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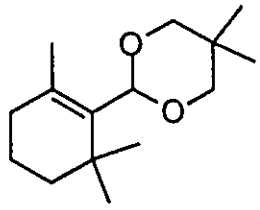
ABSTRACT

PART A

The preparation of a fully functionalized ring A of Taxol® (**1**), its further elaboration to the intramolecular Diels-Alder precursor **272** and the attempted cyclization of this compound are described.

Allylic oxidation of the cyclohexene acetal **138** was accomplished in 65 % yield using buffered selenium dioxide in toluene. Ketone **139** was converted in two steps to the vinyl ketone **197** in 33 % yield. Reduction of ketone **197** occurred with excellent diastereoselectivity to furnish the allylic alcohol **198** in 96 % yield. Protection and subsequent ozonolytic cleavage of **198** furnished the key intermediate aldehyde **200**. Aldehyde **200** was converted through a three step sequence to the fully functionalized TMS cyanohydrin A ring compound **203**. Addition of the vinyl anion derived from the bromo-diene **233** to the aldehyde **225** gave an approximately 5:1 mixture of diastereomeric alcohols **238/239** in 80 % yield. Protection and separation of the major diastereomer followed by deprotection of the acetal gave the aldehyde **265** in 65 % yield. Several methods were evaluated for the preparation of the dienophile component by the addition of the anions derived from dithianes **244** and **260** and (phenylselenomethyl)trimethylsilane **253**. Addition of TBSCN to aldehyde **265** gave a 5:1 mixture of silyl-cyanohydrin diastereomers **268/269** with the major diastereomer **268** being isolated in 67 % yield. X-ray crystallographic analysis of **268** was performed. Reduction of nitrile **268** to the aldehyde **267**, addition of ethynylmagnesium chloride and Dess-Martin periodinane oxidation of the alcohols **270/271** gave the diene-dienophile ketone **272**. Heating of this material in toluene in a sealed tube using "microwave assistance" failed to produce any of the desired cyclized product.



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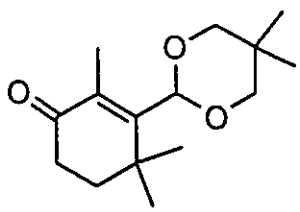

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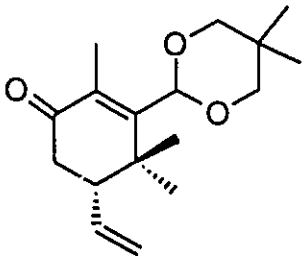

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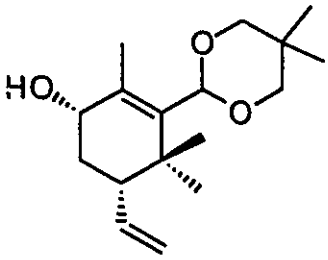

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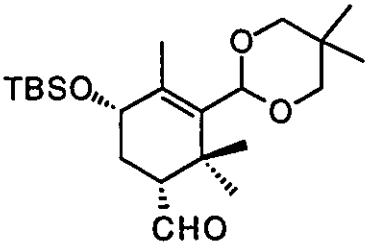

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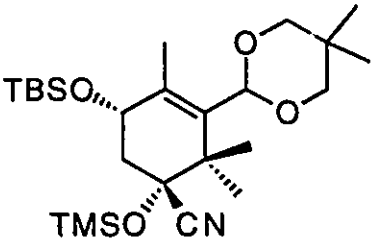

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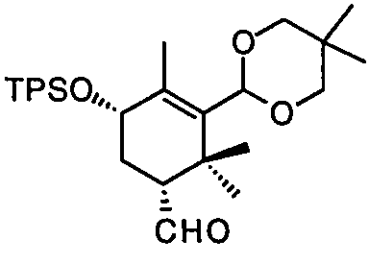

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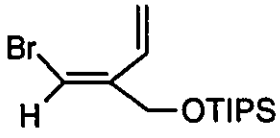

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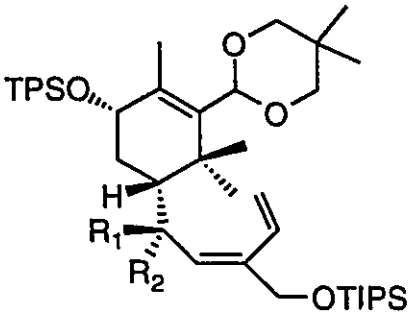
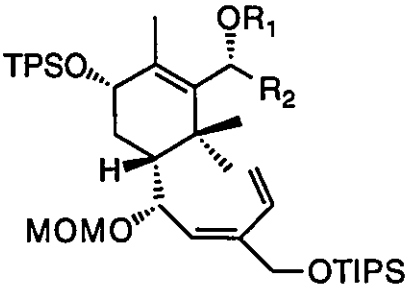
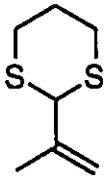


238 R_1 = OH, R_2 = H
239 R_1 = H, R_2 = OH





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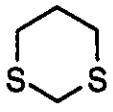
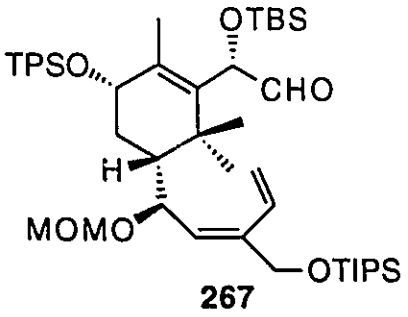


260

268 R_1 = TBS, R_2 = CN
269 R_1 = CN, R_2 = OTBS

268 : 269 = 6 : 1



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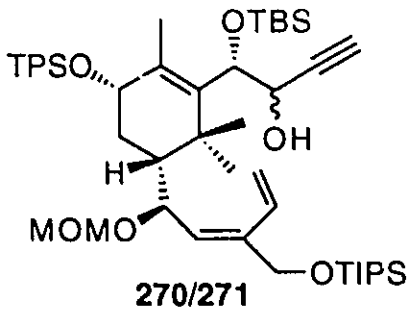

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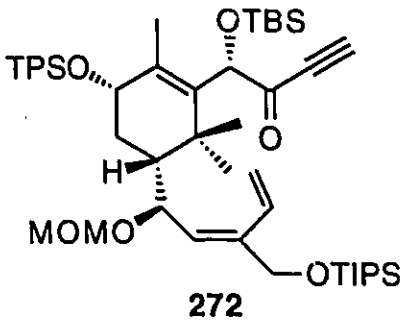

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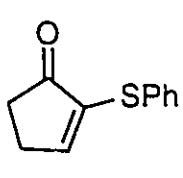
PART B

Preparation of the diene **400** and the attempted Diels-Alder cyclization of this diene to the adduct **398** is described.

β-Keto-sulfone **371** was prepared in 89 % yield in two steps from the vinyl-sulfide **369**. Alkylation of **371** with the allylic bromide **374** followed oy hydrolysis of the enol ether functionality furnished the diketone **378** in 55 % yield for the two steps. Intramolecular aldol-condensation and subsequent reduction gave the diol **380**. Protection of the primary alcohol of **380** as a TBS ether afforded the secondary allylic alcohol **381**. A variety of methods were investigated for the dehydration of alcohol **381** to the diene **383**, with Grieco's procedure giving a yield of about 65 %. Heating of diene **383** at 35 °C was found to give the rearranged product **391/392**. The cycloaddition of diene **383** with a number of dienophiles was investigated. Nitroethylene was found to give a mixture of unstable compounds from which no adduct could be isolated. Diene **383** underwent rearrangement to the exocyclic methylene compound **401** when Lewis acid catalysts were employed. Heating diene **400** with nitroethylene in benzene at reflux followed by treatment of the crude with potassium hydride and dimethyldioxirane gave a mixture of compounds of correct mass for structure **404** but of unproven structure.



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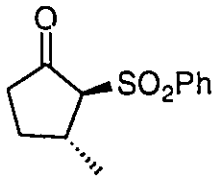

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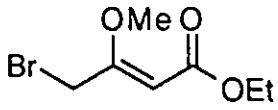

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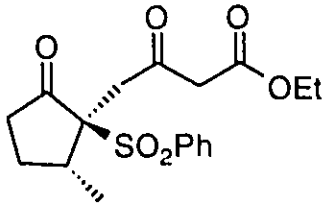

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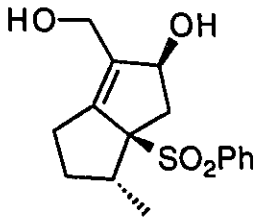

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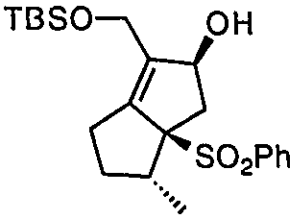

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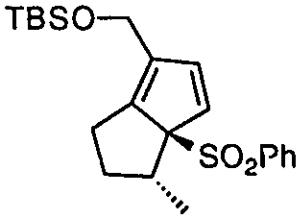

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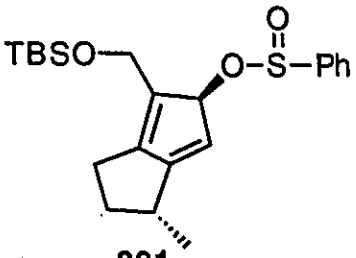

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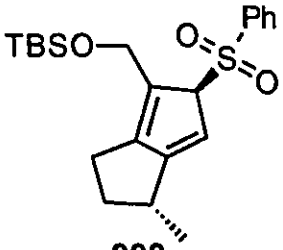

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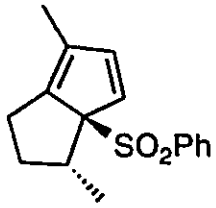

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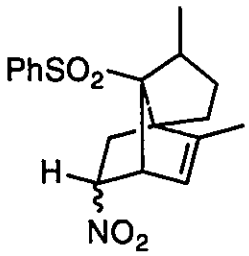

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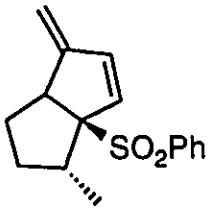

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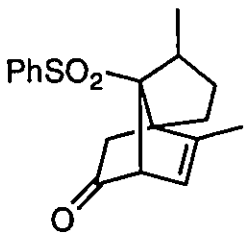

404

To my mother and father.

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azo-*bis*-(isobutyronitrile)
t-AmONa	sodium tertiary-amylate
a.m.u.	atomic mass units
Anal.	analysis
APT	attached proton test
aq	aqueous
Ar	aryl
Bn	benzyl
BOC	tertiary-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
Bu	butyl
Bu_3SnH	tributyltin hydride
n-Bu	primary-butyl
n-BuLi	primary-butyllithium
t-Bu	tertiary butyl
t-BuOK	potassium tertiary-butoxide
t-BuOOH	tertiary-butyl hydroperoxide
Bz	benzoyl
ca.	about
calcd.	calculated
cf.	compare
COSY	H^1-H^1 NMR correlation spectroscopy

m-CPBA	*meta*-chloroperoxybenzoic acid
CSA	(S)–(+)–10–camphorsulfonic acid
Δ	heat
d	doublet
dd	doublet of doublets
DBU	1,8-diazabicyclo [5.4.0.] undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec.	decomposition
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
E.I.	electron impact
e.e.	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethylamine
EtOH	ethanol
g	gram(s)
GC	gas-liquid chromatography
GC/MS	gas-liquid chromatography-mass spectroscopy
gem	geminal
h	hour

HMPA	hexamethylphosphoric triamide
HOAc	acetic acid
HRMS	high resolution mass spectrum
Hz	Hertz
i.d.	inside diameter
Im	imidazole
i-Pr	isopropyl
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LDCA	lithium dicyclohexylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
M^+	molecular ion (mass spectroscopy) or metal cation
Me	methyl
MeI	methyl iodide
MeOH	methanol
mg	milligram(s)
min	minute
mm Hg	millimetres of mercury
mmol	millimole(s)
mol	mole(s)
mp	melting point
MEM	methoxyethyl-
MHz	megahertz
MOM	methoxymethyl-
Ms	methanesulfonyl-
MS	mass spectroscopy

n-	normal (primary)
NaOEt	sodium ethoxide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-morpholine oxide
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
Nu^-	nucleophile
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
Pr	propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
s	singlet
sec	secondary
t	triplet
t-	tertiary
TASF	tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	tetra-*n*-butylammonium fluoride

TBAI	tetra-*n*-butylammonium iodide
TBS	tertiary-butyl dimethylsilyl-
TBSCl	tertiary-butyldimethylsilyl chloride
TBSCN	tertiary-butyldimethylsilyl cyanide
Tf	trifluoromethanesulfonyl-
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl-
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl-
TPAP	tetra-*n*-propyl ammoniumperruthenate
TPS	tertiary-butyldiphenylsilyl-
TS	transition state
Ts	*para*-toluenesulfonyl-
TsOH	*para*-toluenesulfonic acid

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First and foremost I would like to express my gratitude to my supervisor, Dr. Alex Fallis for all his help, patience and understanding and his good natured approach to all the problems the synthetic chemist encounters.

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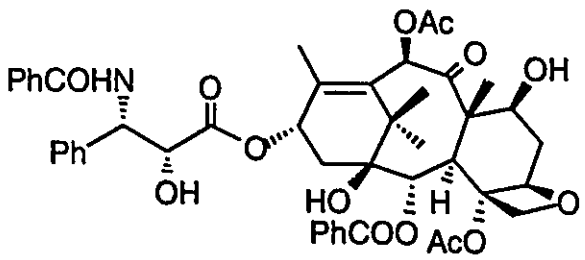
conversations (some about chemistry). Thanks to all for their dinner party invitations. Thanks to Ron Boch (for his views on life, some of which were as bitter as mine!), Christianne Aubrey, Paul Meyer, and Martin Dimitroff and Tham Pham for organizing many of the graduate student social events. Thanks to Mark and Marie Lefebvre for all their understanding. Thanks to Chris Casteldine, Charles Stewart, Tim O'Connor, Toba Miller, Denise Bond and Martin Dimitroff, all six of with whom I've developed lasting friendships. Similar thanks to Cass Guthridge, to whom I owe very much in terms of personal development. Thanks to Dr. Isaac Kennedy for lots of chemistry talk and for the fun time we had at the 1990 CIC conference international beer tasting session (what I remember). I would like to thank my mother and father for all their support throughout the years and for their patience with all my basement experimentation. Thanks to Raj Capoor and Glenn Facey for NMR work. Thanks to Clem Kazikoff for performing the mass spectroscopic analyses. Thanks to the support staff including Eva Szabo (for slide preparation), Monique Levesque, Annette Fournier and Lise Maisoneuve. Last, thanks to Dr. Otto Meresz, for all the encouragement, knowledge and understanding he has given me throughout the past eleven years of my university chemistry career.

FORWORD

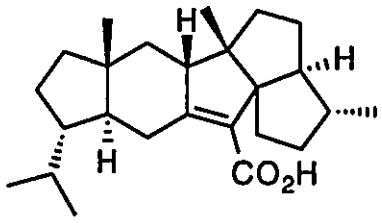
This thesis is in two parts and concerns synthetic approaches to two important natural products:

Part A: TAXOID SYNTHESIS: PREPARATION OF RING A SYNTHONS AND THEIR ELABORATION



Taxol

Part B: SYNTHETIC STUDIES TOWARDS THE PREPARATION OF RETIGERANIC ACID A



Retigeranic Acid A

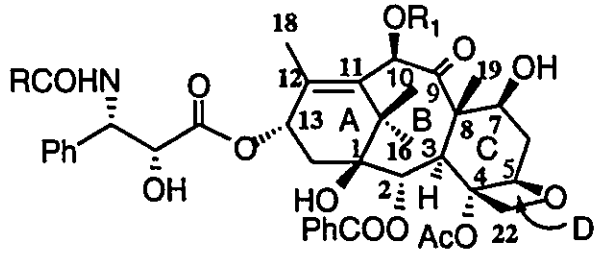
PART A

TAXOID SYNTHESIS: PREPARATION OF RING A SYNTHONS AND THEIR ELABORATION

CHAPTER 1

1.1. INTRODUCTION.

Taxol® (**1**), and its semisynthetic analogue, Taxotere® (**2**), have shown great promise for the treatment of breast and ovarian cancers. In fact, Taxol® (**1**) is regarded by many as "the most promising anticancer agent developed in the last decade".[1] The isolation[2], biosynthesis[3] and the mode of action (biological activity) has been the subject of several reviews.[4] Taxotere® (**2**) possesses an *N-tert*-butoxycarbonyl group in the sidechain compared with the benzamide group in Taxol® (**1**) and also lacks the acetate at C10. This compound has been shown to have greater water solubility than Taxol® (**1**) and recent clinical trials show it to have fewer side effects.[5] In order to produce novel taxane analogues with more potent biological activity and fewer side effects than Taxol® (**1**) there has been much interest in developing efficient ways of preparing the Taxol® (**1**) skeleton.



1 Taxol, R = Ph, R_1 = Ac
2 Taxotere, R = *t*-BuO, R_1 = H

Figure 1

Taxol® (**1**) possesses a number of unusual structural features which make its total synthesis particularly challenging. The molecule consists of a highly oxygenated and sterically congested tricyclic[9.3.1.$0^{3,8}$]pentadecene ring system (rings A, B, C). The

eight membered ring possesses geminal methyl groups which projects into its centre and contributes to the overall strain of the rigid carbocyclic framework. It has been calculated that the presence of the geminal methyl groups as well as the C8 methyl group contribute approximately 10 kcal mol^{-1} to the total strain of the molecule.[6] An additional important structural feature is the C11-C12 "anti-Bredt" double bond. Normally this double bond would increase the strain of such a system with respect to the C11-C12 dihydro-derivative, but in this case, the actual total strain of the molecule is decreased by 1.5 kcal mol^{-1}. The sensitive oxetane functionality (ring D) and the known epimerization of the C7 hydroxyl group by a retro-aldol/aldol process are also of importance.

Holton[7] and Nicolaou[8] have recently completed the first total syntheses of Taxol® (1). There are currently over 30 groups around the world that are engaged in the synthesis of taxanes, driven by the numerous opportunities to be creative in the synthesis of this compound and the potential to develop more potent analogues. Several recent review articles summarize the approaches that are currently under development.[9] Our approach to Taxol® (1) is based on an intramolecular Diels-Alder strategy that simultaneously forms the B and C rings from a preconstructed A-ring.

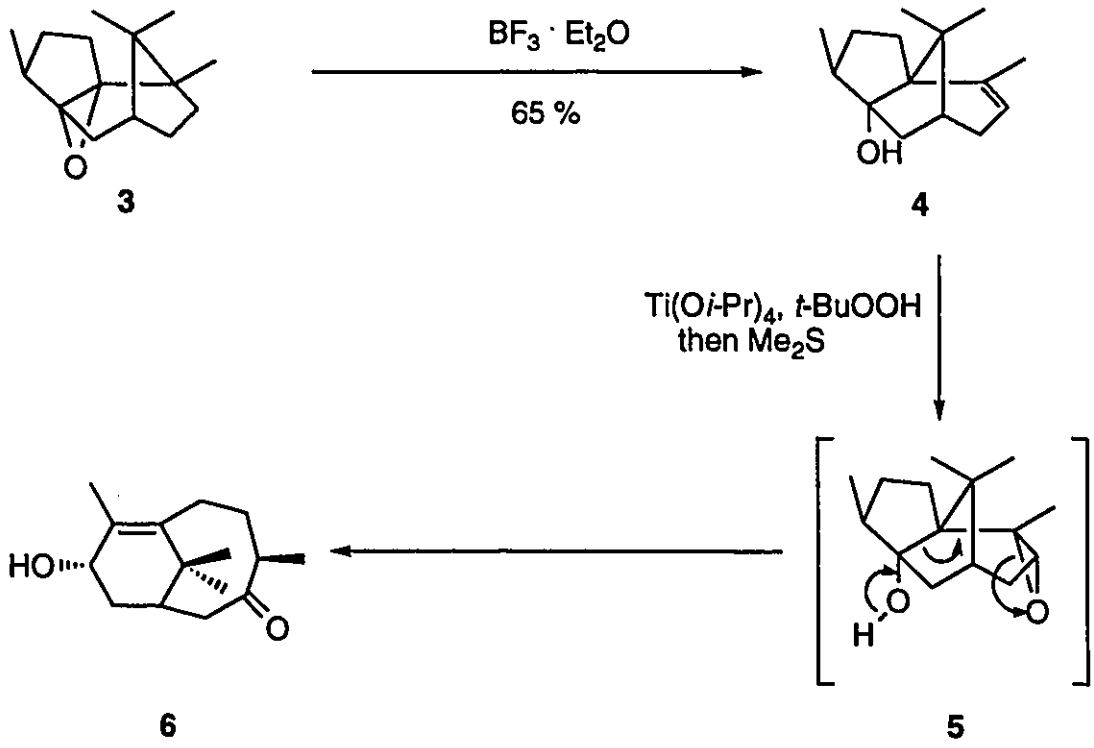
1.2. PREVIOUS TOTAL SYNTHESES.

The problem of functionalization of the eight membered ring was elegantly addressed by Holton through the use of conformational control elements present on the eight membered ring intermediates of his linear synthesis.[7]

Nicolaou's convergent synthesis involved joining highly functionalized A and C rings and performing a ring closure reaction late in the synthesis to form the B ring.[8]

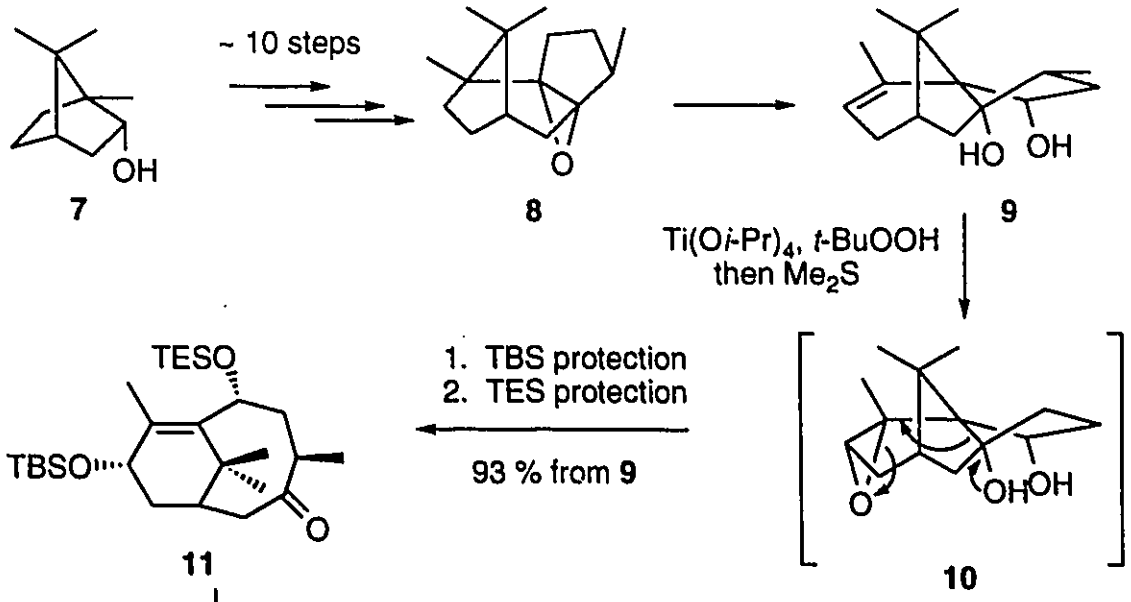
1. 2. 1. Holton's Synthesis.

Holton's synthesis of Taxol® (**1**)[7] was based on his previously developed epoxidation-fragmentation strategy of the tertiary alcohol **4** derived from commercially available and optically active β-patchoulene oxide **3** (Scheme 1) which afforded bicyclic structure **6** via **5**.[10]



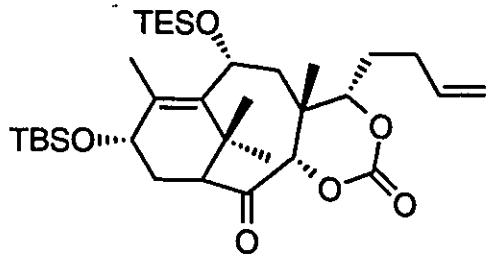
Scheme 1

β-Patchoulene oxide **8** was converted through a 3 step sequence to the functionalized diol **9** (Scheme 2). Holton used this diol for his synthesis of taxusin but the wrong enantiomer was obtained.[11] Use of the commercially available β-patchoulene oxide **3** was therefore not suitable for the synthesis of Taxol® (**1**) and they had to prepare the other enantiomer of β-patchoulene oxide **8** through a lengthy (approximately 10 steps) sequence starting from (-)-borneol **7**.



78 %

1. $HN(i\text{-}Pr)_2$, THF, MeMgBr, 25 °C, then **11**, then 4-pentenal, -23 °C
2. LDA, THF, -35 °C, then (+)-camphorsulfonyl oxaziridine
3. Red-Al®, toluene, -78 to 25 °C
4. Cl_2CO, pyridine, CH_2Cl_2, -78 to 25 °C
5. Swern oxidation

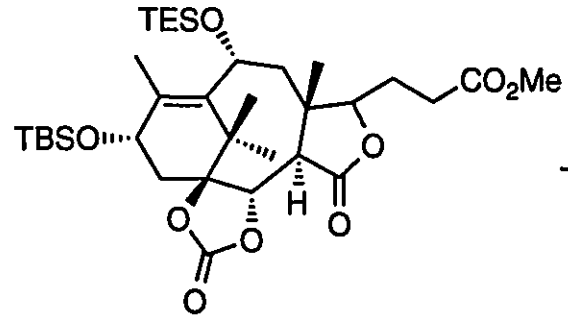


12

1. LiTMP, THF, -25 to 10 °C
2. SmI_2, then SiO_2

3. LTMP, (+)-camphorsulfonyl oxaziridine
4. Red-Al®, THF, - 78 °C
5. Cl_2CO, pyridine, - 23 °C
6. O_3; Me_2S; $KMnO_4$; KH_2PO_4; CH_2N_2

66 %

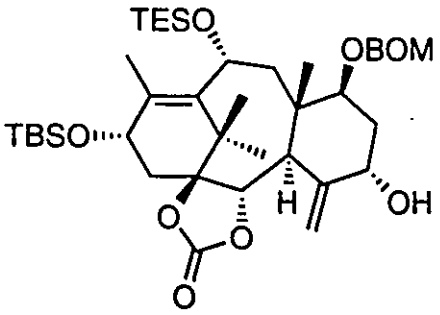


13

1. LDA, THF, -78 °C, then HOAc
2. BOMCl, $EtN(iPr)_2$, $(Bu)_4NI$, CH_2Cl_2
3. PhSK, DMF, 86 °C

4. LDA, -78 °C, TMSCl, then *m*CPBA, hexanes, 25 °C
5. MeMgBr, CH_2Cl_2, -45 °C
6. Burgess reagent

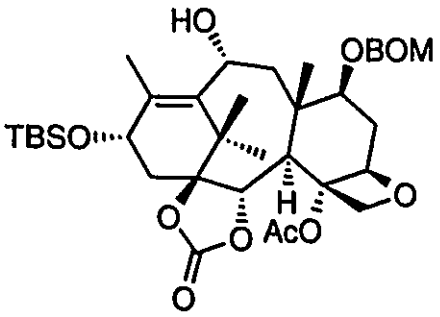
41 %



14

1. OsO_4, Et_2O, pyridine
2. TMSCl, Et_3N, -78 °C
3. LDA, TsCl, -35 °C, then HOAc
4. DBU, toluene, 105 °C
5. Ac_2O, pyridine, DMAP, 25 °C
6. HF · pyridine, CH_3CN, 0 °C

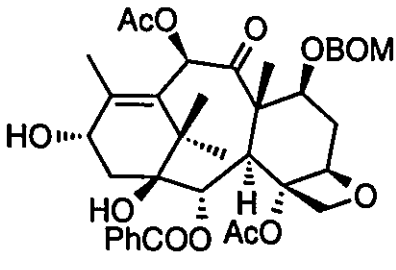
40 %



15

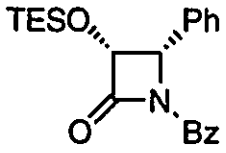
1. PhLi, THF, -78 °C
2. TPAP, NMO, CH_2Cl_2, 25 °C
3. *t*-BuOK, THF, -78 °C, then $(PhSeO)_2O$, THF, 0 °C, then *t*-BuOK, THF, -78 °C
4. Ac_2O, pyridine, DMAP
5. TASF, THF, 25 °C

80 %



16

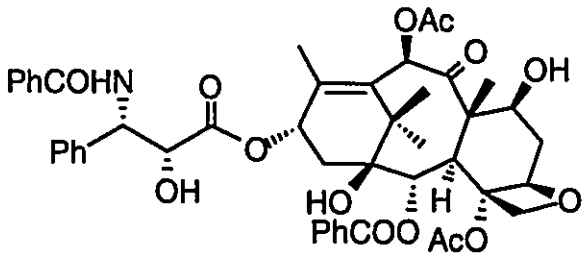
1. $LiN(SiMe_3)_2$, THF, then



THF, 0 °C

2. HF · pyridine, CH_3CN, 0 °C
3. H_2, Pd/C, EtOH, reflux

93 %



1

5.8 % overall from **9**, 0.3 % from **7**

Scheme 2

The epoxidation and fragmentation of **9** proceeded without incident to yield the bicyclic A/B ring compound in 93 % yield. The C13 alcohol was protected as its tertiary-butyldimethylsilyl (TBS) ether and the C10 alcohol protected with a triethylsilyl (TES) group to afford compound **11**. A TES group was employed at C10 to act as a conformational control element. It was known that when a ketone was present at C3 along with a C10 β-alkoxy substituent and C8 β-methyl group the B ring existed in a chair-chair conformation which did not undergo enolization at C3-C8. Employment of the bulky TES group helped shift the conformational equilibrium so that this enolization was now possible. Thus, the magnesium enolate of compound **11** underwent aldol condensation at C8 with 4-pentenal. Hydroxylation at C2 was accomplished with Davis' oxaziridine reagent. The C3 ketone was then reduced with Red-Al® and the resulting triol protected as its cyclic carbonate using phosgene. Oxidation using Swern conditions afforded ketone **12**.

Installation of the *cis*-fused B/C carbonate with an oxygen substituent at C3 was intended to act as another conformational control element and keep the B ring in a boat-chair conformation necessary to enable enolate formation at C1-C2. Epimerization at C3 would then return the B ring to the desired chair-chair conformation with the B/C ring junction being again *trans*-fused. Treatment of carbonate **12** with lithium tetramethylpiperidide (LiTMP) resulted however in deprotonation at C3 instead of C1. A Chan rearrangement then unexpectedly occurred to produce a 5-membered ring lactone bearing a C3 hydroxyl substituent. Reductive removal of this hydroxyl group using samarium (II) iodide furnished the trans-fused lactone. The B ring of this compound was shown to exist in the chair-chair conformation and would not undergo deprotonation at C1. Fortunately, epimerization of this compound catalyzed by silica gel produced the *cis*-fused lactone which existed in the desired boat-chair conformation which subsequently underwent enolate formation and hydroxylation at C1 on deprotonation and treatment with Davis' reagent. Reduction of the C2 carbonyl with Red-Al® followed by a basic

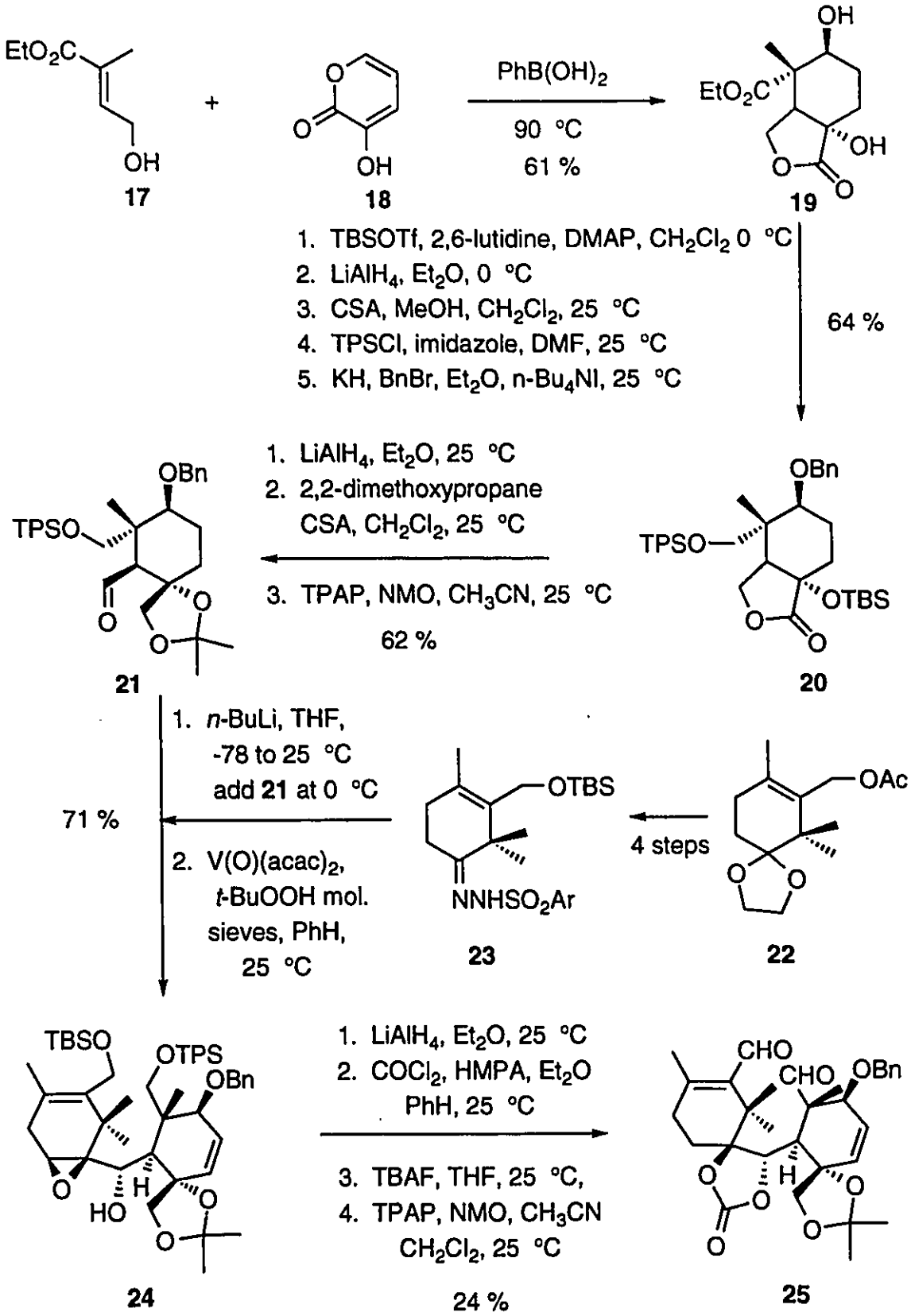
work-up returned the B/C ring junction back to the desired *trans*-fused system. Formation of the carbonate was next accomplished using phosgene. Subsequent ozonolytic cleavage of the terminal alkene yielded the aldehyde which was oxidized and esterified to provide the carbomethoxy compound **13**.

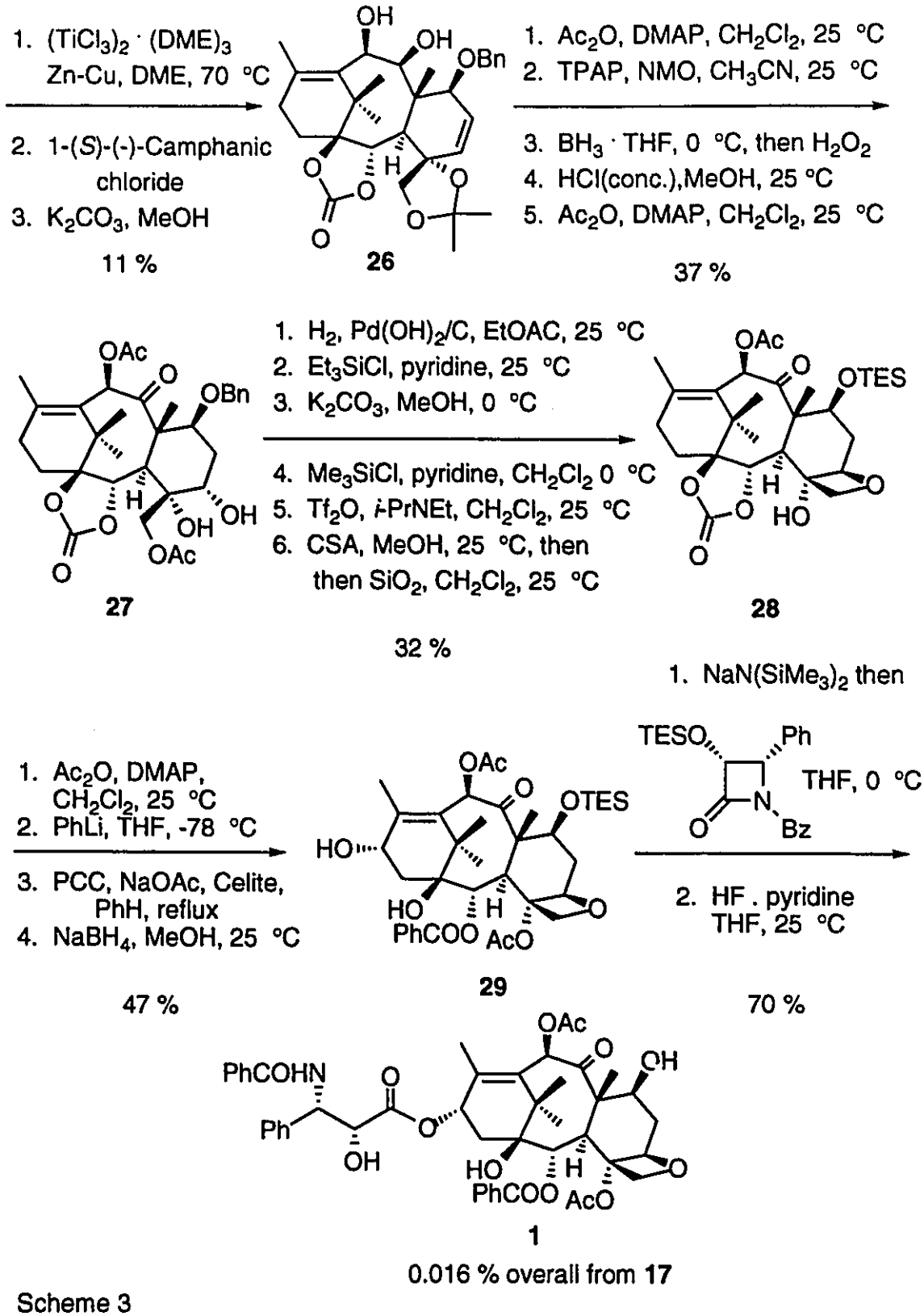
The 5-membered ring lactone was next converted to the 6-membered C ring by a Dieckmann condensation/decarboxylation sequence. Installation of the C5 hydroxyl substituent was accomplished by oxidation of the trimethylsilyl (TMS) enol ether at C4-C5 with *meta*-chloroperoxybenzoic acid (*m*CPBA). Addition of methylmagnesium bromide to the C4 ketone followed by dehydration of the resulting tertiary alcohol using the Burgess reagent furnished the exocyclic methylene compound **14**.

Osmylation of the exocyclic methylene group followed by tosylation or mesylation of the C5 hydroxyl group gave an intermediate which upon treatment with base underwent cyclization to form the oxetane D ring. In order to form the requisite functionality on the upper half of the B ring the C10 hydroxy group was oxidized to a ketone. Subsequent enolate formation followed by treatment with benzeneselenic anhydride/potassium *t*-butoxide and then acetylation gave the desired C9 acetoxy functionality. Deprotection of the C13 TBS group gave the alcohol **16**. Finally, sidechain attachment using Ojima's procedure and deprotection of the C7 hydroxyl afforded Taxol® (**1**) in an overall yield of 5.8 % from **9** and 0.3 % from (-)-borneol **7**.

1. 2. 2. Nicolaou's Synthesis.

Nicolaou's group took a different approach to the synthesis of Taxol® (**1**) by first joining highly functionalized A and C rings and then performing a ring closure to form the B ring late in the synthesis (Scheme 3).[8]


EtO2C
OH
17
+
O
O
OH
18
PhB(OH)2
90 °C
61 %
OH
EtO2C
OH
O
O
19
1. TBSOTf, 2,6-lutidine, DMAP, CH2Cl2 0 °C
2. LiAlH4, Et2O, 0 °C
3. CSA, MeOH, CH2Cl2, 25 °C
4. TPSCl, imidazole, DMF, 25 °C
5. KH, BnBr, Et2O, n-Bu4NI, 25 °C
64 %
OBn
TPSO
OTBS
O
O
20
1. LiAlH4, Et2O, 25 °C
2. 2,2-dimethoxypropane
CSA, CH2Cl2, 25 °C
3. TPAP, NMO, CH3CN, 25 °C
62 %
OBn
TPSO
O
O
O
21
1. n-BuLi, THF,
-78 to 25 °C
add 21 at 0 °C
71 %
2. V(O)(acac)2,
t-BuOOH mol.
sieves, PhH,
25 °C
OTBS
NNHSO2Ar
23
4 steps
OAc
O
O
22
TBSO
OTPS
OBn
O
H
HO
O
24
1. LiAlH4, Et2O, 25 °C
2. COCl2, HMPA, Et2O
PhH, 25 °C
3. TBAF, THF, 25 °C,
4. TPAP, NMO, CH3CN
CH2Cl2, 25 °C
24 %
CHO
CHO
OBn
O
O
H
O
O
O
25


1. $(TiCl_3)_2 \cdot (DME)_3$ Zn-Cu, DME, 70 °C
2. 1-(S)-(-)-Camphanic chloride
3. K_2CO_3, MeOH
11 %
26
1. Ac_2O, DMAP, CH_2Cl_2, 25 °C
2. TPAP, NMO, CH_3CN, 25 °C
3. $BH_3 \cdot THF$, 0 °C, then H_2O_2
4. HCl(conc.),MeOH, 25 °C
5. Ac_2O, DMAP, CH_2Cl_2, 25 °C
37 %
27
1. H_2, $Pd(OH)_2/C$, EtOAC, 25 °C
2. Et_3SiCl, pyridine, 25 °C
3. K_2CO_3, MeOH, 0 °C
4. Me_3SiCl, pyridine, CH_2Cl_2 0 °C
5. Tf_2O, i-PrNEt, CH_2Cl_2, 25 °C
6. CSA, MeOH, 25 °C, then then SiO_2, CH_2Cl_2, 25 °C
32 %
28
1. $NaN(SiMe_3)_2$ then
THF, 0 °C
1. Ac_2O, DMAP, CH_2Cl_2, 25 °C
2. PhLi, THF, -78 °C
3. PCC, NaOAc, Celite, PhH, reflux
4. $NaBH_4$, MeOH, 25 °C
47 %
29
2. HF . pyridine THF, 25 °C
70 %
1
0.016 % overall from 17

Scheme 3

Nicolaou's group began by preparing the A and C rings. In their approach to the C ring, ester-alcohol **17** and 3-hydroxy-2-pyrone **18** underwent a highly regioselective Lewis acid catalyzed Diels-Alder reaction using phenylboronic acid to form the adduct **19**. This compound was subjected to a reduction and a number of protection steps followed by a final oxidation step to afford the aldehyde **21**, ready for addition of the A ring.

Despite having a route to a homochiral A-ring unit (*vide infra*) Nicolaou used the simpler intermediate **22** for this synthesis. Hydrazone **23** was converted via a Shapiro reaction to the corresponding vinyl anion which was added to the C-ring aldehyde **21** to furnish the corresponding alcohol as a single diastereomer. Directed epoxidation with $VO(acac)_2$/*t*-BuOOH afforded the epoxy-alcohol **24**. Regioselective opening of the epoxide with lithium aluminum hydride ($LiAlH_4$) then gave the C1-C2 diol which was protected as its cyclic carbonate on treatment with phosgene and potassium hydride (KH).

The principle purpose of this carbonate was to increase the rigidity of the system to allow for the crucial B ring closure although there was also the additional benefit that this carbonate could later be opened with phenyllithium (PhLi) to give the C1 alcohol and C2 benzoate groups (*vide infra*).

The key reaction to form ring B was accomplished by first removing the TBS and TPS protecting groups and oxidizing the resulting alcohols to the dialdehyde **25**. A pinacol-type coupling was then used to affect the ring closure in 23 % yield.

Resolution of this diol using 1(*S*)-(-)-camphanic chloride gave the diol **26**. Acetylation of the C10 alcohol was then followed by oxidation of the C9 alcohol to the corresponding ketone to give material which was then hydroborated and oxidized so as to install the requisite C5 hydroxyl functionality. Hydrolysis of the acetonide was then carried out and the resultant C20 alcohol acetylated to give compound **27**. This protection was neccessary so that the C7 benzyl group could be replaced by a triethylsilyl group. Cleavage of the C20 acetate followed by protection with a TMS group now set

the stage for oxetane formation using a sequence of steps similar to those used by Holton. Triflation of the C5 hydroxyl group followed by deprotection of the C20 primary alcohol and treatment with SiO_2 gave **28** containing the oxetane ring. Acetylation of the C4 tertiary hydroxyl group then afforded the acetate.

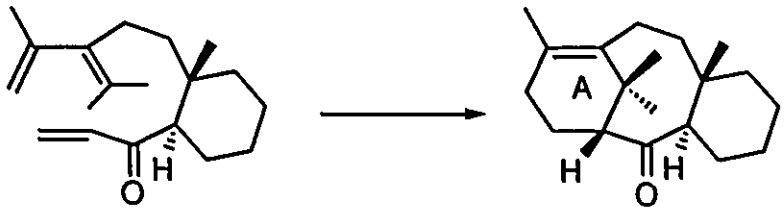
This compound underwent a surpringly regioselective opening with PhLi to give the C2 benzoate and C1 hydroxy group without affecting the other functionality in the molecule and provides testimony to the uniqueness of the taxanes. Additional testimony came from the ability to chemoselectively oxidize the C13 methylene group to a carbonyl in 75 % yield using 30 equivalents of pyridinium chlorochromate (PCC) buffered with sodium acetate. This is quite surprising in light of the high degree of functionality which this system possesses. Reduction of the C13 carbonyl with sodium borohydride gave the alcohol **29**. Finally sidechain attachment (again using the Ojima protocol) followed by C7 deprotection afforded Taxol® (**1**) in 0.016 % overall yield from **17**.

1. 3. REPRESENTATIVE DIELS-ALDER APPROACHES.

In addition to our own approach (*vide infra*), other groups have also examined the potential utility of an intramolecular Diels-Alder cycloaddition to generate the tricyclic skeleton.

1. 3. 1. Diels-Alder Approaches from a Preformed C-Ring.

In independent studies, Jenkins[12] and Shea[13] have generated the A ring with the bridgehead double bond in place through a Diels-Alder reaction using a pre-formed C-ring as a tether for the diene and dienophile. This reaction is illustrated in general terms in Scheme 4.



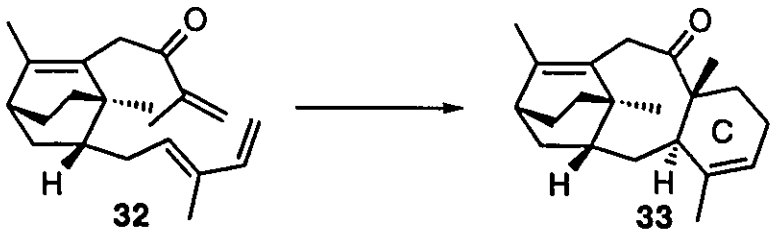
30 **31**

Scheme 4

1. 3. 2. Diels-Alder Approaches from a Preformed A-Ring.

The C ring has been constructed from a bicyclo[2.2.2]octene precursor by Sakan and Craven (Scheme 5).[14] It was assumed that the rigid geometry imparted by this bicyclic framework was required to hold the diene in an axial orientation. This allows the close proximity of the diene and dienophile in order to achieve the proper alignment for the cyclization transition state and overcome the entropic difficulties associated with a conformationally mobile ring system such as a cyclohexene. But is it neccessary to have

this one extra carbon bridging the C17 and C13 carbons? Certainly having the free gem dimethyl groups would simplify the construction of the taxane nucleus.

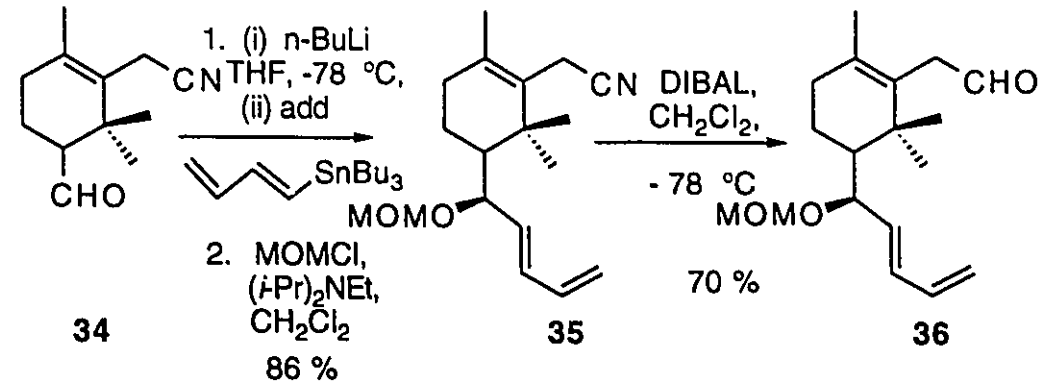


Scheme 5 **32** **33**

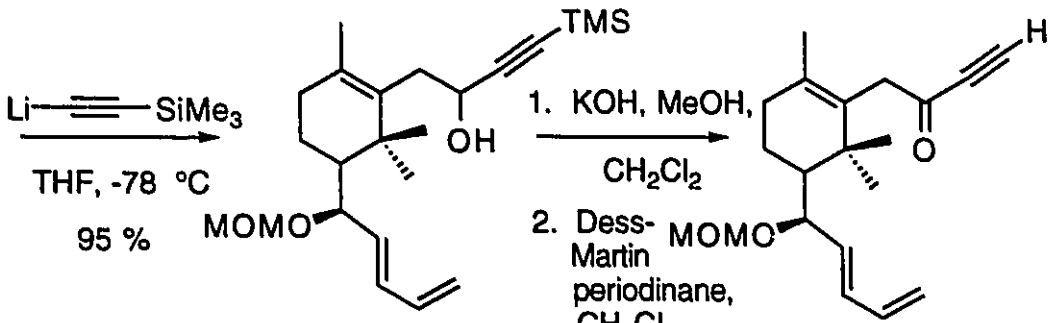
1.3.3. Fallis' Approach.

Previous work in our laboratories demonstrated the feasibility of constructing the taxane nucleus using a preformed A-ring compound as the tether for the diene and dienophile (Scheme 6).[15] The ring A model compound **34** bearing the free gem dimethyl group (*vide infra*) was converted to the Diels-Alder precursor compound **38** through a six step sequence which began by addition of the lithio-butadiene to the aldehyde **34**. The C2 alcohol thus obtained had the opposite stereochemistry of that occurring in Taxol® (**1**). Protection of the alcohol with a methoxymethyl (MOM) group gave the acetal **35** and was followed by reduction with diisobutylaluminum hydride (DIBAL)to afford the aldehyde **36**. Addition of the anion derived from TMS acetylene gave the alcohol **37** which was desilylated and then oxidized with Dess-Martin periodinane to the corresponding ketone **38**.

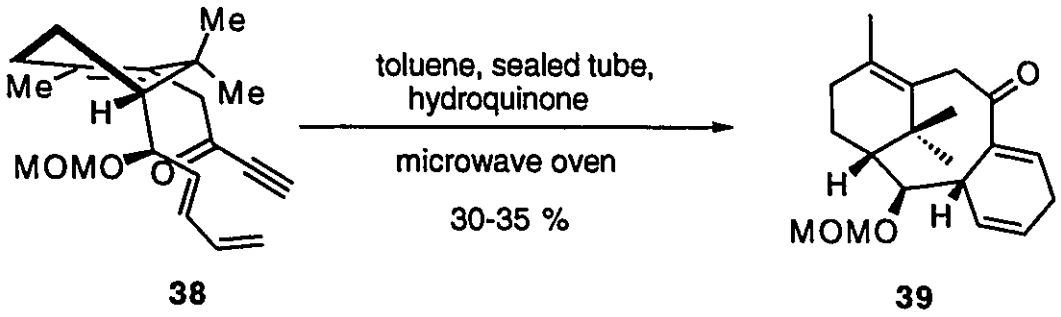
Compound **38** was shown to undergo "microwave assisted" cycloaddition to furnish adduct **39**. Isomerization of the C11-C12 double bond into conjugation with the C9 carbonyl was a competitive reaction and gave compound **40** which was incapable of cyclization and was therefore a factor responsible for lowering the yield. The facial selectivity is governed by the stereochemistry at C-2 which in turn controls the stereochemistry at C-3. Adduct **39** presumably arises through the endo transition state shown. It is apparent then from this work that it is not actually neccessary to tether the C17 methyl by use of a two carbon bridge as with Sakan's synthesis.



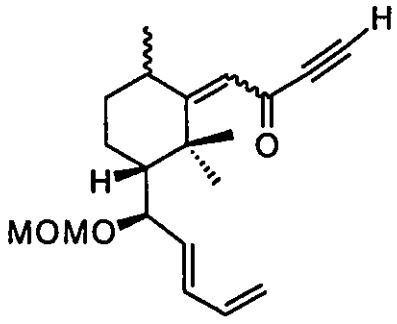
34 35 36



37 38



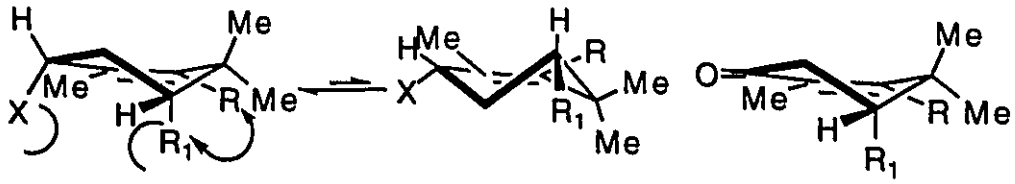
38 39



40

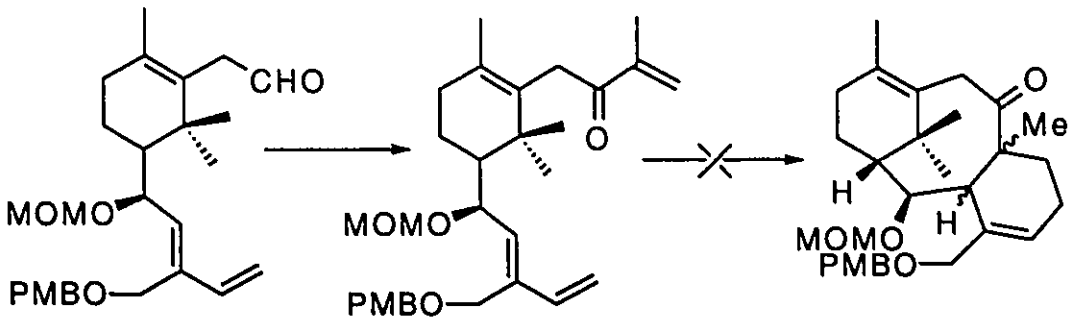
Scheme 6

The success of this approach can be rationalized by the following arguments. The conformer population of cyclohexenes is known to vary with the substitution pattern.[16] Thus, the potential 1,3-diaxial interaction in **41** (Scheme 7) had to be overcome if the reactive components represented by R and R_1 were to cyclize, since the equatorial conformer **42** does not allow the two side chains to interact significantly. However, this



Scheme 7

limitation should not cause undue difficulty provided the reactive conformer comprises a reasonable percentage of the equilibrium mixture at the temperature selected. When X=H the 1,3-interactions should be relatively minor and this would disappear entirely if a cyclohexenone such as **43** was employed. Consistent with this analysis, molecular mechanics calculations indicated that 1,2,3,3,4-pentamethylcyclohexene prefers a conformation related to **42** in which a slight twist minimizes any 1,3-methyl-hydrogen interference.[17] The cycloaddition was also aided by the use of an acetylenic dienophile such that the rotational parameters normally encountered in olefinic dienophiles were minimized. Use of an acetylenic dienophile seems to play an important role in the success of this reaction. Compound **45**, prepared in our laboratory by co-workers and possessing an acrylate as a dienophile, failed to undergo cyclization under similar conditions to that of its acetylenic counterpart (Scheme 8).



44 45 46

Scheme 8

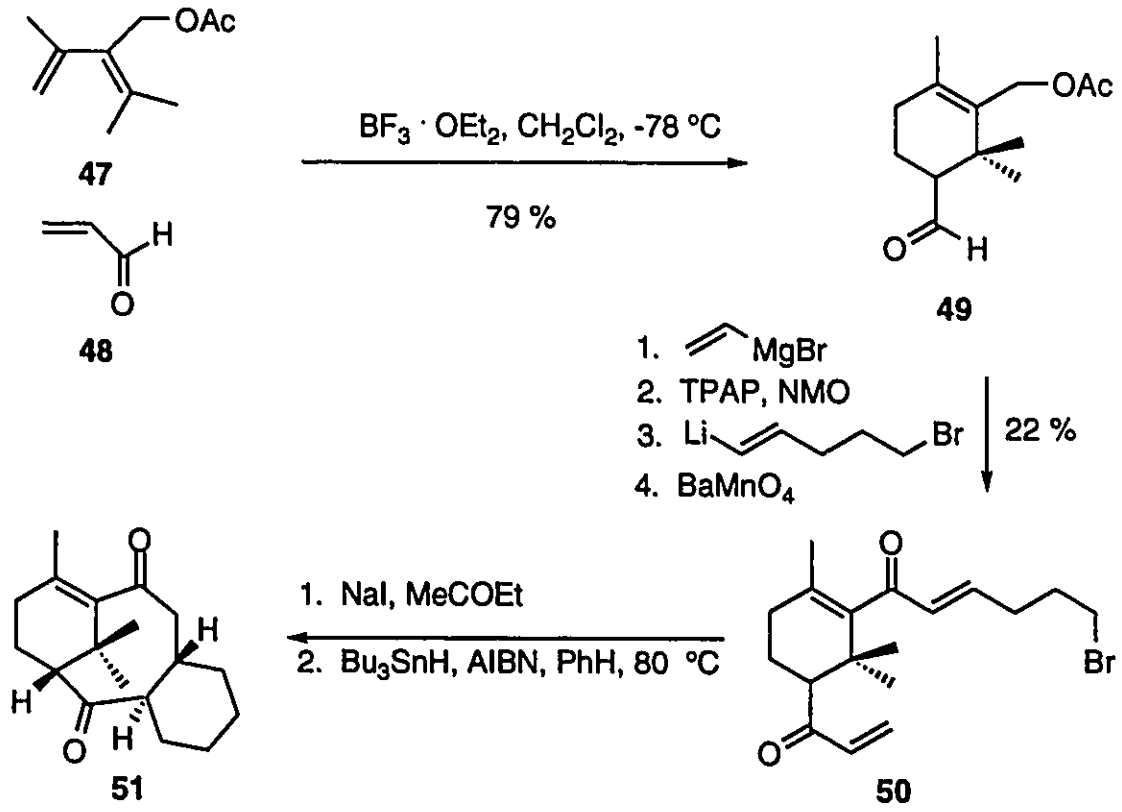
1.4. REPRESENTATIVE TAXOL A-RING SYNTHESES.

A number of groups have synthesized the A ring, generally as part of their overall approach to Taxol® (**1**). Only those approaches which lead to a highly functionalized A ring or those that are considered relevant to the work contained in this thesis are included. It is also not practical to include all the approaches to the taxane ring nucleus although further elaborations of some of these A ring syntheses to the taxane ring system are included.

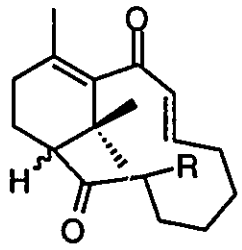
1.4.1. Pattenden's Approach.

Pattenden synthesized a simple A ring model through a Diels-Alder approach (Scheme 9).[18] Readily available diene **47** was reacted with acrolein **48** to produce the adduct **49**. A four step elaboration then produced bromide **50**. Pattenden then made use of a very clever double intramolecular radical cyclization to form the taxane nucleus. Tributyltin hydride mediated radical generation formed a primary alkyl radical by reaction with the iodide which then added to the 'lower' enone to give the more readily formed 12-membered ring. The resulting intermediate radical **52**, due to a conformationally restricted system, then underwent a second intramolecular addition to

the remaining enone to afford the desired taxane nucleus **51** in 19 % yield along with 6 % of the C3 epimer. In addition, 20 % of **53** was formed along with 30 % of material from the reduction of the initially formed radical.



19 % + 6 % of C3 epimer



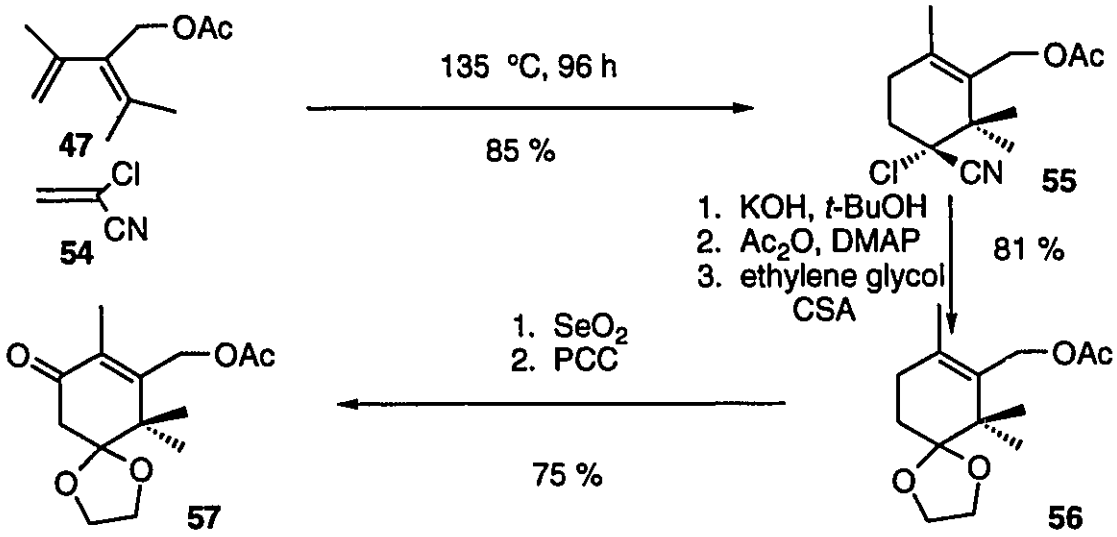
52 R = ·
53 R = H

Scheme 9

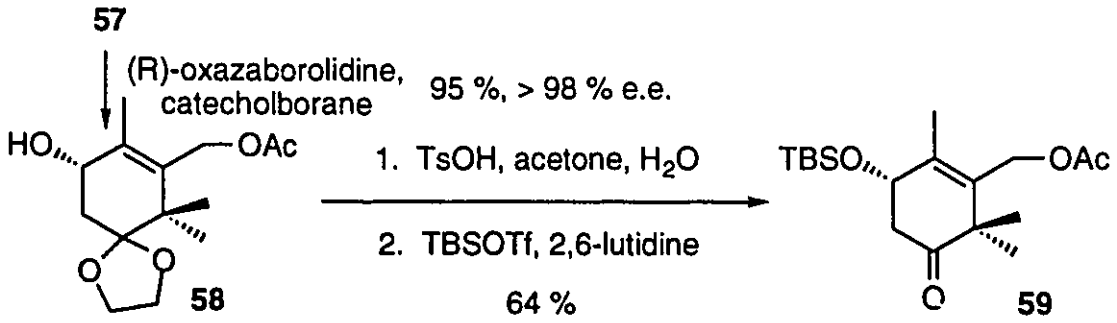
1.4.2. Nicolaou's Approach.

Nicolaou used a similar approach to that of Pattenden to form the A ring (Scheme 10).[19] But instead of acrolein as the ketene equivalent, 2-chloroacrylonitrile **54** was used so that the adduct **55** formed could be hydrolyzed under basic conditions to the

corresponding ketone. Acetylation to reform the acetate cleaved by the preceeding basic hydrolysis was followed by acid catalyzed ketalization of the C1 ketone to give **56**. This material underwent allylic oxidation using selenium dioxide (SeO_2) followed by PCC oxidation of the intermediate alcohol to give the C13 ketone **57**. Corey's oxazaborolidine-catechol borane reduction methodology was then used to form the optically active alcohol **58** in greater than 98 % e.e. excess and 95 % yield. Acid catalyzed hydrolysis of the ketal was accomplished in only moderate yield presumably due to the problem of competing β-elimination of the C13 alcohol. Protection of the alcohol as its TBS ether then completed the sequence to yield **59**. Part of this sequence was used by Nicolaou's group for their total synthesis of Taxol® (**1**) (*vide supra*). As stated earlier, this enantioselective synthesis was not used and a resolution step had to be performed.



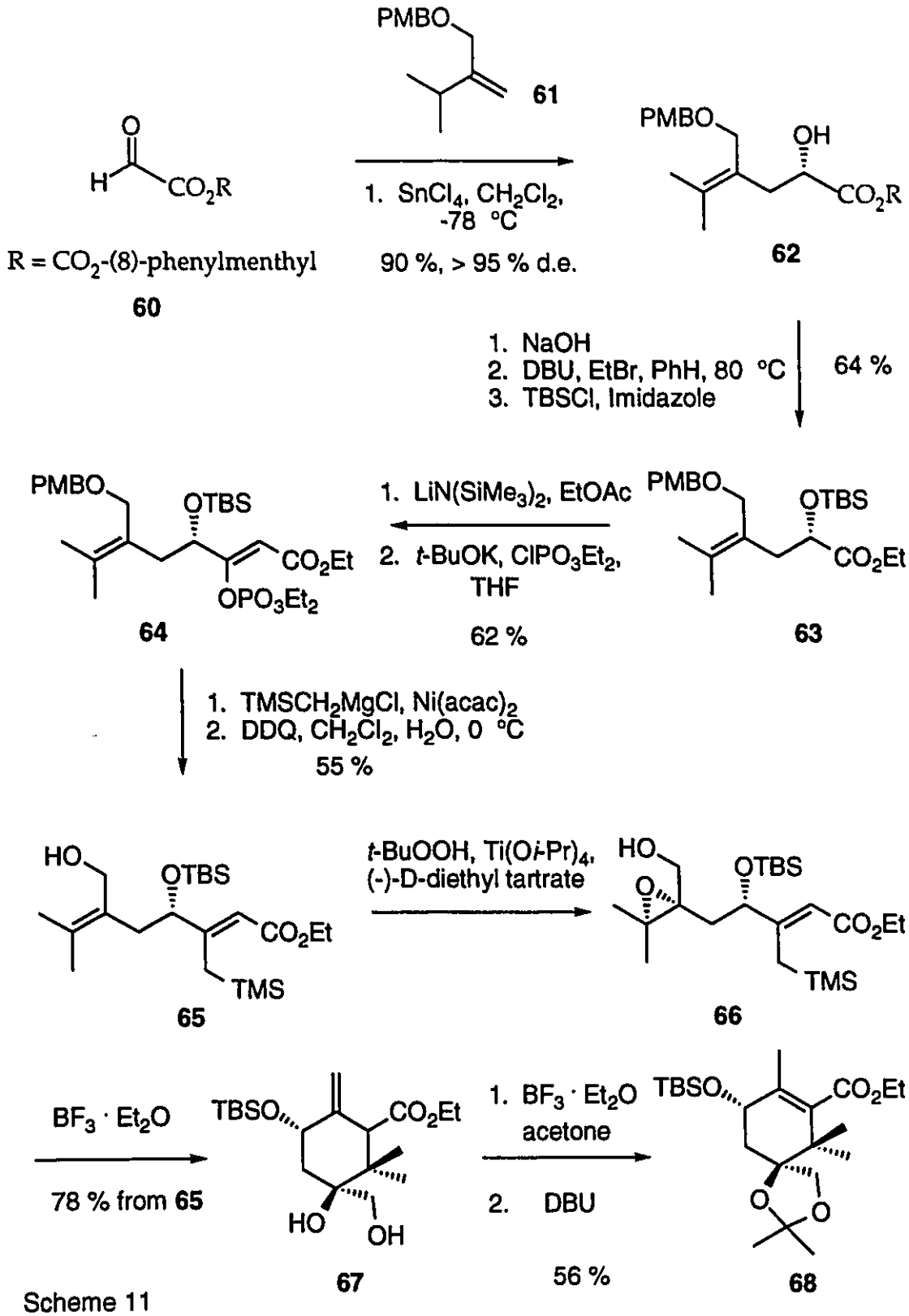
Scheme 10



Scheme 10 continued.

1. 4. 3. Frejd's Approach.

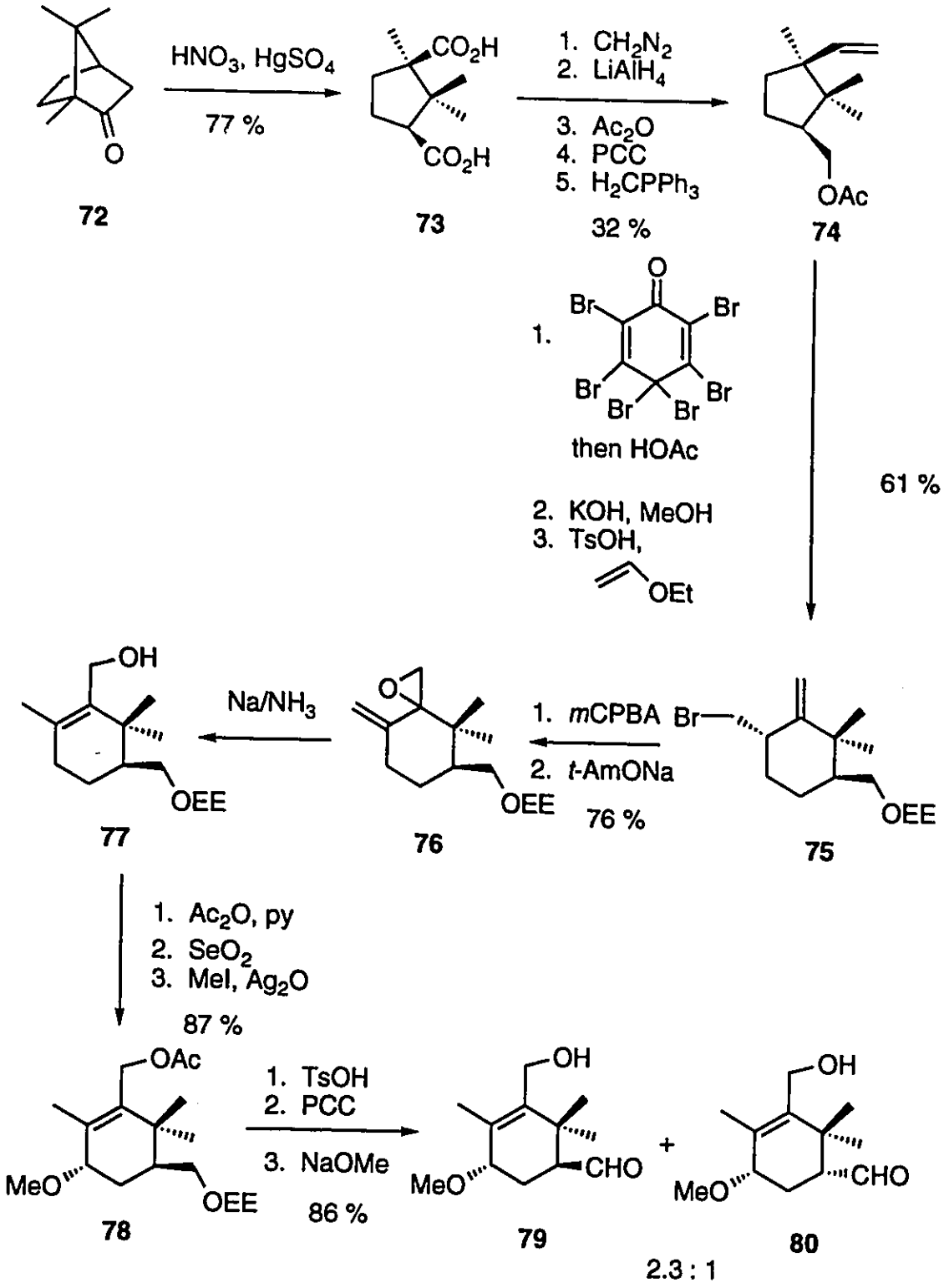
An earlier publication by Frejd disclosed the preparation of an optically active and fully functionalized A ring.[20] Starting from L-arabinose this target was prepared in a lengthy 23 step sequence. In an effort to prepare ring A in a much more efficient manner Frejd's group has recently published a 12 step sequence to **68** (Scheme 11).[21] They began by carrying out an ene reaction of allylic ether **61** with chiral 8-phenylmenthyl glyoxalate **60** such that homoallylic alcohol **62** was obtained in 90 % yield and greater than 95 % diastereomeric excess . This alcohol was then homologated to the enol phosphate **64** in five steps. Enol phosphate **64** underwent a nickel catalyzed addition of TMS methylmagnesium chloride to form the allyl silane. Removal of the para-methoxybenzyl (PMB) group on treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ) gave allylic alcohol **65**. Sharpless epoxidation then set the stage for the cyclization of **66**. This key step involved a boron trifluoride ($BF_3{\cdot}OEt_2$) catalyzed reaction between the allyl silane and epoxide functionality of **66** so as to form cyclohexane **67**. Base treatment to isomerize the exocyclic methylene group into conjugation with the ester followed by protection of the diol as the corresponding acetonide completed the sequence to give acetonide **68**.


PMBO
61
O
H
CO2R
1. SnCl4, CH2Cl2, -78 °C
PMBO
OH
CO2R
R = CO2-(8)-phenylmenthyl
60
90 %, > 95 % d.e.
62
1. NaOH
2. DBU, EtBr, PhH, 80 °C
3. TBSCl, Imidazole
64 %
PMBO
OTBS
CO2Et
OPO3Et2
1. LiN(SiMe3)2, EtOAc
2. t-BuOK, ClPO3Et2, THF
62 %
PMBO
OTBS
CO2Et
64
63
1. TMSCH2MgCl, Ni(acac)2
2. DDQ, CH2Cl2, H2O, 0 °C
55 %
HO
OTBS
CO2Et
TMS
65
t-BuOOH, Ti(Oi-Pr)4, (-)-D-diethyl tartrate
HO
O
OTBS
CO2Et
TMS
66
BF3 · Et2O
78 % from 65
TBSO
CO2Et
HO
OH
67
1. BF3 · Et2O
acetone
2. DBU
56 %
TBSO
CO2Et
O
O
68

Scheme 11

1. 4. 4. Kitagawa's Approach.

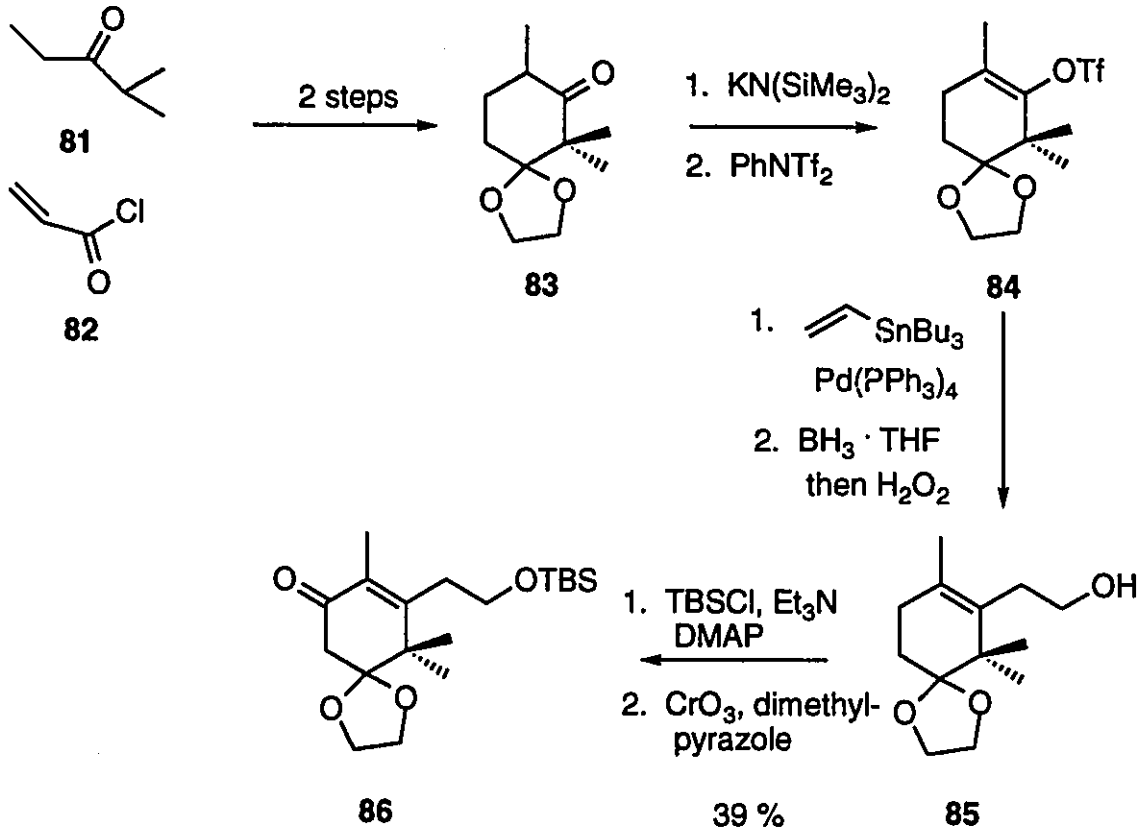
Another homochiral A ring synthesis was carried out by Kitagawa's group who chose camphor **72** as their starting material (Scheme 13).[22] Nitric acid oxidation of this material gave the cyclopentanedicarboxylic acid **73**. This material was converted to the diol *via* reduction with $LiAlH_4$ of the corresponding diester. Selective acetylation of the less hindered alcohol followed by oxidation with PCC of the remaining alcohol gave the aldehyde which was subjected to Wittig olefination conditions to give the vinyl compound **74**. This compound was subjected to bromination conditions using hexabromocyclohexadienone such that a rearrangement occurred to give the ring expanded product which was subsequently deacetylated and protected as its ethoxyethyl (EE) derivative **75**. Epoxidation of the exocyclic methylene group and treatment with the bulky base sodium *t*-amylate gave the exocyclic alkene-epoxide **76**. The epoxide was then rearranged to the alcohol **77** using sodium in ammonia. Allylic oxidation with SeO_2 and protection of the resulting alcohol as the corresponding methyl ether gave **78**. Deprotection of the ethoxyethyl group and oxidation of the resulting alcohol with PCC gave the corresponding aldehyde. This route unfortunately gave material with a trans relationship between the C13 alcohol and the C1 formyl group. Epimerization with base was only partially successsful and gave a 2.3:1 mixture of **79** and **80**, the minor isomer being the desired one. The overall yield was about 6.5 %.


HNO3, HgSO4
77 %
1. CH2N2
2. LiAlH4
3. Ac2O
4. PCC
5. H2CPPh3
32 %
72
73
74
1.
then HOAc
2. KOH, MeOH
3. TsOH,
OEt
61 %
Na/NH3
1. mCPBA
2. t-AmONa
76 %
77
76
75
1. Ac2O, py
2. SeO2
3. MeI, Ag2O
87 %
1. TsOH
2. PCC
3. NaOMe
86 %
78
79
80
2.3 : 1

Scheme 13

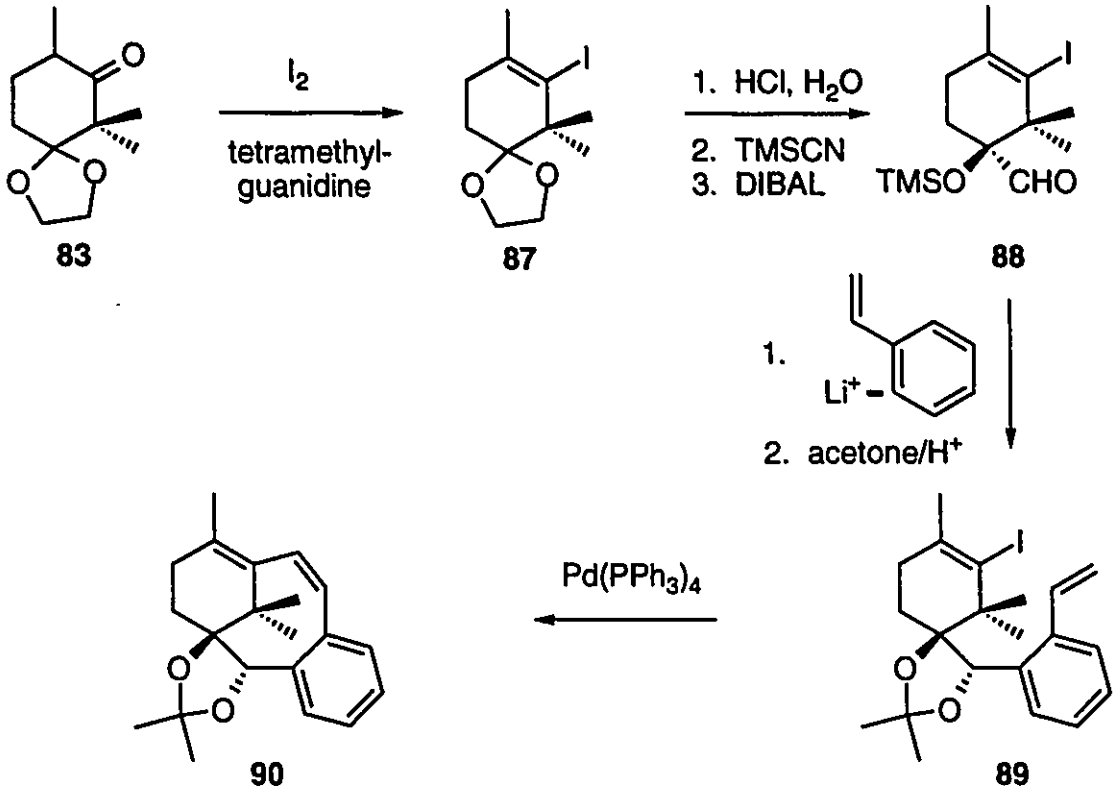
1. 4. 5. Danishefsky's Approach.

Danishefsky's approach to the A ring bears a close resemblance to Nicolaou's route but instead of a Diels-Alder reaction, a Michael addition-condensation approach was used to form the six-membered ring (Scheme 14).[23] Ethyl isopropyl ketone **81** was thus treated with acryloyl chloride to give the trimethylcyclohexane-1,3-dione which was selectively ketalized to form **83**. Formation of the enol triflate and use of a Stille coupling introduced a vinyl group which was hydroborated and oxidized to the alcohol **85**. This alcohol is very similar to compound **56** produced by Nicolaou's route with the exception being the presence of one additional carbon in the sidechain (*vide supra*). Protection of the alcohol **85** as a TBS ether and subsequent oxidation with chromium trioxide/dimethylpyrazole then gave the ketone **86**.



Scheme 14

Ketone **83** has also been converted to the vinyl iodide **87** which was used in a Heck-type olefination sequence to form the taxane nucleus **90** with an aromatic C ring (Scheme 15).[24] Thus deprotection of **87** gave the ketone which was reacted with trimethylsilyl cyanide (TMSCN) to form the trimethylsilyl cyanohydrin. Nitrile reduction with DIBAL then furnished the aldehyde **88** and was followed by the addition of 2-lithiostyrene (derived from 2-bromostyrene) such that the corresponding diol was obtained. This diol was protected as the acetonide **89**. Treatment of **89** with palladium (0) yielded the tricyclic compound **90**.

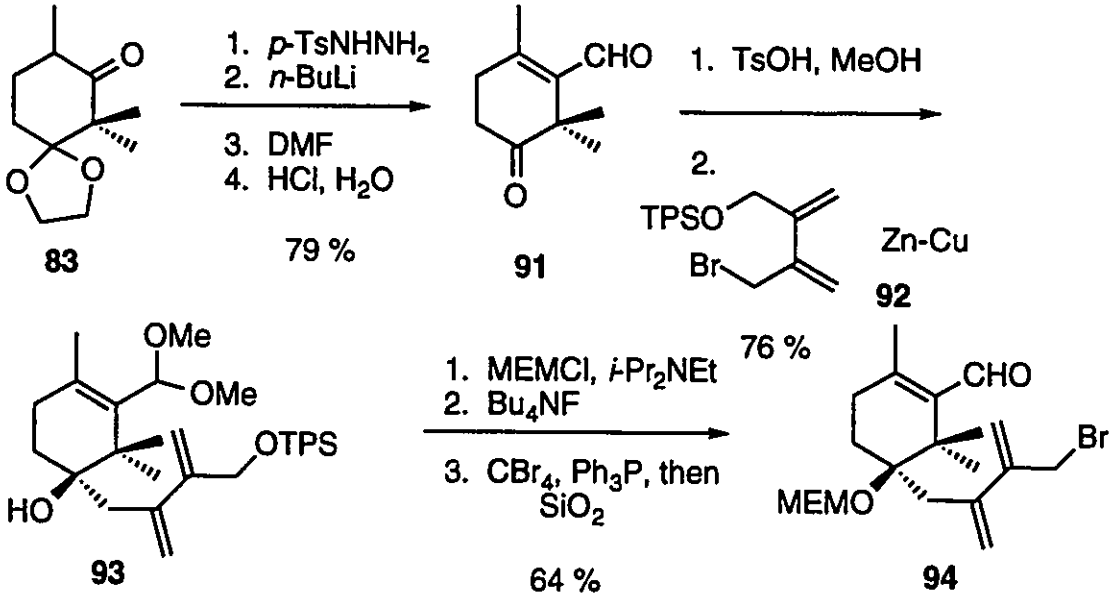


83 **87** **88** **89** **90**

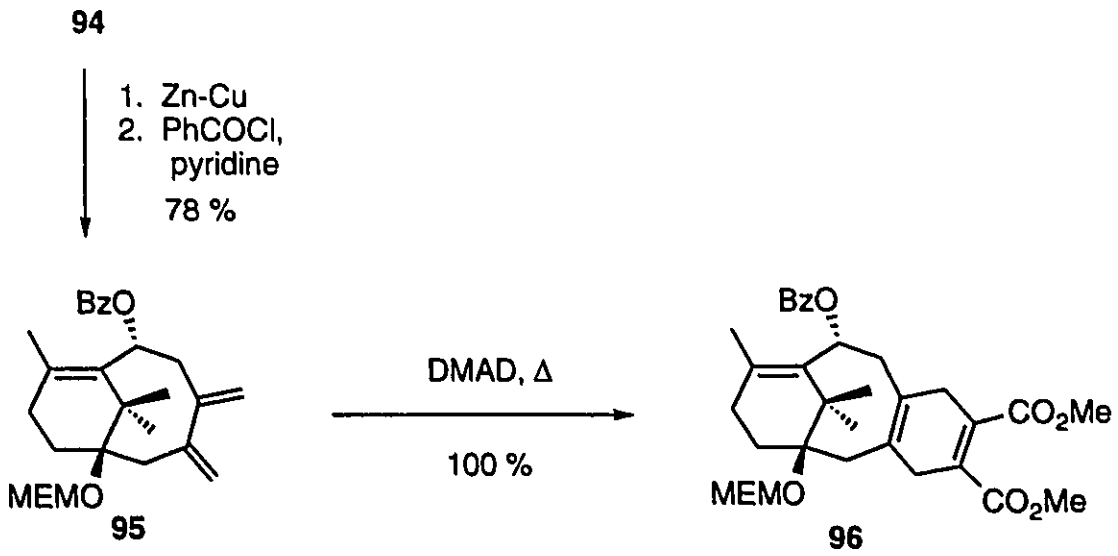
Scheme 15

1.4.6. Wang's Approach.

Wang prepared the enal **91** using the same ketone intermediate **83** that Danishefsky's group used (Scheme 16).[23,24,25] A Shapiro reaction of the hydrazone prepared from this ketone was used to form the corresponding vinyl anion which was then treated with dimethylformamide (DMF) to afford the aldehyde. Deprotection of the ketal functionality then gave the ketone **91** which was followed by protection of the aldehyde as an acetal. The ketone was subsequently reacted with an allyl anion species prepared by treatment of the allyl bromide **92** with a zinc-copper couple to give alcohol **93**. Alcohol **93** was protected with a methoxyethyl (MEM) group and converted to the allyl bromide-aldehyde **94**. Allyl bromide **94** underwent an intramolecular cyclization when treated with a second zinc-copper couple. Benzoylation of the alcohol thus obtained gave the benzoate **95**. Formation of the C-ring was then accomplished by a Diels-Alder reaction using dimethylacetylene dicarboxylate (DMAD) as the dienophile to afford the taxane nucleus **96**.



