THE CHEMISTRY OF THUJONE: ENANTIOSELECTIVE SYNTHESES OF DRIMANE-TYPE ANTIFEEDANTS AND AMBERGRIS FRAGRANCES

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Abstract

This thesis is concerned with the development of thujone (**3**) as an effective chiral building block for natural product synthesis.

Treatment of thujone (**3**) with ozone in solution gave thujonol (**94**) and thujonone (**95**) in a good total yield (70%) via oxidation of the tertiary carbon in the isopropyl side chain. This type of selective oxidation with ozone was generally applicable to a series of thujone derivatives, thus providing versatile intermediates for the syntheses of compounds of interest in the fields of insecticides and perfumery chemicals.

Studies on acid promoted ring cleavage of cyclopropylcarbinols obtained from ozonation revealed three distinct pathways, depending on substrates and reaction conditions. Treatment of **97** with concentrated hydrochloric acid gave chloride **123** while heating alcohol **130**, derived from thujone in five steps, in dioxane:water with a catalytic amount of *p*-toluenesulfonic acid generated homoallylic alcohol **144**. On the other hand, concentrated hydrobromic acid treatment of **120**, obtained from thujonol (**94**) by Robinson annulation, resulted in bromide **322**.

Compound **322** was further reduced with tributyltin hydride to natural (+)-β-cyperone (**8**), thus completing a new four step synthesis from thujone (**3**).

In a projected synthesis of drimane antifeedants (-)-polygodial (**2**) and (-)-warburganal (**10**), a novel radical-mediated ring expansion from **123** to **126** was discovered when the former was treated with tributyltin hydride. However, when a related intermediate **132**, derived by treatment of **130** with hydrochloric acid, was reacted in this manner, no rearrangement but simple reduction to **133** was observed. Clearly, the ring expansion process is critically dependent on the nature of functionality in ring A.

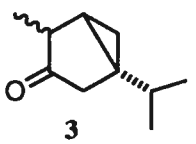
Generation of **126** and, in turn, subsequent intermediates afforded a convenient route to the exclusion of the original isopropyl side chain in many thujone-derived compounds by ozonolysis.

An alternative route developed for the exclusion of the isopropyl side chain involved Baeyer-Villiger oxidation. For example, ketone **131** available from ozonation of alkane **128**, when subjected to *m*-CPBA oxidation, provided acetate **160**, which after hydrolysis to cyclopropanol **161** and treatment of the latter with ferric chloride yielded β-chloroketone **162**.

The enone **163**, obtained from dehydrochlorination of **162**, was converted to dienone **168** with phenylselenenyl chloride and hydrogen peroxide. Birch reduction of **168** generated the crucial intermediate **64**. Since enone **64** had been previously converted to (-)-polygodial (**2**) and (-)-warburganal (**10**), a formal enantioselective synthesis was thus completed.

The enone **163** could also serve as an attractive intermediate for the synthesis of (-)-Ambrox® (**179**). Stereoselective conjugate addition of enone **163** with vinylmagnesium bromide and cuprous iodide yielded compound **245** which was further regioselectively methylated to **246**. Introduction of a double bond into **246** via selenium chemistry as noted above furnished **250** which was reduced to the *trans*-fused decalone **251** by Birch reduction. L-Selectride treatment of **251** produced the axial alcohol **253** and subsequent hydroboration yielded the 1,5-diol **255**. *p*-Toluenesulfonic acid catalyzed cyclization of the 1,5-diol **255** provided the potent ambergris odorants (-)-Ambrox® (**179**) and an interesting rearrangement compound **257** as major products. At lower temperature (80°C), **179** was the major product while **257** became predominant at higher temperature (100°C).

Ring expansion of thujone was also investigated in order to explore alternative routes leading to the synthesis of (**2**) and (**179**). Reaction of thujone (**3**) with ethyl diazoacetate generated β-Ketoester **270**, which upon decarboxylation furnished "homothujone" (**272**). Robinson annulation of compound **272** yielded enone **274**. Alkane **291** was derived from **274** in three steps and its ozonation reaction was performed. Surprisingly, the normally observed attack at the tertiary carbon of the isopropyl side chain did not occur. Instead, ketone **292** was isolated as the major product.



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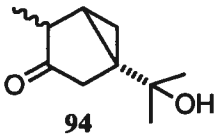

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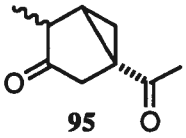

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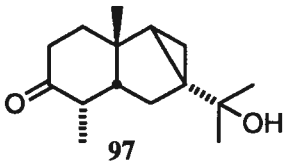

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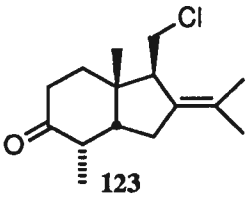

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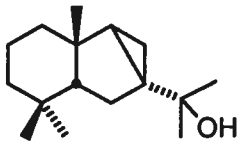

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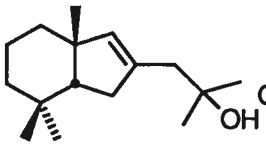

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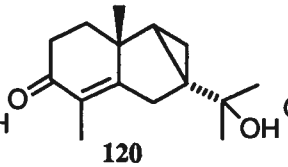

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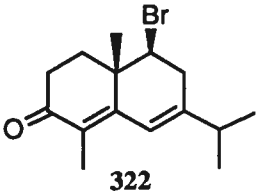

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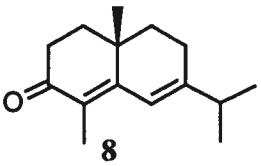

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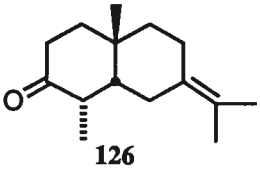

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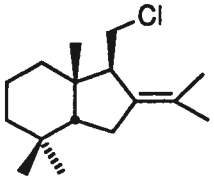

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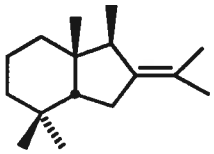

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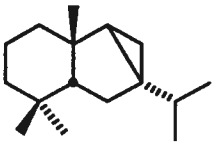

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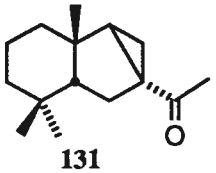

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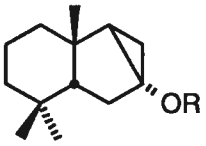

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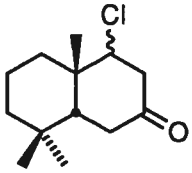
161: R=H



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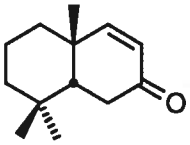

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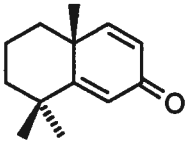

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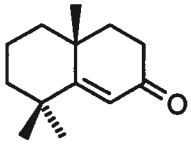

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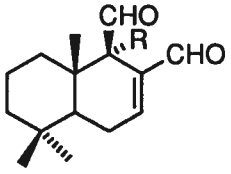
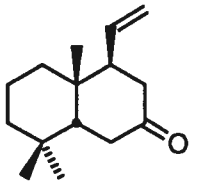


2: R=H
10: R=OH



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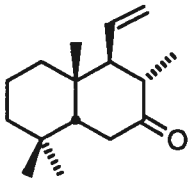

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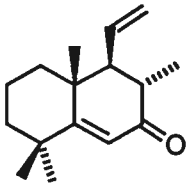

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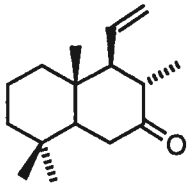

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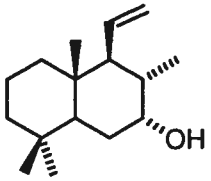

