(8A)	106.95(25)
O(1)-C(1)-C(8A)	120.8(3)	O(4)-C(10)-O(5)	115.1(3)
C(2)-C(1)-C(8A)	119.7(3)	O(5)-C(11)-C(14)	113.5(3)
C(1)-C(2)-C(3)	122.5(3)	O(2)-C(12)-C(13)	103.5(3)
S-C(3)-C(2)	125.8(3)	O(3)-C(13)-C(12)	103.1(3)
S-C(3)-C(4)	112.09(23)	C(11)-C(14)-C(15)	123.2(4)
C(2)-C(3)-C(4)	122.1(3)	C(11)-C(14)-C(19)	119.2(4)
C(3)-C(4)-C(4A)	112.6(3)	C(15)-C(14)-C(19)	117.5(4)
C(4)-C(4A)-C(5)	110.8(3)	C(14)-C(15)-C(16)	121.8(5)
C(4)-C(4A)-C(8A)	112.9(3)	C(15)-C(16)-C(17)	119.9(5)
C(5)-C(4A)-C(8A)	111.9(3)	C(16)-C(17)-C(18)	119.5(5)
C(4A)-C(5)-C(6)	113.0(3)	C(17)-C(18)-C(19)	120.0(5)
C(5)-C(6)-C(7)	110.6(3)	C(14)-C(19)-C(18)	121.3(4)
C(6)-C(7)-C(8)	113.0(3)	S-C(20)-C(21)	120.1(3)
O(2)-C(8)-O(3)	106.07(24)	S-C(20)-C(25)	120.3(3)
O(2)-C(8)-C(7)	108.6(3)	C(21)-C(20)-C(25)	119.6(3)
O(2)-C(8)-C(8A)	110.48(25)	C(20)-C(21)-C(22)	119.5(4)
O(3)-C(8)-C(7)	111.3(3)	C(21)-C(22)-C(23)	120.8(4)
O(3)-C(8)-C(8A)	107.23(24)	C(22)-C(23)-C(24)	119.8(4)
C(7)-C(8)-C(8A)	113.0(3)	C(23)-C(24)-C(25)	119.6(4)
C(1)-C(8A)-C(4A)	111.27(24)	C(20)-C(25)-C(24)	120.6(4)

Table 5. Bond Distances(A) and Angles(Deg) Involving Hydrogen

C(2)-H(2)	0.95(4)	C(12)-H(12A)	0.98(5)
C(4)-H(4A)	0.97(4)	C(12)-H(12B)	0.90(5)
C(4)-H(4B)	1.00(3)	C(13)-H(13A)	1.14(6)
C(4A)-H(4A)	0.93(3)	C(13)-H(13B)	0.95(5)
C(5)-H(5A)	0.91(4)	C(15)-H(15)	1.02(5)
C(5)-H(5B)	0.94(3)	C(16)-H(16)	0.98(6)
C(6)-H(6A)	0.95(4)	C(17)-H(17)	0.95(7)
C(6)-H(6B)	0.98(4)	C(18)-H(18)	0.98(5)
C(7)-H(7A)	0.93(3)	C(19)-H(19)	0.86(5)
C(7)-H(7B)	0.97(4)	C(21)-H(21)	0.99(4)
C(9)-H(9A)	0.96(4)	C(22)-H(22)	0.94(5)
C(9)-H(9B)	0.95(4)	C(23)-H(23)	0.96(4)
C(10)-H(10A)	1.06(3)	C(24)-H(24)	1.00(4)
C(10)-H(10B)	1.01(4)	C(25)-H(25)	1.02(4)
C(11)-H(11A)	0.99(4)		
C(11)-H(11B)	0.98(5)		

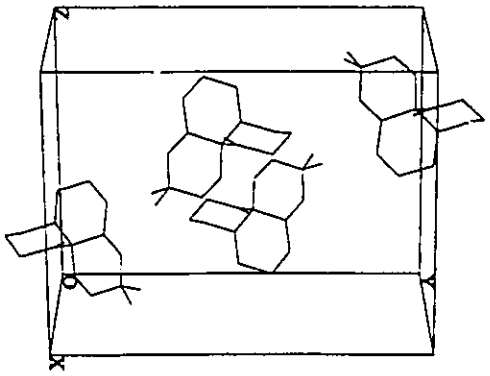
H(4A)-C(4)-H(4B)	106(3)	H(10A)-C(10)-H(10B)	112(3)
H(5A)-C(5)-H(5B)	105(3)	H(11A)-C(11)-H(11B)	120(3)
H(6A)-C(6)-H(6B)	108(3)	H(12A)-C(12)-H(12B)	109(4)
H(7A)-C(7)-H(7B)	114(3)	H(13A)-C(13)-H(13B)	121(4)
H(9A)-C(9)-H(9B)	114(3)		

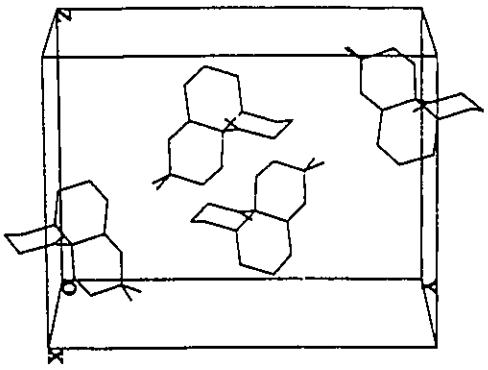
Appendix C

X-ray Structure Report

for

Compound (67)





ANNET1 - AS/CHAN - AUG 91

Space Group and Cell Dimensions Monoclinic, P 21/n
a 6.7423(4) b 16.3538(17) c 12.1489(13)
beta 105.012(7)
Volume 1293.85(21)A**3

Empirical formula : C14 H22 O3

Cell dimensions were obtained from 22 reflections with 2Theta angle in the range 84.00 - 109.00 degrees.