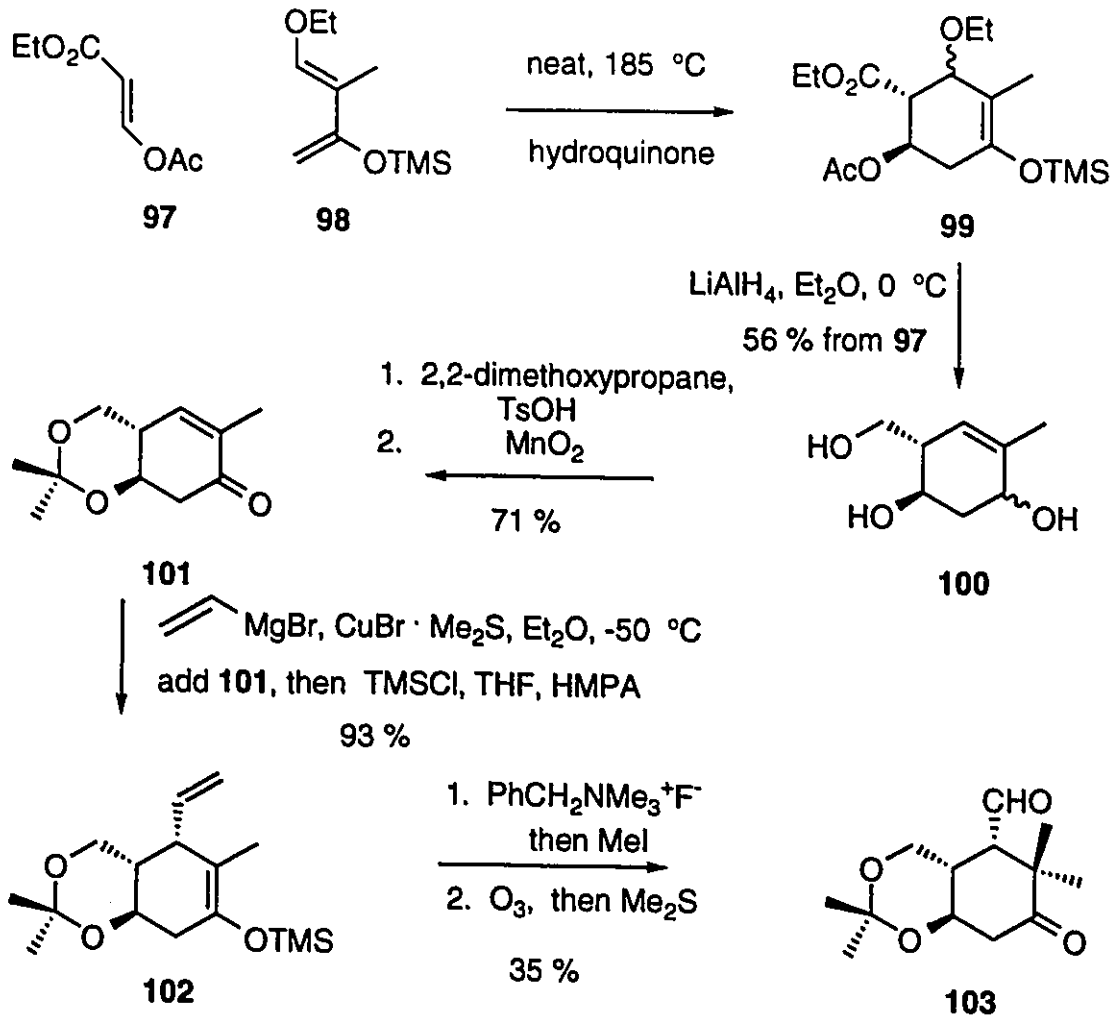
Scheme 16



Scheme 16 continued

1.4.7. Clark's Approach.

Clark used another Diels-Alder approach to form the A ring by a cycloaddition reaction of the enol-ester-acetate **97** with the dienol **98** (Scheme 17).[26] Subsequent reduction of the adduct **99** to the corresponding triol **100** and acetonide formation gave an allylic alcohol which was oxidized with MnO_2 to the enone **101**. 1,4-addition of vinyl cuprate with concomitant trapping of the resulting enolate with TMSCl resulted in formation of the silyl-enol ether **102**. Treatment of the silyl-enol ether with benzyltrimethylammonium fluoride and reaction of the resulting enolate with methyl iodide installated the gem-dimethyl group. Finally, ozonolysis furnished aldehyde **103**.

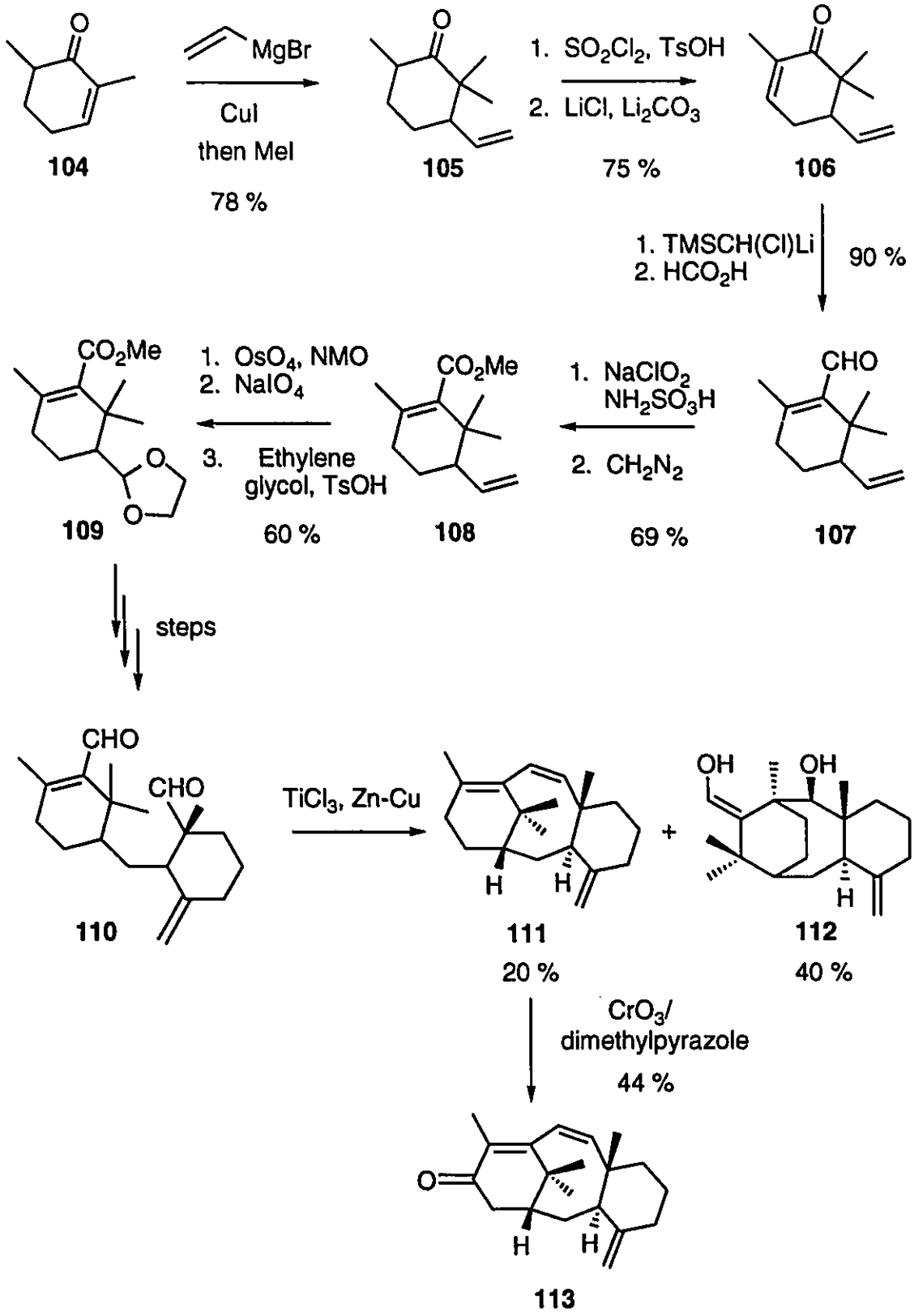


Scheme 17

1.4.8. Kende's Approach.

The work done by Kende's group deserves special mention for they demonstrated the feasibility of using a McMurry coupling to form the B ring.[27] This same method was used later by Nicolaou's group for their total synthesis of Taxol® (1).

For their overall strategy it was necessary to first prepare both A and C rings for subsequent joining (Scheme 18).


104
MgBr
CuI
then MeI
78 %
105
1. SO_2Cl_2, TsOH
2. LiCl, Li_2CO_3
75 %
106
1. TMSCH(Cl)Li
2. HCO_2H
90 %
107
1. $NaClO_2$
NH_2SO_3H
2. CH_2N_2
69 %
108
1. OsO_4, NMO
2. $NaIO_4$
3. Ethylene glycol, TsOH
60 %
109
steps
110
$TiCl_3$, Zn-Cu
111
20 %
112
40 %
CrO_3/
dimethylpyrazole
44 %
113

Scheme 18

The A ring was prepared in a very efficient manner (22 % overall yield) starting from the dimethylcyclohexenone **104**. Addition of vinyl cuprate followed by reaction of the resulting enolate with methyl iodide gave compound **105** possessing the gem-dimethyl group. Chlorination of the α-position of the ketone followed by base catalyzed elimination to regenerate the enone functionality produced **106**. Treatment of **106** with a formyl anion equivalent followed by treatment with formic acid furnished the enal **107**. Subsequent oxidation and esterification gave **108** which when treated with osmium tetroxide (OsO_4) and N-morpholine oxide (NMO) gave the corresponding diol. Treatment of this diol with sodium periodate gave the corresponding aldehyde which was protected as its ketal **109**.

The C ring was attached next and further elaborated to the dialdehyde **110**. This compound, possessing all the methyl groups present in Taxol® (**1**), underwent a McMurry coupling reaction to give the desired coupled product **111** in 20 % yield along with 40 % of **112**, resulting from addition of the C9 aldehyde to the C11-C12 double bond through a Michael-type addition. Allylic oxidation was effected using chromium trioxide and dimethylpyrazole to afford the C13 ketone **113**.

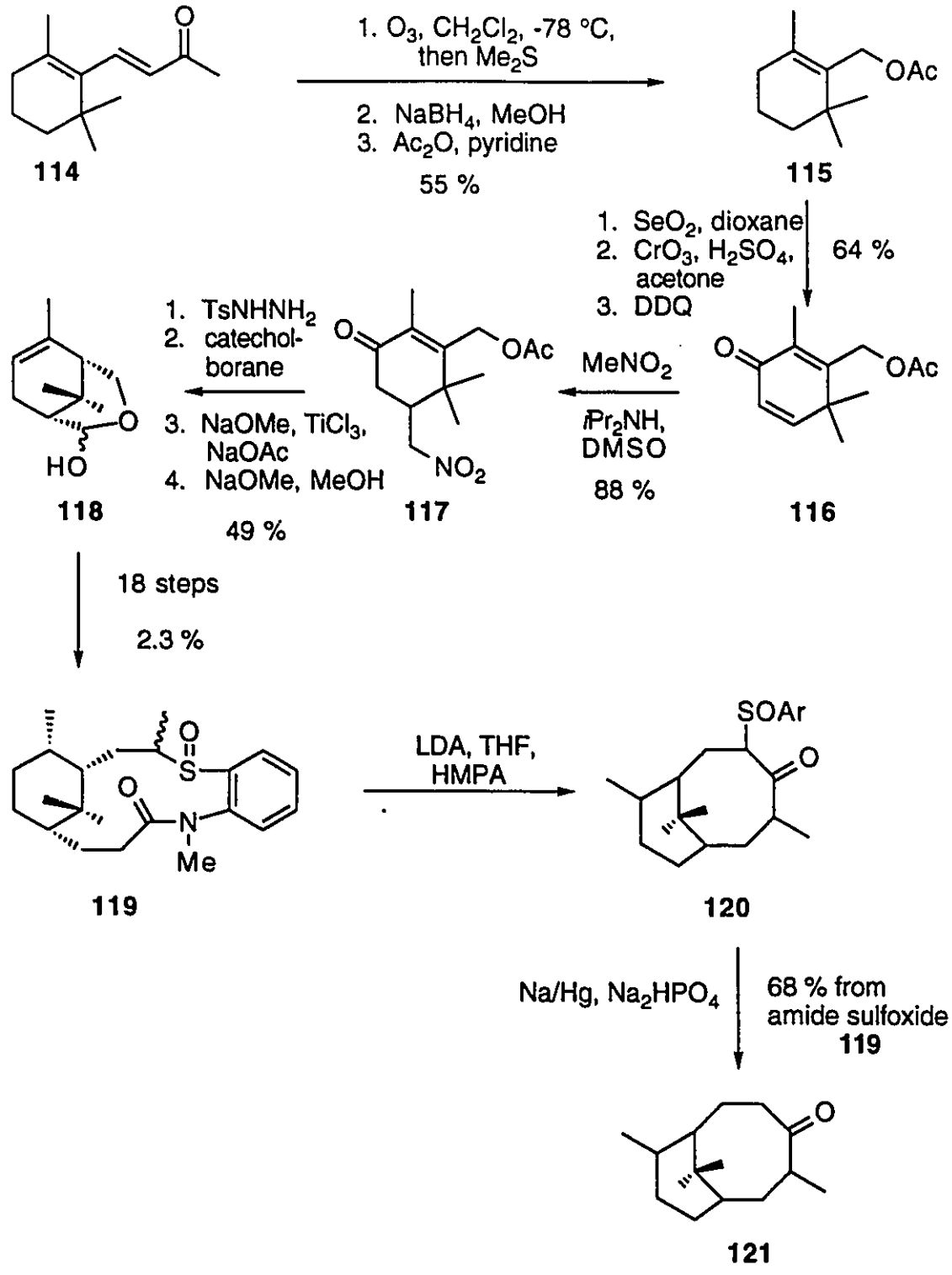
As stated previously, Nicolaou used this procedure to form the B ring but under strictly controlled conditions so that the diol **26** was obtained.

The success of Kende and Nicolaou's approaches are presumably due to the tethering effect of the metal which brings the reactive sites close enough together and overides steric effects.

1.4.9. Oishi's Approach.

Oishi's group used β-ionone (**114**) as a starting material for their synthesis of the bicyclic A/B ring system using their lactam sulfoxide contraction strategy for medium ring synthesis (Scheme 19).[28] The sequence began with ozonolysis of β-ionone to

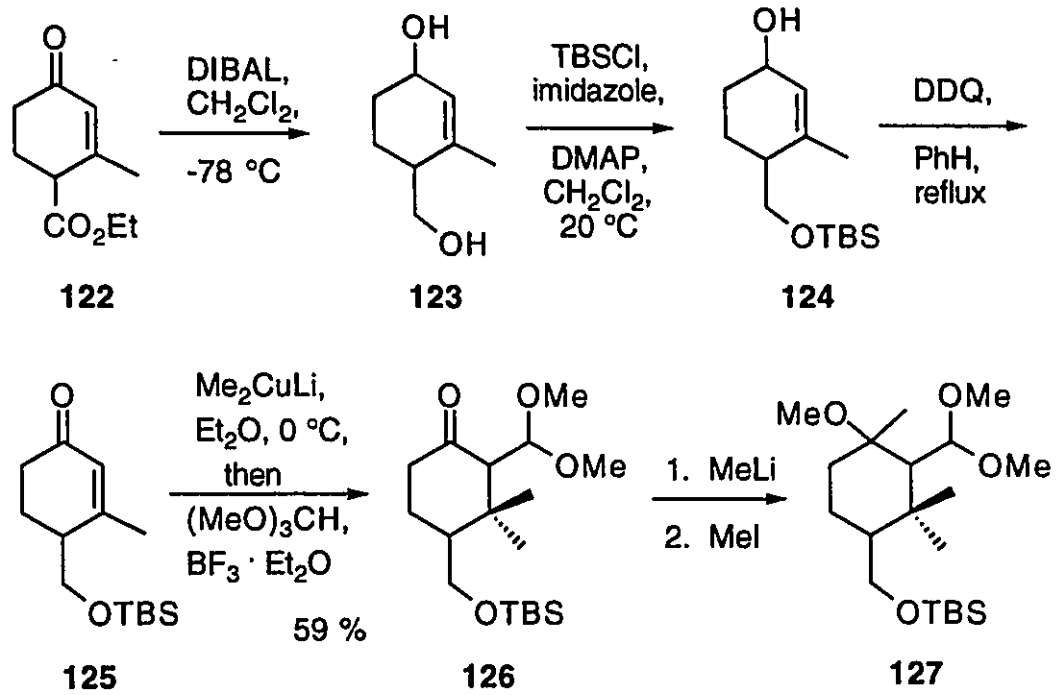
furnish the corresponding aldehyde which was reduced with sodium borohydride and protected to furnish the acetate **115**. Oxidation with selenium dioxide followed by Jones oxidation and dehydrogenation with DDQ then furnished the dienone **116**. This latter step was incredibly slow and required 10 days in refluxing benzene! Addition of nitromethane was again an incredibly slow process requiring 36 days but furnished the nitro compound **117** in good yield. Conversion of the carbonyl group to a methylene group followed by McMurry reduction of the nitro group with simultaneous deprotection of the acetate produced hemi-acetal **118** in modest yield. An additional 18 steps were required to convert compound **118** to the lactam sulfoxide **119** which on treatment with lithium diisopropylamide (LDA) underwent condensation to afford the bicyclic A/B ring system. Unfortunately this sequence of steps resulted in loss of the C11-C12 double bond and also resulted in the positioning of the methyl group at C3 instead of C8. This 30 step sequence may be compared to that of Holton's two step fragmentation of commercially available β-patchoulene oxide to give the optically active compound **6** possessing double bond, C-8 methyl group as well as the C-13 hydroxy group, albeit the wrong enantiomer (*vide supra*)!


1. O_3, CH_2Cl_2, -78 °C, then Me_2S
2. $NaBH_4$, MeOH
3. Ac_2O, pyridine
55 %
114
115
OAc
1. SeO_2, dioxane
2. CrO_3, H_2SO_4, acetone
3. DDQ
64 %
116
$MeNO_2$
iPr_2NH, DMSO
88 %
117
NO_2
1. $TsNHNH_2$
2. catechol-borane
3. NaOMe, $TiCl_3$, NaOAc
4. NaOMe, MeOH
49 %
118
HO
18 steps
2.3 %
119
Me
LDA, THF, HMPA
120
SOAr
Na/Hg, Na_2HPO_4
68 % from amide sulfoxide 119
121

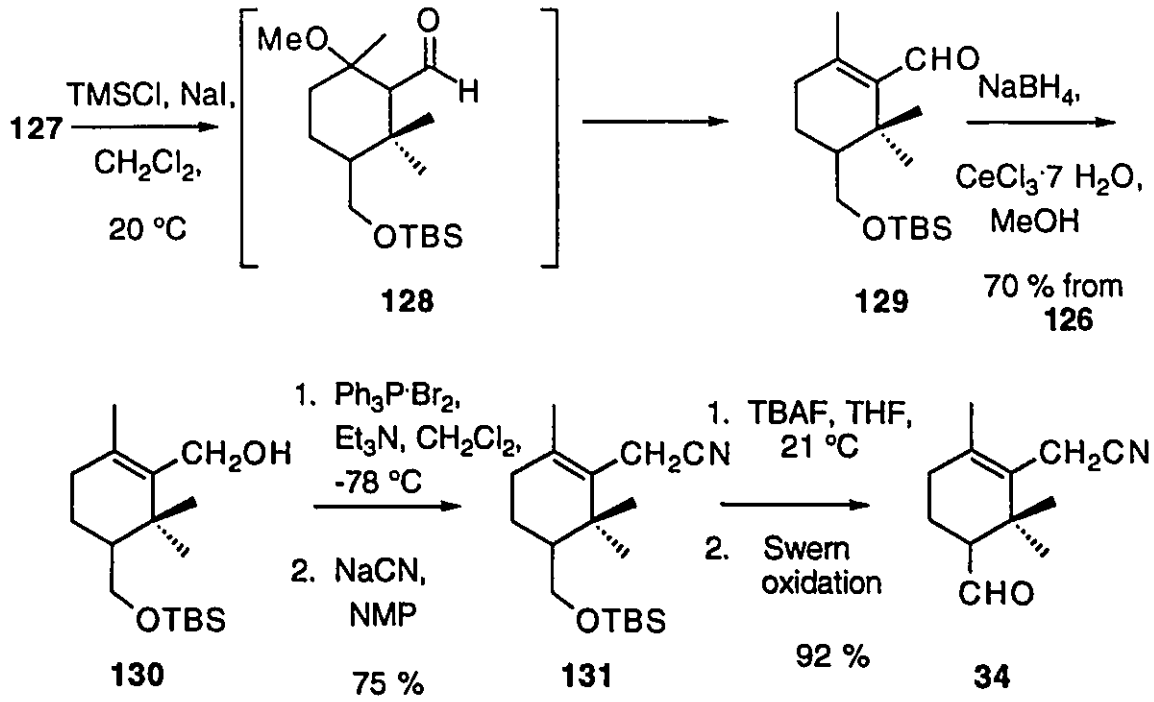
Scheme 19

1. 4. 10. Fallis' Approach.

As discussed previously, the model A ring compound **34** was used to prepare the diene-dienophile **38** which was cyclized to the taxane nucleus **39** (*vide supra*).[15] Starting from Hagemann's ester **122**, the diol **123** was prepared and subsequently mono-protected with *tert*-butyldimethylsilyl chloride (TBSCl) to afford **124** (Scheme 20). The ketone functionality was then regenerated by oxidation with DDQ and methylcuprate was added to install the gem-dimethyl functionality. The enolate resulting from this addition was reacted with trimethyl orthoformate to afford the acetal **126**. Addition of methyllithium to the ketone and methylation of the resulting alcohol gave **127**. Deprotection gave the enal **129** *via* the intermediate aldehyde **128**. Aldehyde **129** was subsequently reduced to the alcohol **130**, converted to the bromide and then to the nitrile **131**. Deprotection of the TBS ether followed by oxidation of the resulting alcohol gave the aldehyde **34**.



Scheme 20



Scheme 20 continued

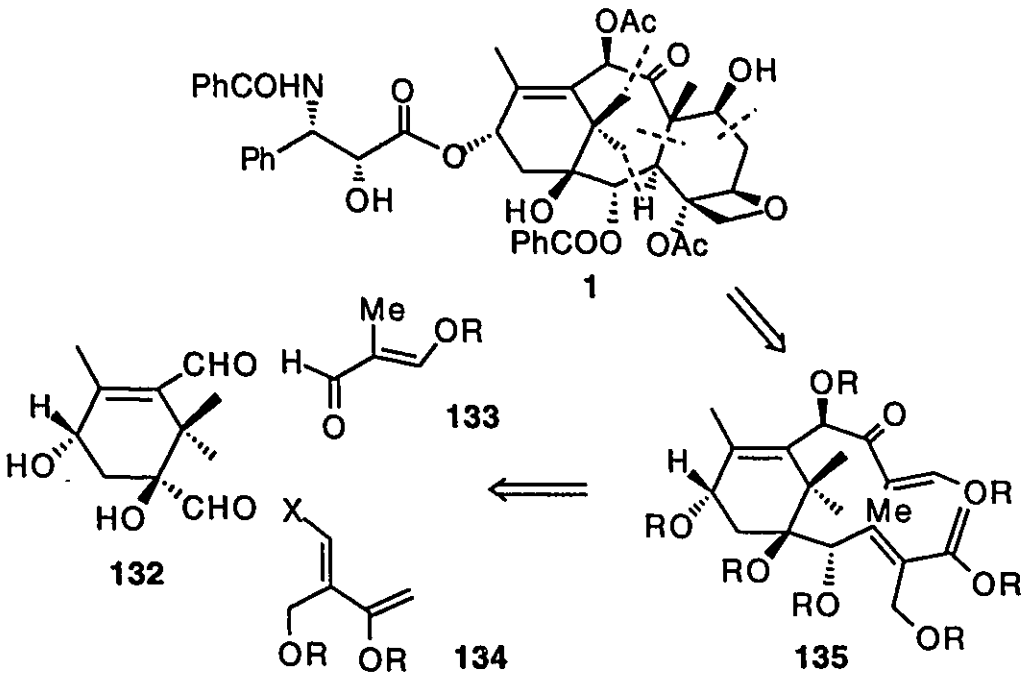
1.5. RESEARCH OBJECTIVES.

1.5.1. Retrosynthetic Plan for Preparing the Taxane Nucleus.

The idea of using an intramolecular Diels-Alder approach to construct the taxane nucleus containing a gem-dimethyl group has been demonstrated to be feasible by our research group. We therefore planned to examine the possibility of constructing a much more highly functionalized Diels-Alder precursor with the goal being the total synthesis of Taxol® (**1**) (Scheme 21). In a retrosynthetic sense removal of the D ring oxetane followed by double disconnection between C6-C7 and C3-C8 in ring C, like that in the model reaction, suggested a Diels-Alder precursor related to tetraene **135**. In principle this could be constructed in a direct manner from further disconnections between C2-C3 and C9-C10. In total this leads to a highly convergent approach to the taxane nucleus

from a suitably functionalized A-ring synthon in the form of a masked dialdehyde related to **132** followed by attachment of the lower diene and upper dienophile units **134** and **133** respectively.

It was thus our goal to first prepare the A-ring synthon and further elaborate this ring to a Diels-Alder precursor which could subsequently be cyclized to the tricyclic framework of Taxol® (**1**).

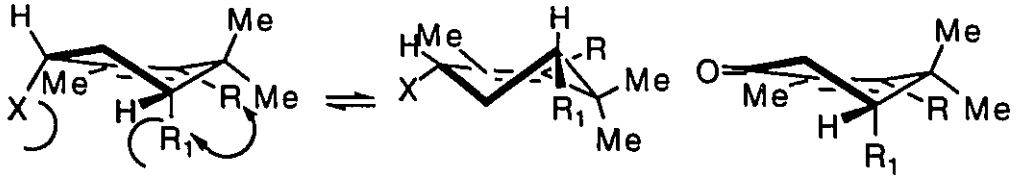


Scheme 21

1. 5. 2. Mechanistic Considerations.

The same factors which enabled a successful outcome for the model reaction also had to be considered for a more complex system. Nevertheless, there was a limitation to this approach for the total synthesis, since the natural α orientation of the C13 ester side chain would increase the nonbonded interactions in the required conformer **41** (X=OR).

Thus for the Diels-Alder step to proceed, either the unnatural C13 epimer or the C13 ketone **43** had to be employed and the A-ring synthon modified accordingly.

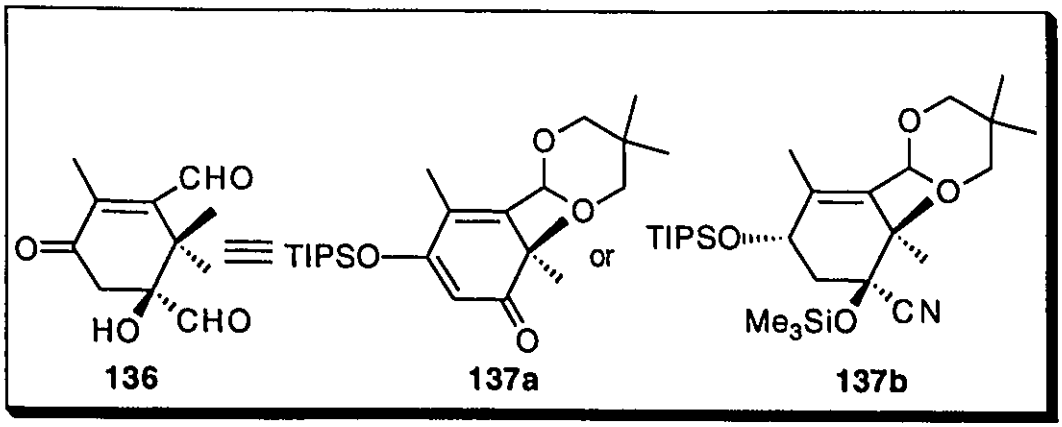


41 **42** **43**

In addition to having to alter the stereochemistry at C13 to the unnatural epimer or avoid the problem by incorporation of a carbonyl at this site, the questions of the stereochemistry and steric demands at both C2 and C10 on the cycloaddition would have to be addressed. From the model reaction (Scheme 6) it appeared that the functionality and stereochemistry at C2 did not adversely affect the Diels-Alder reaction but little was known about how the stereochemistry and size of a substituent at C10 would affect this reaction.

1. 5. 3. Ring A Retrosynthetic Plan

Our overall goal to produce a highly functionalized Diels-Alder precursor required an efficient route to the A-ring synthon. We envisioned the synthesis of compound **137a** or **137b**, **137b** being equivalent to the dialdehyde **136**, where the nitrile and acetal served as masked aldehyde functionalities that could be selectively reacted (Scheme 22).



136 137a 137b

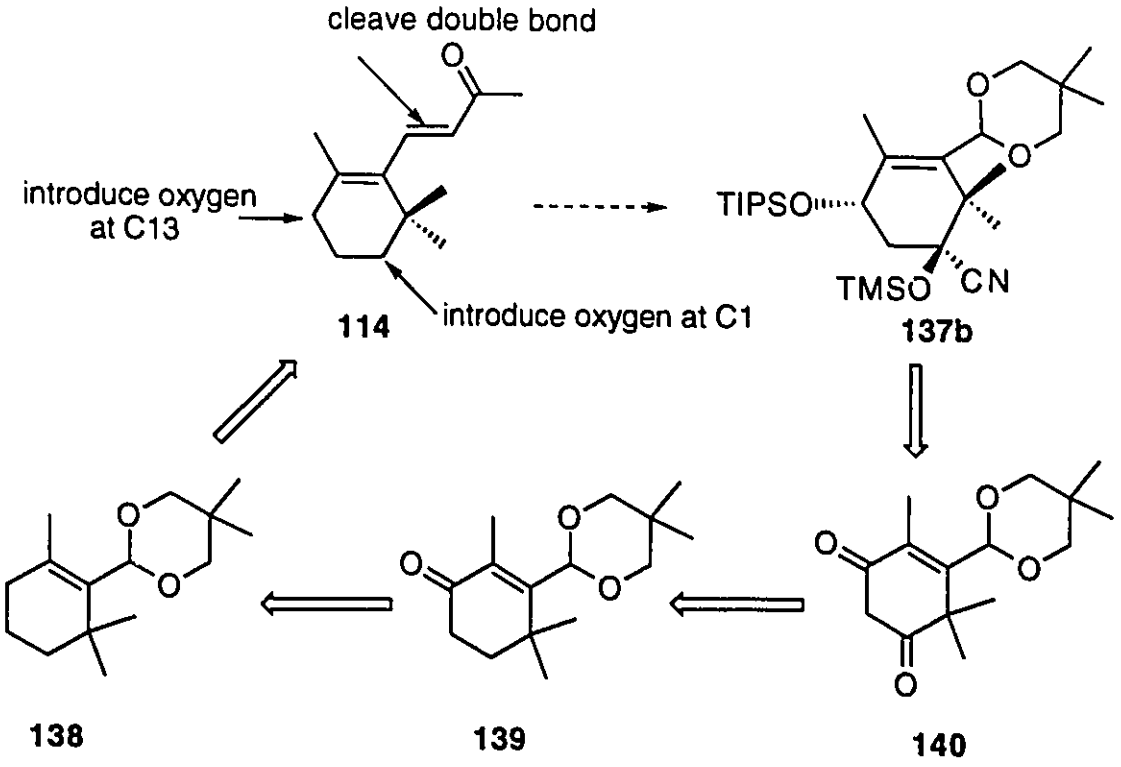
Scheme 22

For our intended A-ring synthesis we, like Oishi's group, also chose β-ionone (**114**) as a starting material. The compound is relatively inexpensive[29] ($ 10/Kg in bulk) and possesses the C15 geminal methyl groups and the C18 vinylic methyl group present in taxanes.

The general strategy was to cleave β-ionone (**114**) to the known compound β-cyclocitral and protect the resulting aldehyde as its acetal **138** (Scheme 23). This would avoid, unlike in Oishi's approach, a reduction and future oxidation step at this center.

What was not known at the time this work was started and is somewhat surprising, is the ability of highly functionalized taxanes to cleanly undergo oxidation at C13. This has now been demonstrated by Nicolaou's total synthesis of Taxol® (**1**).[8] It was thus our intention to incorporate oxygen at C13 at an early stage in our synthesis since often allylic oxidations are problematic and could be especially so at the later stages of a synthesis due to a high degree of functionality present.

Incorporation of oxygen at C13 would also enable the incorporation of functionality at C1, preferably in the form of a ketone like **140**. This ketone in principle could be converted to the silyl cyanohydrin **137b**. Work thus centered on the incorporation of oxygen at C13 and C1.


cleave double bond
introduce oxygen at C13
introduce oxygen at C1
TIPSO
TMSO
CN
114
137b
138
139
140

Scheme 23

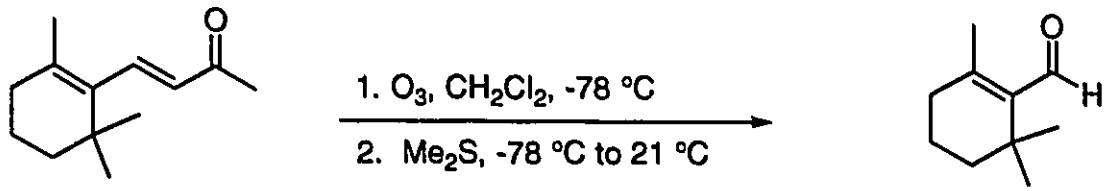
RESULTS AND DISCUSSION

CHAPTER 2

PREPARATION OF RING A

2. 1. Acetal Preparation and Oxidation at C13.

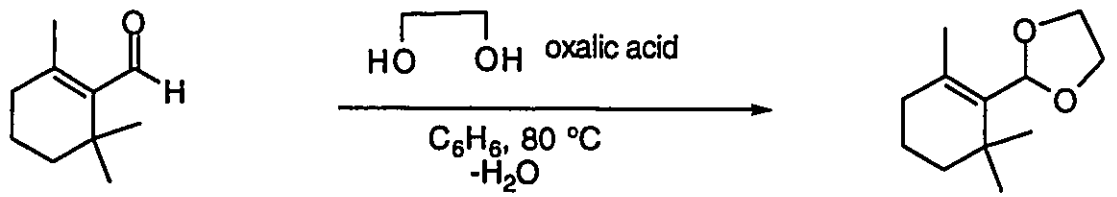
Ozonolysis of β-ionone (**114**) was conducted using a modification of the procedure first reported by Muller and Hoffmann (Scheme 24).[30]



114 **141**

Scheme 24

The crude aldehyde β-cyclocitral (**141**) was protected as its ethylidene acetal **142** using oxalic acid to minimize double bond migration (Scheme 25).[31] Yields by distillation or chromatography were typically 45-60 % depending on the scale of the preparation. This compound displayed a singlet in the ^1H NMR at 5.31 ppm and a resonance at 102.3 ppm in the ^{13}C NMR spectrum, both indicative of the presence of an acetal. No evidence existed of double bond migration.



141

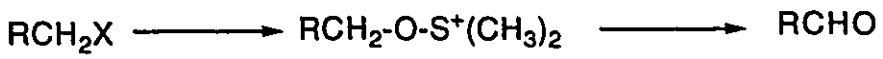
45 to 60 % from **114**

142

Scheme 25

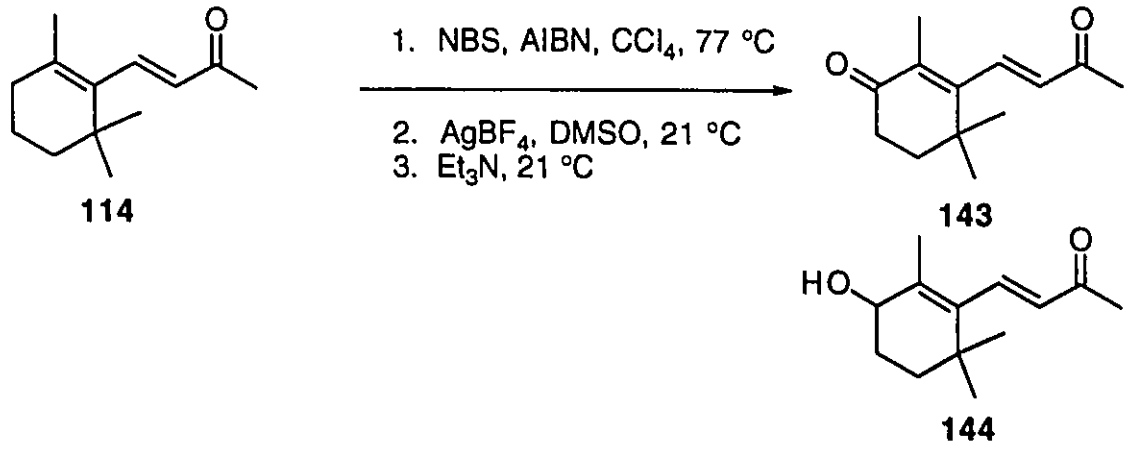
The oxidation of the acetal **142** at C13 (Taxol® (**1**) numbering) was quite problematic. The acetal functionality was quite labile and conditions were developed to avoid its destruction. Initial attempts using SeO_2 in dioxane gave only deprotected starting material.[32] β-Ionone (**114**) was chosen as a model compound to evaluate a number of oxidation methods despite the absence of the acetal functionality.

Work reported by Ganem had shown that primary and secondary alkyl bromides and iodides could be oxidized to aldehydes and ketones respectively using silver tetrafluoroborate ($AgBF_4$) in DMSO followed by addition of triethylamine.[33] The mechanism for this transformation has similarities with other DMSO activated oxidations like the Swern oxidation (Scheme 26). Silver promoted loss of halide followed by nucleophilic attack by the DMSO gives an intermediate which on treatment with triethylamine results in the elimination of dimethylsulfide to generate the carbonyl compound.



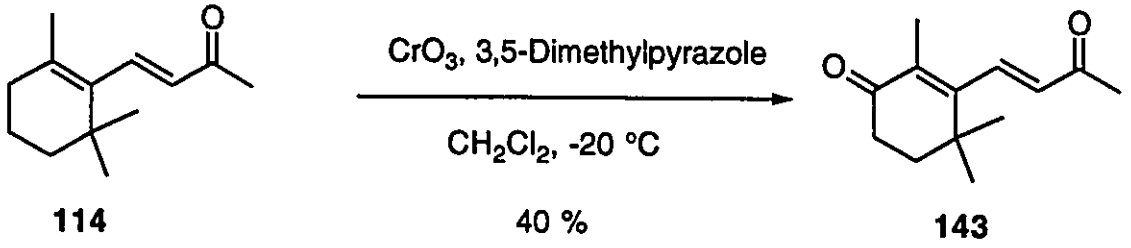
Scheme 26

To evaluate this method β-ionone **114** was treated with N-bromosuccinimide (NBS) and 2,2'-azo-*bis*-(isobutyronitrile) (AIBN) to generate an unstable compound (presumably the bromide) which was treated with $AgBF_4$ in DMSO and then by triethylamine to afford a mixture of alcohol **144** and ketone **143** in low yield as detected by GC/MS (Scheme 27).



Scheme 27

The structure of ketone **143** was verified by comparison with a sample prepared by a different method. The use of CrO_3/dimethylpyrazole to oxidize β-ionone (**114**) gave the keto compound **143** in 40 % isolated yield (Scheme 28).[34] The ^1H NMR of this compound displayed a characterisic multiplet at δ 2.51 ppm (-$COCH_2$-) as well as two resonances in the ^{13}C NMR spectrum at 197.0 and 198.0 ppm, indicating the presence of two carbonyl groups.

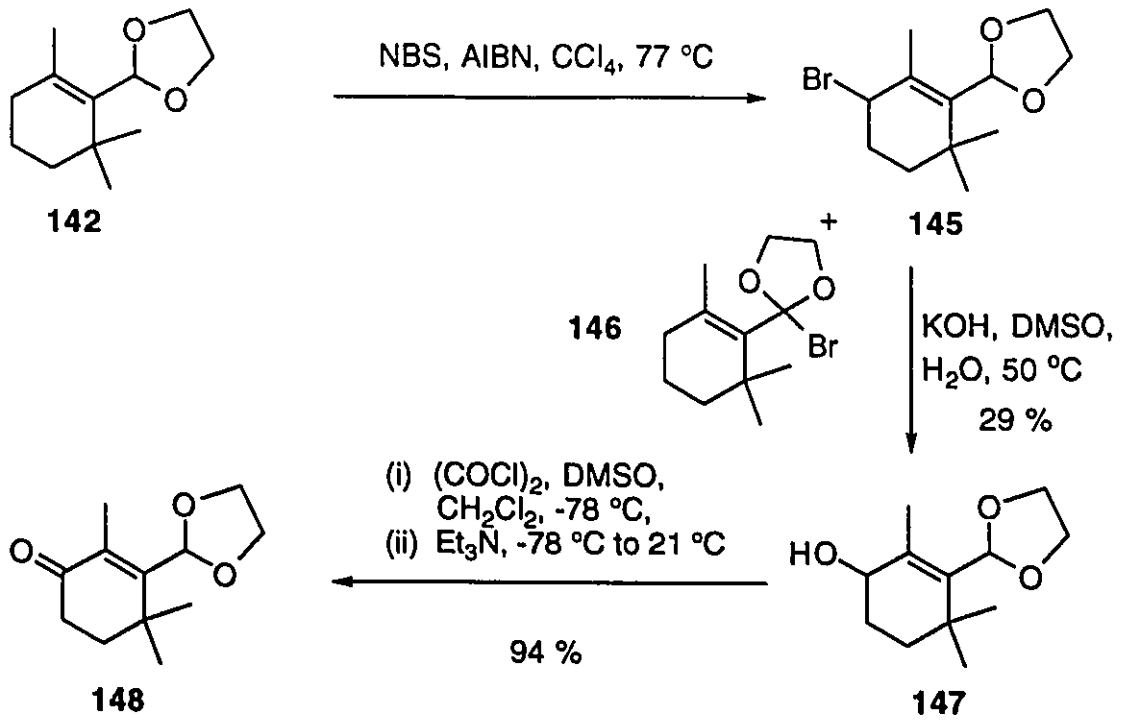


Scheme 28

Application of this method (CrO_3/dimethylpyrazole) to acetal **142** resulted in only a small quantity (< 10 %, GC/MS, ^1H NMR) of ketone **148** with complete consumption of starting material. The structural identity of **148** was later verified through comparison with a sample prepared through a different route (*vide infra*).

Treatment of acetal **142** with NBS/AIBN followed by reaction with $AgBF_4$/DMSO, then triethylamine, also gave poor results like those obtained with β-ionone (**114**).

It was observed that allylic bromination followed by $AgBF_4$/DMSO/Et_3N treatment produced, in addition to the desired ketone, significant quantities of alcohol, presumably due to hydrolysis of the bromide. Partially due to the cost of $AgBF_4$ and the low yields of ketone obtained, a less direct approach was taken where the allylic bromide could be hydrolyzed to the alcohol and then separately oxidized. Treatment of acetal **142** with NBS/AIBN in refluxing carbon tetrachloride in the presence of granular anhydrous K_2CO_3 furnished the unstable bromide **145** which was not isolated but treated immediately with K_2CO_3 in aqueous DMSO at 50 °C for 24 h (Scheme 29). By this procedure it was possible to produce alcohol **147** in 29 % yield. Allylic bromination at C10 to form **146** is apparently a competitive reaction and is partially responsible for the low yield of alcohol **147**. Alcohol **147** displayed a methine proton (C<u>H</u>OH) at 3.85 ppm in the ^1H NMR as well as a characteristic broad band in the IR spectrum at 3409 cm^{-1}. Oxidation using Swern conditions[35] or Dess-Martin periodinane[36] then furnished the ketone **148** in 94 % yield from the alcohol **147**. This ketone displayed two protons as an apparent triplet at 2.46 ppm in the ^1H NMR characteristic of protons next to a carbonyl (RCOC<u>H</u>$_2$-). The ^{13}C NMR spectrum also displayed a resonance at 199.6 ppm indicating the presence of a carbonyl group.

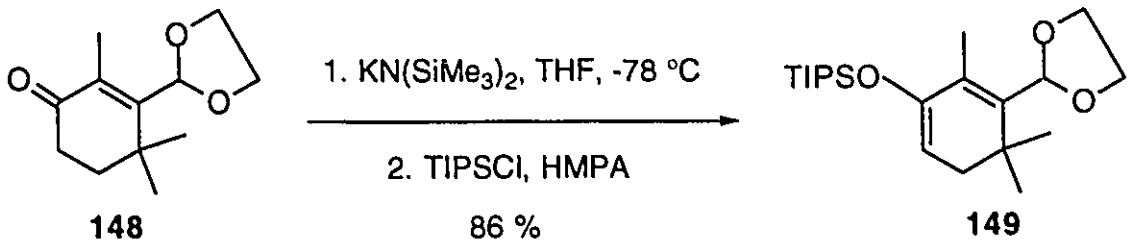


Scheme 29

2.2. Attempted Oxidation at C1: Preparation of a Dienone.

Having secured a route to ketone **148**, attention was next focused on methods for the functionalization of C1. Magnus has shown that when triisopropylsilyl enol ethers are treated with iodosobenzene in the presence of lithium azide it is possible to incorporate an azido group at the allylic position.[37] We therefore examined the possibility of using other allylic oxidants to directly introduce oxygen at C1.

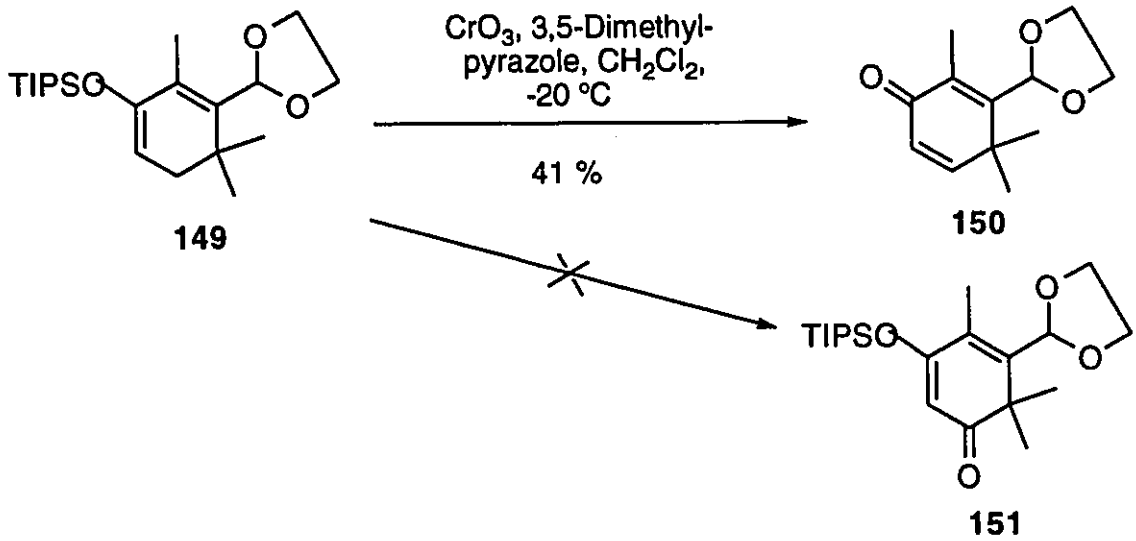
Treatment of ketone **148** with potassium hexamethyldisilazide at -78 °C followed by the addition of triisopropyl silyl chloride and HMPA gave the triisopropylsilyl enol ether **149** in 86 % yield (Scheme 30).[38] This compound displayed a single vinylic proton as an apparent triplet at 4.81 ppm in the ^1H NMR (=C<u>H</u>CH_2-), indicating that the enol ether had been formed.



148 **149**

Scheme 30

When compound **149** was treated with CrO_3/dimethylpyrazole only dienone **150** was isolated in 41 % yield (Scheme 31). Consistent with structure **150** the ^1H NMR indicated the presence of two sets of doublets (J = 10 Hz) at δ 6.06 ppm and 6.69 ppm, integrating to one proton each. Dienone **150** presumably arises through an initial hydride abstraction at the allylic position (perhaps forming the chromate ester) followed by hydrolysis of the silyl group with a concurrent double bond migration to neutralize the positive charge (or β-elimination of the chromate ester). Treatment of enol ether **149** with selenium dioxide in refluxing dioxane in the hopes of producing ketone **151** was similarly ineffective.[32] Nevertheless, it was felt that dienone **150** was useful for a Michael addition strategy for functionalization of C1.

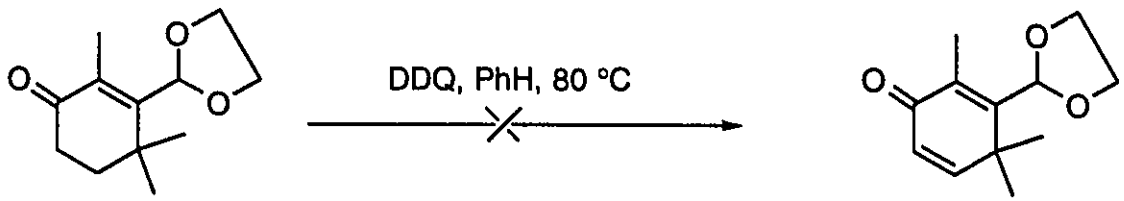


149 **150** **151**

Scheme 31

The yield of 41 % was acceptable, although we felt that a more efficient route to compound **150** would be desirable for large scale preparation of this compound.

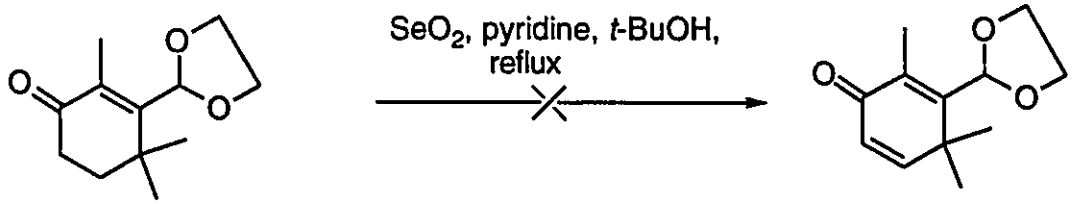
The preparation of dienone **150** by dehydrogenation of the enone **148** using DDQ in refluxing benzene was examined (Scheme 32).[39] Unfortunately despite prolonged heating at reflux only starting material was recovered.



148 **150**

Scheme 32

The use of SeO_2 in refluxing *t*-butanol/pyridine gave a complex mixture with only a small quantity of dienone **150** being produced (Scheme 33).[40]

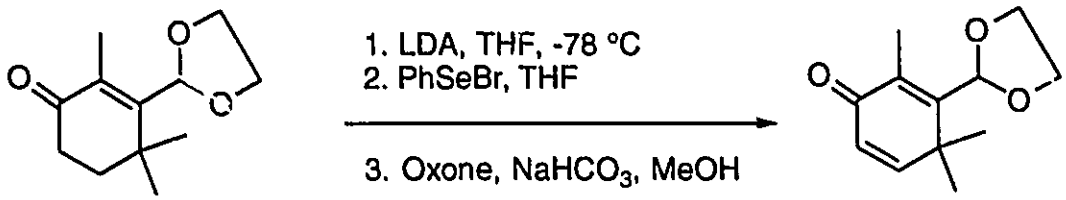


148 **150**

Scheme 33

Significant improvement was achieved by using the method of selenoxide elimination chemistry to introduce the double bond.[41] Treatment of ketone **148** with lithium diisopropylamide (LDA) at -78 °C followed by addition of phenylselenyl bromide gave the α-phenylselenyl ketone which was not isolated but treated directly with aqueous H_2O_2 to afford the dienone **150** (Scheme 34). This method was not reliable

however, with the crude product having a tendency to polymerize readily. This problem presumably arose due to traces of H_2O_2 in the crude product and was solved by using ($KHSO_5 \cdot 2\ KHSO_4 \cdot K_2SO_4$) "Oxone®" buffered with $NaHCO_3$ as the oxidant. Yields were found thereafter to be consistently between 50-60 % depending on the scale of the preparation.

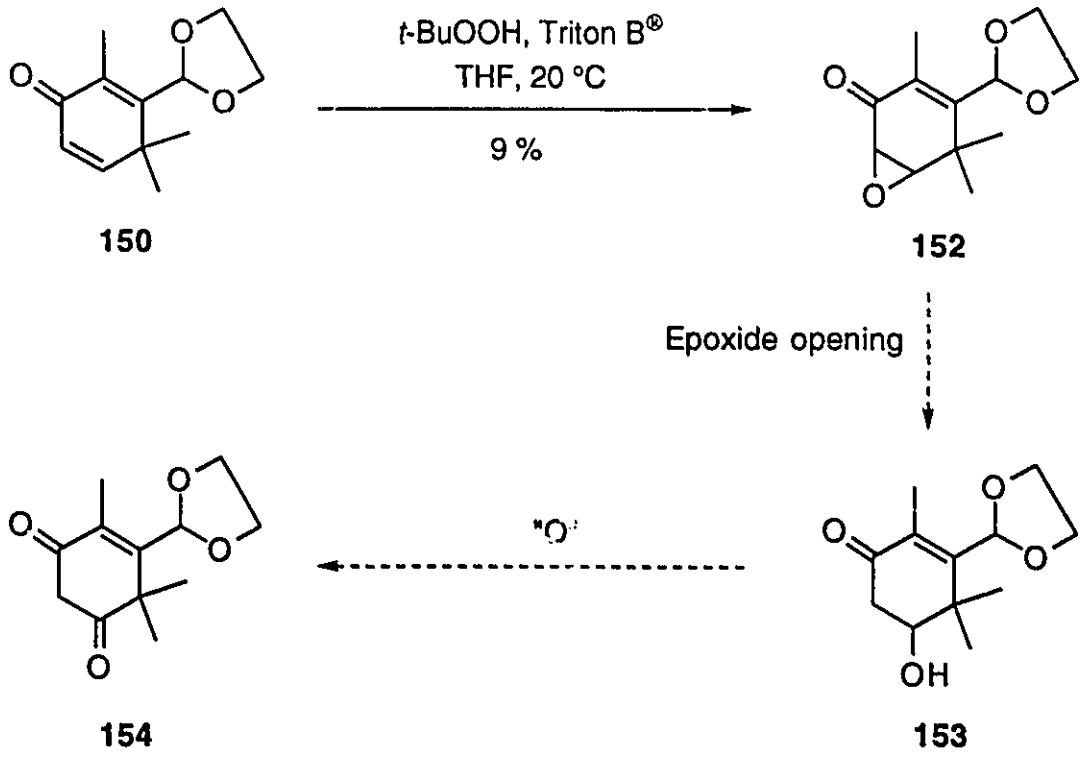


148 **150**

Scheme 34

2. 3. Epoxidation of the Dienone.

An epoxidation route to diketone **154** was investigated next (Scheme 35). Treatment of enone **141** gave epoxide **152** in low yield (< 10 % by GC/MS) and starting material when a combination of *t*-butylhydroperoxide and benzyltrimethylammonium hydroxide in methanol "Triton B®" was employed.[42]



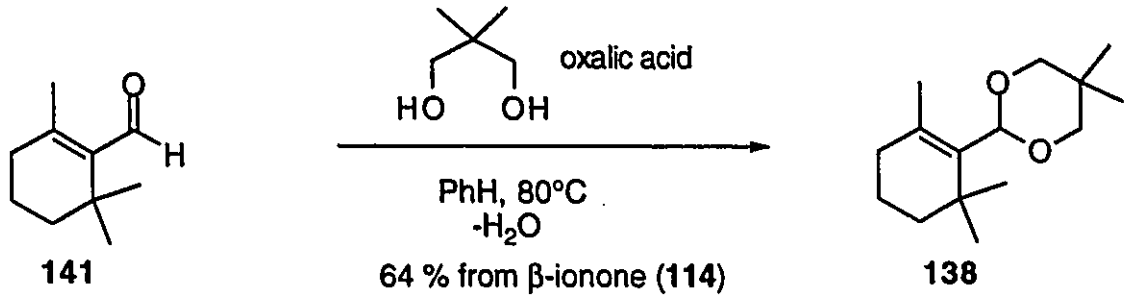
Scheme 35

Compound **152** could not be isolated in pure form because of the very similar polarity between it and the dienone **150**. The epoxide **152** displayed two doublets (J = 4 Hz) at 3.29 and 3.49 ppm in the ^{1}H NMR. Mass spectral data displayed a (M-1) peak consistent with the formation of an epoxide. Information regarding the formation of this compound was subsequently based on ^{1}H NMR and/or GC/MS data only. When the crude mixture was again treated with the same reagent combination complete destruction of the epoxide and dienone occurred. Repeated attempts were made to improve the reaction using a variety of epoxidizing methods (*vide infra*). Unfortunately for reasons not well understood this reaction could not be sufficiently improved to make it practical.

2. 4. Preparation and Oxidation of a more Robust Acetal.

The need for more material prompted us to re-examine the initial steps. Ideally a more robust protecting group for the aldehyde attached at C10 was needed which could withstand allylic oxidizing conditions. It was also desirable to find a new method of oxidation which would eliminate the allylic bromination route, which for the reason stated earlier, gave poor yields.

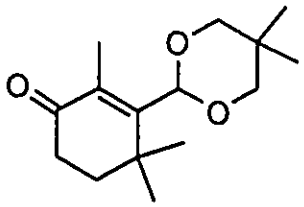
Acetal **138** was prepared from neopentyl glycol using a similar procedure to that for acetal **142** (Scheme 36).



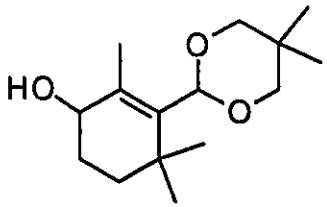
Scheme 36

This compound displayed a singlet at 4.86 ppm in the ^{1}H NMR spectrum and a resonance at 101.8 ppm in the ^{13}C NMR, indicating the presence of the acetal proton and acetal carbon respectively. This acetal proved to be somewhat more stable than its ethylidene counterpart. Treatment of **138** with SeO_2 in refluxing dioxane yielded a mixture of ketone **139** and alcohol **155**.[32] Ketone **139** showed similar spectral characteristics to that of the two carbon acetal **142**, namely, the presence of two protons at 2.45 ppm as an apparent triplet in the ^{1}H NMR spectrum ($COCH_2$) along with a resonance in the ^{13}C NMR at 199.8 ppm, both indicating the presence of a carbonyl group. Alcohol **155** displayed a single proton as an apparent triplet at 3.78 ppm (CHOH) in the ^{1}H NMR. A resonance at 70.2 ppm in the ^{13}C NMR indicated a carbon bearing an

oxygen substituent. A broad band in the IR spectrum at 3431 cm^{-1} was also present verifying the formation of an alcohol.



139

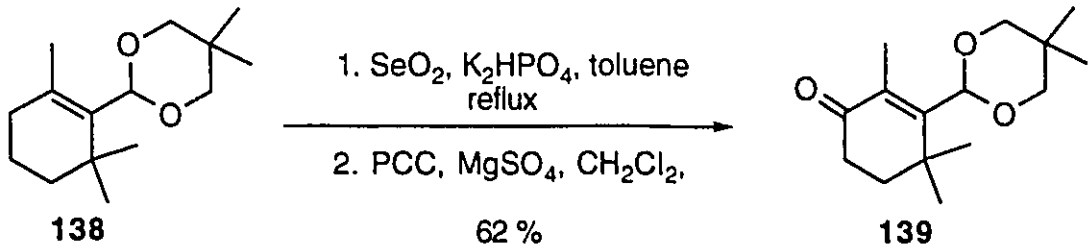


155

Figure 2

Under prolonged heating at reflux of acetal **138** in dioxane (typically 2 hours) using 2.5 equivalents of SeO_2 only ketone **139** was obtained. It was found however that yields varied considerably, anywhere from 20-60 % with deprotection being the main problem. Higher dilution was found to improve yields. However, apart from being impractical for large scale preparations, high dilution still did not always prevent the problem of deprotection.

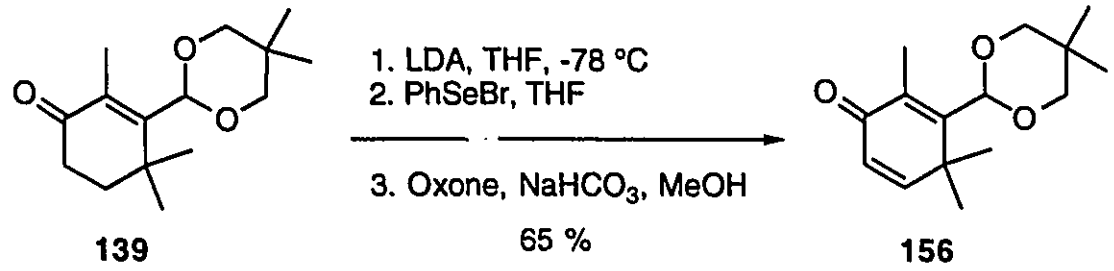
The problem of ketal deprotection with SeO_2 in dioxane for allylic oxidation had also been noticed by Paquette et al.[43] Substitution of toluene for dioxane and employment of KH_2PO_4 as a buffer solved this problem. Employment of the same method with ketal **138** gave a mixture of alcohol **155** and ketone **139** accompanied by very little deprotection (Scheme 37). Under prolonged heating at reflux only ketone is obtained but yields were reduced. Thus the best procedure involved initial oxidation with SeO_2 and treatment of the alcohol/ketone mixture with pyridinium dichromate. Yields thereafter were consistently in the range of 55-65 %.



138 **139**

Scheme 37

Enone **139** was converted to the corresponding dienone **156** using the same conditions employed earlier to prepare dienone **150** (Scheme 38).



139 **156**

Scheme 38

2. 5. Further Attempts at Epoxidation.

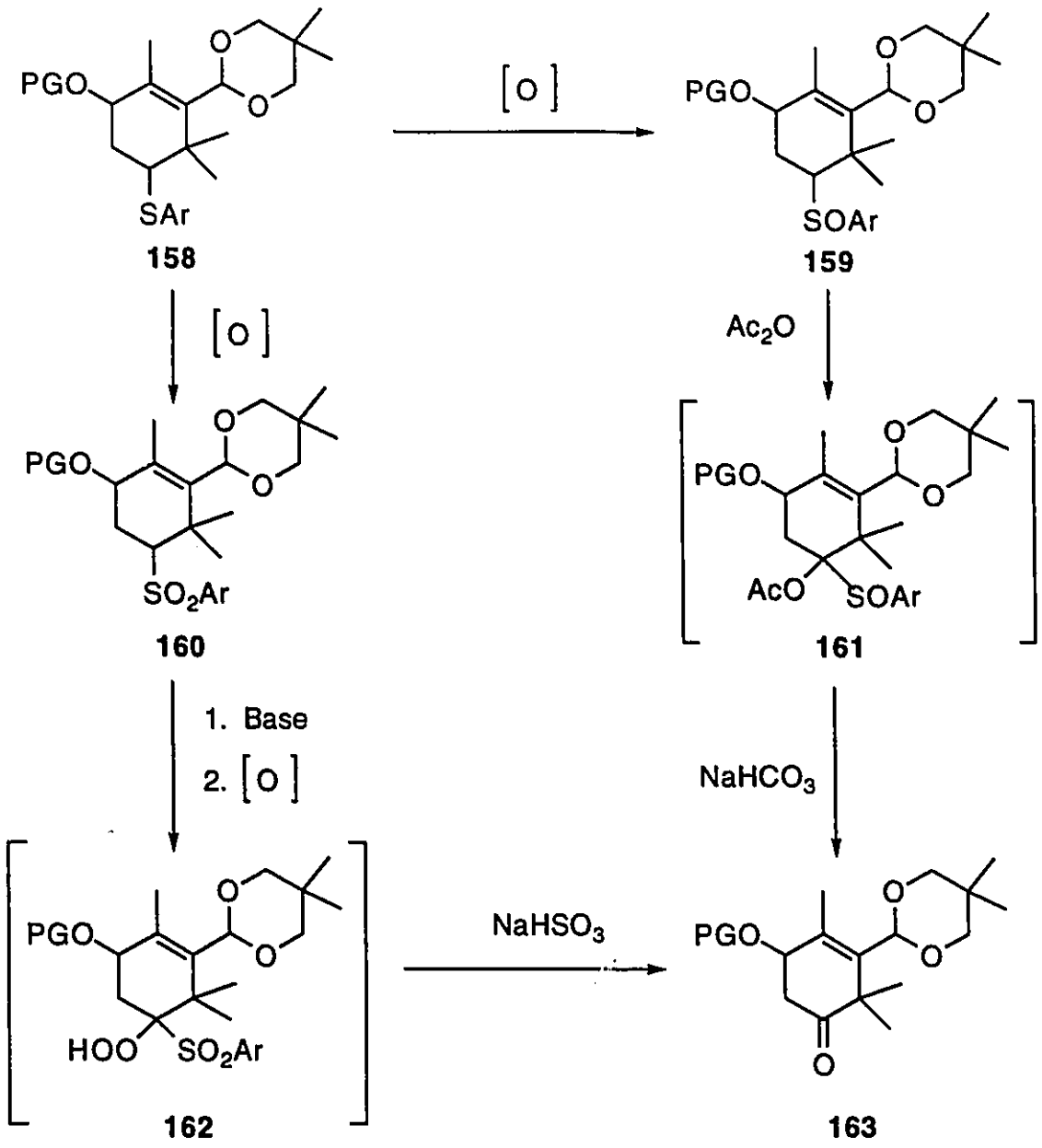
The epoxidation route was also re-examined using dienone **156**. The use of $NaOH/H_2O_2$/MeOH gave only a very small quantity of epoxide.[44] LiO*t*-Bu at -78 °C to 21 °C (from *n*-butyllithium and anhydrous *t*-BuOOH)[45], vanadyl acetylacetonate and *t*-BuOOH in refluxing benzene[46], DBN and *t*-BuOOH in THF[47], and dimethyldioxirane[48] all failed to give any product. Surprisingly, the use of common household bleach (aqueous NaOCl) in dioxane with a small quantity of pyridine gave the best results (ca. 25 % yield).[49] This procedure gave somewhat erratic results however, with complete decomposition of product and starting material occurring frequently.

Several more attempts using *t*-BuOOH/Triton B® reconfirmed the initial observations that this method was problematic. Takahashi's group had also encountered

similar problems with this reagent combination.[50] They suggested that methoxide ion (from the Triton B®) was reacting with the epoxide as it was generated. Substitution of KH for Triton B® and use of anhydrous *t*-BuOOH in THF at 0 °C was found to give good yields for their system, presumably due to the presence of the less nucleophilic *t*-BuOK produced as the by-product. A modification of this reagent combination was tried using potassium hexamethyldisilazide instead of KH. However, this reaction, like the others, only progressed to a certain point or suddenly gave decomposition products (approx. 15-20 % of epoxide by GC/MS). Use of excess reagent, or repeated addition of reagents at periodic intervals did not improve yields.

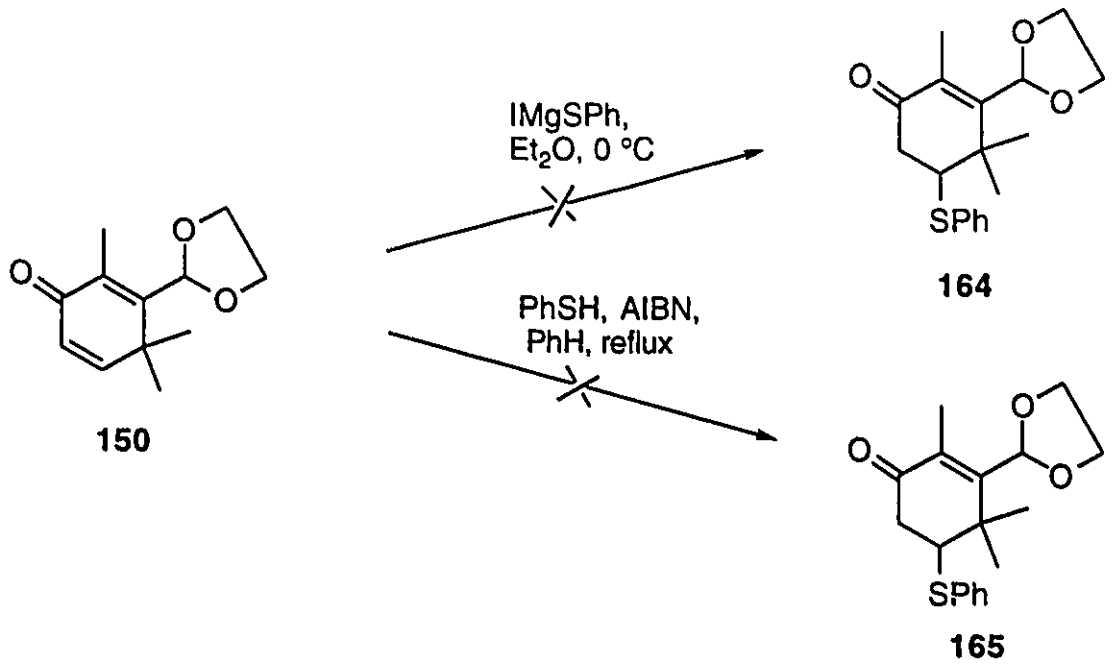
2. 6. Functionalization at C1 with Sulfur.

Due to the disappointing results with the epoxidation of dienone **150/156** we looked at the possibility of using a sulfur nucleophile (eg. RS^-) to functionalize C1. Such a method would have merit since this group could be further transformed to a ketone via Pummerer rearrangement of the sulfoxide.[51] α-Oxygenation of the sulfone could also conceivably produce the ketone **163** (Scheme 39).[52] For this approach to succeed ideally R had to be aromatic so that the reactive site will be at C1 and not on the R group. In addition, the C13 carbonyl would have to be reduced and protected to avoid the competing β-elimination reaction of the acetate or sulfone group (depending on the method). Sufficiently gentle conditions would also have to be used to prevent the β-elimination of the C13 alkoxy group in the product.



Scheme 39

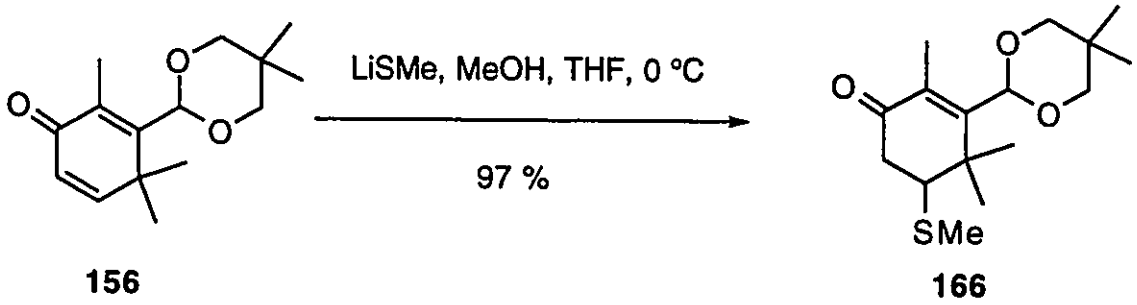
Unfortunately a thiophenyl group could not be introduced on dienone **150** either by way of the magnesium salt of thiophenol[53] or through the thiophenol radical (Scheme 40)[54], presumably due to the steric bulk of this group.



150 164 165

Scheme 40

Modifying the magnesium thiophenolate-addition approach, treatment of dienone **156** with lithium methylthiolate (LiSMe) (prepared from MeSSMe and MeLi) in the presence of 12-crown-4, followed by methanol addition, introduced the SMe group in 87 % yield (97 % based on recovered starting material) so as to afford thio-ether **166** (Scheme 41).

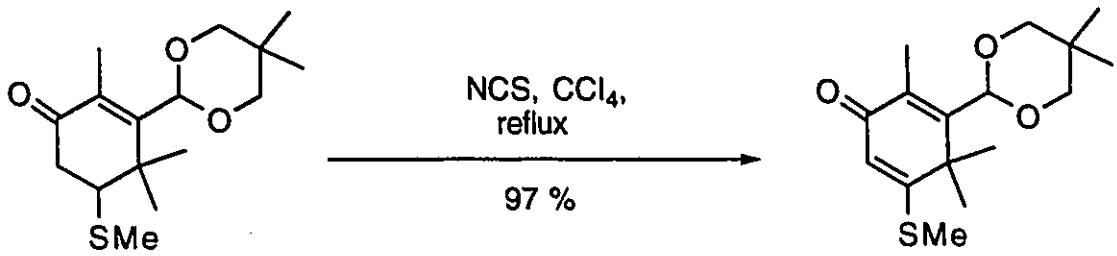


156 166

Scheme 41

After repeated attempts it was found that a large excess of the anion was necessary for good yields. Thioether **166** displayed a singlet (-SC<u>H</u>$_3$) at 2.07 ppm in the ^{1}H NMR spectrum. In addition, a multiplet at 2.59-2.83 ppm was consistent with the presence of the (C<u>H</u>SMe) and (COC<u>H</u>$_2$) protons.

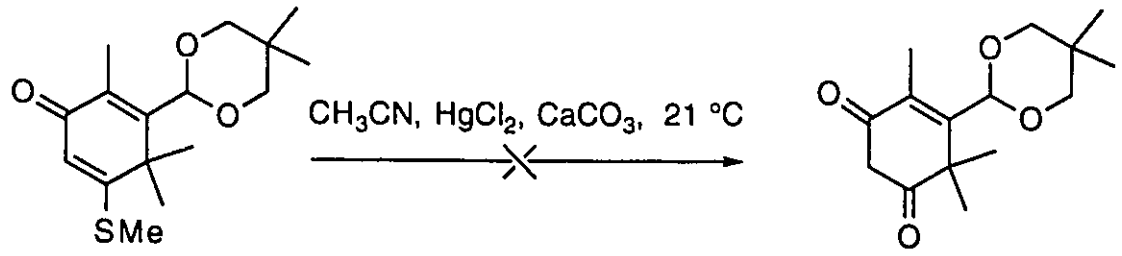
Thioether **166** was treated with *N*-chlorosuccinimide in refluxing CCl_4 in the hope of producing the α-chlorosulfide which could be hydrolyzed to a ketone, but instead vinyl sulfide **167** was obtained, due to the β-elimination of chloride (Scheme 42).[55] This compound displayed a singlet at 6.06 ppm in the ^{1}H NMR spectrum consistent with the formation of a vinylic carbon. Four resonances were also seen in the ^{13}C NMR at 118.2, 134.3, 153.0, 171.7 ppm indicating the presence of two double bonds.



166 **167**

Scheme 42

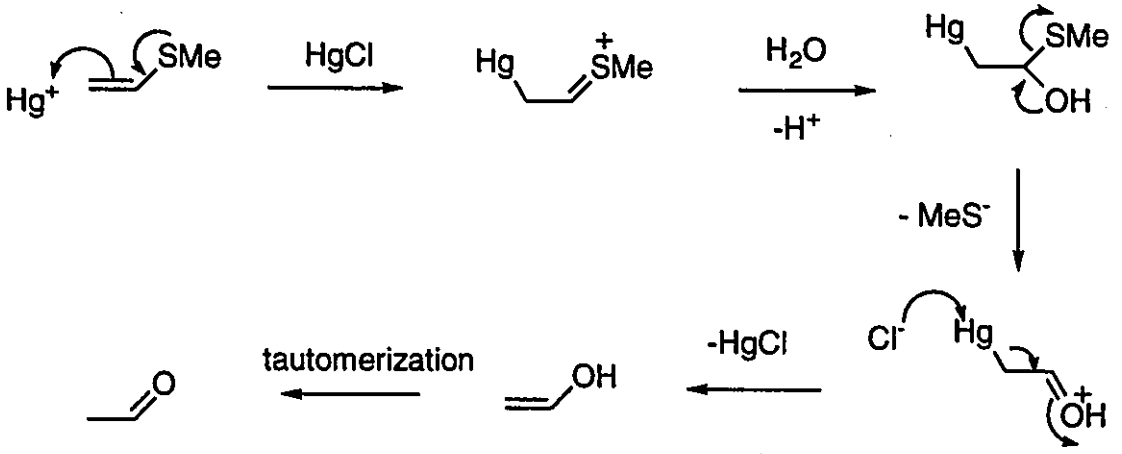
Compound **167** possessed the same oxidation level as β-diketone **140** and hydrolysis of the enol thioether functionality was expected to yield a ketone. Unfortunately compound **167** was resistant to hydrolysis using $HgCl_2$ in aqueous acetonitrile buffered with $CaCO_3$ at 21 °C (Scheme 43).[56]



167 **140**

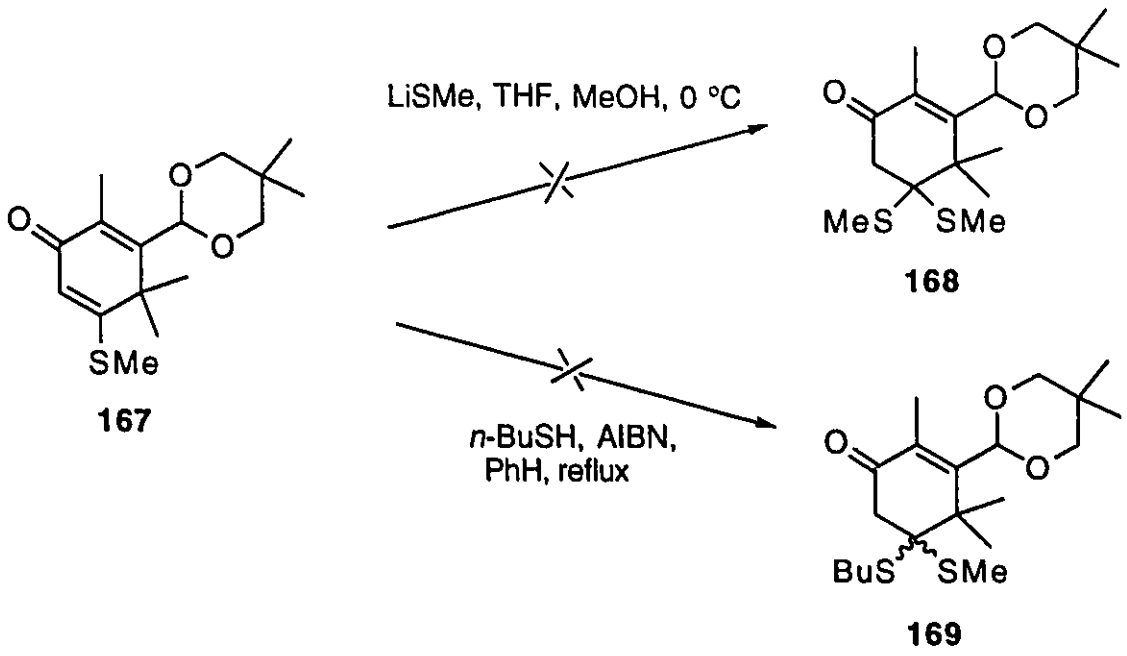
Scheme 43

The use of the much more drastic conditions of $HgCl_2$ in aqueous acetic and trifluoroacetic acids at 100 °C resulted only in deprotection of the acetal. The failure of this method is attributed to the electron deficient nature of the double bond. The proposed mechanism (Scheme 44) of this hydrolysis involves β-addition of Hg^+ to the double bond producing a sulfenium ion which then undergoes attack by water.[57] An electron deficient double bond will therefore not allow this first step to occur.[58]



Scheme 44

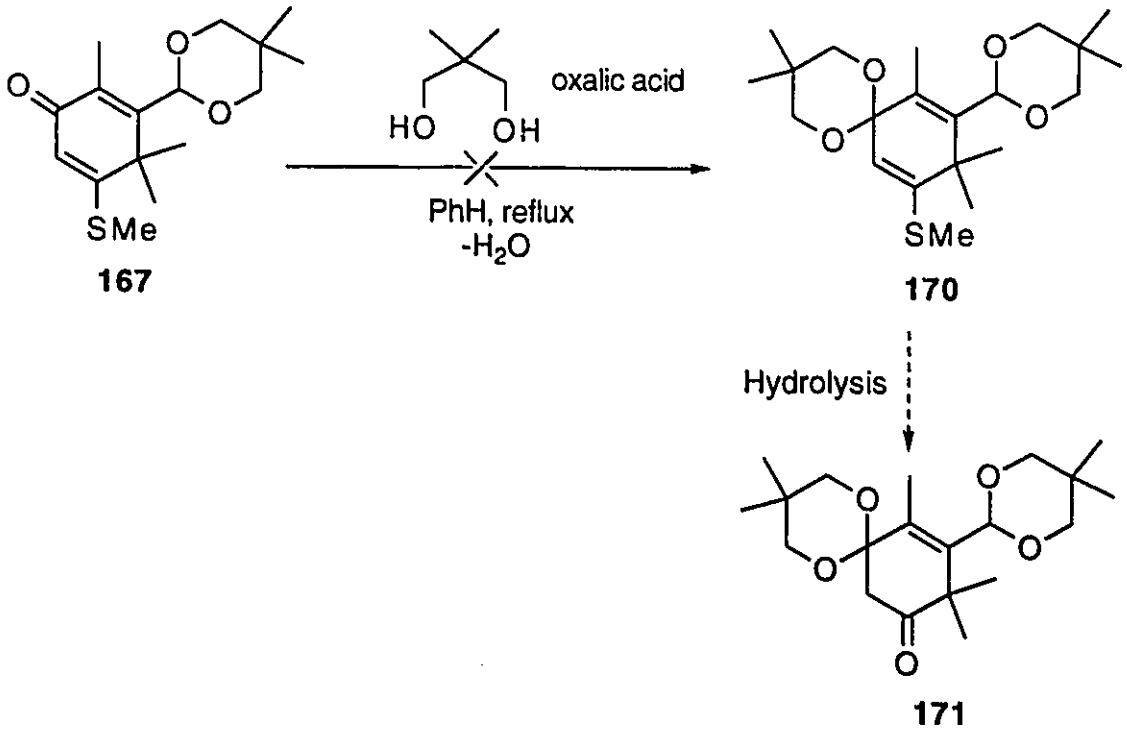
Attempts to convert compound **167** to a thioketal at C1 using a second addition of MeSLi or the addition of butanethiol radical (BuS·) were also unsuccessful (Scheme 45).



167 **168** **169**

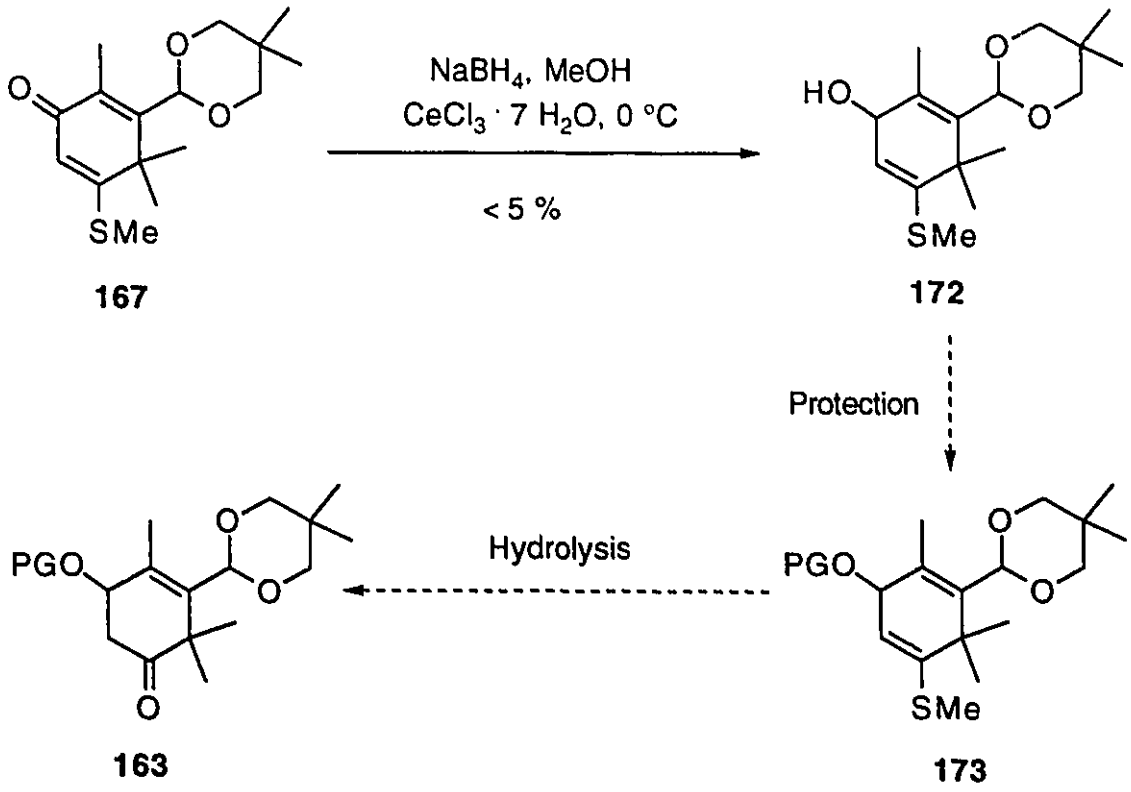
Scheme 45

Ketalization of the carbonyl of **167** using standard conditions, with the intention of making the hydrolysis of the vinyl sulfide more facile by eliminating the effect of the carbonyl group, was unsuccessful (Scheme 46).[31]



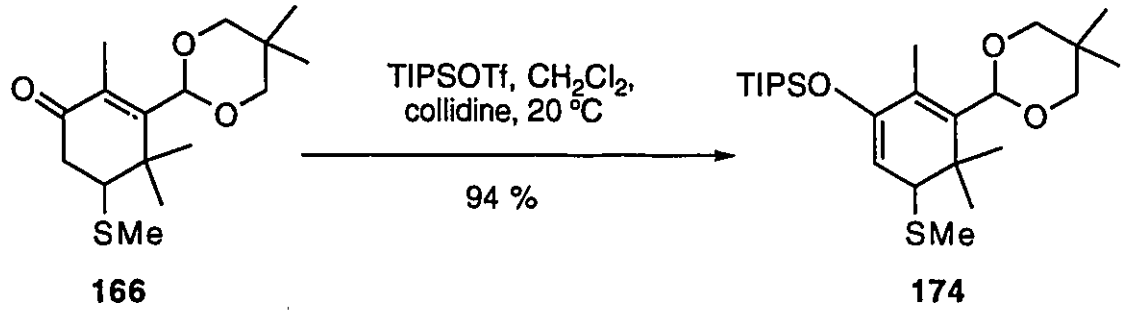
Scheme 46

Reduction of ketone **167** using $CeCl_3/NaBH_4$[59] or DIBAL[60] gave extremely low yields of alcohol **172** (< 5 %). It was hoped that the protected form of this alcohol could be hydrolyzed to the protected keto-alcohol **163** (Scheme 47).