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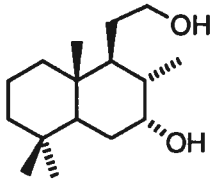

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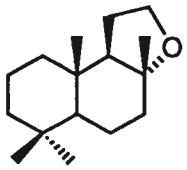

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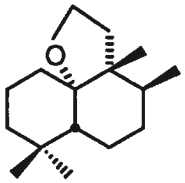

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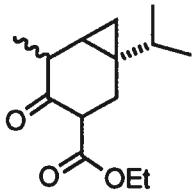

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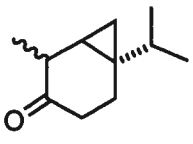

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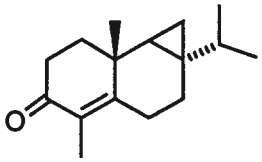

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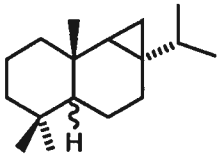

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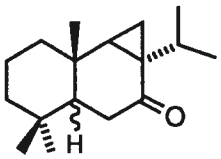

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List of Abbreviations

2D-HETCOR	two dimensional heteronuclear correlation spectroscopy
$[\alpha]_D^{25}$	specific rotation recorded at 25°C using sodium D-line
Ac	acetyl
AIBN	2,2-azoisobutylnitrile
APT	attached proton test (in ^{13}C NMR)
aq.	aqueous
ax	axial
BB	broad band decoupling (in ^{13}C NMR)
Benz.	benzene
bs	broad singlet
c	concentration
CA	Chemical Abstract
CD	circular dichroism
cm^{-1}	wave number
conc.	concentrated
cont.	continue
δ	chemical shift
d	doublet
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$\Delta\varepsilon$	molar circular dichroism
DEG	diethylene glycol
deg	degree (angle)
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq	equatorial
eqv	equivalent

Et	ethyl
EVK	ethyl vinyl ketone
FMO	frontier molecular orbital
g	gram
GC	gas-liquid chromatography
HMPA	hexamethylphosphoramide
hν	light radiation
HOMO	highest occupied molecular orbital (energetically)
Hz	Hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant
λ	wavelength
L-Selectride	lithium tri-*sec*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
log ε	the log of extinction coefficient
LTA	lead tetraacetate
LUMO	lowest unoccupied molecular orbital (energetically)
M	molar
m	multiplet
M^+	molecular ion
m-CPBA	*meta*-chloroperbenzoic acid
m.p.	melting point
m/z	mass to charge ratio
max.	maximum
Me	methyl
mg	milligram
MHz	megahertz
min	minute
µl	microliter
mmol	millimole
MS	mass spectrometry
MVK	methyl vinyl ketone
ν	frequency
NBS	N-bromosuccinimide

nm	nanometer
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
°C	degree Celsius
ORTEP	oak ridge themal ellipsoid program
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	part per million
pyr.	pyridine
θ	ellipticity angle
[θ]	molar ellipticity angle
q	quartet
r.t.	room temperature
s	singlet
SOMO	singly occupied molecular orbital
t	triplet
TBDMS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
v/v	volume to volume ratio
Å	Angstrom

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Especial thanks go to my mother, whose caring, support, and exemplification give me strength and inspiration throughout these years of education.

To the memory of my Father

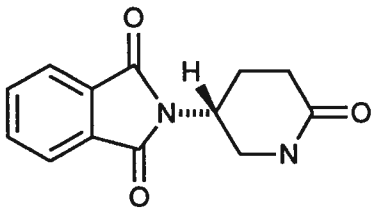
If there is one way better than another,
It is the way of Nature

Aristotle

Chapter 1. General Introduction

1.1. Synthesis of Enantiomerically Pure Compounds

The synthesis of a chiral compound in its enantiomerically pure form has become an important goal for organic chemists in recent years. In addition to aesthetic reasons, the very dependence of various biological activities on absolute stereochemistry[1,2] dictates pure enantiomers to be prepared and investigated in academic research and frequently only enantiomerically pure agents to be produced in industry. A racemic drug, (±)-thalidomide, had to be withdrawn from the market due to a serious side effect of one of the enantiomers. It was reported[3] that (**R**)-(+)-thalidomide (**1**), an effective sedative, had no teratogenic effects when administered to rats and mice even at high doses; but its enantiomer, (S)-(-)-thalidomide, was devoid of sedative effect and resulted in deformities in the animal tested. (-)-Polygodial (**2**), a drimane type sesquiterpene, showed a potent antifeedant activity against African army worms while its enantiomer (+)-polygodial and the racemic mixture exhibited an undesirable phytotoxic effect[4].



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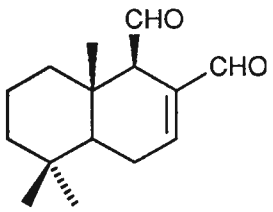

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Three basic methods are available to produce enantiomerically pure compounds, including resolution of racemates, application of asymmetic synthesis, and use of chiral materials as building blocks. Each method has its own advantages and drawbacks[5]:

1. Resolution

The risk associated with a projected synthesis based upon a resolution is evident because of the empirical nature of resolution; resolution is potentially wasteful unless the

undesired enantiomer can be recycled; it has to be performed early in the synthetic sequence to avoid further waste of reagents and labor. However, many resolutions have been successfully carried out. Resolution provides a rapid access to both enantiomers of a compound, which is desirable in biological studies.

2. Asymmetric Synthesis

Asymmetric synthesis holds great promise in producing chiral molecules effectively, as reflected by the vigorous activities in this field in recent years. It has even greater efficiency if the chiral auxiliary is employed catalytically. However, only a few asymmetric syntheses can provide products of high enantiomeric excess reliably without resorting to further enantiomeric enrichment.

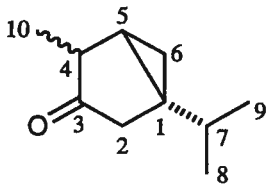
3. Chiral Building Blocks

The third method is to utilize readily available chiral molecules, either naturally occurring products or their derivatives, as starting materials (i.e., chiral templates). If these chiral building blocks are enantiomerically pure and racemization is avoided by choosing reaction conditions carefully, the method is the safest way of obtaining enantiomerically pure compounds. However, the initial chiral molecules have to be consumed during their incorporation into target molecules. Moreover, because of the limited spectrum of readily available chiral compounds, substantial chemistry has to be implemented for their conversion into viable enantiomerically pure intermediates, the preparation of which in racemic form is simpler in perception and / or execution.

All these methods are in some way related to the 'chiral pool' derived from Nature. In resolution, a chiral compound is used to convert enantiomers into two diastereomers or to differentiate them through chemical reactions (i.e., kinetic resolution); in asymmetric synthesis, a chiral auxiliary is employed either catalytically or stoicheometrically to introduce diastereomeric transition states; as a building block, a chiral molecule becomes an integrated part of the target. Therefore, additions to this 'chiral pool' by the introduction of new enantiomerically pure compounds and modification of existing ones are always welcomed.

1.2. Thujone as a Chiral Building Block

The occurrence of thujone (**3**) in Western red cedar (*Thuja plicata* Donn) was reported[7] as early as in 1939 and its absolute stereochemistry was assigned[8] in 1964. This natural product is actually a mixture of two epimers, (-)-α-thujone (**4**) and (+)-β-thujone (**5**) (**4**:**5**=10:1). Of these two epimers, α-thujone is slightly more stable. Treatment of thujone (**3**) with potassium hydroxide in ethanol[9] gave an equilibrium mixture containing α-thujone and β-thujone in a ratio of approximately 2 to 1.