Crystal dimensions : 0.35 X 0.25 X 0.20 mm

FW = 238.32 Z = 4 F(000) = 521.52

Dcalc 1.223Mg.m-3, mu 0.64mm-1, lambda 1.54056A, 2Theta(max) 110.0

The intensity data were collected on a Rigaku diffractometer, using the theta/2theta scan mode.
The h,k,l ranges are :-- -7 6, 0 17, 0 12
No. of reflections measured 1778
No. of unique reflections 1615
No. of reflections with Inet > 2.5sigma(Inet) 1474
No correction was made for absorption

The last least squares cycle was calculated with
39 atoms, 243 parameters and 1474 out of 1615 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000010

The residuals are as follows :--
For significant reflections, RF 0.032, Rw 0.035 GoF 4.82
For all reflections, RF 0.036, Rw 0.035.
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 0.032.

In the last D-map, the deepest hole was -0.130e/A**3,
and the highest peak 0.140e/A**3.

Secondary ext. coeff. = 1.917373 sigma = 0.077671

Standard intensities dropped an average of 2.83%; merging R = 0.9% for 163 symmetry equivalent pairs; solved by direct methods (NRCVAX - all non-H), H's from d-map; refinement: non-H anisotropic, H's isotropic.

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

	x	y	z	Beq
O 1	0.96485(20)	0.40466(7)	0.55569(9)	3.80(6)
O 2	1.19628(20)	0.46458(8)	0.82419(11)	4.96(7)
O 3	0.97896(18)	0.31964(7)	0.71342(9)	3.72(6)
C 1	0.8317 (3)	0.36953(10)	0.74775(14)	3.23(8)
C 2	0.8557 (3)	0.35883(13)	0.87448(15)	3.95(10)
C 3	0.6935 (4)	0.40965(13)	0.90939(18)	4.55(11)
C 4	0.7002 (4)	0.49888(13)	0.87544(16)	4.11(10)
C 4A	0.6785 (3)	0.50959(11)	0.74731(15)	3.51(9)
C 5	0.6849 (3)	0.59947(12)	0.71308(19)	4.37(11)
C 6	0.8938 (3)	0.63813(12)	0.76139(19)	4.45(11)
C 7	1.0649 (3)	0.58839(12)	0.73238(19)	4.07(10)
C 8	1.0524 (3)	0.49947(11)	0.76216(14)	3.24(8)
C 8A	0.84423(25)	0.45849(10)	0.71110(13)	2.88(8)
C 9	0.8101 (3)	0.45419(12)	0.58222(14)	3.53(9)
C10	0.9722 (3)	0.32216(10)	0.59576(14)	3.82(10)
C11	0.7929 (5)	0.27309(15)	0.52525(21)	5.45(14)
C12	1.1771 (5)	0.29018(17)	0.5875 (3)	5.91(14)
H 1	0.6886 (25)	0.3496 (9)	0.7080 (12)	3.1 (4)
H 21	0.996 (3)	0.3782 (10)	0.9146 (14)	4.3 (4)
H 22	0.842 (3)	0.3002 (11)	0.8918 (14)	4.7 (4)
H 31	0.553 (3)	0.3862 (11)	0.8732 (16)	5.9 (5)
H 32	0.709 (3)	0.4051 (11)	0.9907 (17)	5.2 (5)
H 41	0.837 (3)	0.5232 (10)	0.9175 (13)	3.8 (4)
H 42	0.586 (3)	0.5285 (10)	0.8981 (14)	4.3 (4)
H 4A	0.544 (3)	0.4867 (9)	0.7090 (13)	3.6 (4)
H 51	0.654 (3)	0.6050 (10)	0.6285 (15)	4.3 (4)
H 52	0.578 (3)	0.6278 (11)	0.7395 (15)	5.2 (5)
H 61	0.918 (3)	0.6421 (10)	0.8444 (16)	4.8 (4)
H 62	0.895 (3)	0.6968 (12)	0.7288 (15)	5.5 (5)
H 71	1.200 (3)	0.6094 (11)	0.7740 (15)	4.8 (5)
H 72	1.053 (3)	0.5923 (10)	0.6480 (17)	5.1 (5)
H 91	0.820 (3)	0.5076 (10)	0.5463 (13)	4.0 (4)
H 92	0.666 (3)	0.4290 (10)	0.5461 (14)	4.4 (4)
H111	0.654 (4)	0.2909 (13)	0.5354 (18)	7.1 (7)
H112	0.794 (3)	0.2756 (12)	0.4477 (20)	7.2 (6)
H113	0.811 (3)	0.2185 (14)	0.5506 (17)	6.7 (6)
H121	1.284 (4)	0.3210 (15)	0.6355 (21)	8.4 (8)
H122	1.200 (3)	0.2309 (15)	0.6143 (18)	7.8 (6)
H123	1.184 (3)	0.2914 (12)	0.5068 (20)	7.2 (6)

Beq is the mean of the principal axes of the thermal ellipsoid for non-hydrogens. For hydrogens, Beq = Biso.

Table S-2. Anisotropic u(i,j) values *100.
E.S.Ds. refer to the last digit printed