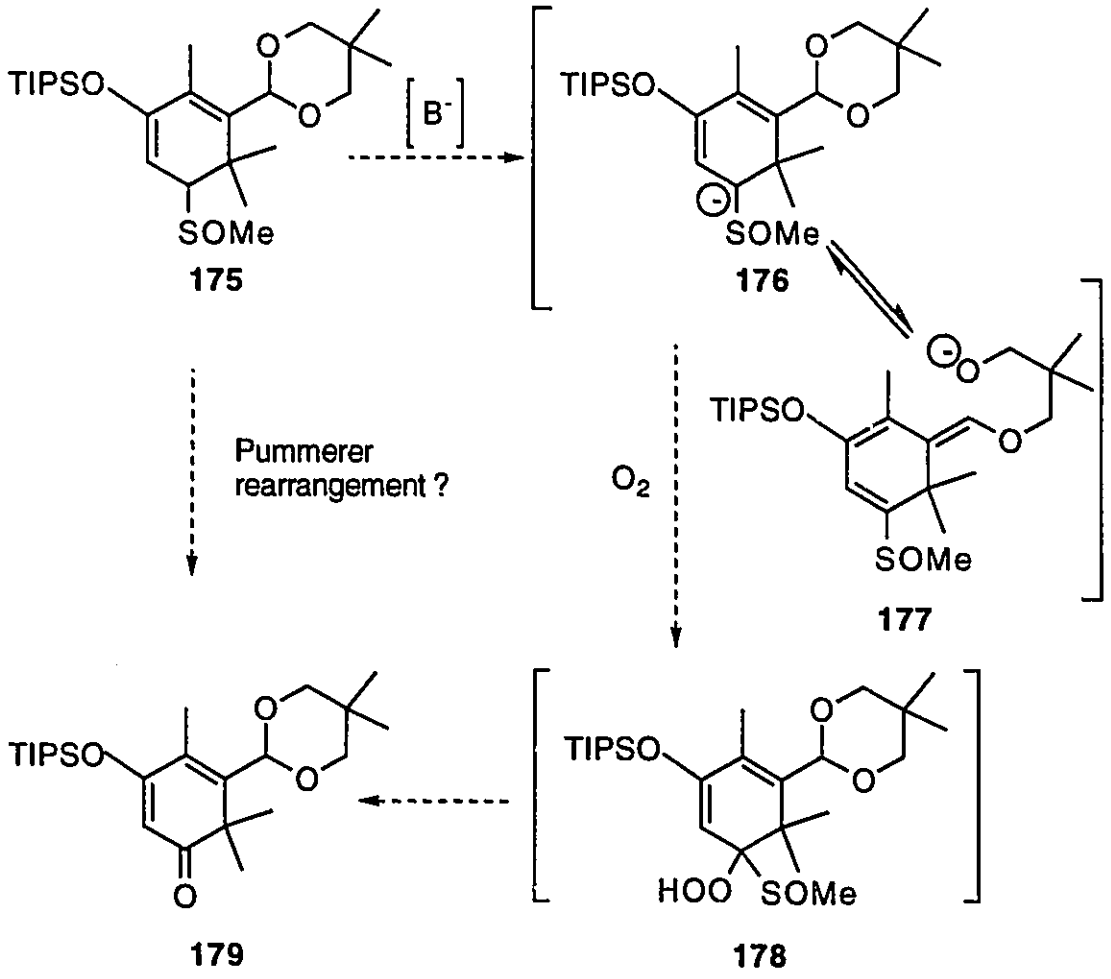
Scheme 47

Compound **166** was converted to the silyl-enol ether **174** by treatment with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) in collidine in 94 % yield (Scheme 48).[61] Enol ether formation was indicated by the presence in the ^{1}H NMR spectrum of a doublet (J = 6.4 Hz) at 3.00 ppm (CHSMe) coupled with a doublet at 4.89 ppm (CH=).



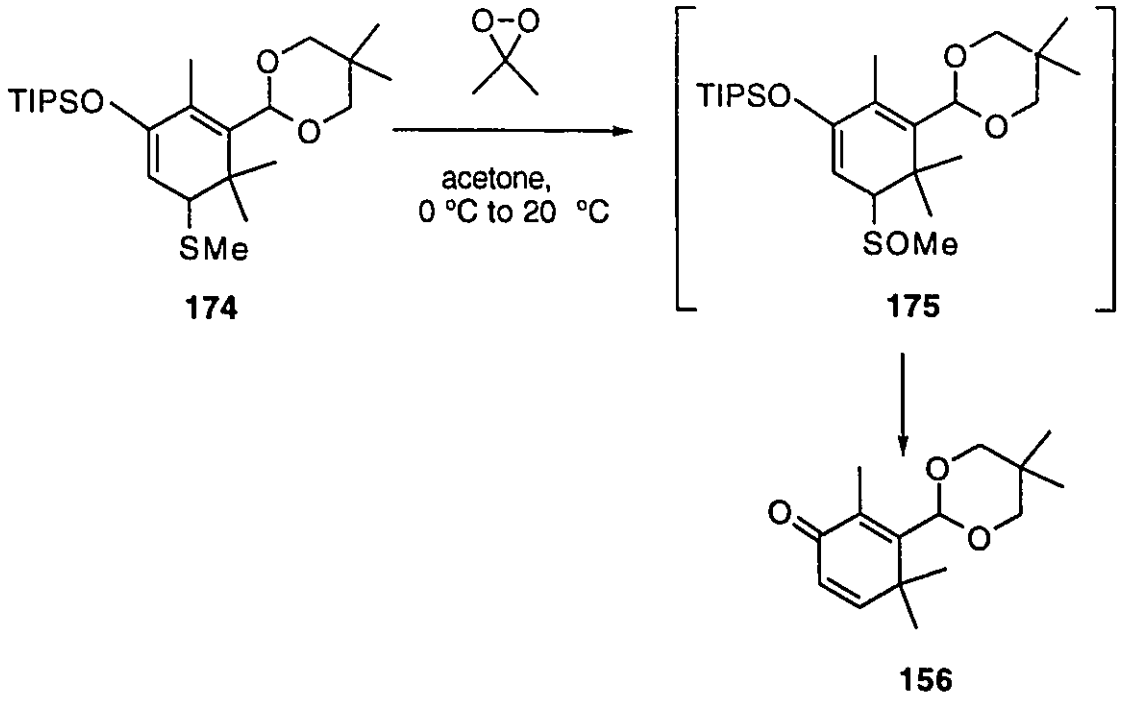
Scheme 48

Compound **174** was prepared with the intention of preparing the corresponding sulfoxide or sulfone and converting this to a ketone using again either a Pummerer rearrangement or hydroxylation at C1 (Scheme 49).



Scheme 49

This methodology had the potential complication of a competing reaction on the methyl group instead of at C1. This was soon found not to be an issue due to the inability to isolate the sulfoxide **175**. Treatment of the sulfide **174** under neutral conditions using dimethyldioxirane at 0 °C gave a polar compound (TLC) which upon warming to 21 °C afforded the dienone **156** (Scheme 50).[62]

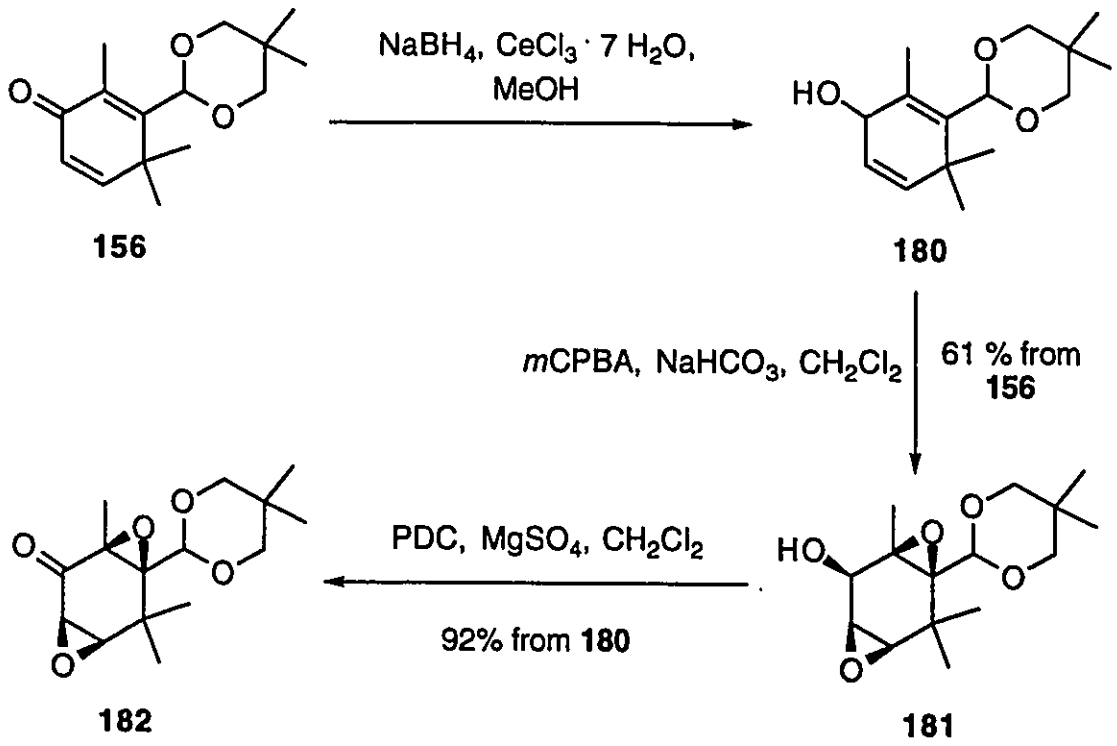


Scheme 50

2. 7. Formation a Bis-Epoxide.

One last attempt was made to epoxidize the dienone **156**. But instead of the past attempts at direct epoxidation, we focused on an indirect route involving epoxidation of the allylic alcohol **180**. This compound was prepared by reduction of dienone **156** using $NaBH_4/CeCl_3 \cdot 7H_2O$ (Scheme 51) (*cf.* contrast the ease of this reduction with the difficulty of reducing vinyl sulfide **167** [*vide supra*]).[59] Epoxidation using *m*CPBA in dichloromethane gave the bis-epoxide **181**, with a two step yield of 61 %. Oxidation of the epoxy-alcohol with pyridinium dichromate (PDC) was quite slow (3 days) but gave the ketone **182** in good yield (77 %).[63] The allylic epoxy-alcohol **181** and the corresponding ketone **182** were assigned the structures shown based on known examples of the hydroxyl directed epoxidation with *m*CPBA where the epoxide is delivered *syn* to the OH group.[64] Ketone **182** diplayed two sets of doublets (J = 4 Hz) at 3.12 and 3.43

ppm in the ^{1}H NMR spectrum indicating the presence of two epoxide protons. Similarly, four resonances in the ^{13}C NMR spectra at 55.8, 64.9, 68.4 and 73.9 ppm were indicative of the four epoxide carbons. A single resonance at 201.4 ppm confirmed the presence of a carbonyl. Conversion of **182** to the vinyl selenide **188** (*vide infra*) further substantiated the presence of the tetrasubstituted epoxide.

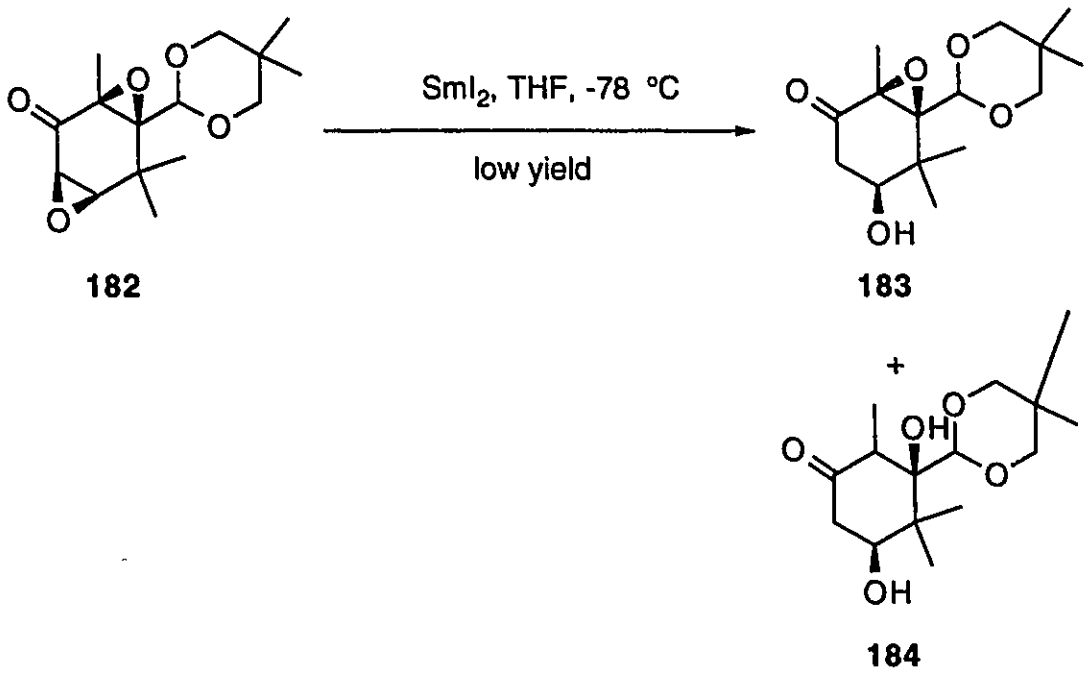


Scheme 51

Despite the disappointment of having obtained the bis-epoxide which created the problem of having to deoxygenate the C11-C12 epoxide, a number of ways to open the less substituted epoxide were examined.

2. 8. Epoxide Opening.

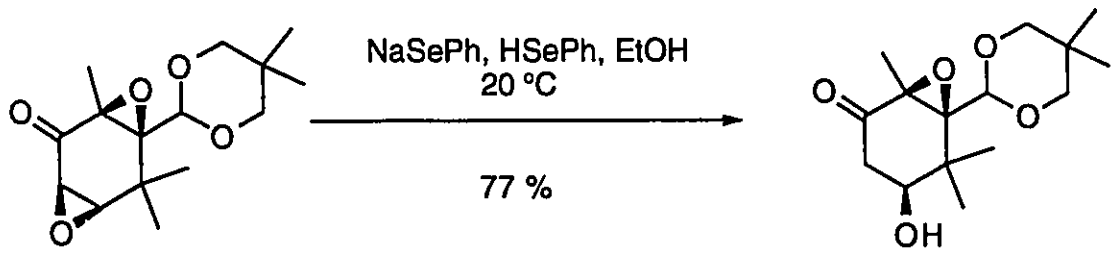
Treatment of **182** with 2.5 equivalents of SmI_2 in THF at -78 °C gave a low yield of keto-alcohol **183**, possibly due to a second competitive ring opening to form the tentatively assigned diol **184** (Scheme 52).[65]



182 **183** **184**

Scheme 52

Use of PhSeNa/PhSeH (prepared from $NaBH_4$/PhSeSePh with subsequent addition of HOAc) gave a good yield of **183** (77 %) (Scheme 53).[66]



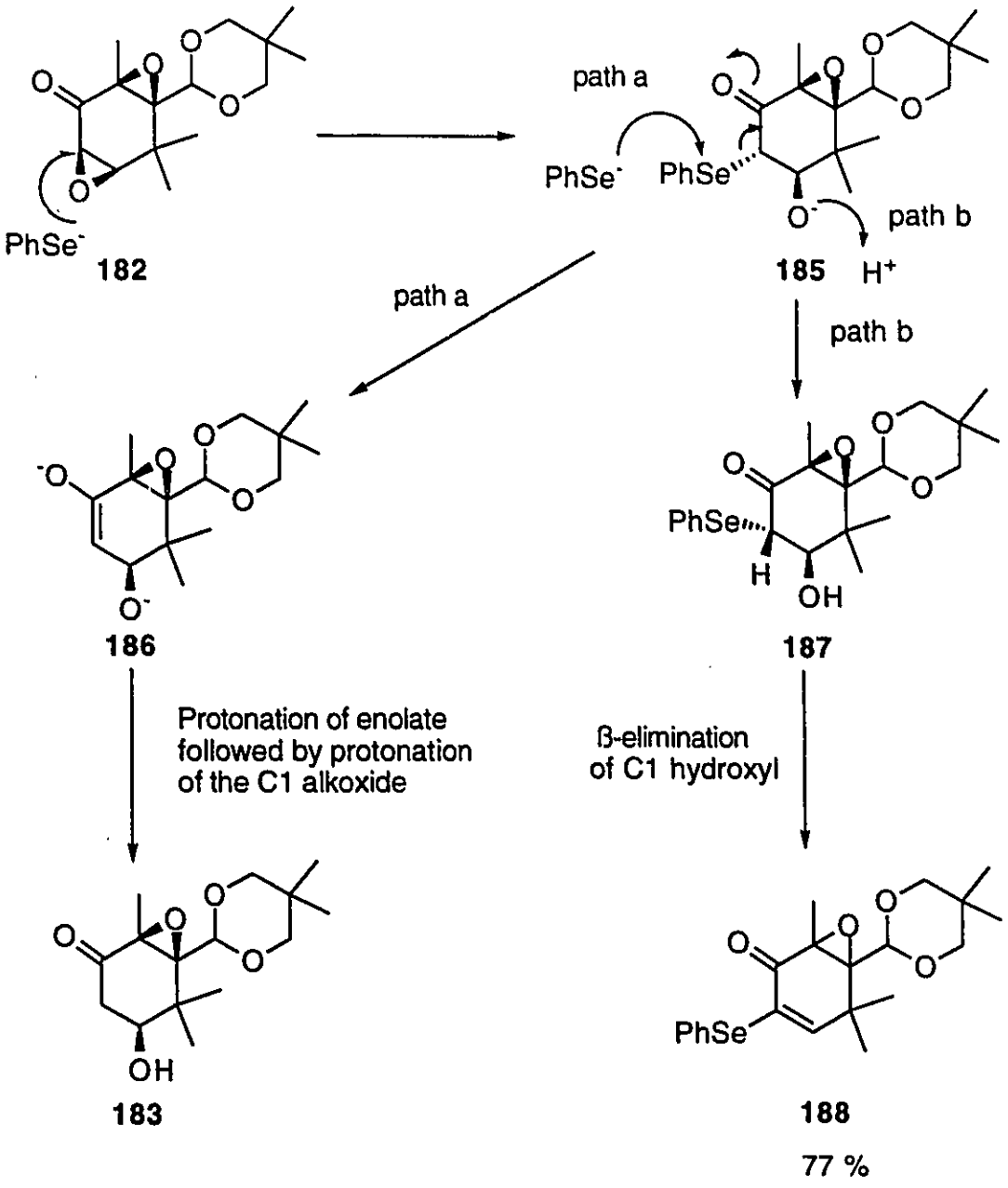
182 **183**

Scheme 53

This compound displayed a broad OH absorption at 3533 cm^{-1} in the IR spectrum as well as three resonances in the ^{13}C NMR at 66.0, 71.9 and 75.2 ppm, indicative of the two epoxide carbons as well as the (CHOH) carbon.

The high regioselectivity of this reaction can be attributed to the proposed mechanism where an initial attack by $PhSe^-$ occcurs on the epoxide carbon α to the carbonyl to form **185** (Scheme 54).[66] A second attack (path a) on the α PhSe group generates the enolate **186** and diphenyldiselenide. The enolate and C1 alkoxide are then sequentially protonated to form **183**.

If the reagent is added very slowly to the epoxide, a second competitive reaction becomes favorable to form vinyl-selenide **188** (path b) in 77 % yield. This competitive reaction is not described by the authors but presumably protonation of the C1 alkoxide gives **187**, followed by β-elimination of hydroxide to afford **188**. Proof of structure of **188** was provided by X-ray crystallographic analysis.

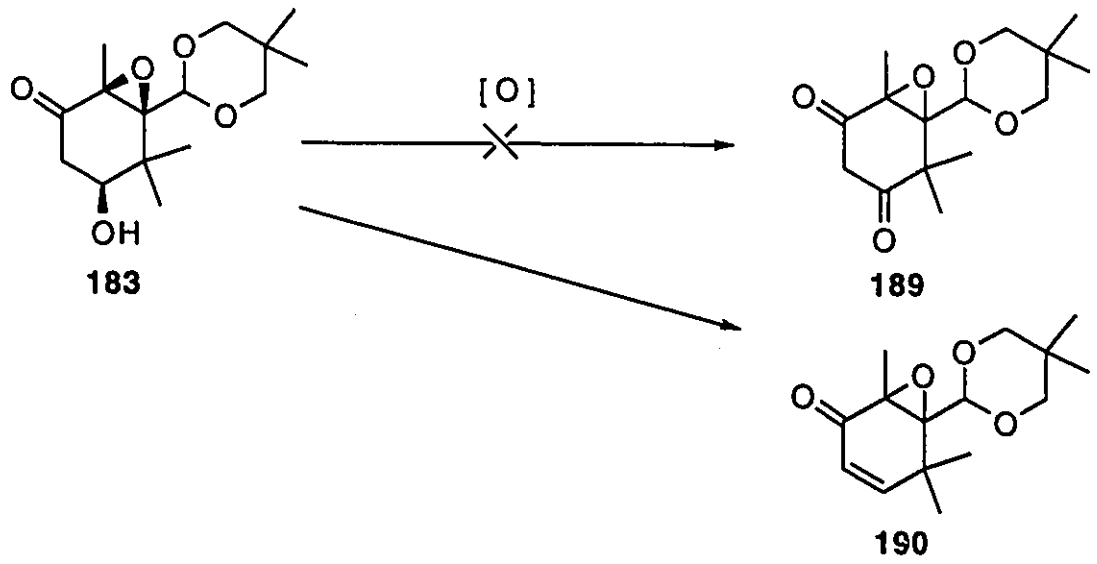


Scheme 54

2. 9. Attempted Oxidation of the C1-Alcohol.

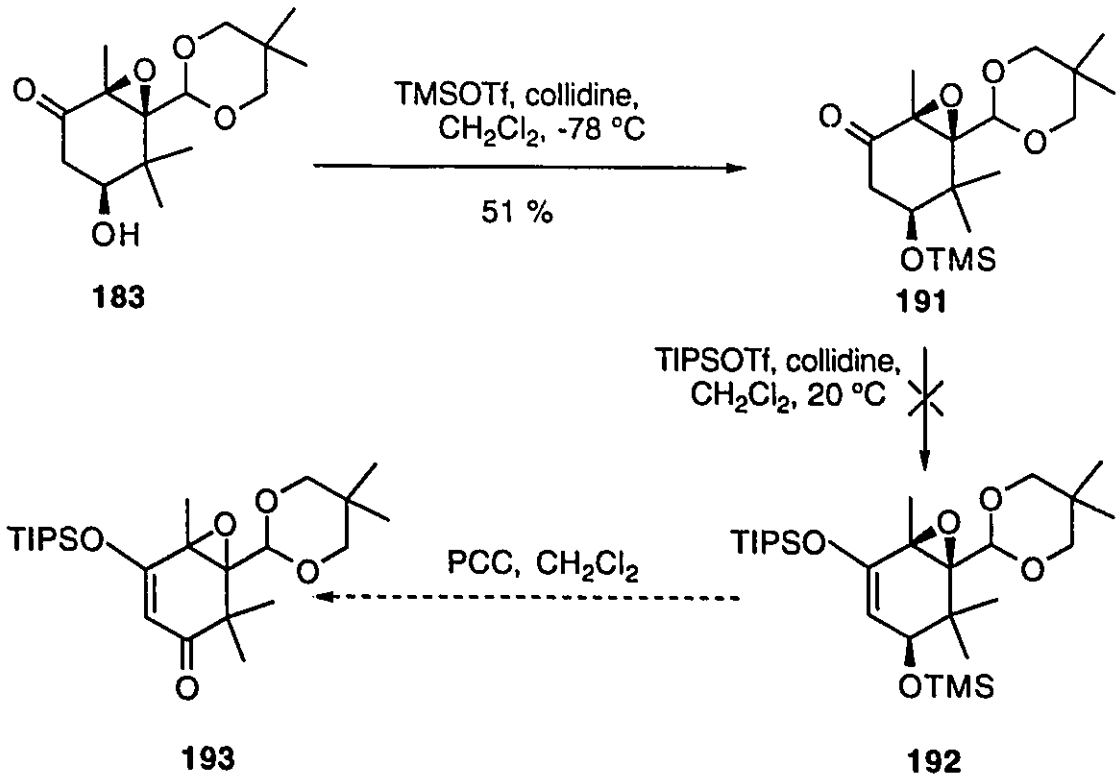
Attempted oxidation of keto-alcohol **183** using a variety of conditions (PCC/NaOAc[67], $(COCl)_2$/DMSO/Et_3N[35], $(CF_3CO)_2O$/DMSO/Et_3N[68]) gave mostly

elimination product **190** (Scheme 55). This compound displayed two doublets (J = 10.5 Hz) at 5.76 and 6.17 ppm in the ^{1}HNMR spectrum.



Scheme 55

To prevent the problem of β-elimination it was thought that a compound such as **191** could be prepared and the ketone temporarily converted to an enol ether and then the C1 alcohol oxidized (Scheme 56).

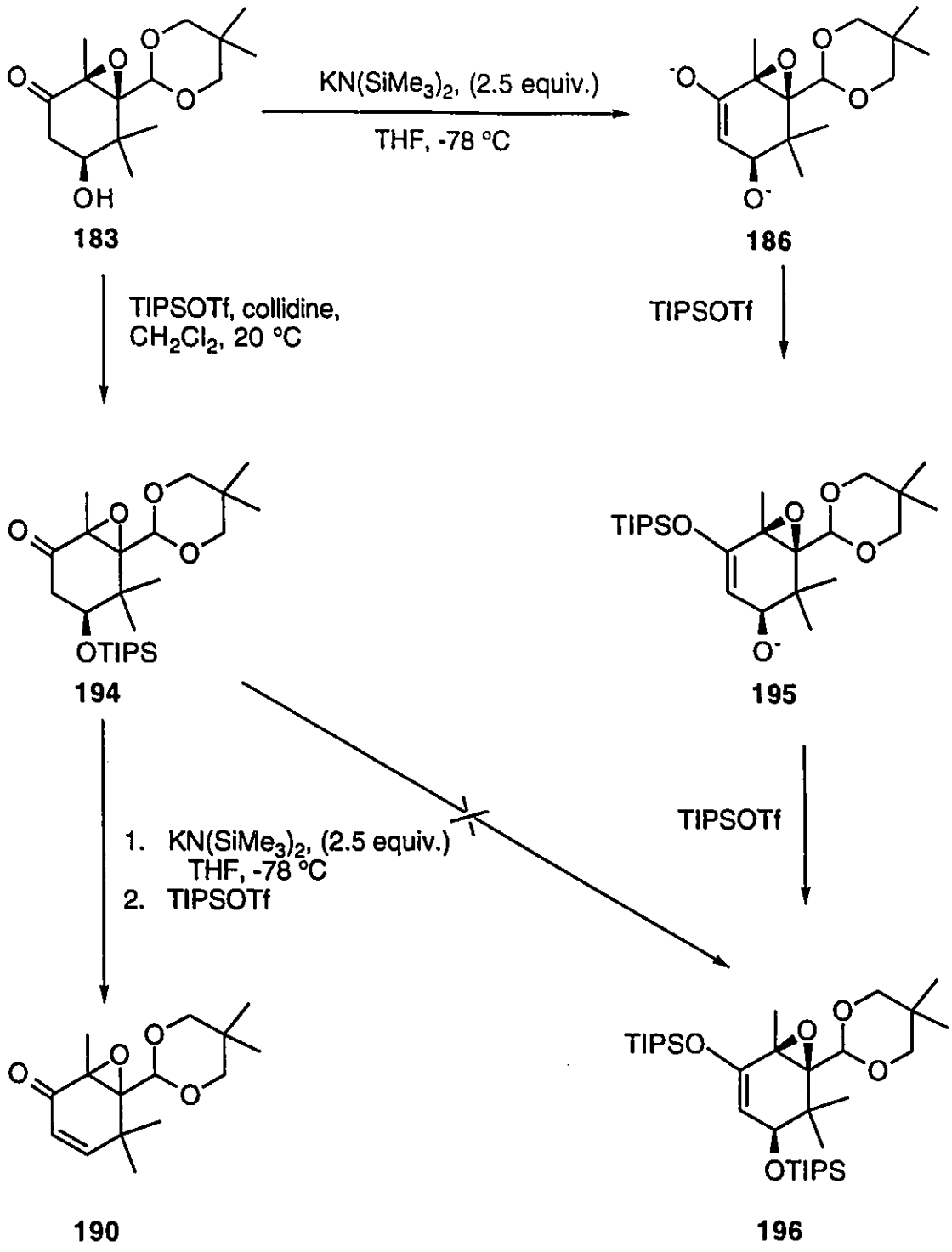


183 **191** **193** **192**

Scheme 56

For this approach to succeed the enolization of the C13 ketone would have to be accomplished without the β-elimination of the the C1 hydroxy group. This should be possible by first protecting the C1 alcohol as its TMS ether followed by treatment with TBS or TIPS triflate and collidine.[61] The C1 TMS ether could then be selectively cleaved with methyllithium and oxidized.[69] This oxidation would also be more facile now that the C1 alcohol was allylic. Precedent for this approach came from the high yield formation of triisopropylsilyl-enol ether **174** upon treatment of the β-keto-sulfide **166** with TIPS triflate and collidine (*vide supra*). Unlike the β-ketosulfide **174** however, enol ether formation did not occur when these conditions were employed with ketone **191** and only the TMS protected alcohol **191** was isolated in 51 % yield. This compound displayed a singlet (9 H) corresponding to the TMS group at 0.07 ppm as well as a doublet of doublets at 3.44 ppm (CHOTMS) in the ^{1}H NMR spectrum. For silylation to

occur by this method it is necessary for a small quantity of ketone to exist in the enol form.[61] Silylation on oxygen followed by proton abstraction from the oxonium ion then completes the process. It therefore appeared that the C11-C12 epoxide was preventing enolization of the C13 ketone. To circumvent this problem it was decided to prepare the dianion **186**, with the idea that the C13 enolate oxygen should be more reactive than the C1 alkoxide, primarily due to their different steric environments (Scheme 57).

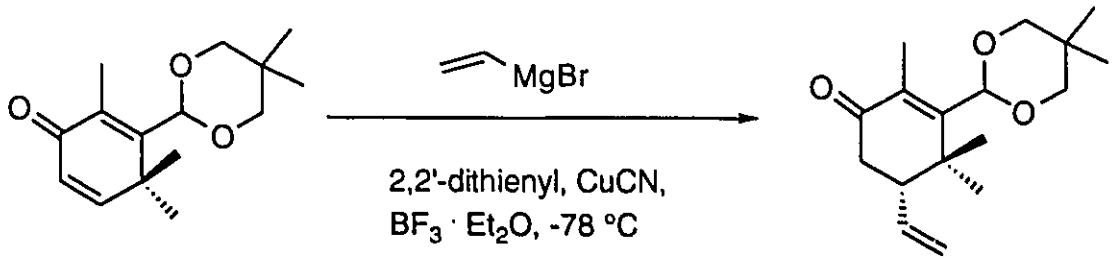

KN(SiMe3)2, (2.5 equiv.)
THF, -78 °C
183
186
TIPSOTf, collidine,
CH2Cl2, 20 °C
TIPSOTf
194
195
1. KN(SiMe3)2, (2.5 equiv.)
THF, -78 °C
2. TIPSOTf
TIPSOTf
190
196

Scheme 57

Thus it might be possible to prepare **195** if only one equivalent of silyl reagent was used. The resulting alcohol (from protonation upon work-up) could then be oxidized to the corresponding ketone **193** (*vide supra*). Treatment of alcohol **183** with 2.5 equivalents of potassium hexamethyldisilazide followed by portionwise addition of TIPS triflate gave however only a mixture of bis-TIPS compound **196** and starting material **183**. Further treatment of the mixture with TIPS triflate gave only **196** in 65 % yield. This compound was characterized by two sets of doublets (J = 5 Hz) at 4.08 and 4.80 ppm in the ^{1}H NMR spectrum characteristic of the methine proton (C<u>H</u>OTIPS) and vinylic proton (C<u>H</u>=) respectively. To rationalize these results it is reasonable to assume that with an excess of base all of the C1 alcohol would exist as the alkoxide and some dianion will also exist. But presumably due to differing steric environments silylation of the C1 alcohol is slower than the C13 enolate oxygen. After silylation of the C13 enolate oxygen, the C1 alkoxide becomes allylic and silylates rapidly. If silylation first occurred on the C1 oxygen, β-elimination would be observed with an excess base. Indeed compound **194**, prepared separately by treatment of alcohol **183** with TIPSOTf and collidine in 69 % yield, upon treatment with 2.5 equivalents potassium hexamethyldisilazide in THF at -78 °C, gave only elimination product **190**.

2. 10. Vinyl Group Addition at C1.

The problem of introducing oxygen functionality at C1 was eventually solved through an indirect route. Vinyl cuprate addition to dienone **156** afforded vinyl ketone **197** in 39 % yield (52 % based on recovered starting material) (Scheme 58).[70]

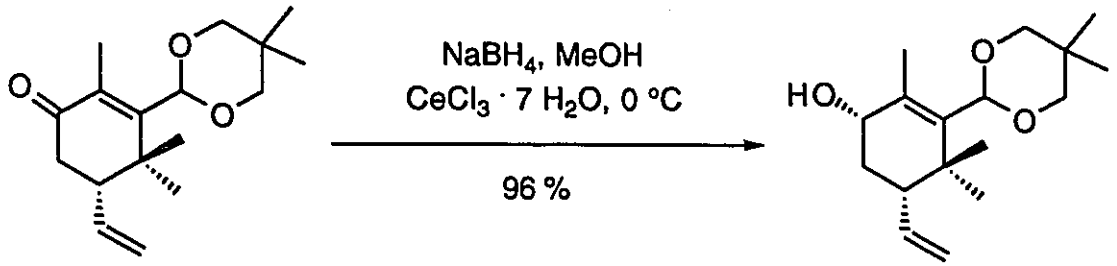


156 **197**

Scheme 58

Compound **197** displayed in the ^1H NMR spectrum a set of multiplets at 4.99-5.34 ppm (2 H) and 5.68-5.86 ppm (1 H) characteristic of the vinyl group. In addition, the presence of an additional double bond in the molecule was confirmed by the total of four resonances in the ^{13}C NMR at 117.2, 133.8, 137.3, and 155.3 ppm. A carbonyl resonance at 199.3 ppm indicated that the desired 1,4-addition had occurred.

Reduction of the ketone **197** under Luche conditions gave the alcohol **198** as a single diastereomer (^1H NMR) in 96 % yield (Scheme 59).[59]

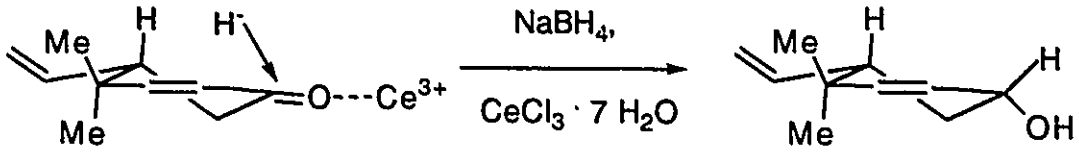


197 **198**

Scheme 59

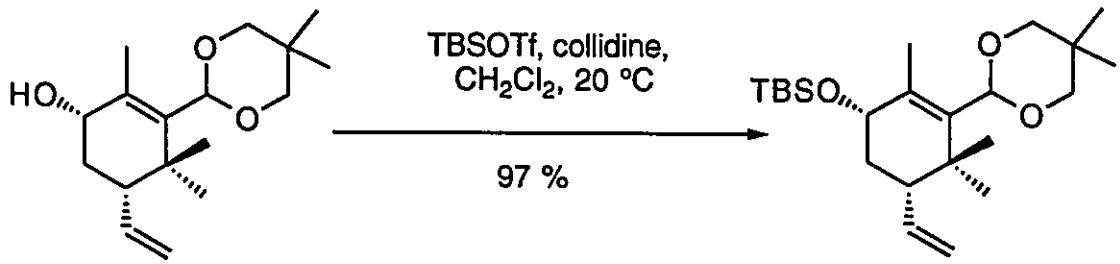
The desired ketone to alcohol conversion was confirmed by the presence of a band in the IR spectrum at 3402 cm^{-1} (OH absorption) and the presence of an apparent broad triplet at 4.04-4.12 ppm in the ^1H NMR spectrum integrating for one proton (C<u>H</u>OH). The presence of four carbon resonances at 115.8, 137.1, 137.3, 139.0 also

indicated that only 1,2-reduction had occurred. The stereochemical assignment of **198** was confirmed by X-ray crystallographic analysis of an advanced intermediate derived from this compound at a later stage of the synthesis (*vide infra*). The assignment is consistent with the mechanism where the vinyl group occupies an equatorial position and attack by hydride occurs axially (Scheme 60). This was also the correct relative stereochemistry at C1 and C13 present in Taxol® (1) but was unsuitable for our intended Diels-Alder approach where it was deemed necessary to have the unnatural C13 stereochemistry.



Scheme 60

Protection of alcohol **198** using TBS triflate in collidine was straightforward and gave the silyl ether **199** in 72 % yield (97 % based on recovered starting material) (Scheme 61).[61]



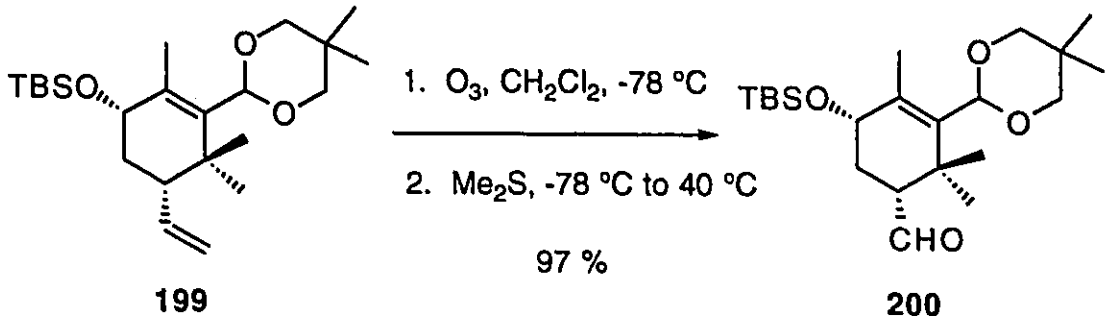
198 **199**

Scheme 61

The presence of two singlets (3 H each) at 0.03 and 0.05 ppm as well as a singlet integrating for 9 hydrogens at 0.87 ppm in the ^1H NMR spectrum indicated the successful incorporation of the TBS group.

2. 11. Preparation of a C2 Aldehyde.

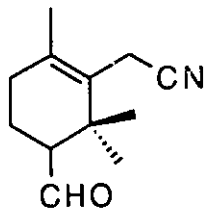
Ozonolysis conducted under closely monitored conditions to avoid C11-C12 double bond cleavage yielded the crude aldehyde **200** in 97 % yield (Scheme 62).[30]



199 **200**

Scheme 62

This compound showed a characteristic absorption in the IR spectrum at 1709 cm^{-1} and a carbonyl resonance at 205.0 ppm in the ^{13}C NMR spectrum. The ozonide of this compound was remarkably stable and slight warming with dimethylsulfide (Me_2S) for 24 hours was required to effect complete decomposition to the aldehyde. Aldehyde **200** was a valuable synthon for further work in our laboratory. It required seven steps for its preparation with an overall yield of approximately 10 %. This is an improvement over our previous (*vide supra*) nine step preparation of the A-ring intermediate **34** (Figure 3) which lacked the C13 protected hydroxyl group.

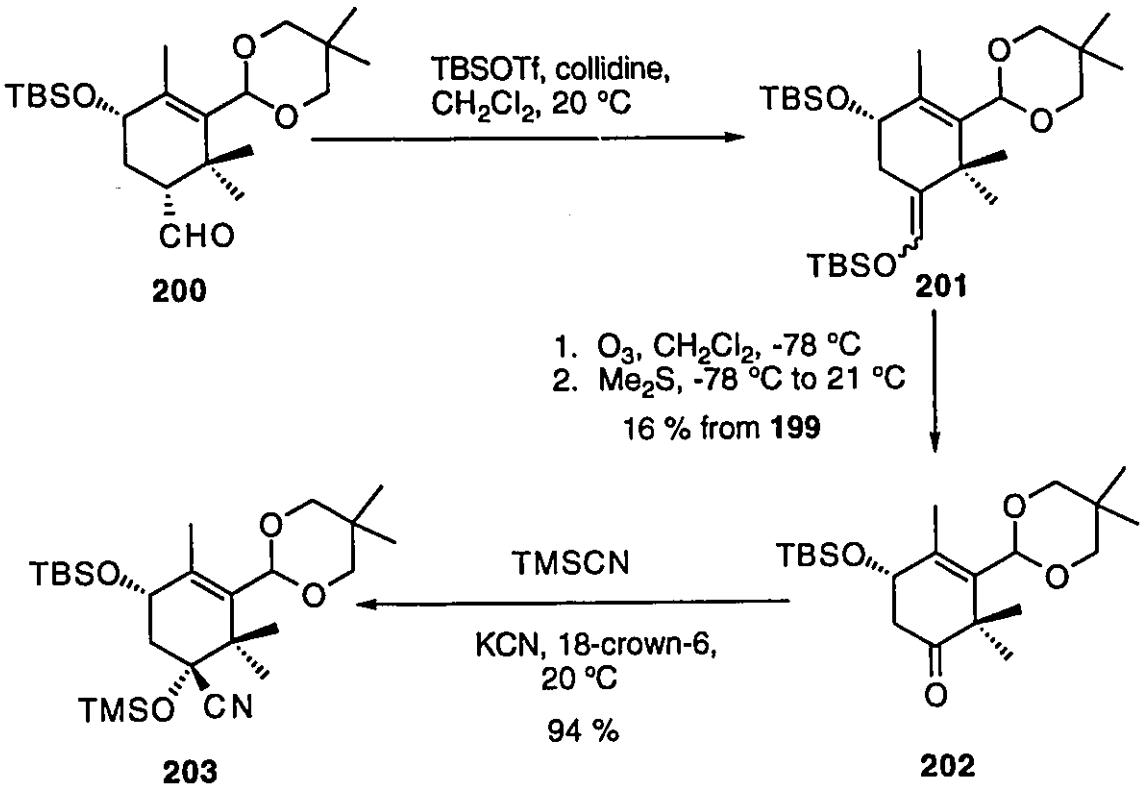


34

Figure 3

2. 12. Preparation of a C1 Ketone.

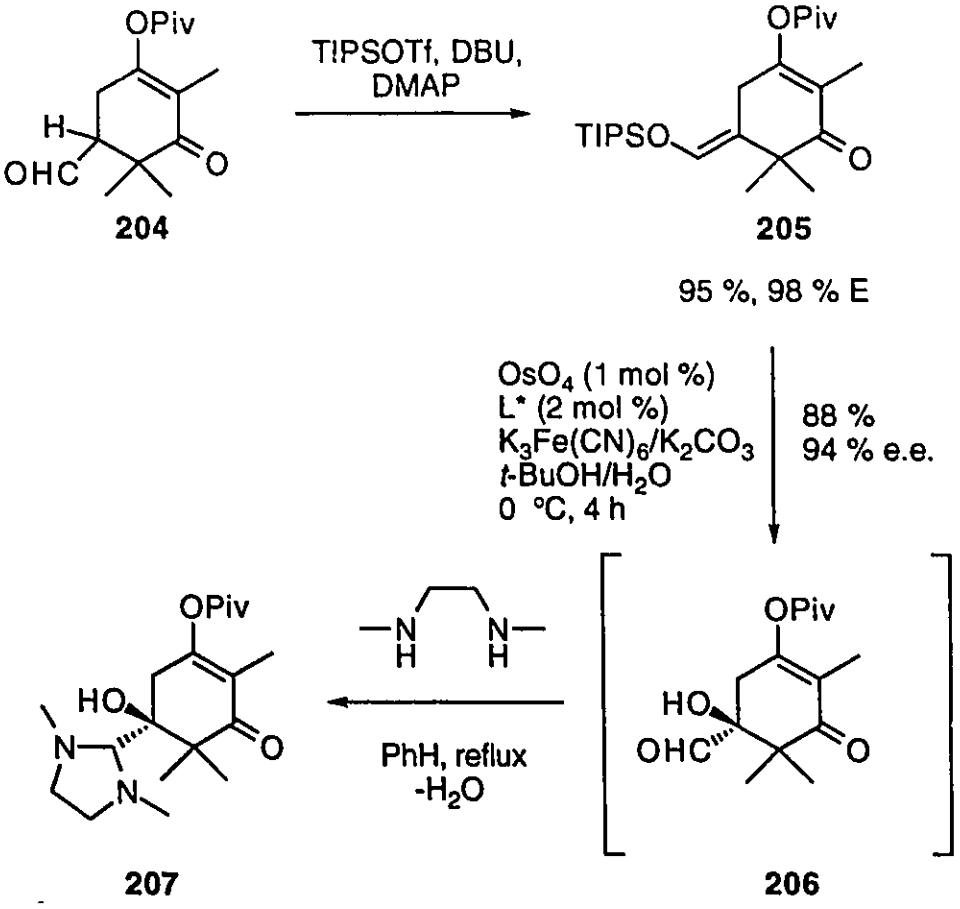
Aldehyde **200** was converted to the corresponding TBS enol ether **201** with TBS triflate and collidine (Scheme 63).[61]

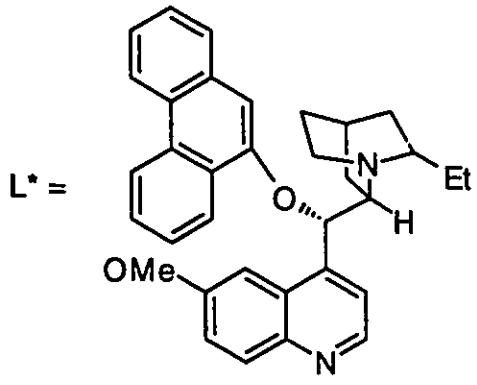


Scheme 63

This silylation step was very slow due to the adjacent gem-dimethyl group and required five equivalents of the reagent and eight hours for completion. Compound **201** displayed a characteristic single vinylic proton at 5.40 ppm in the ^{1}H NMR spectrum, indicative of an enol ether. No attempt was made to determine the geometry of the double bond, although the less sterically crowded E isomer should be favoured. This compound was used immediately in the following step.

Formation of the E isomer can be further substantiated by recent work by Kuwajima's group who prepared the silyl-enol ether **205** (Scheme 64).[71] When the TIPS enol ether was prepared 98 % of the E isomer was formed. Asymmetric dihydroxylation was then used to convert the enol ether to the the α-hydroxy-aldehyde **206**. This material showed a tendency to dimerize under basic conditions and was therefore trapped as its aminal **207**.



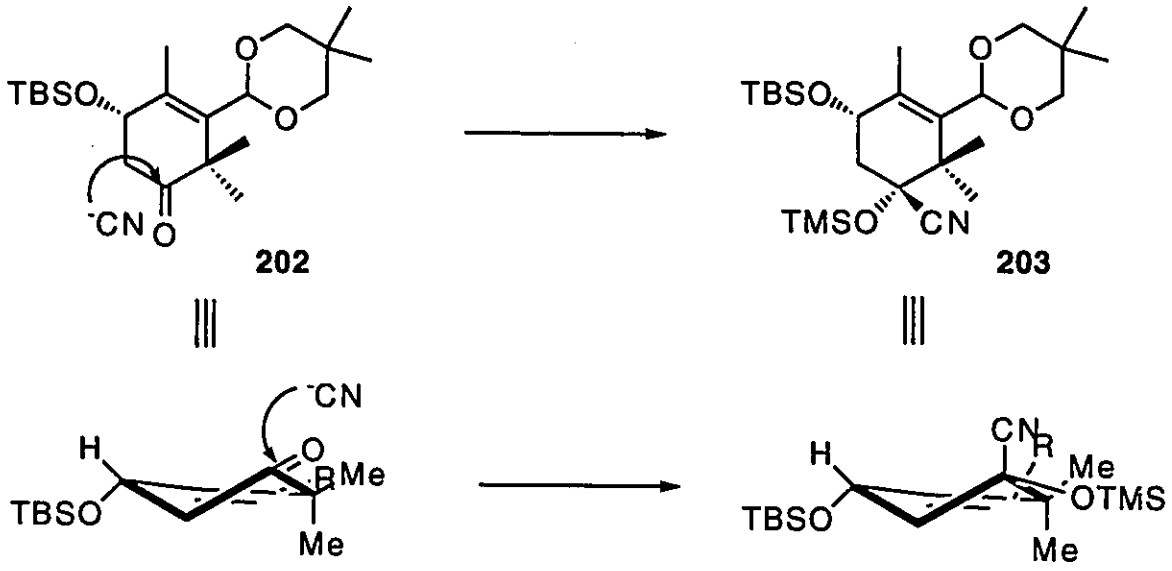


Scheme 64

Carefully controlled ozonolysis of **201** gave the desired ketone **202** in 16 % yield from the vinyl ketone **199** (Scheme 63). The presence of a ketone was indicated by an

absorption at 1718 cm^{-1} in the IR spectrum and a resonance at 212.2 ppm in the ^{13}C NMR.

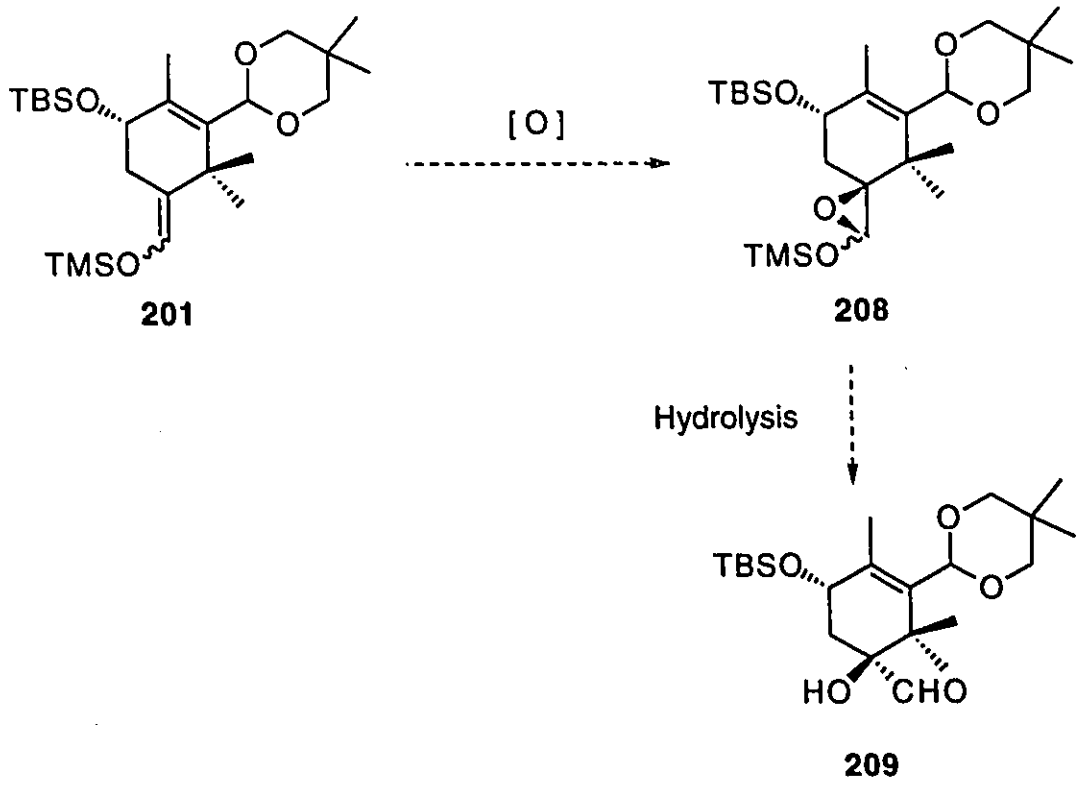
Treatment of the ketone **202** with neat TMSCN, potassium cyanide and a catalytic quantity of 18-crown-6 afforded TMS cyanohydrin **203** in 94 % yield (Scheme 63).[72] Positive proof of stereochemistry can best be determined by X-ray crystallographic analysis. Efforts to produce crystalline material suitable for this method had failed however by the time of this writing. The structure was tentatively assigned as that shown based on the argument that approach of ^{-}CN should occur from the least hindered face opposite the TBS group (Scheme 65). This would result in a *cis* relationship between the C1 and C13 oxygens opposite to that found in Taxol® (**1**) but was desirable for our approach.



Scheme 65

In order to produce material with the naturally occurring stereochemistry it was felt this problem could be overcome by epoxidation of the corresponding TMS enol ether **208** (Scheme 66).[73] Epoxidation should occur from the least hindered face. Subsequent cleavage of the TMS group (H_2O/H^+) should then afford hydroxy-aldehyde **209**. It

should also be possible to use dihydroxylation to effect the same transformation. Using Kuwajima's approach the resulting α-hydroxy-aldehyde can then be trapped as its aminal.

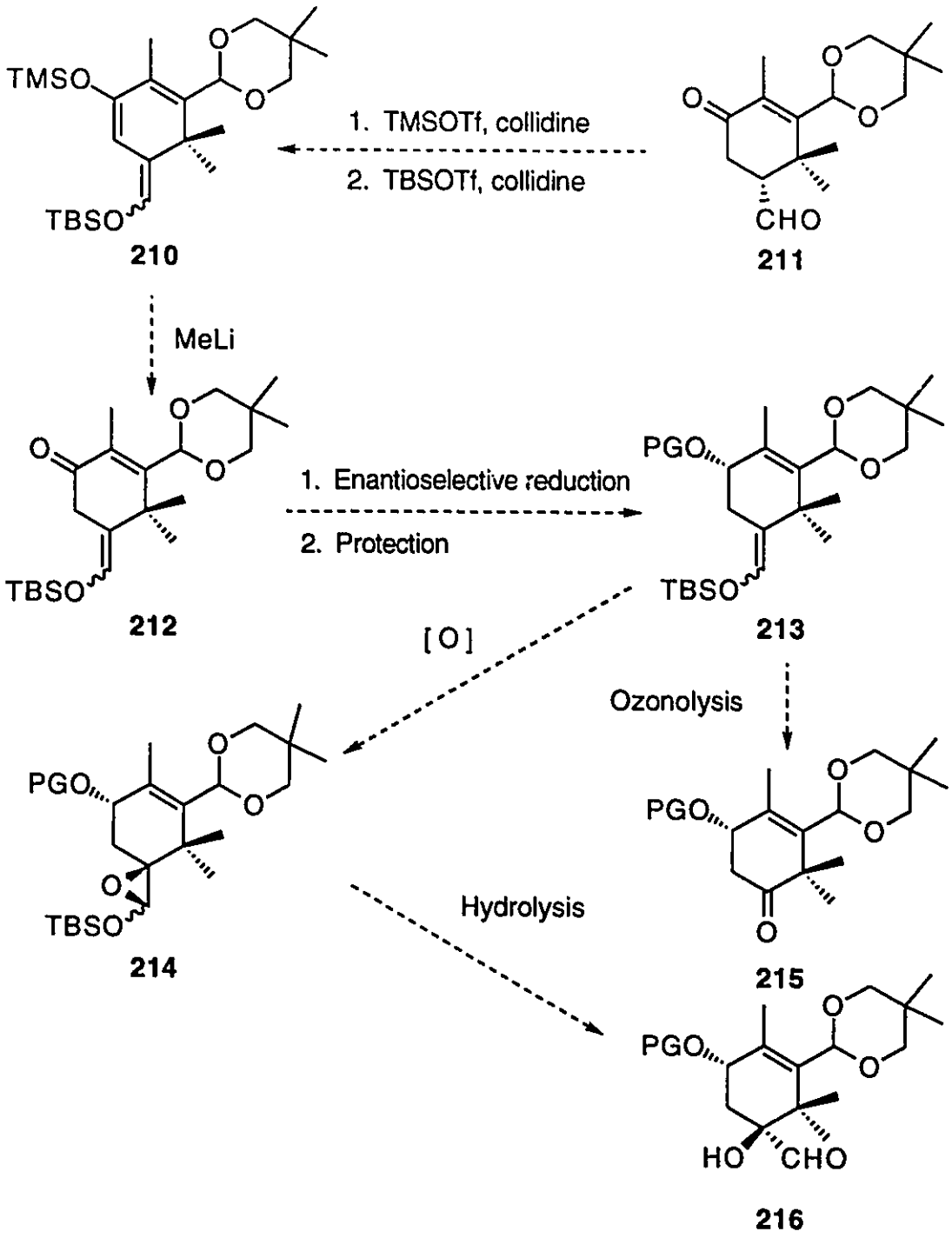


201 **208** **209**

Scheme 66

2. 13. Design of a Homo-Chiral A Ring.

It is conceivable that our synthesis can be adapted to produce homochiral material (Scheme 67).

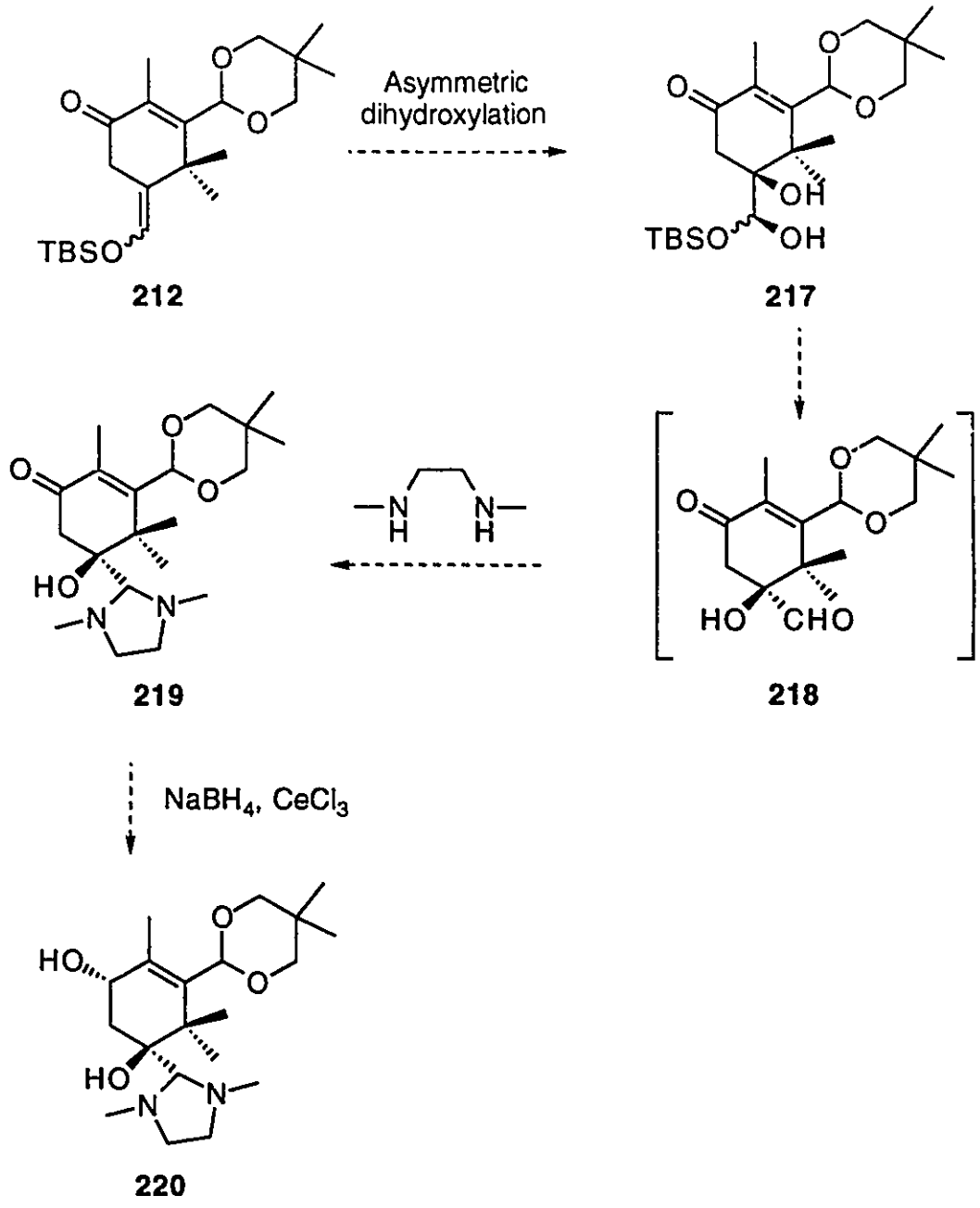


Scheme 67

It was envisioned that keto-aldehyde **211** could be converted to the bis-enol **210**, with the ketone protected as its TMS enol ether and the aldehyde as its TBS enol ether.

Selective cleavage of of the TMS enol ether would then afford ketone **212**, which could be subjected to Corey's oxazaborolidine/catechol borane enantioselective reduction procedure to produce a homochiral alcohol. This material upon protection would furnish **213**. Cleavage with ozone would then give the homochiral β-hydroxy-ketone **215**. Alternatively, epoxidation of **213** would yield the homochiral α-hydroxy aldehyde **216** *via* opening of the epoxide **214.**

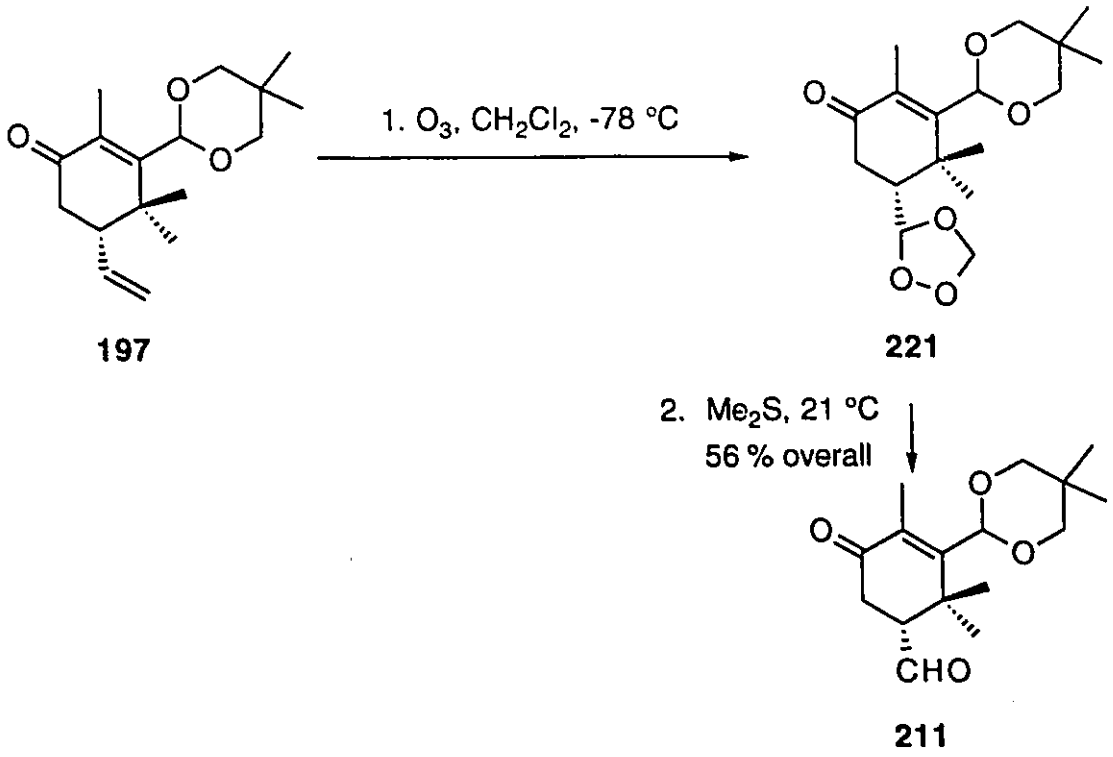
Using the approach taken by Kuwajima, asymmetric dihydroxylation of **212** with subsequent aminal formation could be used to furnish **219** (Scheme 68).[71] This compound when treated with $NaBH_4$ should undergo reduction to give the alcohol **220** possessing the correct absolute stereochemistry at C13 and C1 due to the C1 hydroxyl directed reduction of the carbonyl.



212 **217** **218** **219** **220**

Scheme 68

In order to investigate these approaches keto-aldehyde **211** was prepared in 56 % yield by carefully controlled ozonolysis of vinyl ketone **197** (Scheme 69).



Scheme 69

Compound **211** displayed absorptions in the IR spectrum at 1720 and 1676 cm^{-1} indicating the presence of the enone and aldehyde carbonyls respectively. Resonances in the ^{13}C NMR spectrum at 197.4 and 202.2 ppm also indicated the presence of two carbonyl groups. The ozonide **221** from this reaction, like that seen for the preparation of **200**, was remarkably stable and withstood column chromatography on silica gel. Treatment of compound **221** (Me_2S / CH_2Cl_2 / 21 °C / 48 h) gave the aldehyde **211**.

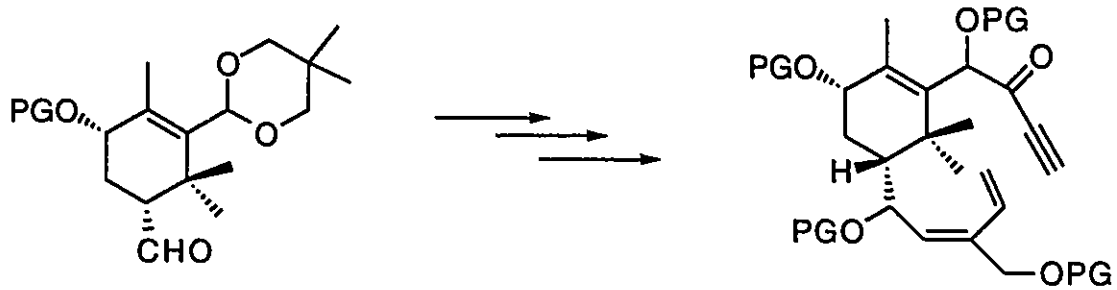
Preparation of the bis-enol ether **210** was not straight forward and a complicated mixture resulted when the keto-aldehye **211** was treated successively with TMS triflate and TBS triflate in collidine.

CHAPTER 3

FURTHER ELABORATION OF RING A

3.1. GENERAL CONSIDERATIONS.

Having secured an efficient synthesis of the A-ring, we next focused our attention on the further elaboration of this intermediate by attaching the diene and dienophile components. This would give rise to a compound such as **223** (Scheme 70).



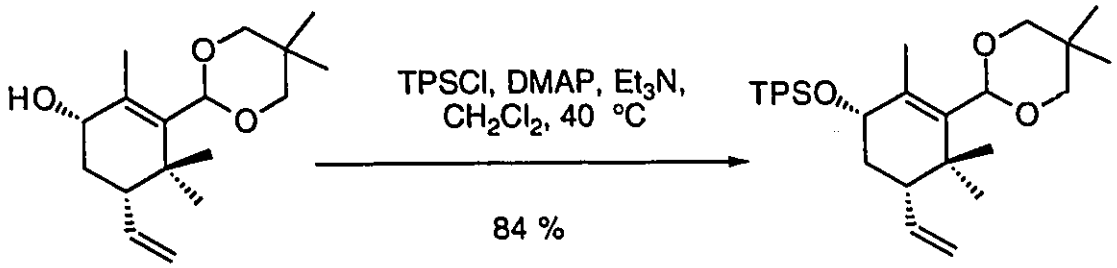
222 **223**

Scheme 70

The aldehyde for this approach could be obtained from alcohol **198**. Alcohol **198** possessed a *syn* relationship between C1 and C13 and it was therefore anticipated that use of this aldehyde would adversely affect the Diels-Alder reaction. Development of methods to further elaborate the A-ring to the diene-dienophile, despite this potential future complication, were nonetheless still neccessary in order to ascertain the ease with which the relative stereochemistry could be controlled.

3. 2. Preparation of Ring A with a C13-OTPS Group.

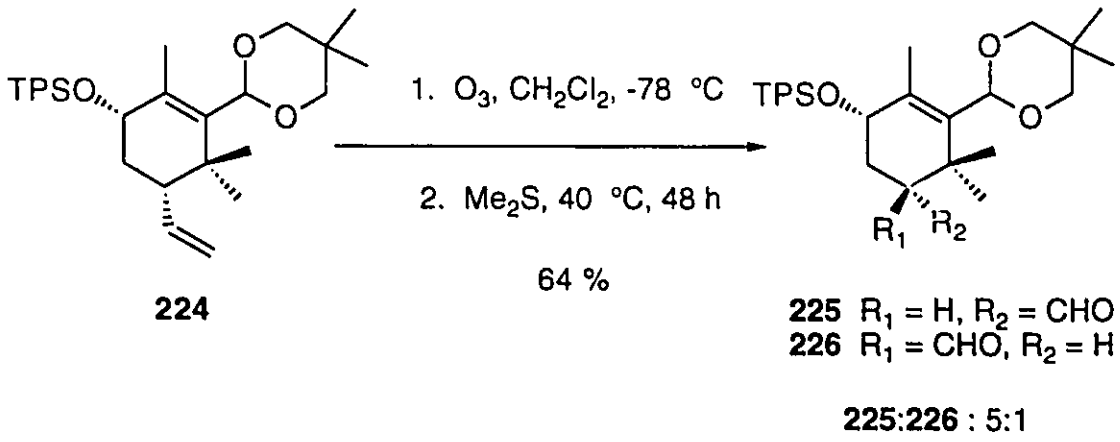
The overall goal of producing Taxol® (1) made it necessary to selectively protect and deprotect various intermediates. The side chain attachment to the C13 alcohol would likely be one of the last steps of the synthesis, thus we chose to protect alcohol **198** with a group which shows stability to a variety of reaction conditions. Protection of alcohol **198** with a *tert*-butyldiphenylsilyl (TPS) group gave the silyl ether **224** in 69 % yield (84 % based on recovered starting material) (Scheme 71).[74]



198 **224**

Scheme 71

The presence of a singlet in the ^{1}H NMR spectrum at 1.05 ppm integrating for 9 hydrogens and two multiplets at 7.30-7.46 and 7.51-7.76 ppm integrating for 10 hydrogens indicated incorporation of the TPS group. Ozonolysis of **224** followed by silica gel chromatography gave, due to partial epimerization, a 5:1 mixture of the aldehydes **225** and **226** in 64 % yield (Scheme 72). The major isomer displayed an absorption in the IR spectrum at 1718 cm^{-1} and a resonance in the ^{13}C NMR at 204.4 ppm, both characteristic of an aldehyde carbonyl group.



Scheme 72

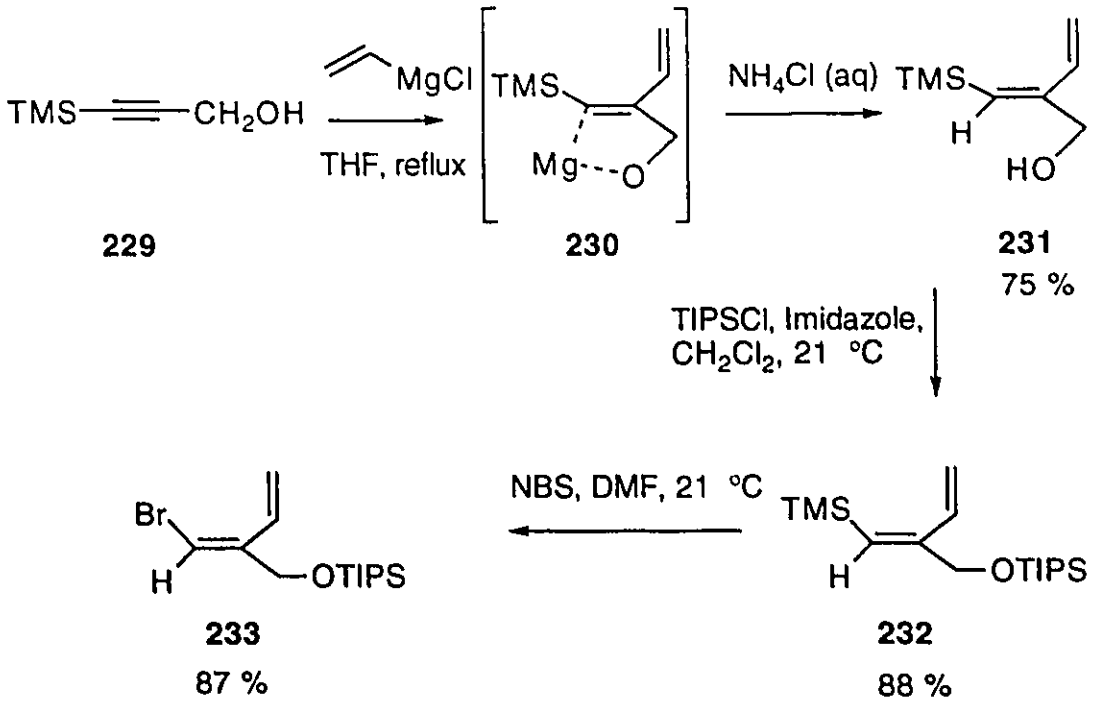
3. 3. Attachment of the Diene Component.

At the time this work was in progress, considerable effort had been made in our laboratory towards the development of the requisite diene component. We envisioned a diene such as **227** where a methyloxy substituent at C4 would later serve as a handle for further elaboration to the oxetane D ring (Figure 4).

227 **228**

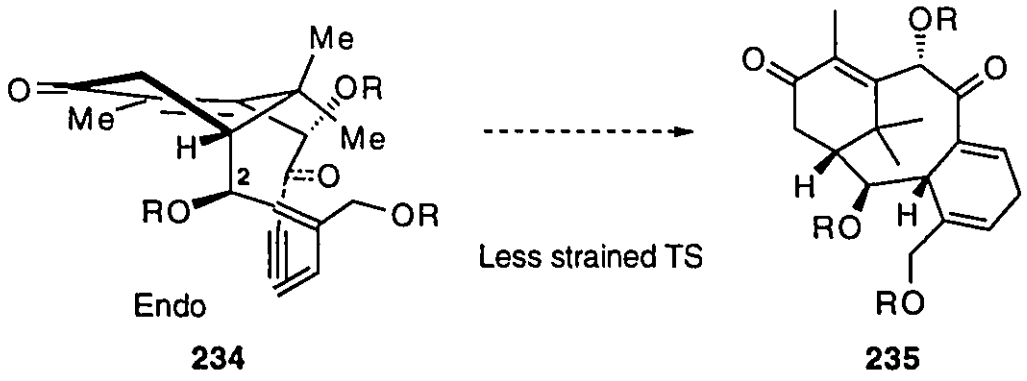
Figure 4

An efficient route to diene **233** was developed by my colleagues. This diene was of the opposite geometry (*cf.* compound **228**) to that used in the original model (*vide supra*) (Scheme 73). This procedure has recently been published.[75]



Scheme 73

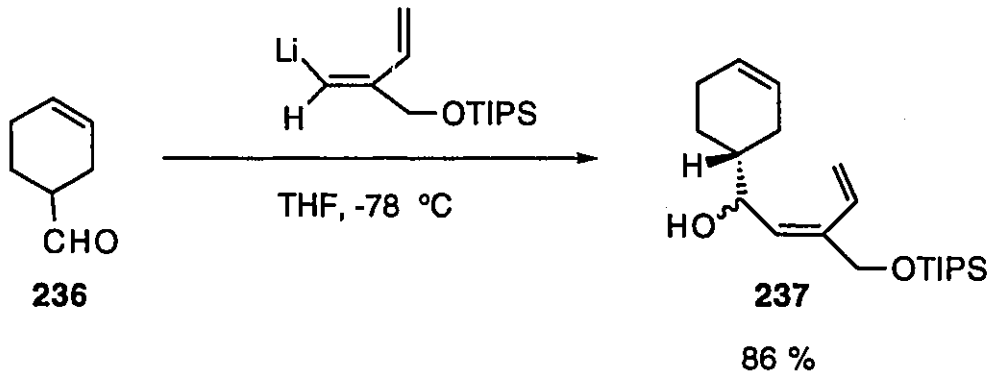
Despite our initial focus on the preparation of a diene with the same geometry as that of the model, molecular models indicated the use of diene **233** and an acetylenic dienophile provided a favourable overlap of these two reactive components. As seen previously with the model reaction it was expected that the C2 stereochemistry would also influence the facial selectivity. The most favourable transition state for this diene was predicted for a system where the C2 stereochemistry is 'unnatural' and the transition state is endo (Scheme 74).



Scheme 74

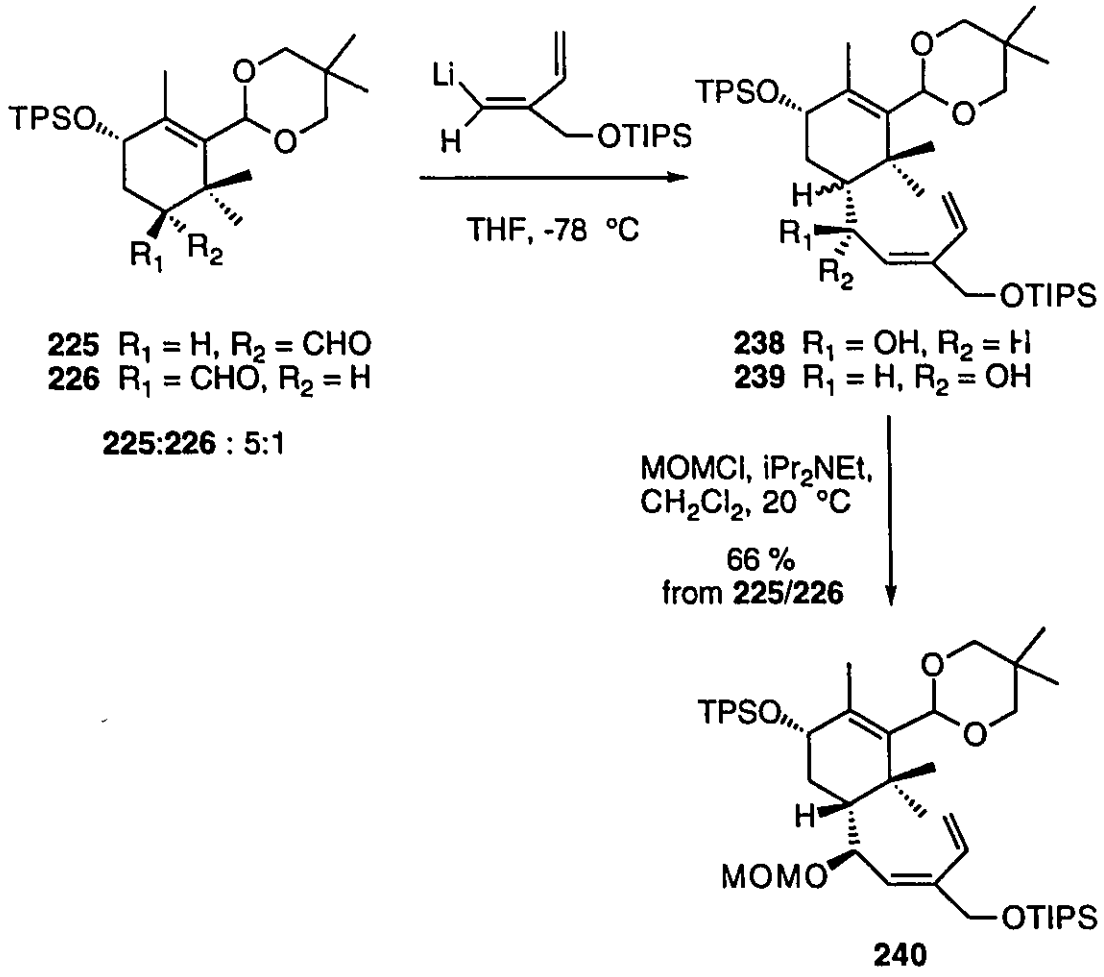
A possible complication with the use of diene **233** was the potential for sigmatropic rearrangement at the temperatures neccessary to affect the [4+2] cycloaddition. The rearrangement of such systems is well documented.[76] However, rearrangement versus cycloaddition should be competitive and the success of the Diels-Alder reaction would largely depend on the accessibility to the transition state of this reaction.

Diene **233** was shown by a co-worker to cleanly undergo metal/halogen exchange. Addition to the model compound tetrahydrobenzaldehyde **236** gave alcohol **237** in 86 % yield (Scheme 75).



Scheme 75

Addition of the lithio-diene, derived from bromide **233**, to a 5:1 mixture of aldehydes **225** and **226** gave an 80 % yield of alcohols **238/239** (Scheme 76).



Scheme 76

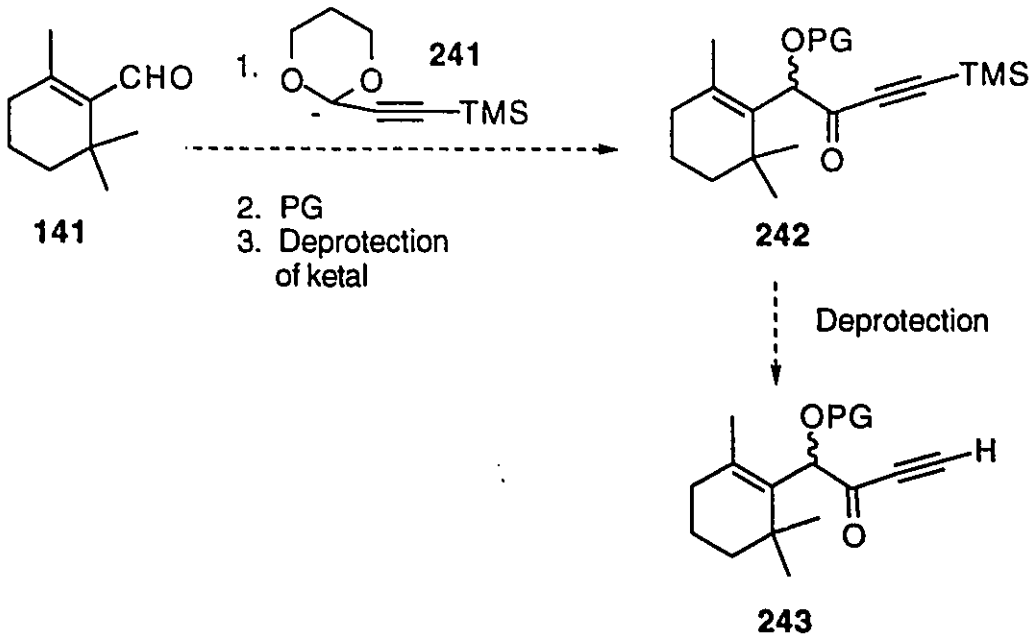
The presence of an alcohol was confirmed by a weak absorption in the IR spectrum at 3606 cm^{-1}. It was not possible to separate the diastereomers at the alcohol stage, but the protection of these alcohols as their MOM ethers gave material that was readily separated. The major isomer **240** was obtained in 66 % yield. The MOM protected compound **240** was characterized by the presence in the ^1H NMR spectrum of a singlet at 3.15 ppm (OCH_3) and two doublets at 4.26 and 4.46 ppm (J = 6.7 Hz)

($C\underline{H}_2OCH_3$) from the methoxymethyl group. Signals characteristic of the presence of the diene were two sets of doublets at 5.06 and 5.15 ppm (J = 11.4 and 17.7 Hz respectively) ($=C\underline{H}_2$), a doublet at 5.49 ppm (J = 9.8 Hz) ($C\underline{H}$=CR-CH=CH_2) and a doublet of doublets at 6.58 ppm (J = 17.7, 11.4 Hz) (CH=CR-$C\underline{H}$=CH_2). A singlet at 4.31 ppm integrating for two hydrogens was characteristic of the methylene group next to the TIPS group ($C\underline{H}_2$OTIPS). The stereochemistry at C2 was later verified by X-ray crystallographic analysis of a more complex derivative (*vide infra*) to be that shown and was the same as that obtained for the model system. This result can be rationalized by the tendency for the carbonyl oxygen to orient itself away from the sterically demanding gem-dimethyl groups (Scheme 77). Addition of the diene then gives rise to the C2 alcohol on the β-face.

Scheme 77

3.4. Preparation of the Dienophile Component.

In addition to the synthesis of the diene component, methods were also being developed by co-workers for the addition of the dienophile component to the aldehyde attached at C10. It was our intention to introduce the C9 carbonyl and a double (or triple) bond in one step. In our first approach we envisioned the addition of acetylenic ketal **241** to the model aldehyde **141** with subsequent *in situ* protection of the resulting C10 alkoxide (Scheme 78).



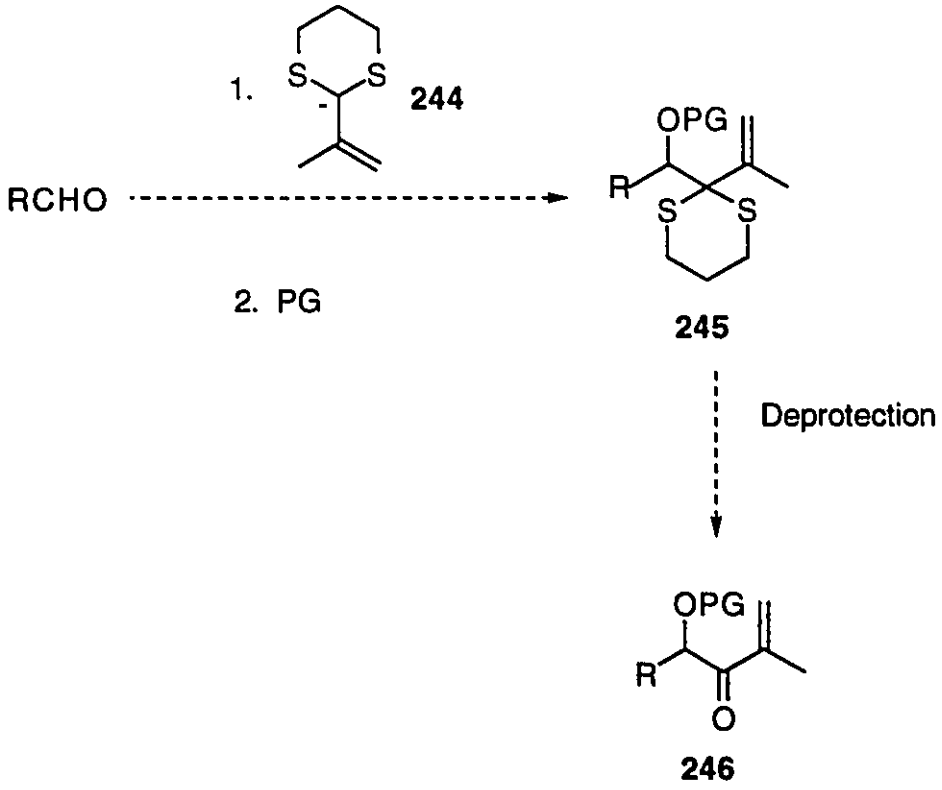
141 242 243

Scheme 78

Deprotection of the ketal followed by removal of the TMS group would result in a three step sequence for introduction of the dienophile with the requisite functionality at C9 and C10. This approach was prompted by previous difficulties encountered with the oxidation of the propargylic alcohol **37** used for the original model studies. Ironically, oxidation of the propargylic alcohol of a more complex system proved to be facile (*vide infra*).

Acetylenic ketal **241** is a known compound and has been shown to add to a variety of electrophiles.[77] No mention was made however of the addition to carbonyl compounds. Unfortunately a co-worker found that the addition of **241** to model aldehyde **141** gave a number of compounds difficult to identify.

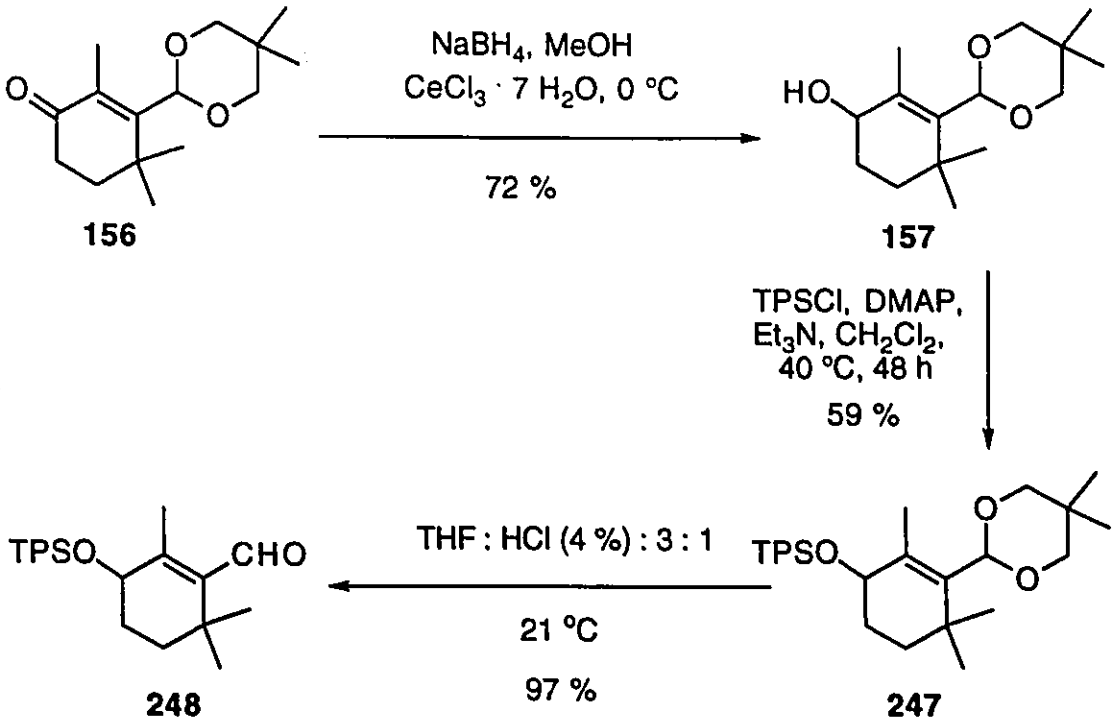
In the second approach we looked at the introduction of an isopropenyl group as a dienophile with a dithiane protected C9 carbonyl (Scheme 79). In principle, nucleophilic addition of **244** with protection of the resulting C10 alkoxide, followed by dithiane deprotection, results in a two step procedure to introduce an acrylate dienophile.