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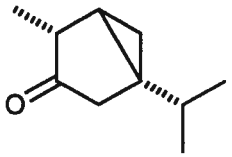

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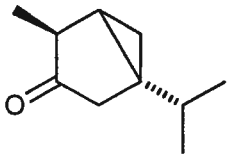

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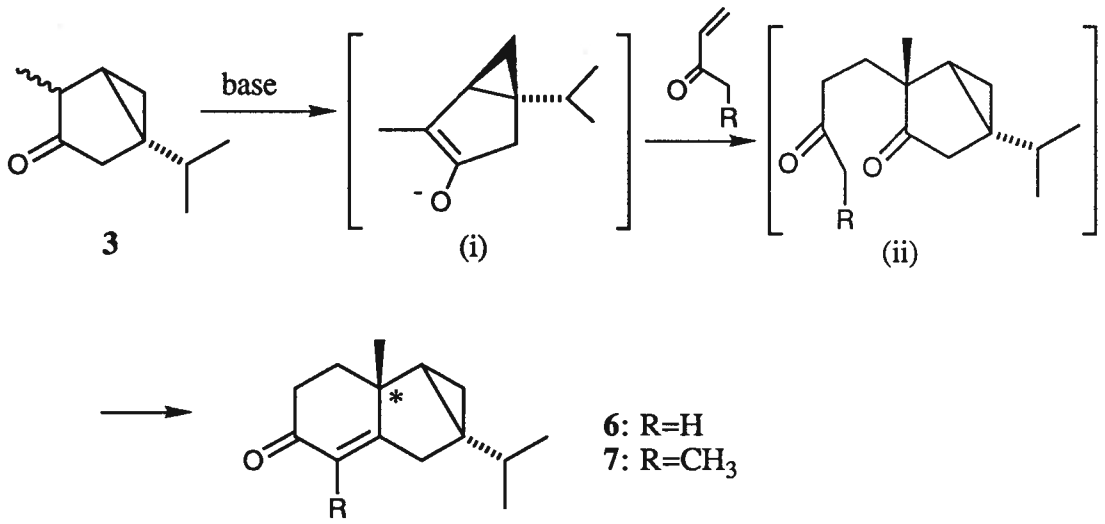
The logging practice of Western red cedar which is abundant in British Columbia forests generates a waste product, generally called "slash". The 'slash' consists of the left-over branches, and leaves. It often must be removed for reforestation and elimination of the potential fire hazard. Alternatively, "on-site" steam distillation of the slash produces an essential oil containing thujone up to 88%, thus providing an inexpensive source of thujone while also serving as a means of removing the left-over slash[7]. Although the oil obtained can be sold for use in the perfumery industry, higher grade chemical products originating from it are well sought after in recent years from the viewpoints of both economic opportunity and environmental concern. In fact, recent synthetic work in our laboratories has proven that thujone is a viable chiral starting material for the enantioselective synthesis of biologically active natural products and their analogues including juvenile hormone analogues[10], pyrethroid insecticides[11], aryl terpenoids[12], sesquiterpenes[13], steroids[14], and insect antifeedants[15]

The novelty of thujone chemistry stems from its unique structural features. The bicyclo[3.1.0]hexane moiety is a *cis*-fusion[#] of the two smallest odd-membered rings (i.e., 3-membered ring and 5-membered ring). The inherent cyclopropane ring should manifest the close relevance of thujone chemistry to the chemistry of cyclopropyl group[17] since its transformation is a necessity for most synthetic efforts. The carbonyl group would lend its versatility to a great range of synthetic elaborations.

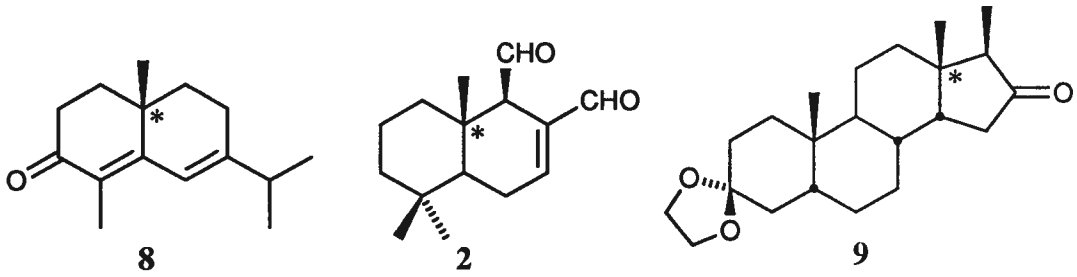
The Robinson annulation of thujone (**3**) is a pivotal transformation in which a quaternary carbon center was generated in a highly stereoselective manner[13a,18] (Scheme 1). Presumably, the approach of Michael acceptors (e.g., MVK and EVK) took place exclusively from the less hindered convex side of the more stable enolate (i). Subsequent aldol condensation of the products (ii) generated tricyclic enones **6** and **7**.



Scheme 1 Robinson Annulation of Thujone

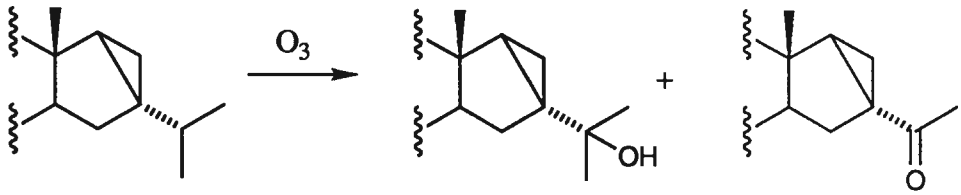
This newly generated quaternary center became a reference point in correlating the thujone structure with chosen target molecules, for example, (+)-β-cyperone (**8**)[13a], (-)-polygodial (**2**)[15], and the steroid analogue **9**.[14b]

[#] There is no organic molecule known to possess a *trans*-fused bicyclo[3.1.0]hexane moiety (see ref. 16).



8 2 9

Another important transformation recently discovered is the selective functionalization of the tertiary carbon at the isopropyl side chain of thujone and its derivatives by ozonation (Scheme 2). The importance of such a functionalization lies in the possible utilization of two operations required in the synthesis of different target molecules by using intermediates derived from the ozonation process. These two operations are the exclusion of the isopropyl side chain and the regioselective ring cleavage of the cyclopropyl group. The ozonation reaction has been applied to synthesis of drimane antifeedants[15], rose oil fragrances[46], and more recently, ambergris fragrances (to be described in this thesis).



Scheme 2 Ozonation of Thujone and Its Derivatives

This thesis is divided into three parts: the first part deals with a formal enantioselective synthesis of (-)-polygodial (**2**), a potent insect antifeedant; the second part describes the synthetic studies leading to products of ambergris fragrance, one of the most valuable animal fragrances; the third part discusses some exploratory studies of new strategies to develop thujone as a more versatile chiral building block.

Chapter 2. Studies Directed to the Synthesis of (-)-Polygodial and (-)-Warburganal

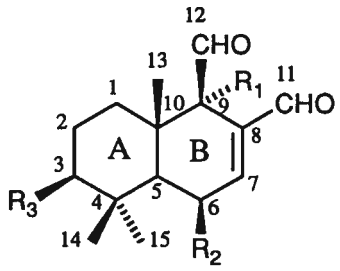
2.1. Introduction

2.1.1. Drimane-type Antifeedants

Along with herbicides, insecticides are presently the most useful agrochemicals to protect food and crops[19a,19c,20]. Insecticides can be divided into two groups. The first group includes synthetic organochlorines, organophosphates, dinitrophenols, formamidines, carbamates, and pyrethroids together with the naturally occuring nicotine, rotenone (*Derris*), sabadilla, and ryania. They have wide applications due to their effectiveness, low cost, and easy usage. However, there are certain disadvantages associated with them: many are quite toxic to vertebrates, fish or beneficial lower forms of life, and are non-selective, killing both pest insects and beneficial insects; some are extremely persistent in the environment and are likely to accumulate in animals; higher and possibly phytotoxic dosages are required because of the developed resistance of some pest insects. The second group of insecticides consist of repellents, attractants, pheromones, insect growth regulators, oviposition inhibitors, and antifeedants. They promise to overcome drawbacks of the first group agents and are attracting the attention of researchers worldwide[21,22]. These compounds are readily degradable and thus friendly to the environment. They are highly specific in insect-plant, insect-insect relations or certain processes within the insect, and therefore less toxic to human beings and useful insects. Many of them are mimics of or even the same as compounds which are essential in the life processes of the pest insect, thus making it more difficult for the insect to restrict the uptake and detoxify such molecules than in the case of synthetic insecticides. In other words, the development of resistance from the target insect is less likely to happen.