	u11	u22	u33	u12	u13	u23
O 1	6.98(9)	3.59(7)	4.52(7)	-0.24(7)	2.66(7)	0.03(5)
O 2	4.07(8)	6.39(9)	7.53(10)	0.21(7)	-0.05(7)	0.29(7)
O 3	6.22(9)	4.02(7)	4.11(7)	0.86(6)	1.74(6)	0.42(5)
C 1	4.10(11)	4.37(11)	3.86(10)	-0.14(9)	1.12(9)	0.19(8)
C 2	5.91(14)	5.23(13)	3.96(11)	-0.14(11)	1.44(10)	0.84(9)
C 3	6.40(16)	7.27(15)	4.12(12)	-0.22(12)	2.28(12)	0.42(11)
C 4	4.80(13)	6.47(14)	4.76(12)	0.34(12)	1.96(11)	-0.40(10)
C 4A	3.65(11)	5.01(12)	4.50(11)	0.21(10)	0.73(9)	-0.10(9)
C 5	5.92(15)	5.12(13)	5.41(13)	1.61(11)	1.19(12)	0.04(10)
C 6	7.16(16)	3.91(12)	5.83(14)	0.22(11)	1.68(12)	-0.33(10)
C 7	5.70(14)	4.49(12)	5.39(13)	-1.12(10)	1.66(11)	-0.70(10)
C 8	4.25(12)	4.41(11)	3.85(10)	0.05(9)	1.42(9)	-0.47(8)
C 8A	3.83(11)	3.89(10)	3.12(9)	0.03(8)	0.72(8)	0.12(7)
C 9	5.81(14)	3.86(11)	3.64(10)	-0.03(10)	1.08(10)	0.17(8)
C10	7.03(14)	3.56(10)	4.39(11)	-0.03(10)	2.35(10)	-0.01(8)
C11	10.53(23)	5.01(14)	5.18(15)	-2.17(15)	2.04(15)	-0.80(11)
C12	9.50(22)	6.37(17)	7.69(18)	1.73(16)	4.23(17)	-0.27(15)

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

Table S-3. Bond Distances(A) and Angles(Degrees)
Involving Hydrogens

C(1)-H(1)	1.015(17)	C(7)-H(71)	0.982(19)
C(2)-H(21)	0.995(19)	C(7)-H(72)	1.009(20)
C(2)-H(22)	0.991(18)	C(9)-H(91)	0.987(17)
C(3)-H(31)	1.012(21)	C(9)-H(92)	1.042(19)
C(3)-H(32)	0.969(20)	C(11)-H(111)	1.019(24)
C(4)-H(41)	1.016(19)	C(11)-H(112)	0.944(23)
C(4)-H(42)	1.007(19)	C(11)-H(113)	0.942(23)
C(4A)-H(4A)	0.978(17)	C(12)-H(121)	0.95(3)
C(5)-H(51)	0.999(18)	C(12)-H(122)	1.022(24)
C(5)-H(52)	0.977(21)	C(12)-H(123)	0.993(24)
C(6)-H(61)	0.981(19)		
C(6)-H(62)	1.039(20)		

H(21)-C(2)-H(22)	109.4(14)	H(111)-C(11)-H(112)	110.6(18)
H(31)-C(3)-H(32)	104.7(15)	H(111)-C(11)-H(113)	106.0(18)
H(41)-C(4)-H(42)	109.7(13)	H(112)-C(11)-H(113)	109.5(17)
H(51)-C(5)-H(52)	108.7(14)	H(121)-C(12)-H(122)	106.2(19)
H(61)-C(6)-H(62)	108.4(13)	H(121)-C(12)-H(123)	111.9(19)
H(71)-C(7)-H(72)	108.6(14)	H(122)-C(12)-H(123)	107.0(17)
H(91)-C(9)-H(92)	109.0(13)		

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

O(1)-C(9)	1.4224(23)	C(4A)-C(5)	1.531(3)
O(1)-C(10)	1.4307(20)	C(4A)-C(8A)	1.5476(24)
O(2)-C(8)	1.2068(23)	C(5)-C(6)	1.517(3)
O(3)-C(1)	1.4281(21)	C(6)-C(7)	1.526(3)
O(3)-C(10)	1.4188(20)	C(7)-C(8)	1.506(3)
C(1)-C(2)	1.5160(24)	C(8)-C(8A)	1.5338(24)
C(1)-C(8A)	1.5300(23)	C(8A)-C(9)	1.5241(22)
C(2)-C(3)	1.519(3)	C(10)-C(11)	1.517(3)
C(3)-C(4)	1.520(3)	C(10)-C(12)	1.505(3)
C(4)-C(4A)	1.535(3)		

C(9)-O(1)-C(10)	114.99(13)	O(2)-C(8)-C(8A)	123.32(15)
C(1)-O(3)-C(10)	115.73(12)	C(7)-C(8)-C(8A)	115.29(16)
O(3)-C(1)-C(2)	109.34(14)	C(1)-C(8A)-C(4A)	109.42(14)
O(3)-C(1)-C(8A)	111.31(13)	C(1)-C(8A)-C(8)	114.29(14)
C(2)-C(1)-C(8A)	113.95(15)	C(1)-C(8A)-C(9)	104.48(13)
C(1)-C(2)-C(3)	108.98(16)	C(4A)-C(8A)-C(8)	107.54(13)
C(2)-C(3)-C(4)	112.03(17)	C(4A)-C(8A)-C(9)	112.88(14)
C(3)-C(4)-C(4A)	112.51(16)	C(8)-C(8A)-C(9)	108.34(14)
C(4)-C(4A)-C(5)	112.51(16)	O(1)-C(9)-C(8A)	109.55(14)
C(4)-C(4A)-C(8A)	109.91(15)	O(1)-C(10)-O(3)	111.07(13)
C(5)-C(4A)-C(8A)	111.60(16)	O(1)-C(10)-C(11)	110.76(16)
C(4A)-C(5)-C(6)	112.56(17)	O(1)-C(10)-C(12)	104.85(16)
C(5)-C(6)-C(7)	111.74(17)	O(3)-C(10)-C(11)	111.50(16)
C(6)-C(7)-C(8)	111.49(17)	O(3)-C(10)-C(12)	105.45(17)
O(2)-C(8)-C(7)	121.37(17)	C(11)-C(10)-C(12)	112.92(20)

Table S-4. Torsion Angles (Degrees)