Scheme 79

Dithiane **244** was originally used by Seebach[78] to prepare α-hydroxy ketones and was previously used in our laboratory for the preparation of (+)-longifolene.[79] For our approach to succeed the problem of α versus γ alkylation had to be addressed. α-Alkylation versus γ-alkylation of carbonyl compounds using dithianes of the type **244** has been shown to be dependent on a number of factors. These include hardness or softness of the carbonyl group[80], solvent polarity and steric effects.[81] Soft carbonyls (typically ketones), low solvent polarity as well as a sterically hindered reactive site all favour γ-alkylation.

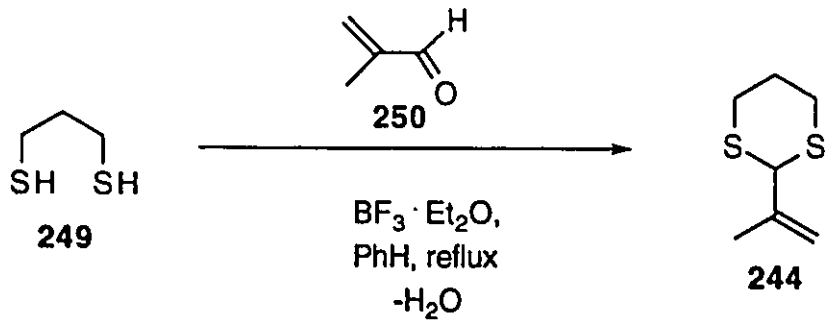
The model aldehyde **248** was used in order to evaluate the addition of compound **244** and was prepared in three steps. Reduction of ketone **156** with sodium borohydride under Luche conditions gave alcohol **157** in 72 % yield (Scheme 80).[59]



Scheme 80

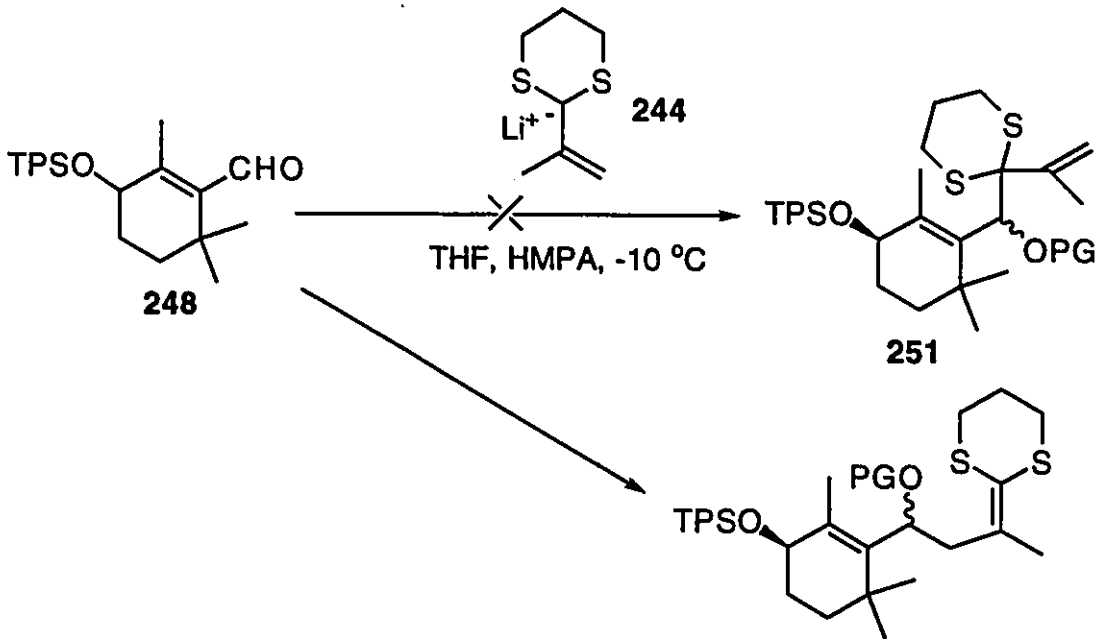
This alcohol showed an absorption in the IR spectrum at 3431 cm^{-1} and an apparent triplet in the ^1H NMR spectrum at 3.78 ppm characteristic of the methine proton (CHOH). Protection of the alcohol gave the TPS ether **247**[74] in 59 % yield and was followed by essentially quantitative deprotection of the ketal group to furnish aldehyde **248**.[82] Compound **248** displayed a resonance at 194.2 ppm in the ^{13}C NMR spectrum and a single proton at 10.02 ppm in the ^1H NMR spectrum consistent with the formation of an aldehyde. An absorption in the IR spectrum at 1678 cm^{-1} confirmed that the aldehyde was unsaturated. In addition, the presence of a singlet at 0.98 ppm (9 H) and two sets of multiplets at 7.25-7.41 ppm (6 H) and 7.58-7.68 ppm (4 H) indicated that the TPS group had been incorporated.

Dithiane **244** was prepared by a co-worker by condensation of 1,3-propanedithiol **249** with methacrolein **250** (Scheme 81).[83]



Scheme 81

Disappointingly, the addition of dithiane **244** to aldehyde **248**, with or without HMPA in THF, gave mostly the γ-alkylated product **252** as a 1.5:1 mixture of diastereomers in 62 % yield (Scheme 82).

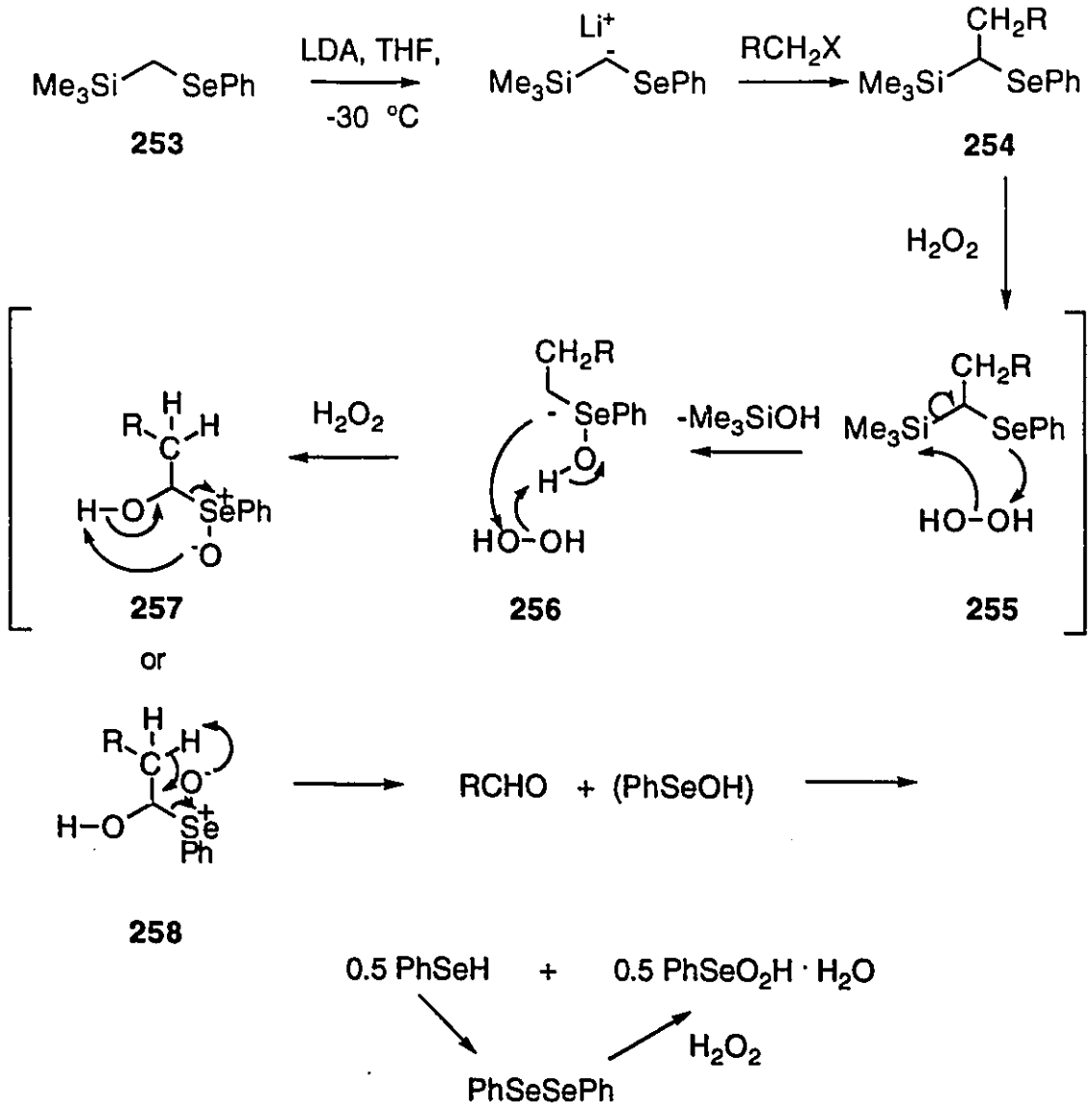


Scheme 82

Due to these difficulties we looked at using a formyl anion equivalent which could be used to furnish an α-hydroxy-aldehyde upon addition to the aldehyde at C10. Addition of an acetylene or vinyl Grignard reagent to the new aldehyde followed by

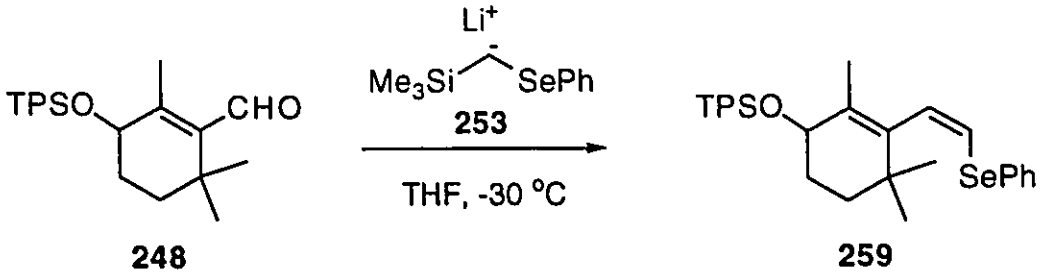
oxidation of the resulting alcohol would then give the dienophile 'upper half' described in Scheme 79.

(Phenylselenomethyl)trimethylsilane **253** has been used as a formyl anion equivalent.[84] Typically this reagent has only been reacted with alkyl halides. The resulting product, upon reaction with hydrogen peroxide undergoes an interesting rearrangement to form an aldehyde (Scheme 83).



Scheme 83

The compound has also been added to aldehydes and ketones with only minor quantities of vinylselenide being formed from a Peterson type olefination.[85] However, in our hands, addition of lithiated **253** gave exclusively *cis*-vinyl selenide **259** in 65 % yield (Scheme 84).

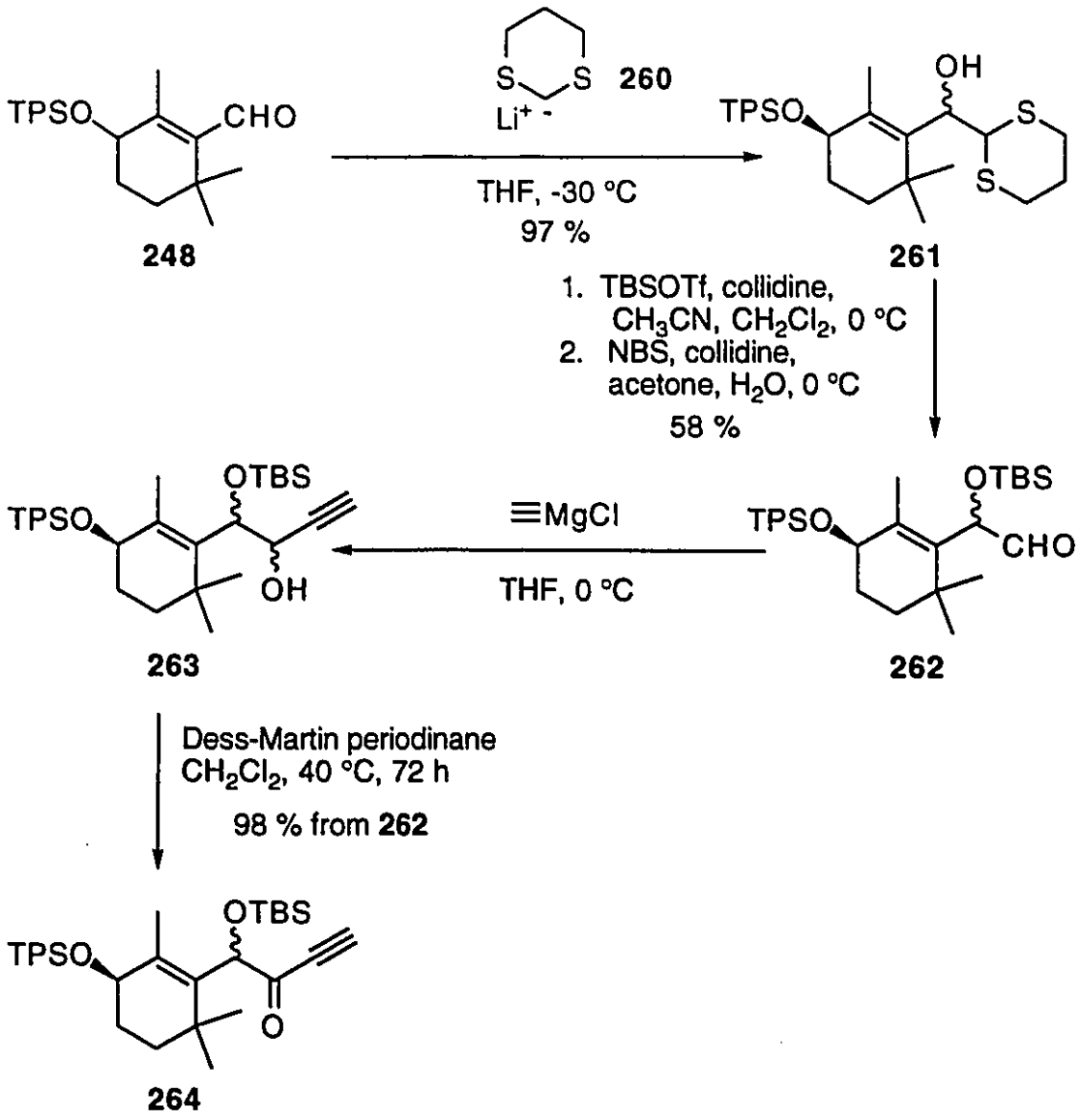


248 **259**

Scheme 84

This result showed that it was not possible to use this reagent for the preparation of α-hydroxy-aldehydes. However, the reagent shows good potential for the preparation of vinyl-selenides and co-workers are currently using it to examine a radical based approach to the taxane ring system (*vide infra*).

Using more conventional methodology, 1,3-dithiane **260** was added to aldehyde **248** to give a 2:1 mixture of alcohols **261** in 97 % yield (Scheme 85).[83]

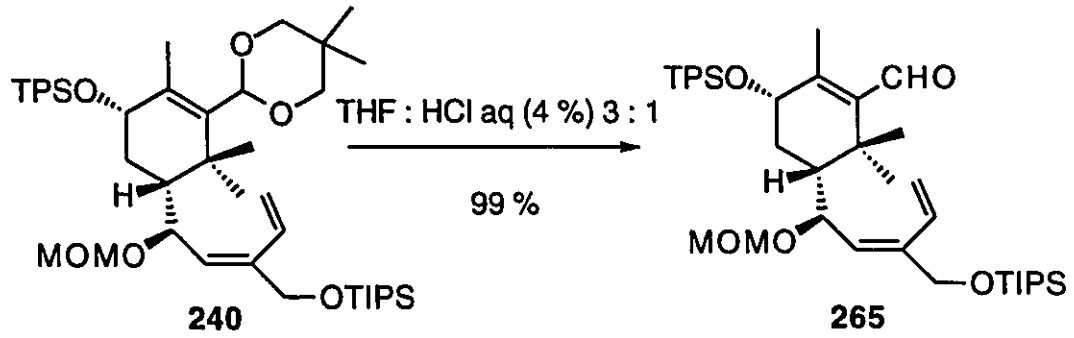


Scheme 85

This work was intended for model studies, thus these compounds were characterized by ^{1}H NMR only (major isomer). The major isomer of alcohol **261** displayed two doublets (J = 11 Hz) at 4.32 and 4.39 ppm in the ^{1}H NMR spectrum corresponding to the methine proton between the two sulfurs of the dithiane (-SCHRS-) and the methine proton of the alcohol (CHOH) respectively. Protection of the alcohol as the TBS ether[74] followed by deprotection of the dithiane functionality with NBS[86] gave

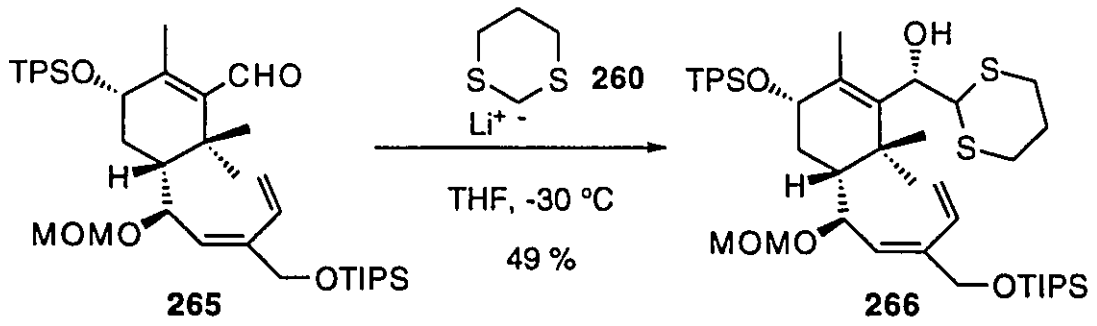
the α-siloxy-aldehyde **262** with a combined two step yield of 58 %. The α-siloxy-aldehyde **262** displayed a singlet at 4.66 ppm (CHOTBS) and a singlet at 9.62 ppm (CHO) in the ^{1}H NMR. In addition, two singlets at 0.02 and 0.12 ppm indicated the presence of the TBS group. Addition of the acetylenic Grignard followed by oxidation with Dess-Martin periodinane[36] then gave acetylenic ketone **264** in 98 % yield. Acetylenic ketone **264** showed a characteristic singlet at 3.28 ppm (COC≡CH) as well as a singlet at 4.80 ppm (CHOTBS). The downfield shift of the terminal acetylene proton is accounted for by the transmission of the electron withdrawing effect of the carbonyl group through the triple bond.

Using the actual system, acetal **240** was deprotected using acidic hydrolysis with a 99 % yield of the enal **265** being obtained (Scheme 86).[82] Enal **265** displayed similar spectral characteristics to that of the model compound **248** with a band in the IR spectrum at 1677 cm^{-1} and resonances in the ^{1}H NMR and ^{13}C NMR at 10.06 ppm (singlet, 1 H) and 193.4 ppm respectively.



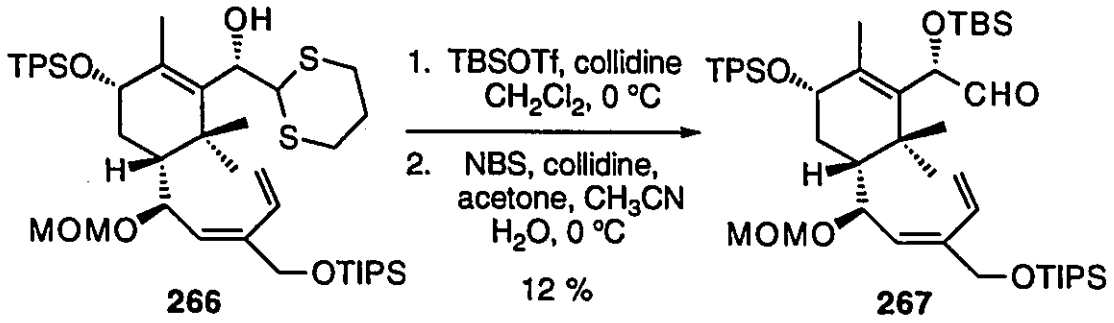
Scheme 86

Addition of dithiane to enal **265** gave alcohol **266** as a single diastereomer in 49 % yield (64 % based on recovered starting material) (Scheme 87).[83] This isomer was tentatively assigned the stereochemistry shown based on other nucleophilic additions to this center (*vide infra*).



Scheme 87

Protection of the alcohol as the TBS ether was not straightforward and gave the desired silyl ether **267** and an inseparable unidentified by-product in a 1:2 ratio in a combined yield of only 40 % (Scheme 88).

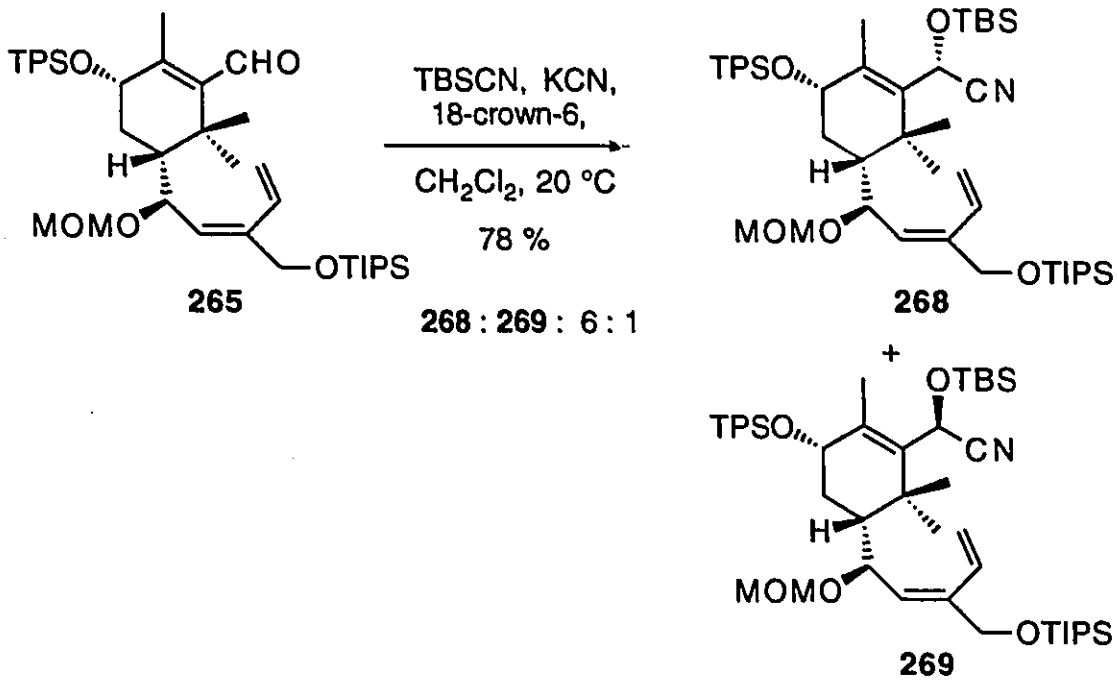


Scheme 88

Deprotection of the dithiane with NBS[86] gave the desired aldehyde **267**, but the overall yield for protection/deprotection was only 12 %. Proof of structure of **267** came at a later stage by comparison with an authentic sample prepared by a separate route (*vide infra*). Clearly the problem with this method was the protection step. This reaction was very slow requiring eight hours to go to completion and significant decomposition resulted.

3. 5. Preparation of a Silyl Cyanohydrin.

Seeking to avoid these problems we looked at the addition of tertiary-butyldimethylsilyl cyanide (TBSCN) to the aldehyde **265**. Reduction of the nitrile would then furnish the previously prepared α-siloxy-aldehyde **267**. Addition of freshly prepared TBSCN[87] under basic catalysis afforded a 6:1 mixture of cyanohydrins **268** and **269** in 78 % yield (Scheme 89).[88]

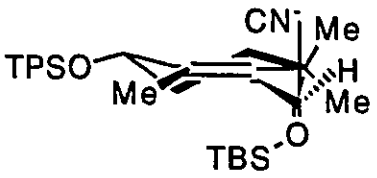


Scheme 89

Chromatography afforded the major diastereomer **268** as a crystalline solid in 67 % yield. This was rather fortunate as all compounds prepared from the starting aldehyde **225** were oils or glassy solids. It was therefore possible to obtain proof of structure by X-ray crystallographic analysis. TBS cyanohydrin **268** displayed a single proton at 4.95 ppm in the ^{1}H NMR spectrum that was characteristic of the silyl-cyanohydrin proton (TBSOCH(R)CN). The nitrile carbon gave a signal at 120.0 ppm in the ^{13}C NMR

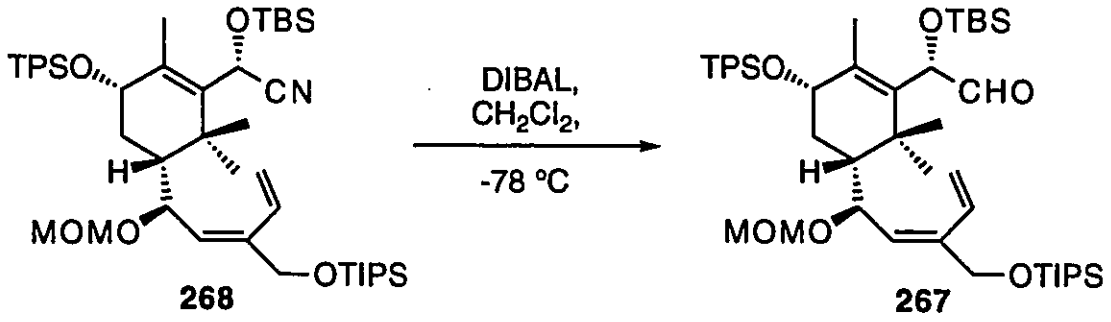
spectrum. In addition, the characteristic signals of the TBS group were evident at 0.13 (s, 3 H), 0.26 ppm (s, 3 H) (diastereotopic methyls) and 0.88 ppm (s, 9 H) (tertiary butyl group). The formation of the major isomer **268** can be rationalized on the basis of the carbonyl oxygen orienting itself away from the gem-dimethyl groups and the CN^- approaching from the top face of the A-ring opposite the OTPS group (Scheme 90).

The unnatural stereochemistry at C10 was predicted to be favourable for the subsequent Diels-Alder reaction due to reduced interaction of the OTBS group with the gem-dimethyl group.

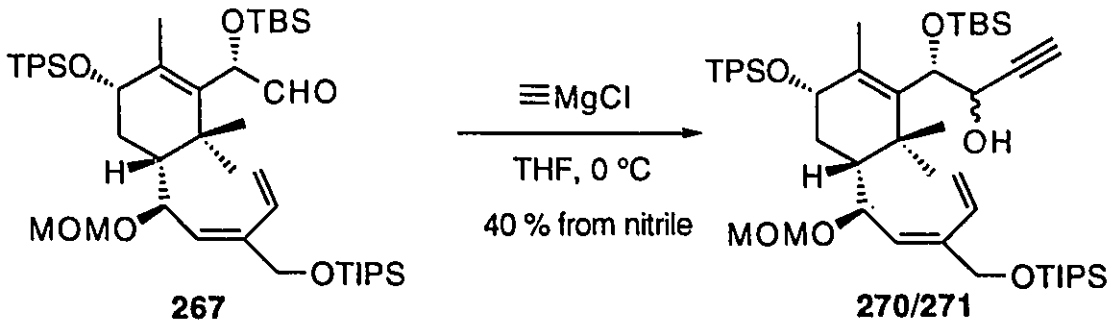


Scheme 90

Reduction of the nitrile **268** with DIBAL gave the crude aldehyde **267**[89] (Scheme 91) which was treated directly with ethynylmagnesium chloride to yield a 2:1 mixture of propargylic alcohols **270** and **271** in 40 % yield (Scheme 92).



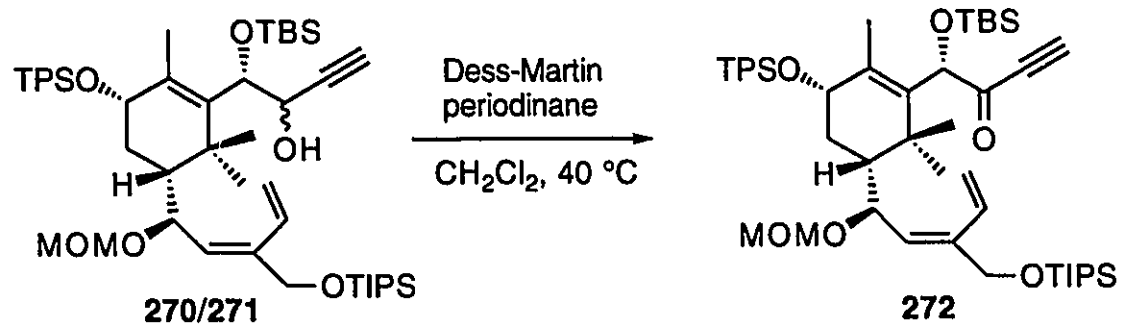
Scheme 91



Scheme 92

The major isomer **270** displayed a proton at 2.43 ppm in the ^{1}H NMR, (J = 2 Hz), characteristic of an acetylenic hydrogen. A broad band in the IR spectrum at 3309 cm^{-1} indicated the presence of an alcohol. A multiplet at 4.46-4.54 ppm integrating for two protons was indicative of the newly formed alcohol as well as the methine under the OTBS group (≡CRHOH and CRHOTBS)

Alcohols **270/271** were oxidized separately with Dess-Martin periodinane[36] to produce ketone **272** with an overall yield of 80 % (Scheme 93).



Scheme 93

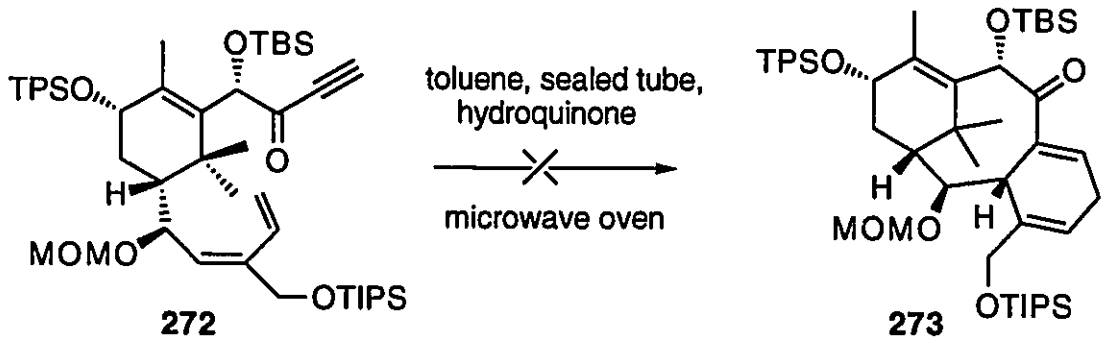
Compound **272** displayed a single proton in the ^{1}H NMR as a doublet (J = 2.4 Hz) at 3.23 ppm, as well as an absorption in the IR at 1690 cm^{-1}, both characteristic of a propargylic ketone. A carbonyl signal in the ^{13}C NMR at 125 MHz at 21 °C could not be detected. Upon cooling to -40 °C however, a carbonyl signal was clearly seen at 188.3

ppm. More surprising was the doubling of signals seen in both the carbon and proton spectra at this temperature. Clearly this compound is quite conformationally restricted and at -40 °C two distinct conformers 'freeze out'.[90]

3. 6. The Diels-Alder Reaction.

As discussed earlier, models suggested that when both the hydroxyl substituents at C2 and C10 are of the unnatural stereochemistry, steric interactions are minimized in the Diels-Alder transition state. It should also be recalled (*vide supra*) that in an effort to avoid the problems associated with a 1,3-diaxial interaction between the C13 OTPS and C1 axial diene components, it would be neccessary for these components to have a *trans* relationship. This was not the case with our system but nevertheless the cyclization still had to be attempted.

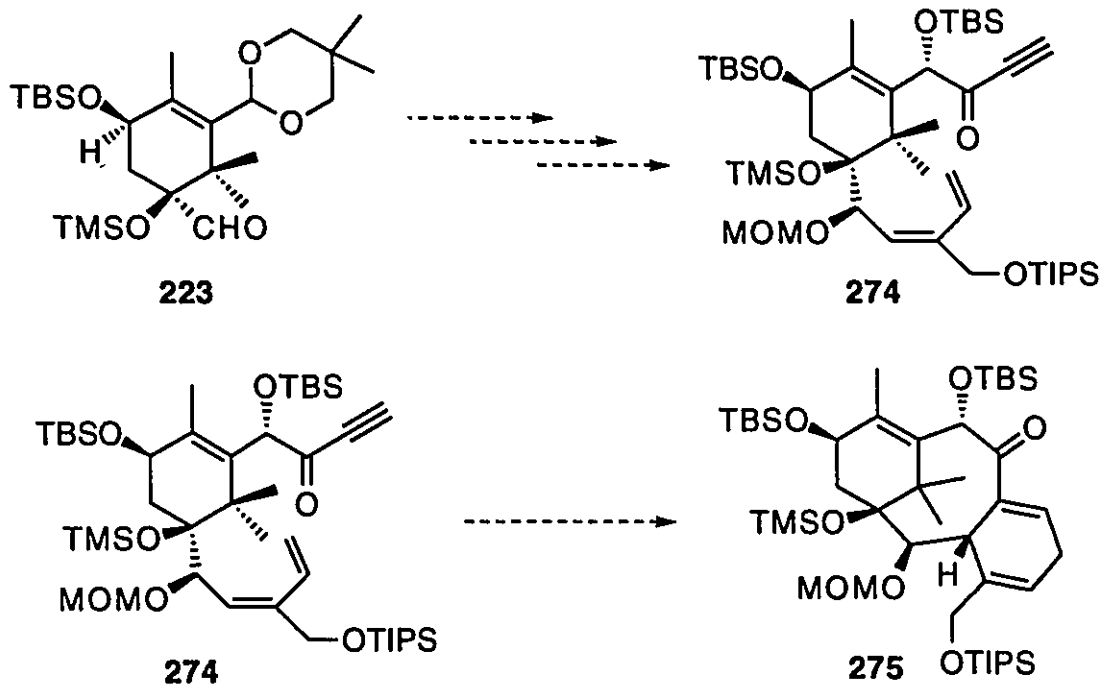
Using our microwave assisted Diels-Alder methodology, compound **272** was heated in degassed toluene with 10 mol % hydroquinone in a sealed tube at approximately 300 °C for eight hours until all starting material was consumed (Scheme 94). Unfortunately a complex mixture resulted from which no adduct could be detected.



272 **273**

Scheme 94

As discussed previously, a carbonyl at C13 should facilitate the Diels-Alder reaction due to the elimination of any 1,3-diaxial interactions. It is therefore conceivable that the use of a protecting group at C13 which can be selectively removed would allow for oxidation of the C13 alcohol to a carbonyl. There is also possibility of epimerizing the aldehyde attached at C1 in compound **225**. This belief has not been evaluated experimentally but precedent exists for this transformation based on the work of Kitagawa who tried to epimerize the *trans* compound **79** to the less stable *cis* compound **80**, with only partial success (recall Scheme 13).[22] In our case we desire the opposite transformation to the more stable *trans* isomer. It is also likely that silyl-cyanohydrin **223** where the C13 OTBS and C1 nitrile possess a *trans* relationship to one another, will be favourable for the Diels-Alder approach (Scheme 95).

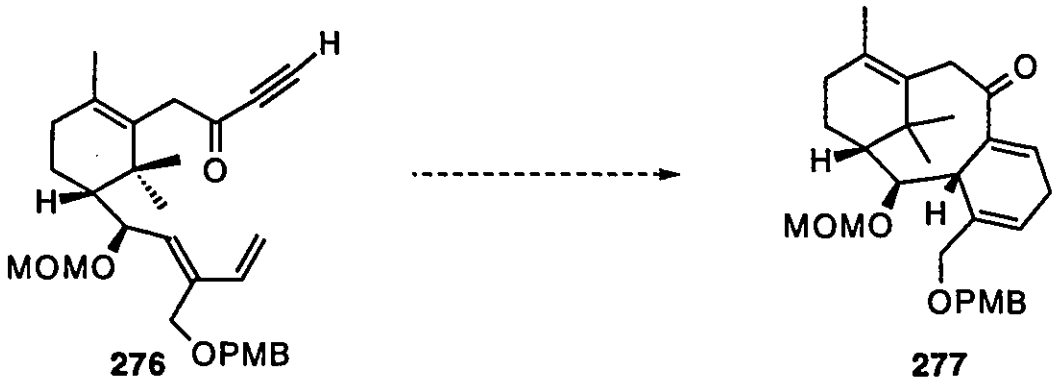


Scheme 95

3.7. CONLUSIONS.

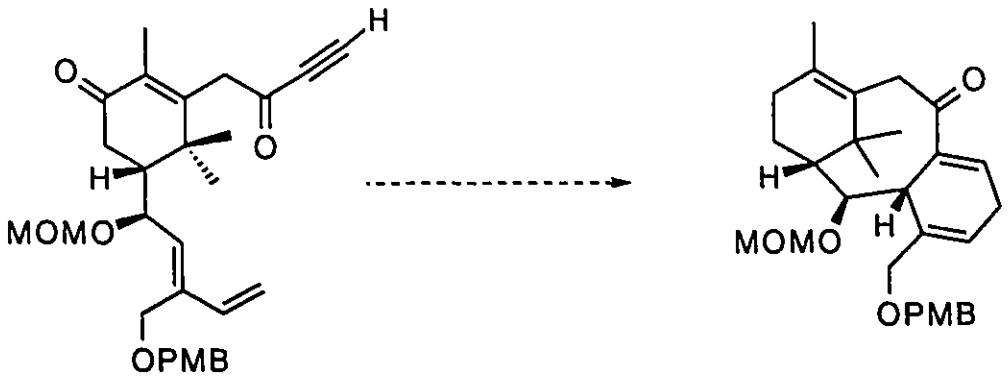
Through the formation of one stereocenter at C1 through the Michael addition of the vinyl group, good stereocontrol at C13, C2 and C10 was also achieved.

As a continuation of this project, a number of questions remain to be answered. The stereochemistry at C13 seems to be a key factor in this approach, but the effect of changing the diene geometry is also unknown. Compound **276** has thus been prepared by co-workers and is currently being tested for its ability to undergo cycloaddition (Scheme 96).



Scheme 96

Similarly, compound **278** is being prepared, which approximates the original model **38** with the exception of the C13 ketone and the C4 substituent on the diene (Scheme 97). This compound will evalute the validity that the presence of a ketone at C13 will help the Diels-Alder reaction by eliminating the problem of 1,3-diaxial interactions and also prevent the double bond migration.

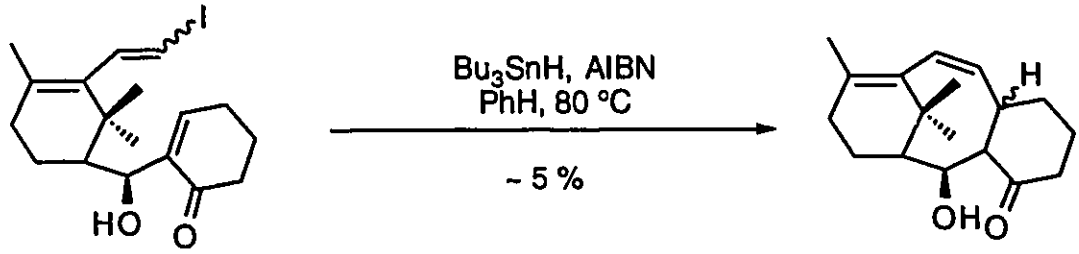


278 **279**

Scheme 97

In addition to the Diels-Alder approach to the taxane ring system, work in our laboratory has also focused on a radical based approach to this ring system (Scheme 98).

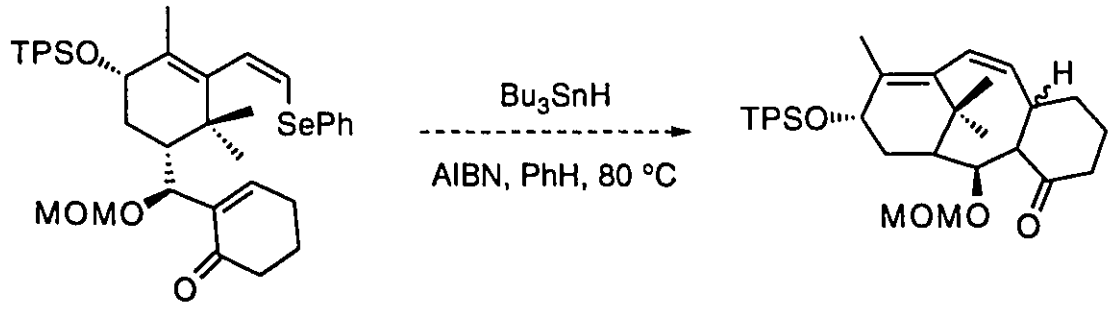
Vinyl iodide **280** has previously been prepared and treated with tributyltin hydride/AIBN. Results have been inconclusive due to problems identifying the small quantities of products isolated from this reaction.



280 **281**

Scheme 99

Using the method obtained for preparation of the vinyl-selenide **259** (*vide supra*), a slightly modified radical precursor **282** has been prepared by a co-worker (Scheme 100). Models indicate that the stereochemistry of the C2 and C13 substituents do not appear to interfere with the intended cyclization. Attempted radical cyclization is currently underway.



282 **283**

Scheme 100

EXPERIMENTAL

CHAPTER 4

General Experimental

Infrared spectra were obtained either as neat thin films or as a thin film of a chloroform solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR)(internal calibration).

All nuclear magnetic resonance (NMR) spectra were obtained from deuterochloroform solutions. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz on a Varian Gemini spectrometer, at 300 MHz on a Varian XL-300 spectrometer, or at 500 MHz on a Bruker WM500 spectrometer relative to an internal lock on the deuterium from $CDCl_3$. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (δ scale). The multiplicity, number of protons and coupling constants are indicated in parentheses.

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 50 MHz on a Varian Gemini spectrometer, at 75 MHz on a Varian XL-300 spectrometer, or at 125 MHz on a Bruker WM500 spectrometer relative to an internal lock on deuterium from $CDCl_3$. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ scale).

Gas chromatography was performed on a Varian 6000 Gas chromatograph equipped with a 25 m X 0.25 mm i.d. silicone gum capillary column. Gas chromatography-mass spectroscopy (GC-MS) determinations were performed on a Hewlett Packard 5890 Series II gas chromatograph equipped with a 25 m polysiloxane coated glass capillary column connected to a Hewlett Packard 5971A mass selective detector. Low resolution mass spectroscopy (MS) using either electron impact (E.I.), or chemical ionization (CI) mode was performed on a V.G. Micromass 7070 HS mass

spectrometer with an electron beam energy of 70 eV (for E.I.). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-IIA mass spectrometer with an electron beam energy of 70 eV. All compounds were homogeneous by GC-MS and TLC.

Microanalyses were performed at M-H-W Laboratories, Phoenix, Arizona, or were performed in house.

Analytical thin layer chromatography (TLC) was performed on commercial aluminum-backed silica gel plates (E. Merck, type 5554). Visualization was accomplished with ultraviolet light, iodine vapour, and/or heating the plate after immersion in either a 5 % solution of ammonium molybdate in 10 % aqueous H_2SO_4 (w/v) or a 2.5 % solution of p-anisaldehyde in ethanol containing 3 % H_2SO_4. Conventional (drip) and flash chromatography were performed with E. Merck Silica Gel 60 (70-230 or 230-400 mesh respectively).

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Distillation temperatures are uncorrected.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry oxygen-free nitrogen or argon in oven-dried glassware equipped with a magnetic stirring bar and rubber septa. Standard inert atmosphere techniques were used in handling all air and/or moisture sensitive compounds. 'Drying' during the work-up procedure refers to drying with anhydrous magnesium sulfate ($MgSO_4$). 'Concentration' during work-up refers to concentration *in vacuo* using a Buchi R110 Rotovapour, unless otherwise stated.

Solvents and Reagents

Petroleum ether refers to a hydrocarbon mixture with a boiling range of 30-60 °C. Ether refers to diethyl ether (Et_2O). Tetrahydrofuran (THF) and diethyl ether were freshly distilled from potassium and benzophenone ketyls, respectively.

Dichloromethane (CH_2Cl_2), benzene, and toluene were freshly distilled from calcium hydride (CaH_2).

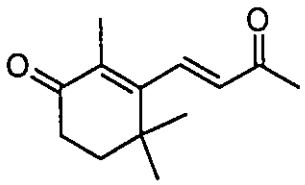
Methanol (MeOH), hexamethylphosphoramide (HMPA), triethylamine (Et_3N), acetonitrile (CH_3CN) and diisopropylamine (i-Pr_2NH) were distilled from CaH_2 and stored over activated 4 Å molecular sieves.

Pyridine was distilled from lithium aluminum hydride ($LiAlH_4$) and stored over activated 4 Å molecular sieves.

Potassium hexamethyldisilazide refers to potassium bis(trimethylsilyl)amide.

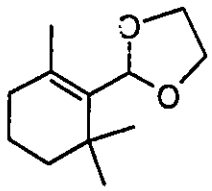
t-Butyldimethylsilyl cyanide (TBSCN) was prepared according to the procedure described by Baker et al.[87] Dimethyldioxirane solutions in acetone were prepared as described by Murray.[62] Nitroethylene was prepared according to the procedure of Noland.[129] 2-Nitrophenylselenylcyanate was prepared as described by Bauer.[121]

4-(2,2,6-trimethyl-5-oxo-cyclohex-6-en-1-yl)-3-buten-2-one (**143**).



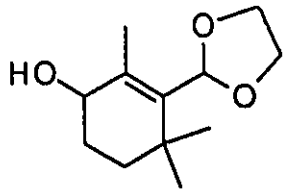
3,5-Dimethylpyrazole (28.8 g, 300 mmol) was added in one portion to a mechanically stirred -15 to -20 °C suspension of chromium trioxide (30.0 g, 300 mmol) in dichloromethane (150 mL). The mixture was stirred for 20 minutes and then β-ionone **114** (10.0 mL, 49.1 mmol) was added. After warming to 0 °C stirring was continued for 2 h. Sodium hydroxide solution (125 mL, 5 M) was then added and the mixture stirred at 0 °C for 1 h. The dichloromethane was removed under reduced pressure and the aqueous layer extracted with ether (5 X 400 mL). The combined ether extracts were concentrated under reduced pressure to approximately 800 mL and then washed with HCl (4 X 125 mL, 1 N), saturated $NaHCO_3$ solution (2 X 25 mL), brine (2 X 50 mL), dried, filtered and concentrated to a residual oil which was chromatographed (10 % ethyl acetate/hexanes) to afford the ketone **143** (4.0 g, 39.5 %) as a pale yellow crystalline solid; mp 50.5-53 °C; IR ($CHCl_3$) 3019, 2967, 1667, 1358, 1216 cm^{-1}; ^1H NMR (200 MHz) δ 1.16 (s, 6 H), 1.77 (s, 3 H), 1.86 (apparent t, 2 H), 2.32 (s, 3 H), 2.51 (apparent t, 2 H), 6.16 (d, 1 H, J = 16.5 Hz), 7.20 (d, 1 H, J = 16.5 Hz); ^{13}C NMR (75 MHz) δ 13.0, 26.9, 27.4, 33.7, 35.1, 36.9, 130.9, 133.2, 139.9, 157.4, 197.0, 198.0; HRMS (EI) calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1308; Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; found: C, 75.52; H, 8.66.

2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde ethylidene acetal (**142**).



Ozone was passed into a stirred -78 °C solution of β-ionone (**114**) (10.0 mL, 49.0 mmol) in dichloromethane (125 mL) until all the starting material was consumed (TLC). Dimethylsulfide (20 mL, large excess) was added and the mixture allowed to warm to 21 °C over a 12 h period. The dichloromethane and excess dimethylsulfide were removed under reduced pressure and then ethylene glycol (30 mL), oxalic acid (100 mg) and benzene (150 mL) were added to the crude aldehyde **141**. The mixture was heated at reflux for 22 h using a Dean-Stark water separator and then cooled to 21 °C. Saturated $NaHCO_3$ solution (20 mL) and ether were then added and the organic phase separated, washed with saturated $NaHCO_3$ solution (25 mL), brine (2 X 50 mL), dried, filtered and concentrated to a residual oil which was distilled (bulb to bulb) to afford the acetal **142** (4.3 g, 44.7 %) as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.06 (s, 6 H), 1.37-1.49 (m, 2 H), 1.52-1.55 (m, 2 H), 1.74 (s, 3 H), 1.93-2.02 (m, 2 H), 3.82-4.06 (m, 4 H), 5.31 (s, 1 H); ^{13}C NMR δ 19.1, 23.9, 28.2, 34.1, 35.1, 40.1, 64.4, 102.3, 132.2, 137.3; HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1464, found 196.1462.

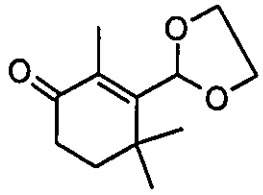
5-hydroxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde ethylidene acetal (147).



Granular potassium carbonate (2.0 g, anhydrous), N-bromosuccinimide (5.50 g, 30.8 mmol) and 2,2'-azobis(isobutyronitrile) (AIBN) (100 mg, 0.610 mmol) were added sequentially to a solution of the acetal **142** (5.50 g, 28.0 mmol) in carbon tetrachloride (50 mL) and the mixture heated to reflux. During the first 30 minutes of reflux additional AIBN (4 X 50 mg, 1.22 mmol total) was added at 5-10 minute intervals. Heating at reflux was continued for a total of 2 h. The mixture was cooled to 21 °C, powdered potassium carbonate (2.0 g, anhydrous) was added, and the mixture filtered through a small plug of $MgSO_4$ onto more potassium carbonate (2.0 g). The filtrate was concentrated, water (5 mL) and dimethylsulfoxide (20 mL) were added and the mixture heated at 50 °C for 48 h. The mixture was cooled and ether (300 mL) was added. The ether layer was separated and the aqueous layer further extracted with ether (5 X 100 mL). The combined ether extracts were washed with water (5 X 40 mL), brine (2 X 40 mL), dried, filtered and concentrated to a residual oil which was used in the following step without further purification. An analytical sample was obtained by chromatography (230-400 mesh silica pretreated with 0.3 % v/v triethylamine in 30 % ethyl acetate in hexanes) of a portion of the total crude (300 mg) to afford the alcohol **147** (92 mg, 29.0 %, based on the total crude) as a colourless oil; IR (neat) 3409, 2920, 1449, 1226, 1050 cm^{-1}; ^1H NMR (200 MHz) δ 1.40 (s, 3 H), 1.10 (s, 3 H), 1.30-1.40 (m, 1 H), 1.48-1.95 (m, 3 H), 1.86 (s, 3 H), 3.82-3.97 (m, 3 H), 4.02-4.10 (m, 2 H), 5.30 (s, 1 H); ^{13}C NMR

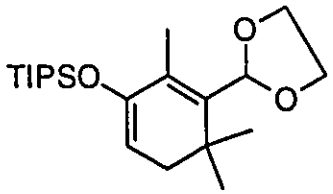
(50 MHz) δ 16.6, 27.0, 27.9, 28.3, 34.2, 35.4, 64.5, 64.6, 70.6, 102.0, 136.0, 137.7; HRMS (EI) calcd $C_{12}H_{20}O_3$ 212.1413, found 212.1389.

5-oxo-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde ethylidene acetal (**148**).



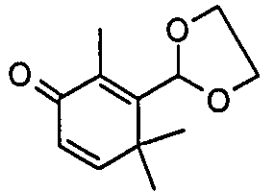
Oxalyl chloride (1.90 mL, 21.8 mmol)) was added to a stirred -78 °C solution of dimethylsulfoxide (1.70 mL, 24.0 mmol) in dichloromethane (200 mL) with noticeable evolution of gas. The mixture was stirred at -78 °C for 15 minutes and a solution of the alcohol **147** (1.23 g, 5.78 mmol) in dichloromethane (25 mL) was added over a period of 5 minutes. Stirring was continued for an additional 15 minutes and then triethylamine (13.0 mL, 93.0 mmol) was added. After 30 minutes the mixture was warmed to 21 °C and saturated $NaHCO_3$ solution (50 mL) and ether (400 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (50 mL), brine (2 X 50 mL), dried, filtered and concentrated to a residual oil which was chromatographed (230-400 mesh silica pretreated with 0.3 % v/v triethylamine in 15 % ethyl acetate/petroleum ether) to afford the ketone **148** (1.08 g, 93.6 %) as a colourless oil; IR ($CHCl_3$) 2940, 1673, 1460, 1228, 1027 cm^{-1}; ^1H NMR (200 MHz) δ 1.22 (s, 6 H), 1.29 (apparent t, 2 H), 1.32 (s, 3 H), 2.46 (apparent t, 2 H), 3.86-4.12 (m, 4 H), 5.45 (s, 1 H); ^{13}C NMR (75 MHz) δ 11.2, 26.4, 34.1, 38.2, 64.8, 101.8, 135.3, 154.7, 199.6; HRMS (EI) calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1256.

5-triisopropylsiloxy-2,2,6-trimethylcyclohexa-4,6-diene-1-carboxaldehyde ethylidene acetal (**149**).



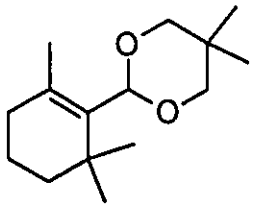
Potassium hexamethyldisilazide (3.3 mL, 0.5 M in toluene, 1.67 mmol) and HMPA were added sequentially to a stirred -78 °C solution of the ketone **148** (273 mg, 1.29 mmol) in THF (80 mL). The mixture was stirred for 15 minutes at -78 °C and then triisopropylsilyl chloride (357 uL, 1.67 mmol) was added and the mixture allowed to warm to 0 °C. Saturated $NaHCO_3$ (20 mL) was added and the THF removed under reduced pressure. The aqueous layer was extracted with ether (200 mL) and the extract was washed with saturated $NaHCO_3$ (25 mL), brine (2 X 25 mL), dried, filtered and then concentrated to give a residual oil which was chromatographed (5% ethyl acetate/hexanes) to afford the silyl-enol ether **149** (407 mg, 86.3%) as a colourless oil; IR (neat) 2947, 2867, 1655, 1465, 1221, 1069 cm^{-1}; ^1H NMR 200 MHz) δ 1.02-1.22 (m, 27 H), 1.85 (s, 3H), 2.00 (apparent d, 1H, J = 4.7 Hz), 3.82-4.08 (m, 4 H), 4.81 (apparent t, 1 H, J = 4.7 Hz), 5.59 (s, 1 H); ^{13}C NMR (75 MHz) δ 12.7, 13.0, 18.1, 26.2, 33.4, 39.4, 69.4, 100.7, 102.8, 134.1, 134.3, 149.0; HRMS (EI) calcd for $C_{21}H_{38}O_3Si$ 366.2592, found 366.2590.

2,2,6-trimethyl-3,6-cyclohexadien-5-one-1-carboxaldehyde ethylidene acetal (150).



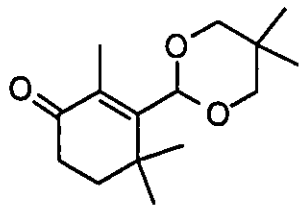
Dimethylpyrazole (276 mg, 2.88 mmol) was added in one portion to a stirred -23 °C suspension of chromium trioxide (288 mg, 2.88 mmol) in dichloromethane. The mixture was stirred at -23 °C for 20 minutes and then a solution of silyl-enol ether **149** (85.0 mg, 0.23 mmol) in dichloromethane was added. Stirring was continued at -23 °C for 1 h, potassium hydroxide solution (1.2 mL, 5 N) was added, and the mixture was warmed to 0 °C and stirred for an additional 1 h . The dichloromethane was removed under reduced pressure and water (10 mL) and ether (100 mL) were added. The organic phase was separated, washed with potassium hydroxide solution (1.2 mL, 5 N), brine (10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (10 % ethyl acetate in petroleum ether) to afford the dienone **150** (20.0 mg, 41.3 %) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6 H), 1.98 (s, 3 H), 3.90-4.13 (m, 4 H), 5.56 (s, 1 H), 6.06 (d, 1 H, J = 10 Hz), 6.69 (d, 1 H, J = 10 Hz).

2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**138**).



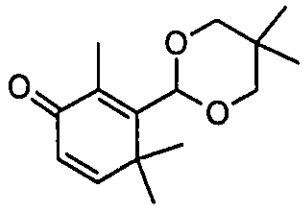
Ozone was passed into a stirred -78 °C solution of β-ionone **114** (20.0 g, 104 mmol) until all starting material was consumed (TLC). Dimethylsulfide (5-10 mL) was added and the mixture slowly warmed to 21 °C over a 12 h period. The solvent was removed under reduced pressure to afford the crude enal **141** which was protected as follows: Benzene (150 mL) was added to a mixture of the crude enal **141**, 2,2-dimethyl-1,3-propanediol (44.0 g, 422 mmol) and oxalic acid dihydrate (0.50 g) and the mixture heated at reflux for 10 h using a Dean-Stark water separator for azeotropic removal of water. After cooling to 21 °C, saturated $NaHCO_3$ solution (100 mL) was added and the mixture was stirred for 15 minutes. The organic phase was diluted with ether (500 mL), separated and washed with water (5 X 50 mL), brine (2 X 25 mL), dried, filtered and concentrated to give a residual oil which was chromatographed (100 % hexanes) to afford acetal **138** (15.8 g, 63.8 %) as a light yellow oil which could be recrystallized from hexanes; mp 38.0-40.5 °C; IR ($CHCl_3$) 3011, 2935, 1658, 1464, 1220, 1090 cm^{-1}; ^1H NMR (200 MHz) δ 0.73 (s, 3 H), 1.03 (s, 6 H), 1.27 (s, 3 H), 1.38-1.43 (m, 2 H), 1.51-1.58 (m, 2 H), 1.94-2.00 (m, 2 H), 1.96 (s, 3 H), 3.47-3.69 (m, 4 H), 4.86 (s, 1 H); ^{13}C NMR (50 MHz) δ 19.1, 20.7, 22.0, 23.9, 28.1, 30.0, 33.6, 39.5, 78.3, 101.8, 134.3, 135.2; HRMS (EI) calcd for $C_{15}H_{26}O_2$ 238.1934, found 238.1918.

5-oxo-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (139).



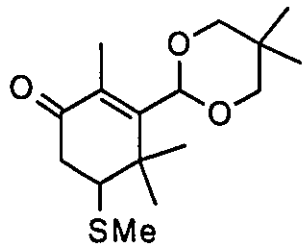
Toluene (280 mL) was added to a mixture of the acetal **138** (4.80 g, 20.0 mmol), potassium dihydrogen phosphate (8.59 g, 63.1 mmol) and selenium dioxide (4.95 g, 47.0 mmol) and the mixture stirred at reflux until all starting material was consumed (TLC/GC/MS). This typically required 2 h. After cooling saturated $NaHCO_3$ solution (100 mL) was cautiously added and the organic phase diluted with ether (250 mL). The organic phase was then separated, washed with saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried, filtered and concentrated to afford a mixture of alcohol **155** and ketone **139** as a viscous black oil which was used without purification in the next step: Magnesium sulfate (1.75 g, 14.6 mmol) and pyridinium dichromate (7.52 g, 20.0 mmol) were added sequentially to a solution of the crude alcohol **155** and ketone **139** in dichloromethane (50 mL). The mixture was stirred at 21 °C for 3.5 h and then passed through a short column of Florasil® using ether as the eluant. The eluate was concentrated under reduced pressure and chromatographed (10 % ethyl acetate/hexanes) to afford the ketone **139** (3.10 g, 61.5 %) as a light yellow oil which crystallized on standing; mp 67.5-69.5 °C; IR ($CHCl_3$) 2946, 1673, 1466, 1086, 1017 cm^{-1}; ^1H NMR (200 MHz) δ 0.75 (s, 3 H), 1.23 (s, 6 H), 1.28 (s, 3 H), 1.79 (apparent t, 2 H), 2.45 (apparent t, 2 H), 3.50 (apparent d, 2 H, J = 11.1 Hz), 3.72 (apparent d, 2 H, J = 11.1 Hz), 5.07 (s, 1 H); ^{13}C NMR (50 MHz) δ 11.9, 22.0, 23.8, 26.4, 30.2, 34.0, 35.0, 37.8, 78.1, 101.5, 133.8, 155.3, 199.8; HRMS (EI) calcd for $C_{15}H_{24}O_3$ 252.1726, found 252.1742.

2,2,6-trimethyl-3,6-cyclohexadien-5-one-1-carboxaldehyde neopentylidene acetal (156).



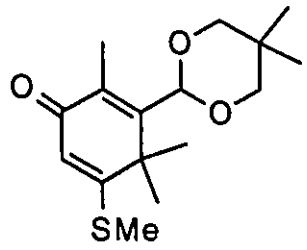
n-Butyllithium (6.0 mL, 2.5 M in hexanes, 15.0 mmol) was added dropwise to a stirred 0 °C solution of diisopropylamine (2.50 mL, 19.1 mmol) in THF (250 mL). The mixture was stirred at 0 °C for 15 minutes, cooled to -78 °C and then a solution of the ketone **139** (3.50 g, 13.9 mmol) in THF (50 mL) was added. Stirred at -78 °C for 15 minutes and then a solution of phenylselenyl bromide (3.58 g, 15.2 mmol) in THF (35 mL) was added dropwise until a slight orange colouration persisted. The mixture was warmed to 21 °C and saturated $NaHCO_3$ solution (50 mL) was added. The THF was removed under reduced pressure and methanol (400 mL) then added. Solid $NaHCO_3$ (20 g) and Oxone® (20 g) (CAUTION! CO_2 EVOLUTION!) were added sequentially and the mixture stirred at 21 °C for 12 h. Most of the methanol was then removed under reduced pressure and the aqueous extracted with ether (4 X 100 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (20 mL), brine (2 X 20 mL), dried, filtered and concentrated to a residual oil which was chromatographed (10 % ethyl acetate in hexanes) to afford the dienone **156** (1.80 g, 51.8 %, 69.5 % recycled); mp 84-86 °C; IR ($CHCl_3$) 2950, 1662, 1633, 1169, 1088 cm^{-1}; ^1H NMR (200 MHz) δ 0.76 (s, 3 H), 1.30 (s, 9 H), 2.13 (s, 3 H), 3.49-3.77 (m, 4 H), 5.17 (s, 1 H), 6.14 (d, 1 H, J = 9.9 Hz), 6.67 (d, 1 H, J = 9.9 Hz); ^{13}C NMR (75 MHz) δ 11.8, 22.1, 23.9, 25.3, 30.3, 39.2, 78.3, 101.5, 125.1, 135.0, 153.0, 157.5, 187.2; HRMS (EI) calcd for $C_{15}H_{22}O_3$ 250.1570, found 250.1564; Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; found: C, 71.79; H, 8.78.

5-oxo-3-methylthio-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**166**).



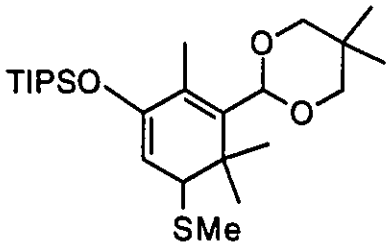
A solution of lithium methylthiolate (prepared by adding methyllithium (17.2 mL, 1.4 M in ether, 24.1 mmol) to a stirred 0 °C solution of methyldisulfide (6.00 mL, 66.6 mmol) in THF (100 mL)) was added to a stirred 0 °C solution of the dienone **156** (400 mg, 1.60 mmol) and 12-crown-4 (48 uL, 0.30 mmol) in THF (20 mL). Methanol (1.00 mL) was added and the mixture warmed to 21 °C and stirred for 12 h. Saturated NH_4Cl solution (50 mL) was then added and the THF removed under reduced pressure. The aqueous solution was extracted with ether (200 mL) and the extract was washed with brine (2 X 25 mL), dried, filtered and concentrated to give a residual oil which was chromatographed (10 % ethyl acetate/hexanes) to afford the thio-ether **166** (414, 86.7 %) as a colourless viscous oil which solidified on standing; mp 76.5-78.5 °C; IR ($CHCl_3$) 3019, 1672, 1469, 1321, 1217, 1082 cm^{-1}; ^1H NMR (200 MHz) δ 0.73 (s, 3 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 1.41 (s, 3 H), 2.00 (s, 3 H), 2.07 (s, 3 H), 2.59-2.83 (m, 3 H), 3.44-3.50 (m, 2 H), 3.67-3.73 (m, 2 H), 5.07 (s, 1 H); ^{13}C NMR (75 MHz) δ 11.9, 15.5, 20.9, 22.1, 23.9, 25.4, 30.3, 40.4, 40.7, 54.0, 78.2, 101.6, 134.0, 155.0, 198.2; HRMS (EI) calcd for $C_{16}H_{26}O_3S$ 298.1610, found 298.1605; Anal. Calcd for $C_{16}H_{26}O_3S$: C, 64.39; H, 8.78; found: C, 64.25; H, 8.47.

3-methylthio-2,2,6-trimethylcyclohexa-3,6-dien-5-one-1-carboxaldehyde neopentylidene acetal (**167**).



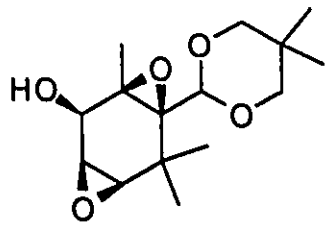
Carbon tetrachloride (50 mL) was added to a mixture of keto-sulfide **166** (204 mg, 0.685 mmol) and N-chlorosuccinimide (129 mg, 0.966 mmol) and the mixture heated at vigorous reflux for 3.5 h. The cooled mixture was filtered through a small plug of $MgSO_4$ and the eluant concentrated to a residual oil which was chromatographed (60 % ether/hexanes) to afford the thio-enol ether **167** (196 mg, 96.7 %) as a colourless oil which solidified on standing; mp 89-91.5 °C; IR ($CHCl_3$) 3016, 2961, 1647, 1620, 1348, 1216, 1170, cm^{-1}; ^1H NMR (200 MHz) δ 0.77 (s, 3 H), 1.31 (s, 3 H), 1.41 (s, 6 H), 2.20 (s, 3 H), 2.32 (s, 3 H), 3.50-3.79 (m, 4 H), 5.15 (s, 1 H), 6.06 (s, 1 H); ^{13}C NMR (75 MHz) δ 11.9, 14.3, 22.1, 24.0, 27.0, 30.3, 42.9, 78.5, 101.6, 118.2, 134.3, 153.3, 171.7, 183.6; HRMS (EI) calcd for $C_{16}H_{24}O_3S$ 296.1447, found 296.1442.

3-methylthio-5-triisopropylsiloxy-2,2,6-trimethylcyclohexa-4,6-diene-1-carboxaldehyde neopentylidene acetal (**174**).



Collidine (67 uL, 0.51 mmol) and triisopropylsilyl trifluoromethanesulfonate (90.0 uL, 0.33 mmol) were added sequentially to a stirred 0 °C solution of the keto-sulfide **166** (50.0 mg, 0.168 mmol). After 5 minutes saturated $NaHCO_3$ solution (5 mL) and ether (50 mL) were added and the organic layer separated. The organic layer was washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to give a residual oil which was chromatographed (10 % ethyl acetate/hexanes) to afford the silyl-enol ether **174** (72.0 mg, 94.5 %) as a colourless oil; IR (neat) 2947, 2867, 1649, 1596, 1465, 1238, 1090 cm^{-1}; ^1H NMR (200 MHz) δ 0.72 (s, 3 H), 1.05-1.15 (m, 21 H), 1.20 (s, 3 H), 1.25 (s, 3H), 1.43 (s, 3 H), 1.93 (s, 3 H), 1.94 (s, 3 H), 3.00 (d, 1 H, J = 6.4 Hz), 3.41-3.72 (m, 4 H), 4.89 (d, 1 H, J = 6.4 Hz), 5.17 (s, 1 H); ^{13}C NMR (75 MHz) δ 12.7, 12.8, 13.4, 18.1, 22.2, 23.9, 24.4, 28.2, 30.2, 38.1, 54.9, 78.3, 100.9, 102.2, 131.3, 135.8, 150.0; HRMS (EI) calcd for $C_{24}H_{43}O_3Si$ (M^+ - CH_3S) 407.2983, found 407.2949.

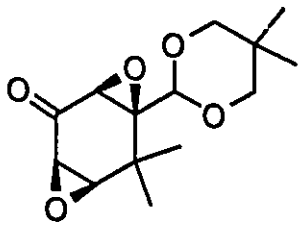
1,6,3,4-di-epoxy-2,2,6-trimethyl-5-hydroxy-cyclohexane-1-carboxaldehyde-neopentylidene acetal (**181**).



Cerium trichloride heptahydrate (373 mg, 1.00 mmol) was added to a stirred 0 °C solution of the dienone **156** (250 mg, 1.00 mmol) in methanol (2.5 mL). The mixture was stirred until all the cerium trichloride was dissolved and then sodium borohydride (38 mg, 1.00 mmol) was added. Stirring was continued at 0 °C for 0.5 h and then additional sodium borohydride (25 mg, 0.66 mmol) was added. After stirring for an additional 3 h at 0 °C, saturated NH_4Cl solution (5 mL) and water (5 mL) were added, and stirring was continued for another 0.5 h. The methanol was then removed under reduced pressure and the aqueous layer was extracted with dichloromethane (50 mL). The organic extract was washed with saturated NH_4Cl solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to afford the crude alcohol **180** which was used in the following step; $NaHCO_3$ (119 mg, 1.42 mmol) and meta-chloroperoxybenzoic acid (369 mg, 50 %, 1.07 mmol) were added sequentially to a solution of the crude alcohol **180** in dichloromethane (5 mL). The mixture was stirred at 21 °C for 0.45 h and then sodium thiosulfate (50 mg, 0.31 mmol) and water (2 mL) were added. The mixture was rapidly stirred for 1 h and then saturated $NaHCO_3$ solution (5 mL) and dichloromethane (40 mL) were added. The organic phase was separated and the aqueous further extracted with dichloromethane (3 X 40 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (2 X 5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was

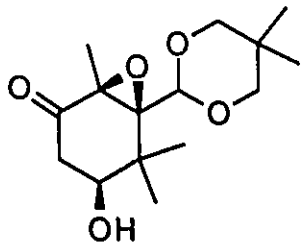
chromatographed (50 % ethyl acetate in petroleum ether) to afford the bis-epoxy-alcohol **181** (174 mg, 61.3 %) as a white solid; ^{1}H NMR (200 MHz) δ 0.71 (s, 3 H), 1.18 (s, 3 H), 1.27 (s, 3 H), 1.37 (s, 3 H), 1.57 (s, 3 H), 2.89 (d, 1 H, J = 4.0 Hz), 3.31-3.40 (m, 3 H), 3.60-3.72 (m, 2 H), 4.00 (d, 1 H, J = 3.2 Hz), 4.40 (s, 1 H).

1,6,3,4-di-epoxy-2,2,6-trimethyl-5-oxo-cyclohexane-1-carboxaldehyde-neopentylidene acetal (**182**).



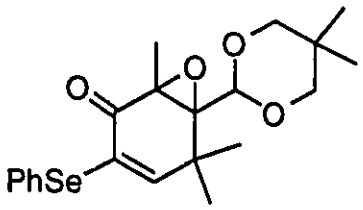
Magnesium sulfate (87 mg, 0.72 mmol) and pyridinium dichromate (480 mg, 1.30 mmol) were added sequentially to a solution of the epoxy-alcohol **181** (147 mg, 0.518 mmol) in dichloromethane (2.5 mL). The mixture was stirred at 21 °C until all starting material was consumed (TLC). This typically required 60 h. The mixture was then passed through a small column of Florasil® using ether as the eluant and the eluate concentrated to afford the epoxy-ketone **182** (118 mg, 80.8 %) as a white solid; mp 109-111.5 °C; IR ($CHCl_3$) 3022, 2965, 1704, 1468, 1219, 1027 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.71 (s, 3 H), 1.18 (s, 3 H), 1.28 (s, 3 H), 1.55 (s, 3 H), 1.56 (s, 3 H), 3.12 (d, 1 H, J = 4.1 Hz), 3.24-3.39 (m, 2 H), 3.43 (d, 1 H, J = 4.1 Hz), 3.64-3.69 (m, 1 H), 4.44 (s, 1 H); ^{13}C NMR (125 MHz) δ 13.4, 21.8, 22.0, 22.5, 23.8, 30.2, 33.9, 55.8, 64.9, 68.4, 73.9, 77.9, 78.2, 103.5, 201.4; HRMS (EI) calcd for $C_{15}H_{22}O_5$ 282.1468, found 282.1475; Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; found: C, 64.01; H, 7.95.

1,6-epoxy-3-hydroxy-2,2,6-trimethyl-5-oxo-cyclohexane-1-carboxaldehyde neopentylidene acetal (183).



Sodium borohydride (57 mg, 1.5 mmol) was added to a stirred 21 °C suspension of diphenyldiselenide (234 mg, 0.75 mmol) in ethanol (3 mL, 99 %). The mixture was stirred for 20 minutes, acetic acid (15 uL, 0.25 mmol) added and then an aliquot (0.40 mL) of this solution was added to a stirred 0 °C solution of epoxy-ketone **182** (28 mg, 0.11 mmol) in ethanol (1.0 mL, 99 %). The mixture was warmed to 21 °C and brine (1 mL) and saturated $NaHCO_3$ solution (1 mL) were added. After stirring for 15 minutes most of the ethanol was removed under reduced pressure and the aqueous residue extracted with dichloromethane (4 X 20 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (5 mL), brine (10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (100 % benzene then 100 % ethyl acetate) to afford the alcohol **183** (21.8 mg, 77.3 %) as a colourless oil; IR ($CHCl_3$) 3533, 3020, 1713, 1470, 1217, 1088 cm^{-1}; ^1H NMR (200 MHz) δ 0.69 (s, 3 H), 1.09 (s, 3 H), 1.16 (s, 3 H), 1.40 (s, 3 H), 1.62 (s, 3 H), 2.55-2.80 (m, 2 H), 3.20-3.42 (m, 4 H), 3.62-3.69 (m, 2 H), 4.69 (s, 1 H); ^{13}C NMR (75 MHz) δ 12.1, 21.8, 22.5, 23.6, 24.0, 30.2, 38.1, 43.3, 66.0, 71.9, 75.2, 77.7, 78.0, 101.4, 204.7; HRMS (EI) calcd for $C_{15}H_{24}O_5$ 284.1624, found 284.1602.

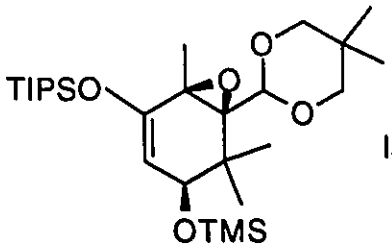
2-phenylseleno-2,2,6-trimethylcyclohexa-3,6-dien-5-one-1-carboxaldehyde neopentylidene acetal (188).



Sodium borohydride (57 mg, 1.5 mmol) was added to a stirred 21 °C suspension of diphenyldiselenide (234 mg, 0.75 mmol) in ethanol (8.0 mL, 99 %). The mixture was stirred for 20 minutes, acetic acid (15 uL, 0.25 mmol) added and then this solution was transferred portionwise (10 X 0.15 mL) at 15-20 minute intervals to a stirred 21 °C solution of the epoxy-ketone **182** (200 mg, 0.75 mmol) and diphenyldiselenide (212 mg, 0.68 mmol) in ethanol (3 mL, 99 %). The ethanol was removed under reduced pressure and the residual solid chromatographed (100 % benzene) to afford the vinyl-selenide **188** (231 mg, 77.2 %) as a crystalline yellow solid; mp 121.5-123.5 °C; IR ($CHCl_3$) 3020, 2965, 1672, 1611, 1216 cm^{-1}; ^1H NMR (500 MHz) δ 0.74 (s, 3 H), 1.21 (s, 3 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.68 (s, 3 H), 3.41-3.73 (m, 4 H), 4.62 (s, 1 H), 5.90 (s, 1 H), 7.29-7.35 (m, 3 H), 7.49-7.51 (m, 2 H); ^{13}C NMR (125 MHz) δ 12.3, 21.6, 23.5, 24.0, 24.2, 29.9, 39.9, 63.2, 68.6, 77.5, 77.8, 102.8, 126.1, 127.4, 127.9, 129.2, 134.7, 153.5, 191.7; HRMS (EI) calcd for $C_{21}H_{26}O_4Se$ 422.0996, found 422.0967; Anal. Calcd for $C_{21}H_{26}O_4Se$: C, 59.86; H, 6.22; found: C, 59.80; H, 6.40.

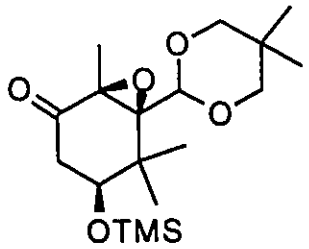
1,6-epoxy-3-trimethylsiloxy-2,2,6-trimethyl-5-oxo-cyclohexane-1-carboxaldehyde neopentylidene acetal (**191**).

Attempted preparation of



192

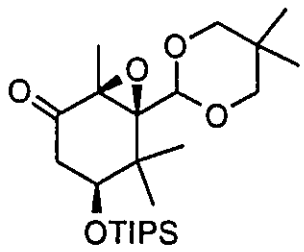
Isolation of



191

Collidine (57 uL, 0.44 mmol) and trimethylsilyl trifluoromethane sulfonate (30 uL, 0.11 mmol) were added sequentially to a stirred 21 °C solution of the hydroxy-ketone **183** (29 mg, 0.10 mmol) in dichloromethane (2 mL). The mixture was stirred for 5 minutes whereupon TLC analysis indicated all starting material was consumed. Triisopropylsilyl trifluoromethanesulfonate (30 uL, 0.11 mmol) was then added and the reaction stirred for 0.5 h. TLC analysis indicated no change had occurred so more triisopropylsilyl trifluoromethane sulfonate (30 uL, 0.11 mmol) was added and stirring continued for a further 0.5 h. Again no change could be seen by TLC. Saturated $NaHCO_3$ solution (2 mL) and ether (50 mL) were then added and the organic phase separated, washed with saturated $NaHCO_3$ (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (5 % ethyl acetate/petroleum ether) to afford silyl-ether **191** (18.4 mg, 50.6 %) as a colourless oil; IR ($CHCl_3$) 2954, 1721, 1468, 1254, 1091 cm^{-1}; ^1H NMR (200 MHz) δ 0.07 (s, 9 H), 0.71 (s, 3 H), 1.15 (s, 3 H), 1.20 (s, 3 H), 1.35 (s, 3 H), 1.52 (s, 3 H), 2.13 (dd, 1 H, J = 12.8, 3.4 Hz), 2.94 (apparent t, 1 H, J = 12.8 Hz), 3.44 (dd, 1 H, J = 12.8, 3.4 Hz), 3.34-3.71 (m, 4 H), 4.42 (s, 1 H); ^{13}C NMR (75 MHz) δ 0.2, 11.4, 16.9, 22.0, 23.3, 23.9, 30.3, 38.9, 42.5, 65.4, 70.8, 75.9, 77.9, 78.2, 104.4, 205.8; HRMS (EI) calcd for $C_{18}H_{32}O_5Si$ 356.2020, found 356.2019.

1,6-epoxy-3-triisopropylsiloxy-2,2,6-trimethyl-5-oxo-cyclohexane-1-carboxaldehyde neopentylidene acetal (**194**).

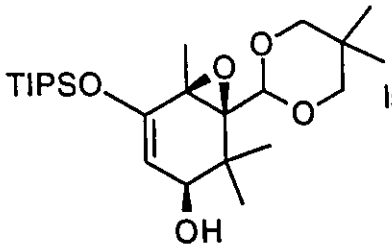


194

Collidine (40 uL, 37 mg, 0.30 mmol) and triisopropylsilyl trifluoromethanesulfonate (45 uL, 51 mg, 0.17 mmol) were added sequentially to a stirred 21 °C of the keto-alcohol **183** (20.9 mg, 0.0736 mmol) in dichloromethane (2 mL). The mixture was stirred at 21 °C for 5 minutes and then saturated $NaHCO_3$ solution (5 mL) and ether (50 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (5 % ethyl acetate/petroleum ether) to afford the silyl-ether **194** (22.4 mg, 69.2 %) as a colourless oil; IR ($CHCl_3$) 2954, 2868, 1718, 1466, 1216, 1086 cm^{-1}; ^1H NMR (500 MHz) δ 0.74 (s, 3 H), 1.03 (m, 21 H), 1.23 (s, 6 H), 1.48 (s, 3 H), 1.54 (s, 3 H), 2.27 (dd, 1 H, J = 12.8, 3.4 Hz), 3.00 (apparent t, 1 H, J = 12.8 Hz), 3.38-3.72 (m, 4 H), 3.65 (dd, 1 H, J = 12.8, 3.4 Hz), 4.45 (s, 1 H); ^{13}C NMR (125 MHz) δ 11.4, 12.8, 16.8, 18.1, 18.2, 22.1, 23.4, 23.9, 30.4, 39.6, 42.6, 65.5, 70.8, 76.5, 78.0, 78.2, 104.6, 205.8; HRMS (EI) calcd for $C_{21}H_{37}O_5Si$ (M^+ - isopropyl) 397.2411, found 397.2457.

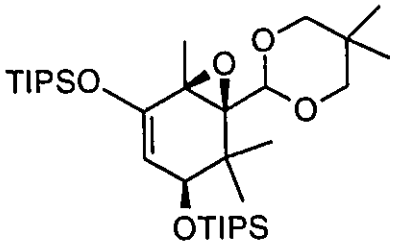
1,6-epoxy-2,2,6-trimethyl-3-triisopropylsiloxy-5-triisopropylsiloxycyclohex-4-ene-1-carboxaldehyde neopentylidene acetal (196).

Attempted preparation of



195

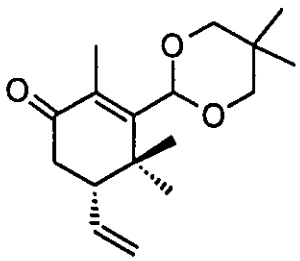
Isolation of



196

Potassium hexamethyldisilazide (410 uL, 0.5 M in toluene, 0.205 mmol) was added to a stirred -78 °C solution of the hydroxy-ketone **183** (22.0 mg, 0.077 mmol) in THF (2.0 mL). The mixture was stirred for 5 minutes at -78 °C and then triisopropylsilyl trifluoromethanesulfonate (25 uL, 28 mg, 0.10 mmol) was added. Analysis by TLC revealed an approximately 50:50 mixture of the alcohol **195** and the bis-silyl-enol-ether **196**. Additional triisopropylsilyl trifluoromethanesulfonate (25 uL, 28 mg, 0.10 mmol) was added and the mixture warmed to 0 °C. Saturated $NaHCO_3$ solution (5 mL) and ether (100 mL) were added and the organic phase separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to a residual oil which was chromatograhed (5 % ethyl acetate/petroleum ether) to afford the bis-silylated compound **196** (30.0 mg, 65.0 %) as a colourless oil; IR (neat) 2948, 2867, 1661, 1464, 1093 cm^{-1}; ^1H NMR (200 MHz) δ 0.70 (s, 3 H), 1.03-1.23 (m, 51 H), 1.61 (s, 3 H), 3.36-3.72 (m, 4 H), 4.08 (d, 1 H, J = 5.0 Hz), 4.69 (s, 1 H), 4.80 (d, 1 H, J = 5.0 Hz); ^{13}C NMR (75 MHz) δ 12.4, 12.7, 14.2, 17.7, 17.9, 18.0, 20.7, 21.8, 23.2, 23.5, 30.0, 39.5, 59.4, 68.1, 75.0, 77.5, 77.8, 102.9, 105.3, 150.3.

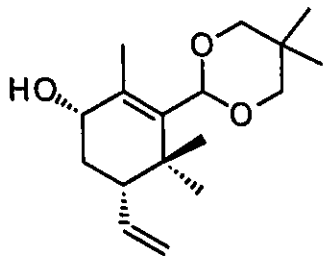
5-oxo-2,2,6-trimethyl-3-vinyl-cyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (197).



Vinylmagnesium bromide (50.0 mL, 1.0 M in THF, 50.0 mmol) was added to a stirred -10 °C solution of lithium 2-thienylcyanocuprate (200 mL, 0.25 M in THF, 50.0 mmol) in THF (275 ml). The mixture was stirred at -10 °C for 0.5 h and then cooled to -78 °C. Boron trifluoride etherate (6.0 mL, 49 mmol) was added and stirring continued for 0.5 h and then the dienone **156** (7.40 g, 29.6 mmol) in THF (40 mL) was added dropwise over a 10 minute period. Stirring was continued at -78 °C for 5.25 h and then the cooling bath was removed for 5 minutes. Saturated pH 9 NH_4Cl/NH_4OH solution (300 mL) was added and the mixture was transferred to a 2 L Erlenmeyer flask. Ether (400 mL) and additional pH 9 NH_4Cl/NH_4OH solution (300 mL) were added and the mixture rapidly stirred for 12 h while exposed to the air. The organic phase was separated and the aqueous layer further extracted with ether (3 X 500 mL). The combined organic extracts were concentrated under reduced pressure to remove all THF and then the residual oil was redissolved in ether (1000 mL). The ether solution was washed with saturated $NaHCO_3$ solution (100 mL), brine (2 X 100 mL), dried, filtered and concentrated to a residual oil which was chromatographed (10 % ethyl acetate/hexanes) to afford the vinyl ketone **197** (3.2g, 38.9 %, 52.3 % recycled); mp 85.5-87 °C; IR ($CHCl_3$) 3018, 2964, 1671, 1468, 1218, 1085 cm^{-1}; ^1H NMR (200 MHz) δ 0.75 (s, 3 H), 1.09 (s, 3 H), 1.23 (s, 3 H), 1.28 (s, 3 H), 2.04 (s, 3 H), 2.45 (m, 2 H), 2.46 (m, 1 H), 3.47-3.75 (m, 4 H), 4.99-5.34 (m, 2 H), 5.10 (s, 1 H), 5.68-5.86 (m, 1 H); ^{13}C NMR δ 11.9, 20.5, 22.1, 23.9, 25.4, 30.3, 38.1, 39.4, 49.2, 101.6, 117.2, 133.8, 137.3, 155.3,

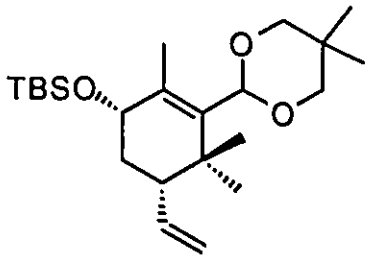
199.3; HRMS (EI) calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1870; Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41; found: C, 73.34; H, 9.26.

5-hydroxy-2,2,6-trimethyl-3-vinyl-cyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**198**).