According to Munaka[23a], an antifeedant is defined as a chemical which does not kill the insect directly but inhibits feeding, the insect often remaining near the treated plant material and

possibly dying through starvation. An antifeedant is different from an olfactory repellent which is usually a volatile compound that repels the insect before it starts to eat. The exact mode of action of these antifeedants is still largely speculative[23b,23c]. They are believed to play a major role in the ever continuing battle for survival between insects and plants[24]. Probably all plants contain one or more substances which are unpalatable to insects. Plants selection programmes in the evolution process have often chosen varieties with higher contents of antifeedants. The use of these compounds as crop protection agents seems to bear considerable promise[22,25].



2: R_1=R_2=R_3=H
10: R_1=OH, R_2=R_3=H
11: R_1=OH, R_2=H, R_3=OH
12: R_1=OH, R_2=OAc, R_3=H

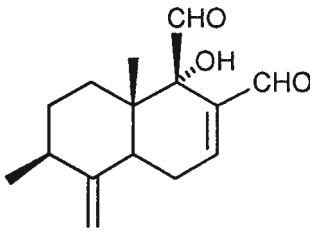


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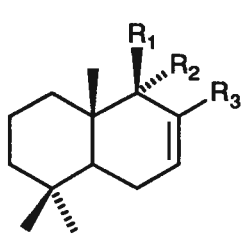
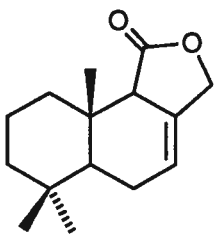
Figure 1 Drimane Antifeedants

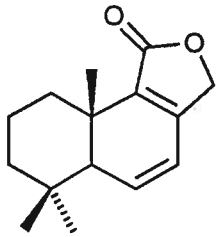
Several sesquiterpenes, mostly of the drimane type, were isolated from the bark of East African medical plants *Warburgia ugandensis* and *W. stuhmannii* (Cannellaceae). Some of these sesquiterpenes (Figure 1)[26], (-)-polygodial (**2**), (-)-warburganal (**10**), 3-hydroxywarburganal (**11**), ugandensidial (**12**), and muzigadial (**13**), possess strong antifeedant activity against the African army worms, *Spodoptera exempta* and *S. littoralis* . More recently, (-)-polygodial (**2**) and (-)-warburganal (**10**) were shown to inhibit feeding and colonization of the aphid of *Myzus persicae* and to decrease the transmission of different plant

viruses by the aphid[27]. Among many other biological activities exhibited by these antifeedants, the hot taste to humans appears the most interesting. Kubo and Ganjain[28] suggested a correlation between the antifeedant activity and the pungent taste experienced by human beings. It should be noted that some of these compounds had also been isolated from other sources even before they were tested positive of antifeedant activity, including (-)-polygodial (**2**) from marsh pepper *Polyonum hydropiper* (Polygonaceae)[29a,b] and *Drimys lanceolata* (Winteraceae)[29c], muzigadial (**13**) identical with canellal from *Canella winterana* (Winteraceae)[29d], and ugandensidial (**12**) identical with cinnamodial isolated from *Cinnmosma fragrans* (Canellaceae)[29e,f].

In order to elucidate the relationship between structure and antifeedant activity, a large number of compounds, either isolated from plants or prepared by chemical synthesis, have been evaluated (Figure 2). The fact that *epi*-polygodial (**14**), polygodial derivatives **15**, **16**, **17**, **18**, cinnamolide (**19**), and betadiennolide (**20**), are devoid of any activity, reveals the necessity of both the C-9β equatorial aldehyde and the enal moiety for the activity in the A/B*trans*-fused series[26]. The (+)-polygodial (**21**) is as active as naturally occurring (-)-polygodial (**2**)[30c], although, earlier, **21** was shown to be highly phytotoxic. Of the two *cis*-fused analogues **22** and **23**, only **23** which has a C-9α aldehyde group, has strong activity; this apparent inversion compared with the corresponding *trans*-fused **2** and **14** was rationalized[30c] (see below). The structure and activity of the diastereoisomers saccalutal (**24**) and isosaccalutal (**25**) parallel that of (-)-polygodial (**2**) and *epi*-polygodial (**14**): compound **24** like compound **2** is active while compound **25** like compound **14** is inactive. Taking the very active muzigodial (**13**) into consideration, it is apparent that modification in the ring A exerts little effect on the activity. Hydroxylation at C9α enhances the activity, while the introduction of an acetoxy group at C6 reduces the activity, possibly by steric hindrance.







14: R_1=H, R_2=R_3=CHO
15: R_1=R_3=CH_2OH, R_2=H
16: R1=CH_2OH, R_2=H, R_3=CHO
17: R_1=R_3=CO_2H, R_2=H
18: R_1=R_3=CO_2Me, R_2=H

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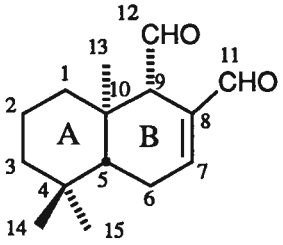

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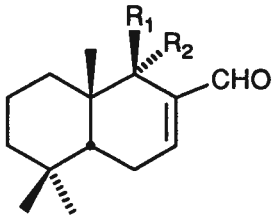
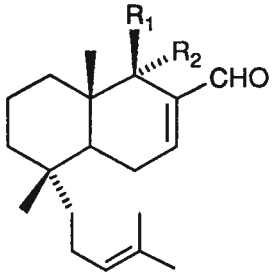


22: R_1=CHO, R_2=H
23: R_1=H, R_2=CHO



24: R_1=CHO, R_2=H
25: R_1=H, R_2=CHO

Figure 2 Analogues of Drimane Antifeedants

Based on the above studies of relationship between structure and antifeedant activity, electrophysiological experiments[31a], and biomimetic studies[30], two main hypotheses concerning the actual molecular mechanism were brought forward to correlate structure to activity. The first suggests (Figure 3) that the enal moiety may act as a thiol acceptor of the insect's chemoreceptor membranes in a way similar to the Michael reaction and inhibits the

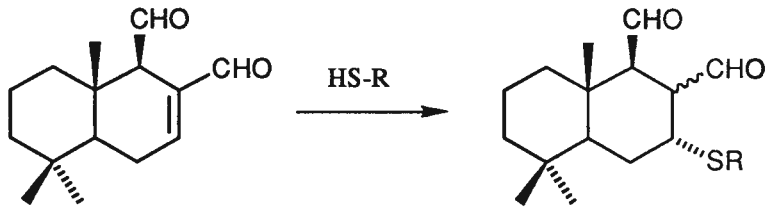


Figure 3 Interaction between Drimane Antifeedants and the Insect's Receptor: the first hypothesis

stimuli transduction[31a]. The lack of activity of *epi*-polygodial (**14**) is explained on the basis of the steric hindrance of its C-9α aldehyde to the approaching free thiol function on the receptor surface[31b].