C10	O 1	C 9	C 8A	59.8(1)		C 9	O 1	C10	O 3	-51.2(1)
C 9	O 1	C10	C11	73.2(2)		C 9	O 1	C10	C12	-164.7(2)
C10	O 3	C 1	C 2	178.8(2)		C10	O 3	C 1	C 8A	-54.4(1)
C 1	O 3	C10	O 1	48.2(1)		C 1	O 3	C10	C11	-75.9(1)
C 1	O 3	C10	C12	161.2(2)		O 3	C 1	C 2	C 3	-177.9(2)
C 8A	C 1	C 2	C 3	56.8(1)		O 3	C 1	C 8A	C 4A	178.5(2)
O 3	C 1	C 8A	C 8	-60.8(1)		O 3	C 1	C 8A	C 9	57.4(1)
C 2	C 1	C 8A	C 4A	-57.2(1)		C 2	C 1	C 8A	C 8	63.4(1)
C 2	C 1	C 8A	C 9	-178.4(2)		C 1	C 2	C 3	C 4	-54.8(1)
C 2	C 3	C 4	C 4A	56.1(1)		C 3	C 4	C 4A	C 5	179.9(2)
C 3	C 4	C 4A	C 8A	-55.1(1)		C 4	C 4A	C 5	C 6	67.5(2)
C 8A	C 4A	C 5	C 6	-56.6(1)		C 4	C 4A	C 8A	C 1	54.2(1)
C 4	C 4A	C 8A	C 8	-70.5(1)		C 4	C 4A	C 8A	C 9	170.1(2)
C 5	C 4A	C 8A	C 1	179.7(2)		C 5	C 4A	C 8A	C 8	55.1(1)
C 5	C 4A	C 8A	C 9	-64.4(1)		C 4A	C 5	C 6	C 7	53.1(1)
C 5	C 6	C 7	C 8	-50.5(1)		C 6	C 7	C 8	O 2	-124.6(2)
C 6	C 7	C 8	C 8A	53.7(1)		O 2	C 8	C 8A	C 1	1.4(1)
O 2	C 8	C 8A	C 4A	123.1(2)		O 2	C 8	C 8A	C 9	-114.6(2)
C 7	C 8	C 8A	C 1	-176.9(2)		C 7	C 8	C 8A	C 4A	-55.2(1)
C 7	C 8	C 8A	C 9	67.1(1)		C 1	C 8A	C 9	O 1	-59.7(1)
C 4A	C 8A	C 9	O 1	-178.5(2)		C 8	C 8A	C 9	O 1	62.5(1)

Appendix D

X-ray Structure Report

for

Compound (77)

TABLE OF CONTENTS

DATA COLLECTION

A colorless plate crystal of $C_{13}H_{22}O_3$ having approximate dimensions of 0.400 X 0.400 X 0.100 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 16 carefully centered reflections in the range $21.22 < 2\theta < 37.88°$ corresponded to a triclinic cell with dimensions:

a =	8.455 (6)Å	α =	96.8 (1)°
b =	12.68 (1)Å	β =	105.25 (8)°
c =	6.241 (8)Å	γ =	101.94 (8)°
V =	621 (1)Å^3		

For Z = 2 and F.W. = 226.31, the calculated density is 1.210 g/cm^3. Based on packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P\bar{1}$ (#2)

The data were collected at a temperature of 20 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 119.6°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.59° with a take-off angle of 6.0°. Scans of (1.78 + 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 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 1443 reflections which were collected, 1315 were unique (R_{int} = .033). 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 0.61 to 1.49. The data were corrected for Lorentz and polarization effects.

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 1015 observed reflections ($I > 3.00\sigma(I)$) and 145 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \; ||Fo| - |Fc|| \; / \; \Sigma \; |Fo| = 0.055$$

$$R_w = [(\Sigma \; w \; (|Fo| - |Fc|)^2 \; / \; \Sigma \; w \; Fo^2)]^{1/2} = 0.037$$

The standard deviation of an observation of unit weight[5] was 4.04. The weighting scheme was based on counting statistics and included a factor (p = 0.00) 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 0.18 and -0.21 $e^-/Å^3$, 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	$C_{13}H_{22}O_3$
Formula Weight	226.31
Crystal Color, Habit	colorless, plate
Crystal Dimensions (mm)	0.400 X 0.400 X 0.100
Crystal System	triclinic
No. Reflections Used for Unit Cell Determination (2θ range)	16 (21.2 - 37.9°)
Omega Scan Peak Width at Half-height	0.59
Lattice Parameters:	
	a = 8.455 (6)Å
	b = 12.68 (1)Å
	c = 6.241 (8)Å
	α = 96.8 (1)°
	β = 105.25 (8)°
	γ = 101.94 (8)°
	V = 621 (1)Å^3
Space Group	$P\bar{1}$ (#2)
Z value	2
D_{calc}	1.210 g/cm^3
F_{000}	248
$\mu_{(CuK\alpha)}$	6.40 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) (2 rescans)
Scan Width	(1.78 + 0.30 tanθ)°
$2\theta_{max}$	119.6°
No. of Reflections Measured	Total: 1443 Unique: 1315 (R_{int} = .033)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.61 - 1.49)

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	0.00
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1015
No. Variables	145
Reflection/Parameter Ratio	7.00
Residuals: R; R_w	0.055; 0.037
Goodness of Fit Indicator	4.04
Max Shift/Error in Final Cycle	0.00
Maximum Peak in Final Diff. Map	0.18 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-0.21 $e^-/Å^3$