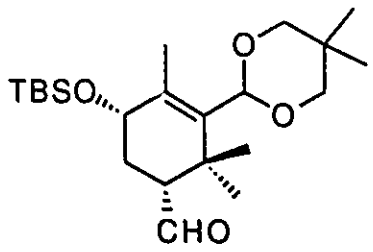
Methanol was added to a mixture of ketone **197** (252 mg, 0.906 mmol) and cerium trichloride heptahydrate (353 mg, 0.950 mmol) and the mixture stirred for 10 minutes at 21 °C. The mixture was then cooled to 0 °C and sodium borohydride (76.0 mg, 2.00 mmol) was added in one portion. After hydrogen evolution ceased saturated NH_4Cl solution (2 mL) was added, the mixture stirred for 15 minutes, and then most of the methanol was removed under reduced pressure. The aqueous residue was extracted with ether (4 X 25 mL) and the combined extracts were concentrated and placed under high vacuum to remove all the methanol. The residual oil was dissolved in ether (100 mL), dried, filtered and concentrated to afford alcohol **198** (245 mg, 96.0 %) as a single diastereomer ; mp 42-44 °C ; IR ($CHCl_3$) 3402, 2955, 1639, 1464, 1387, 1089 cm^{-1}; ^1H NMR (200 MHz) δ 0.73 (s, 3 H), 0.93 (s, 3 H), 1.05 (s, 3 H), 1.28 (s, 3 H), 1.41-1.63 (m, 1 H), 1.89-2.14 (m, 2 H), 2.09 (s, 3 H), 3.45-3.73 (m, 4 H), 4.04-4.12 (apparent br t), 4.86 (s, 1 H), 4.96-5.07 (m, 2H), 5.69-5.87 (m, 1 H); ^{13}C NMR (50 MHz) δ 15.7, 21.5, 22.0, 23.9, 25.7, 30.0, 34.2, 37.4, 47.7, 71.1, 78.3, 115.8, 137.1, 137.3, 139.0; HRMS (EI) calcd for $C_{17}H_{28}O_3$ 280.2039, found 280.2038.

5-tert-butyldimethylsiloxy-2,2,6-trimethyl-3-vinyl-cyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**199**).



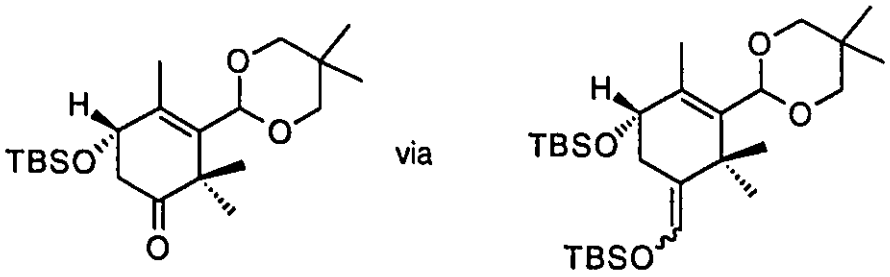
Collidine (2.00 mL, 15.2 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (2.20 mL, 9.58 mmol) were added sequentially to a stirred 0 °C solution of the alcohol **198** (2.25 g, 8.04 mmol) in dichloromethane (50 mL). The mixture was stirred for 5 minutes and then saturated $NaHCO_3$ solution (100 mL) and ether (350 mL) were added. The organic phase was separated, washed with $NaHCO_3$ (50 mL), brine (50 mL), dried, filtered and concentrated under high vacuum to remove most of the residual collidine. Chromatography of the residual oil (5 % ethyl acetate/hexanes) afforded recovered alcohol **198** (0.57 g, 25.3 %) and the desired silyl-ether **199** (2.29 g, 72.1 %) as a white solid; mp 100-102 °C; IR ($CHCl_3$) 2952, 2857, 1639, 1468, 1215, 1083 cm^{-1}; ^1H NMR (200 MHz) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.73 (s, 3 H), 0.87 (s, 9 H), 0.92 (s, 3 H), 1.04 (s, 3 H), 1.27 (s, 3 H), 1.56-1.72 (m, 3 H), 2.01 (s, 3 H), 3.49-3.73 (m, 4 H), 4.06-4.15 (m, 1H), 4.85 (s, 1 H), 4.94-5.05 (m, 2 H), 5.68-5.86 (m, 1 H); ^{13}C NMR (75 MHz) δ -4.9, -4.1, 16.4, 18.1, 21.7, 22.1, 24.1, 25.9, 30.1, 34.7, 37.4, 48.1, 71.9, 78.4, 78.5, 102.2, 115.6, 136.2, 138.4, 139.5; HRMS (EI) calcd for $C_{23}H_{42}O_3Si$ 394.2905, found 394.2887; Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73; found: C, 70.04; H, 10.73.

5-tert-butyldimethylsiloxy-3-formyl-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**200**).



Ozone was passed into a stirred -78 °C solution of vinyl compound **199** (2.28 g, 5.79 mmol) in dichloromethane (100 mL) until all the starting material was consumed (TLC). Dimethylsulfide (10 mL, large excess) was added and the mixture warmed to 21 °C over a 12 h period and then further warmed to near reflux for 24 h until all ozonide was consumed. The dichloromethane and excess dimethylsulfide were removed under reduced pressure to afford the crude aldehyde **200** (2.22 g, 96.8 %) as a light yellow viscous oil which was used directly in the following step; IR ($CHCl_3$) 2957, 2858, 1709, 1467, 1216, 1086 cm^{-1}; ^1H NMR (200 MHz) δ 0.07 (s, 3 H), 0.10 (s, 3 H), 0.74 (s, 3 H), 0.88 (s, 9 H), 1.15 (s, 3 H), 1.70–1.80 (m, 1 H), 2.02 (s, 3 H), 2.08–2.13 (m, 1 H), 2.20–2.29 (m, 1 H) 2.28 (s, 3 H), 2.29 (s, 3 H), 3.47-3.77 (m, 4 H), 4.07 (apparent t, 1 H), 4.91 (s, 1 H), 9.83 (d, 1 H, J = 3.1 Hz); ^{13}C NMR (75 MHz) δ 205.0 (CO); HRMS (EI) calcd for $C_{22}H_{40}O_4Si$ 396.2697, found 396.2705.

5-tert-butyldimethylsiloxy-2,2,6-trimethyl-3-oxo-cyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (202).

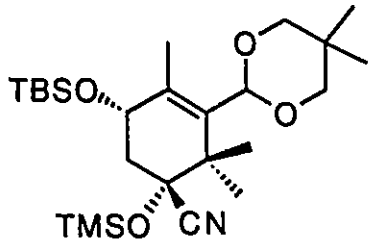


202 **201**

Collidine (580 uL, 4.39 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (500 uL, 2.18 mmol) were added sequentially to a stirred 21 °C solution of the crude aldehyde **200** (206 mg, 0.523 mmol) in dichloromethane (5 mL). The mixture was stirred at 21 °C for 8 h and then saturated $NaHCO_3$ solution (5 mL) and ether (100 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution, brine (2 X 10 mL), dried, filtered and concentrated under high vacuum (to facilitate the removal of excess collidine) to afford the crude enol ether **201**; ^1H NMR (200 MHz) δ 0.05 (s, 6 H), 0.71, (s, 3 H), 0.84 (s, 9 H), 1.10 (s, 3 H), 1.15 (s, 3 H), 1.24 (s, 3 H), 1.82-1.90 (m, 2 H), 2.02 (s, 3 H), 3.38-3.72 (m, 4 H), 4.07 (d, J = 5 Hz), 4.74 (s, 1 H), 5.40 (s, 1 H); Crude enol ether **201** was used directly in the following step: Ozone was passed through a stirred -78 °C solution of the crude enol ether **201** in dichloromethane (10 mL) until all starting material was consumed (TLC). This only required approximately 40 seconds! Dimethylsulfide (2 mL, large excess) was added and the mixture warmed to 21 °C over a 12 h period. The dichloromethane and excess dimethylsulfide were removed under reduced pressure and the residual oil chromatographed (5 % to 20 % ethyl acetate/petroleum ether) to afford the ketone **202** (33.0 mg, 16.5 %) as a white solid; mp 88-90.5 °C; IR ($CHCl_3$) 2958, 1718, 1468, 1216, 1083 cm^{-1}; ^1H NMR (200 MHz) δ 0.048 (s, 6 H), 0.74 (s, 3 H), 0.84 (s, 9 H), 1.20 (s, 3

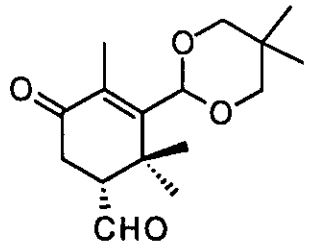
H), 1.24 (s, 3 H), 1.28 (s, 3 H), 2.10 (s, 3 H), 2.57 (dd, 1 H, J = 13.4, 6.0 Hz), 2.74 (dd, 1 H, J = 13.4, 4.6 H z), 3.45-3.74 (m, 4 H), 4.25 (apparent t, 1 H), 4.90 (s, 1 H); ^{13}C NMR (75 MHz) δ -4.8, -4.6, 17.7, 17.9, 22.2, 23.8, 24.0, 24.6, 25.7, 30.2, 45.7, 47.1, 72.1, 78.5, 101.7, 134.7, 137.4, 212.2; HRMS (EI) calcd for $C_{17}H_{29}O_4Si$ (M^+ - t-butyl) 325.1836, found 325.1806; Anal. Calcd for $C_{21}H_{38}O_4Si$: C, 65.92; H, 10.01; found: C, 66.09; H, 9.87.

5-tert-butyldimethylsiloxy-3-cyano-2,2,6-trimethyl-3-trimethylsiloxy-cyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**203**).



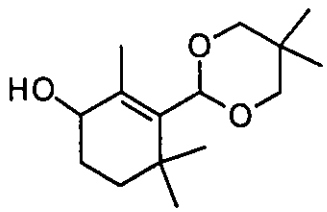
Trimethylsilyl cyanide (500 uL, 3.75 mmol) was added to mixture of the ketone **202** (23.0 mg, 0.060 mmol), 18-crown-6 (5.0 mg, 0.019 mmol) and potassium cyanide (1.0 mg, 0.015 mmol). The mixture was stirred at 21 °C for 3 h and then the excess trimethylsilylcyanide was removed under reduced pressure. Saturated $NaHCO_3$ solution (5 mL) and ether (100 mL) were added and the organic phase separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to afford the cyanohydrin **203** (27.2 mg, 93.9 %) as a pale yelow oil; ^1H NMR ($CDCl_3$) d 0.22 (s, 6 H), 0.72 (s, 3 H), 0.87 (s, 9 H), 1.08 (s, 3 H), 1.25 (s, 3 H), 1.33 (s, 3 H), 1.95 (s, 3 H), 1.95-2.00 (m, 1 H), 2.18-2.29 (m, 1 H), 3.38-3.3.72 (m, 4 H), 4.30-4.40 (m, 1 H), 4.90 (s, 1 H); HRMS (EI) calcd $C_{25}H_{47}O_4NSi$ 481.3046, found 481.3030.

3-formyl-5-oxo-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**211**).



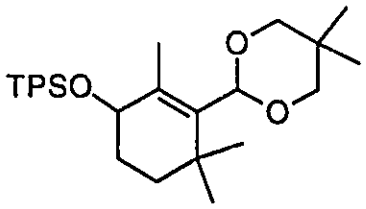
Ozone was passed into a stirred -78 °C solution of the vinyl ketone **197** (107 mg, 0.385 mmol) in dichloromethane (10 mL) until all starting material was consumed (TLC). Dimethylsulfide (2 mL, large excess) was added and the mixture warmed to 21 °C over a 12 h period. The mixture was kept at 21 °C for 36-48 h to decompose the ozonide completely. Slight warming could also be used to accelerate this process. The dichloromethane and excess dimethylsulfide were removed under reduced pressure and the residual oil chromatographed (15 % ethyl acetate/petroleum ether) to afford the keto-aldehyde **211** (60.0 mg, 55.7 %) as a pale yellow solid; mp 67-69 °C; IR ($CHCl_3$) 2958, 2720, 1720, 1676, 1223, 1086 cm^{-1}; ^1H NMR (200 MHz) δ 0.76 (s, 3 H), 1.27 (s, 3 H), 1.34 (s, 3 H), 1.51 (s, 3 H), 1.99 (s, 3 H), 2.53-2.78 (m, 3 H), 3.46-3.75 (m, 4 H), 5.12 (s, 1 H), 9.87 (d, 1 H, J = 1.6 Hz); ^{13}C NMR (75 MHz) δ 11.8, 21.9, 22.1, 23.9, 26.5, 30.3, 33.7, 37.6, 56.5, 78.2, 101.3, 134.4, 153.4, 197.4, 202.2; HRMS (EI) calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1672.

5-hydroxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (155).



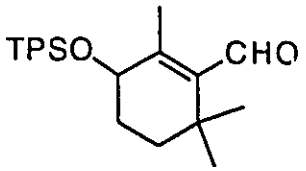
Methanol (50 mL) was added to a mixture of the ketone **139** (0.91 g, 3.6 mmol) and cerium trichloride heptahydrate (1.41 g, 3.78 mmol) and the mixture stirred for 10 minutes at 21 °C. The mixture was then cooled to 0 °C and sodium borohydride (304 mg, 8.04 mmol) added in one portion. After hydrogen evolution ceased saturated NH_4Cl solution (10 mL) was added and then most of the methanol was removed under reduced pressure. The aqueous residue was extracted with ether (4 X 100 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (2 X 25 mL), brine (2 X 25 mL), dried, filtered and then concentrated to afford the alcohol **155** (660 mg, 72.0 %) as a colourless oil which solidified on standing; mp 71.5-74 °C ; IR ($CHCl_3$) 3431, 2948, 1670, 1463, 1219, 1087 cm^{-1}; ^1H NMR (200 MHz) δ 0.63 (s, 3 H), 0.91 (s, 3 H), 0.97 (s, 3 H), 1.16 (s, 3 H), 1.20-1.31 (m, 1 H), 1.41-1.62 (m, 2 H), 1.63-1.82 (m, 1 H), 1.97 (s, 3 H), 3.33-3.62 (m, 4 H), 3.78 (apparent t, 1 H), 4.76 (s, 1 H); ^{13}C NMR (75 MHz) δ 17.1, 21.9, 23.7, 26.7, 27.6, 27.9, 29.9, 33.9, 34.5, 70.2, 78.1, 101.4, 135.7, 137.6; HRMS (EI) calcd for $C_{15}H_{26}O_3$ 254.1883, found 254.1875. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30; found: C, 70.87; H, 10.15.

5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (**247**).



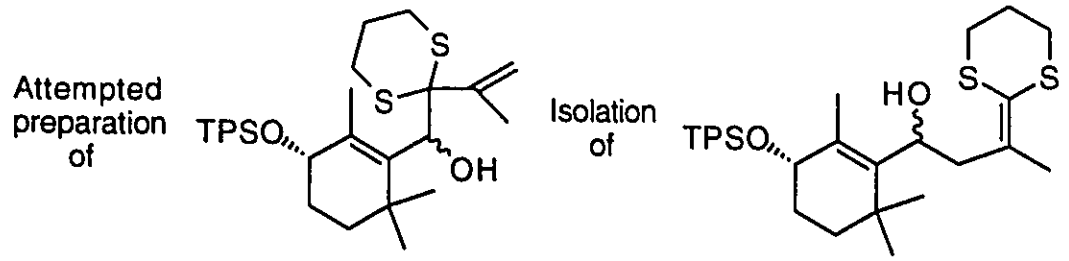
tert-Butylchlorodiphenylsilane (2.55 g, 9.28 mmol) and triethylamine (1.62 mL, 11.6 mmol) were added sequentially to a stirred solution of the alcohol **155** (660 mg, 2.60 mmol) and 4-dimethylaminopyridine (20.0 mg, 0.164 mmol) in dichloromethane (10 mL). The mixture was heated at reflux for 72 h, cooled to 21 °C and then saturated $NaHCO_3$ solution (10 mL) and ether (100 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (10 % ethyl acetate in hexanes) to afford the silyl-ether **247** (58.6 %) as a colourless oil; ^1H NMR (200 MHz); 0.74 (s, 3 H), 0.96 (s, 3 H), 1.05 (s, 9 H), 1.08 (s, 3 H), 1.28 (s, 3 H), 1.42-1.55 (m, 4 H), 2.03 (s, 3 H), 3.41-3.78 (m, 4 H), 4.00 (m, 1 H), 4.83 (s, 1 H), 7.32-7.45 (m, 6 H), 7.56-7.75 (m, 4 H).

5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde (248).



A 3:1 mixture of THF : HCl (4 %) (40 mL) was added to the acetal **247** (750 mg, 1.52 mmol) and the mixture stirred at 21 °C for 3 h. Saturated $NaHCO_3$ solution (20 mL) was added cautiously and the THF removed under reduced pressure. The aqueous was extracted with ether (3 X 100 mL) and the combined extracts were washed with saturated $NaHCO_3$ solution (20 mL), brine (2 X 20 mL), dried, filtered and concentrated to afford the aldehyde **248** (602 mg, 97.2 %) as a colourless oil; IR (neat) 2942, 2858, 1678, 1427, 1109, 1085 cm^{-1}; ^1H NMR (200 MHz) δ 0.98 (s, 9 H), 1.00 (s, 3 H), 1.13 (s, 3 H), 1.12-1.18 (m, 1 H), 1.41-1.62 (m, 3 H), 1.98 (s, 3 H), 3.91-4.00 (m, 1 H), 7.25-7.41 (m, 6 H), 7.58-7.68 (m, 4 H), 10.02 (s, 1 H); ^{13}C NMR (50 MHz) δ 16.8, 20.1, 23.3, 27.6, 28.1, 29.7, 34.1, 36.8, 73.5, 128.1, 128.3, 130.3, 130.4, 134.0, 134.7, 136.6, 141.6, 155.1, 194.2; HRMS (EI) calcd for $C_{26}H_{34}O_2Si$ 406.2330, found 406.2316.

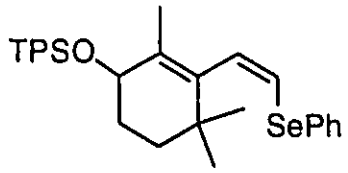
2-(5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)-4-hydroxy-2-methyl-butanoic acid dithiopropylidene ketene acetal (252).



251 **252**

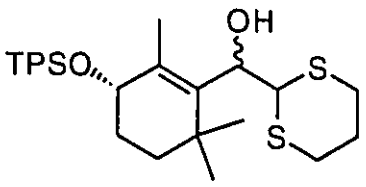
n-Butyllithium (100 uL, 2.5 M in hexanes, 0.25 mmol) was added to a stirred -10 °C solution of dithiane **260** (37 mg, 0.25 mmol) in THF (1 mL). The mixture was stirred at -10 °C for 0.5 h and then HMPA (220 uL) was added with the original bright amber colour becoming even more intense. A solution of the aldehyde **248** (53 mg, 0.13 mmol) in THF (1 mL) was then added and the mixture stirred for an additional 15 minutes. Saturated $NaHCO_3$ solution (5 mL) and ether (100 mL) were then added and the organic phase was separated, washed with water (5 X 5 mL), saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was shown to be an approximately 17:1 mixture of γ-alkylated product (consisting of an approximately 1.5:1 mixture of isomers) **252** and α-alkylated product **251**. Major isomer (γ-isomer); ^{1}HNMR (200 MHz) δ 0.93 (s, 3 H), 0.95 (s, 12 H), 1.10-1.70 (m, 4 H), 1.82 (s, 3 H), 1.92 (s, 3 H), 2.01-2.06 (m, 2 H), 2.33 (dd, 1 H, J = 14, 4 Hz), 2.65-2.85 (m, 4 H), 3.14 (dd, 1 H), J = 14, 11 Hz), 3.81-3.86 (m, 1 H), 4.24-4.34 (m, 1 H), 7.21-7.34 (m, 6 H), 7.56-7.65 (m, 4 H).

2-(5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)-1Z]-1-phenylseleno-ethene (**259**).



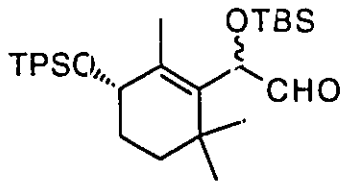
n-Butyllithium (190 uL, 1.6 M in hexanes, 0.30 mmol) was added to a stirred 0 °C solution of diisopropylamine (50.0 uL, 0.36 mmol) in THF (2 mL). The mixture was cooled to -30 °C and (phenylselenomethyl)trimethylsilane (64 uL, 0.31 mmol) was then added. Stirring was continued at -30 °C for 0.5 h and then a solution of the aldehyde **248** (40.0 mg, 0.10 mmol) in THF (1.0 mL) was added. After stirring for an additional 10 minutes saturated $NaHCO_3$ solution (5 mL) and ether (50 mL) were added. The mixture was warmed to 21 °C and the organic phase separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was shown to be cis-vinyl selenide **259**; ^1H NMR ($CDCl_3$) d 0.88 (s, 3 H), 0.98 (s, 9 H), 1.00 (s, 3 H), 1.96 (s, 3 H), 3.95-4.02 (m, 1 H), 6.42 (d, 1 H, J = 9.5 Hz), 6.65 (d, 1 H, J = 9.5 Hz).

2-(5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)-2-hydroxy-acetaldehyde propylidene dithioacetal (**261**).



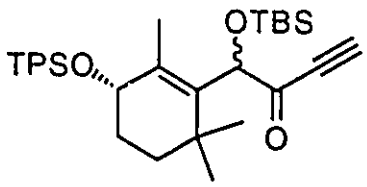
n-Butyllithium (100 uL, 2.5 M in hexanes, 0.25 mmol) was added to a stirred -20°C solution of 1,3-dithiane **260** (30 mg, 0.25 mmol) in THF (2.5 mL). The mixture was stirred at -20 °C for 1 h and then a solution of the aldehyde **248** (50 mg, 0.12 mmol) in THF (1 mL) was added. The mixture was stirred for 5 minutes and then saturated $NaHCO_3$ solution (5 mL) and ether (50 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to afford the hydroxy-dithiane **261** (63 mg, 97.2 %) as a 2:1 mixture of diastereomers. Major diastereomer; ^1H NMR (200 MHz) δ 0.99 (s, 3 H), 1.02 (s, 9 H), 1.15 (3 H), 1.21-1.32 (m, 1 H), 1.55-1.64 (m, 3 H), 1.78 (s, 3 H), 2.00-2.13 (m, 2 H), 2.70-2.96 (m, 4 H), 3.94-4.02 (m, 1 H), 4.32 (d, 1 H, J = 11.2 Hz), 4.59 (d, 1 H, J = 11.2 Hz), 7.32-7.43 (m, 6 H), 7.66-7.77 (m, 4 H).

2-(5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)-2-tert-butyldimethylsiloxy-acetaldehyde (262).



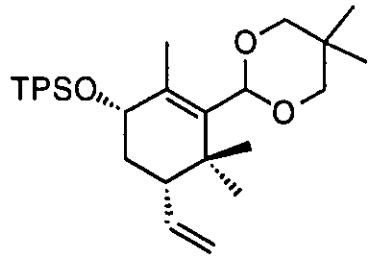
Collidine (150 uL, 1.14 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (150 uL, 0.65 mmol) were added sequentially to a stirred 21 °C of the crude alcohol **261** (63 mg, 0.12 mmol) in dichloromethane (2 mL). The mixture was stirred for 3 h and then saturated $NaHCO_3$ solution (5 mL) and ether (50 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was passed through a small plug of silica (5 % ethyl acetate in petroleum ether) to afford the crude silyl ether (52 mg, 67.8 %) as a colourless oil which was used without further purification in the following step: Freshly recrystallized N-bromosuccinimide (75 mg, 0.42 mmol) was added to a stirred 21 °C solution of the crude silyl-ether (52 mg, 0.080 mmol) in acetone:acetonitrile:water (4 mL, 5:4:1). The solution quickly turned reddish and then faded to yellow. Saturated $NaHCO_3$ solution (5 mL) and ether were then added and the organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was passed through a small plug of silica (5 % ethyl acetate in petroleum ether) to afford the aldehyde **262** (22 mg, 85.6 %) (2:1 mixture of diastereomers) as a colourless oil; Major diastereomer; ^1H NMR (200 MHz) δ 0.04 (s, 3 H), 1.12 (s, 3 H), 0.90 (s, 9 H), 0.98 (s, 3 H), 1.06 (s, 9 H), 1.11 (s, 3 H), 1.21-1.31 (m, 1 H), 1.52-1.75 (m, 3 H), 1.65 (s, 3 H), 3.80-3.90 (m, 1 H), 4.65 (s, 1 H), 7.33-7.45 (m, 6 H), 7.66-7.73 (m, 4 H), 9.53 (s, 1 H).

4-(5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)-4-tert-butyldimethylsiloxy-but-1-yn-3-one (**264**).



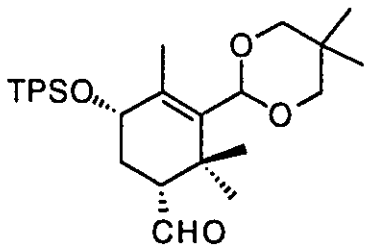
Ethynylmagnesium chloride (400 uL, 0.5 M in THF, 0.20 mmol) was added to a stirred 0 °C solution of the aldehyde **262** (22 mg, 0.04 mmol) in THF (2 mL). The mixture was warmed to 21 °C and stirred for 15 minutes. Saturated $NaHCO_3$ solution (5 mL) and ether were then added and the organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to afford the alcohol **263** (28.9 mg) as a residual oil which was used without further purification in the following step: Dichloromethane (2 mL) was added to a mixture of the alcohol **263** (21.6 mg, 0.038 mmol) and Dess-Martin periodinane (250 mg, 0.59 mmol) and the mixture heated at reflux for 42 h. The mixture was then cooled to 21 °C and ether (40 mL), saturated $NaHCO_3$ solution (40 mL) and sodium thiosulfate (1.1 g, 7.0 mmol) were added and the mixture rapidly stirred for 1 h. The organic phase was separated, washed with sodium thiosulfate solution (15 mL, 20 %) combined with saturated $NaHCO_3$ solution (15 mL), brine (20 mL), dried, filtered and concentrated to afford the ketone **264** (23.0 mg, 98 %) as a residual oil; ^1H NMR (200 MHz) δ 0.05 (s, 3 H), 1.18 (s, 3 H), 0.92 (s, 9 H), 0.98 (s, 3 H), 1.06 (s, 9 H), 1.11 (s, 3 H), 1.21-1.32 (m, 1 H), 1.54-1.73 (m, 3 H), 1.65 (s, 3 H), 3.97-4.05 (m, 1 H), 4.80 (s, 1 H), 7.34-7.47 (m, 6 H), 7.65-7.75 (m, 4 H).

5-tert-butyldiphenylsiloxy-2,2,6-trimethyl-3-vinyl-cyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (224).



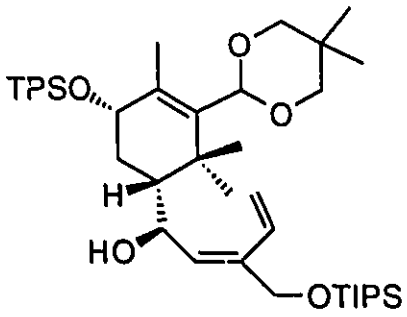
Dichloromethane (10 mL) was added to a mixture of the alcohol **198** (1.20 g, 4.28 mmol), tert-butyldiphenylchlorosilane (6.30 g, 22.1 mmol), 4-dimethylaminopyridine (1.00 g, 8.20 mmol) and triethylamine (4.20 mL, 30.0 mmol) and the mixture heated at reflux for 24 h. Saturated $NaHCO_3$ solution (100 mL) and ether (100 mL) were added and the mixture stirred for 12 h to hydrolyze the excess chlorosilane. The organic phase was separated, washed with saturated $NaHCO_3$ solution (10 mL), brine (2 X 10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (10 % ether/hexanes) to afford the silyl-ether **224** (1.52 g, 68.5 %, 83.8 % recycled) as a white solid; mp 119.0-122.0 °C; IR ($CHCl_3$) 3017, 2954, 2859, 1639, 1426, 1216 cm^{-1}; ^1H NMR (200 MHz) δ 0.74 (s, 3 H), 0.92 (s, 3 H), 0.98 (s, 3 H), 1.05 (s, 9 H), 1.26 (s, 3 H), 1.57-1.85 (m, 3 H), 2.07 (s, 3 H), 3.44-3.78 (m, 4 H), 4.11-4.19 (m, 1 H), 4.73-4.96 (m, 2 H), 4.85 (s, 1 H), 5.59-5.77 (m, 1 H), 7.30-7.46 (m, 6 H), 7.51-7.76 (m, 4 H); ^{13}C NMR (75 MHz) δ 16.6, 19.2, 21.6, 21.9, 23.8, 25.4, 26.9, 29.9, 33.9, 37.0, 47.4, 72.9, 78.1, 78.3, 101.9, 115.2, 127.0, 127.3, 129.1, 129.3, 133.3, 134.4, 135.9, 136.0, 138.2, 138.9; HRMS (EI) calcd for $C_{33}H_{46}O_3Si$ 518.3218, found 518.3199; Anal. Calcd for $C_{33}H_{46}O_3Si$: C, 76.40; H, 8.94; found: C, 76.44; H, 8.88.

5-tert-butyldiphenylsiloxy-3-formyl-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (225).



Ozone was passed into a stirred -78 °C solution of the vinyl compound **224** (1.51 g, 2.92 mmol) in dichloromethane until all starting material was consumed (TLC). Dimethylsulfide (10 mL, large excess) was added and the mixture was warmed to 21 °C over a 2 h period and then further warmed to about 40 °C for a 12h period. The dichloromethane and excess dimethylsulfide were removed under reduced pressure and the residual oil chromatographed (100 % hexanes to 5 % ethyl acetate in hexanes) to afford the aldehydes **225/226** (971 mg, 63.9 %) as a white foam containing approximately 85 % of the major diastereomer **225**; IR ($CHCl_3$) 3018, 2955, 2858, 2754, 1718, 1675, 1216 cm^{-1}; ^1H NMR (200 MHz) δ 0.75 (s, 3 H), 1.05 (s, 9 H), 1.14 (s, 3 H), 1.19 (s, 3 H), 1.27 (s, 3 H), 1.80-1.98 (m, 3 H), 1.98 (s, 3 H), 3.44-3.77 (m, 4 H), 4.07 (apparent t, 1 H), 4.87 (s, 1 H), 7.31-7.46 (m, 6 H), 7.64-7.74 (m, 4 H), 9.63 (d, 1 H, J = 3.1 Hz); ^{13}C NMR (75 MHz) δ 17.1, 19.4, 22.1, 23.0, 24.0, 26.7, 27.0, 29.3, 30.1, 36.3, 55.7, 71.9, 78.4, 78.5, 101.5, 127.4, 127.5, 127.6, 127.8, 129.6, 129.7, 133.2, 136.0, 136.1, 138.5, 204.4; HRMS (EI) calcd for $C_{32}H_{44}O_4Si$ 520.3010, found 520.3028.

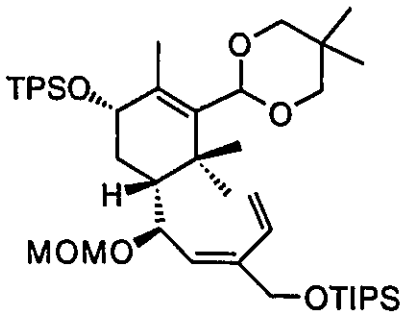
3-(1-hydroxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (238).



A solution of the vinyl bromide **233** (577 mg, 1.81 mmol) in THF (3.0 mL) was added to a stirred -78 °C solution of sec-butyllithium (3.20 mL, 1.21 M in hexanes, 3.86 mmol) in THF (10 mL) over a period of two minutes. The mixture was stirred at -78 °C for 20 minutes and then a solution of the aldehyde **225/226** (664 mg, 1.27 mmol) in THF (3.5 mL) was added over a period of 1 minute. The reaction mixture was stirred at -78 °C for 10 minutes and then warmed to 21 °C and stirred a further 10 minutes. Water was added, the organic phase separated and the aqueous phase further extracted ether (3 X 30 mL). The combined organic extracts were dried, filtered and concentrated to a residual oil which was chromatographed (3:1 petroleum ether:ether) to afford the alcohols **238/239** as an approximately 5:1 mixture of diastereomers). Major isomer ; IR ($CHCl_3$) 3607, 3017, 1466, 1427, 1216, 1065 cm^{-1}; ^1H NMR (200 MHz) δ 0.72, (s, 3 H), 0.99-1.08 (m, 36 H), 1.25-1.30 (m, 1 H), 1.26 (s, 3 H), 1.61-1.69 (m, 1 H), 1.95-2.01 (m, 1 H), 2.04 (s, 3 H), 3.43-3.75 (m, 4 H), 4.13 (dd, 1 H, J = 10.2, 5.0 Hz), 4.30 (s, 2 H), 4.72 (m, 1 H), 4.78 (s, 1 H), 5.05 (d, 1 H, J = 11.3 Hz), 5.15 (d, 1 H, J = 17.5 Hz), 5.50 (d, 1 H, J = 10.0 Hz), 6.70 (dd, 1 H, J = 17.5, 11.3 Hz), 7.31-7.40 (m, 6 H), 7.67-7.72 (m, 4 H); ^{13}C NMR (50 MHz) δ 11.9, 14.1, 16.9, 18.0, 19.5, 21.0, 22.2, 22.4, 24.1, 26.3, 27.2, 30.1, 38.0, 48.8, 60.4, 63.5, 65.8, 73.8, 77.2, 78.5, 78.6, 102.1, 115.2, 127.3, 127.4, 129.5,

130.4, 130.8, 133.9, 134.6, 135.0, 136.1, 136.2, 138.6; HRMS (EI) calcd for $C_{46}H_{70}O_4Si_2$ (M+ - H_2O) 742.4718, found 742.4764.

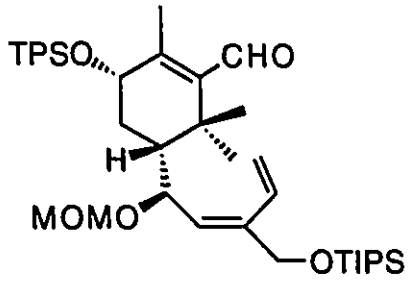
3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde neopentylidene acetal (240).



N,N-diisopropylethylamine (1.25 mL, 7.19 mmol) and chloromethyl methyl ether (460 uL, 6.06 mmol) were added sequentially to a stirred 21 °C solution of the alcohols **238/239** (497 mg, 0.654 mmol, 5:1 mixture of diastereomers) and 4-dimethylaminopyridine (50.0 mg, 0.409 mmol) in dichloromethane (3 mL). The mixture was stirred for 14 h and then saturated $NaHCO_3$ solution (10 mL) and ether (100 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (100 % hexanes to 20 % ether in hexanes) to afford the major diastereomer **240** (354 mg, 65.6 %) as a colourless oil; IR ($CHCl_3$) 2915, 1465, 1427, 1216, 1067 cm^{-1}; ^1H NMR (500 MHz) δ 0.72 (s, 3 H), 0.99-1.08 (m, 36 H), 1.25-1.30 (m, 1 H), 1.26 (s, 3 H), 1.60-1.68 (m, 1 H), 1.95-2.01 (m, 1 H), 2.05 (s, 3 H), 3.15 (s, 3 H), 3.42-3.74 (m, 4 H), 4.12 (dd, 1 H, J = 10.3, 5.1 Hz), 4.26 (d, 1 H, J = 6.7 Hz), 4.31 (s, 2 H), 4.46 (d, 1 H, J = 6.7 Hz), 4.50 (dd, 1 H, J = 9.8, 4.0 Hz), 4.77 (s, 1 H), 5.06 (d, 1 H, J = 11.4 Hz), 5.15 (d, 1 H, 17.7 Hz), 5.49 (d, 1 H, J = 9.8 Hz), 6.58 (dd, 1 H, J = 17.7 Hz,

11.4 Hz), 7.31-7.40 (m, 6 H), 7.67-7.72 (m, 4 H); ^{13}C NMR (125 MHz) δ 12.0, 16.8, 17.9, 18.0, 19.5, 21.8, 22.2, 24.1, 26.7, 27.2, 30.0, 30.2, 38.1, 48.5, 56.0, 63.2, 69.8, 74.0, 78.5, 78.6, 93.5, 102.3, 114.7, 127.2, 127.5, 128.2, 129.3, 129.4, 130.9, 133.9, 134.8, 136.2, 136.3, 136.7, 139.1.

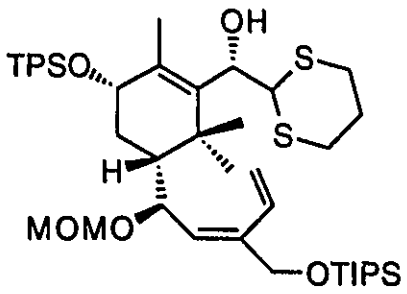
3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-ene-1-carboxaldehyde (**265**).



HCl (300 uL, 4 %) was added to a stirred 21 °C solution of acetal **240** (30.0 mg, 0.037 mmol) in THF (1 mL). The mixture was stirred at 21 °C for 3 h and then saturated $NaHCO_3$ solution (2 mL) was added. Stirring was continued for 10 minutes and then the THF was removed under reduced pressure. The aqueous layer was extracted with ether and the extract was washed with water (5 X 10 mL), saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to afford the aldehyde **265** (26.8 mg, 99.9 %) as a colourless oil; IR (neat) 2913, 2758, 1677, 1464, 1076 cm^{-1}; ^1H NMR (200 MHz) δ 1.01-1.08 (m, 30 H), 1.19 (s, 3 H), 1.22 (s, 3 H), 1.67-1.74 (m, 1 H), 2.04-2.12 (m, 1H), 2.07 (s, 3 H), 3.17 (s, 3 H), 4.20 (apparent t, 1 H), 4.27 (d, 1H, J = 6.7 Hz), 4.33 (s, 2 H), 4.49 (d, 1 H, J = 6.7 Hz), 4.57 (dd, 1 H, J = 9.8, 3.7 Hz), 5.09 (d, 1 H, J = 11.3 Hz), 5.17 (d, 1 H, J = 18.1 Hz), 5.52 (d, 1 H, J = 9.8 Hz), 6.60 (dd, 1 H, J = 18.1, 11.3 Hz), 7.32-7.44 (m, 6 H), 7.67-7.75 (m, 4 H), 10.06 (s, 1 H); ^{13}C NMR (75 MHz) δ 11.9, 15.0, 17.9, 19.5, 21.1, 26.7, 27.0, 27.1, 29.3, 37.5, 48.3, 56.0, 62.9, 68.9, 74.3, 93.4,

114.8, 127.4, 127.5, 127.6, 129.6, 129.7, 130.6, 133.4, 134.1, 136.0, 136.8, 141.2, 155.6, 193.9.

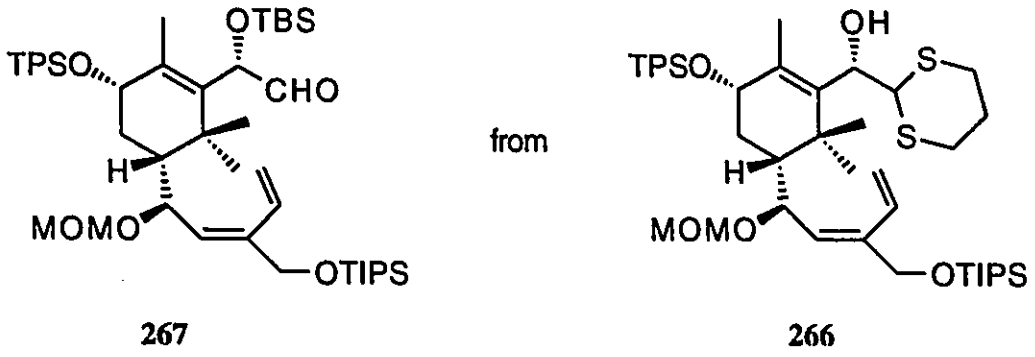
2-[-3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)]-2-hydroxy-acetaldehyde propylidene dithioacetal (**266**).



n-Butyllithium (180 uL, 2.5 M in hexanes, 0.45 mmol) was added to a stirred -20°C of 1,3-dithiane **260** (54.0 mg, 0.45 mmol) in THF (3.5 mL) and the mixture stirred at -20 °C for 1h. The mixture was then cooled to -78 °C and a solution of the aldehyde **265** (154 mg, 0.214 mmol) in THF (1 mL) added and stirring continued for 1 h. The reaction was warmed to -20 °C and then saturated $NaHCO_3$ solution (10 mL) was added. The THF was removed under reduced pressure and the aqueous residue extracted with ether (100 mL). The ether extract was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (100 % hexanes to 20 % ether in hexanes) to afford starting aldehyde **265** (37.3 mg, 24.2 %) and the alcohol **266** (87.7 mg, 48.8 %) as a single diastereomer; IR ($CHCl_3$) 3451, 2947, 2865, 1593, 1464, 1379, 1216, 1107 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (s, 3 H), 1.00-1.03 (m, 30 H), 1.05 (s, 3 H), 1.10-1.30 (m, 1 H), 1.48-1.63 (m, 1 H), 1.82 (s, 3 H), 1.91-2.09 (m, 3 H), 2.74-2.79 (m, 2 H), 2.87-2.91 (m, 2 H), 3.13 (s, 3 H), 4.16 (dd, 1 H, J = 10.3, 5.7 Hz), 4.22 (d, 1 H, J = 10.2 Hz), 4.23 (d, 1 H, J = 6.7 Hz), 4.32

(s, 2 H), 4.48 (d, 1 H, J = 6.7 Hz), 4.49 (dd, 1 H, J = 10.0, 4.0 Hz), 4.52 (d, 1 H, J = 10.2 Hz), 5.07 (d, 1 H, J = 11.4 Hz), 5.15 (d, 1 H, J = 17.9 Hz), 5.53 (d, 1 H, J = 10.0 Hz), 6.58 (dd, 1 H, J = 17.9, 11.4 Hz), 7.29-7.40 (m, 6 H), 7.68-7.73 (m, 4 H); ^{13}C NMR (125 MHz) δ 12.0, 17.7, 18.0, 19.7, 22.4, 22.6, 25.4, 27.1, 27.2, 28.3, 29.4, 29.7, 29.9, 39.5, 48.5, 51.6, 56.0, 63.1, 69.8, 71.1, 74.9, 93.4, 114.7, 127.3, 127.5, 128.1, 129.3, 129.4, 130.9, 134.4, 134.9, 136.0, 136.1, 136.7, 138.1, 138.6.

2-[3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)]-2-tert-butyldimethylsiloxy-acetaldehyde (**267**).

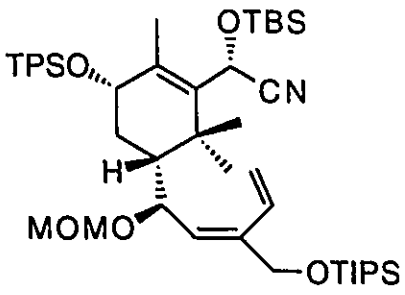


267 **266**

Collidine (100 uL, 0.75 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (100 uL, 0.44 mmol) were added sequentially to a stirred 0 °C solution of the alcohol **266** (76.8 mg, 0.0916 mmol) in dichloromethane (2 mL). The mixture was stirred at 0 °C for 10 h and then saturated $NaHCO_3$ solution (5 mL) and ether (100 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was chromatographed (100 % hexanes to 5 % ether in hexanes) to afford the desired silylated alcohol (37.5 mg, 43.0 %) and an impurity in a 1:2 ratio; ^1H NMR (500 MHz) δ 0.11 (s, 3 H), 0.21 (s, 3 H), 0.81-1.04 (m, 39 H), 1.25-1.30 (m, 1 H), 1.33 (s, 3 H), 1.41

(s, 3 H), 1.60-1.68 (m, 1 H), 1.62 (s, 3 H), 1.91-2.09 (m, 3 H), 2.74-2.91 (m, 4 H), 3.28 (s, 3 H), 4.16-4.22 (m, 2 H), 4.30 (s, 2 H), 4.32-4.50 (m, 5 H), 4.81 (d, 1 H, J = 8.0 Hz), 5.02 (d, 1 H, J = 11.4 Hz), 5.12 (d, 1 H, J = 17.0 Hz), 5.57 (d, 1 H, 10.0 Hz), 6.53-6.61 (m, 1 H), 7.29-7.40 (m, 6 H), 7.68-7.73 (m, 4 H). This material was converted directly to the aldehyde: Collidine (60 uL, 0.45 mmol) was added to a stirred 0 °C solution of the crude dithiane (35 mg, 0.037 mmol) in 80 % (v/v) aqueous acetonitrile (1.5 mL) and acetone (2.5 mL). N-bromosuccinimide (60 mg, 0.33 mmol) was then added in one portion with the solution turning yellow. The mixture was stirred for 5 minutes at 0 °C and then saturated $NaHCO_3$ solution (5 mL), sodium thiosulfate solution (5 mL, 20 %) and ether (100 mL) were added. The organic layer was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (5 % ether in hexanes) to afford the aldehyde **267** (7.0 mg, 22.1 %) as a colourless oil; ; IR (neat) 2912, 2720, 1737, 1592, 1465, 1080 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.02 (s, 3 H), 0.13 (s, 3 H), 0.82-1.04 (m, 45 H), 1.31-1.39 (m, 1 H), 1.65-1.70 (m, 1 H), 1.69 (s, 3 H), 1.98-2.08 (m, 1 H), 3.15 (s, 3 H), 4.15 (dd, 1 H, J = 9.9, 6.6 Hz), 4.27 (d, 1 H, J = 6.6 Hz), 4.33 (s, 3 H), 4.48 (d, 1 H, J = 6.6 Hz), 4.52 (dd, 1 H, J = 10.4, 4.4 Hz), 4.60 (s, 1 H), 5.09 (d, 1 H, J = 11.6 Hz), 5.18 (d, 1 H, J = 18.3 Hz), 5.53 (d, 1 H, J = 10.4 Hz), 6.59 (dd, 1 H, J = 18.3, 11.6 Hz), 7.35-7.42 (m, 6 H), 7.66-7.73 (m, 4 H), 9.57 (s, 1 H); ^{13}C NMR (75 MHz) δ -4.7, -4.3, 11.9, 16.5, 18.0, 18.3, 19.5, 22.3, 25.7, 25.9, 27.0, 27.1, 29.9, 38.8, 48.4, 56.0, 63.1, 69.7, 73.8, 77.4, 93.4, 114.8, 127.3, 127.5, 128.2, 129.3, 129.5, 130.7, 134.1, 134.8, 136.0, 136.4, 136.7, 201.2.

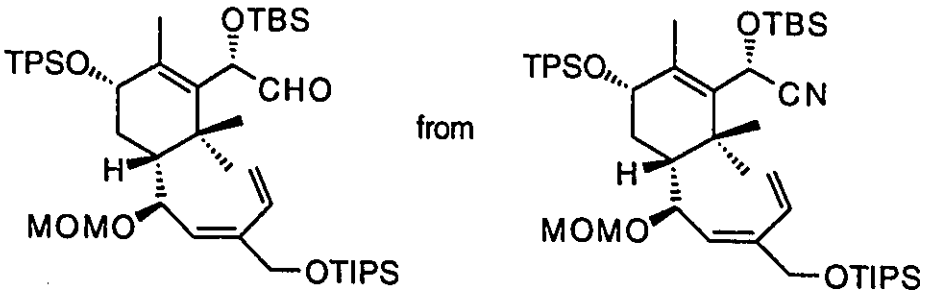
2-[3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)]-2-tert-butyldimethylsiloxy-acetonitrile (**268**).



Dichloromethane (2 mL) was added to a mixture of aldehyde **265** (212 mg, 0.295 mmol), 18-crown-6 (30.0 mg, 0.12 mmol), potassium cyanide (27.0 mg, 0.42 mmol) and tert-butyldimethylsilyl cyanide (87.0 mg, 0.62 mmol). The mixture was stirred at 21 °C for 7 h and then saturated $NaHCO_3$ solution (5 mL) and ether (100 mL) were added. The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 10 mL), dried, filtered and concentrated to give the crude product as a 6:1 mixture of diastereomers. Chromatography (100 % hexanes to 5% ether in hexanes) afforded the major diastereomer **268** (170 mg, 67.0 %) as a crystalline solid along with an oil (28 mg, 11 %) which is tentatively assigned as the minor diastereomer **269**. Major diastereomer **268**; mp 132.0-134.5 °C; IR ($CHCl_3$) 3019, 2947, 2863, 1467, 1216, 1109 cm^{-1}; ^1H NMR (200 MHz) δ 0.13 (s, 3 H), 0.26 (s, 3 H), 0.88 (s, 9 H), 0.82-1.06 (m, 36 H), 1.30-1.38 (m, 1 H), 1.58-1.64 (m, 1 H), 1.92-2.05 (m, 1 H), 1.98 (s, 3 H), 3.12 (s, 3 H), 4.11 (dd, 1 H, J = 9.7, 5.4 Hz), 4.25 (d, 1 H, J = 6.7 Hz), 4.32 (s, 2 H), 4.45 (d, 1 H, J = 6.7 Hz), 4.47 (dd, 1 H, J = 10.0, 4.2 Hz), 4.95 (s, 1 H), 5.09 (d, 1 H, J = 11.6 Hz), 5.17 (d, 1 H, J = 18.3 Hz), 5.49 (d, 1 H, J = 10.0 Hz), 6.56 (dd, 1 H, J = 18.3, 11.6 Hz), 7.32-7.43 (m, 6 H), 7.67-7.76 (m, 4 H); ^{13}C NMR (75 MHz) δ -5.2, -5.1, 11.9, 16.5, 18.0, 19.5, 22.3, 25.4, 25.5, 26.3, 27.1, 29.8, 38.9, 48.1, 56.0, 58.9, 63.0, 69.4, 73.6, 93.3, 115.0, 120.0, 127.3, 127.5,

127.9, 129.4, 129.5, 130.6, 133.9, 134.7, 135.7, 135.9, 136.0, 136.1, 136.9, 141.0; Anal. Calcd for $C_{50}H_{82}O_6Si$: C, 69.79; H, 9.49; found: C, 69.96; H, 9.23.

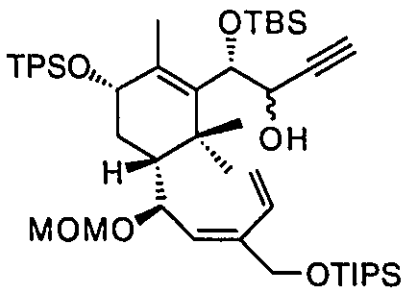
2-[3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)]-2-tert-butyldimethylsiloxy-acetaldehyde (267).



267 **268**

Diisobutylaluminum hydride (70.0 uL, 1.0 M in toluene, 0.070 mmol) was added to a stirred -78 °C solution of the nitrile **268** (40.0 mg, 0.047 mmol) in dichloromethane (2 mL). The mixture was stirred at -78 °C for 0.5 h and then warmed to 21 °C and held at 21 °C for 5 minutes. Saturated NH_4Cl solution (5 mL) was added and the mixture rapidly stirred for 3 h. The aqueous layer was extracted with ether (100 mL) and the extract was washed with saturated NH_4Cl solution (5 mL), brine (10 mL), dried, filtered and concentrated to afford the crude aldehyde **267** (34.0 mg, 84.7 %) as a colourless oil used directly in the next step. All spectral data was identical to the material obtained from the dithiane route (*vide supra*).

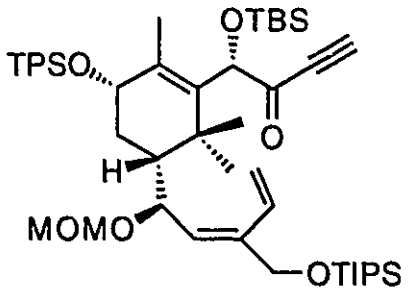
4-[3-(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)]-4-tert-butyldimethylsiloxy-but-1-yn-3-ol (**270/271**).



Ethynylmagnesium chloride (850 uL, 0.5 M in THF, 0.42 mmol) was added to a stirred 0 °C solution of the aldehyde **267** (170.0 mg, 0.197 mmol) in THF (10.0 mL). The mixture was stirred at 0 °C for 0.5 h and then saturated NH_4Cl solution (10 mL) was added. The THF was removed under reduced pressure and the aqueous layer extracted with ether (100 mL). The ether extract was washed with saturated NH_4Cl solution (5 mL), saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to give a residual oil consisting of a 2:1 mixture of diastereomeric alcohols **270/271**. Chromatography (100 % hexanes to 20 % ether in hexanes) afforded the minor diastereomer **271** (31.0 mg, 15.2 %) followed by the major diastereomer **270** (51.0 mg, 25.0 %), both as colourless oils; Major diastereomer; IR (neat) 3309, 2944, 2862, 1593, 1465, 1105, 1039 cm^{-1}; ^1H NMR (200 MHz) δ 0.02 (s, 3 H), 0.16 (s, 3 H), 0.84 (s, 9 H), 0.97 (s, 3 H), 1.01-1.07 (m, 33 H), 1.25-1.30 (m, 1 H), 1.50-1.62 (m, 1 H), 1.96 (s, 3 H), 2.01-2.10 (m, 1 H), 2.43 (d, 1 H, J = 2.0 Hz), 3.14 (s, 3 H), 4.12 (dd, 1 H, J = 10.0, 5.7 Hz), 4.24 (d, 1 H, J = 6.8 Hz), 4.33 (s, 2 H), 4.38 (d, 1 H, J = 8.2 Hz), 4.46 (d, 1 H, J = 6.8 Hz), 4.46-4.54 (m, 2 H), 5.10 (d, 1 H, J = 11.7 Hz), 5.18 (d, 1 H, J = 18.4 Hz), 5.49 (d, 1 H, J = 11.2 Hz), 6.59 (dd, 1 H, J = 18.4, 11.7 Hz), 7.34-7.43 (m, 6 H), 7.66-7.76 (m, 4 H); ^{13}C NMR (75 MHz) δ -4.2, -3.8, 11.9, 16.7, 18.0, 18.4, 19.5, 22.3, 25.9, 26.2, 27.2,

27.9, 30.0, 39.4, 48.3, 56.0, 63.1, 66.0, 69.5, 73.3, 74.6, 74.8, 85.0, 93.3, 114.9, 127.3, 127.5, 128.0, 129.4, 129.5, 130.7, 134.0, 134.7, 136.0, 136.8, 138.6, 139.3.

4-[(1-methoxymethyloxy-3-triisopropylsiloxymethyl-(Z)-2,4-pentadienyl)-5-tert-butyldiphenylsiloxy-2,2,6-trimethylcyclohex-6-en-1-yl)]-4-tert-butyldimethylsiloxy-but-1-yn-3-one (**272**).



Dichloromethane (6 mL) was added to a mixture of the acetylenic alcohols **270/271** and Dess-Martin periodinane (597 mg, 1.40 mmol). The mixture was heated at reflux for 16 h and then cooled to 21 °C. Saturated $NaHCO_3$ solution (25 mL), sodium thiosulfate (1.0 g) and ether (100 mL) were added and the mixture rapidly stirred for 0.5 h. The organic phase was separated and washed with saturated $NaHCO_3$ solution (5 mL), brine (2 X 5 mL), dried, filtered and concentrated to a residual oil which was chromatographed (100 % hexanes to 10 % ether in hexanes) to afford the ketone **272** (63.9 mg, 80.1 %) as a colourless oil; IR ($CHCl_3$) 3299, 3020, 2948, 2862, 1690, 1467, 1216 cm^{-1}; ^1H NMR (500 MHz) δ 0.02 (br s, 3 H), 0.15 (s, 3 H), 0.89 (s, 9 H), 1.01-1.07 (m, 45 H), 1.30-1.35 (m, 1 H), 1.58-1.64 (m, 1 H), 1.62 (br s, 3 H), 1.99-2.04 (m, 1 H), 3.17 (s, 3 H), 3.23 (d, 1 H, J = 2.4 Hz), 4.15-4.18 (m, 1 H), 4.27 (d, 1 H, J = 6.7 Hz), 4.32 (s, 2 H), 4.47 (d, 1 H, J = 6.7 Hz), 4.55 (m, 1 H), 4.58 (br s, 1 H), 5.08 (d, 1 H, J = 11.3 Hz), 5.17 (d, 1 H, J = 17.7 Hz), 5.53 (d, 1 H, J = 9.8 Hz), 6.57 (dd, 1 H, J = 17.7, 11.3 Hz), 7.30-7.42 (m, 6 H), 7.67-7.71 (m, 4 H); ^{13}C NMR (125 MHz) δ -4.6, -4.0, 12.0,

14.1, 15.3, 18.0, 18.5, 19.6, 22.3, 25.9, 26.0, 27.1, 29.8, 31.6, 39.1, 56.0, 63.1, 65.8, 69.6, 73.9, 80.6, 81.1, 93.5, 114.8, 127.3, 127.5, 127.6, 128.2, 129.3, 129.5, 130.8, 134.3, 134.9, 136.0, 136.1, 136.8, 165.8, (CO δ 188.3 (230 K)); Anal. Calcd for $C_{52}H_{82}O_6Si_3$: C, 70.38; H, 9.31; found: C, 70.51; H, 9.34.

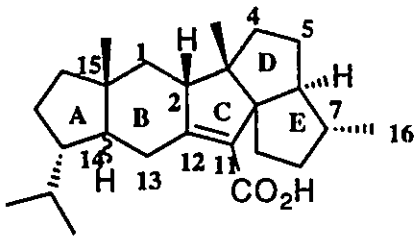
PART B

SYNTHETIC STUDIES TOWARDS THE PREPARATION OF RETIGERANIC ACID A

CHAPTER 5

5. 1. INTRODUCTION.

Retigeranic acid A **284** and B **285** were first isolated as a mixture by Sheshadri in 1965 from the lichens of the *Lobaria retigera* group found in the Western Himalayas.[91] Successful structural elucidation of this compound was not completed until 1972 when the group of Shibata crystallized the *p*-bromoanilide derivative and obtained retigeranic acid A **284**.[92] Unknown at the time however was that they had fractionally crystallized the minor component of a 2:1 mixture of retigeranic acids. Thus the designation retigeranic acid A since it was the first component isolated. Not until 1986 was it discovered that retigeranic acid consisted of two components and all syntheses were therefore only of retigeranic A **284**.[93] Retigeranic acid A **284** is a structurally unique member of the rare class of sesterterpenes possessing a high degree of stereochemical information as well as associated *trans*-hydrindane and triquinane subunits. It has therefore been the subject of much synthetic interest.



284 = α-H = Retigeranic Acid A

285 = β-H = Retigeranic Acid B

Figure 5

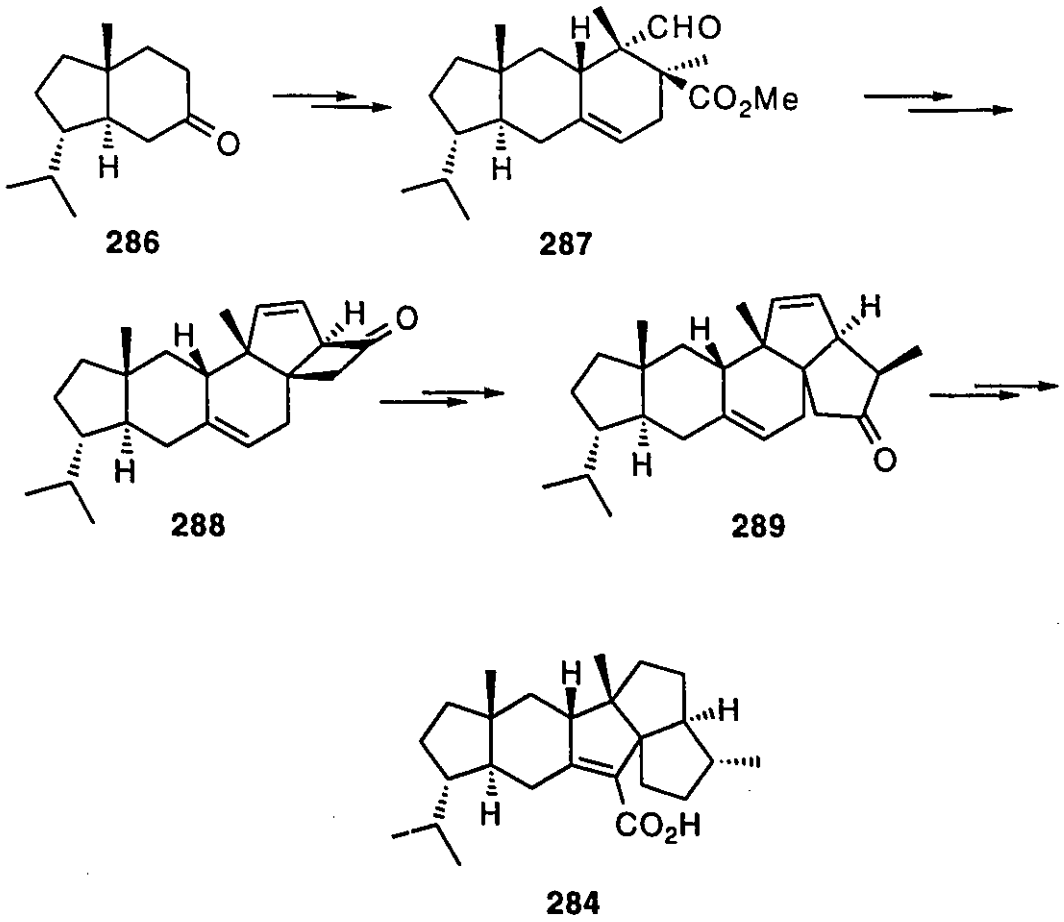
To date the biological activity of retigeranic acid A **284** has not been evaluated although members of the *genus Lobaria* are considered to be important in perfumery and tanning and have been used as vegetable drugs for the cure of eczema and lung disorders.[94]

5. 2. PREVIOUS TOTAL SYNTHESES.

The total synthesis of retigeranic acid A **284** has been imaginatively addressed by the groups of Corey[95], Paquette[96], Hudlicky[97] and Wender[98].

5. 2. 1. Corey's Approach.

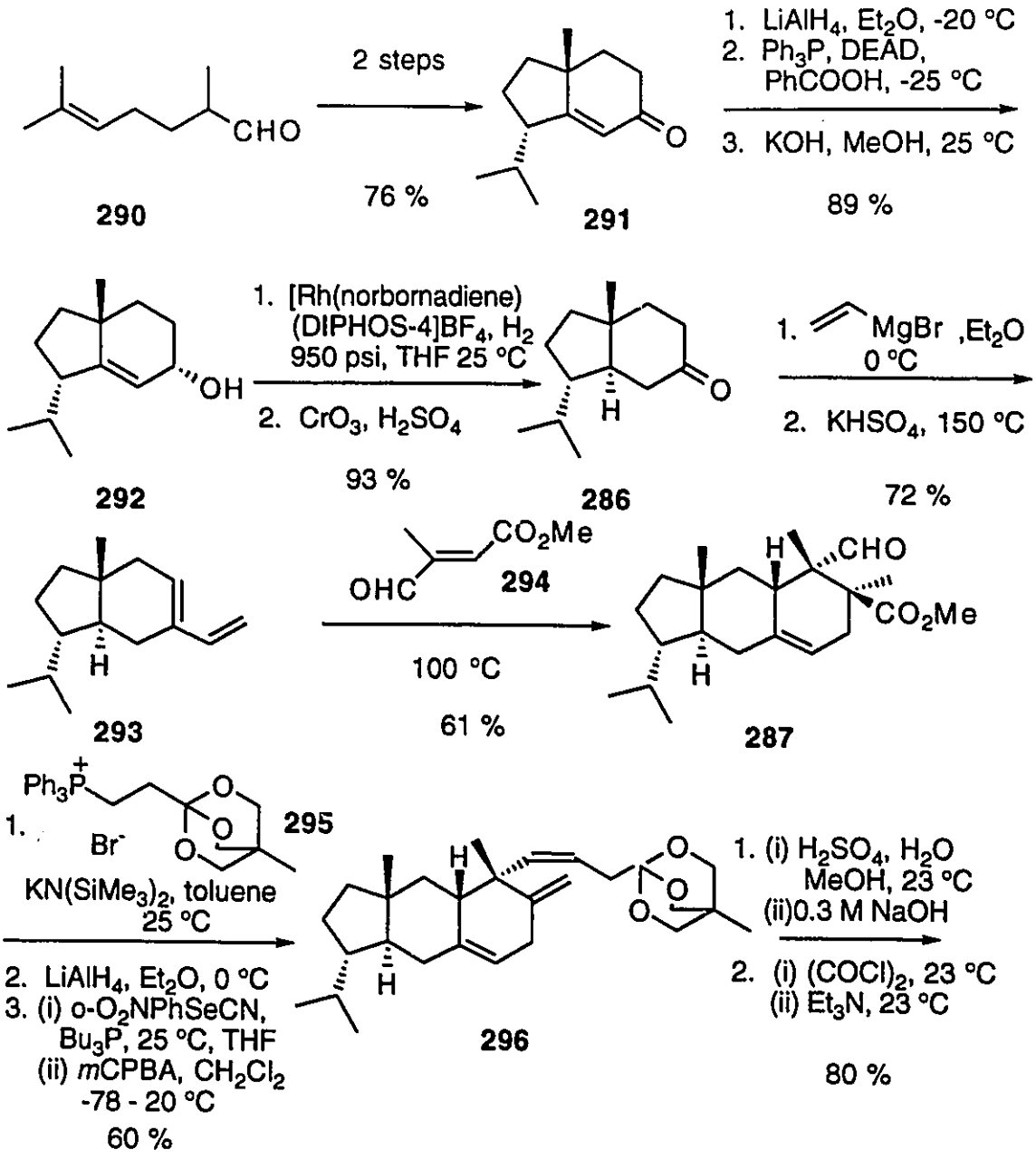
Corey was first to succeed in the preparation of **284** in racemic form.[95] The general strategy he used was to start with the hydrindanone **286** and then form the C-ring compound **287** using a Diels-Alder reaction (Scheme 101). Further elaboration simultaneously generated the D and E rings using an intramolecular 2+2 ketene addition to form cyclobutanone **288**. Expansion of the cyclobutanone E ring followed by a ring contraction of the six membered C ring completed the synthesis of **284**.

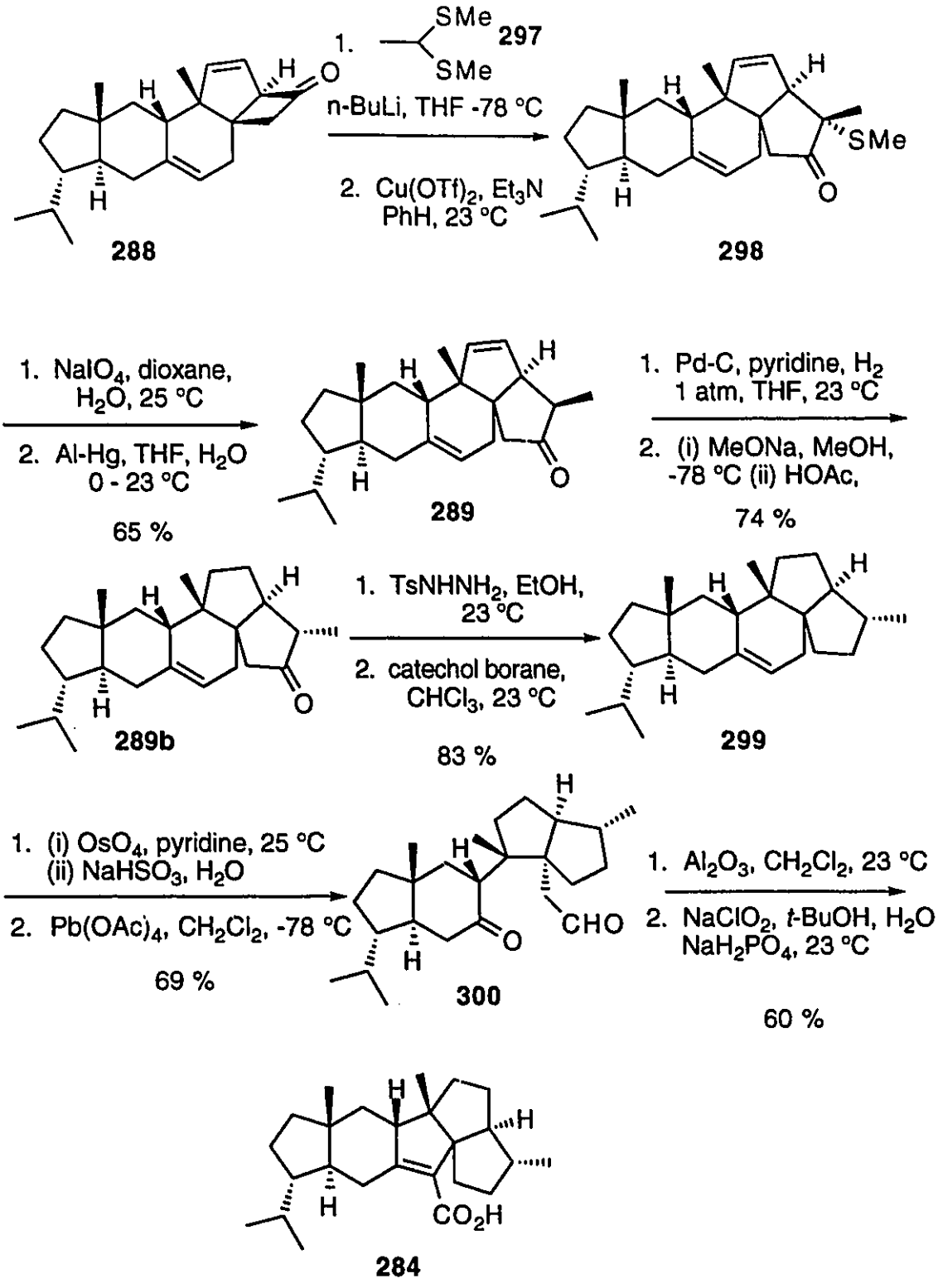


Retigeranic Acid A

Scheme 101

The starting point for the synthesis was the hydrindenone **291** which was prepared in two steps from the 2,6-dimethyl-5-heptenal **290** (Scheme 102).


2 steps
76 %
1. LiAlH4, Et2O, -20 °C
2. Ph3P, DEAD, PhCOOH, -25 °C
3. KOH, MeOH, 25 °C
89 %
1. [Rh(norbornadiene)(DIPHOS-4]BF4, H2 950 psi, THF 25 °C
2. CrO3, H2SO4
93 %
1. MgBr ,Et2O 0 °C
2. KHSO4, 150 °C
72 %
100 °C
61 %
KN(SiMe3)2, toluene 25 °C
2. LiAlH4, Et2O, 0 °C
3. (i) o-O2NPhSeCN, Bu3P, 25 °C, THF
(ii) mCPBA, CH2Cl2 -78 - 20 °C
60 %
1. (i) H2SO4, H2O MeOH, 23 °C
(ii)0.3 M NaOH
2. (i) (COCl)2, 23 °C
(ii) Et3N, 23 °C
80 %
290
291
292
286
293
294
287
295
296


1.
SMe
SMe
297
n-BuLi, THF -78 °C
2. Cu(OTf)2, Et3N
PhH, 23 °C
288
298
1. NaIO4, dioxane,
H2O, 25 °C
2. Al-Hg, THF, H2O
0 - 23 °C
65 %
289
1. Pd-C, pyridine, H2
1 atm, THF, 23 °C
2. (i) MeONa, MeOH,
-78 °C (ii) HOAc,
74 %
289b
1. TsNHNH2, EtOH,
23 °C
2. catechol borane,
CHCl3, 23 °C
83 %
299
1. (i) OsO4, pyridine, 25 °C
(ii) NaHSO3, H2O
2. Pb(OAc)4, CH2Cl2, -78 °C
69 %
300
1. Al2O3, CH2Cl2, 23 °C
2. NaClO2, t-BuOH, H2O
NaH2PO4, 23 °C
60 %
284

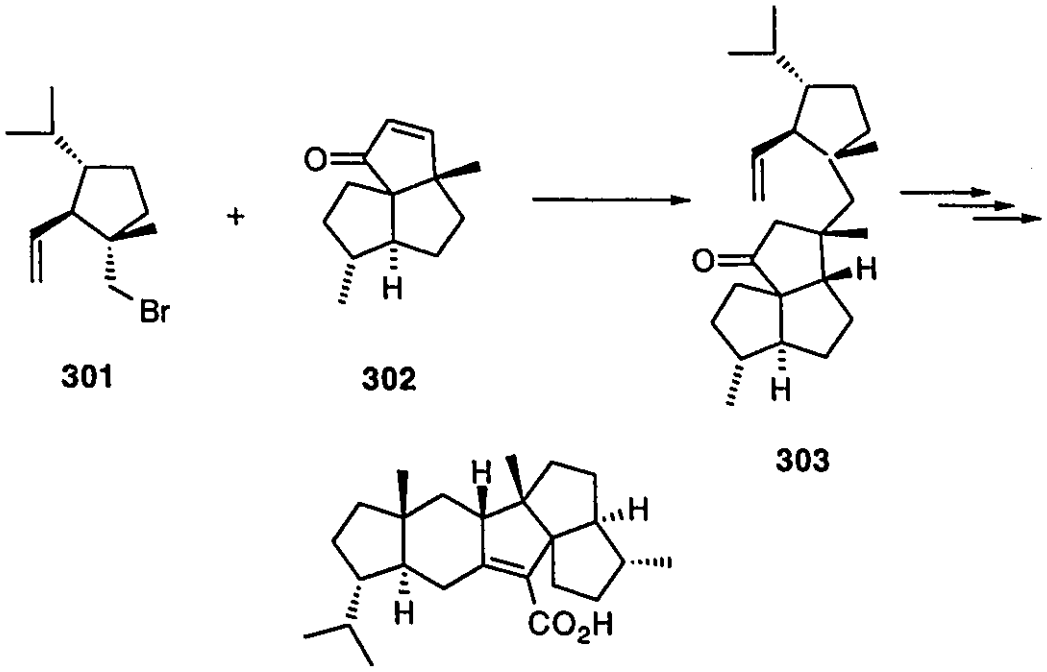
Scheme 102

To form the desired trans relationship between rings A and B the ketone **291** was first reduced and then subjected to a Mitsunobu inversion so that the resulting, stereospecifically generated alcohol **292** could serve as a handle for a directed hydrogenation. The resulting saturated alcohol was then oxidized to the ketone **286**. A Diels-Alder reaction was used to form the C-ring and therefore the diene **293** was prepared by vinylmagnesium bromide addition to the ketone **286** and subsequent dehydration. Cycloaddition using 3-formyl-*cis*-crotonate **294** as the dienophile gave the adduct **287** which was subjected to Wittig olefination conditions using the phosphonium salt **295**. Reduction of the ester and formation of the exocyclic methylene compound **296** from the alcohol set the stage for formation of rings D and E. Thus deprotection of **296** and formation of the ketene from the resulting acid was followed by a 2+2 cycloaddition which simultaneously formed the cyclopentene D-ring and cyclobutanone E ring of compound **288**. Ring E was expanded by addition of the lithio-anion of acetaldehyde dithioacetal **297** followed by a copper catalyzed rearrangement to the sulfide **298**. Oxidation to the sulfone and treatment with sodium amalgam served to form the desulfurized product **289**. The D ring double bond was then selectively hydrogenated and the C16 methyl group was epimerized under basic catalysis to afford the sulfide **289b**. Reduction of the carbonyl to a methylene group was followed by dihydroxylation of the C-ring double bond with subsequent oxidative cleavage to form the keto-aldehyde **300**. Finally, aldol condensation of **300** gave the α,β-unsaturated aldehyde which was oxidized to afford racemic retigeranic acid A **284**.

5.2.2. Paquette's Approach.

Paquette took a more convergent approach to the synthesis of optically active natural retigeranic acid A **284** by choosing to join the A-ring compound **301** to the

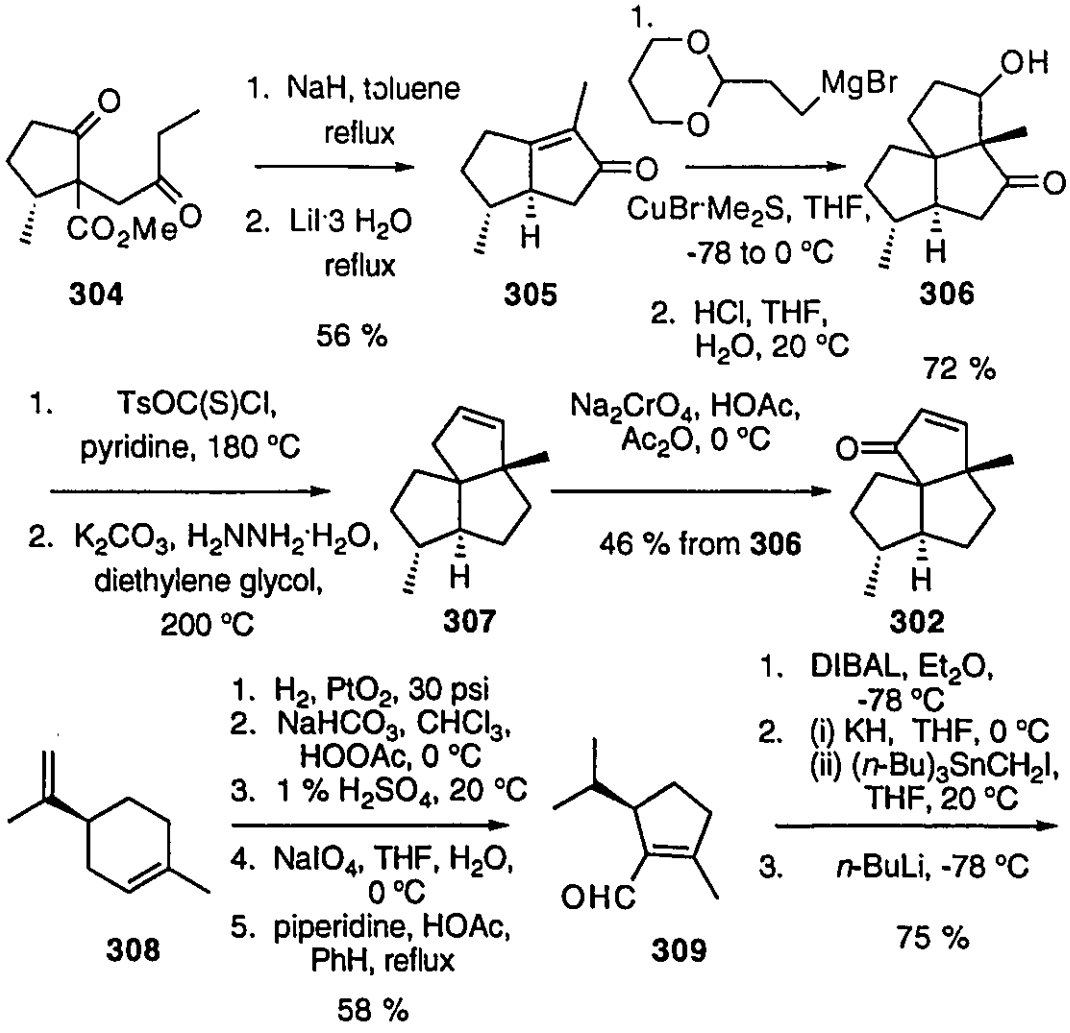
triquinane unit **302** (Scheme 103).[96] The B-ring was then formed followed by further elaboration to retigeranic acid A **284**.

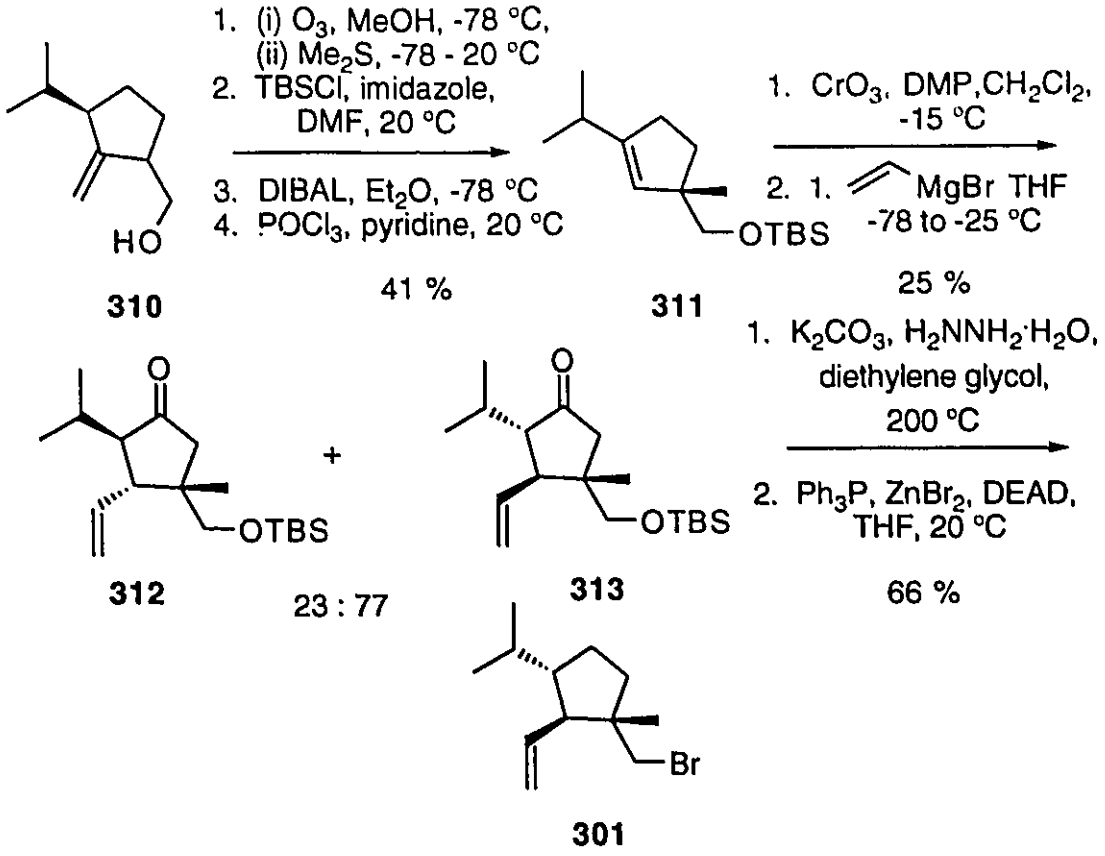


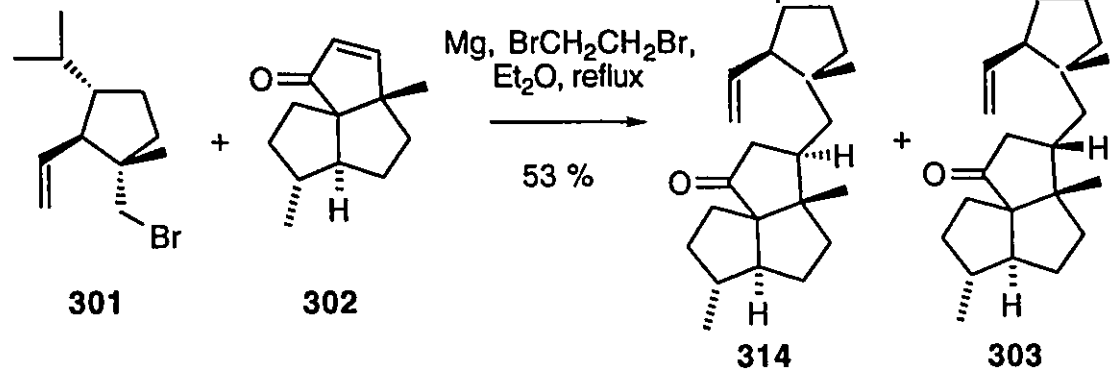
301 **302** **303** **284**

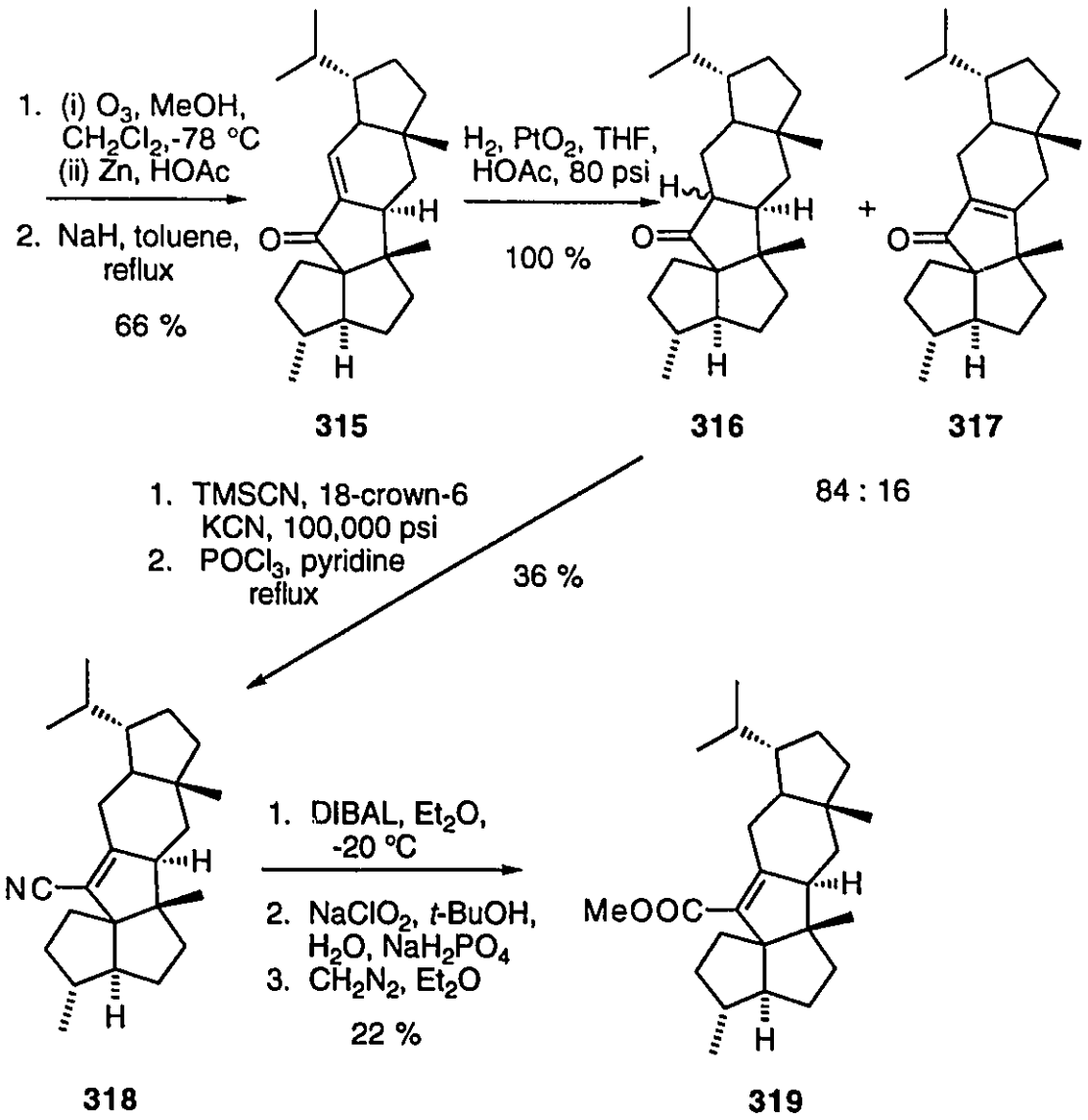
Scheme 103

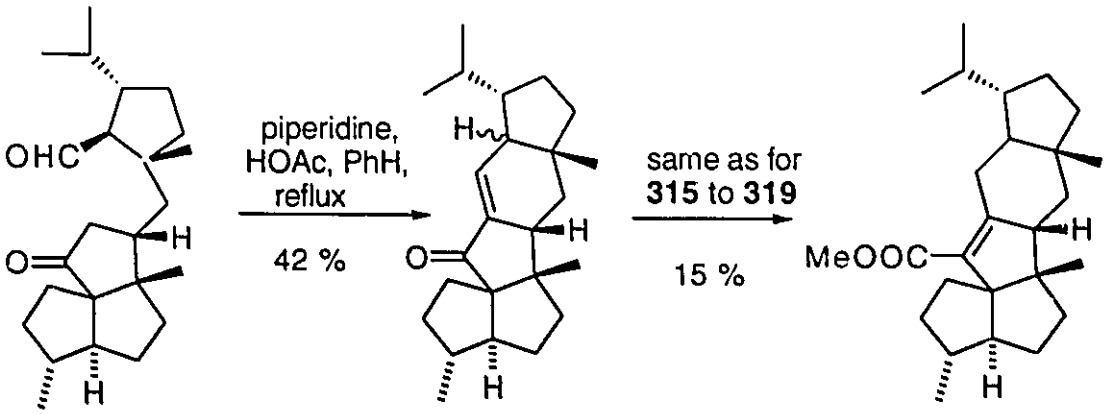
Triquinane **302** was prepared from the optically active β-keto-ester **304** derived from (R)-(+)-pulegone (Scheme 104). Aldol condensation of **304** gave after decarboxylation the diquinane **305**. Diquinane **305** was then subjected to a second annulation by Grignard addition and condensation of the resulting keto-aldehyde to form alcohol **306**. Dehydration through the xanthate ester followed by Wolff-Kishner reduction of the carbonyl gave the alkene **307** which underwent allylic oxidation to the ketone **302**.