The second hypothesis, suggested by Sodano et al.[30], assumes that pyrrole formation by reaction of the C8 and C9 dialdehyde moieties with a primary amine of the receptor site is responsible for the antifeedant activity (Figure 4). Under biomimetic conditions, only the active (-)-9β-polygodial (**2**) instead of the *epi*-polygodial (**14**) reacts with a variety of amines, including L-cysteine, L-lysine, L-alanine, and methyl amine, to give pyrrole derivatives[30a,b]. The shorter distance between the C-8 and C-9 aldehyde groups in (-)-polygodial (**2**) relative to *epi*-polygodial (**14**) is considered to be responsible for its ease of pyrrole ring closure and therefore the antifeedant activity[30a]. The strong activity of the *cis*-fused dial **23** with an α aldehyde group at C-9, in contrast to the *cis*-fused dial **22** with a β aldehyde group at C-9, is rationalized in a similar way using their more stable steroid-like conformations[30c].

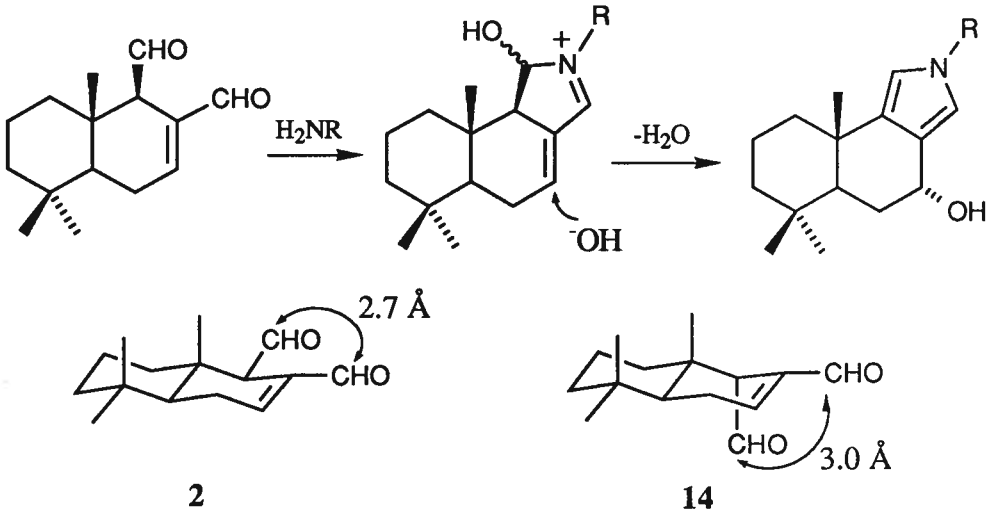


Figure 4 Interaction between Drimane Antifeedants and the Insect's Receptor: the second hypothesis

Based on these two earlier hypotheses, a new proposal was brought forward recently[31c], which assumes that a three-pronged interaction between the receptor and the

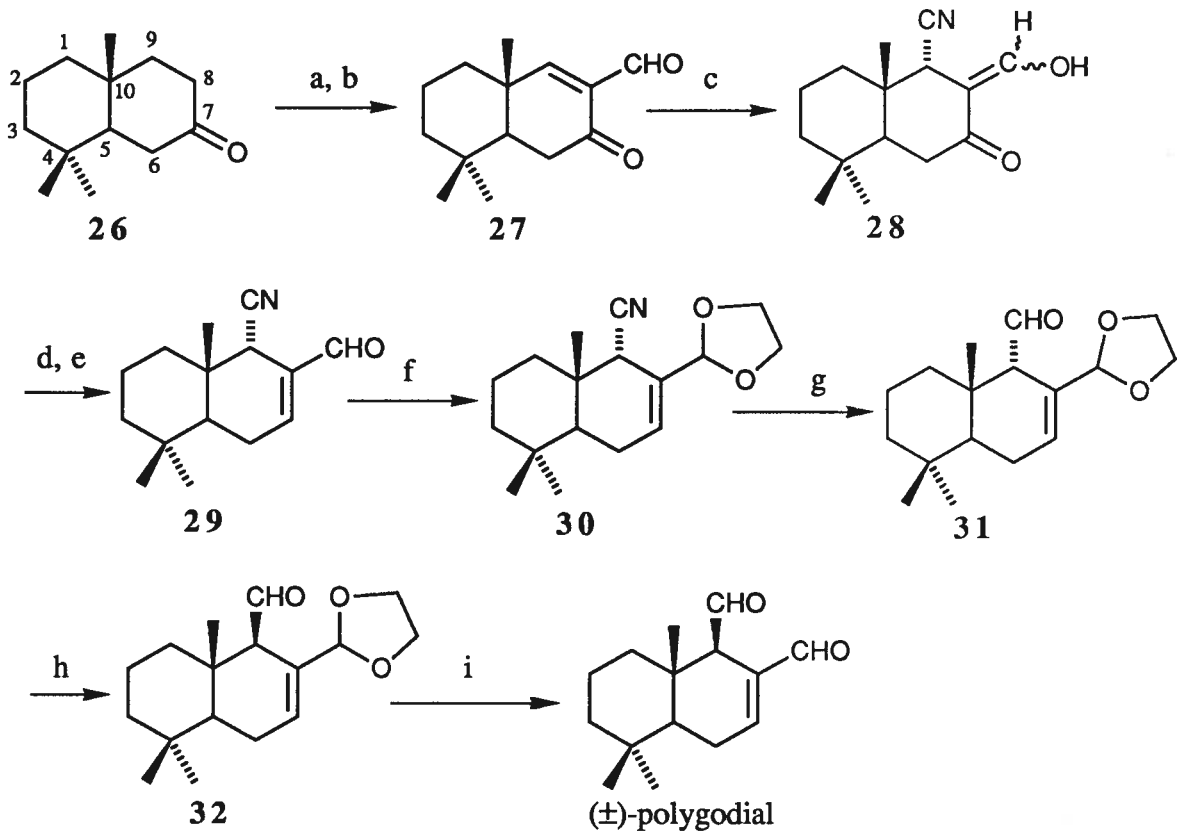
substrate, involving pyrrole formation, Michael addition of the thiol group to the enal moiety, and van der Waals interactions involving the ring **A** (especially at C1), is responsible for the antifeedant activity.

2.1.2. Total Synthesis of Drimane-type Antifeedants

The discovery of the antifeedant activity of drimane-type sesquiterpenes has stimulated a surging interest in their synthesis in the past decade. An excellent review by de Groot and T. A. van Beek[19b] summarizes all studies prior to 1987. More recently, an updated version by de Groot and Jansen[19d] describes in detail all published synthetic work prior to early 1990 . So far, the syntheses of polygodial[32,33], warburganal[34,35], cinnamidial[36], and muzigodial[37] in their racemic and enantiomerically pure forms have been achieved by different research groups. The following discussion will focus on the enantioselective synthesis of (-)-polygodial and (-)-warburganal. A few racemic syntheses of these two compounds will also be discussed since they have direct relevance to our strategy towards the synthesis of drimane-type antifeedants.