Positional parameters for AS IV-2

atom	x	y	z
O(1)	0.1293(3)	0.0375(2)	-0.1532(5)
O(2)	0.4725(4)	0.1200(3)	-0.1048(5)
O(3)	0.1913(4)	0.0563(3)	0.4266(5)
C(1)	0.1723(5)	0.1387(4)	-0.0016(7)
C(2)	0.1690(5)	0.2341(4)	-0.1248(8)
C(3)	0.2088(6)	0.3448(4)	0.0271(9)
C(4)	0.3772(6)	0.3590(4)	0.2107(8)
C(4A)	0.3826(5)	0.2657(4)	0.3458(8)
C(5)	0.5554(6)	0.2884(4)	0.5268(8)
C(6)	0.7008(6)	0.2828(5)	0.4240(9)
C(7)	0.6630(6)	0.1732(4)	0.2649(9)
C(8)	0.4892(6)	0.1454(4)	0.0932(8)
C(8A)	0.3405(5)	0.1524(4)	0.1893(7)
C(9)	0.3198(6)	0.0563(4)	0.3192(7)
C(10)	0.2304(6)	0.4360(4)	-0.1098(9)
C(11)	0.0646(6)	0.3524(4)	0.1331(9)
H(1)	0.0648	0.1289	0.1057
H(2)	0.4459	0.0728	0.4583
H(3)	0.2755	-0.0220	0.1767
H(4)	0.2612	0.2312	-0.2027
H(5)	0.1088	0.4272	0.2422
H(6)	0.0645	0.2939	0.2503
H(7)	0.2436	0.5183	-0.0354
H(8)	0.1206	0.4253	-0.2409
H(9)	0.3444	0.4185	-0.1881
H(10)	0.4316	0.4415	0.3366
H(11)	0.4957	0.3671	0.1303
H(12)	0.2813	0.2577	0.4475
H(13)	0.7155	0.3406	0.3422
H(14)	0.8019	0.2903	0.5426
H(15)	0.7455	0.1769	0.1859
H(16)	0.6687	0.1167	0.3515
H(17)	0.1957	0.0260	-0.2926
H(18)	0.0383	0.2215	-0.2603
H(19)	-0.0568	0.3480	0.0011
H(20)	0.0855	0.0507	0.3059
H(21)	0.5783	0.3596	0.6134
H(22)	0.5494	0.2355	0.6219

Positional parameters and B(eq) for AS IV-2

atom	x	y	z	B(eq)
O(1)	0.1293(3)	0.0375(2)	-0.1532(5)	3.8(1)
O(2)	0.4725(4)	0.1200(3)	-0.1048(5)	4.9(2)
O(3)	0.1913(4)	0.0563(3)	0.4266(5)	4.3(1)
C(1)	0.1723(5)	0.1387(4)	-0.0016(7)	3.4(2)
C(2)	0.1690(5)	0.2341(4)	-0.1248(8)	3.7(2)
C(3)	0.2088(6)	0.3448(4)	0.0271(9)	4.4(2)
C(4)	0.3772(6)	0.3590(4)	0.2107(8)	4.0(2)
C(4A)	0.3826(5)	0.2657(4)	0.3458(8)	3.8(2)
C(5)	0.5554(6)	0.2884(4)	0.5268(8)	5.0(2)
C(6)	0.7008(6)	0.2828(5)	0.4240(9)	5.5(3)
C(7)	0.6630(6)	0.1732(4)	0.2649(9)	5.0(2)
C(8)	0.4892(6)	0.1454(4)	0.0932(8)	3.8(2)
C(8A)	0.3405(5)	0.1524(4)	0.1893(7)	3.1(2)
C(9)	0.3198(6)	0.0563(4)	0.3192(7)	3.9(2)
C(10)	0.2304(6)	0.4360(4)	-0.1098(9)	5.5(3)
C(11)	0.0646(6)	0.3524(4)	0.1331(9)	5.7(3)
H(1)	0.0648	0.1289	0.1057	4.5
H(2)	0.4459	0.0728	0.4583	4.9
H(3)	0.2755	-0.0220	0.1767	4.9
H(4)	0.2612	0.2312	-0.2027	4.7
H(5)	0.1088	0.4272	0.2422	6.2
H(6)	0.0645	0.2939	0.2503	6.2
H(7)	0.2436	0.5183	-0.0354	6.5
H(8)	0.1206	0.4253	-0.2409	6.5
H(9)	0.3444	0.4185	-0.1881	6.5
H(10)	0.4316	0.4415	0.3366	4.9
H(11)	0.4957	0.3671	0.1303	4.9
H(12)	0.2813	0.2577	0.4475	4.9
H(13)	0.7155	0.3406	0.3422	6.6
H(14)	0.8019	0.2903	0.5426	6.6
H(15)	0.7455	0.1769	0.1859	6.1
H(16)	0.6687	0.1167	0.3515	6.1
H(17)	0.1957	0.0260	-0.2926	4.7
H(18)	0.0383	0.2215	-0.2603	4.5
H(19)	-0.0568	0.3480	0.0011	6.7
H(20)	0.0855	0.0507	0.3059	5.2
H(21)	0.5783	0.3596	0.6134	6.0
H(22)	0.5494	0.2355	0.6219	6.0

U values for AS IV-2

atom	U11	U22	U33	U12	U13	U23
O(1)	0.049(2)	0.043(2)	0.049(2)	0.005(2)	0.014(2)	-0.001(2)
O(2)	0.062(2)	0.083(3)	0.048(2)	0.027(2)	0.022(2)	0.011(2)
O(3)	0.051(2)	0.067(3)	0.042(2)	0.009(2)	0.014(2)	0.014(2)
C(1)	0.045(3)	0.040(3)	0.044(3)	0.011(3)	0.014(3)	0.005(3)
C(2)	0.041(3)	0.050(4)	0.051(3)	0.014(3)	0.010(3)	0.012(3)
C(3)	0.057(4)	0.048(4)	0.069(4)	0.020(3)	0.023(3)	0.018(3)
C(4)	0.049(3)	0.039(3)	0.057(4)	0.009(3)	0.008(3)	0.009(3)
C(4A)	0.046(3)	0.046(4)	0.048(3)	0.009(3)	0.009(3)	0.006(3)
C(5)	0.067(4)	0.062(4)	0.053(4)	0.013(3)	0.009(3)	0.006(3)
C(6)	0.050(4)	0.075(5)	0.070(4)	0.011(3)	-0.003(3)	0.014(4)
C(7)	0.043(3)	0.081(5)	0.067(4)	0.016(3)	0.014(3)	0.017(3)
C(8)	0.049(3)	0.039(3)	0.058(4)	0.014(3)	0.012(3)	0.015(3)
C(8A)	0.037(3)	0.042(3)	0.042(3)	0.010(3)	0.014(2)	0.011(3)
C(9)	0.044(3)	0.056(4)	0.048(3)	0.008(3)	0.018(3)	0.014(3)
C(10)	0.080(4)	0.047(4)	0.086(5)	0.027(3)	0.016(3)	0.027(3)
C(11)	0.070(4)	0.073(5)	0.080(4)	0.037(3)	0.022(3)	0.008(3)
H(1)	0.0570					
H(2)	0.0626					
H(3)	0.0626					
H(4)	0.0600					
H(5)	0.0782					
H(6)	0.0782					
H(7)	0.0820					
H(8)	0.0820					
H(9)	0.0820					
H(10)	0.0623					
H(11)	0.0623					
H(12)	0.0617					
H(13)	0.0836					
H(14)	0.0836					
H(15)	0.0769					
H(16)	0.0769					
H(17)	0.0590					
H(18)	0.0565					
H(19)	0.0846					
H(20)	0.0664					