1. NaH, toluene
reflux
2. LiI·3 H2O
reflux
56 %
304
305
1.
MgBr
CuBr·Me2S, THF,
-78 to 0 °C
2. HCl, THF,
H2O, 20 °C
72 %
306
1. TsOC(S)Cl,
pyridine, 180 °C
2. K2CO3, H2NNH2·H2O,
diethylene glycol,
200 °C
307
Na2CrO4, HOAc,
Ac2O, 0 °C
46 % from 306
302
1. H2, PtO2, 30 psi
2. NaHCO3, CHCl3,
HOOAc, 0 °C
3. 1 % H2SO4, 20 °C
4. NaIO4, THF, H2O,
0 °C
5. piperidine, HOAc,
PhH, reflux
58 %
308
309
1. DIBAL, Et2O,
-78 °C
2. (i) KH, THF, 0 °C
(ii) (n-Bu)3SnCH2I,
THF, 20 °C
3. n-BuLi, -78 °C
75 %


1. (i) O_3, MeOH, -78 °C,
(ii) Me_2S, -78 - 20 °C
2. TBSCl, imidazole,
DMF, 20 °C
3. DIBAL, Et_2O, -78 °C
4. $POCl_3$, pyridine, 20 °C
41 %
1. CrO_3, DMP,CH_2Cl_2,
-15 °C
2. 1. MgBr THF
-78 to -25 °C
25 %
1. K_2CO_3, $H_2NNH_2{\cdot}H_2O$,
diethylene glycol,
200 °C
2. Ph_3P, $ZnBr_2$, DEAD,
THF, 20 °C
66 %
HO
OTBS
O
Br
310
311
312
313
301
23 : 77


Mg, $BrCH_2CH_2Br$,
Et_2O, reflux
53 %
O
H
Br
301
302
314
303
74 : 26


1. (i) O3, MeOH, CH2Cl2,-78 °C
(ii) Zn, HOAc
2. NaH, toluene, reflux
66 %
H2, PtO2, THF, HOAc, 80 psi
100 %
315
316
317
84 : 16
1. TMSCN, 18-crown-6 KCN, 100,000 psi
2. POCl3, pyridine reflux
36 %
1. DIBAL, Et2O, -20 °C
2. NaClO2, t-BuOH, H2O, NaH2PO4
3. CH2N2, Et2O
22 %
318
319



320

from **303**

321 =β-H, **322** = α-H

321 : **322** = 75 : 25

323

Scheme 104

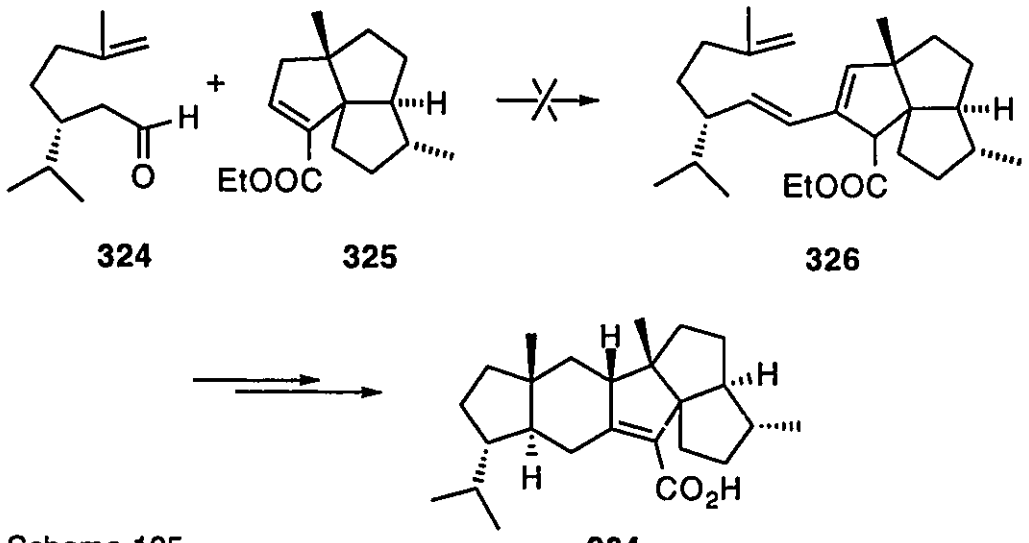
The A-ring was prepared from (S)-limonene **308**. Hydrogenation of the isopropenyl group followed by epoxidation, opening to the diol, cleavage to the keto-aldehyde and aldol condensation afforded the cyclopentene **309**. Subsequent reduction to the alcohol followed by base induced rearrangement of the corresponding tributyltin derivative gave the exocyclic methylene compound **310**. Ozonolysis to the ketone followed by protection, reduction and dehydration resulted in the olefin **311**. Allylic oxidation and subsequent vinyl cuprate addition afforded vinyl ketone **312/313**. Reduction of the carbonyl group of **313** using Wolff-Kishner conditions occurred with simultaneous desilylation and was followed by bromide formation to yield the desired coupling partner **301**.

The crucial coupling step was accomplished by conversion of the bromide **301** to the Grignard reagent followed by the addition of the triquinane **302**. This reaction gave a 3:1 mixture of **314** and **315** with a preference for addition to the β-face syn to the methyl group. This was explained on the basis that this was the least sterically hindered mode of addition. Conversion of the major isomer **314** to the pentacyclic ketone **315** was accomplished by ozonolysis of the vinyl group of **314** with a subsequent aldol

condensation. Further conversion of **315** *via* hydrogenated product **316** to the cyanohydrin was followed by dehydration to the nitrile **318**. This nitrile was reduced and then oxidized to the acid which was esterified to C-2 epimeric retigeranic acid methyl ester **319**. All attempts to epimerize **319** at C-2 to retigeranic acid methyl ester **323** failed. Preparation of (-)-retigeranic acid **323** methyl ester was accomplished however by repeating the conversion of the minor isomer **303** to **323**. In this case however, aldol condensation of **320** (derived from **303**) gave a 75:25 mixture of β to α isomers **321/322**, the minor isomer again being the desired one with the consequence that the overall yield was quite poor.

5. 2. 3. Hudlicky's Approach.

Originally Hudlicky had planned to form retigeranic acid A **284** by using a Diels-Alder approach to simultaneously form the A and B rings of the trans-hydrindane portion of the molecule (Scheme 105).[99] The Diels-Alder triene precursor **326** was to be formed via attachment of the acyl anion equivalent of **324** to the triquinane portion **325** of the molecule. Unfortunately attempts to affect this coupling were unsuccessful.

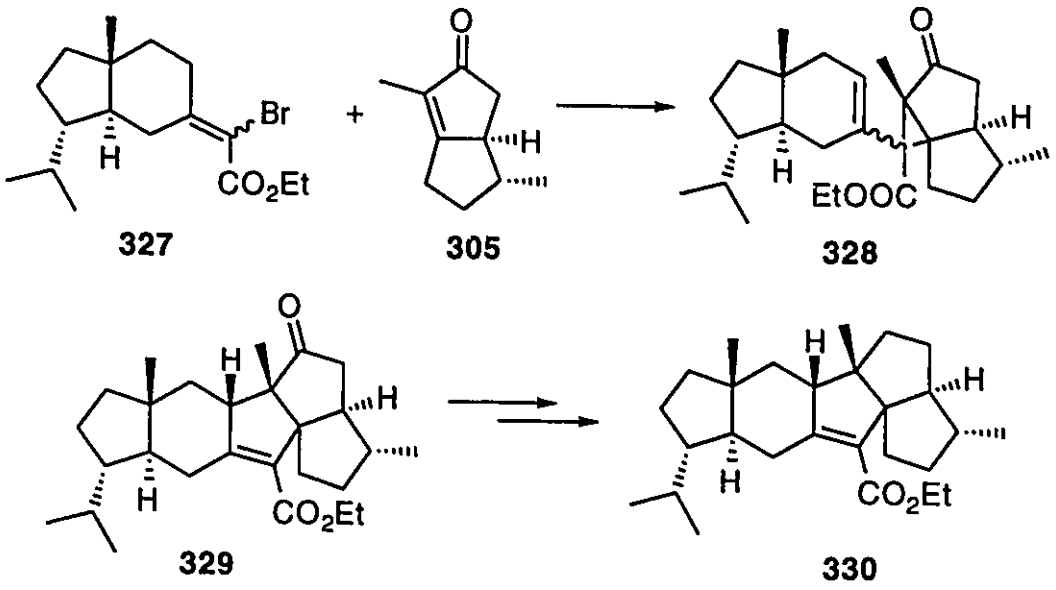


324 **325** **326**

284

Scheme 105

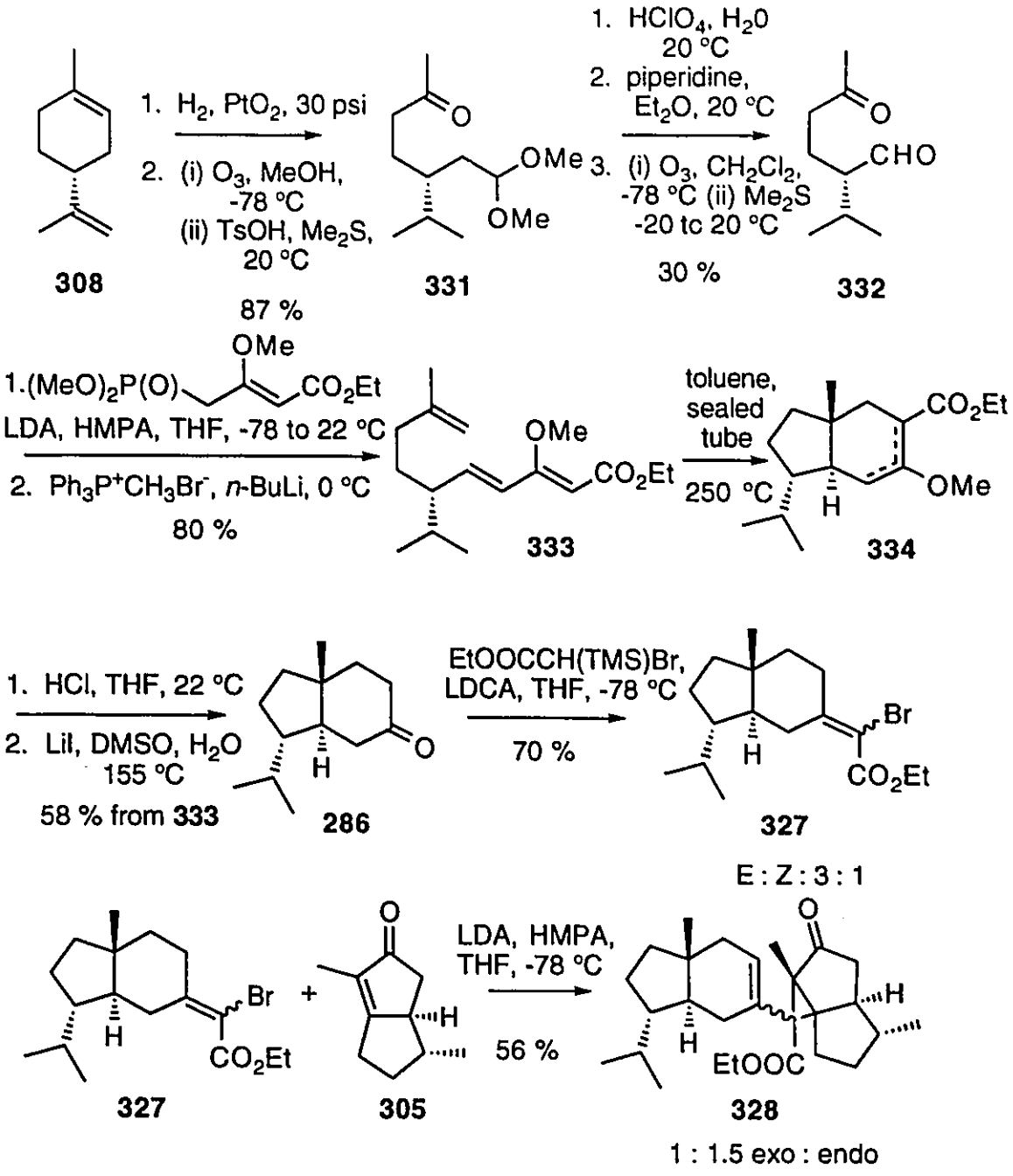
Hudlicky did succeed however in preparing optically active 'natural' retigeranic acid A **284** using his vinyl cyclopropanation strategy to prepare the pentacycle **329** in what can be described as a highly efficient and rapid approach to this compound (Scheme 106).[97] Hudlicky's approach was highly convergent and involved joining the trans-hydrindane vinyl bromide **327** and the diquinane **305** so as to form the vinyl cyclopropane **328**. Thermolysis then gave the pentacycle **329**. Removal of the ketone in the D-ring gave (-)-retigeranic acid A ethyl ester **330**.

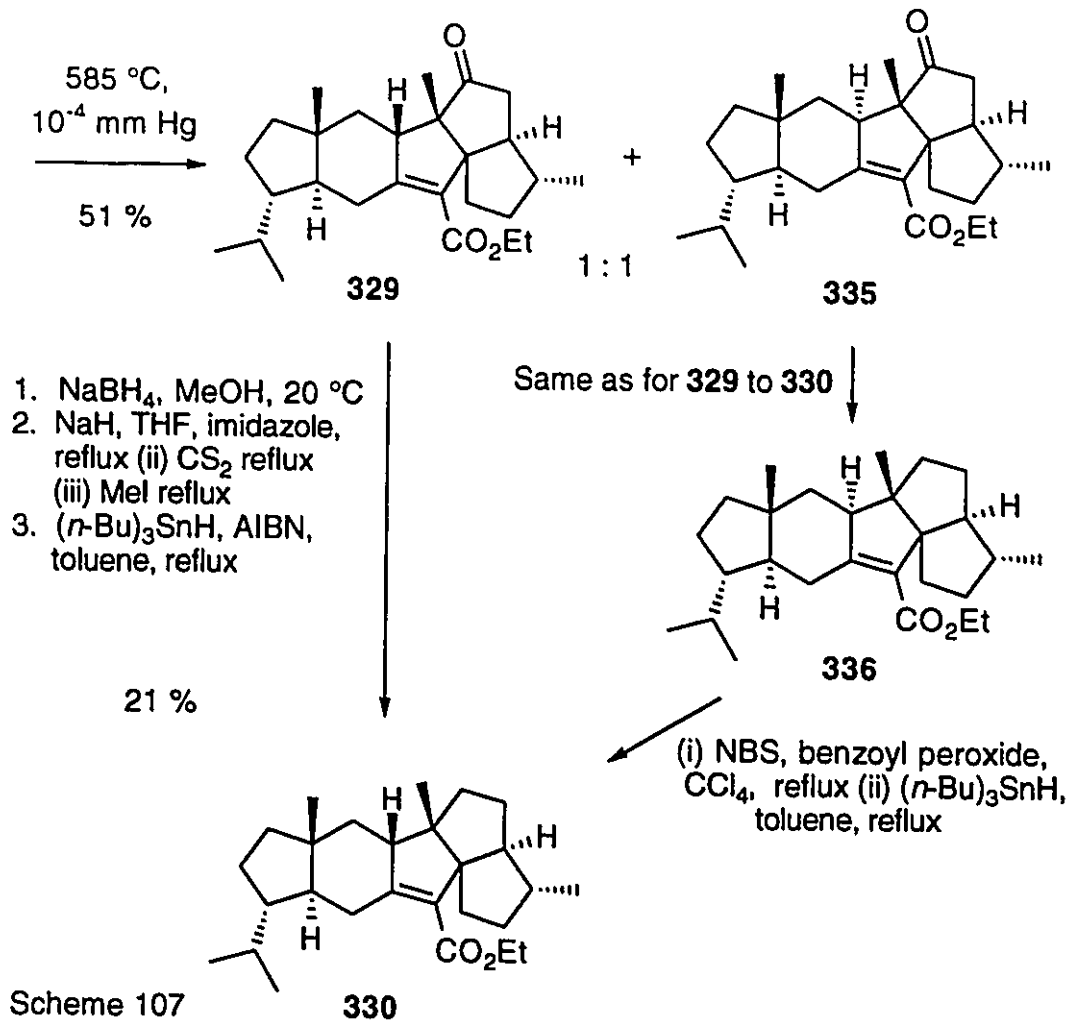


327 **305** **328** **329** **330**

Scheme 106

The trans-hydrindane component **327** was prepared using Fallis' route to ketone **286** but was prepared in optically pure form using limonene **308** as the starting material (Scheme 107).[100]


1. H2, PtO2, 30 psi
2. (i) O3, MeOH, -78 °C (ii) TsOH, Me2S, 20 °C
87 %
1. HClO4, H2O 20 °C
2. piperidine, Et2O, 20 °C
3. (i) O3, CH2Cl2, -78 °C (ii) Me2S -20 to 20 °C
30 %
308
331
332
1.(MeO)2P(O)
OMe
CO2Et
LDA, HMPA, THF, -78 to 22 °C
2. Ph3P+CH3Br-, n-BuLi, 0 °C
80 %
333
toluene, sealed tube
250 °C
334
1. HCl, THF, 22 °C
2. LiI, DMSO, H2O 155 °C
58 % from 333
286
EtOOCCH(TMS)Br, LDCA, THF, -78 °C
70 %
327
E : Z : 3 : 1
LDA, HMPA, THF, -78 °C
56 %
327
305
328
1 : 1.5 exo : endo



Scheme 107

Hydrogenation of (S)-limonene **308** to menthene and ozonolysis gave the keto-aldehyde which was isolated as the acetal **331**. Dehomologation of the free aldehyde by ozonolysis of the enamine afforded the keto-aldehyde **332**. Emmons-Horner olefination of the aldehyde and simple Wittig methenylation of the ketone then gave the triene **333**. Heating of the triene in toluene then afforded the Diels-Alder adduct **334** along with recovered starting material. Attempts to improve the yield of this reaction proved to be difficult and recourse was made to recycling the starting material such that sufficient quantities of the adduct **334** could be prepared. Hydrolysis and decarboxylation of this adduct followed by treatment of the resulting ketone with ethyl

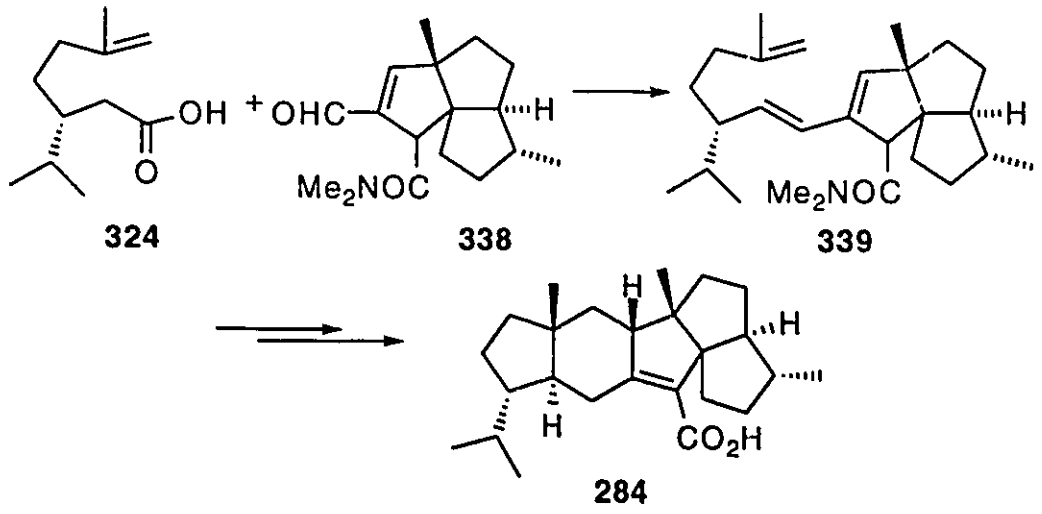
(trimethylsilyl)bromoacetate gave the requisite vinyl bromide coupling partner **327** as a 3:1 mixture of E : Z products.

Preparation of the diquinane **305** was accomplished according to Paquette's procedure (*vide supra*).

The stage was now set for the coupling of **305** and **327**. Treatment of vinyl bromide **327** with base and addition of diquinane **305** furnished the adduct **328** as a 1:1.5 mixture of exo and endo isomers. Thermolysis then gave the epimeric pentacycles **329** and **335**. Reduction of the D-ring carbonyl and Barton deoxygenation of the resulting alcohol gave retigeranic acid ethyl ester **330**. 2-Epi-retigeranic acid ethyl ester **336** was prepared through the same set of transformations from **335**. However, unlike Paquette, Hudlicky succeeded in epimerizing the C-2 center by a combination of NBS bromination/tributyltin hydride reduction so as to increase the overall yield of **330**.

5. 2. 4. Wender's Approach.

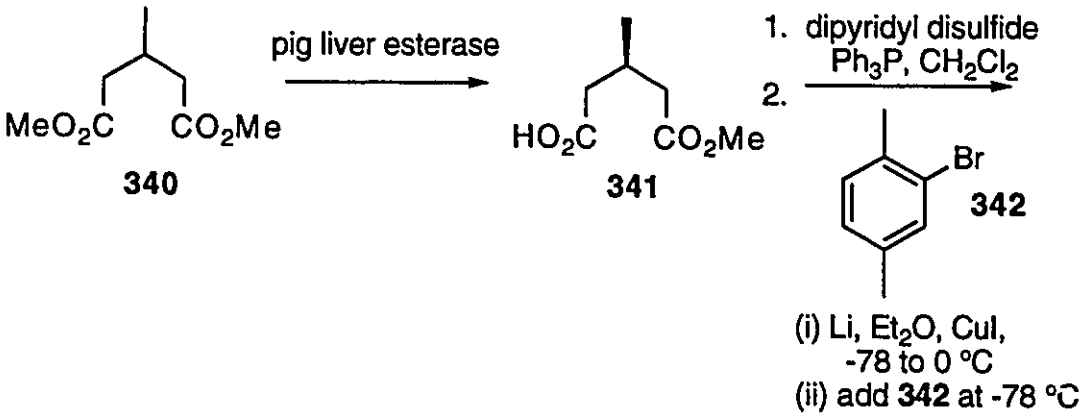
Wender was successful in using an almost identical approach to that of Hudlicky's first attempt to retigeranic acid A **284** (*vide supra*) but instead of using a Michael addition of an acyl anion equivalent to a C-ring enone as Hudlickly had attempted, Wender prepared the triquinane **338** with an aldehyde 'handle' for attachment of the alkene **324** (Scheme 108).[98] Transformation to the triene **339** and a subsequent Diels-Alder reaction then gave the pentacycle which was further transformed to retigeranic acid A **284**.



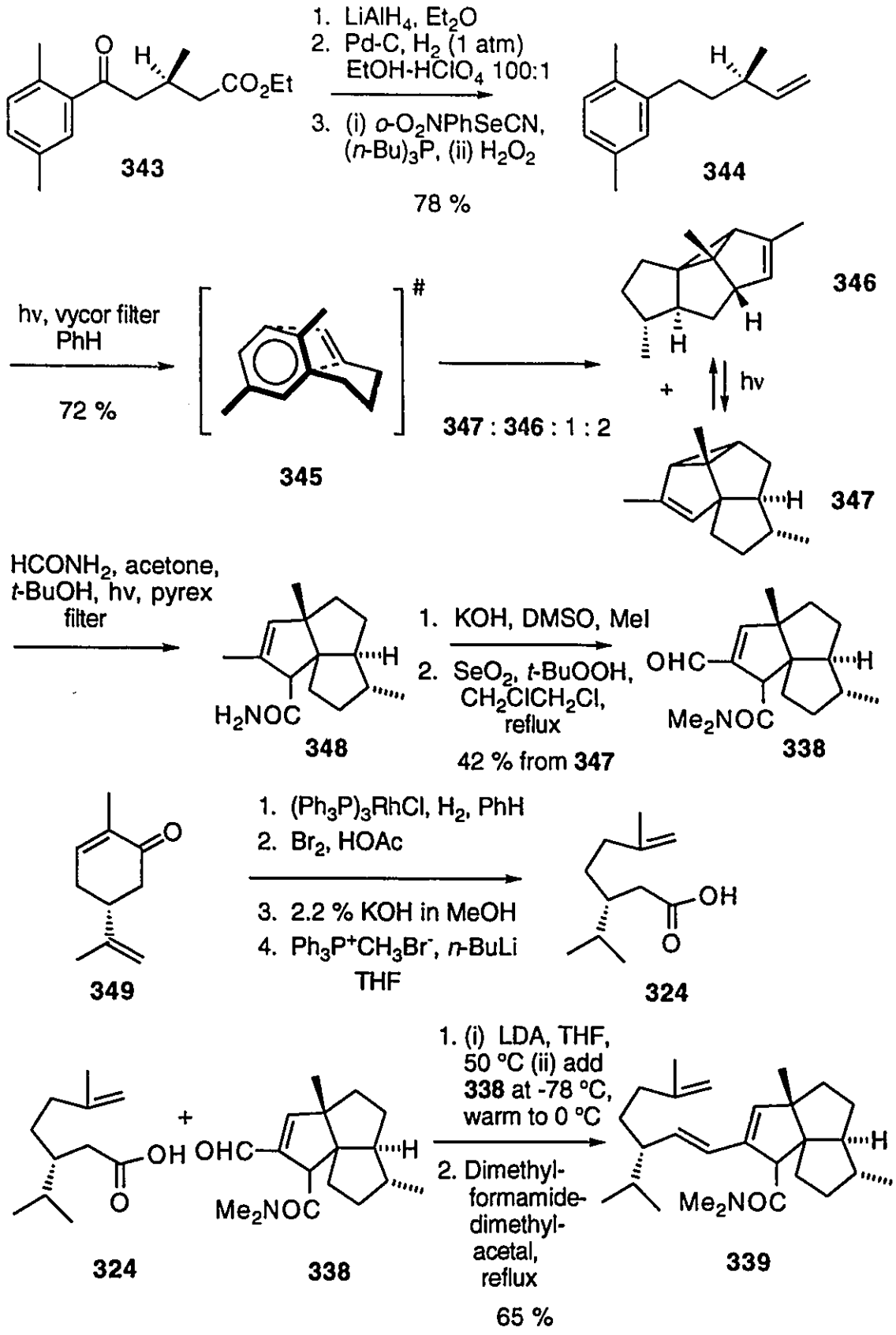
324 338 339 284

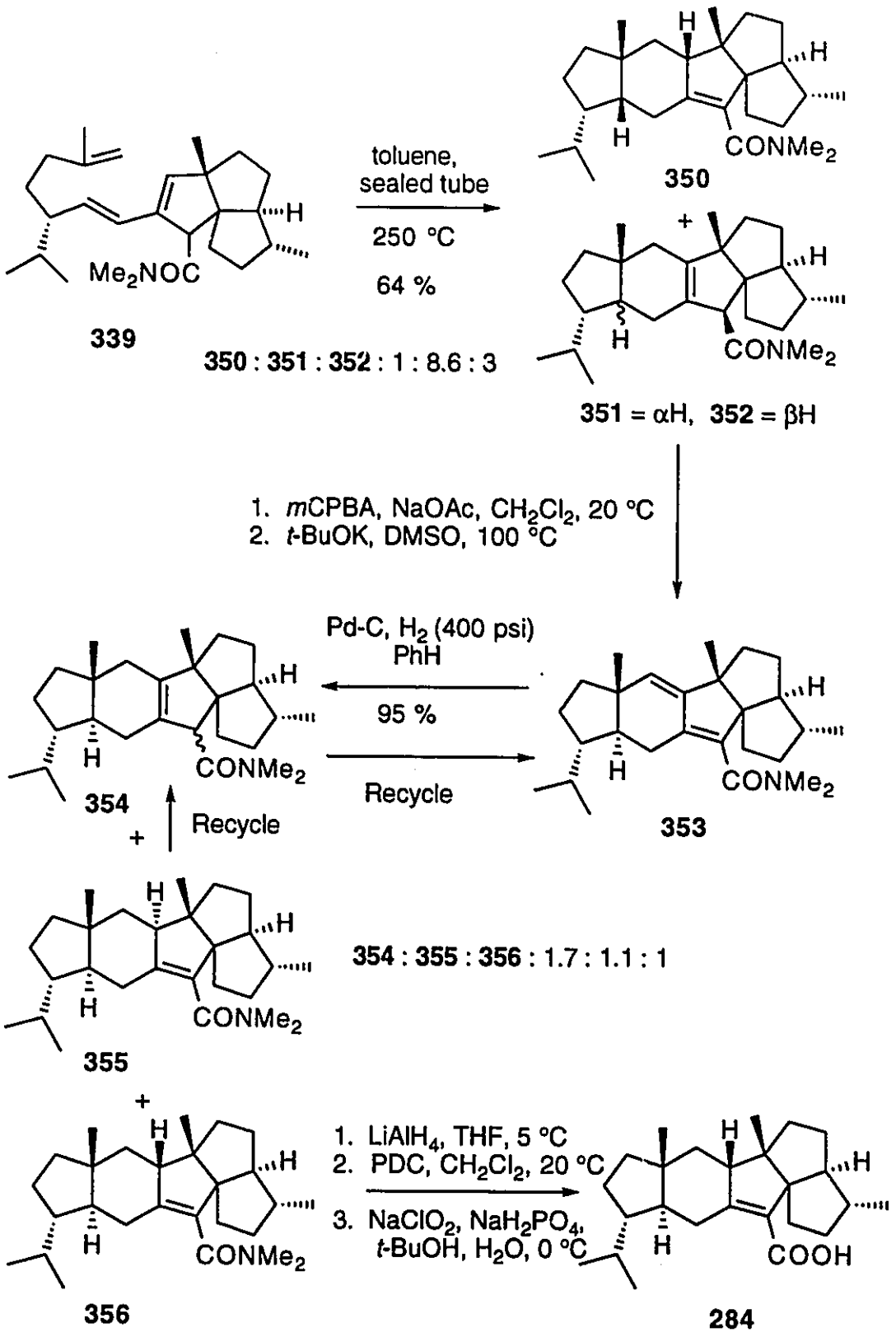
Scheme 108

Key to Wender's approach for forming the triquinane **338** was use of his arene-alkene photo-induced cyclization methodology (Scheme 109).



340 **341** **342**


1. LiAlH4, Et2O
2. Pd-C, H2 (1 atm) EtOH-HClO4 100:1
3. (i) o-O2NPhSeCN, (n-Bu)3P, (ii) H2O2
78 %
343
344
hv, vycor filter PhH
72 %
345
347 : 346 : 1 : 2
346
347
hv
HCONH2, acetone, t-BuOH, hv, pyrex filter
348
1. KOH, DMSO, MeI
2. SeO2, t-BuOOH, CH2ClCH2Cl, reflux
42 % from 347
338
349
1. (Ph3P)3RhCl, H2, PhH
2. Br2, HOAc
3. 2.2 % KOH in MeOH
4. Ph3P+CH3Br-, n-BuLi THF
324
1. (i) LDA, THF, 50 °C (ii) add 338 at -78 °C, warm to 0 °C
2. Dimethyl-formamide-dimethyl-acetal, reflux
65 %
339

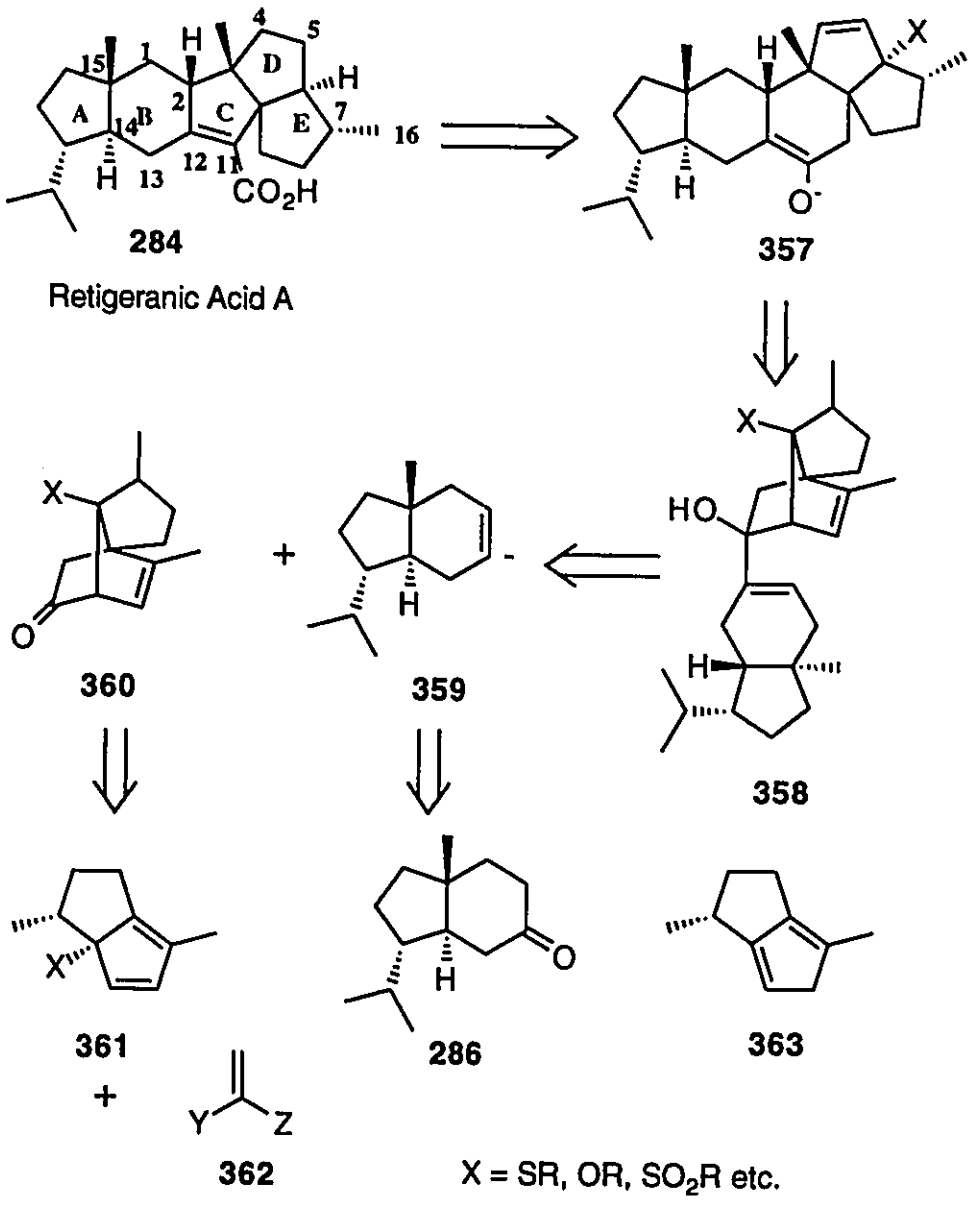

toluene,
sealed tube
250 °C
64 %
339
350
350 : 351 : 352 : 1 : 8.6 : 3
351 = αH, 352 = βH
1. mCPBA, NaOAc, CH2Cl2, 20 °C
2. t-BuOK, DMSO, 100 °C
Pd-C, H2 (400 psi)
PhH
95 %
Recycle
Recycle
354
353
354 : 355 : 356 : 1.7 : 1.1 : 1
355
356
1. LiAlH4, THF, 5 °C
2. PDC, CH2Cl2, 20 °C
3. NaClO2, NaH2PO4,
t-BuOH, H2O, 0 °C
284

Scheme 109

The synthesis began with optically pure ester-acid **341** which was prepared by treatment of 3-methylglutaric acid dimethyl ester **340** with pig liver esterase. The acid was then coupled with the aryl bromide **342** to give the keto-ester **343** which was reduced to the diol. Hydrogenation of the benzylic alcohol and conversion of the primary alcohol to the terminal olefin **344** gave material which was ready to be cyclized. Irradiation of **344** gave the exciplex **345** which resulted in the formation of the two cyclopropyl triquinanes **346** and **347** in a 2:1 ratio. These two compounds could be interconverted by further irradiation and thus multigram quantities of **347** were easily prepared. Light induced formamide radical addition to **347** with concurrent cyclopropyl ring fragmentation furnished the triquinane **348**. Dimethylation of the amide of **348** and allylic oxidation of the vinylic methyl group gave the triquinane aldehyde **338**. Acid **324** was prepared in four steps from R-(-)-carvone **349**. Hydrogenation of **349** followed by bromination and base treatment gave the keto-acid which was then methylenated under Wittig conditions to form **324**. Acid **324** was coupled with the aldehyde **338** to give a hydroxy-acid which underwent decarboxylative dehydration with dimethylformamide dimethylacetal to give the triene **339**. Diels-Alder reaction of this triene gave a mixture of pentacycle **350** and the double bond isomerized product **351/352**. Alkene **351** was epoxidized and treated with base to give the diene **353** which was then hydrogenated to give the three products **354, 355** and **356** in a ratio of 1.7:1.1:1, with **356** possessing the correct stereochemistry. Reduction of the amide group to the corresponding alcohol gave retigeranic acid A **284** upon oxidation. C2 epi-pentacycle **355** could be converted back to **354** and this in turn converted back into diene **353**. Recycling through this route made it possible to increase the overall yield of retigeranic acid A **284**.

5.3. Our Approach.

Our approach to retigeranic acid A **284** was derived from the observation that if ring C was a six-membered ring ketone and the D ring possessed a double bond at C4,5 (retigeranic acid numbering) the corresponding C11,12 enolate from this ketone would give rise to a 1,5-diene (Scheme 110).



Scheme 110

An anionic oxy-Cope rearrangement can therefore be used to prepare ketone **357** from the dienol **358**. Compound **358** can in turn be obtained by addition of vinyl anion **359** to the ketone **360**. Vinyl anion **359** can be derived from the trans-hydrindanone **286** using the Shapiro reaction. The tricyclic ketone **360** can be further disconnected to yield the diene **361** and a ketene equivalent **362**.

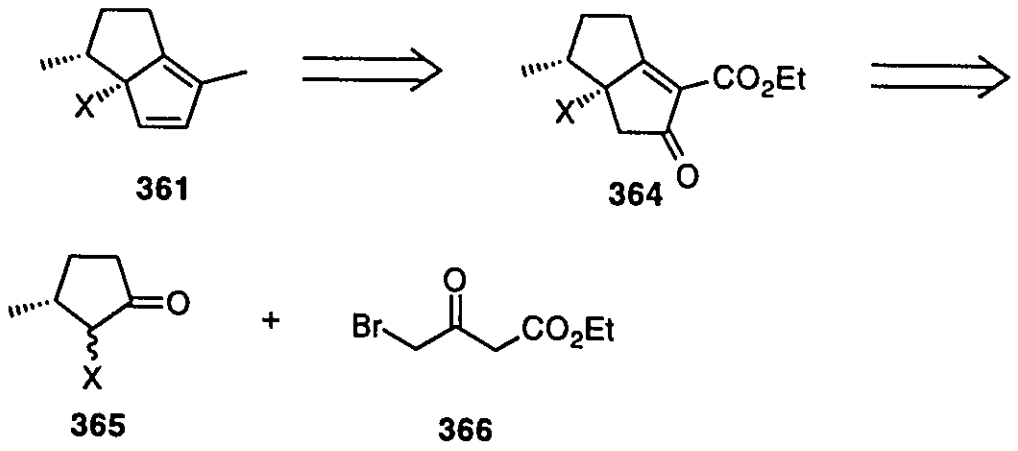
Earlier work in our laboratory focused on preparation of the 'left-hand' trans-hyrindane portion of the molecule through preparation of the trans-hydrindanone **286** (Scheme 107). The route to this compound has been published.[100]

The preparation of the tricyclic compound **360** was the prime focus. As stated previously, it was envisioned that tricyclic ketone **360** could be derived through a Diels-Alder reaction of a ketene equivalent **362** with a diene like **361**. Diene **361** is an annulated cyclopentadiene, and it was thus neccessary to incorporate a group X which would prevent sigmatropic rearrangement to the more substituted (and more stable) isomer **363**. It would also be necessary for the group X and the C16 methyl group (retigeranic acid numbering) to possess a *syn* relationship in order to obtain the correct stereochemistry in the final product **284**. Furthermore, in order to obtain the desired stereochemistry in the final target, dienophile addition would have to occur on the face *syn* to the group X and the methyl group. This is also the convex face and should be the favoured face of addition provided that the group X is not too large.

5.3.1. Preparation of the Cyclopentanone.

Diene **361** can be derived from the keto-ester **364** (Scheme 111). Disconnection of the double bond indicates that **364** can in turn be derived from a cyclopentanone such as **365** *via* an annulation sequence involving addition and aldol condensation of component **366**.

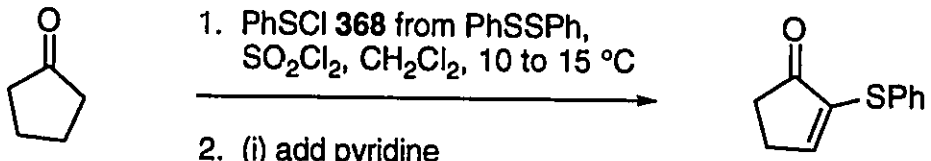
As stated earlier, the group X of the cyclopentadiene **365** is neccessary to prevent sigmatropic rearrangement of the cyclopentadiene to the more stable diene **363**. In addition, the group X would have to be readily removable, stable to a wide variety of reaction conditions and not so bulky so as to interfere with the *syn* addition of the dienophile. The group X should also facilitate the preparation of large quantities of the cyclopentanone **365** in an efficient manner.



361 **364** **365** **366**

Scheme 111

With these considerations in mind we chose the vinyl keto-sulfide **369** as the starting material. This is a known compound and is readily prepared on a large scale in 30-40 % yield from the addition of phenylsulfenyl chloride **368** to cyclopentanone **367** (Scheme 112).[101] Phenylsulfenyl chloride **368** in turn is easily prepared by the addition of sulfuryl chloride (SO_2Cl_2) to diphenyldisulfide.

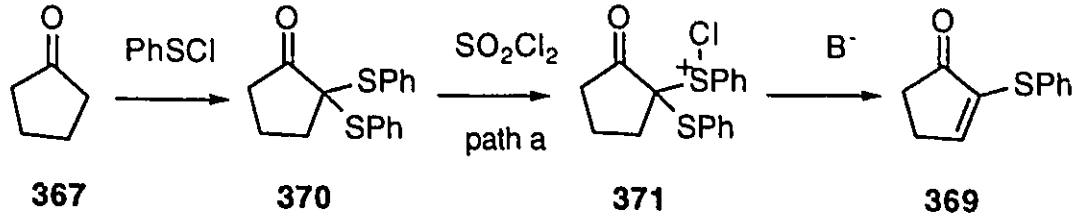


367 **369**

30 %

Scheme 112

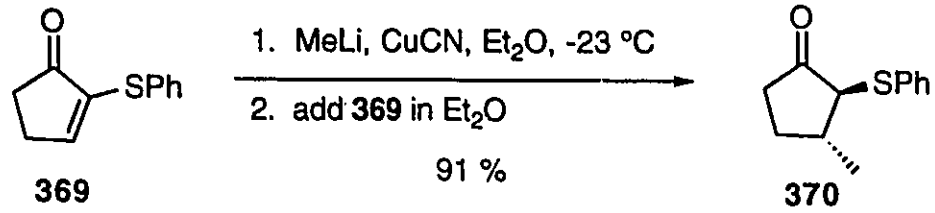
Formation of **369** takes place by an initial dithiolation followed by chlorination and elimination of phenylsulfenyl chloride (path a) (Scheme 113).



367 **370** **371** **369**

Scheme 113

Introduction of the C16 methyl group was accomplished by methylcyanocuprate addition to the vinyl keto-sulfide **369** (Scheme 14).[102]



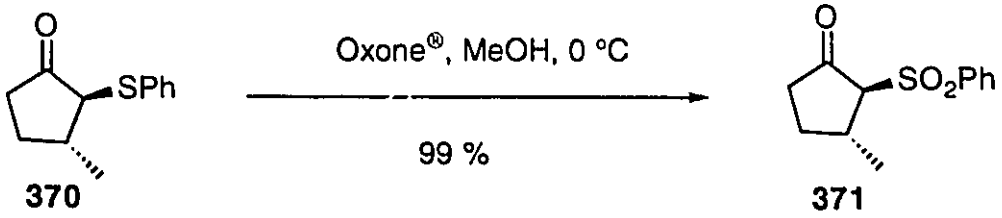
369 **370**

Scheme 114

The higher order cyanocuprate was chosen only from the practical standpoint that technical grade copper (I) cyanide can be used in place of the tedious to purify copper (I) iodide. The resulting crude methylated product **370** was obtained as a 6:1 mixture of *trans* to *cis* products in 91 % yield. Evidence for incorporation of the methyl group came from the presence of a doublet (J = 6.5 Hz) at 1.18 ppm in the ^1H NMR spectrum integrating for three protons. Evidence for the presence of a ketone was seen by a carbonyl resonance in the ^{13}C NMR at 215 ppm.

Sulfide **370** was found to have limited stability and earlier attempts by a co-worker to alkylate this material gave complex mixtures. Sulfide **370** was therefore

immediately oxidized with Oxone® to the corresponding sulfone **371** in a crude yield of 99 % (Scheme 115).[103]



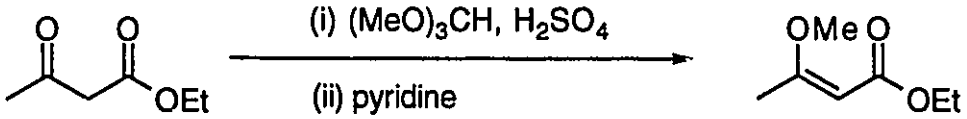
370 **371**

Scheme 115

This material was sufficiently pure to be used in the next step without need for further purification. Sulfone **371** was characterized by the presence of a strong absorption in the IR spectrum at 1312 cm^{-1}. In addition, the methine proton next to the sulfur was shifted downfield by approximately 0.3 ppm to 3.31 ppm in the ^1H NMR spectrum (-COC<u>H</u>RSO_2Ph). Formation of the strong electron withdrawing sulfone group also had the effect of shifting all the aromatic protons downfield, in particular the *ortho* protons which were seen at 7.83-7.89 ppm.

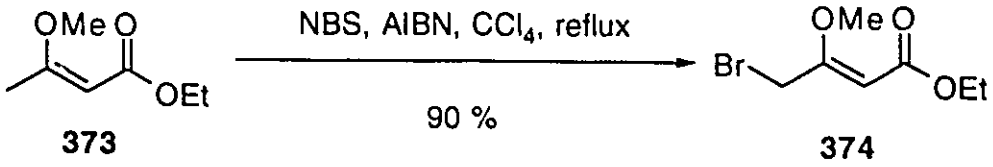
5. 3. 2. Alkylation of the Cyclopentanone.

For the alkylation and subsequent aldol condensation, the allylic bromide **374** was prepared in two steps starting from ethyl acetoacetate **372**. Preparation of the methyl enol ether **373**[100] was readily accomplished (Scheme 116) as was the preparation of the allylic bromide[100] (Scheme 117) in an overall yield of 80 %.



372 90 % **373**

Scheme 116

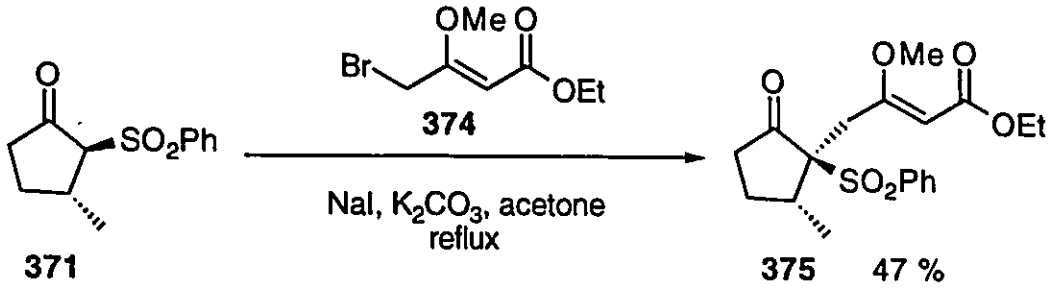


373 **374**

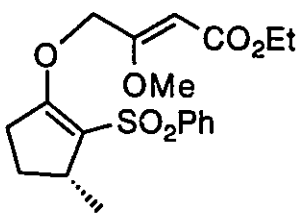
Scheme 117

Bromide **374** was previously used by Fallis for the preparation of the Wittig reagent **333** which in turn was used to prepare the hydrindanone **286** (Scheme 107).

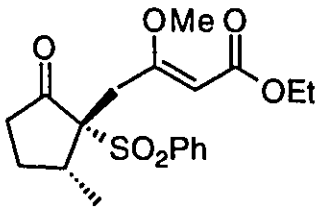
Alkylation of sulfone **371** was accomplished using the bromide **374** which was converted *in situ* to the iodide via a Finkelstein reaction in acetone (Scheme 118).[105] Potassium carbonate had the advantage that unlike strong lithium bases like LDA, it required no special handling precautions and enabled the reaction to be readily scaled up.



371 **375** 47 %



376 15 %



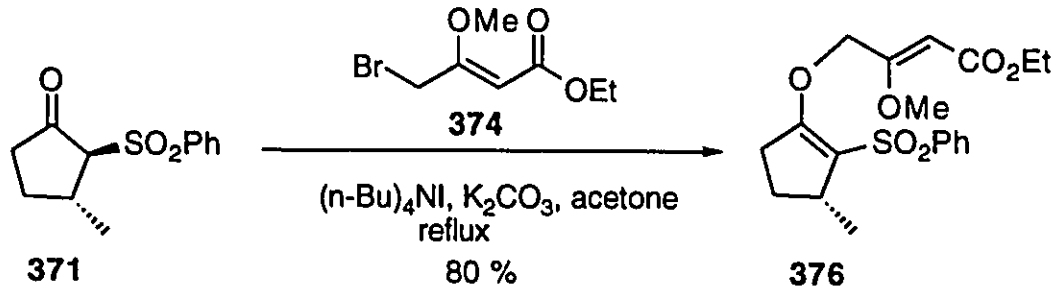
377 10 %

Scheme 118

From the alkylation reaction a 47 % yield of **375** was obtained by recrystallization. In addition, approximately 15 % of O-alkylated product **376** was

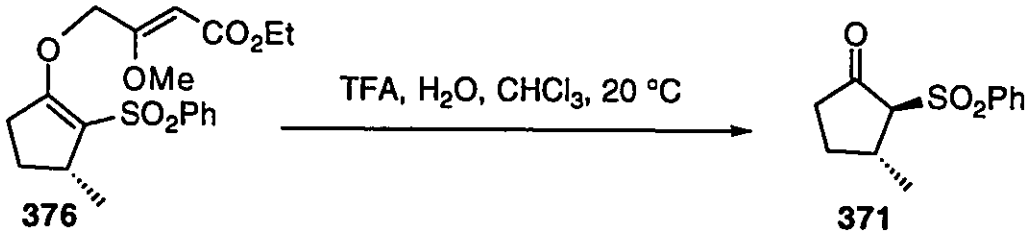
isolated accompanied by approximately 10 % of what is tentatively assigned the minor diastereomer **377**.

Alkylation was also attempted using approximately 5 mol % of tetra-*n*-butylammonium iodide so as to avoid the use of a large quantity of sodium iodide in this procedure (Scheme 119).



Scheme 119

Unfortunately an approximate 80 % yield of O-alkylated material **376** was obtained. A large cation apparently tends to favour O-alkylation. No attempt was made to fully characterize the O-alkylated product **376** but the structural assignment of this compound was made on the basis of an experiment which showed that acid catalyzed hydrolysis of this compound gave back sulfone **371** (Scheme 120).



Scheme 120

The stereochemistry of the sulfone **375** was later established through X-ray crystallographic analysis of the diol **380** (*vide infra*) and showed that the phenylsulfone and methyl groups possessed an *anti* relationship to one another. This was a surprising

result for it was anticipated that alkylation would occur opposite the methyl group. One explanation for this apparent anomaly is offered by Takahashi who has suggested that a strong steric interaction, due to the eclipsing of the methyl group and sulfone group as the sp center rehybridizes, is avoided if the electrophile approaches *syn* to the methyl group.[106] Another explanation which can be offered is based more on electronic effects than steric effects. Cieplak has developed a theory which postulates that alkylation should occur *anti* to the best sigma donor, which in this case is the C-H bond opposite the methyl group (Figure 6).[107] The investigation of Cieplak's ideas have been the subject of much interest in our laboratory and came about as a result of this 'anomalous' alkylation result. Extension of his ideas to enable control over the facial selectivity of the Diels-Alder reaction by varying the heteroatom on simple substituted cyclopentadienes has been investigated.[108]

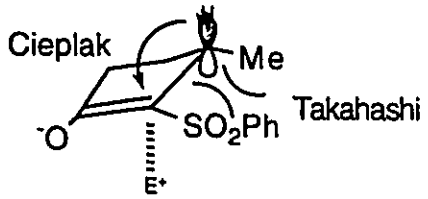


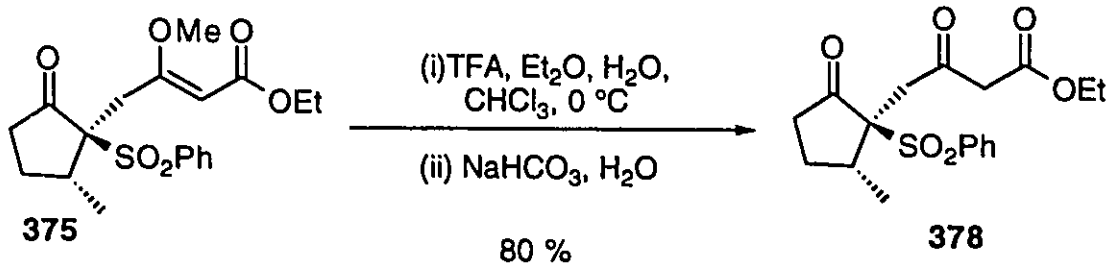
Figure 6

Despite the consequences of increasing the steric environment on both faces of the diene, it was anticipated that the *trans* relationship between the methyl and sulfone group should not affect the Diels-Alder reaction such that the dienophile should favour addition on the concave face opposite the sterically more demanding phenylsulfone group. The Diels-Alder facial selectivity studies (*vide supra*) also indicated that a sulfone group directs dienophiles *anti* to this group and as such should complement the steric effect.[108]

The *anti* relationship between the methyl and sulfone group also made it neccessary to correct the stereochemistry of the final product after removal of the sulfone group at C6. It was anticipated this could be accomplished at the time of removal of the

sulfone. Reductive removal of the sulfone with sodium amalgam should be followed by protonation to form the more stable natural stereochemistry.[109]

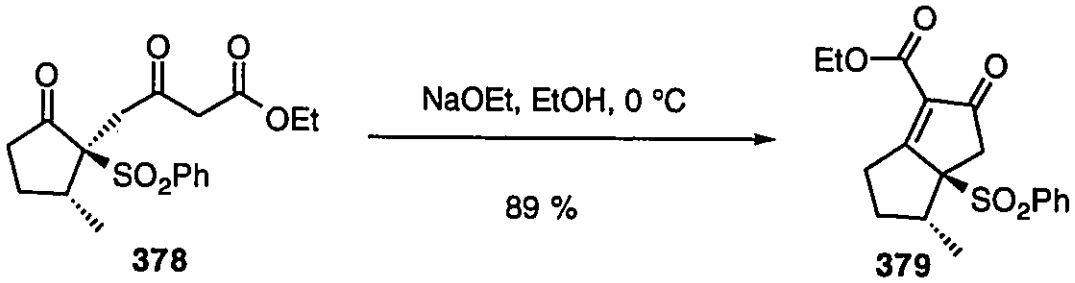
The major alkylated product **375** underwent hydrolysis of the enol ether functionality to give the diketone **378** in a recrystallized yield of 80 % (Scheme 121).[110]



Scheme 121

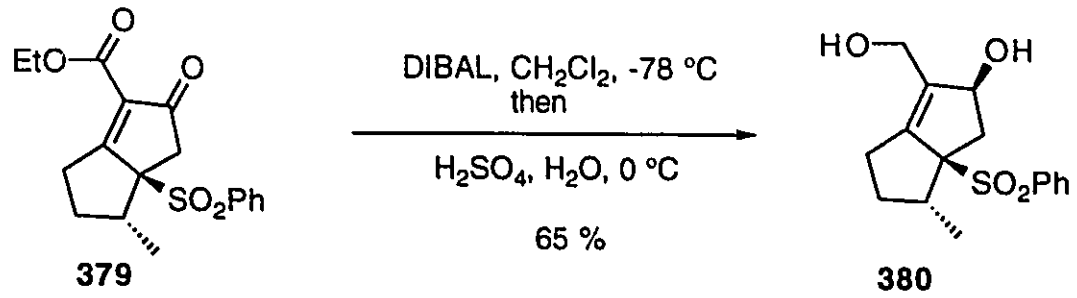
5. 3. 3. Annulation of the Cyclopentanone.

Attempts to use silica gel chromatography to purify **378** revealed that this compound underwent acid catalyzed aldol condensation to give the annulated keto-ester **379**. Unfortunately, although this was the desired product of the next step, significant decomposition also resulted. Recourse was therefore made to the use of a base catalyzed condensation to yield the keto-ester **379** (Scheme 122). By this method a crude yield of 89 % was obtained. The material was of sufficiently high purity for use in the next step.



Scheme 122

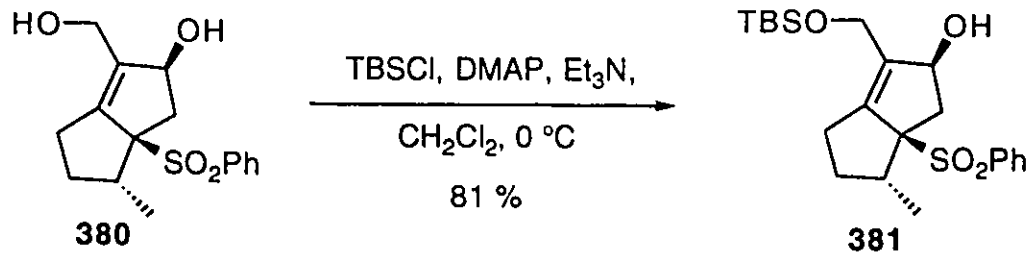
Reduction of the keto-ester **379** was effected by the use of DIBAL in dichloromethane at -78 °C (Scheme 123).[60]



Scheme 123

In order to obtain good yields of the alcohol **380** it was neccessary to quench the reaction shortly after warming to around 0 °C. It was discovered for the work-up procedure that stirring the reaction with either saturated ammonium chloride solution or sodium potassium tartrate solution did not give an aluminum free product. A wash with 10 % sulfuric acid at 0 °C was found to eliminate this problem. Yields were typically 60-70 % using this set of conditions. Positive proof of structure for diol **380** came from X-ray crystallographic analysis of this compound. Diol **380** was characterized by the presence of a broad band in the IR spectrum at 3428 cm^{-1}. In the ^1H NMR spectrum a singlet at 4.35 ppm integrating for two protons ($HOC\underline{H}_2$-) as well as a doublet of doublets (J = 12.8, 6.4 Hz) was indicative of the methine proton under the secondary alcohol ($HOC\underline{H}RR'$).

Diol **380** was then protected as its mono TBS ether in 81 % yield (Scheme 124).[111]

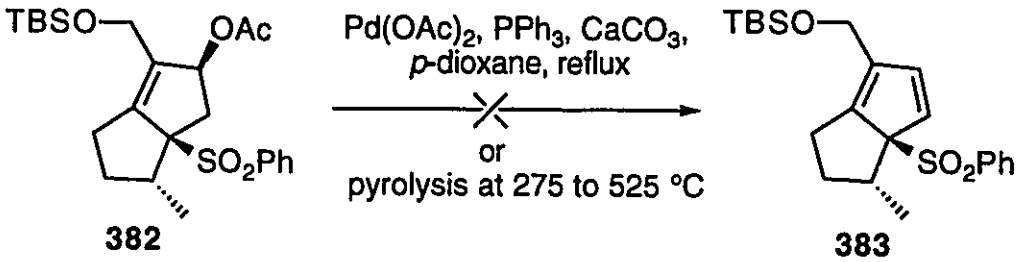


Scheme 124

Protection of the primary alcohol was considered necessary to avoid the problems with the subsequent elimination of the secondary alcohol. Silyl ether **381** displayed two singlets integrating for three protons each at 0.06 and 0.07 ppm in the ^{1}H NMR spectrum which represented the two diastereotopic methyl groups of the TBS group. The presence of the *tert*-butyl group was indicated by a singlet at 0.88 ppm integrating for nine protons.

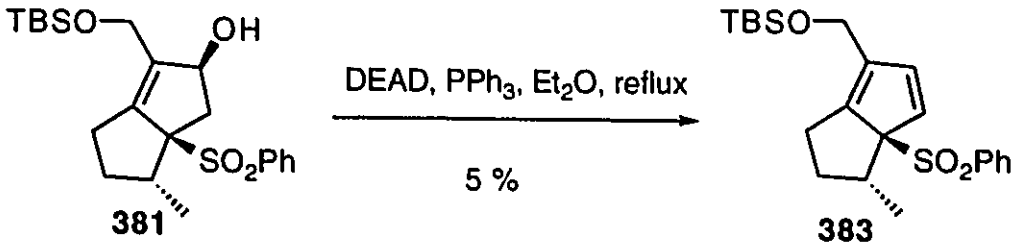
5. 3. 4. Preparation of the Diene.

A variety of methods were used to try to prepare the diene **383**. Preparation of the acetate **382** and treatment with $Pd(OAc)_2/PPh_3/CaCO_3$ in refluxing THF or *p*-dioxane returned starting material only. Use of $Pd(PPh_3)_4$ similarly resulted in only starting material being recovered unaffected (Scheme 125).[112]



Scheme 125

Treatment of the alcohol **381** using Mitsunobu-type reaction conditions in the absence of an acid in refluxing toluene gave a trace of fairly non-polar material as seen by TLC.[113] Analysis by ^{1}H NMR did not reveal any of the desired diene **383** however. Substitution of THF or ether proved to be beneficial due to reduced reaction temperatures and a small quantity of diene **383** was isolated (Scheme 126).

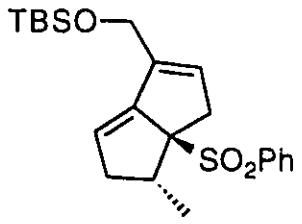


Scheme 126

Similar treatment of the lithium alkoxide of **381** with DEAD/PPh_3 did not improve results. What could not be reconciled at the time however was that no matter how many equivalents of DEAD/PPh_3 were used or no matter how long the reaction was refluxed, the yield could not be improved. In addition, the starting material was usually completely consumed in these reactions.

Diene **383** was characterized by two sets of doublets (J = 5.1 Hz) at 6.02 and 6.11 ppm in the ^{1}H NMR spectrum. Eight carbon resonances at 127.0, 129.4, 130.6, 133.2, 135.0, 140.4, 141.5 and 146.8 in the ^{13}C NMR indicated two double bonds being present plus four aromatic carbons.

In addition to the diene **383**, material tentatively assigned as the trans-diene **384** was also recovered from the Mitsunobu-type reaction. This material showed two complex multiplets at 5.48 and 5.71 ppm, both integrating for one proton each (Figure 7).

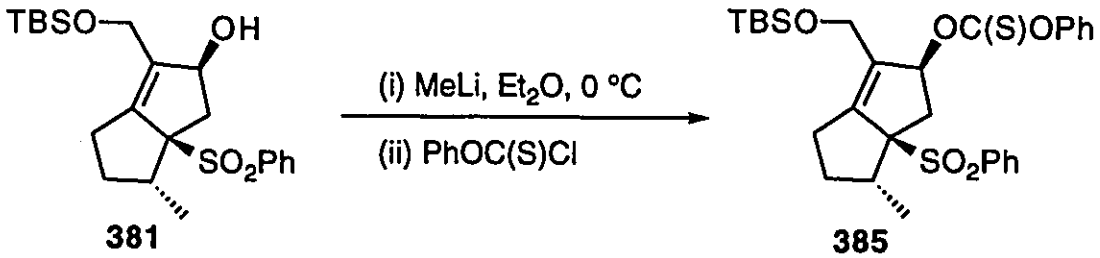


384

Figure 7

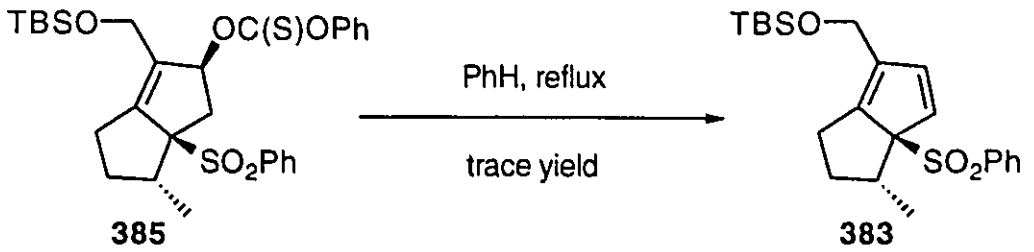
Many of the standard methods for the elimination of secondary alcohols were examined with poor results. For example, pyrolysis of the acetate **382** at a range of temperatures from 275 to 525 °C gave only unidentifiable material.[79] Treatment with $SOCl_2$[114] or tosyl chloride[115] in pyridine gave traces of the diene **383** as did treatment with mesyl chloride and triethylamine.[116] Conversion of alcohol **381** to the corresponding lithium alkoxide and treatment with tosyl chloride gave material which when heated with $NaHCO_3$ in DMSO gave only *trans*-diene **384**.

Formation of the thionocarbonate **385** was accomplished by treatment of the alcohol **381** sequentially with methyllithium and phenylthionochloroformate (Scheme 127). This material when heated in benzene gave a small quantity of the diene **383** as determined by ^1H NMR analysis (Scheme 128).[117]



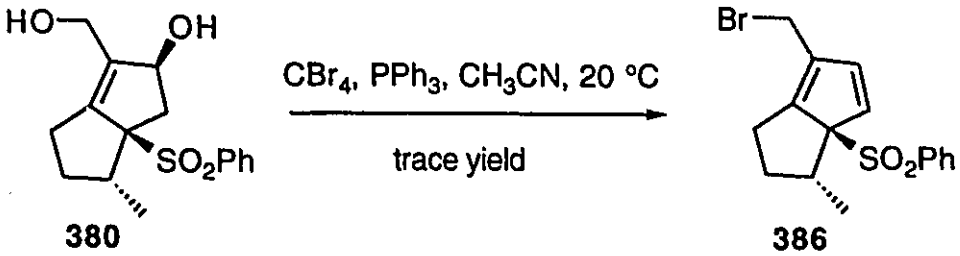
381 **385**

Scheme 127



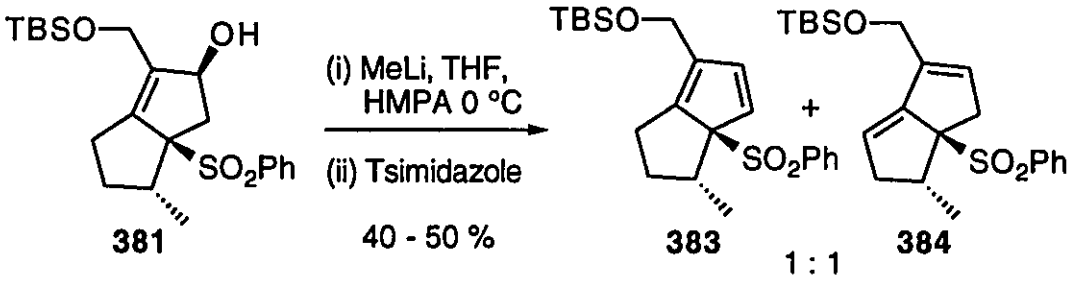
Scheme 128

Treatment of the diol **380** with 1.5 equivalents of CBr_4/PPh_3 in acetonitrile gave only a small quantity of diene as the bromo-diene **386** (Scheme 129).[118] Structural assignment of **386** was later verified by preparation of this compound through a separate route (*vide infra*).



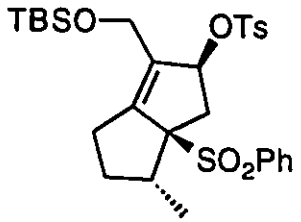
Scheme 129

One of the more successful reactions for the preparation of diene **383** involved treatment of the lithium alkoxide of the alcohol **381** with tosylimidazole in THF/HMPA (Scheme 130).[119]



Scheme 130

From this reaction an approximately 50 : 50 mixture of *cis* and *trans* dienes **383** and **384** was isolated in 40-50 % yield. The conditions employed for this reaction came about as a result of attempts to prepare the tosylate **387** (Figure 8). Initial attempts using ether as the solvent resulted in the slow formation of what was believed to be the tosylate **387**. In an attempt to increase the rate of this reaction, THF was substituted for ether and HMPA was added so as to make up 20 % of the solvent. Under this set of conditions no tosylate was isolated but only dienes **383** and **384** were formed.

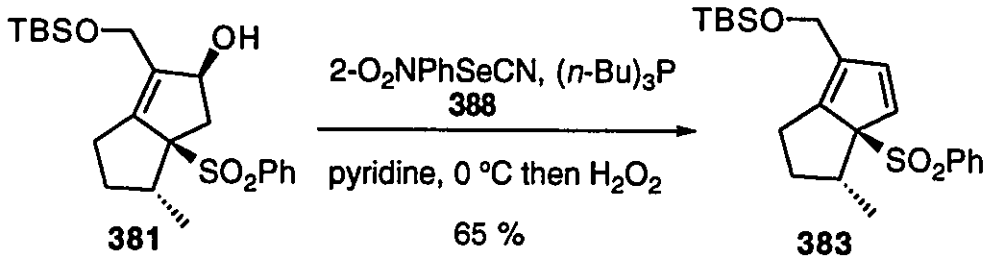


387

Figure 8

If the synthesis of retigeranic acid A **284** was to be accomplished however, a yield of 20 - 25 % for diene **383** was clearly unacceptable and would have to be improved.

Application of Grieco's procedure successfully overcame this hurdle and yields of the diene **383** could now be obtained in yields of 60-65 % (Scheme 131).[120]



381 **383**

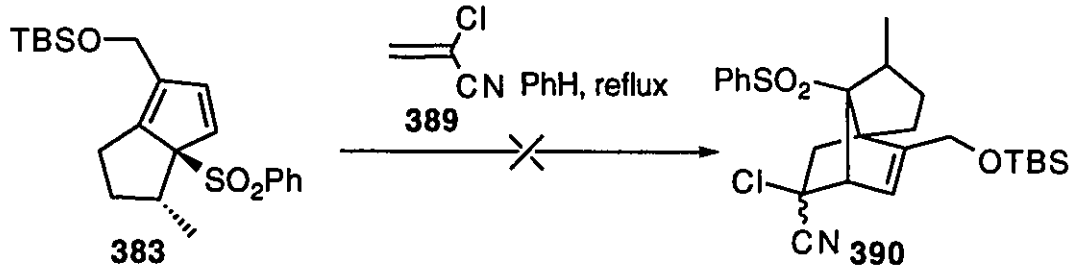
Scheme 131

Ortho-nitrophenylselenylcyanate **388** was freshly prepared according to the procedure of Bauer.[121] Reagent **388** was found to be unstable under prolonged storage conditions (- 30 °C/6 months) despite the fact that no change occurred in its ^{1}H NMR spectrum. Initially it was thought that the tri-*n*-butylphosphine or hydrogen peroxide were of poor quality. Use of new H_2O_2, tri-*n*-butylphosphine, or freshly distilled pyridine still did not correct this problem. Resort was thus made to the use of freshly prepared **388** with a successful outcome.

5. 3. 5. Attempted Cycloaddition of the Diene with Chloroacrylonitrile.

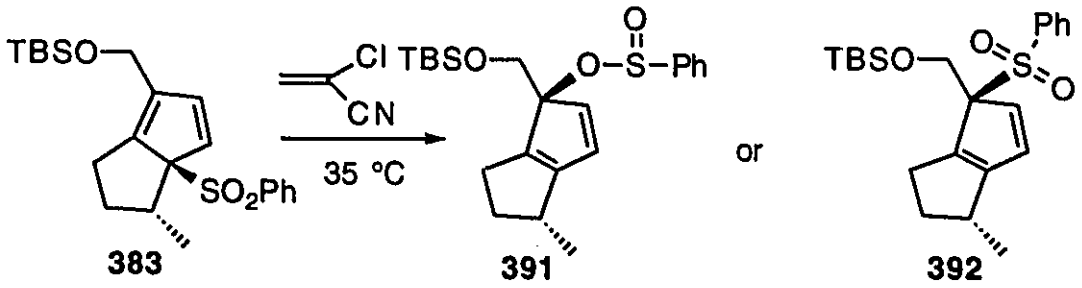
The question of the cycloaddition of diene **383** with a ketene equivalent was the next aspect to be addressed. Chloroacrylonitrile **389** was chosen as an ideal ketene equivalent for both its reactivity and ease by which its Diels-Alder adducts can be converted to ketones.[122]

Heating chloroacrylonitrile with the diene **383** in benzene unfortunately gave a complex mixture from which adduct **390** could not be detected. This adduct would be expected to display one vinylic proton as a doublet yet this signal was not observed (Scheme 132).



Scheme 132

Heating the diene **383** with chloroacrylonitrile **389** at 35 °C gave after several days what initially appeared to be the adduct **390**. Quantitative ^{13}C NMR showed however that the number of carbons detected was the same as for the diene **383**. Further analysis showed that diene **383** had undergone a rearrangement to compound **391**, presumably through a 2,3-sigmatropic rearrangement (Scheme 133). The rearrangement of an allylic sulfinate to an allylic sulfone has been documented.[123] The rearrangement of diene **383** was not prevented by heating the sample in benzene containing the radical inhibitor hydroquinone, thereby supporting a sigmatropic rearrangement mechanism.



Scheme 133

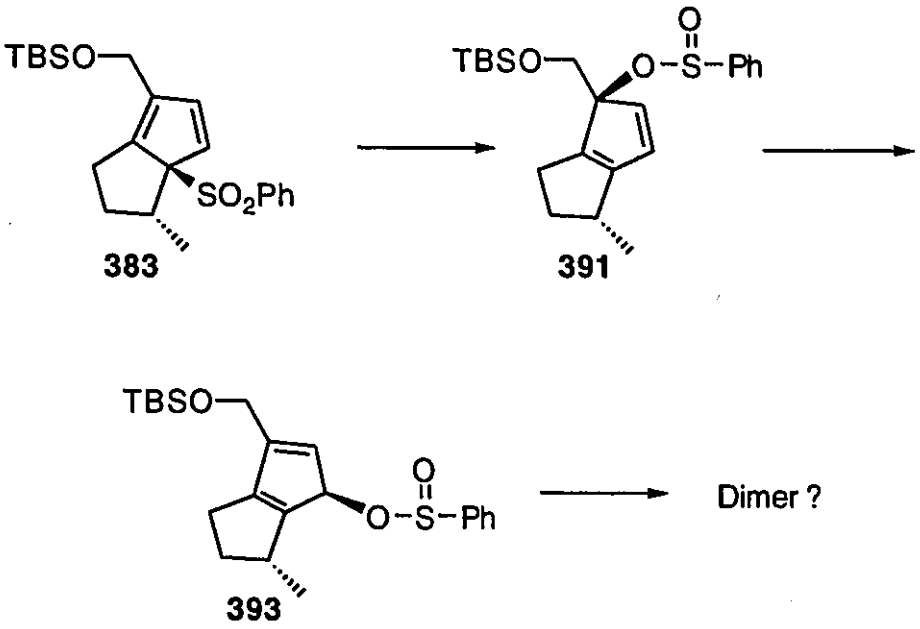
Diene **391** was characterized by an apparent triplet and apparent doublet at 5.58 and 5.79 ppm respectively in the ^{1}H NMR spectrum. Eight carbon resonances at 125.4, 127.4, 129.2, 133.5, 134.0, 134.6, 146.7 and 161.8 ppm indicated that four aromatic carbons as well as four double bond carbons were present. ^{1}H COSY, HETCOR and DEPT experiments further supported this structure.

The possibility of a different structural assignment for the rearrangement product also existed however, based on the IR spectrum of this compound. Two characteristic absorptions for compound **391** at 1298 and 1145 cm^{-1} differed little from the two characteristic bands at 1296 and 1147 cm^{-1} of the sulfone functionality of diene **383**. The structural assignment for diene **392** containing a sulfone group therefore existed based on this information as well as the observation that the compound was found to be only

slightly less polar than the starting diene **383** by TLC. This is consistent with the retention of the less polar sulfone functionalility compared with that of **391**.

The structure is thus tentatively assigned as either **391** or **392**. Unfortunately compound **391/392** was an oil and positive proof of structure through X-ray crystallographic analysis could therefore not be obtained.

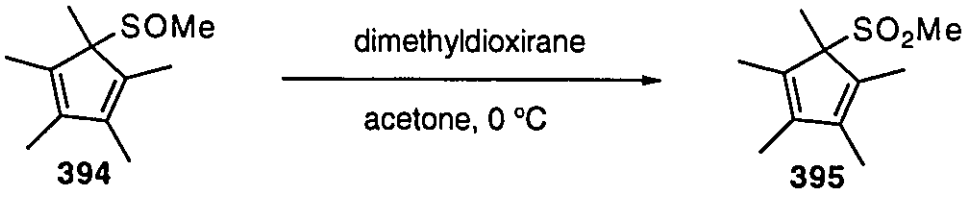
Heating the diene **383** alone in refluxing benzene verified the rearrangement to **391/392** (only **391** is shown in Scheme 134) but showed that at this temperature (80 °C) a further transformation occurred to produce material which was unstable and began to rapidly change into another compound (approximately 20 % conversion in 10 minutes) (Scheme 134).



Scheme 134

It is believed that this material is cyclopentadiene **393** which contains the most highly substituted double bonds of the cyclopentadiene and therefore is the most favoured. This material may dimerize readily.

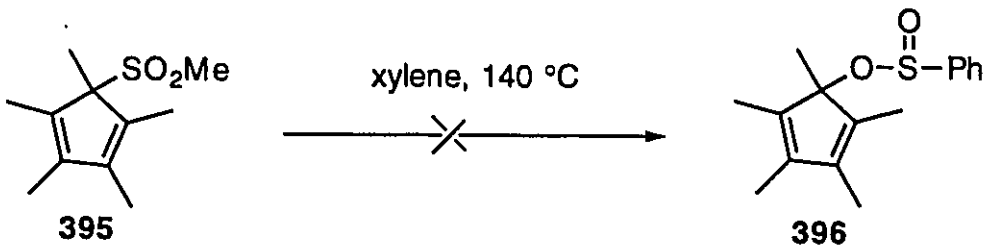
To see whether this rearrangement was a peculiarity to the diene **383**, the sulfone **395** was prepared by oxidation of the sulfoxide **394** (Scheme 135).



394 **395**

Scheme 135

Heating of this sulfone to 140 °C in *o*-xylene afforded only recovered starting material (Scheme 136). This experiment did not comfirm however that rearrangement to the sulfone was not occurring since the product would have the same structure. Nevertheless, it is apparent that there is something unusual about diene **383** which reduces the barrier to rearrangement.



395 **396**

Scheme 136

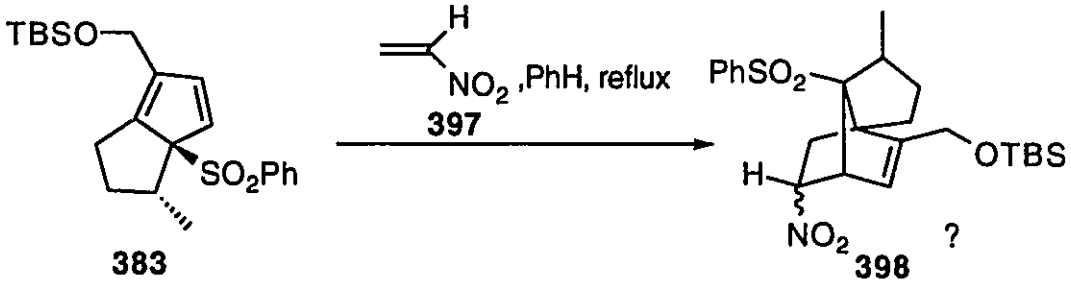
This disheartening result now provided an explanation as to why no new vinylic proton was observed by the heating of **383** with chloroacrylonitrile **379** in refluxing benzene. Rearangement to **391** and **393** must occur first followed by cycloaddition so that several products are obtained. This result also provided the explanation why the diene could not be prepared using a temperature greater than about 30 °C. Clearly rearrangement of the diene was occurring as soon as it was formed.

Attempts to promote the cycloaddition by using neat chloroacryonitrile **379** with ultrasound[124] failed as did the use of Lewis acids such as $ZnCl_2$, copper (II) tetrafluoroborate or copper (II) triflate.[125] The latter two Lewis acids resulted in desilylation only. Extremely high pressures (10,000 atmospheres)[126] or Grieco's procedure utilizing 5 M lithium perchlorate in ether as solvent were similarly ineffective.[127]

5. 3. 6. Attempted Cycloaddition of the Diene with Nitroethylene.

Unfortunately rearrangement of the diene **383** at such a low temperature imposed severe limitations on the number of dienophiles which could be used and therefore only very reactive ones could be used. Nitroethylene **397** is known to react with cyclopentadiene at -150 °C.[128] This compound was prepared according to the procedure of Noland but was found to be unreactive with the diene **383** even at room temperature.[129] Reaction at very high pressures was again ineffective as were Lewis acids which simply served to promote polymerization of the nitroethylene.

Heating of nitroethylene **397** with diene **383** in refluxing benzene gave a mixture of compounds, one of which displayed a doublet (J = 5.5 Hz) at 6.03 ppm in the vinylic region and accounted for approximately 40 % of the crude material in the ^1H NMR spectrum (Scheme 137).

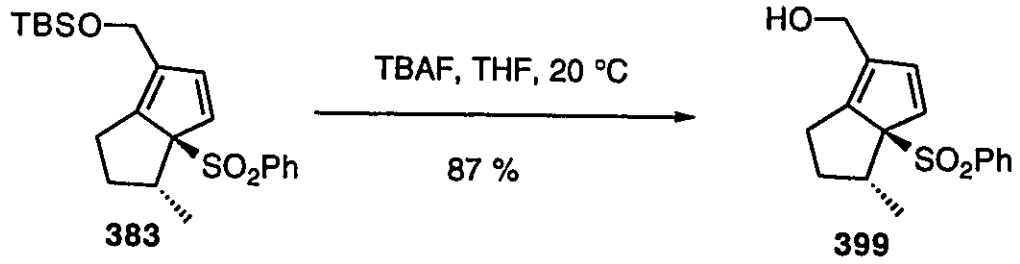


Scheme 137

This was an encouraging result for adduct **398** was expected to display one vinylic hydrogen as a doublet. It was also known that the complete rearrangement of diene **383** took several hours in refluxing benzene and it was thus possible that the desired cycloaddition might have occurred before rearrangement to **391** or **392**. Unfortunately the material from this reaction was unstable and could not be isolated by silica gel chromatography.

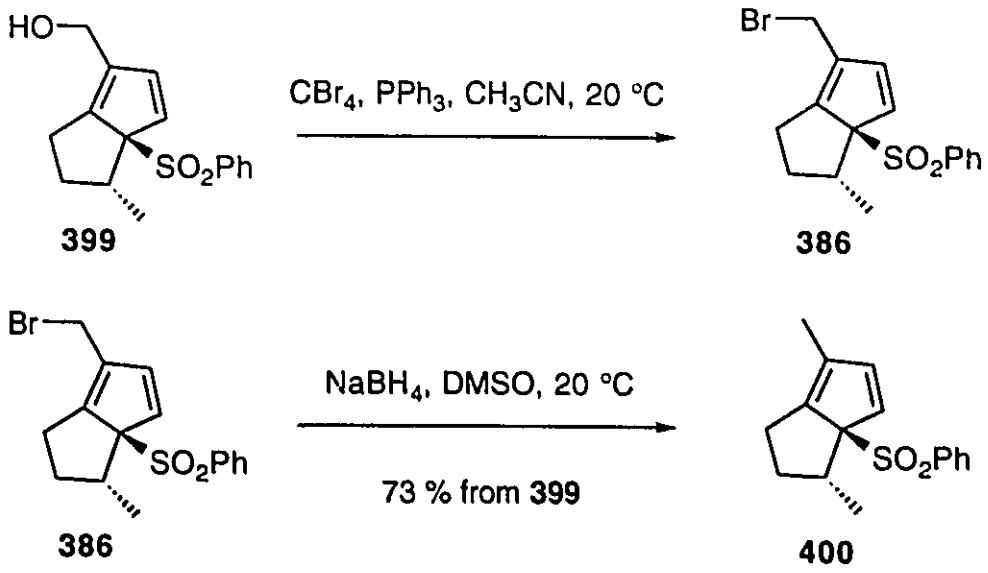
As discussed previously, several Lewis acid catalyzed reactions simply resulted in desilylation of the diene **383** and thus the conversion of **383** to the dimethyldiene **400** was undertaken. In principle a more robust protecting group could simply have been employed to solve this problem but it was felt that this conversion would be straightforward and would furnish the necessary methyl group in the final product. There was also the benefit that the ^{1}H NMR would be simplified.

Desilylation of **383** gave the alcohol **399** in 87 % yield (Scheme 138)[130] which was converted to the bromide **386** and then reduced to the dimethyl diene **400** with a combined yield of 73 % (Scheme 139).[131]



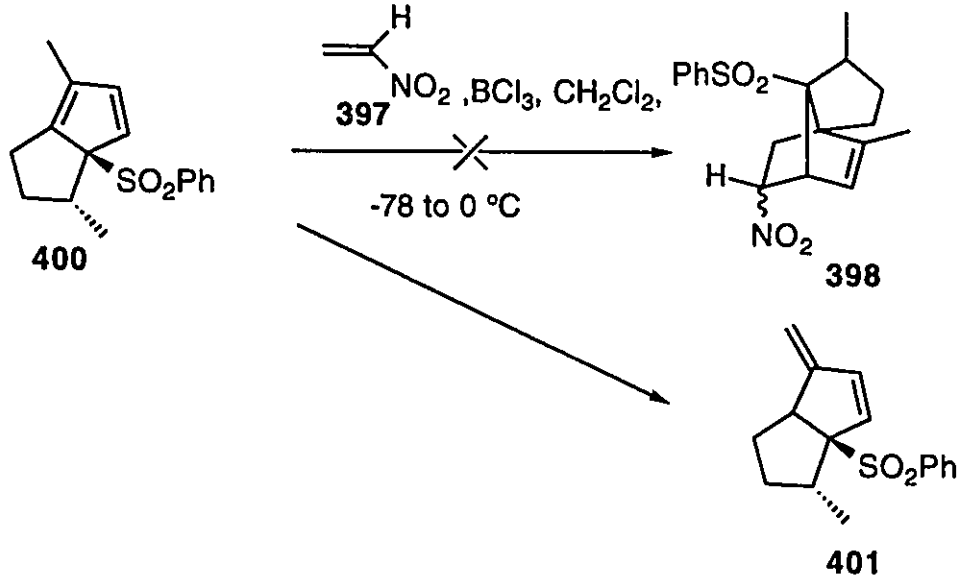
383 **399**

Scheme 138



Scheme 139

Disappointingly, when diene **400** was treated with nitroethylene **397** at low temperature with boron trichloride (BCl_3), rearrangement occurred to give exocyclic methylene compound **401** (Scheme 140).



Scheme 140

This rearrangement presumably occurs to relieve the strain of the diene. Diene **401** was characterized by two doublets (J = 2.2 Hz) integrating for one hydrogen each at 4.72 and 4.85 ppm repectively in the ^{1}H NMR spectrum representing the exocyclic methylene group. Two doublets (J = 5.6 Hz) at 5.94 and 6.30 ppm indicated the presence of the endocyclic double bond. Further confirmation of structure was obtained through ^{1}H COSY and ADEPT experiments.