2.1.2.(a). Polygodial

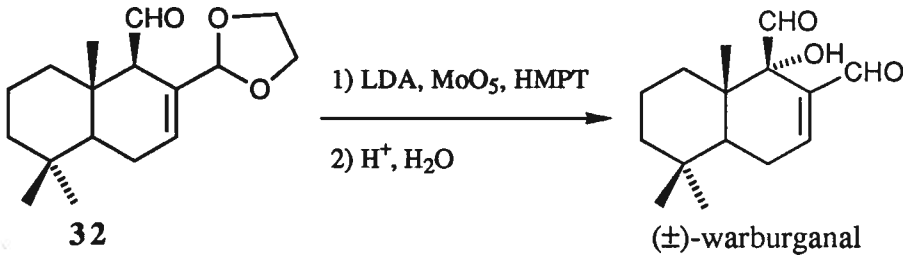
A synthesis of (±)-polygodial and (±)-warbuganal was developed by de Groot et al.[32f] starting from the decalone **26** (Scheme 3). The carbonyl function at C7 was used first to introduce the necessary functionalized carbon atoms at C8 and C9 and subsequently to generate the C7, C8 double bond. The formylation of **26** and the subsequent dehydrogenation gave the unsaturated keto-aldehyde **27**, which underwent a stereoselective conjugate addition by cyanide to **28**. The resulting keto-aldehyde **28** was converted to the unsaturated aldehyde **29** by reduction of its (*n*-butylthio)methylene derivative, followed by mild hydrolysis. Protection of the aldehyde group in **29** and the reduction of the nitrile group in **30** gave compound **31**. The epimerization of **31** to **32** was effected by potassium *t*-butoxide in *t*-butanol. Acidic hydrolysis of **32** then provided (±)-polygodial.



a) NaH, HCOOMe; b) PhSeCl, H_2O_2; c) CN^-; d) H^+, HSBu; e) $NaBH_4$, H^+, H_2O; f) H^+, $(HOCH_2)_2$; g) DIBAL; h) KO^tBu, HO^tBu; i) H^+, H_2O.

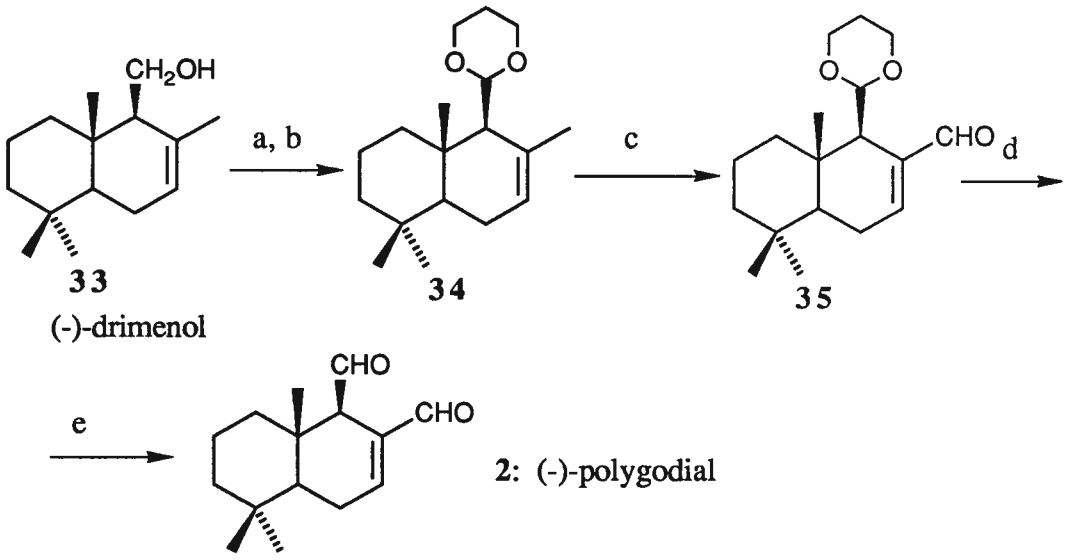
Scheme 3 de Groot's Synthesis of (±)-Polygodial

Since the conversion of **32** to (±)-warbuganal had been accomplished by MoO_5 α-hydroxylation of the enolate from **32** followed by the hydrolysis of the resulting compound[32b,34b], the above sequence also provided a route to (±)-warburganal.



32 (±)-warburganal

The conversion of (-)-drimenol (**33**) into the natural enantiomer (-)-polygodial (**2**) was reported by Cortes et al[33b] (Scheme 4). Oxidation of **33** and the subsequent protection of the aldehyde gave **34**, which was then oxidized with a catalytic amount of selenium dioxide and bis-(4-methoxyphenyl) selenoxide as co-oxidant to give **35** in 45% yield. Deprotection of **35** generated (-)-polygodial (**2**) in an overall yield of 30%.

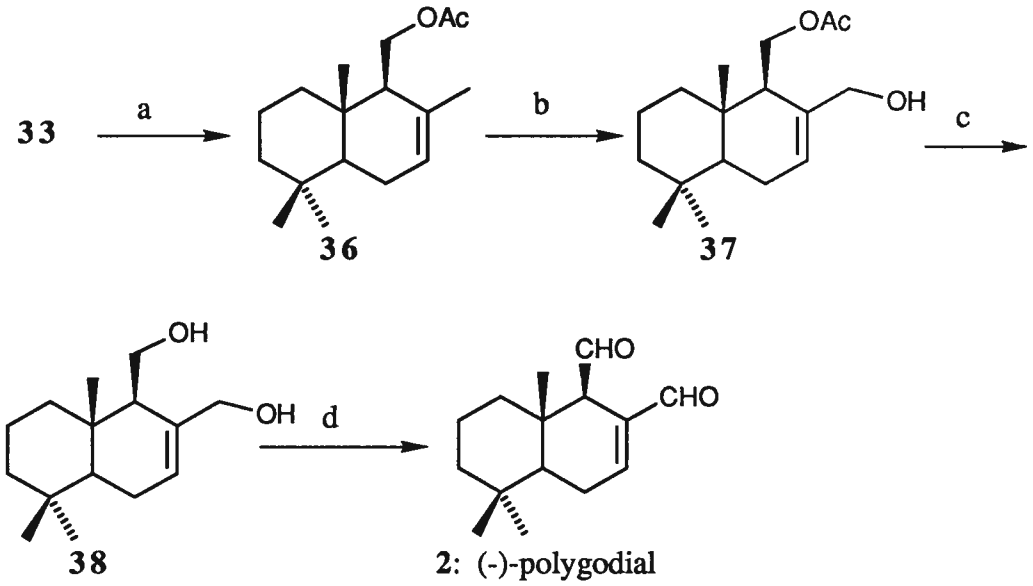


a) PCC; b) $HO(CH_2)_3OH$, H^+; c) SeO_2, $(4\text{-}MeOPh)_2SeO$; d) H^+, H_2O.

Scheme 4 Cortes' First Synthesis of (-)-Polygodial (2)

An alternative sequence from (-)-drimenol (**33**) was published by the same group of authors[33c] (Scheme 5). Acetylation of (-)-drimenol (**33**) provided acetate **36** which was then oxidized to produce the allylic alcohol **37**. Saponification of **37** by means of potassium

carbonate in methanol resulted in diol **38**. Swern oxidation of the diol gave (-)-polygodial (**2**) in almost quantitative yield. The overall yield of (-)-polygodial was 30% from (-)-drimenol (**33**).