U values for AS IV-2

atom	U11	U22	U33	U12	U13	U23
H(21)	0.0756					
H(22)	0.0756					

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.419(5)	C(4)	C(4A)	1.533(6)
O(2)	C(8)	1.203(5)	C(4A)	C(5)	1.541(6)
O(3)	C(9)	1.418(5)	C(4A)	C(8A)	1.556(6)
C(1)	C(2)	1.510(6)	C(5)	C(6)	1.539(7)
C(1)	C(8A)	1.558(6)	C(6)	C(7)	1.530(7)
C(2)	C(3)	1.519(7)	C(7)	C(8)	1.516(6)
C(3)	C(4)	1.536(6)	C(8)	C(8A)	1.542(6)
C(3)	C(10)	1.526(6)	C(8A)	C(9)	1.547(6)
C(3)	C(11)	1.547(7)			

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(1)	H(17)	1.164	C(6)	H(14)	0.951
O(3)	H(20)	0.990	C(7)	H(15)	0.950
C(1)	H(1)	1.258	C(7)	H(16)	0.950
C(2)	H(4)	1.026	C(9)	H(2)	1.145
C(2)	H(18)	1.168	C(9)	H(3)	1.175
C(4)	H(10)	1.158	C(10)	H(7)	1.063
C(4)	H(11)	1.225	C(10)	H(8)	1.035
C(4A)	H(12)	1.189	C(10)	H(9)	1.236
C(5)	H(21)	0.950	C(11)	H(5)	1.034
C(5)	H(22)	0.949	C(11)	H(6)	1.103
C(6)	H(13)	0.948	C(11)	H(19)	1.120

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
O(1)	C(1)	C(2)	111.7(4)	C(4A)	C(5)	C(6)	112.6(4)
O(1)	C(1)	C(8A)	111.5(4)	C(5)	C(6)	C(7)	111.0(4)
C(2)	C(1)	C(8A)	114.1(4)	C(6)	C(7)	C(8)	112.5(4)
C(1)	C(2)	C(3)	114.6(4)	O(2)	C(8)	C(7)	120.6(5)
C(2)	C(3)	C(4)	108.1(4)	O(2)	C(8)	C(8A)	123.5(4)
C(2)	C(3)	C(10)	109.8(5)	C(7)	C(8)	C(8A)	115.9(4)
C(2)	C(3)	C(11)	110.5(4)	C(1)	C(8A)	C(4A)	108.9(4)
C(4)	C(3)	C(10)	108.2(4)	C(1)	C(8A)	C(8)	111.8(4)
C(4)	C(3)	C(11)	111.0(4)	C(1)	C(8A)	C(9)	108.8(4)
C(10)	C(3)	C(11)	109.1(4)	C(4A)	C(8A)	C(8)	109.2(4)
C(3)	C(4)	C(4A)	114.6(4)	C(4A)	C(8A)	C(9)	112.2(4)
C(4)	C(4A)	C(5)	110.5(4)	C(8)	C(8A)	C(9)	106.0(4)
C(4)	C(4A)	C(8A)	111.8(4)	O(3)	C(9)	C(8A)	112.0(4)
C(5)	C(4A)	C(8A)	111.4(4)				

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(1)	O(1)	H(17)	121.07	C(7)	C(6)	H(13)	109.18
C(9)	O(3)	H(20)	106.50	C(7)	C(6)	H(14)	108.89
O(1)	C(1)	H(1)	105.22	H(13)	C(6)	H(14)	109.57
C(2)	C(1)	H(1)	111.56	C(6)	C(7)	H(15)	108.90
C(8A)	C(1)	H(1)	102.05	C(6)	C(7)	H(16)	109.03
C(1)	C(2)	H(4)	102.40	C(8)	C(7)	H(15)	108.46
C(1)	C(2)	H(18)	111.31	C(8)	C(7)	H(16)	108.47
C(3)	C(2)	H(4)	110.27	H(15)	C(7)	H(16)	109.45
C(3)	C(2)	H(18)	108.30	O(3)	C(9)	H(2)	107.43
H(4)	C(2)	H(18)	109.87	O(3)	C(9)	H(3)	108.25
C(3)	C(4)	H(10)	117.71	C(8A)	C(9)	H(2)	104.90
C(3)	C(4)	H(11)	111.34	C(8A)	C(9)	H(3)	103.68
C(4A)	C(4)	H(10)	108.33	H(2)	C(9)	H(3)	120.56
C(4A)	C(4)	H(11)	107.05	C(3)	C(10)	H(7)	120.00
H(10)	C(4)	H(11)	95.92	C(3)	C(10)	H(8)	109.61
C(4)	C(4A)	H(12)	112.24	C(3)	C(10)	H(9)	102.22
C(5)	C(4A)	H(12)	105.17	H(7)	C(10)	H(8)	99.16
C(8A)	C(4A)	H(12)	105.54	H(7)	C(10)	H(9)	116.41
C(4A)	C(5)	H(21)	108.48	H(8)	C(10)	H(9)	109.24
C(4A)	C(5)	H(22)	108.56	C(3)	C(11)	H(5)	104.11
C(6)	C(5)	H(21)	108.72	C(3)	C(11)	H(6)	107.42
C(6)	C(5)	H(22)	108.90	C(3)	C(11)	H(19)	111.53
H(21)	C(5)	H(22)	109.53	H(5)	C(11)	H(6)	102.29
C(5)	C(6)	H(13)	109.22	H(5)	C(11)	H(19)	111.79
C(5)	C(6)	H(14)	108.92	H(6)	C(11)	H(19)	118.42