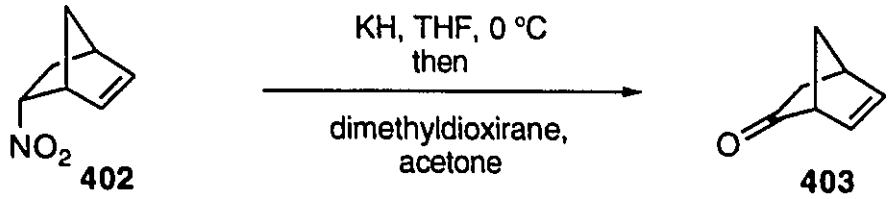
Use of 5 M lithium perchlorate in ether with nitroethylene **397** and the diene **400** at room temperature gave only starting material. Recourse was made to the treatment of diene **400** with nitroethylene in refluxing benzene. As was seen with the TBS diene **383**, an unstable compound was formed which displayed a vinylic doublet (J = 5.5 Hz) at 6.03 ppm.

5. 3. 7. Conversion of the Nitro-adduct to a Ketone.

The inability to isolate the Diels-Alder adduct from the reaction of diene **400** with nitroethylene **397** implied that the crude material should be converted directly to the ketone.

To avoid wasting valuable material the model compound nitronorbornylene **402** was prepared according to the literature method.[132] A number of literature methods were then evaluated for the conversion of **402** to the ketone norbornenone **403**. These methods included $TiCl_3$ buffered with NH_4OAc[133], K_2CO_3/H_2O_2,[134] conversion to the TBS silyl nitronate and cleavage to the ketone with *m*CPBA[135], *t*-BuOK then $V(O)(acac)_2$/*t*-BuOOH[136] and $KOH/KMnO_4$.[137] Even with these known methods it was difficult to obtain good yields of ketone **403**. Bartlett's procedure using *t*-BuOK to first generate the nitronate anion followed by oxidation with $V(O)(acac)_2$ and *t*-BuOOH showed some promise. Modification of this procedure by using KH in THF to generate the nitronate

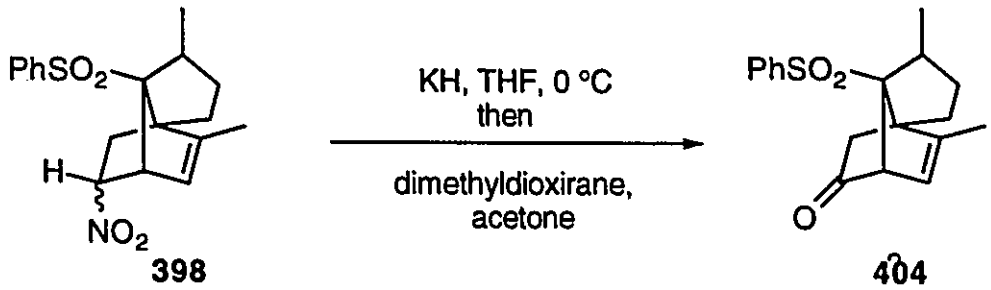
anion followed by treatment with freshly prepared dimethyldioxirane solution in acetone was found to improve yields of ketone **403** (Scheme 141).



402 **403**

Scheme 141

Using the same set of conditions on the mixture of crude Diels-Alder adducts obtained from the diene **400** and nitroethylene **397**, a mixture of three compounds as determined by GC were obtained in very low yield. Each of these compounds possessed the correct mass of 316 a.m.u. (Scheme 142).



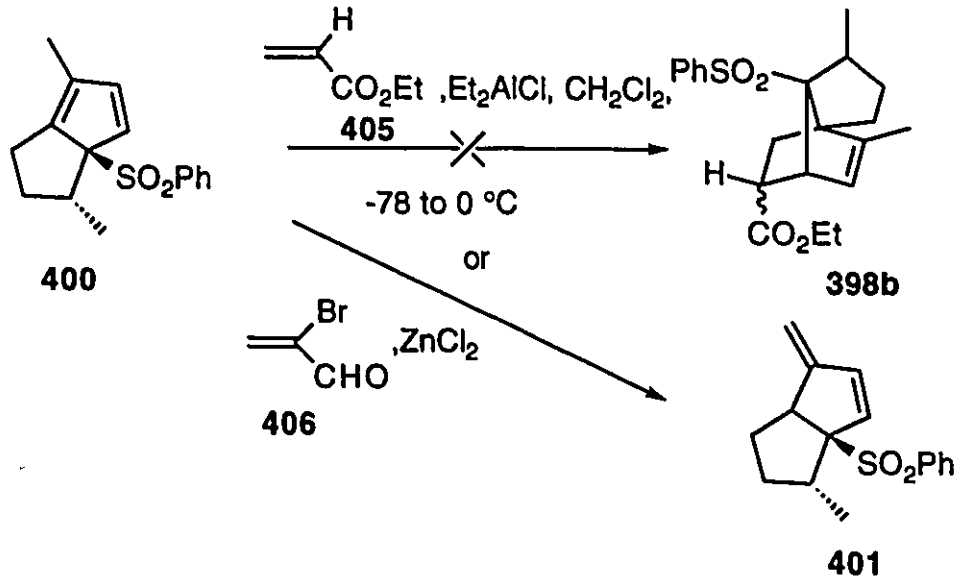
398 **404**

Scheme 142

Part of this low yield can be explained on the basis of the unpredictable nature of nitroethylene, which on a large scale reaction with the diene **400** was found to give substantial quantities of polymer and very little adduct as compared with several smaller scale reactions performed earlier. Less than 2 mg of the three compounds of mass 316 were obtained from 72 mg of diene **400**. It was therefore very difficult to separate and characterize these compounds and no claim is made as to the formation of the desired ketone **404**.

5. 3. 8. Attempted Cycloaddition of the Diene with Other Dienophiles.

The use of ethyl acrylate **405** under Lewis acid catalysis using diethylaluminum chloride and dichloromethane at low temperature again only resulted in rearrangement to the diene **401** (Scheme 143). Use of bromo-acrolein **406** with BCl_3 was similarly ineffective with diene **401** being formed.[138]

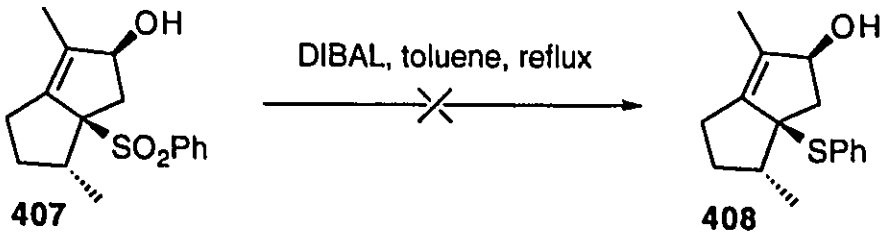


Scheme 143

5. 3. 9. Attempted Conversion of the Sulfone Group to a Sulfde.

Conversion of the sulfone **400** to the sulfide **409** in an effort to prevent the thermal rearrangement of the diene met with much difficulty. Sulfones are extremely difficult to reduce and the use of 'high' temperatures would only serve to rearrange diene **400** before reduction of the sulfone can occur. Thus the use of DIBAL in refluxing toluene, which is known to effect this transformation in certain cases, could not be employed.[139] Reduction of the thermally stable sulfone-alcohol **407** was therefore

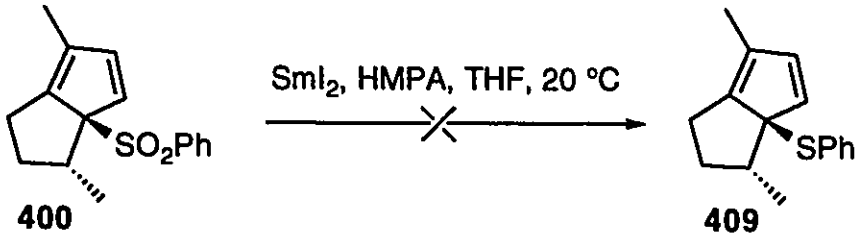
attempted under these conditions but none of the desired sulfide **408** could be detected (Scheme 144).



407 **408**

Scheme 144

A more recent publication using the powerful reducing ability of samarium (II) iodide with HMPA claimed that sulfones could be quickly reduced to sulfides at 0 °C in THF in several minutes.[140] Treatment of diene **400** under the same set of conditions failed to give any of the desired sulfide **409** and only a complex mixture resulted (Scheme 145).



400 **409**

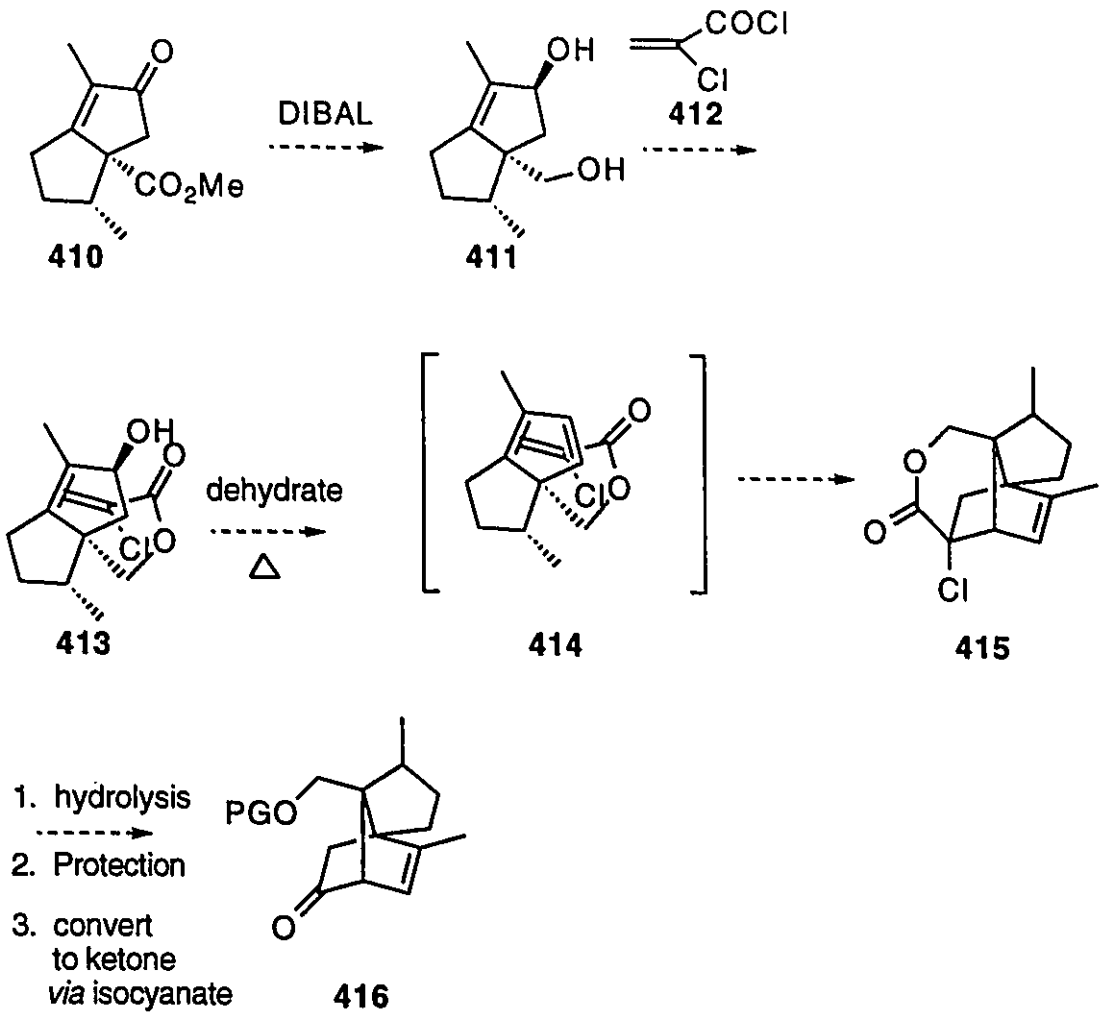
Scheme 145

5. 4. CONCLUSIONS.

5. 4. 1. Future work.

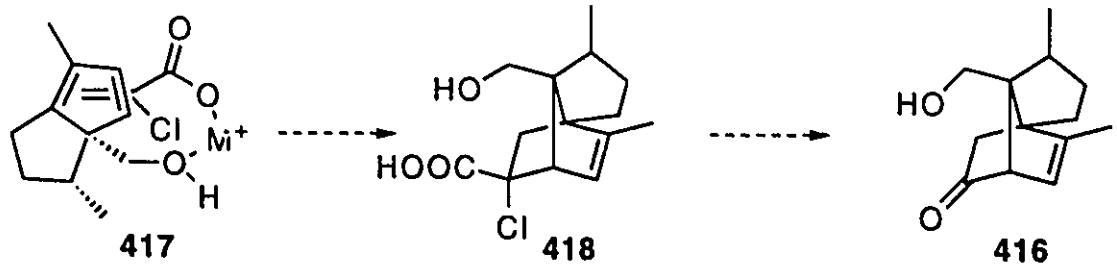
The facile rearrangement of diene **383/400** unfortunately limited the temperature at which the cycloaddition could be carried out. It therefore appears necessary to replace the sulfone with a more suitable group which will not facilitate rearrangement. Should an effort be made to prepare a modified diquinane, the original plan to incorporate a *syn* relationship between the C16 methyl group and the group X should be followed. This would avoid the neccessity of correcting the stereochemistry in the final product at C6. More importantly, through the knowledge gained from the π-facial selectivity studies carried out in our laboratory, the group X can be chosen which can direct the addition of the dienophile syn to the group X. Addition would also be to the less hindered convex face such that these two factors would be complementary.

The opportunity also exists to use an intramolecular Diels-Alder reaction to prepare the tricylcic framework. For example, the diol **411** should be readily available by reduction of the keto-ester **410** (Scheme 146). The resulting primary alcohol could then be esterified to afford the α-chloroacrylate **413**.[141] Conversion to the diene **414** followed by cycloaddition would then afford the adduct **415**. Hydrolysis of the lactone, protection of the alcohol, followed by conversion of the carboxyl group to the acid chloride and treatment with sodium azide would then provide the isocyanate via a Curtius degradation. Hydrolysis of the isocyanate would then afford the ketone **416**.



Scheme 146

Similarly, an intermolecular reaction with the diene-alcohol **417** using a metal chelate bond for good regiocontrol could be employed (Scheme 147). These possibilities remain for future work.



417 418 416

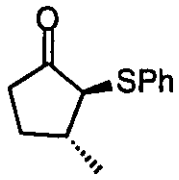
Scheme 147

EXPERIMENTAL

CHAPTER 6

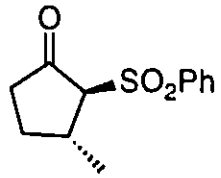
See Chapter 4 for the General Experimental.

3-methyl-2-phenylthiocyclopentanone (370).



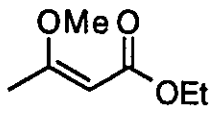
Methyllithium (402 mL, 1.4 M in ether, low halide, 563 mmol) was added to a stirred -23 °C suspension of copper (I) cyanide (26.0 g, 290 mmol) in ether (400 mL). After addition of approximately 50 mL of methyllithium all the copper cyanide had dissolved, producing a light yeliow solution. Further addition of methyllithium resulted in a dark green solution. A solution of cyclopentenone **369** (44.5 g, 234 mmol) in ether (300 mL) was then added over a 45 minute period. After stirring at -23 °C for 1 h the cooling bath was removed and stirring continued for 1 h. The mixture was then cooled to 0 °C and pH 8 NH_4Cl/NH_4OH solution (200 mL) cautiously added (Gas Evolution!). The ether layer was then separated and the aqueous layer further extracted with ether (5 X 200 mL). The combined organic extracts were washed with saturated NH_4Cl solution (200 mL), brine (200 mL), dried, filtered and concentrated to afford the ketone **370** (43.8 g, 90.9 %) as an approximately 6:1 mixture of trans vs cis isomers; Major isomer; IR (neat) 3040, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 1.18 (d, 3 H, J = 6.5 Hz), 1.41-1.61 (m, 1 H), 1.96-2.45 (m, 4 H), 2.95 (d, 1 H, J = 9.6 Hz), 7.22-7.28 (m, 3 H), 7.40-7.46 (m, 2 H); ^{13}C NMR (50 MHz) δ 18.7, 28.5, 36.7, 37.2, 60.7, 127.8, 128.9, 133.0, 214.7.

3-methyl-2-phenylsulfonylthiocyclopentanone (371).



A solution of keto-thio-ether **370** (43.2 g, 208 mmol) in methanol (1.0 L) was added dropwise over 0.5 h to a stirred 0 °C solution of Oxone® (240 g, 781 mmol) in methanol (1.0 L). The mixture was warmed to 21 °C and stirred for 18 h after which the methanol was removed under reduced pressure, water added (200 ml) and the aqueous layer extracted with dichloromethane (5 X 350 mL). The combined extracts were washed with brine (200 mL), dried, filtered and concentrated to afford keto-sulfone **371** (48.8 g, 98.6 %) as a pale yellow solid which was sufficiently pure for use in the next step; mp 125-126°C (recrystallized from dichloromethane/ether); IR ($CHCl_3$) 3022, 1749, 1448, 1312, 1216, 1152 cm^{-1}; ^1H NMR (200 MHz) δ 1.25 (d, 3 H, J = 6.7 Hz), 1.35-1.59 (m, 1 H), 2.18-2.37 (m, 3 H), 2.86-3.02 (m, 1 H), 3.31 (d, 1 H, J = 8.0 Hz), 7.50-7.70 (m, 3 H), 7.83-7.89 (m, 2 H); ^{13}C NMR 20.5, 28.5, 33.3, 38.8, 75.7, 129.1, 134.2, 138.1, 207.1; HRMS (EI) calcd for $C_{11}H_{11}O_3S$ (M^+ - CH_3) 223.0429, found 223.0429; Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; found: C, 60.70; H, 5.78.

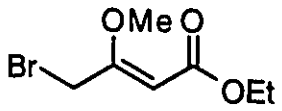
ethyl-(3-methoxy)-(Z)-but-2-enoate (373).



Sulfuric acid (6 drops, 95 %) was added to a stirred 21 °C mixture of ethyl acetoacetate (26.0 g, 200 mmol) and trimethyl orthoformate (23.4 g, 220 mmol). The

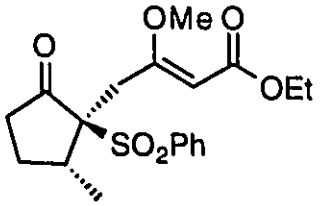
mixture was stirred for 24 h at 21 °C, pyridine (6 drops) added and then the mixture distilled to afford the enol ether **373** (23.8 g, 82.6 %) as a colourless, mobile liquid; bp 62°C (20 mm Hg) IR (neat) 2967, 1710, 1630, 1445, 1278, 1143 cm^{-1}; ^1H NMR (200 MHz) δ 1.19 (t, 3 H, J = 7.1 Hz), 2.21 (s, 3 H), 3.55 (s, 3 H), 4.06 (q, 2 H, J = 7.1 Hz), 4.94 (s, 1 H); ^{13}C NMR (50 MHz) δ 13.9, 18.2, 54.9, 58.8, 90.5, 167.6, 172.8; HRMS (EI) calcd for $C_7H_{12}O_3$ 144.0787, found 144.0765.

ethyl-(4-bromo-3-methoxy)-(Z)-but-2-enoate (374).



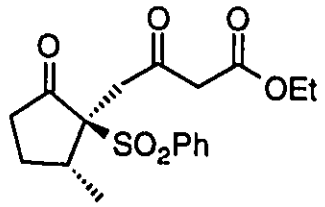
Enol ether **373** (21.6 g, 150 mmol) was added to a stirred 21 °C suspension of N-bromosuccinimide (28.8 g, 162 mmol) and 2,2'-azobis(isobutyronitrile) (20 mg, 0.12 mmol) and the mixture heated at reflux for 1.45 h. The mixture was cooled to 21 °C, filtered through a glass frit, concentrated to an oil under reduced pressure and then distilled to afford the bromo-enol ether **374** (29.8 g, 89.1 %) as a colourless oil; bp 99-101 °C (1.0 mm Hg); IR (neat) 2980, 1708, 1631, 1443, 1295, 1147 cm^{-1}; ^1H NMR (200 MHz) δ 1.23 (t, 3 H, J = 7.1 Hz), 3.65 (s, 3 H), 4.12 (q, 2 H, J = 7.1 Hz), 4.47 (s, 2 H), 5.07 (s, 1 H); ^{13}C NMR (50 MHz) δ 13.9, 25.4, 55.9, 59.7, 93.1, 166.2, 169.0; HRMS (EI) calcd for $C_7H_{11}O_3Br$ 221.9891, found 221.9896.

ethyl-4-[5-methyl-2-oxo-1-phenylsulfonylcyclopent-1-yl]-3-methoxy-but-2-enoate (375).



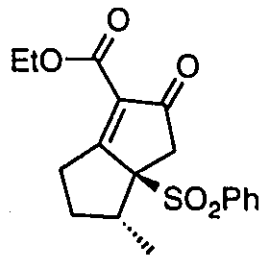
Sodium iodide (37.2 g, 248 mmol), anhydrous potassium carbonate (33.8 g, 245 mmol) and the bromo-enol ether **374** (54.8 g, 246 mmol) were added sequentially to a stirred 21 °C solution of the sulfone **371** (47.8 g, 201 mmol) in anhydrous acetone (3.5 L). The mixture was stirred at 21 °C for 2 h and then heated at reflux for 30 h. The acetone was removed under reduced pressure and water (300 mL) and sodium sulfite (5 g) were added. The aqueous phase was extracted with dichloromethane (4 X 500 mL) and the combined extracts were washed with water (100 mL), saturated NH_4Cl solution (100 mL), brine (100 mL), dried, filtered and concentrated to a dark brown residual oil which was chromatographed (30 % ethyl acetate/hexanes followed by 100 % dichloromethane) to give an orange solid which was further purified by recrystallization from dichloromethane/ether to afford the alkylated product **375** (35.5 g, 46.5 %) as white needles; mp 123-125 °C; IR ($CHCl_3$) 3021, 1747, 1705, 1300, 1216, 1144 cm^{-1}; ^1H NMR (200 MHz) δ 1.08 (d, 3 H, J = 6.9 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 1.31-1.45 (m, 1 H), 2.08-2.22 (m, 1 H), 2.28-2.57 (m, 2 H), 2.91 (d, 1 H, J = 16.1 Hz), 3.28-3.42 (m, 1 H), 3.45 (s, 3 H), 4.20 (q, 2 H, J = 7.1 Hz), 4.29 (d, 1 H, J = 16.1 Hz), 4.95 (s, 1 H), 7.51-7.69 (m, 3 H), 7.84-7.86 (m, 2 H); ^{13}C NMR (75 MHz) δ 14.3, 15.8, 28.4, 32.4, 35.9, 38.9, 55.2, 59.8, 75.3, 92.6, 128.6, 131.1, 134.1, 135.3, 166.5, 169.0, 210.1; HRMS (EI) calcd for $C_{13}H_{19}O_4$ (M^+ - $PhSO_2$) 239.1284, found 239.1276; Anal. Calcd for $C_{19}H_{24}O_6S$: C, 59.98; H, 6.36; found: C, 60.14; H, 6.53.

ethyl-4-[5-methyl-2-oxo-1-phenylsulfonylcyclopent-1-yl]-3-oxo-but-2-enoate (378).



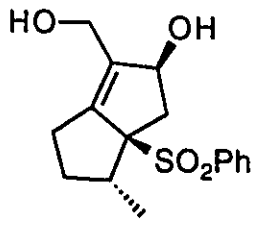
Trifluoroacetic acid (87 mL, 1.13 mol) and water saturated ether (22.0 mL, 7.5 % w/v water, 1.65 g H_2O, 91.7 mmol) were added sequentially to a stirred 21 °C solution of the enol ether **375** (34.5 g, 90.8 mmol) in chloroform (500 mL). The mixture was stirred for 18 h, cooled to 0 °C and then saturated $NaHCO_3$ solution (800 mL) was cautiously added. The organic phase was separated and the aqueous layer extracted with dichloromethane (3 X 250 mL). The combined extracts were washed with saturated $NaHCO_3$ (100 mL), brine (100 mL), dried, filtered and concentrated to give a residual oil which was recrystallized from dichloromethane/methanol to afford the diketone **378** (26.1 g, 78.5 %) as white needles; mp 136-137.5 °C; IR ($CHCl_3$) 3024, 1738, 1708, 1310, 1217, 1143 cm^{-1}; ^1H NMR (200 MHz) δ 0.98 (d, 3 H, J = 6.8 Hz), 1.19 (t, 3 H, J = 7.1 Hz), 1.72-1.84 (m, 1 H), 2.05-2.20 (m, 1 H), 2.30-2.61 (m, 2 H), 3.21-3.45 (m, 5 H), 4.21 (q, 2 H, J = 7.1 Hz), 7.51-7.58 (m, 2 H), 7.65-7.77 (m, 1 H), 7.75-7.88 (m, 2 H); ^{13}C NMR (75 MHz) δ 13.9, 16.4, 28.0, 34.7, 39.2, 44.8, 48.4, 61.6, 74.4, 128.9, 130.8, 134.4, 134.7, 166.1, 198.6, 209.8; HRMS (EI) calcd for $C_{12}H_{17}O_4$ (M^+ - $PhSO_2$) 225.1127, found 225.1129; Anal. Calcd for $C_{18}H_{22}O_6S$: C, 59.00; H, 6.05; found: C, 58.46; H, 5.85.

4-carboethoxy-8-methyl-3-oxo-1-phenylsulfonyl-bicyclo[3.3.0]oct-4-ene (379).



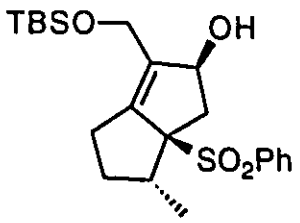
A suspension of the diketone **375** (200 mg, 0.545 mmol) in ethanol (20.0 mL) was added dropwise over a 15 minute period to a stirred 0 °C solution of freshly prepared sodium ethoxide solution (prepared by addition of sodium metal (13.5 mg, 0.587 mmol) to ethanol (1.90 mL)). The mixture was stirred at 0 °C for 1 h and then saturated NH_4Cl solution (10 mL) was added. The ethanol was removed under reduced pressure, the mixture diluted with water (10 mL) and the aqueous layer extracted with dichloromethane (3 X 50 mL). The combined extracts were washed with water (10 mL), brine (2 X 10 mL), dried, filtered and concentrated to afford the aldol-condensation product **379** (169 mg, 88.7 %) as a pale yellow solid which was used directly in the following step; mp 149-151 °C (dec); IR ($CHCl_3$) 3023, 1730, 1709, 1649, 1301, 1217, 1143 cm^{-1}; ^1H NMR (200 MHz) δ 0.97 (d, 3 H, J = 6.8 Hz), 1.20-1.30 (m, 1 H), 1.32 (t, 3 H, J = 7.1 Hz), 1.50-1.68 (m, 1 H), 2.55 (d, 1 H, J = 19.2 Hz), 2.80-2.95 (m, 1 H), 2.82 (d, 1 H, J = 19.2 Hz), 3.10-3.26 (m, 2 H), 4.25 (q, 2 H, J = 7.1 Hz), 7.48-7.57 (m, 2 H), 7.62-7.80 (m, 3 H); ^{13}C NMR (75 MHz) δ 14.2, 19.1, 28.4, 33.0, 33.9, 42.6, 61.1, 129.1, 130.4, 131.5, 133.3, 134.8, 161.1, 187.2, 198.6; HRMS (EI) calcd for $C_{12}H_{15}O_3$ (M^+ - $PhSO_2$) 207.1021, found; Anal. Calcd for $C_{18}H_{20}O_5S$: C, 62.05; H, 5.79; found: C, 62.26; H, 5.94.

3-hydroxy-4-hydroxymethyl-8-methyl-1-phenylsulfonyl-bicyclo[3.3.0]oct-4-ene (380).



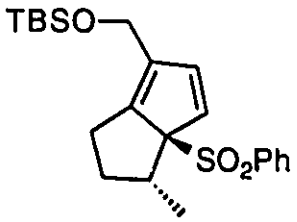
Diisobutylaluminum hydride (3.50 mL, 1.5 M in toluene, 5.25 mmol) was added to a stirred -78 °C solution of the keto-ester **379** (531 mg, 1.53 mmol) in dichloromethane (10.0 mL). The mixture was stirred at -78 °C for 1 h and then warmed to 0 °C and held at this temperature for 5 minutes. Saturated NH_4Cl solution (10 mL) was added and the mixture stirred for 15 minutes. Dichloromethane (25 mL) was added and the mixture washed with 0 °C sulfuric acid (20 mL, 10 %). The organic phase was separated and the aqueous layer further extracted with dichloromethane (6 X 30 mL). The combined organic extracts were washed with 0 °C sulfuric acid (25 mL, 10 %), saturated $NaHCO_3$ solution (20 mL) (CAUTION !), dried, filtered and concentrated to a residual oil which was chromatographed (100 % ethyl acetate) to afford the diol **380** (296 mg, 62.8 %) as a white solid; mp 138-139 °C (dec); IR ($CHCl_3$) 3428, 3020, 1278, 1216, 1134 cm^{-1}; ^1H NMR (200 MHz) δ 0.69 (d, 3 H, J = 7.0 Hz), 2.11-2.39 (m, 6 H), 2.57-2.66 (m, 1 H), 4.20 (d, 1 H, J = 11.9 Hz), 4.35 (s, 2 H), 4.92 (dd, 1 H, J = 12.8, 6.4 Hz), 7.53-7.66 (m, 3 H), 7.85-7.95 (m, 2 H); ^{13}C NMR (75 MHz) δ 17.9, 24.2, 34.3, 36.4, 58.1, 79.5, 88.3, 129.1, 130.0, 134.0, 136.9, 142.9, 144.2; HRMS (EI) calcd for $C_{10}H_{15}O_2$ (M^+ - $PhSO_2$) 167.1072, found 167.1071; Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54; found: C, 62.25; H, 6.52.

4-tert-butyldimethylsiloxymethyl-3-hydroxy-8-methyl-1-phenylsulfonyl-bicyclo[3.3.0]oct-4-ene (**381**).



Dichloromethane (40 mL) was added to a mixture of the diol **380** (405 mg, 1.31 mmol), 4-dimethylaminopyridine (224 mg, 1.83 mmol) and t-butyldimethylsilyl chloride (272 mg, 1.81 mmol). The mixture was stirred for 10 h at 21 °C and then concentrated to an oil which was chromatographed (80% ethyl acetate/hexanes) to afford the mono-silylated alcohol **381** (452 mg, 81.2 %) as a colourless oil which crystallized on standing; mp 61-63 °C ; IR ($CHCl_3$) 3480, 3018, 1445, 1280, 1215, 1135 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.70 (d, 3 H, J = 7.1 Hz), 0.88 (s, 9 H), 1.21-1.45 (m, 1 H), 2.10-2.50 (m, 5 H), 2.58-2.75 (m, 1 H), 3.89 (d, 1 H, J = 12.1 Hz), 4.36 (s, 2 H), 4.80-4.90 (dd, 1 H, J = 11.2, 5.6 Hz), 7.52-7.72 (m, 3 H, 7.91-7.98 (m, 2 H); ^{13}C NMR (75 MHz) δ -5.5, -5.4, 18.1, 18.3, 24.4, 25.8, 34.2, 36.4, 36.5, 59.1, 79.1, 88.6, 129.1, 130.1, 133.9, 137.2, 142.6, 143.6; HRMS (EI) calcd for $C_{16}H_{29}O_2Si$ (M^+ - $PhSO_2$) 281.1938, found 281.1899; Anal. Calcd for $C_{22}H_{34}O_4SSi$: C, 62.52; H, 8.11; found: C, 62.80; H, 8.17.

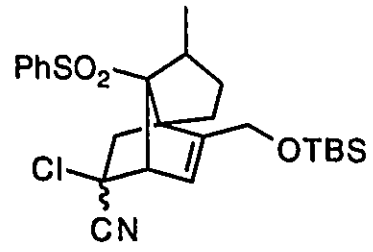
4-tert-butyldimethylsiloxymethyl-8-methyl-1-phenylsulfonyl-bicyclo[3.3.0]octa-2,4-diene (383).



Tri-n-butylphosphine (882 uL, 3.54 mmol) was added to a stirred 21 °C solution of the alcohol **381** (500 mg, 1.18 mmol) and 2-nitrophenylselenylcyanate (804 mg, 3.54 mmol) in pyridine (10.0 mL). The mixture was cooled to 0 °C and stirred for 2.5 h. Hydrogen peroxide (1.50 mL, 30 %) was added and stirring continued at 0 °C for 4 h after which the pyridine and excess hydrogen peroxide were removed under reduced pressure. Saturated $NaHCO_3$ solution (10 mL) was added and the aqueous layer extracted with ether (100 mL). The ether extract was washed with saturated $NaHCO_3$ solution (15 mL), brine (15 mL), dried, filtered and concentrated to give a residual oil which was chromatographed (30 % ethyl acetate/hexanes) to afford the diene **383** (308 mg, 64.3 %) as a colourless oil which crystallized on standing; mp 52-54 °C; IR ($CHCl_3$) 2946, 2858, 1643, 1448, 1296, 1147, 910 cm^{-1}; ^1H NMR (200 MHz) δ -0.052 (s, 6 H), 0.80 (d, 3 H, J = 7.1 Hz), 0.81 (s, 9 H), 1.80-1.93 (m, 1 H), 2.36-2.50 (m, 1 H), 2.62-2.79 (m, 1 H), 2.92-3.17 (m, 2 H), 3.94 (d, 1 H, J = 14.0 Hz), 4.13 (d, 1 H, J = 14.0 Hz), 6.02 (d, 1 H, J = 5.1 Hz), 6.11 (d, 1 H, J = 5.1 Hz), 7.23-7.34 (m, 2 H), 7.46-7.54 (m, 1 H), 7.68-7.74 (m, 2 H); ^{13}C NMR (75 MHz) δ -5.6, 18.1, 18.9, 21.3, 25.6, 31.3, 39.9, 59.0, 92.6, 127.0, 129.4, 130.6, 133.2, 135.0, 140.4, 141.5, 146.8; HRMS (EI) calcd for $C_{18}H_{23}O_3SSi$ (M^+ - t-butyl) 347.1138, found 347.1134.

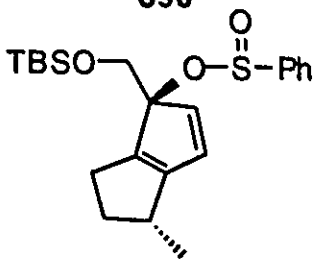
6-methyl-2-tert-butyldimethylsiloxymethyl-1-phenylsulfinyl-bicyclo[3.3.0]octa-2,7-diene (391).

Attempted preparation of



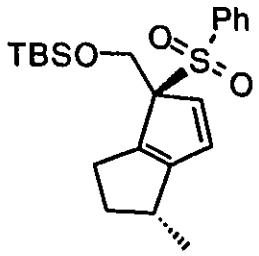
390

Isolation of



391

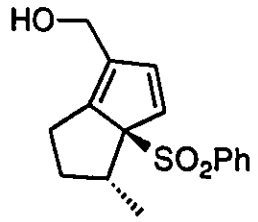
or



392

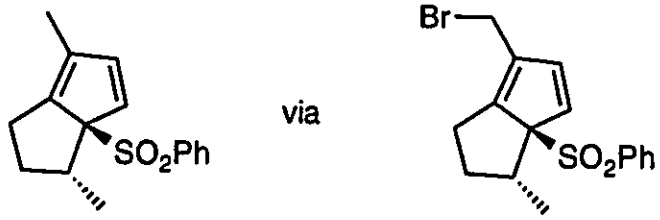
A mixture of the diene **383** (935 mg, 2.31 mmol) and chloroacrylonitrile (2.00 mL, 25.2 mmol) was heated at 35 °C for 11 days. The excess chloroacrylonitrile was removed under reduced pressure and the residual oil was chromatographed (40 % to 100 % dichloromethane in hexanes) to afford pure **391/392** (161 mg, 17.2 %) as a colourless oil, a mixed fraction of **391/392** and diene **383** (80 mg, 8.56 %) and pure diene **383** (550 mg, 58.8 %); IR ($CHCl_3$) 2957, 2930, 2858, 1458, 1382, 1298, 1256, 1145 cm^{-1}; ^1H NMR (500 MHz) δ 0.00 (s, 6 H), 0.81 (s, 9 H), 1.14 (d, 1 H, J = 7.0 Hz), 1.72-1.86 (m, 2 H), 2.65-2.71 (m, 1 H), 2.84-2.93 (m, 1 H), 3.30-3.47 (m, 1 H), 4.51 (s, 2 H), 5.58 (apparent t, 1 H), 5.79 (d, 1 H, J = 1.8 Hz), 7.32-7.36 (m, 2 H), 7.51-7.55 (m, 1 H), 7.70-7.79 (m, 2 H); ^{13}C NMR (75 MHz) δ –5.4, –5.3, 18.3, 18.6, 23.6, 25.9, 30.4, 40.8, 60.9, 86.8, 125.4, 127.4, 129.2, 133.5, 134.0, 134.6, 146.7, 161.8; HRMS (EI) calcd for $C_{22}H_{32}O_3SSi$ 404.1843, found 404.1820.

4-hydroxymethyl-8-methyl-1-phenylsulfonyl-bicyclo[3.3.0]octa-2,4-diene (383).



Tetra-n-butylammonium fluoride (1.0 mL, 1.0 M in THF, 1.0 mmol) was added to a stirred 0 °C solution of the diene **383** (328 mg, 0.811 mmol) in THF (20 mL). The mixture was stirred at 0 °C for 2 h and then the THF was removed under reduced pressure and the residual oil chromatographed (20 % to 80 % ethyl acetate in hexanes) to afford the alcohol **399** (205 mg, 87.1 %) as a colourless oil; ^{1}H NMR (200 MHz) δ 1.32 (d, 3 H, J = 7.2 Hz), 1.78-1.93 (m, 1 H), 2.35-2.52 (m, 1 H), 2.64-2.82 (m, 1 H), 2.93-3.20 (m, 2 H), 3.96 (d, 1 H, J = 12.5 Hz), 4.13 (d, 1 H, J = 12.5 Hz), 6.07 (d, 1 H, J = 6.5 Hz), 6.14 (d, 1 H, J = 6.5 Hz).

4-bromomethyl-8-methyl-1-phenylsulfonyl-bicyclo[3.3.0]octa-2,4-diene (383).

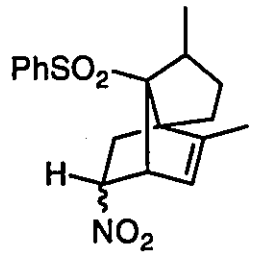


Acetonitrile (3 mL) was added to a mixture of the alcohol **399** (34.7 mg, 0.120 mmol), triphenylphosphine (37.0 mg, 0.140 mmol) and freshly sublimed carbon tetrabromide (46.5 mg, 0.140 mmol). The mixture was stirred at 21 °C for 1 h, and then

the acetonitrile was removed under reduced pressure and the residual oil chromatographed (20 % ethyl acetate in hexanes) to afford the bromide **386** (38.0 mg, 90.0 %) as a white solid; ^{1}H NMR (200 MHz) δ 1.30 (d, 3 H, J = 7.1Hz), 1.32-1.99 (m, 1 H), 2.36-2.51 (m, 1 H), 2.65-2.83 (m, 1 H), 2.97-3.04 (m, 2 H), 3.79 (d, 1 H, J = 10.4 Hz), 3.90 (d, 1 H, J = 10.4 Hz), 6.02 (d, 1 H, J = 5.1 Hz), 6.16 (d, 1 H, J = 5.1 Hz), 7.30-7.38 (m, 2 H), 7.48-7.57 (m, 1 H), 7.68-7.72 (m, 2 H). Reduction of bromide **386** to dimethyldiene **400**: A solution of the bromodiene **386** (38.0 mg, 0.108 mmol) in DMSO (4 mL) was added to a stirred 21°C solution of sodium borohydride (8.0 mg, 0.21 mmol) in DMSO (2.5 mL). The mixture was stirred at 21 °C for 4 h and then water was added (10 mL). The aqueous layer was extracted with ether (5 X 10 mL) and the combined extracts were washed with water (2 X 5 mL), brine (2 X 5 mL), dried and concentrated to afford the dimethyldiene **400** (23.9 mg, 80.8 %) as a colourless solid; mp 98-99 °C; ^{1}H NMR (200 MHz) δ 0.77 (d, 1 H, J = 6.4 Hz), 1.57 (s, 3 H), 1.76-1.91 (m, 1 H), 2.24-2.40 (m, 1 H), 2.59-2.77 (m, 1 H), 2.91-3.13 (m, 2 H), 5.82 (d, 1 H, J = 5.1 Hz), 6.07 (d, 1 H, J = 5.1 Hz), 7.28 (m, 2 H), 7.47-7.55 (m, 1 H), 7.70-7.75 (m, 2 H); ^{13}C NMR (75 MHz) δ 12.7, 18.7, 20.7, 31.6, 39.7, 91.9, 126.8, 129.2, 130.4, 133.0, 135.0, 137.6, 143.3, 146.8; HRMS (EI) calcd for $C_{16}H_{18}O_2S$ 274.1028, found 274.1020.

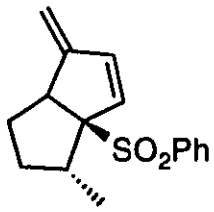
4-methylene-8-methyl-1-phenylsulfonyl-bicyclo[3.3.0]octa-2,4-diene (383).

Attempted preparation of



398

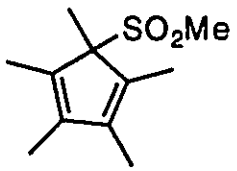
Isolation of



401

Freshly prepared nitroethylene (30.0 mg, 0.411 mmol) was added to a stirred 21 °C solution of the diene **383** (23.4 mg, 0.0854 mmol) in dichloromethane (2 mL). TLC analysis after 6 h indicated no reaction had occurred. The mixture was then cooled to -78 °C and boron trichloride (50.0 uL, 1 M in hexanes, 0.050 mmol) was added. After warming to 21 °C over a 12 h period saturated $NaHCO_3$ solution (5 mL) and dichloromethane (20 mL) were added. The organic phase was then separated and the aqueous layer further extracted with dichloromethane (4 X 10 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), dried, filtered and concentrated to a residual oil which was chromatographed (100 % dichloromethane) to afford none of the desired adduct **398** but only rearranged diene **401** (14.0 mg, 59.8 %) as an oil; ^1H NMR (300 MHz) δ 0.98 (d, 3 H, J = 6.8 Hz), 1.10-1.18 (m, 1 H), 1.55-1.61 (m, 1 H), 1.75-1.95 (m, 2 H), 2.75-2.83 (m, 1 H), 3.46 (d, 1 H, J = 8.5 Hz), 4.72 (d, 1 H, J = 2.2 Hz), 4.85 (d, 1 H, J = 2.2 Hz), 5.94 (d, 1 H, J = 5.6 Hz), 6.30 (d, 1 H, J = 5.6 Hz), 7.45-7.61 (m, 3 H), 7.80-7.84 (m, 2 H); ^{13}C NMR (75 MHz) δ 16.0, 32.6, 33.9, 38.6, 50.0, 87.2, 107.1, 128.6, 129.9, 131.3, 133.4, 137.0, 141.1, 155.9; HRMS (EI) calcd for $C_{16}H_{18}O_2S$ 274.1028, found 274.1032.

1,2,3,4,5-pentamethyl-1-methylsulfonyl-cyclopenta-2,4-diene (**395**).



Freshly prepared dimethyldioxirane solution (6 ml, ca 0.1 M in acetone) was added to a stirred 21 °C solution of sulfoxide **394** (100 mg, 0.56 mmol) in acetone (2 mL). The acetone was removed under reduced pressure and the residual oil chromatographed (50 % ethyl acetate in hexanes) to afford the sulfone **395** (68.0 mg, 62.0

%) as a white solid; mp 112-114.5 °C; IR ($CHCl_3$) 3021, 1655, 1443, 1292, 1149, 1073 cm^{-1}; ^1H NMR (200 MHz) δ 1.40 (s, 3 H), 1.80 (s, 3 H), 1.89 (s, 3 H), 1.90 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (75 MHz) δ 10.7, 11.4, 33.8, 78.0, 134.2, 140.9; HRMS (EI) calcd for $C_{11}H_{18}O_2S$ 214.1028, found 214.1031.

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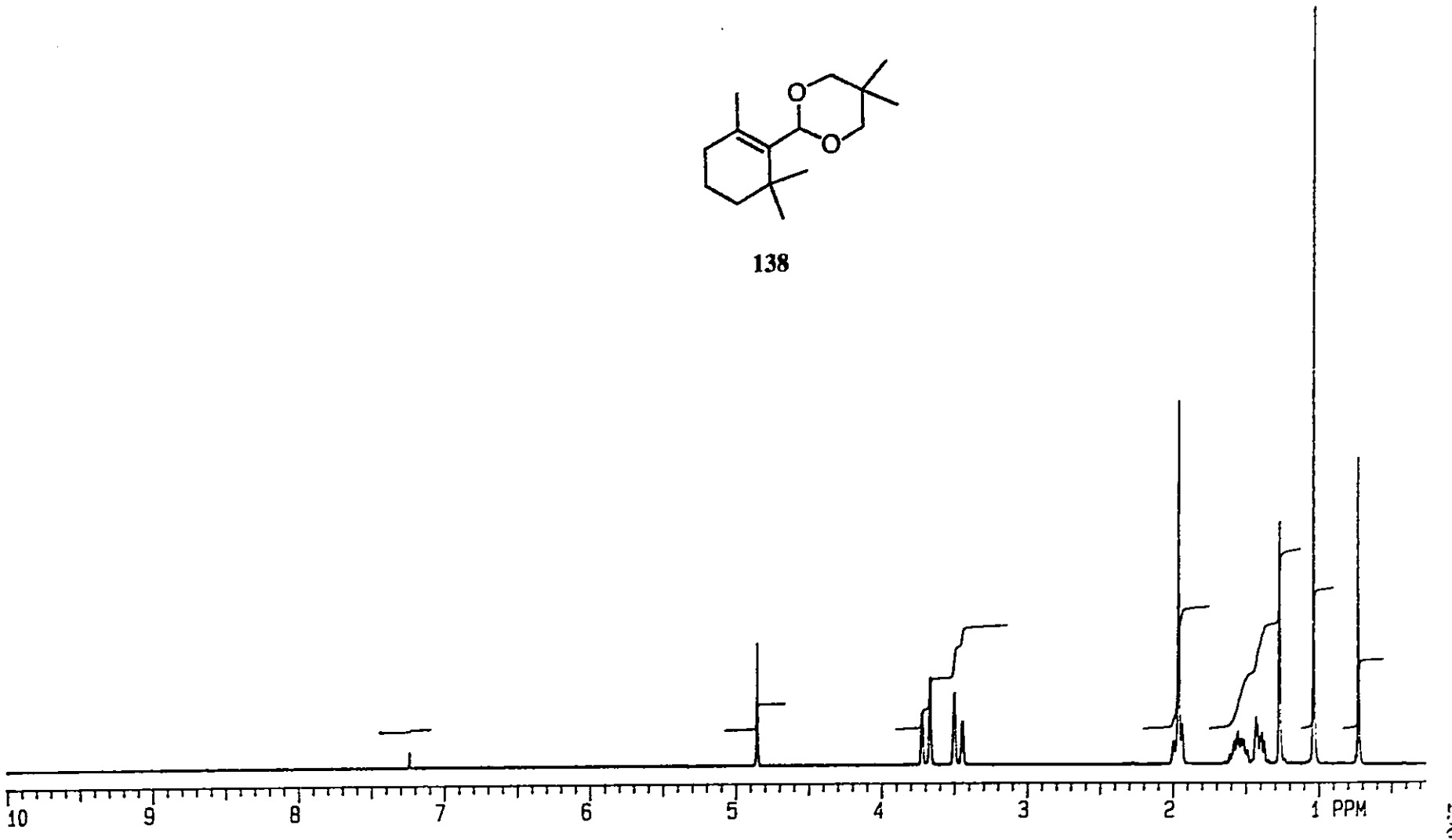
CLAIMS TO ORIGINAL RESEARCH

1. Fully functionalized Taxol A ring building block **203** was prepared possessing a C10 acetal.
2. It was demonstrated that excellent diastereoselectivity could be obtained from the reduction of the carbonyl group of ketone **139**.
3. Good diastereoselectivity was obtained for the TBSCN addition to the C10 carbonyl group of enal **265**.
4. The Diels-Alder precursor **272** was prepared using a highly convergent approach by the sequential addition of the diene and dienophile components.
5. Progress has been achieved in the development of a convergent route to taxoids.
6. The novel diene **383** was prepared via treatment of the allylic alcohol **381** with ortho-nitrophenylselenyl cyanate, tri-*n*-butylphosphine followed by addition of hydrogen peroxide.
7. Dienes **383** and **400** were found to undergo an unusual rearrangement upon heating at 35 °C.
8. Compound **400** was shown to rearrange to the exocyclic methylene compound **401** when treated with Lewis acids.

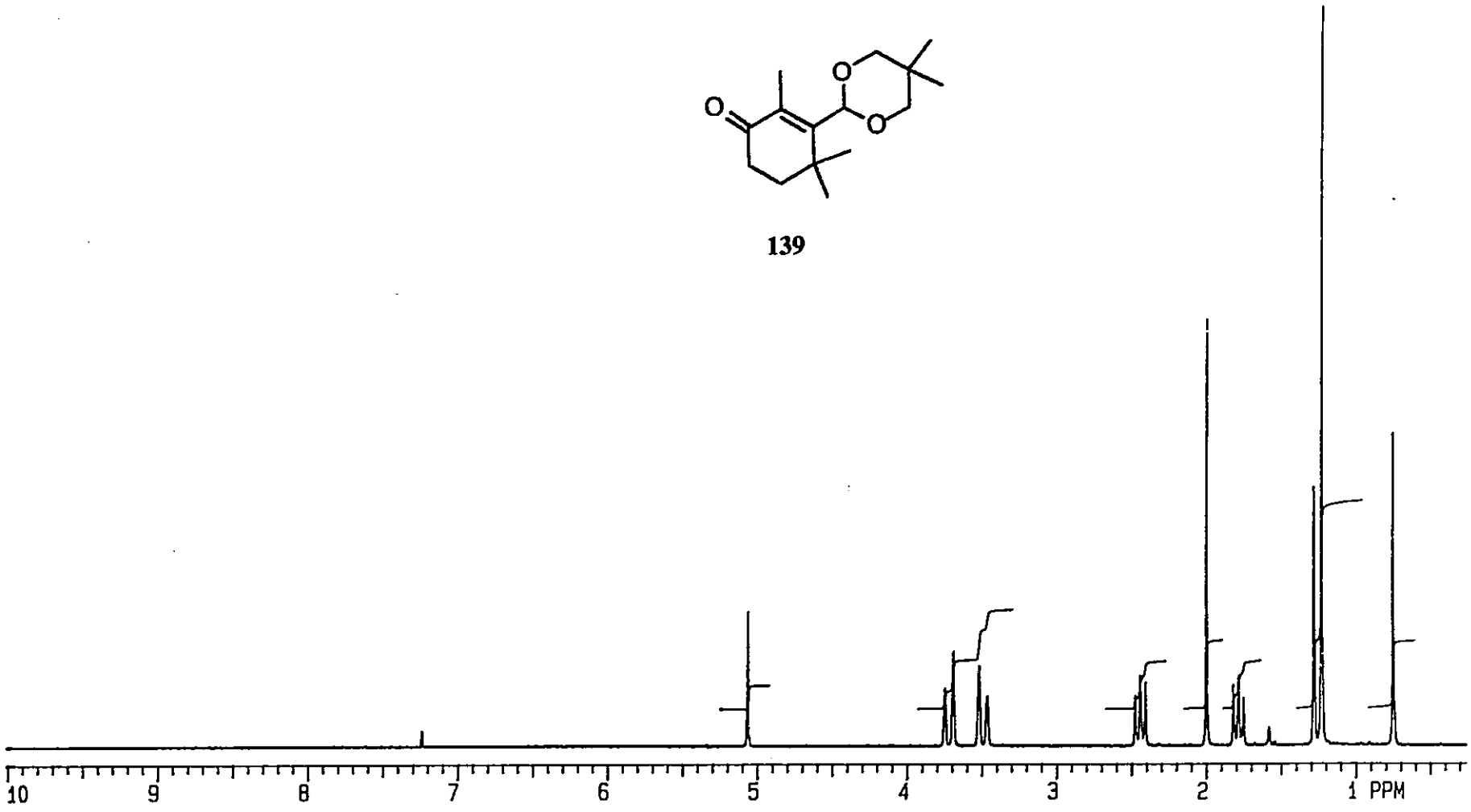
APPENDIX I

REPRODUCTION OF THE ORIGINAL SPECTRA OF SOME KEY COMPOUNDS DESCRIBED IN THIS THESIS



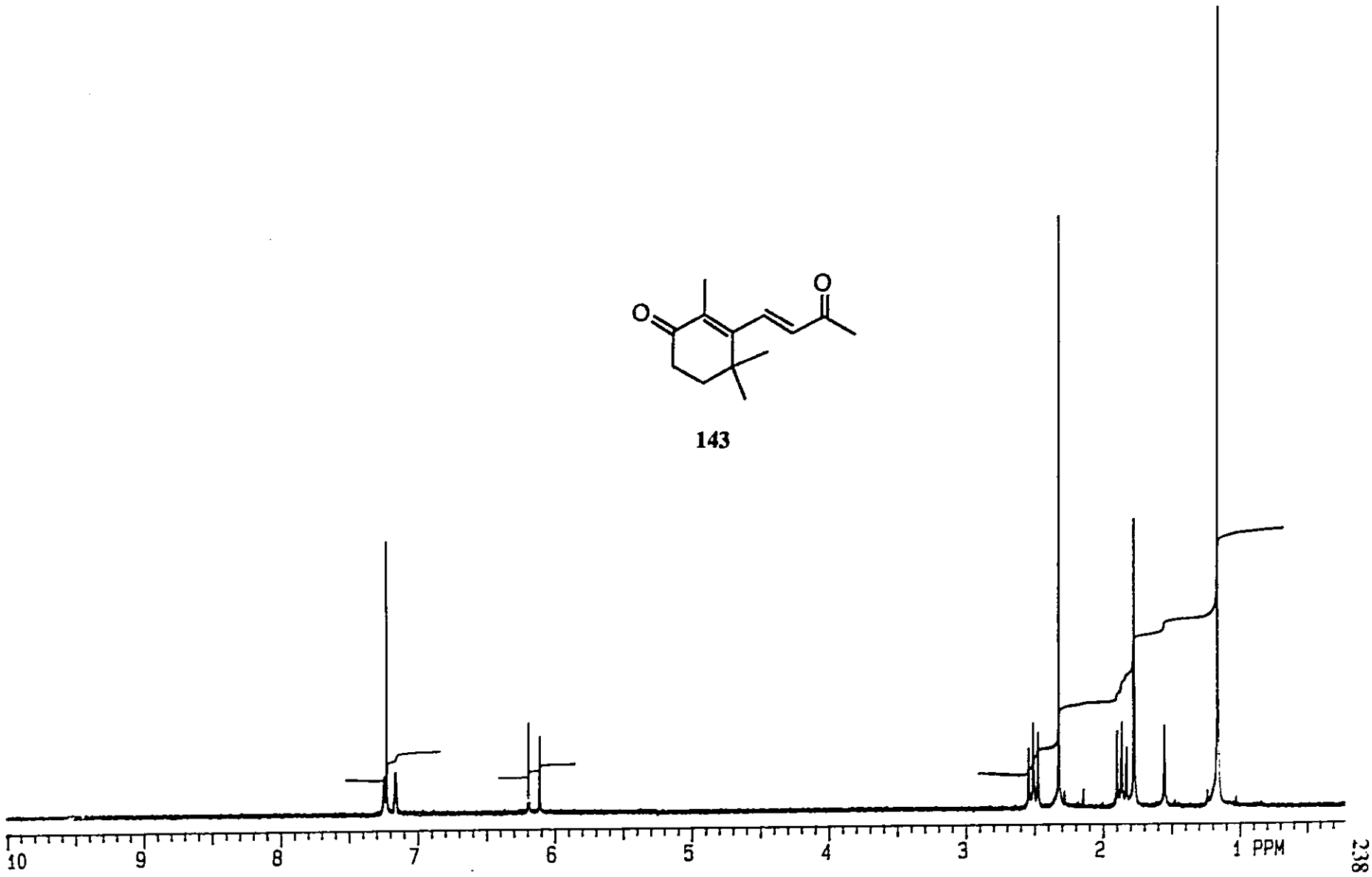
138

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **138**



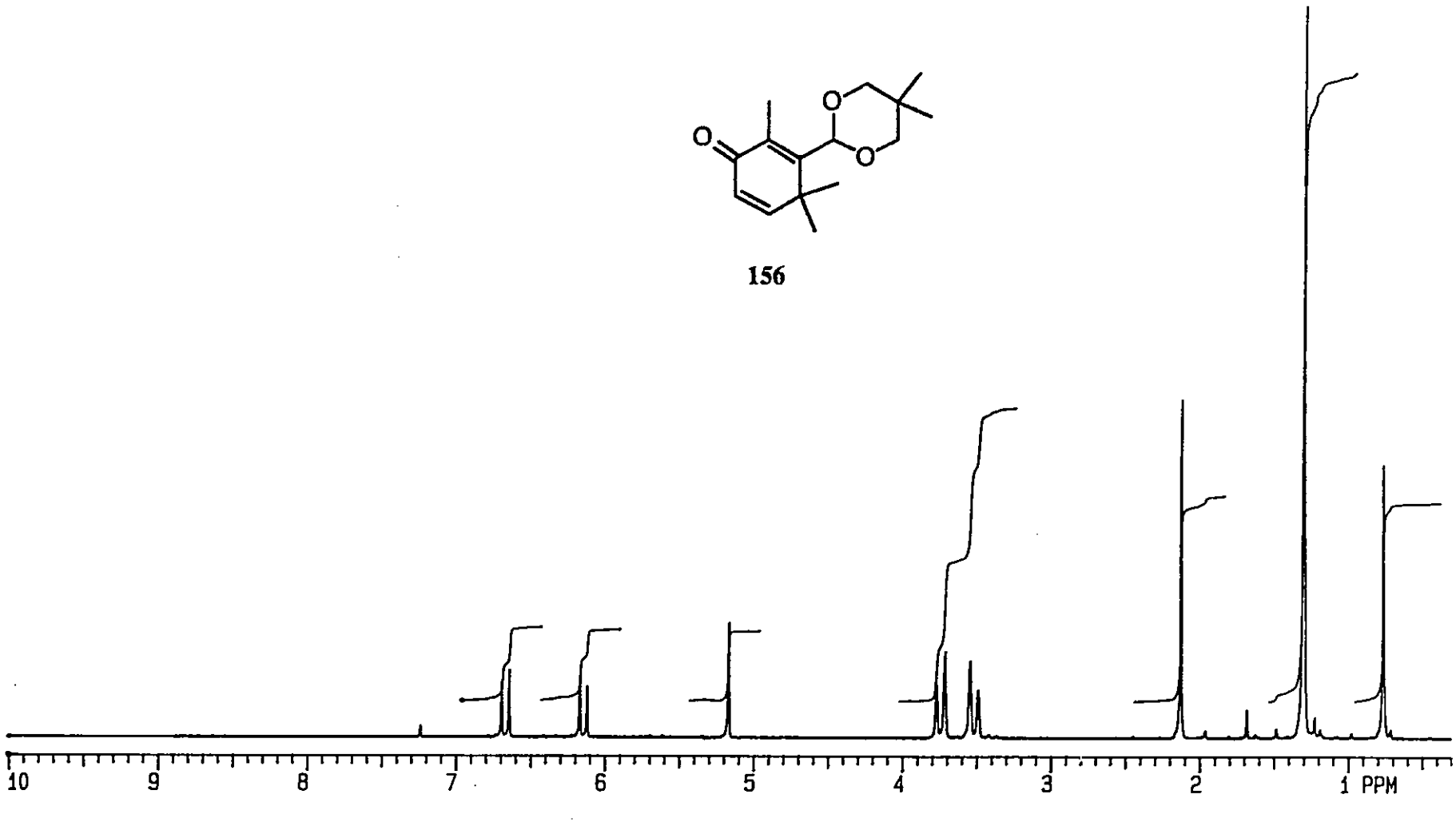
139

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **139**



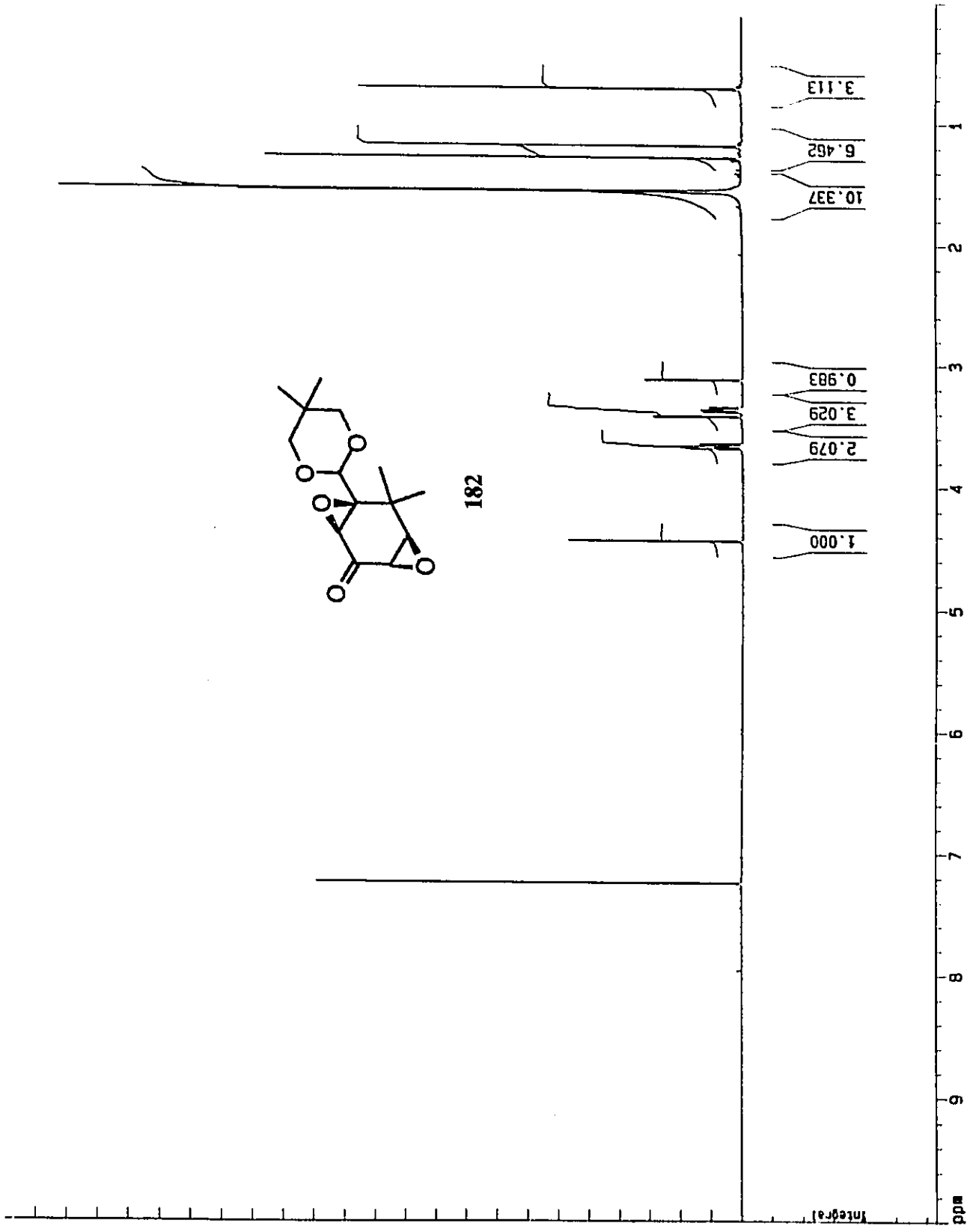
143

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **143**

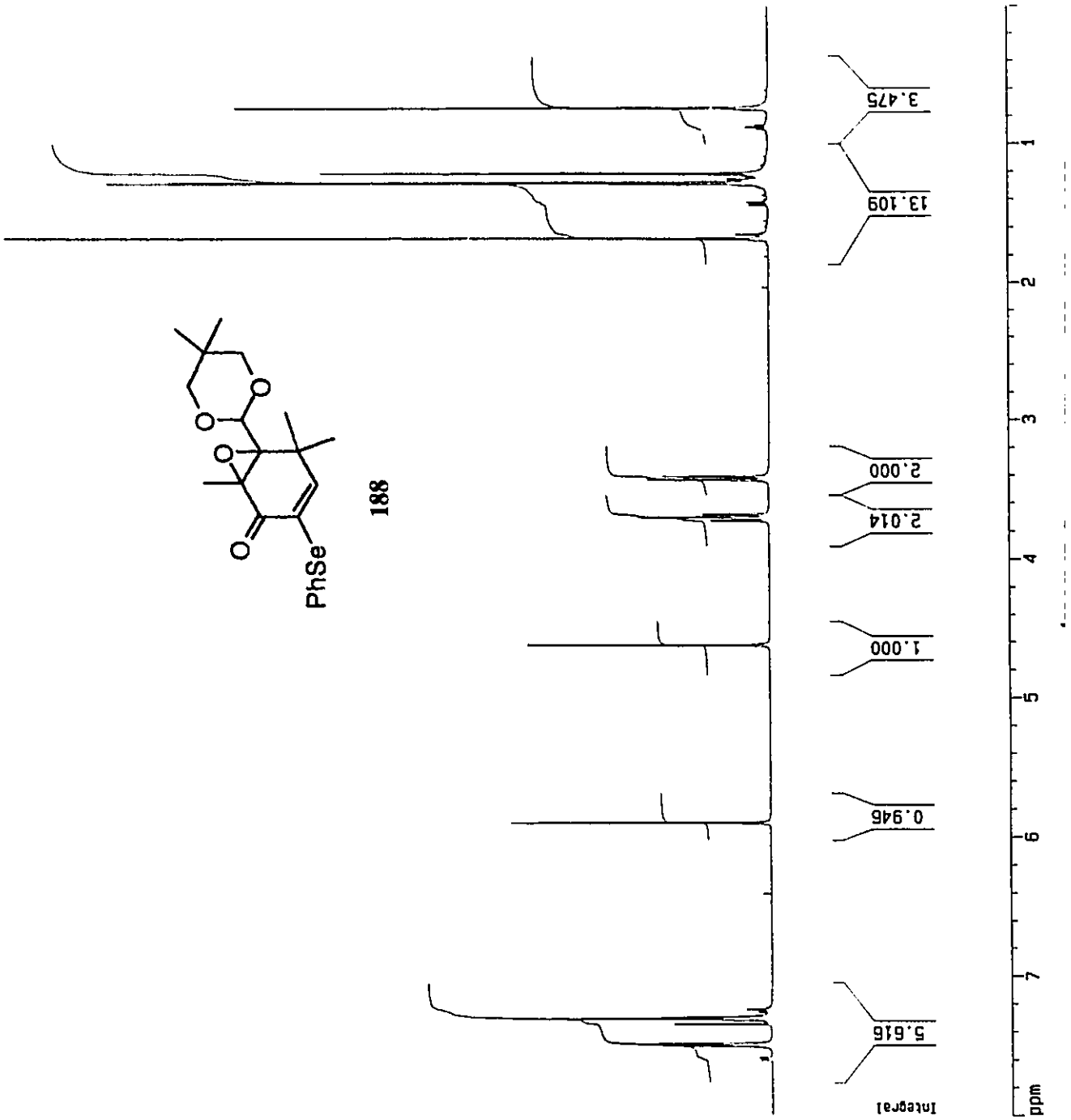


156

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **156**



182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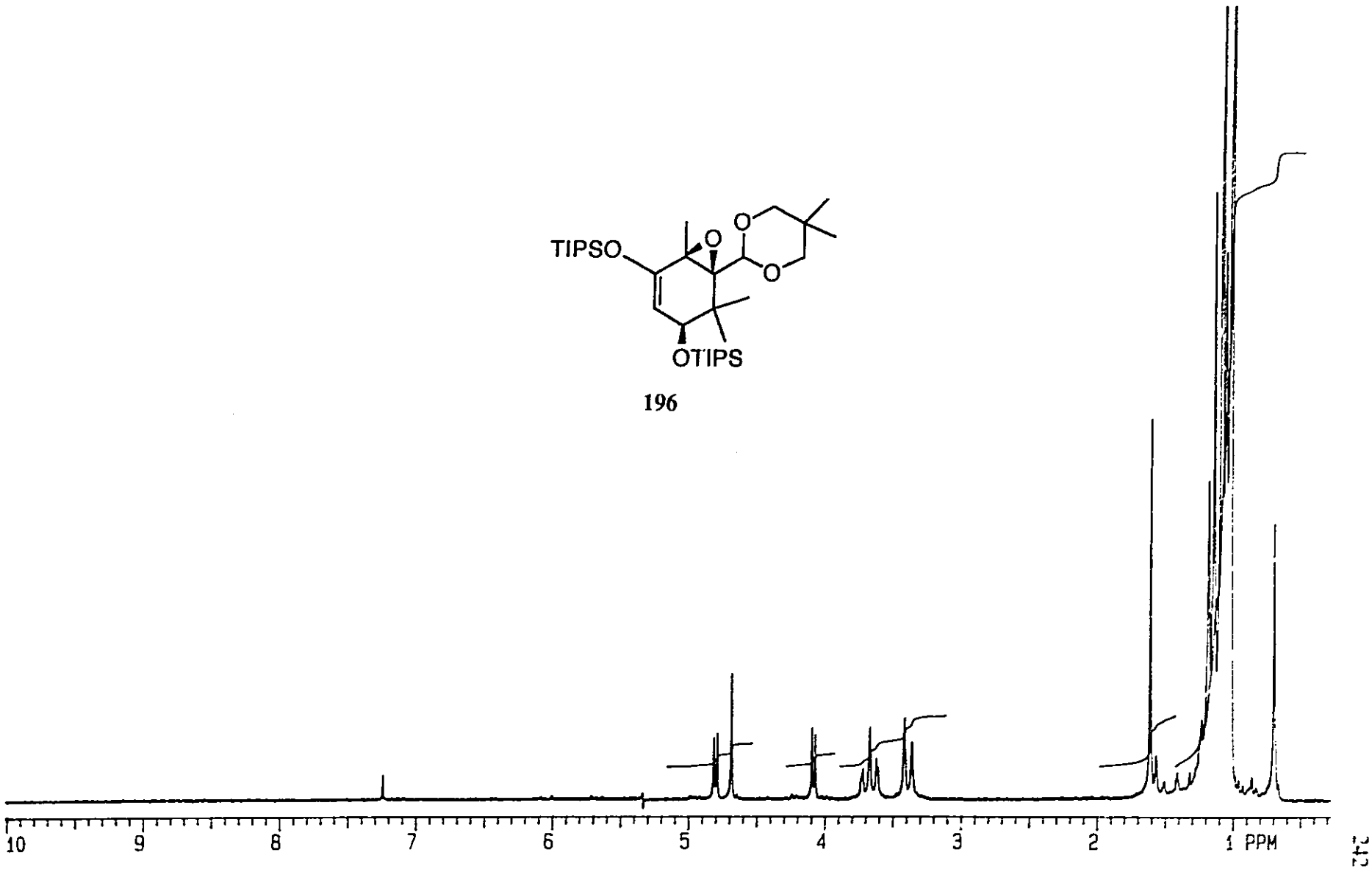
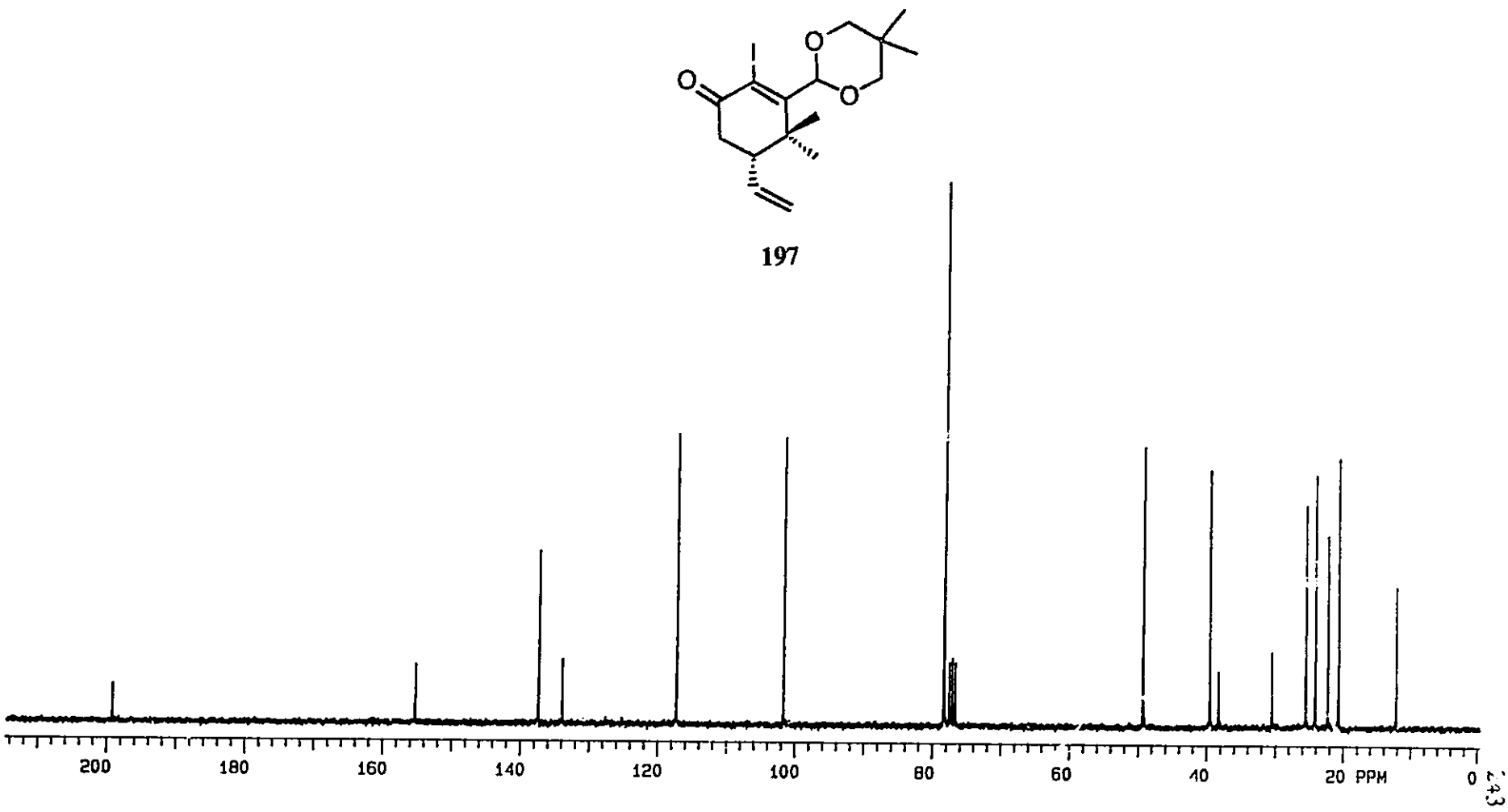
5.616
Integral
ppm
1
2
3
4
5
6
7



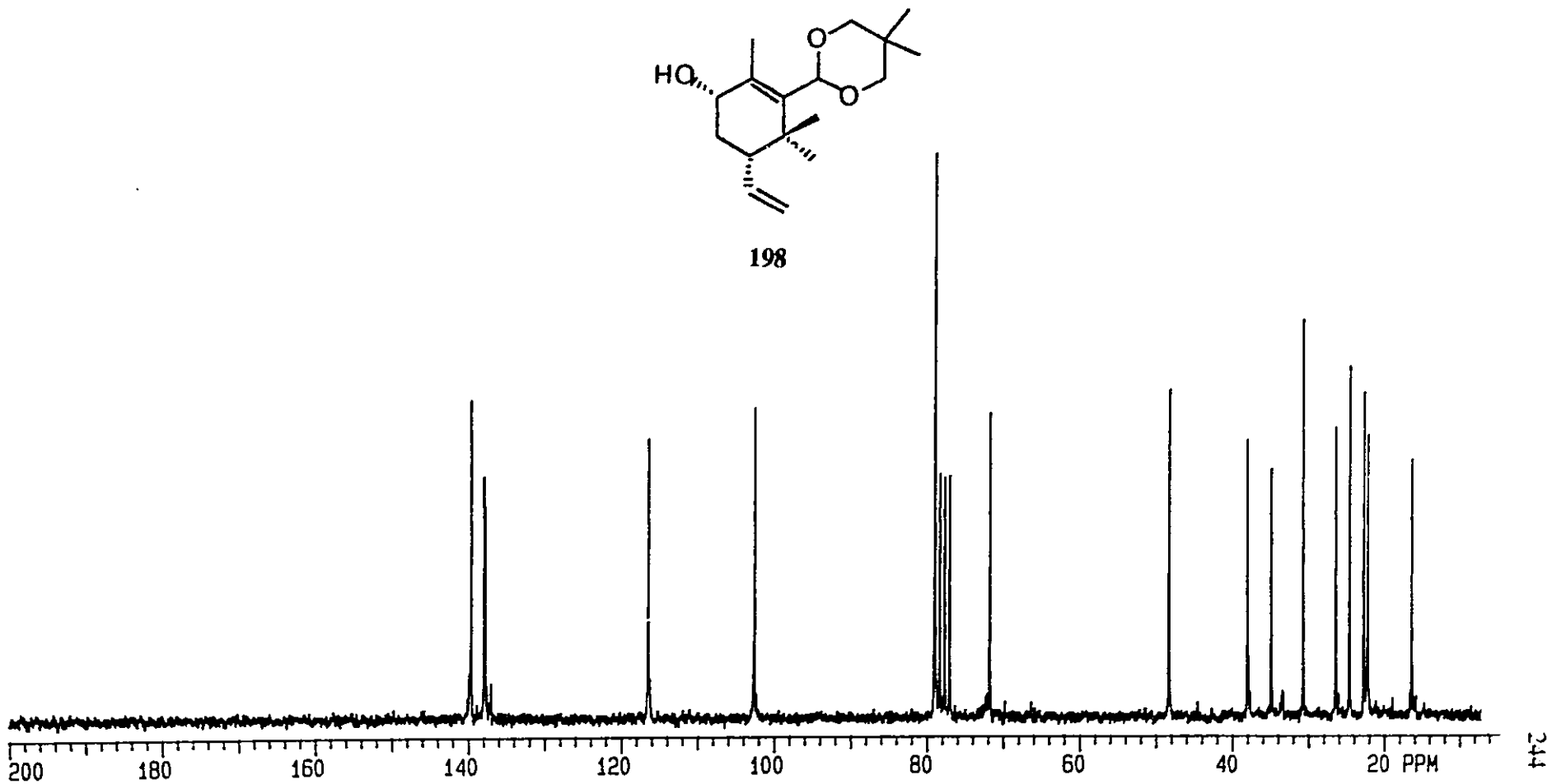
196

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **196**



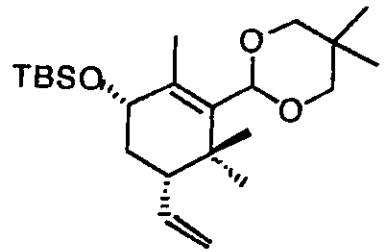
197

^{13}C NMR Spectrum ($CDCl_3$, 75 MHz) of **197**

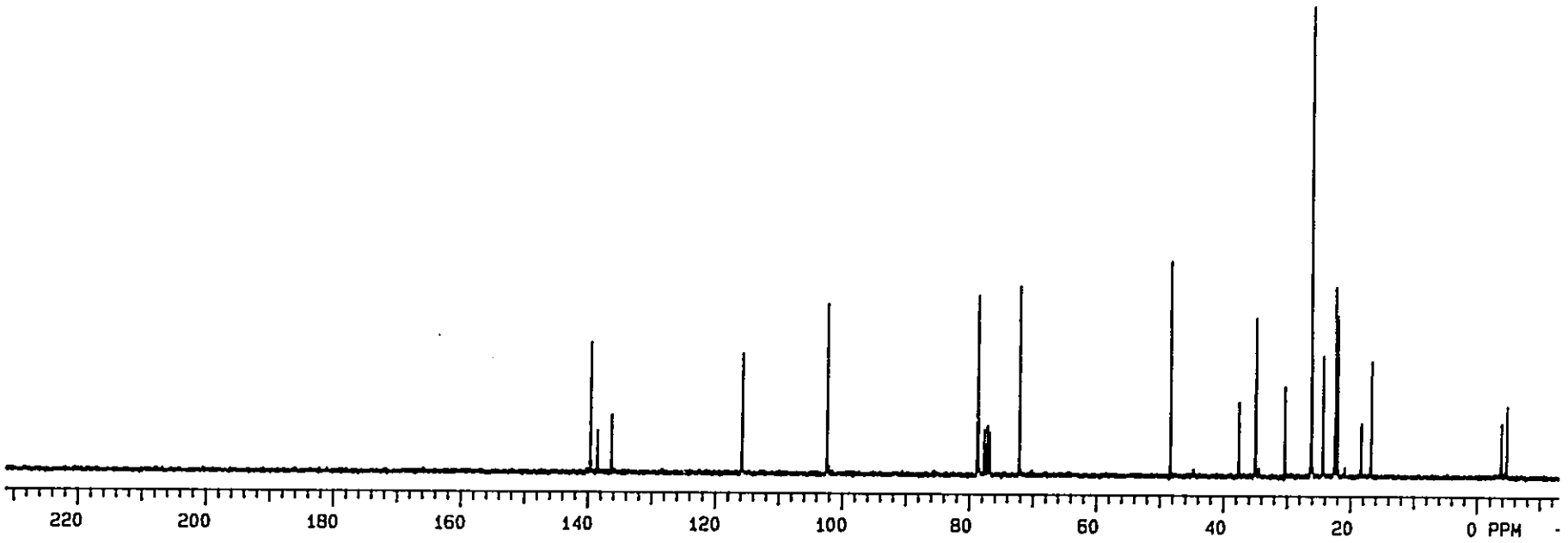


198

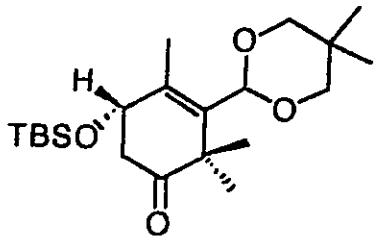
^{13}C NMR Spectrum ($CDCl_3$, 50 MHz) of **198**