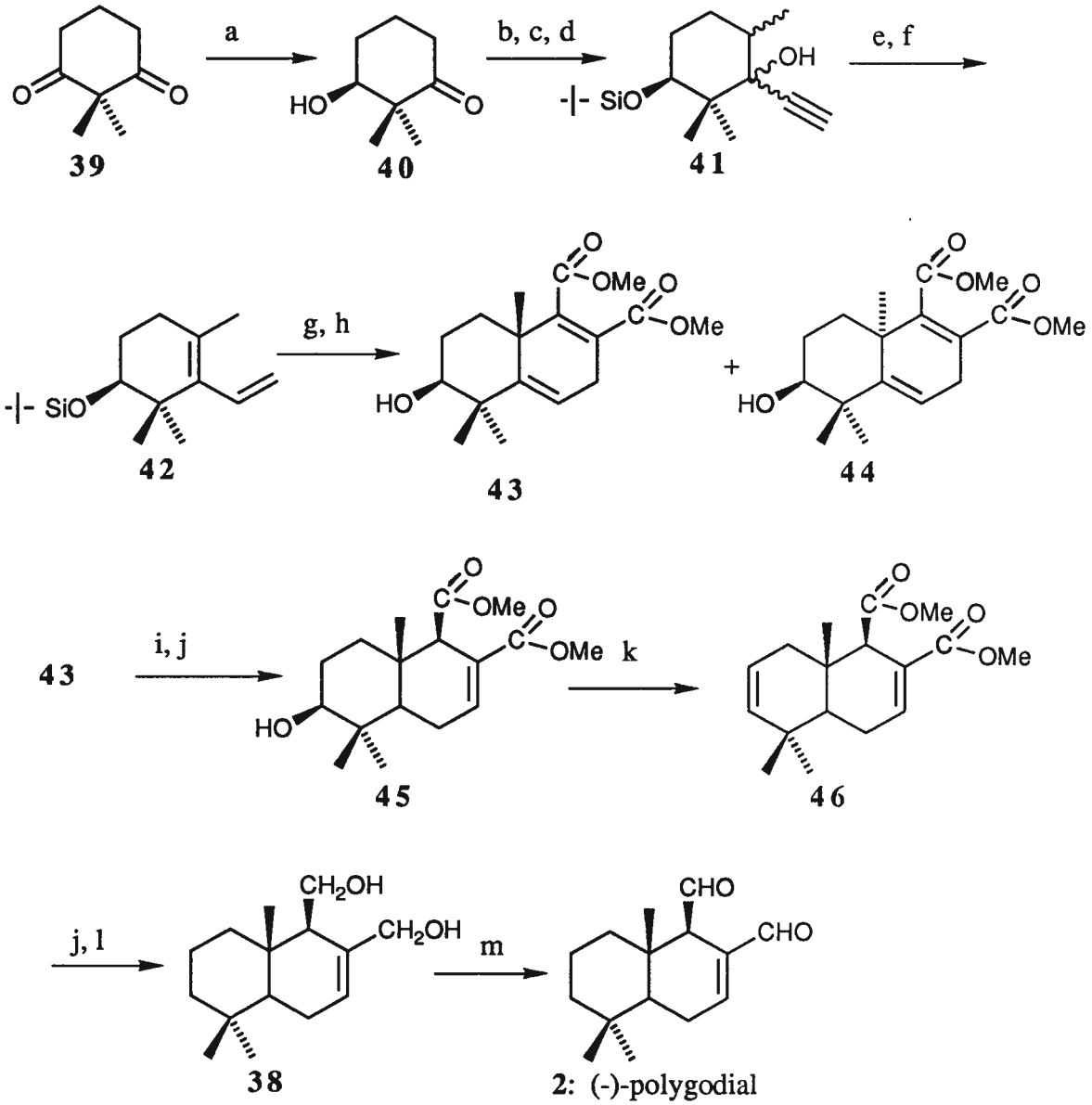
a) Ac_2O, Pyr.; b) SeO_2 (cat.), $(4\text{-MeOPh})_2SeO$; c) KOH, MeOH; d) $(COCl)_2$, DMSO.

Scheme 5 Cortes' Second Synthesis of (-)-Polygodial (**2**)

A synthesis of both enantiomers of polygodial has been developed by Mori et al.[33a] starting from (**S**)-3-hydroxy-2,2-dimethylcyclohexanone (**40**), which was obtained by reduction of dione **39** using Baker's yeast. The (**S**)-ketol **40** was converted to diene **42** as indicated in Scheme 6. The Diels-Alder reaction of this diene **42** with dimethyl acetylenecarboxylate yielded a 1:1 mixture of **43** and **44**. The diastereomeric diesters **43** and **44** were separated in 32% and 35% yield by HPLC. They were then utilized as starting materials for the preparation of both enantiomers of polygodial.

Diester **43** was reduced to *trans*-fused diester **45**. Treatment of **45** with CF_3SO_2Cl and DMPA eliminated the axial hydroxyl group. Hydrogenation of **46** over Pd-C and

reduction of the diester functions gave diol **38**. Swern oxidation of this diol **38** provided the natural (-)-polygodial in an overall yield of 3.0%.

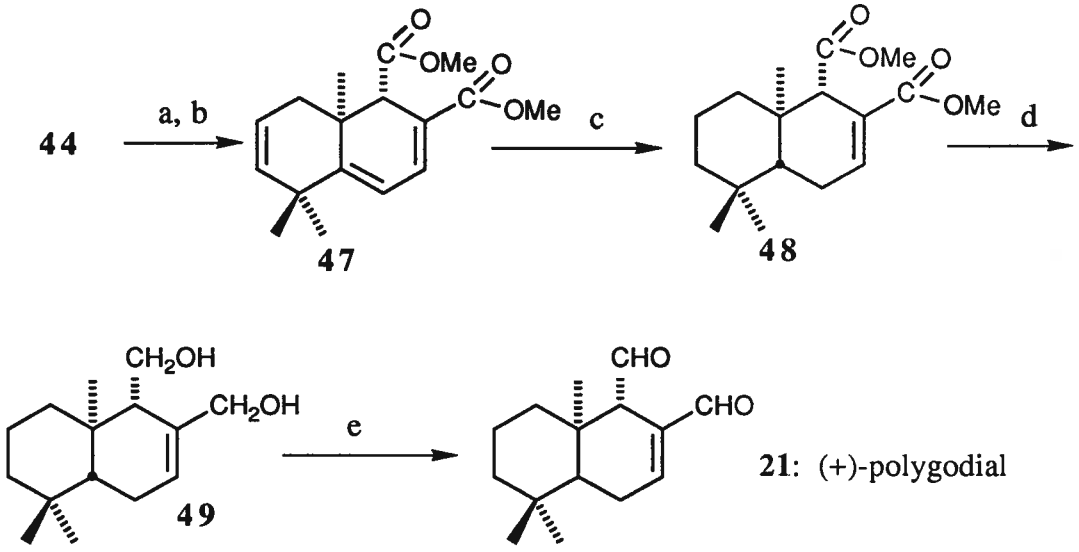


a) baker's yeast; b) Me_3CMe_2SiCl; c) MeI, LDA; d) HC≡CNa; e) $CuSO_4$; f) H_2, Pd-$CaCO_3$; g) MeO_2C-≡-CO_2Me; h) HF, CH_3CN; i) DBU; j) H_2, Pd-C; k) CF_3SO_2Cl, DMAP; l) LAH; m) $(COCl)_2$, DMSO.

Scheme 6 Mori's Synthesis of (-)-Polygodial (2)

The diastereomeric diester **44** was transformed into the unnatural (+)-polygodial through a slightly different route (Scheme 7). Base-catalyzed isomerization of **44** to a

conjugated diene was followed by elimination of the hydroxyl group to give triene **47**. Hydrogenation of this triene afforded the *trans*-fused diester **48** in 70% yield. LAH reduction of the diester functions produced diol **49** which was then converted to the unnatural (+)-polygodial **21** by Swern oxidation in an overall yield of 2.9%.