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

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	angle
O(1)	C(1)	C(2)	C(3)	178.3(4)
O(1)	C(1)	C(8A)	C(4A)	178.7(4)
O(1)	C(1)	C(8A)	C(8)	57.9(5)
O(1)	C(1)	C(8A)	C(9)	-58.8(5)
O(2)	C(8)	C(7)	C(6)	128.8(5)
O(2)	C(8)	C(8A)	C(1)	-7.8(7)
O(2)	C(8)	C(8A)	C(4A)	-128.4(5)
O(2)	C(8)	C(8A)	C(9)	110.6(5)
O(3)	C(9)	C(8A)	C(1)	-62.5(5)
O(3)	C(9)	C(8A)	C(4A)	58.0(5)
O(3)	C(9)	C(8A)	C(8)	177.1(4)
C(1)	C(2)	C(3)	C(4)	52.9(5)
C(1)	C(2)	C(3)	C(10)	170.7(4)
C(1)	C(2)	C(3)	C(11)	-68.8(5)
C(1)	C(8A)	C(4A)	C(4)	-51.2(5)
C(1)	C(8A)	C(4A)	C(5)	-175.3(4)
C(1)	C(8A)	C(8)	C(7)	171.9(4)
C(2)	C(1)	C(8A)	C(4A)	51.0(5)
C(2)	C(1)	C(8A)	C(8)	-69.7(5)
C(2)	C(1)	C(8A)	C(9)	173.5(4)
C(2)	C(3)	C(4)	C(4A)	-54.4(6)
C(3)	C(2)	C(1)	C(8A)	-54.2(5)
C(3)	C(4)	C(4A)	C(5)	-179.3(4)
C(3)	C(4)	C(4A)	C(8A)	56.0(5)
C(4)	C(4A)	C(5)	C(6)	-68.0(6)
C(4)	C(4A)	C(8A)	C(8)	71.2(5)
C(4)	C(4A)	C(8A)	C(9)	-171.6(4)
C(4A)	C(4)	C(3)	C(10)	-173.2(4)
C(4A)	C(4)	C(3)	C(11)	67.0(6)
C(4A)	C(5)	C(6)	C(7)	-54.5(6)
C(4A)	C(8A)	C(8)	C(7)	51.3(6)
C(5)	C(4A)	C(8A)	C(8)	-52.9(5)
C(5)	C(4A)	C(8A)	C(9)	64.3(5)
C(5)	C(6)	C(7)	C(8)	50.4(6)
C(6)	C(5)	C(4A)	C(8A)	56.8(6)
C(6)	C(7)	C(8)	C(8A)	-50.9(6)
C(7)	C(8)	C(8A)	C(9)	-69.7(5)

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

Intermolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(1)	O(3)	2.725(5)	2	O(2)	C(9)	3.418(7)	55401
O(1)	O(3)	2.833(5)	55401	O(2)	C(5)	3.425(7)	55401
O(1)	O(1)	3.333(7)	2	O(2)	C(8)	3.455(6)	65502
O(1)	C(1)	3.447(6)	2	O(2)	C(9)	3.469(7)	65502
O(1)	C(9)	3.560(6)	2	O(2)	O(2)	3.523(8)	65502
O(1)	C(7)	3.586(7)	65502	O(2)	C(7)	3.592(8)	65502
O(2)	O(3)	3.138(6)	55401	O(3)	C(2)	3.453(7)	55601

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) -X , -Y , -Z

Intermolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(1)	H(20)	1.858	2	C(4A)	H(4)	3.289	55601
O(1)	H(1)	2.491	2	C(4A)	H(9)	3.427	55601
O(1)	H(15)	3.120	65502	C(5)	H(9)	3.357	55601
O(1)	H(16)	3.192	65502	C(5)	H(4)	3.364	55601
O(1)	H(20)	3.326	55401	C(5)	H(10)	3.403	66602
O(1)	H(3)	3.350	2	C(5)	H(7)	3.546	66602
O(2)	H(22)	2.502	55401	C(6)	H(18)	3.309	65601
O(2)	H(2)	2.661	55401	C(6)	H(6)	3.501	65501
O(2)	H(3)	2.785	65502	C(6)	H(19)	3.546	65601
O(2)	H(16)	3.044	65502	C(6)	H(8)	3.576	65601
O(2)	H(2)	3.398	65502	C(7)	H(17)	3.014	65502
O(3)	H(17)	1.831	55601	C(7)	H(3)	3.385	65502
O(3)	H(4)	2.855	55601	C(7)	H(6)	3.452	65501
O(3)	H(16)	3.010	65602	C(8)	H(22)	3.400	55401
O(3)	H(17)	3.072	2	C(8)	H(3)	3.416	65502
O(3)	H(18)	3.371	55601	C(9)	H(17)	2.917	55601
O(3)	H(20)	3.374	55602	C(9)	H(2)	2.995	65602
O(3)	H(18)	3.536	2	C(9)	H(16)	3.178	65602
C(1)	H(20)	2.951	2	C(10)	H(11)	3.076	66502
C(1)	H(1)	3.455	2	C(10)	H(13)	3.337	66502
C(1)	H(3)	3.584	2	C(10)	H(19)	3.445	56502
C(2)	H(12)	3.086	55401	C(10)	H(12)	3.533	55401
C(2)	H(14)	3.511	45401	C(10)	H(21)	3.559	66602
C(4)	H(9)	3.324	66502	C(10)	H(9)	3.566	66502
C(4)	H(10)	3.349	66602	C(11)	H(15)	3.241	45501
C(4)	H(21)	3.520	66602	C(11)	H(7)	3.319	56502