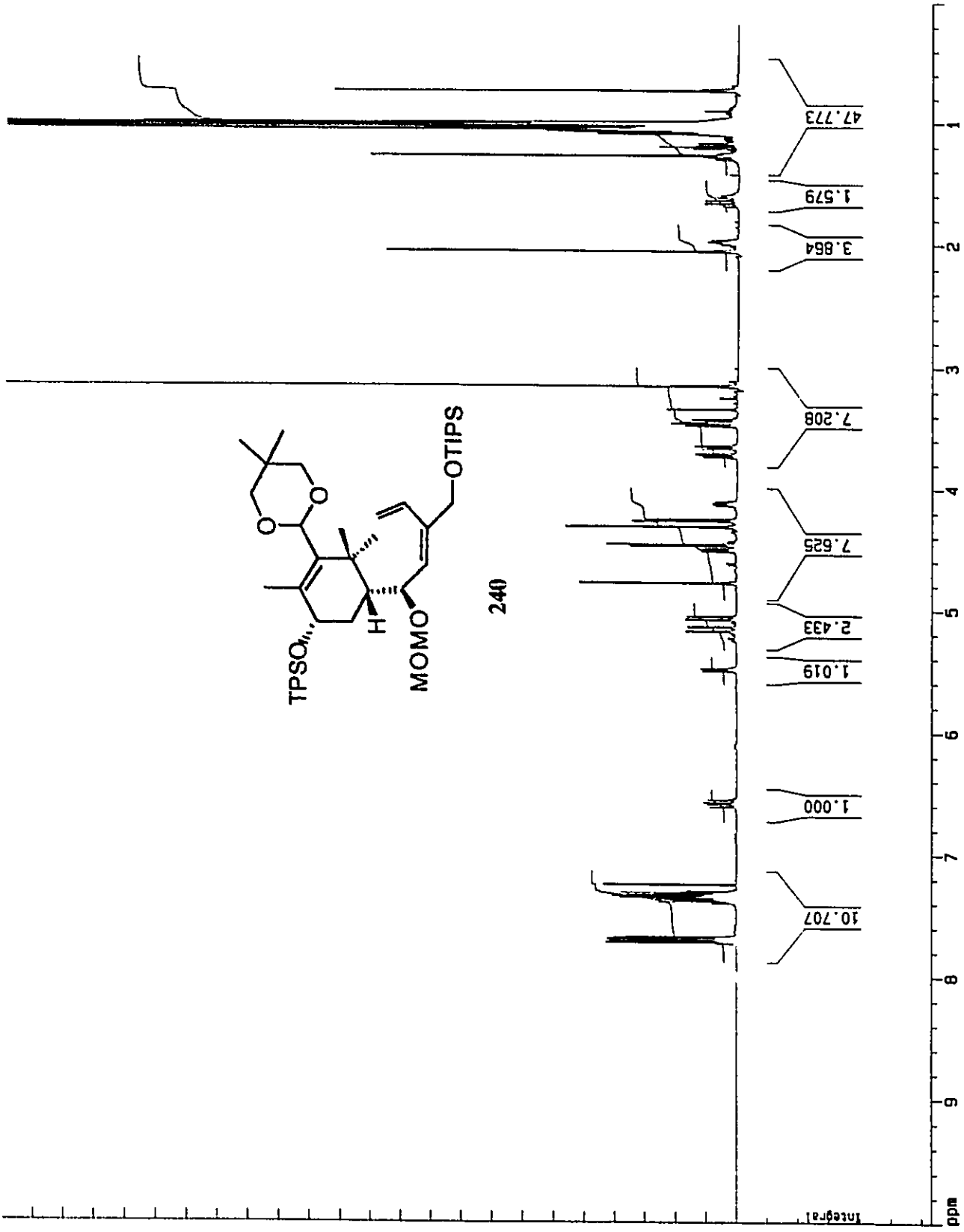
199

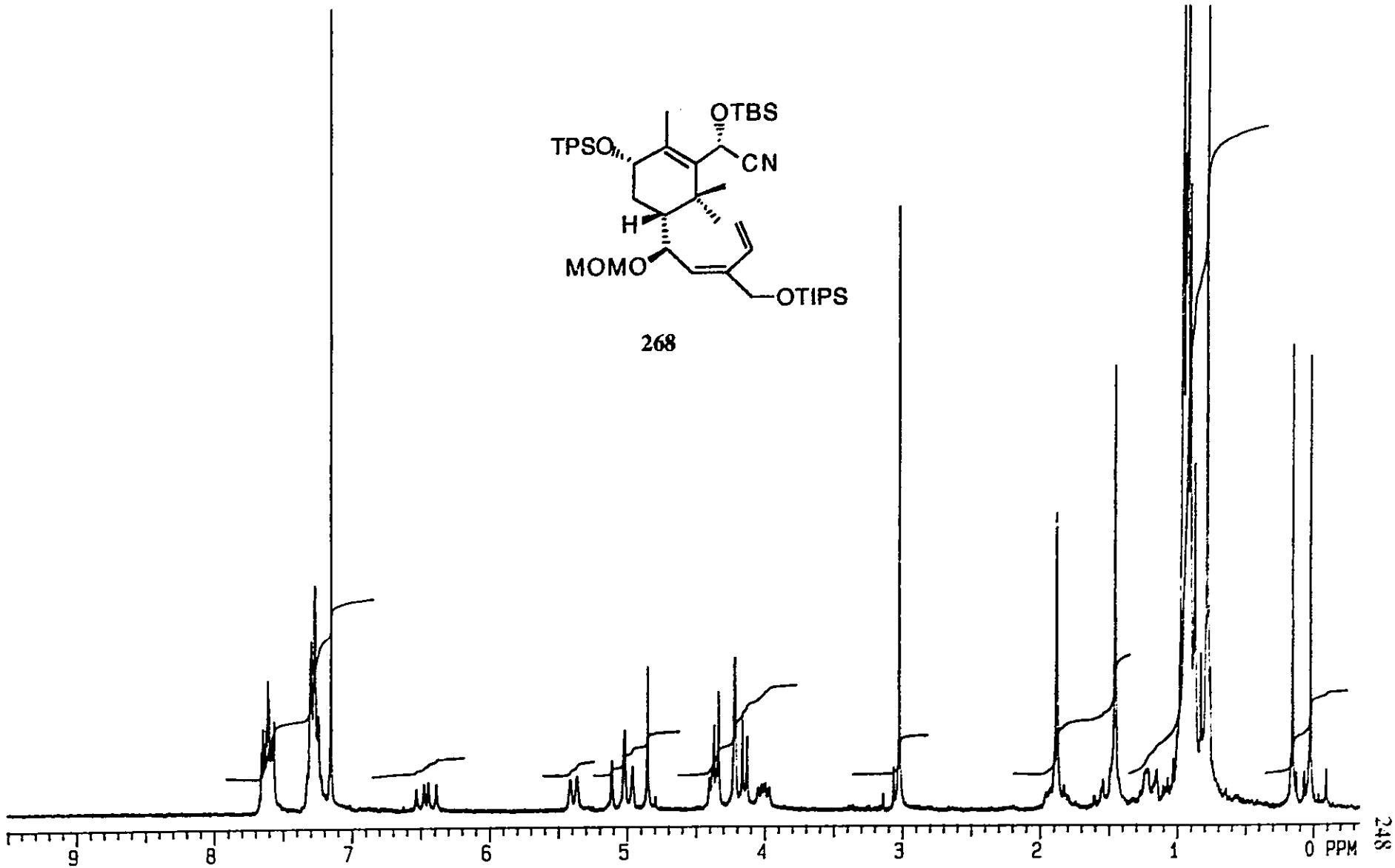


^{13}C NMR Spectrum ($CDCl_3$, 75 MHz) of **199**

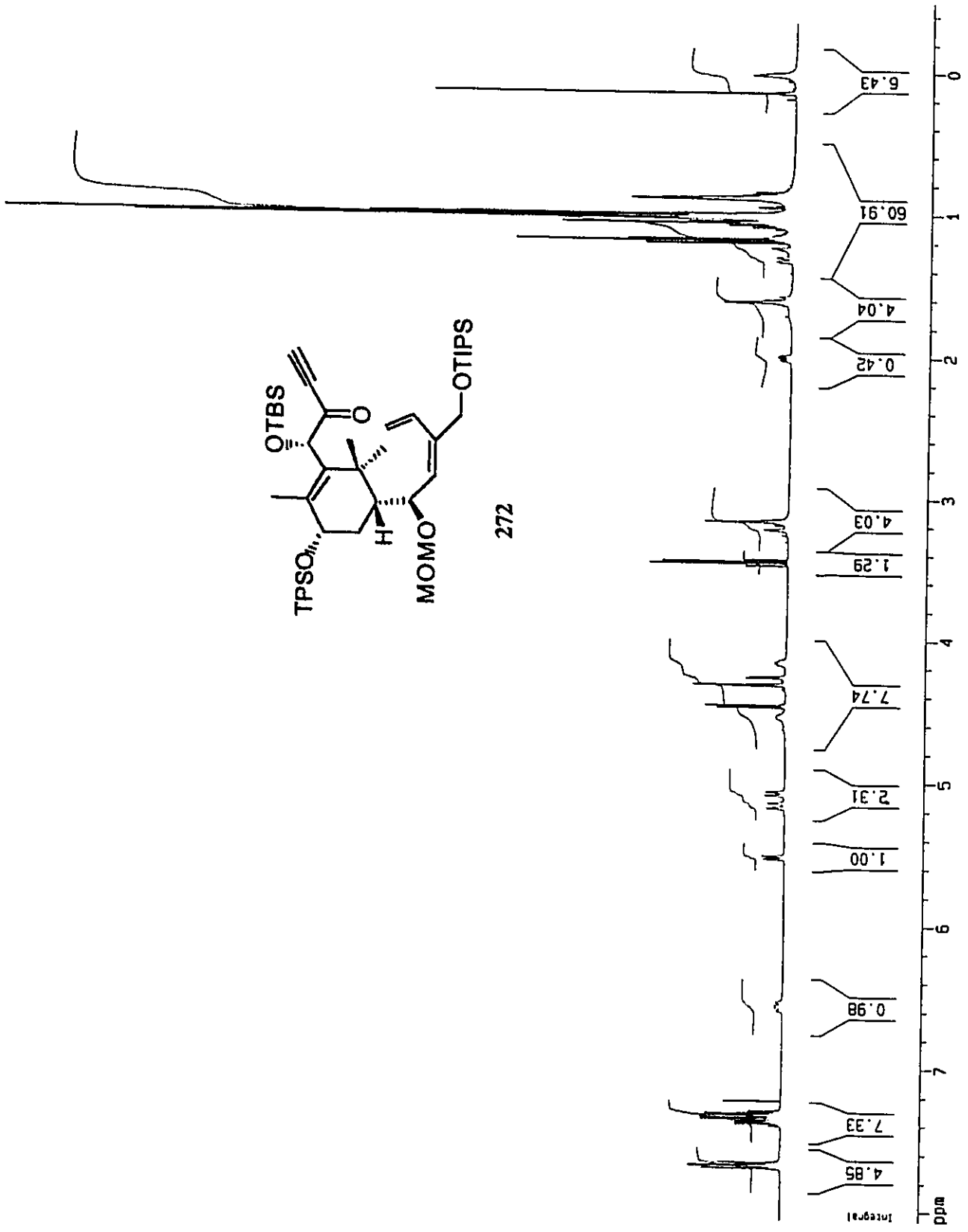


202

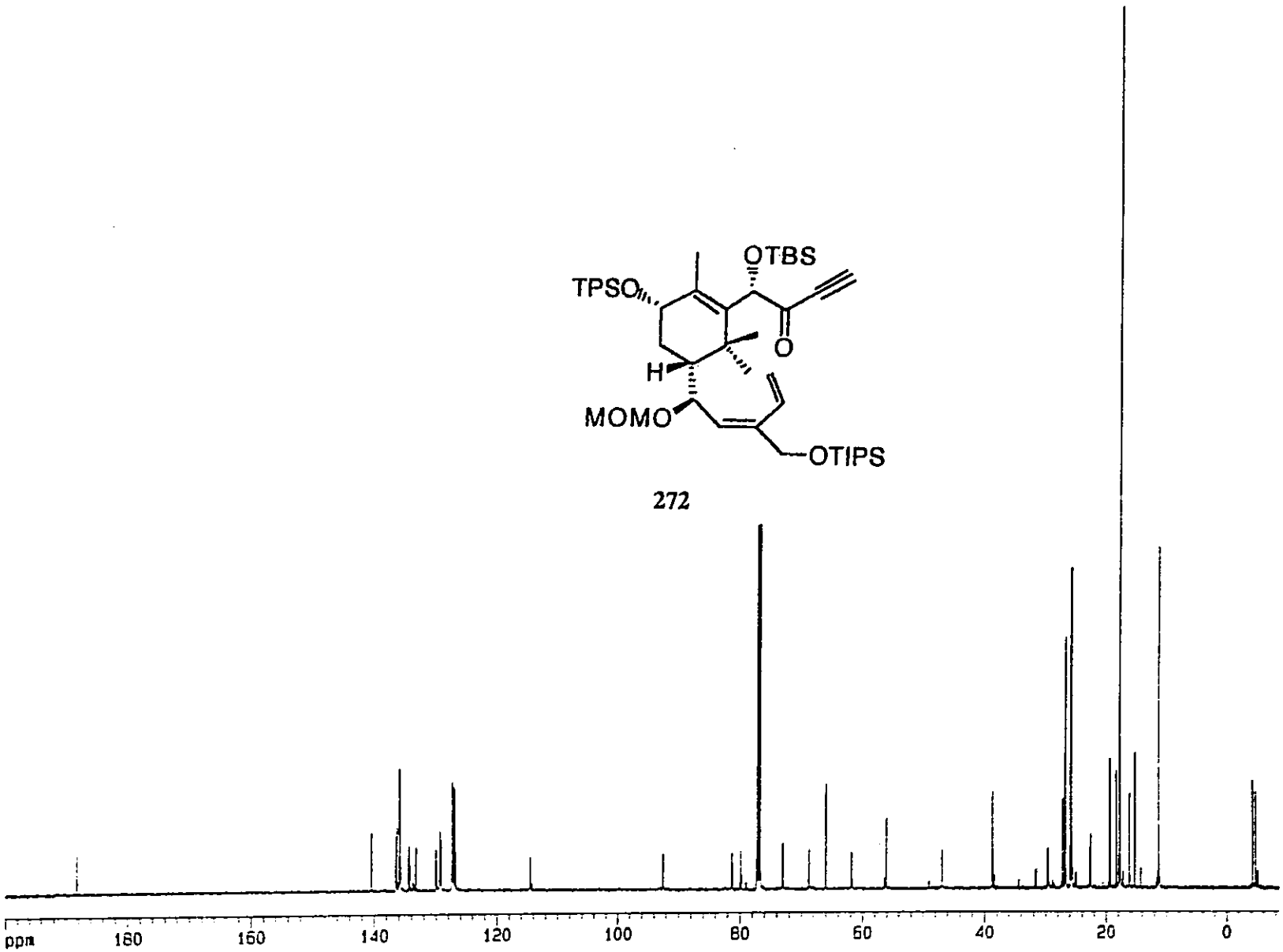

47.773
1.579
3.864
7.208
7.625
2.433
1.019
1.000
10.707
Integral
ppm
1
2
3
4
5
6
7
8
9
OTIPS
MOMO
H
TPSO
240



^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **268**

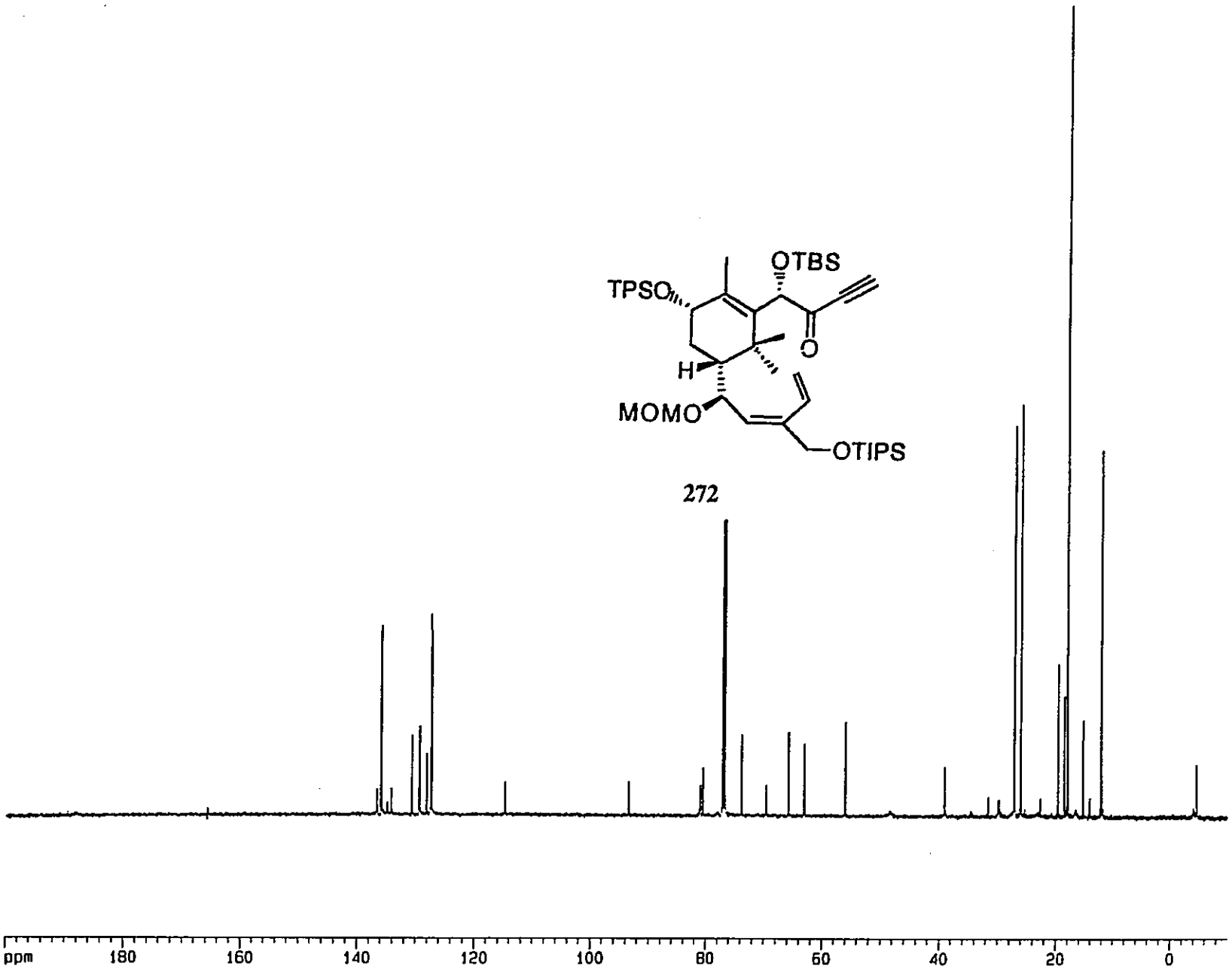


^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of 272 @ 298 K

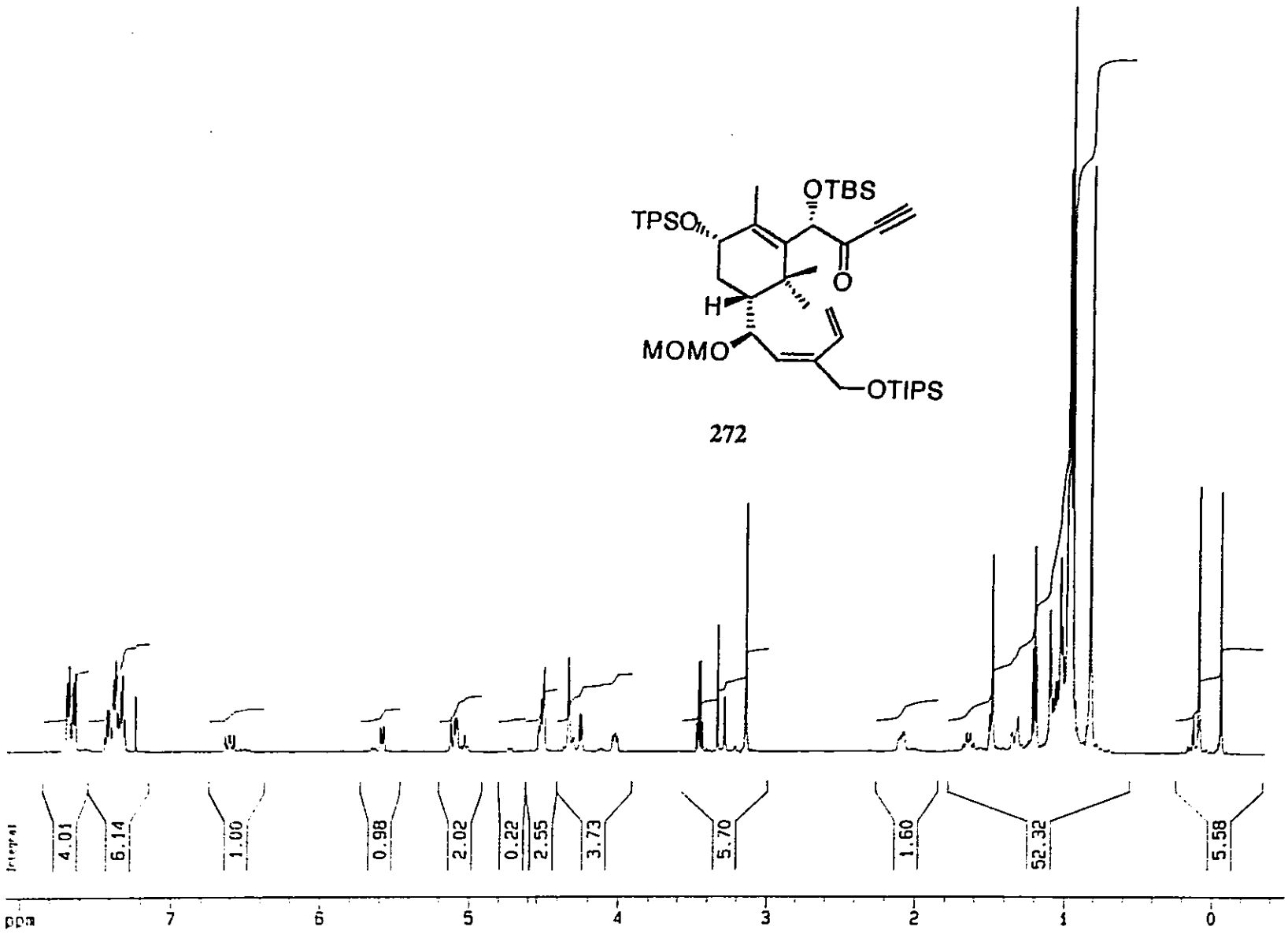


272

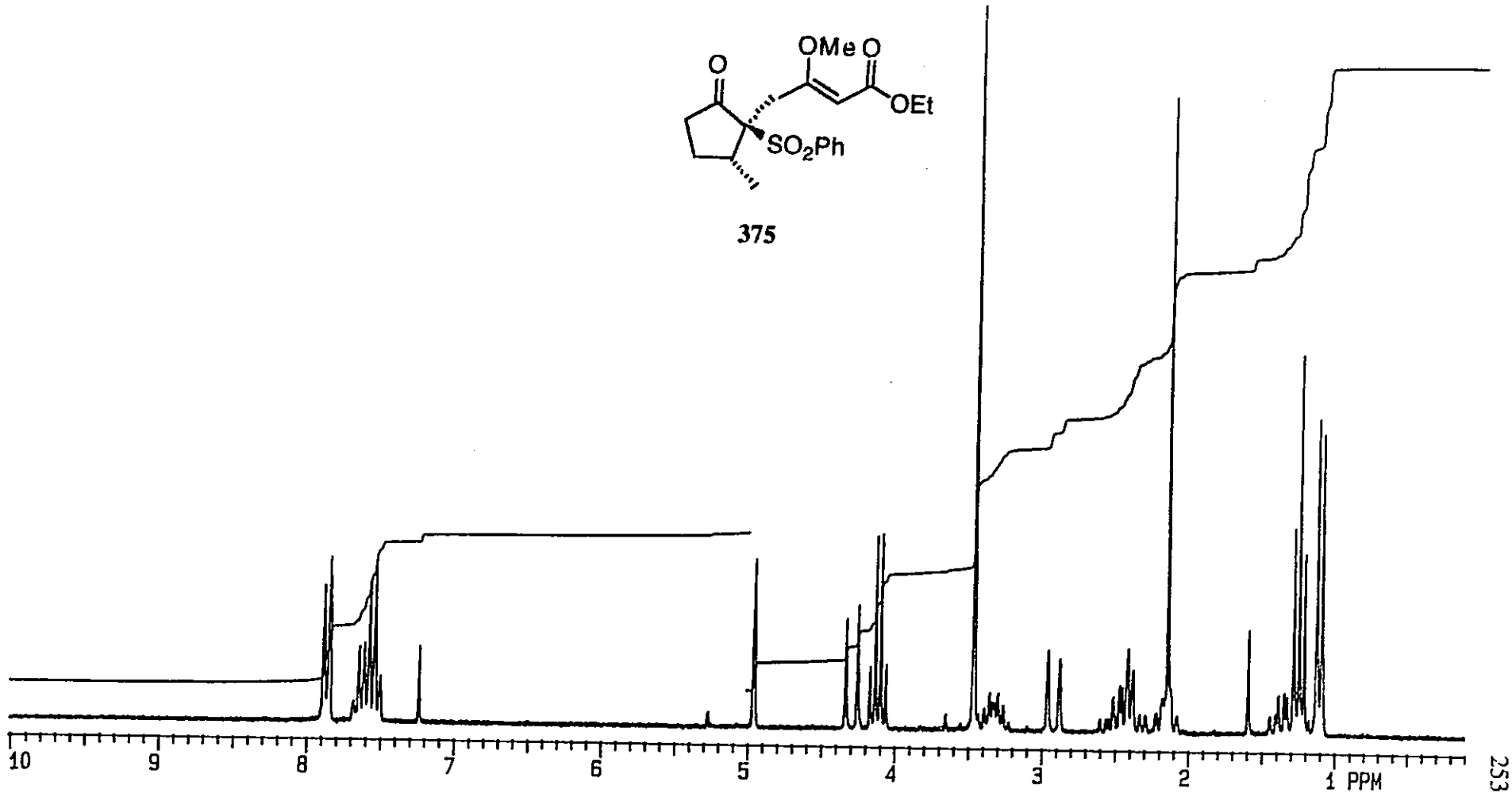
^{13}C NMR Spectrum (CDCl$_3$, 125 MHz) of 272 @ 220 K



^{13}C NMR Spectrum ($CDCl_3$, 125 MHz) of 272 @ 298 K

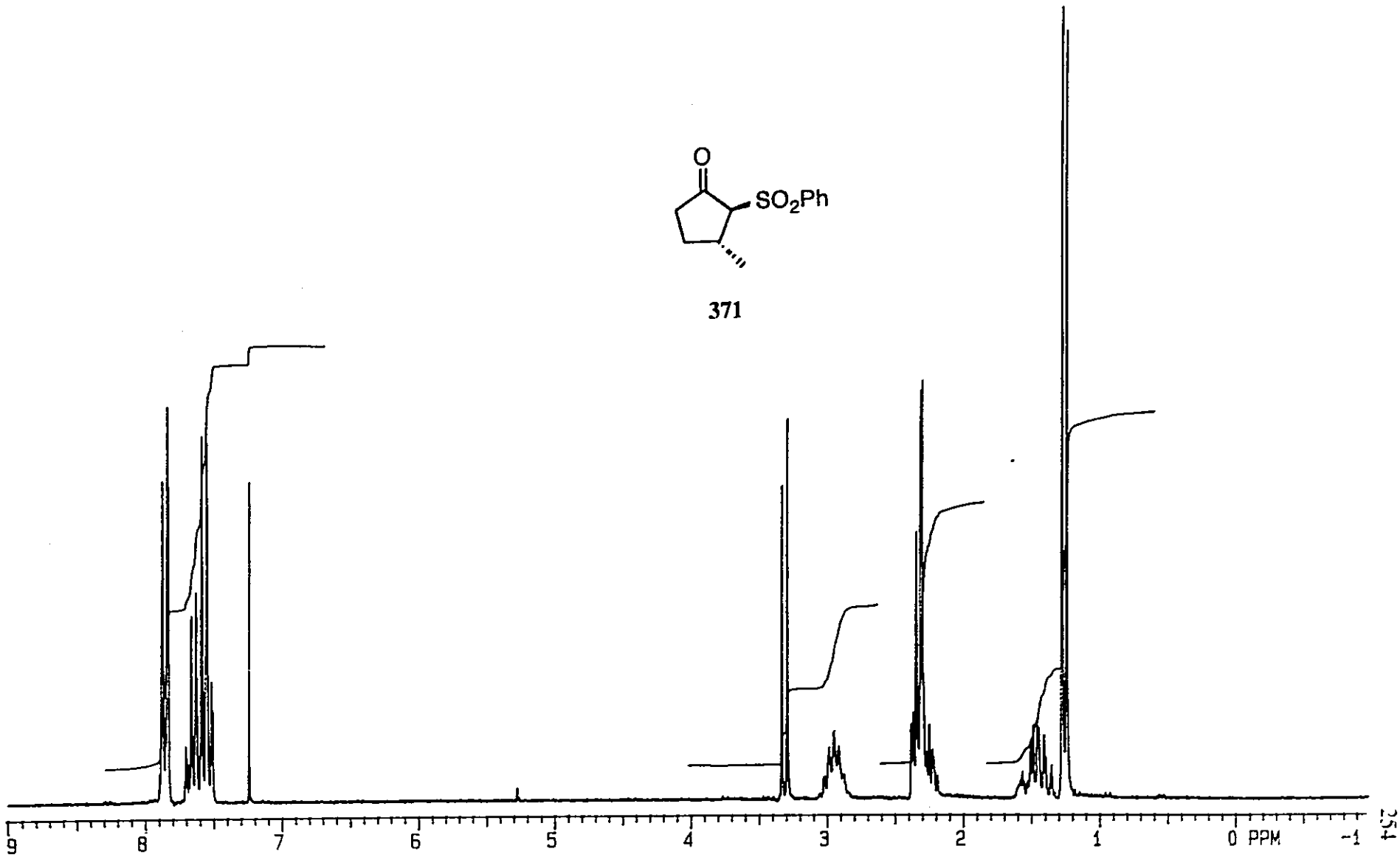


^{1}H NMR Spectrum ($CDCl_3$, 500 MHz) of 272 @ 230 K



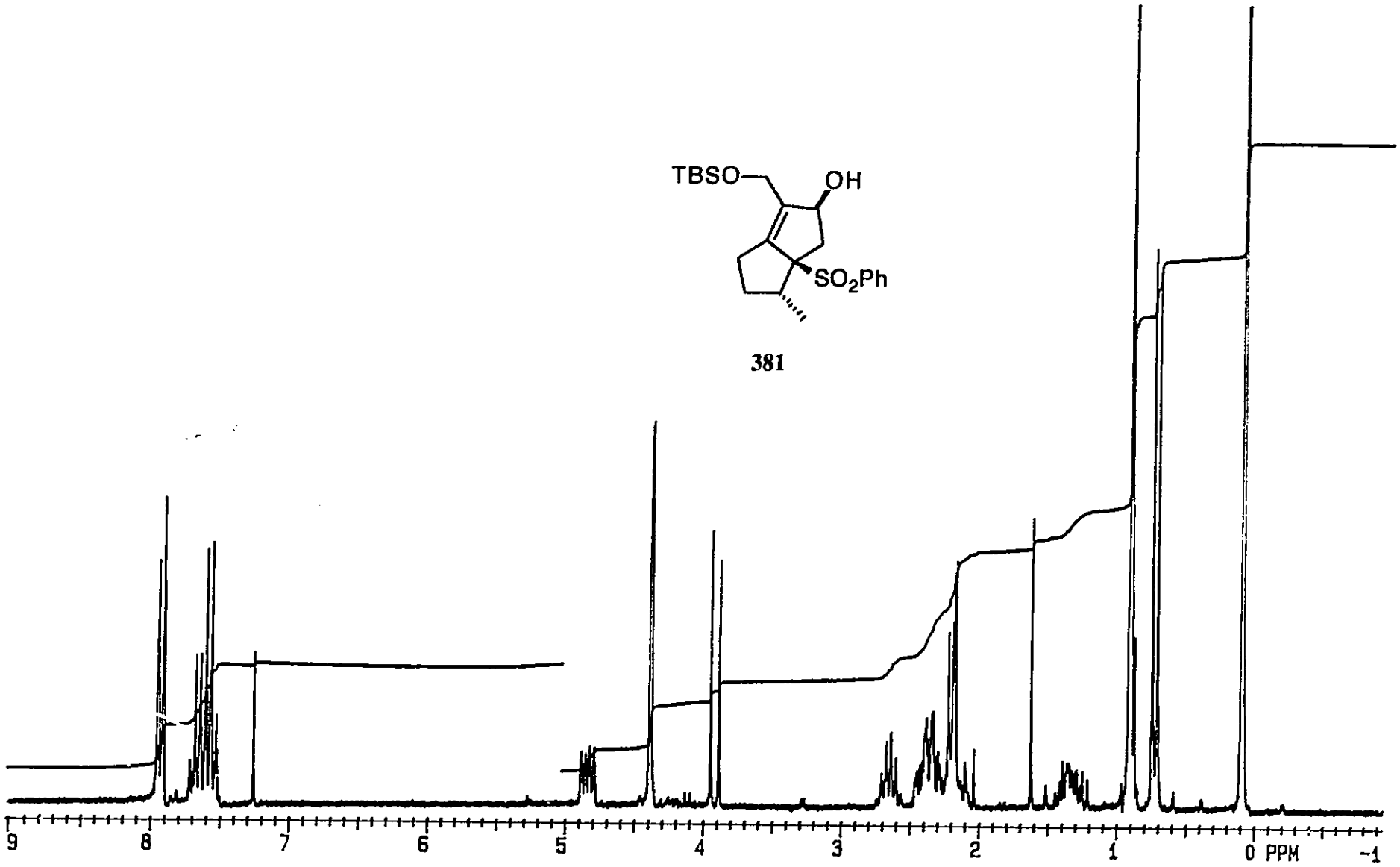
375

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of 375



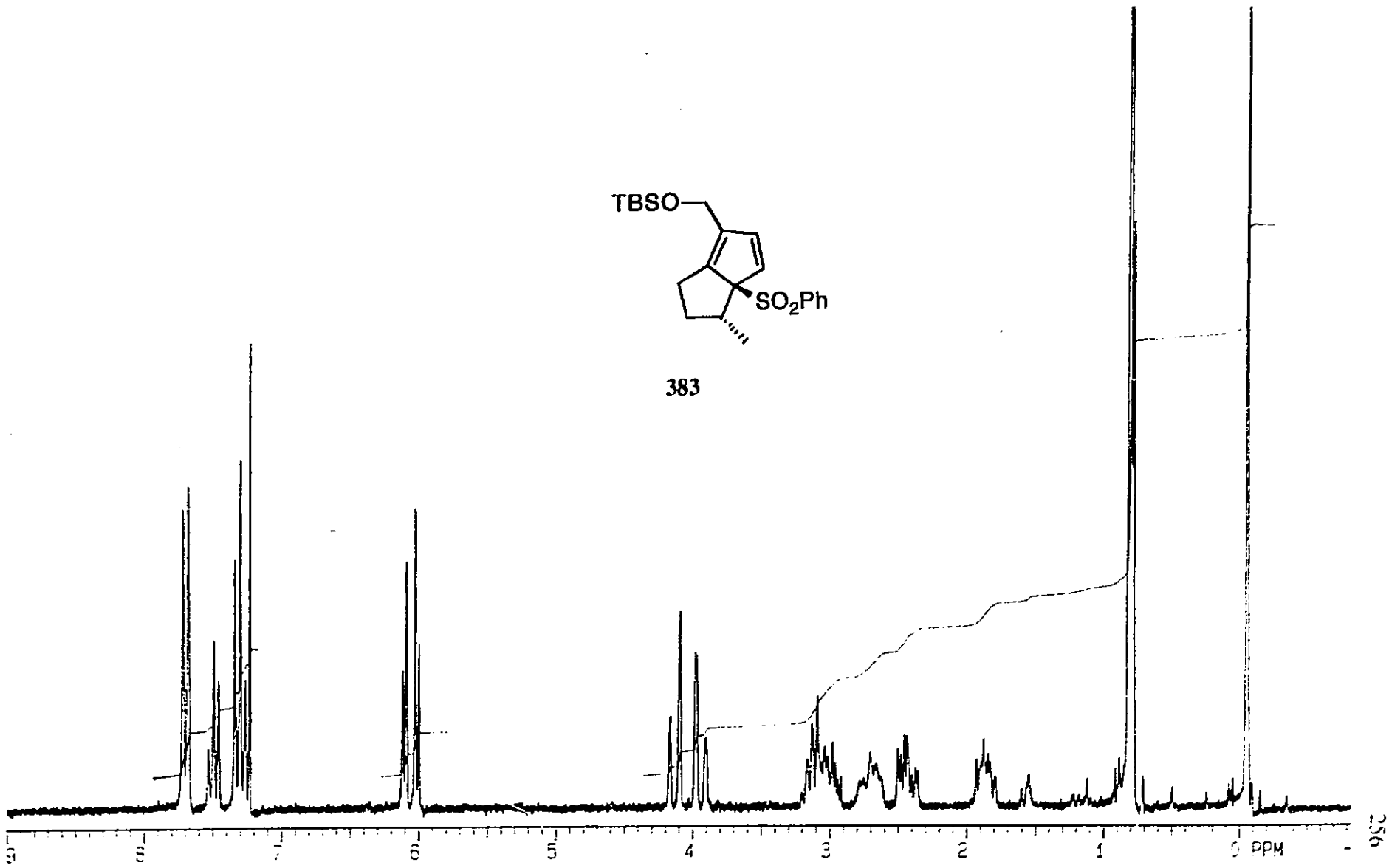
371

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **371**



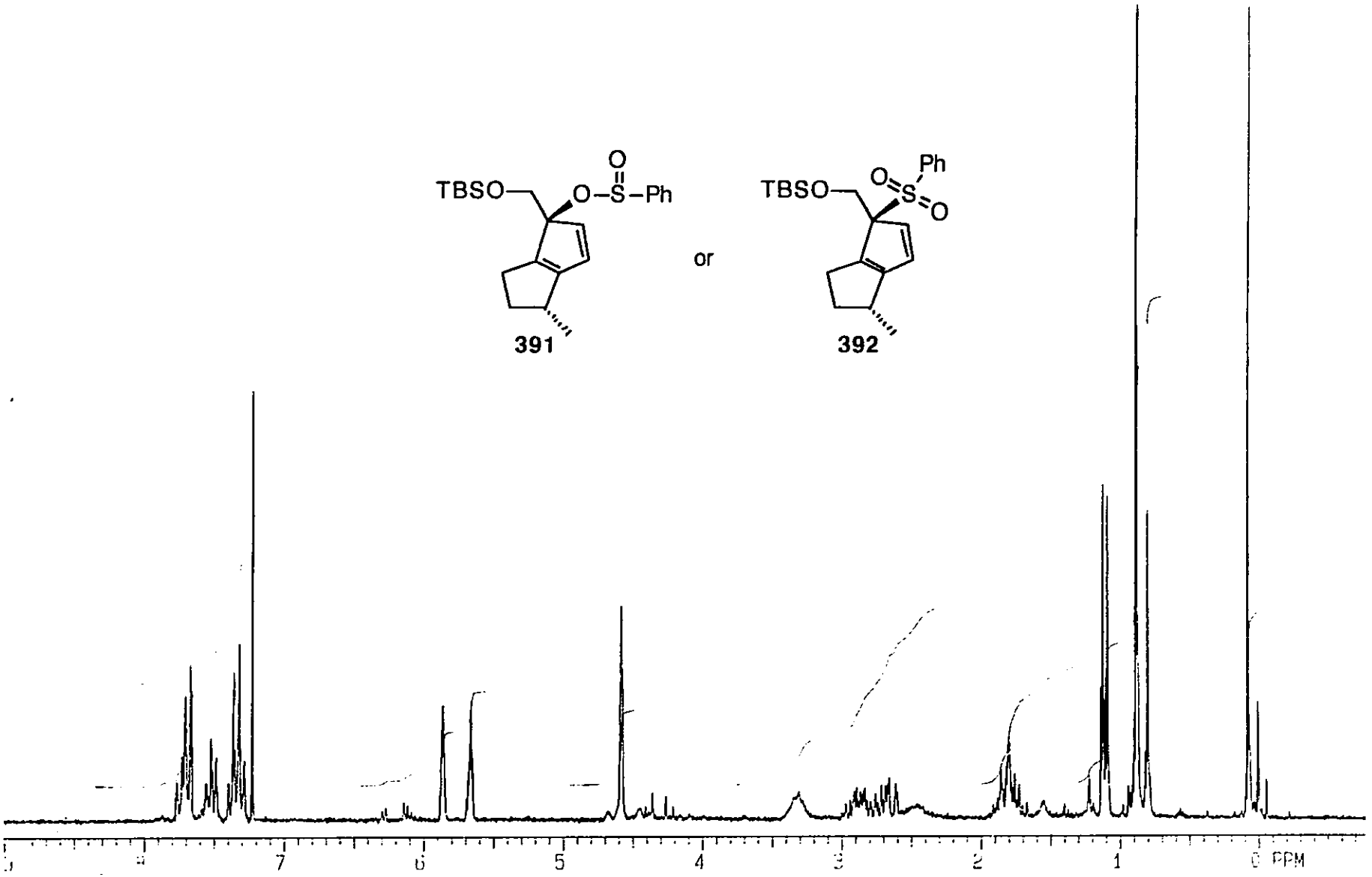
381

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **381**

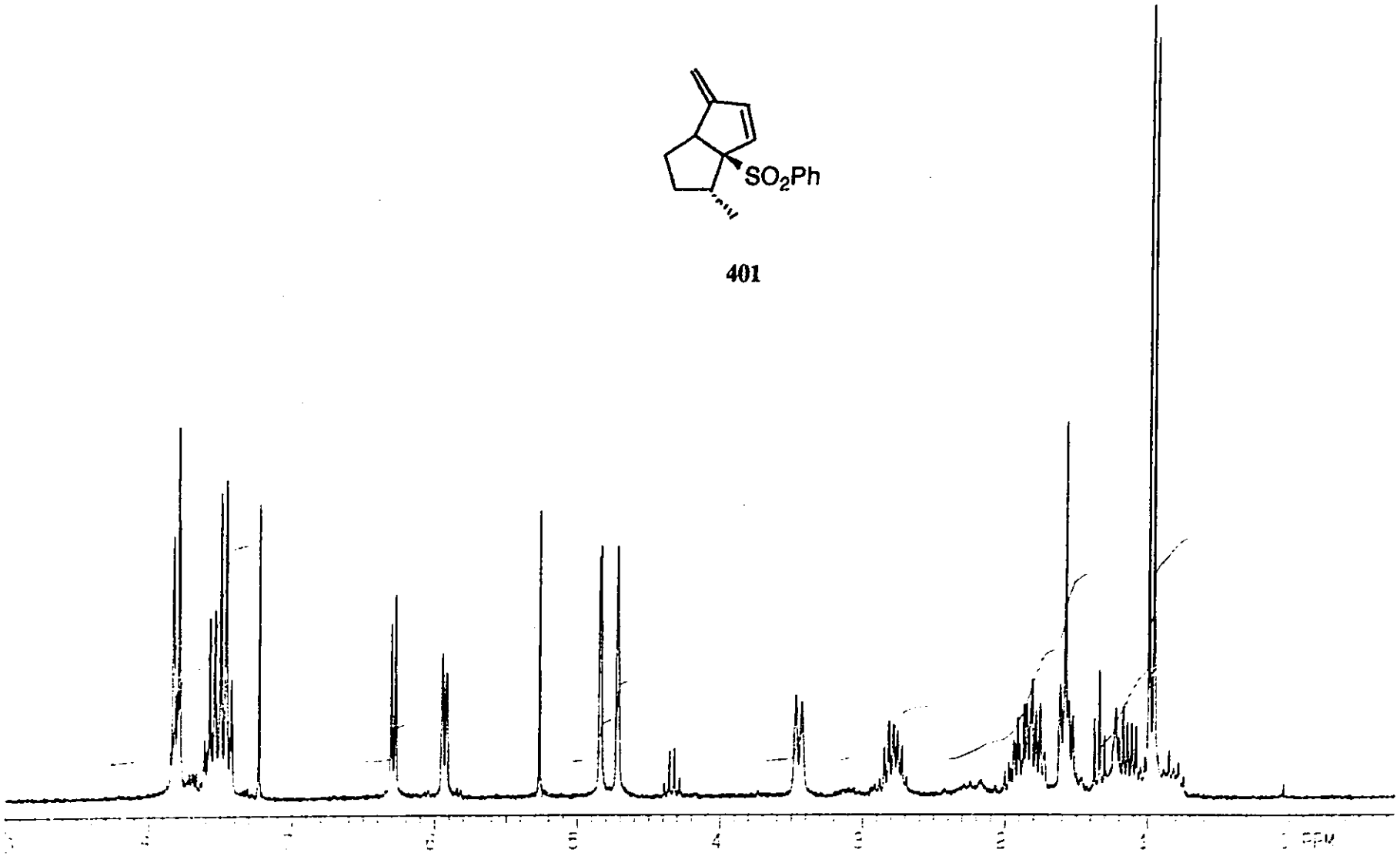


383

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **383**



^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **391/392**

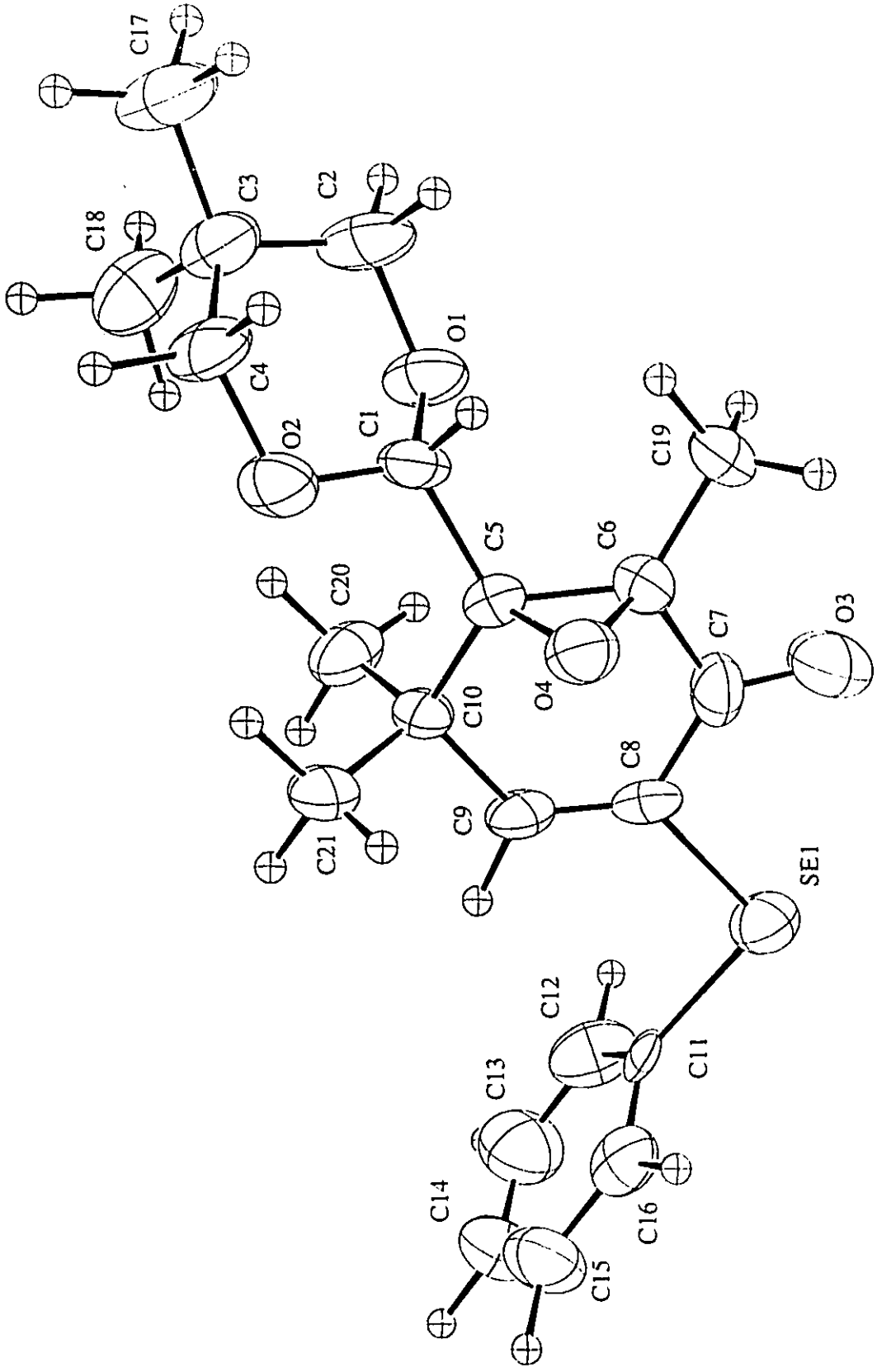


401

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz) of **401**

APPENDIX II

X-RAY DATA OF COMPOUNDS 188 AND 268



ORTEP Drawing of compound 188

EXPERIMENTAL

1. Data Collection

A crystal of SeO4C21H26 having approximate dimensions of .2,.2,.2mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo Kalpha radiation.

Cell constants and an orientation matrix for data collection, were obtained from least-squares refinement using the setting angles of 25 reflections in the range 40<2theta<50 corresponded to a monoclinic cell with dimensions:

a = 12.023(5)
b = 10.331(3)
c = 17.829(6)
beta= 108.27(4)

For Z= 4 and FW= 421.39, the calculated density is 1.331g/cm3. Based on the systematic absences, the space group was determined to be P 21/n.

The data was collected at a temperature of 20 degrees using the omega-2theta scan technique to a maximum 2theta value of 49.9 degrees.

2. Data reduction

A total of 3495 reflections was collected. The unique set contains only 3307 reflections. The standards were measured after every 150 reflections. No crystal decay was noticed. The data were corrected for Lorentz and polarisation effects (1). Absorption correction was made. The minimum and maximum transmission factors are 0.464 and 0.666.

3. Solution and refinement:

The structure was solved by direct methods. All the atoms were refined anisotropically except the hydrogen. The hydrogen atoms were calculated. The benzene ring was refined as rigid group to increase the ratio reflections/parameter. The refinement was made using the unobserved data, because of the small ratio reflections/parameter. The final cycle of full matrix least-squares refinement was based on 1921 observed reflections (I>2.5 sigma(I)) and 224 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final differences Fourier map corresponded to .730 and -1.210 e/a3, respectively.

All the calculations were performed using the NRCVAX crystallographic software package (2).

EXPERIMENTAL DETAILS

Empirical formula	$Se_4C_{21}H_{26}$
Formula weight	421.39
Crystal shape	cube
Crystal dimensions (mm)	.2,.2,.2
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40-50
Lattice parameters	a=12.023(5) b=10.331(3) c=17.829(6) beta=108.27(4)
Space group	P 21/n
Z value	4
Dcalc (g.cm-3)	1.331
F(000)	871.88
mu (mm-1)	1.79
No of reflection measured No of reflection unique No of reflection observed No of atoms	3495 3307 1921 52
No of variables	224
Rf (sign refl)	.079
Rw (sign refl)	.030

Rf (all refl)	.173
Rw (all refl)	.041
Goodness of fit	5.28

Last difference fourier map

max peak	0.730
min peak	-1.210

Space Group and Cell Dimensions Monoclinic, P 21/n
a 12.023(5) b 10.331(3) c 17.829(6)
beta 108.27(4)
Volume 2102.8(12)A**3

Empirical formula : Se O4 C21 H26

Cell dimensions were obtained from 2· reflections with 2Theta angle in the range 40.00 - 50.00 degrees.

Crystal dimensions : 0.20 X 0.20 X 0.20 mm

FW = 421.39 Z = 4 F(000) = 871.88

Dcalc 1.331Mg.m-3, mu 1.79mm-1, lambda 0.70930A, 2Theta(max) 49.9

The intensity data were collected on a Rigaku diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -12 12; Kmin,max 0 12; Lmin,max 0 21
No. of reflections measured 3495
No. of unique reflections 3307
No. of reflections with Inet > 2.5sigma(Inet) 1921
Merging R-value on intensities 0.050
Absorption corrections were made.
The minimum and maximum transmission factors are 0.464187 and 0.666196.

The last least squares cycle was calculated with
52 atoms, 224 parameters and 1921 out of 3307 reflections.
Weights based on counting-statistics were used.

The residuals are as follows :--
For significant reflections, RF 0.079, Rw 0.030 GoF 5.28
For all reflections, RF 0.173, Rw 0.031.
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 0.055.

In the last D-map, the deepest hole was -1.210e/A**3,
and the highest peak 0.730e/A**3.

Secondary ext. coeff. 0.349871 sigma 0.037634

The following references are relevant to the NRCVAX System.

1. Full System Reference :
Gabe, E.J., Le Page, Y., Charland, J.-P., Lee, F.L. and White, P.S.
(1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :

Table of Atomic Bond Distances in Angstroms

Se1-C8	1.928(9)	C10-C21	1.563(12)
Se1-C11	1.939(7)	C17-H17C	1.046(8)
O1-C1	1.430(12)	C17-H17A	1.132(10)
O1-C2	1.467(12)	C17-H17B	1.089(10)
O2-C1	1.353(11)	C18-H18C	1.118(10)
O2-C4	1.461(11)	C18-H18A	1.129(10)
O3-C7	1.223(11)	C18-H18B	1.121(9)
O4-C5	1.468(12)	C19-H19C	1.113(8)
O4-C6	1.461(11)	C19-H19A	1.070(9)
C1-C5	1.569(13)	C19-H19B	1.086(9)
C1-H1	1.141(10)	C20-H20C	1.099(9)
C2-C3	1.450(15)	C20-H20A	1.069(8)
C2-H2A	1.162(11)	C20-H20B	1.103(9)
C2-H2B	1.075(10)	C21-H21C	1.084(8)
C3-C4	1.554(15)	C21-H21A	1.102(9)
C3-C17	1.522(14)	C21-H21B	1.069(10)
C3-C18	1.474(17)	H12-C12	1.107(7)
C4-H4A	1.085(8)	H13-C13	1.083(7)
C4-H4B	1.081(9)	H14-C14	1.069(8)
C5-C6	1.496(13)	H15-C15	1.075(7)
C5-C10	1.525(14)	H16-C16	1.137(7)
C6-C7	1.546(15)	C11-C12	1.395(13)
C6-C19	1.487(13)	C11-C16	1.395(11)
C7-C8	1.415(16)	C12-C13	1.395(12)
C8-C9	1.303(14)	C13-C14	1.395(12)
C9-C10	1.511(13)	C14-C15	1.395(14)
C9-H9	1.114(9)	C15-C16	1.395(11)
C10-C20	1.533(13)		

Table of Atomic Bond Angles in Degrees

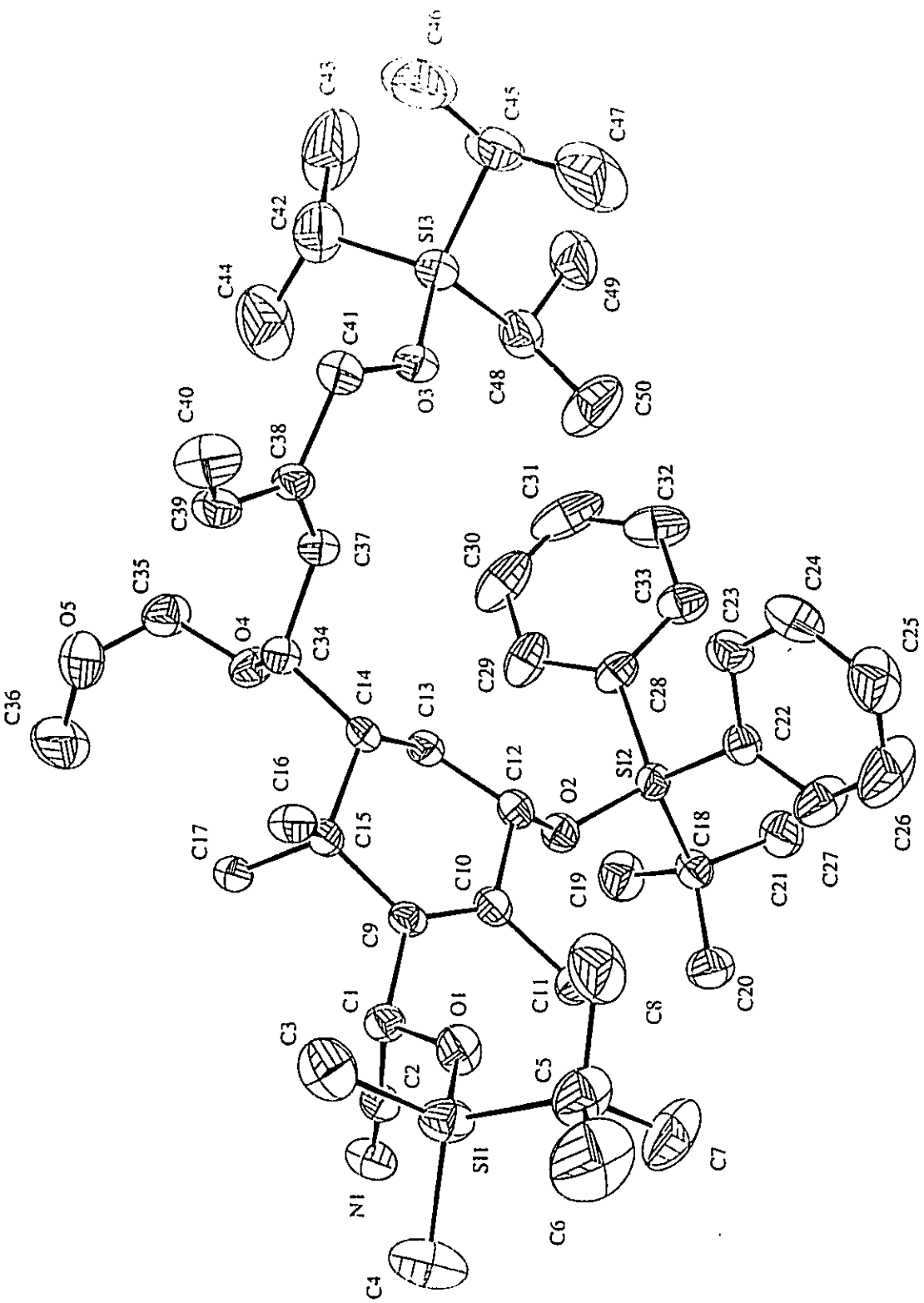
C8-Se1-C11	98.6(4)	C9-C10-C20	109.1(7)
C1-O1-C2	108.0(6)	C9-C10-C21	107.2(7)
C1-O2-C4	110.4(7)	C20-C10-C21	110.2(7)
C5-O4-C6	61.4(6)	C3-C17-H17C	113.3(9)
O1-C1-O2	112.8(8)	C3-C17-H17A	108.4(8)
O1-C1-C5	106.2(7)	C3-C17-H17B	110.2(8)
O1-C1-H1	109.1(7)	H17C-C17-H17A	108.1(7)
O2-C1-C5	114.2(8)	H17C-C17-H17B	111.3(8)
O2-C1-H1	108.0(8)	H17A-C17-H17B	105.1(8)
C5-C1-H1	106.4(8)	C3-C18-H18C	114.5(9)
O1-C2-C3	113.7(8)	C3-C18-H18A	115.4(8)
O1-C2-H2A	104.9(8)	C3-C18-H18B	114.8(9)
O1-C2-H2B	108.1(8)	H18C-C18-H18A	103.5(9)
C3-C2-H2A	110.0(9)	H18C-C18-H18B	103.9(8)
C3-C2-H2B	115.2(10)	H18A-C18-H18B	103.2(8)
H2A-C2-H2B	104.1(8)	C6-C19-H19C	109.9(7)
C2-C3-C4	107.7(9)	C6-C19-H19A	112.3(8)
C2-C3-C17	111.2(9)	C6-C19-H19B	110.3(8)
C2-C3-C18	110.6(9)	H19C-C19-H19A	107.7(8)
C4-C3-C17	107.1(8)	H19C-C19-H19B	106.6(7)
C4-C3-C18	109.9(9)	H19A-C19-H19B	109.8(7)
C17-C3-C18	110.2(9)	C10-C20-H20C	109.7(8)
O2-C4-C3	109.2(7)	C10-C20-H20A	113.5(8)
O2-C4-H4A	108.0(8)	C10-C20-H20B	109.6(7)
O2-C4-H4B	107.6(8)	H20C-C20-H20A	108.8(7)
C3-C4-H4A	111.3(9)	H20C-C20-H20B	106.4(8)
C3-C4-H4B	111.5(9)	H20A-C20-H20B	108.5(8)
H4A-C4-H4B	109.0(7)	C10-C21-H21C	111.4(7)
O4-C5-C1	110.4(8)	C10-C21-H21A	108.5(8)
O4-C5-C6	59.1(6)	C10-C21-H21B	110.7(7)
O4-C5-C10	113.3(7)	H21C-C21-H21A	107.6(7)
C1-C5-C6	113.7(8)	H21C-C21-H21B	110.0(9)
C1-C5-C10	120.5(8)	H21A-C21-H21B	108.6(7)
C6-C5-C10	122.7(8)	Se1-C11-C12	120.2(5)
O4-C6-C5	59.5(6)	Se1-C11-C16	119.6(7)
O4-C6-C7	110.0(7)	C12-C11-C16	120.0(6)
O4-C6-C19	115.4(8)	H12-C12-C11	121.0(7)
C5-C6-C7	114.7(8)	H12-C12-C13	119.0(8)
C5-C6-C19	126.4(8)	C11-C12-C13	120.0(6)
C7-C6-C19	116.0(8)	H13-C13-C12	119.2(8)
O3-C7-C6	114.7(10)	H13-C13-C14	120.8(9)
O3-C7-C8	126.1(10)	C12-C13-C14	120.0(7)
C6-C7-C8	119.2(8)	H14-C14-C13	118.6(9)
Se1-C8-C7	109.5(7)	H14-C14-C15	121.4(7)
Se1-C8-C9	127.2(8)	C13-C14-C15	120.0(7)
C7-C8-C9	123.4(9)	H15-C15-C14	119.0(7)
C8-C9-C10	125.9(9)	H15-C15-C16	121.0(8)
C8-C9-H9	117.9(8)	C14-C15-C16	120.0(6)
C10-C9-H9	116.0	H16-C16-C11	118.9(8)
C5-C10-C9	112.0	H16-C16-C15	121.1(8)
C5-C10-C20	109.4	C11-C16-C15	120.0(7)

C5-C10-C21 108.9(8)

Torsion angles

C11	SE1	C8	C7	178.1(7)	C11	SE1	C8	C9	-3.7(4)
C8	SE1	C11	C12	94.7(5)	C8	SE1	C11	C16	90.7(5)
C2	O1	C1	O2	61.3(6)	C2	O1	C1	C5	173.0(9)
C2	O1	C1	H1	-58.8(6)	C1	O1	C2	C3	-56.2(7)
C1	O1	C2	H2A	64.0(6)	C1	O1	C2	H2B	174.5(11)
C4	O2	C1	O1	-64.8(6)	C4	O2	C1	C5	173.9(9)
C4	O2	C1	H1	55.8(6)	C1	O2	C4	C3	58.9(7)
C1	O2	C4	H4A	-179.9(10)	C1	O2	C4	H4B	-62.4(6)
C6	O4	C5	C1	-106.1(8)	C6	O4	C5	C6	0.0(5)
C6	O4	C5	C10	115.4(8)	C5	O4	C6	C5	0.0(5)
C5	O4	C6	C7	-107.5(8)	C5	O4	C6	C19	118.9(8)
O1	C1	C5	O4	136.5(10)	O1	C1	C5	C6	72.3(7)
O1	C1	C5	C10	-88.4(8)	O2	C1	C5	O4	-98.6(8)
O2	C1	C5	C6	-162.8(11)	O2	C1	C5	C10	36.5(5)
H1	C1	C5	O4	20.4(3)	H1	C1	C5	C6	-43.8(5)
H1	C1	C5	C10	155.5(11)	O1	C2	C3	C4	52.9(6)
O1	C2	C3	C17	169.9(11)	O1	C2	C3	C18	-67.3(7)
H2A	C2	C3	C4	-64.5(7)	H2A	C2	C3	C17	52.6(6)
H2A	C2	C3	C18	175.4(13)	H2B	C2	C3	C4	178.4(13)
H2B	C2	C3	C17	-64.5(8)	H2B	C2	C3	C18	58.2(7)
C2	C3	C4	O2	-52.3(6)	C2	C3	C4	H4A	-171.5(13)
C2	C3	C4	H4B	66.5(8)	C17	C3	C4	O2	-172.1(11)
C17	C3	C4	H4A	68.8(8)	C17	C3	C4	H4B	-53.3(6)
C18	C3	C4	O2	68.3(7)	C18	C3	C4	H4A	-50.9(6)
C18	C3	C4	H4B	-172.9(13)	C2	C3	C17	H17C	179.8(13)
C2	C3	C17	H17A	-60.2(7)	C2	C3	C17	H17B	54.3(7)
C4	C3	C17	H17C	-62.7(7)	C4	C3	C17	H17A	57.3(7)
C4	C3	C17	H17B	171.8(12)	C18	C3	C17	H17C	56.8(7)
C18	C3	C17	H17A	176.8(12)	C18	C3	C17	H17B	-68.7(8)
C2	C3	C18	H18C	-60.9(7)	C2	C3	C18	H18A	59.1(7)
C2	C3	C18	H18B	179.0(13)	C4	C3	C18	H18C	-179.7(12)
C4	C3	C18	H18A	-59.7(7)	C4	C3	C18	H18B	60.1(7)
C17	C3	C18	H18C	62.5(7)	C17	C3	C18	H18A	-177.5(12)
C17	C3	C18	H18B	-57.6(7)	O4	C5	C6	O4	0.0(3)
O4	C5	C6	C7	99.6(8)	O4	C5	C6	C19	-100.6(8)
C1	C5	C6	O4	100.4(8)	C1	C5	C6	C7	-159.9(10)
C1	C5	C6	C19	-0.1(4)	C10	C5	C6	O4	-99.3(8)
C10	C5	C6	C7	0.3(5)	C10	C5	C6	C19	160.1(10)
O4	C5	C10	C9	-57.0(6)	O4	C5	C10	C20	-178.2(10)
O4	C5	C10	C21	61.3(6)	C1	C5	C10	C9	169.0(10)
C1	C5	C10	C20	47.9(6)	C1	C5	C10	C21	-72.6(7)
C6	C5	C10	C9	10.1(5)	C6	C5	C10	C20	-111.1(9)
C6	C5	C10	C21	128.5(9)	O4	C6	C7	O3	-127.7(11)
O4	C6	C7	C8	52.7(6)	C5	C6	C7	O3	167.6(12)
C5	C6	C7	C8	-12.1(5)	C19	C6	C7	O3	5.6(4)
C19	C6	C7	C8	-174.1(11)	O4	C6	C19	H19C	-49.6(5)
O4	C6	C19	H19A	70.3(7)	O4	C6	C19	H19B	-166.9(11)
C5	C6	C19	H19C	20.0(4)	C5	C6	C19	H19A	140.0(11)
C5	C6	C19	H19B	-97.3(9)	C7	C6	C19	H19C	179.6(11)

C7	C6	C19	H19A	-60.4(7)	C7	C6	C19	H19B	62.3(7)
O3	C7	C8	SE1	11.6(4)	O3	C7	C8	C9	-166.6(12)
C6	C7	C8	SE1	-168.7(9)	C6	C7	C8	C9	13.1(5)
SE1	C8	C9	C10	-178.8(9)	SE1	C8	C9	H9	-3.9(3)
C7	C8	C9	C10	-0.9(5)	C7	C8	C9	H9	174.0(12)
C8	C9	C10	C5	-10.6(5)	C8	C9	C10	C20	110.7(9)
C8	C9	C10	C21	-129.9(10)	H9	C9	C10	C5	174.4(11)
H9	C9	C10	C20	-64.3(6)	H9	C9	C10	C21	55.1(6)
C5	C10	C20	H20C	179.1(11)	C5	C10	C20	H20A	-58.9(6)
C5	C10	C20	H20B	62.6(6)	C9	C10	C20	H20C	56.3(6)
C9	C10	C20	H20A	178.2(11)	C9	C10	C20	H20B	-60.2(6)
C21	C10	C20	H20C	-61.2(6)	C21	C10	C20	H20A	60.7(6)
C21	C10	C20	H20B	-177.7(11)	C5	C10	C21	H21C	57.7(6)
C5	C10	C21	H21A	175.9(11)	C5	C10	C21	H21B	-65.0(7)
C9	C10	C21	H21C	179.0(11)	C9	C10	C21	H21A	-62.8(6)
C9	C10	C21	H21B	56.3(6)	C20	C10	C21	H21C	-62.3(6)
C20	C10	C21	H21A	55.9(6)	C20	C10	C21	H21B	175.0(11)
SE1	C11	C12	H12	-4.9(2)	SE1	C11	C12	C13	174.6(7)
C16	C11	C12	H12	-179.4(9)	C16	C11	C12	C13	0.0(4)
SE1	C11	C16	H16	0.6(2)	SE1	C11	C16	C15	-174.6(7)
C12	C11	C16	H16	175.1(9)	C12	C11	C16	C15	0.0(4)
H12	C12	C13	H13	-1.0(0)	H12	C12	C13	C14	179.4(9)
C11	C12	C13	H13	179.6(9)	C11	C12	C13	C14	0.0(4)
H13	C13	C14	H14	0.9(0)	H13	C13	C14	C15	-179.6(10)
C12	C13	C14	H14	-179.5(10)	C12	C13	C14	C15	0.0(4)
H14	C14	C15	H15	0.0(0)	H14	C14	C15	C16	179.5(9)
C13	C14	C15	H15	-179.5(10)	C13	C14	C15	C16	0.0(4)
H15	C15	C16	H16	4.5(0)	H15	C15	C16	C11	179.5(9)
C14	C15	C16	H16	-175.0(9)	C14	C15	C16	C11	0.0(4)



ORTEP Drawing of compound 268

EXPERIMENTAL

1. Data Collection

A crystal of Si3O5N1C50H81 having approximate dimensions of .2,.2,.2 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo Kalpha radiation.

Cell constants and an orientation matrix for data collection, were obtained from least-squares refinement using the setting angles of 25 reflections in the range 40<2theta<45 corresponded to a monoclinic cell with dimensions:

a = 15.1273(24)
b = 19.174(8)
c = 18.622(4)
beta=91.43(8)

For Z=4 and FW=861.63, the calculated density is 1.058 g/cm3. Based on the systematic absences, the space group was determined to be P 21/c.

The data was collected at a temperature of -130 degrees using the omega-2theta scan technique to a maximum 2theta value of 44.9 degrees.

2. Data reduction

A total of 6726 reflections was collected. The unique set contains only 6412 reflections. The standards were measured after every 150 reflections. No crystal decay was noticed. The data were corrected for Lorentz and polarisation effects (1). No absorption correction was made.

3. Solution and refinement:

The structure was solved by direct methods. All the atoms were refined anisotropically except the hydrogen. The hydrogen atoms were calculated. The final cycle of full matrix least-squares refinement was based on 4549 observed reflections (I>2.5 sigma(I)) and 533 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final differences Fourier map corresponded to 0.310 and -.380 e/a3, respectively.

All the calculations were performed using the NRCVAX crystallographic software package (2).

EXPERIMENTAL DETAILS

Empirical formula	Si3O5N1C50H81
Formula weight	861.63
Crystal shape	cube
Crystal dimensions (mm)	.2,.2,.2
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 40-45
Lattice parameters	a=15.1273(24) b=19.174(8) c=18.622(4) beta=91.43(8)
Space group	P 21/c
Z value	4
Dcalc (g.cm-3)	1.058
F(000)	1881.44
mu (mm-1)	0.12
No of reflection measured	6726
No of reflection unique	6412
No of reflection observed	4549
No of atoms	140
No of variables	533
Rf (sign refl)	.052
Rw (sign refl)	.035
Rf (all refl)	.087
Rw (all refl)	.036
Goodness of fit	2.86
Last difference fourier map	
max peak	.310
min peak	-.380

Space Group and Cell Dimensions Monoclinic, P 21/c
a 15.1273(24) b 19.174(8) c 18.622(4)
beta 91.43(8)
Volume 5407(3)A**3

Empirical formula : Si3 O5 N C50 H81

Cell dimensions were obtained from 24 reflections with 2Theta angle
in the range 40.00 - 50.00 degrees.

Crystal dimensions : 0.20 X 0.20 X 0.20 mm

FW = 861.63 Z = 4 F(000) = 1881.44

Dcalc 1.058Mg.m-3, mu 0.12mm-1, lambda 0.70930A, 2Theta(max) 44.9

The intensity data were collected on a Rigaku diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -14 14; Kmin,max 0 20; Lmin,max 0 20
No. of reflections measured 6726
No. of unique reflections 6412
No. of reflections with Inet > 2.5sigma(Inet) 4549
Merging R-value on intensities 0.055
No correction was made for absorption

The last least squares cycle was calculated with
140 atoms, 533 parameters and 4549 out of 6412 reflections.
Weights based on counting-statistics were used.

The residuals are as follows :--
For significant reflections, RF 0.052, Rw 0.035 GoF 2.86
For all reflections, RF 0.087, Rw 0.036.
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 0.291.

In the last D-map, the deepest hole was -0.380e/A**3,
and the highest peak 0.310e/A**3.

Secondary ext. coeff. 0.469240 sigma 0.018851

The following references are relevant to the NRCVAX System.

1. Full System Reference :
Gabe, E.J., Le Page, Y., Charland, J.-P., Lee, F.L. and White, P.S.
(1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :
International Tables for X-ray Crystallography, Vol. IV, (1974)

Table of Atomic Bond Distances in Angstroms

Si1-O1	1.658(3)	C20-H20A	1.085(4)
Si1-C3	1.866(5)	C20-H20B	1.089(5)
Si1-C4	1.866(5)	C21-H21C	1.087(5)
Si1-C5	1.881(5)	C21-H21A	1.078(4)
Si2-O2	1.654(3)	C21-H21B	1.088(5)
Si2-C18	1.897(4)	C22-C23	1.418(6)
Si2-C22	1.877(4)	C22-C27	1.386(6)
Si2-C28	1.880(4)	C23-C24	1.380(6)
Si3-O3	1.651(3)	C23-H23	1.096(4)
Si3-C42	1.890(5)	C24-C25	1.381(7)
Si3-C45	1.889(5)	C24-H24	1.091(4)
Si3-C48	1.890(5)	C25-C26	1.359(7)
O1-C1	1.417(5)	C25-H25	1.095(5)
O2-C12	1.427(5)	C26-C27	1.392(7)
O3-C41	1.412(5)	C26-H26	1.108(5)
O4-C34	1.446(5)	C27-H27	1.095(4)
O4-C35	1.406(5)	C28-C29	1.398(6)
O5-C35	1.401(6)	C28-C33	1.415(6)
O5-C36	1.420(6)	C29-C30	1.390(7)
N1-C2	1.142(5)	C29-H29	1.094(5)
C1-C2	1.489(6)	C30-C31	1.377(8)
C1-C9	1.533(6)	C30-H30	1.079(5)
C1-H1	1.098(4)	C31-C32	1.396(8)
C3-H3C	1.087(5)	C31-H31	1.098(5)
C3-H3A	1.090(5)	C32-C33	1.381(6)
C3-H3B	1.073(5)	C32-H32	1.103(5)
C4-H4C	1.084(5)	C33-H33	1.104(5)
C4-H4A	1.085(5)	C34-C37	1.509(6)
C4-H4B	1.081(5)	C34-H34	1.091(4)
C5-C6	1.531(7)	C35-H35A	1.090(4)
C5-C7	1.529(7)	C35-H35B	1.086(4)
C5-C8	1.552(7)	C36-H36C	1.087(6)
C6-H6C	1.089(6)	C36-H36A	1.104(6)
C6-H6A	1.104(6)	C36-H36B	1.082(5)
C6-H6B	1.077(5)	C37-C38	1.321(6)
C7-H7C	1.069(5)	C37-H37	1.085(4)
C7-H7A	1.087(5)	C38-C39	1.479(6)
C7-H7B	1.101(5)	C38-C41	1.514(6)
C8-H8C	1.090(6)	C39-C40	1.315(6)
C8-H8A	1.091(5)	C39-H39	1.095(4)
C8-H8B	1.073(5)	C40-H40C	1.111(5)
C9-C10	1.341(6)	C40-H40B	1.108(5)
C9-C15	1.538(6)	C41-H41A	1.078(4)
C10-C11	1.515(6)	C41-H41B	1.093(4)
C10-C12	1.521(6)	C42-C43	1.523(8)
C11-H11C	1.074(4)	C42-C44	1.531(8)
C11-H11A	1.077(4)	C42-H42	1.106(5)
C11-H11B	1.085(4)	C43-H43C	1.088(7)
C12-C13	1.521(6)	C43-H43A	1.101(6)
C12-H12	1.086(4)	C43-H43B	1.072(6)
C13-C14	1.530(5)	C44-H44C	1.087(6)
C13-H13A	1.081(4)	C44-H44A	1.078(5)

C13-H13B	1.081(4)	C44-H44B	1.071(6)
C14-C15	1.557(6)	C45-C46	1.523(7)
C14-C34	1.541(6)	C45-C47	1.534(8)
C14-H14	1.086(4)	C45-H45	1.098(5)
C15-C16	1.559(6)	C46-H46C	1.101(7)
C15-C17	1.548(6)	C46-H46A	1.096(6)
C16-H16C	1.071(4)	C46-H46B	1.076(5)
C16-H16A	1.086(4)	C47-H47C	1.089(6)
C16-H16B	1.080(4)	C47-H47A	1.077(5)
C17-H17C	1.081(4)	C47-H47B	1.087(6)
C17-H17A	1.083(4)	C48-C49	1.532(7)
C17-H17B	1.079(4)	C48-C50	1.523(7)
C18-C19	1.547(6)	C48-H48	1.090(4)
C18-C20	1.529(6)	C49-H49C	1.082(5)
C18-C21	1.537(6)	C49-H49A	1.080(5)
C19-H19C	1.086(5)	C49-H49B	1.091(5)
C19-H19A	1.077(4)	C50-H50C	1.090(5)
C19-H19B	1.092(5)	C50-H50A	1.077(5)
C20-H20C	1.092(5)	C50-H50B	1.093(6)

Table of Atomic Bond Angles in Degrees

O1-Si1-C3	110.50(19)	C18-C21-H21C	109.9(4)
O1-Si1-C4	109.21(20)	C18-C21-H21A	110.5(4)
O1-Si1-C5	101.81(19)	C18-C21-H21B	109.9(4)
C3-Si1-C4	110.20(24)	H21C-C21-H21A	109.1(4)
C3-Si1-C5	112.96(21)	H21C-C21-H21B	108.4(4)
C4-Si1-C5	111.84(24)	H21A-C21-H21B	109.0(4)
O2-Si2-C18	105.41(17)	Si2-C22-C23	119.0(3)
O2-Si2-C22	108.62(17)	Si2-C22-C27	124.6(3)
O2-Si2-C28	110.47(18)	C23-C22-C27	116.3(4)
C18-Si2-C22	116.33(19)	C22-C23-C24	121.7(4)
C18-Si2-C28	109.33(19)	C22-C23-H23	118.3(4)
C22-Si2-C28	106.67(19)	C24-C23-H23	120.0(4)
O3-Si3-C42	109.19(20)	C23-C24-C25	120.0(4)
O3-Si3-C45	110.80(19)	C23-C24-H24	120.2(4)
O3-Si3-C48	102.43(19)	C25-C24-H24	119.8(4)
C42-Si3-C45	109.13(23)	C24-C25-C26	119.6(4)
C42-Si3-C48	112.37(23)	C24-C25-H25	119.4(4)
C45-Si3-C48	112.03(21)	C26-C25-H25	121.1(5)
Si1-O1-C1	129.4(3)	C25-C26-C27	121.0(5)
Si2-O2-C12	127.40(25)	C25-C26-H26	118.9(4)
Si3-O3-C41	130.3(3)	C27-C26-H26	120.0(5)
C34-O4-C35	112.9(3)	C22-C27-C26	121.5(4)
C35-O5-C36	112.0(4)	C22-C27-H27	118.4(4)
O1-C1-C2	110.8(3)	C26-C27-H27	120.1(4)
O1-C1-C9	110.9(3)	Si2-C28-C29	121.5(3)
O1-C1-H1	109.0(3)	Si2-C28-C33	120.4(3)
C2-C1-C9	110.5(3)	C29-C28-C33	118.0(4)
C2-C1-H1	108.0(3)	C28-C29-C30	120.8(5)
C9-C1-H1	107.4(3)	C28-C29-H29	119.5(4)
N1-C2-C1	176.1(4)	C30-C29-H29	119.7(4)
Si1-C3-H3C	109.7(3)	C29-C30-C31	120.5(5)
Si1-C3-H3A	109.6(3)	C29-C30-H30	121.3(5)
Si1-C3-H3B	110.5(3)	C31-C30-H30	118.2(5)
H3C-C3-H3A	108.2(4)	C30-C31-C32	119.7(4)
H3C-C3-H3B	109.5(4)	C30-C31-H31	121.0(5)
H3A-C3-H3B	109.3(4)	C32-C31-H31	119.3(5)
Si1-C4-H4C	109.9(4)	C31-C32-C33	120.2(5)
Si1-C4-H4A	109.8(4)	C31-C32-H32	119.2(4)
Si1-C4-H4B	110.0(3)	C33-C32-H32	120.6(5)
H4C-C4-H4A	108.9(4)	C28-C33-C32	120.7(4)
H4C-C4-H4B	109.1(5)	C28-C33-H33	119.1(4)
H4A-C4-H4B	109.1(5)	C32-C33-H33	120.2(4)
Si1-C5-C6	110.4(4)	O4-C34-C14	108.0(3)
Si1-C5-C7	110.2(3)	O4-C34-C37	109.9(3)
Si1-C5-C8	109.1(3)	O4-C34-H34	110.6(3)
C6-C5-C7	110.1(4)	C14-C34-C37	110.9(3)
C6-C5-C8	108.6(4)	C14-C34-H34	108.4(3)
C7-C5-C8	108.3(4)	C37-C34-H34	108.9(3)
C5-C6-H6C	111.1(5)	O4-C35-O5	113.4(4)
C5-C6-H6A	109.4(4)	O4-C35-H35A	108.2(4)
C5-C6-H6B	111.8(5)	O4-C35-H35B	108.2(4)

H6C-C6-H6A	107.1(5)
H6C-C6-H6B	109.1(5)
H6A-C6-H6B	108.3(5)
C5-C7-H7C	110.8(5)
C5-C7-H7A	110.5(4)
C5-C7-H7B	109.5(4)
H7C-C7-H7A	109.8(4)
H7C-C7-H7B	108.8(4)
H7A-C7-H7B	107.5(5)
C5-C8-H8C	109.9(4)
C5-C8-H8A	109.8(4)
C5-C8-H8B	110.3(4)
H8C-C8-H8A	107.9(5)
H8C-C8-H8B	109.2(5)
H8A-C8-H8B	109.1(4)
C1-C9-C10	119.9(4)
C1-C9-C15	114.3(3)
C10-C9-C15	125.8(4)
C9-C10-C11	124.7(4)
C9-C10-C12	121.2(4)
C11-C10-C12	114.0(3)
C10-C11-H11C	109.7(4)
C10-C11-H11A	109.1(4)
C10-C11-H11B	108.9(4)
H11C-C11-H11A	110.2(4)
H11C-C11-H11B	109.6(4)
H11A-C11-H11B	109.4(4)
O2-C12-C10	108.1(3)
O2-C12-C13	109.8(3)
O2-C12-H12	109.1(3)
C10-C12-C13	112.4(3)
C10-C12-H12	108.4(3)
C13-C12-H12	108.9(3)
C12-C13-C14	110.1(3)
C12-C13-H13A	109.5(3)
C12-C13-H13B	109.9(3)
C14-C13-H13A	109.5(3)
C14-C13-H13B	109.3(3)
H13A-C13-H13B	109.4(4)
C13-C14-C15	112.6(3)
C13-C14-C34	111.4(3)
C13-C14-H14	106.4(3)
C15-C14-C34	113.9(3)
C15-C14-H14	106.6(3)
C34-C14-H14	106.7(3)
C9-C15-C14	109.8(3)
C9-C15-C16	108.9(3)
C9-C15-C17	109.6(3)
C14-C15-C16	107.7(3)
C14-C15-C17	112.4(3)
C16-C15-C17	108.7(3)
C15-C16-H16C	109.4(3)
C15-C16-H16A	109.6(3)
C15-C16-H16B	109.7(3)

O5-C35-H35A	108.6(4)
O5-C35-H35B	110.0(4)
H35A-C35-H35B	108.3(4)
O5-C36-H36C	110.7(5)
O5-C36-H36A	110.7(4)
O5-C36-H36B	111.6(4)
H36C-C36-H36A	107.2(4)
H36C-C36-H36B	108.8(5)
H36A-C36-H36B	107.5(5)
C34-C37-C38	126.0(4)
C34-C37-H37	116.6(3)
C38-C37-H37	117.5(4)
C37-C38-C39	123.2(4)
C37-C38-C41	121.5(4)
C39-C38-C41	115.3(3)
C38-C39-C40	126.1(4)
C38-C39-H39	116.2(4)
C40-C39-H39	117.6(4)
C39-C40-H40C	108.5(4)
C39-C40-H40B	108.0(4)
H40C-C40-H40B	105.3(4)
O3-C41-C38	110.8(3)
O3-C41-H41A	109.5(4)
O3-C41-H41B	108.8(3)
C38-C41-H41A	109.8(4)
C38-C41-H41B	109.2(4)
H41A-C41-H41B	108.7(4)
Si3-C42-C43	113.5(4)
Si3-C42-C44	112.8(4)
Si3-C42-H42	104.2(3)
C43-C42-C44	110.8(5)
C43-C42-H42	106.9(4)
C44-C42-H42	108.1(4)
C42-C43-H43C	110.9(5)
C42-C43-H43A	108.6(5)
C42-C43-H43B	111.7(5)
H43C-C43-H43A	107.4(5)
H43C-C43-H43B	109.5(5)
H43A-C43-H43B	108.5(5)
C42-C44-H44C	109.3(4)
C42-C44-H44A	109.8(5)
C42-C44-H44B	108.8(5)
H44C-C44-H44A	109.1(5)
H44C-C44-H44B	109.6(5)
H44A-C44-H44B	110.3(5)
Si3-C45-C46	112.6(3)
Si3-C45-C47	111.8(3)
Si3-C45-H45	105.0(3)
C46-C45-C47	109.5(4)
C46-C45-H45	109.0(4)
C47-C45-H45	108.8(4)
C45-C46-H46C	110.8(5)
C45-C46-H46A	110.2(5)
C45-C46-H46B	112.1(5)

H16C-C16-H16A	109.[illegible](4)
H16C-C16-H16B	110.[illegible](4)
H16A-C16-H16B	109.[illegible](4)
C15-C17-H17C	109.[illegible](3)
C15-C17-H17A	109.[illegible](3)
C15-C17-H17B	109.9(3)
H17C-C17-H17A	109.2(3)
H17C-C17-H17B	109.5(4)
H17A-C17-H17B	109.3(4)
Si2-C18-C19	108.0(3)
Si2-C18-C20	113.4(3)
Si2-C18-C21	110.5(3)
C19-C18-C20	107.5(4)
C19-C18-C21	107.7(4)
C20-C18-C21	109.5(4)
C18-C19-H19C	110.1(4)
C18-C19-H19A	110.6(4)
C18-C19-H19B	109.9(4)
H19C-C19-H19A	109.3(4)
H19C-C19-H19B	108.2(4)
H19A-C19-H19B	108.8(4)
C18-C20-H20C	110.7(4)
C18-C20-H20A	110.9(4)
C18-C20-H20B	110.7(4)
H20C-C20-H20A	108.2(4)
H20C-C20-H20B	107.9(4)
H20A-C20-H20B	108.4(4)

H46[illegible]-C46-H46A	106.7(5)
H46[illegible]-C46-H46B	108.2(5)
H46A-C46-H46B	108.6(5)
C45-C47-H47C	110.4(4)
C45-C47-H47A	110.6(5)
C45-C47-H47B	109.3(5)
H47C-C47-H47A	109.0(5)
H47C-C47-H47B	108.3(5)
H47A-C47-H47B	109.2(5)
Si3-C48-C49	113.6(3)
Si3-C48-C50	112.5(3)
Si3-C48-H48	104.7(3)
C49-C48-C50	110.5(4)
C49-C48-H48	107.6(4)
C50-C48-H48	107.5(4)
C48-C49-H49C	110.3(4)
C48-C49-H49A	110.0(4)
C48-C49-H49B	110.1(4)
H49C-C49-H49A	109.3(4)
H49C-C49-H49B	108.5(4)
H49A-C49-H49B	108.7(4)
C48-C50-H50C	110.1(4)
C48-C50-H50A	111.5(4)
C48-C50-H50B	109.7(4)
H50C-C50-H50A	109.0(5)
H50C-C50-H50B	107.8(5)
H50A-C50-H50B	108.7(4)

Torsion angles

C3	SI1	O1	C1	-48.8(2)	C4	SI1	O1	C1	72.6(3)
C5	SI1	O1	C1	-169.1(3)	O1	SI1	C3	H3C	-58.7(2)
O1	SI1	C3	H3A	60.0(2)	O1	SI1	C3	H3B	-179.5(4)
C4	SI1	C3	H3C	-179.5(4)	C4	SI1	C3	H3A	-60.7(3)
C4	SI1	C3	H3B	59.7(3)	C5	SI1	C3	H3C	54.6(3)
C5	SI1	C3	H3A	173.4(4)	C5	SI1	C3	H3B	-66.2(3)
O1	SI1	C4	H4C	-68.1(3)	O1	SI1	C4	H4A	51.7(2)
O1	SI1	C4	H4B	171.7(5)	C3	SI1	C4	H4C	53.5(3)
C3	SI1	C4	H4A	173.2(5)	C3	SI1	C4	H4B	-66.7(3)
C5	SI1	C4	H4C	-180.0(5)	C5	SI1	C4	H4A	-60.2(3)
C5	SI1	C4	H4B	59.8(3)	O1	SI1	C5	C6	179.4(4)
O1	SI1	C5	C7	-58.7(3)	O1	SI1	C5	C8	60.1(3)
C3	SI1	C5	C6	60.9(3)	C3	SI1	C5	C7	-177.2(4)
C3	SI1	C5	C8	-58.4(3)	C4	SI1	C5	C6	-64.1(3)
C4	SI1	C5	C7	57.8(3)	C4	SI1	C5	C8	176.6(4)
C18	SI2	O2	C12	160.4(3)	C22	SI2	O2	C12	35.1(2)
C28	SI2	O2	C12	-81.6(2)	O2	SI2	C18	C19	67.5(3)
O2	SI2	C18	C20	-51.6(2)	O2	SI2	C18	C21	-174.9(4)
C22	SI2	C18	C19	-172.1(4)	C22	SI2	C18	C20	68.8(3)
C22	SI2	C18	C21	-54.6(3)	C28	SI2	C18	C19	-51.3(3)
C28	SI2	C18	C20	-170.3(4)	C28	SI2	C18	C21	66.3(3)
O2	SI2	C22	C23	-83.4(3)	O2	SI2	C22	C27	92.5(3)
C18	SI2	C22	C23	157.9(4)	C18	SI2	C22	C27	-26.1(2)
C28	SI2	C22	C23	35.6(2)	C28	SI2	C22	C27	-148.4(4)
O2	SI2	C28	C29	-22.9(2)	O2	SI2	C28	C33	159.0(4)
C18	SI2	C28	C29	92.7(3)	C18	SI2	C28	C33	-85.5(3)
C22	SI2	C28	C29	-140.8(4)	C22	SI2	C28	C33	41.1(2)
C42	SI3	O3	C41	-47.3(2)	C45	SI3	O3	C41	72.9(3)
C48	SI3	O3	C41	-166.7(3)	O3	SI3	C42	C43	180.0(5)
O3	SI3	C42	C44	-53.0(3)	O3	SI3	C42	H42	64.1(3)
C45	SI3	C42	C43	58.7(3)	C45	SI3	C42	C44	-174.2(4)
C45	SI3	C42	H42	-57.2(3)	C48	SI3	C42	C43	-67.8(3)
C48	SI3	C42	C44	60.0(3)	C48	SI3	C42	H42	177.1(5)
O3	SI3	C45	C46	-72.6(3)	O3	SI3	C45	C47	51.1(3)
O3	SI3	C45	H45	168.9(4)	C42	SI3	C45	C46	47.7(3)
C42	SI3	C45	C47	171.4(4)	C42	SI3	C45	H45	-70.8(3)
C48	SI3	C45	C46	173.3(4)	C48	SI3	C45	C47	-62.9(3)
C48	SI3	C45	H45	54.9(2)	O3	SI3	C48	C49	-162.7(4)
O3	SI3	C48	C50	-36.1(2)	O3	SI3	C48	H48	80.3(3)
C42	SI3	C48	C49	80.2(3)	C42	SI3	C48	C50	-153.2(4)
C42	SI3	C48	H48	-36.8(2)	C45	SI3	C48	C49	-43.6(3)
C45	SI3	C48	C50	82.9(3)	C45	SI3	C48	H48	-160.7(4)
SI1	O1	C1	C2	-89.8(3)	SI1	O1	C1	C9	147.0(4)
SI1	O1	C1	H1	29.0(1)	SI2	O2	C12	C10	-135.5(4)
SI2	O2	C12	C13	101.4(3)	SI2	O2	C12	H12	-17.2(1)
SI3	O3	C41	C38	135.8(4)	SI3	O3	C41	H41A	-102.8(4)
SI3	O3	C41	H41B	15.8(1)	C35	O4	C34	C14	167.9(4)
C35	O4	C34	C37	-70.9(3)	C35	O4	C34	H34	49.4(3)
C34	O4	C35	O5	-75.5(3)	C34	O4	C35	H35A	45.0(2)