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

Intermolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
C(11)	H(13)	3.511	45501	H(5)	H(13)	3.459	66602
C(11)	H(8)	3.575	56502	H(5)	H(13)	3.520	45501
H(1)	H(3)	2.894	2	H(5)	H(14)	3.525	66602
H(1)	H(20)	3.017	2	H(6)	H(15)	2.697	45501
H(1)	H(15)	3.039	45501	H(6)	H(14)	3.220	45501
H(1)	H(17)	3.190	2	H(6)	H(8)	3.274	55601
H(1)	H(1)	3.220	2	H(6)	H(13)	3.304	45501
H(2)	H(2)	2.280	65602	H(6)	H(18)	3.340	55601
H(2)	H(16)	2.906	65602	H(7)	H(19)	2.572	56502
H(2)	H(17)	2.945	55601	H(7)	H(11)	2.624	66502
H(2)	H(3)	3.051	65602	H(7)	H(21)	2.755	66602
H(3)	H(15)	2.758	65502	H(7)	H(13)	2.809	66502
H(3)	H(16)	3.267	65602	H(7)	H(9)	3.278	66502
H(3)	H(18)	3.461	2	H(7)	H(22)	3.596	66602
H(3)	H(22)	3.549	65602	H(8)	H(14)	2.766	45401
H(3)	H(16)	3.556	65502	H(8)	H(13)	3.215	66502
H(3)	H(17)	3.559	55601	H(8)	H(19)	3.293	56502
H(4)	H(12)	2.292	55401	H(8)	H(12)	3.429	55401
H(4)	H(22)	2.915	55401	H(8)	H(13)	3.575	45401
H(4)	H(20)	3.375	55401	H(8)	H(11)	3.577	66502
H(4)	H(21)	3.378	55401	H(9)	H(11)	2.711	66502
H(5)	H(8)	2.960	56502	H(9)	H(12)	2.726	55401
H(5)	H(7)	3.172	56502	H(9)	H(10)	2.742	66502
H(5)	H(8)	3.204	55601	H(9)	H(21)	2.773	55401
H(5)	H(21)	3.215	66602	H(9)	H(9)	3.172	66502
H(5)	H(19)	3.438	56502	H(9)	H(10)	3.271	55401

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

Intermolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
H(9)	H(13)	3.406	66502				
H(9)	H(22)	3.448	55401				
H(10)	H(10)	2.243	66602				
H(10)	H(21)	2.527	66602				
H(11)	H(21)	3.471	55401				
H(11)	H(22)	3.588	55401				
H(12)	H(18)	3.088	55601				
H(12)	H(17)	3.558	55601				
H(13)	H(19)	3.221	65501				
H(14)	H(18)	2.440	65601				
H(14)	H(19)	2.738	65601				
H(15)	H(17)	2.841	65502				
H(15)	H(19)	2.991	65501				
H(15)	H(20)	3.527	65501				
H(15)	H(18)	3.585	65601				
H(16)	H(17)	2.376	65502				
H(16)	H(18)	3.307	65601				
H(17)	H(20)	2.351	2				
H(17)	H(20)	2.515	55401				
H(17)	H(17)	3.504	55402				
H(18)	H(20)	3.349	2				
H(18)	H(20)	3.423	55401				
H(19)	H(21)	3.426	45401				
H(19)	H(22)	3.437	45401				
H(20)	H(20)	3.381	55602				

Contacts out to 3.60 angstroms. 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(3)	2.725(5)	2	O(1)	O(3)	3.489(6)	1
O(1)	O(2)	2.796(5)	1	O(2)	O(3)	3.138(6)	55401
O(1)	O(3)	2.833(5)	55401	O(2)	O(2)	3.523(8)	65502
O(1)	O(1)	3.333(7)	2	O(3)	O(3)	3.647(7)	55602

Contacts out to 3.90 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Cartesian coordinates

atom	x	y	z
O1	1.2462	0.6341	-0.9071
O2	3.8519	1.6052	-0.6207
O3	0.7692	0.2280	2.5255
C1	1.0958	1.7226	-0.0093
C2	1.0194	3.0424	-0.7387
C3	0.8162	4.2494	0.1602
C4	1.9008	4.2229	1.2473
C4A	1.9696	2.9166	2.0469
C5	3.0744	2.9982	3.1183
C6	4.4873	3.0418	2.5097
C7	4.7164	1.8582	1.5679
C8	3.6019	1.7012	0.5517
C8A	2.1683	1.6824	1.1206
C9	2.0315	0.3471	1.8899
C10	0.9839	5.5312	-0.6500
C11	-0.5974	4.2272	0.7877
H1	0.0363	1.4832	0.6256
H2	2.8265	0.3986	2.7129
H3	2.0970	-0.4678	1.0461
H4	1.9347	3.0926	-1.1998
H5	-0.5991	5.0343	1.4337
H6	-0.6371	3.3712	1.4816
H7	0.7577	6.4714	-0.2097
H8	0.2992	5.5437	-1.4260

H9	2.1224	5.4008	-1.1135
H10	1.9380	5.1083	1.9925
H11	3.0139	4.4118	0.7712
H12	0.9673	2.7046	2.6492
H13	4.5908	3.8508	2.0226
H14	5.1282	3.0098	3.2102
H15	5.5349	1.9914	1.1044
H16	4.7714	1.0632	2.0851
H17	2.0669	0.6450	-1.7321
H18	0.1704	3.0353	-1.5412
H19	-1.3955	4.3179	0.0068
H20	0.0872	0.2927	1.8108
H21	2.9408	3.7849	3.6338
H22	3.0091	2.2359	3.6814