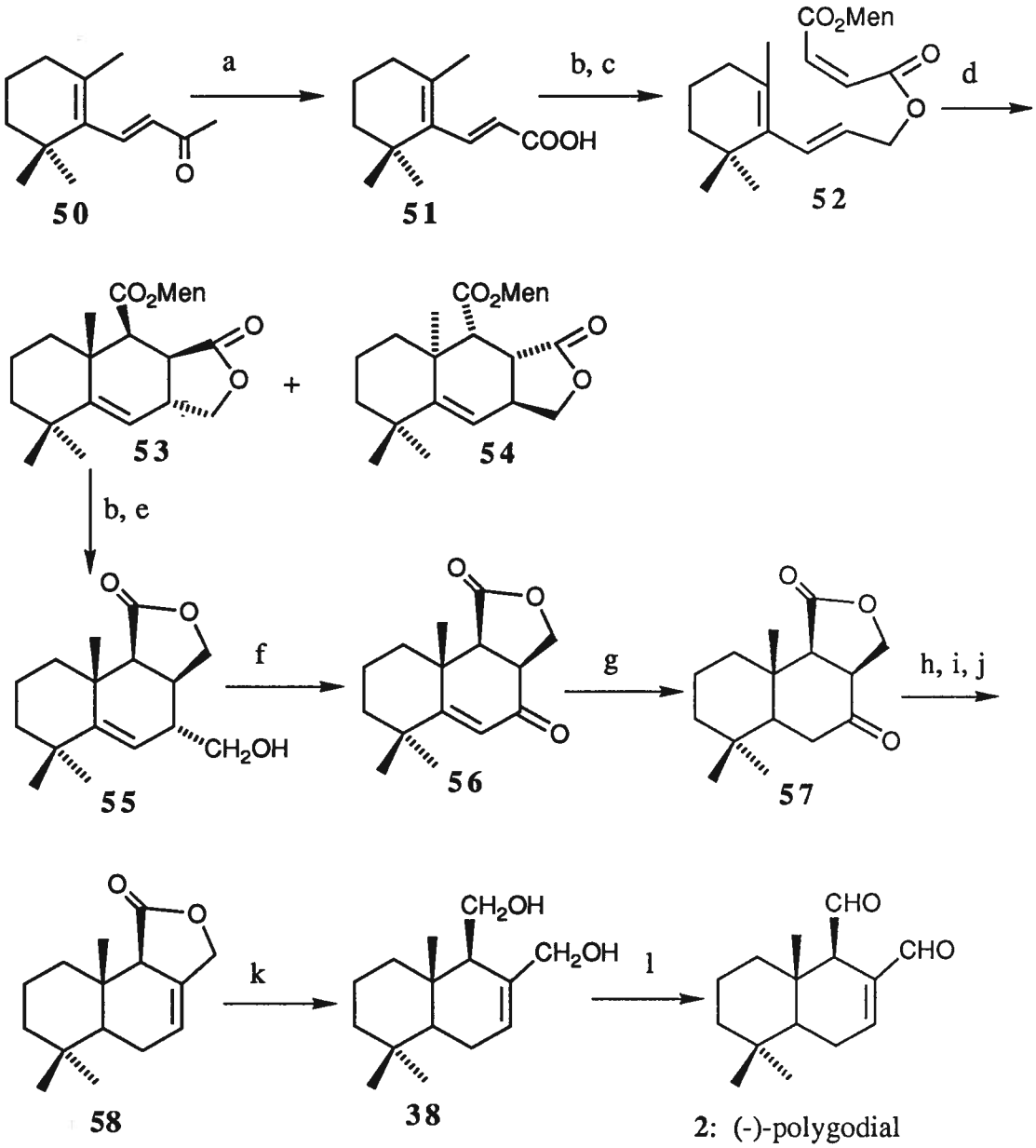


a) DBU; b) CF_3SO_2Cl, DMAP; c) H_2, Pd-C; d) LAH; e) $(COCl)_2$, DMSO.

Scheme 7 Mori's Synthesis of (+)-Polygodial (**21**)

A sequence to (-)-polygodial (**2**) involving an intramolecular Diels-Alder reaction was developed by He and Wu[33d] (Scheme 8). β-Ionone (**50**) was treated with sodium hypobromite to produce **51**. Reduction of **51** with LAH, followed by condensation with maleic acid mono-1-menthyl ester gave **52** in 36% overall yield. Refluxing of **52** in xylene afforded diastereomers **53** and **54** in 79% yield at a ratio 1.75:1. The lactone **53** was then reduced to a diol which was cyclized to lactone **55** by *p*-toluenesulfonic acid in benzene in 76% yield. Oxidative cleavage of **55** with CrO_3 furnished **56** in 65% yield which was then hydrogenated to **57**. The carbonyl group in **57** was converted into an olefinic double bond as shown in **58** by a three-step sequence in 66% overall yield. LAH treatment of **58** produced the diol **38**

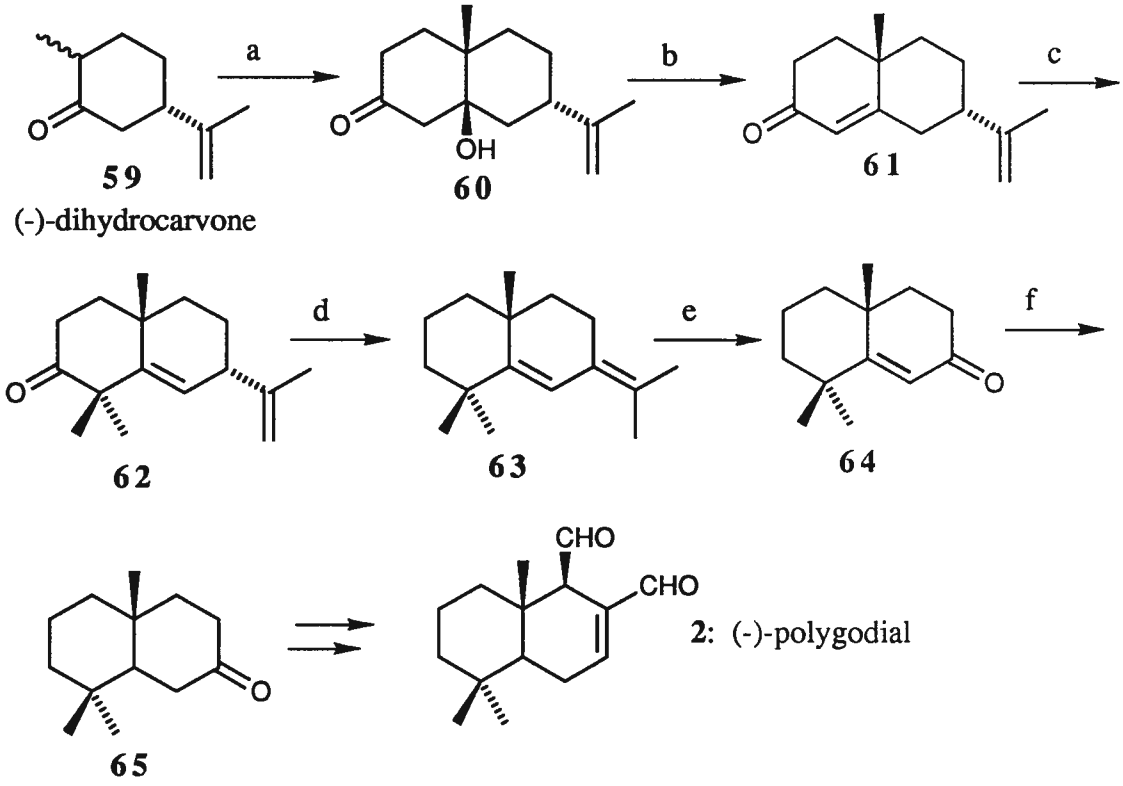
which was finally converted to (-)-polygodial (**2**) by Swern oxidation[33b]. The overall yield was 4.1% from β-ionone (**50**).



a) NaClO; b) LAH, 0°C; c) HO_2C-C≡C-CO_2Men, DCC ; d) xylene, reflux, N_2; e) p-TsOH, benzene; f) CrO_3; g) H_2, Pd-C, MeOH; h) $NaBH_4$; i) $MeSO_2Cl$, Pyr.; j) DMSO; k) LAH; l) DMSO, $(COCl)_2$.

Scheme 8 He and Wu's Synthesis of (-)-Polygodial (**2**)

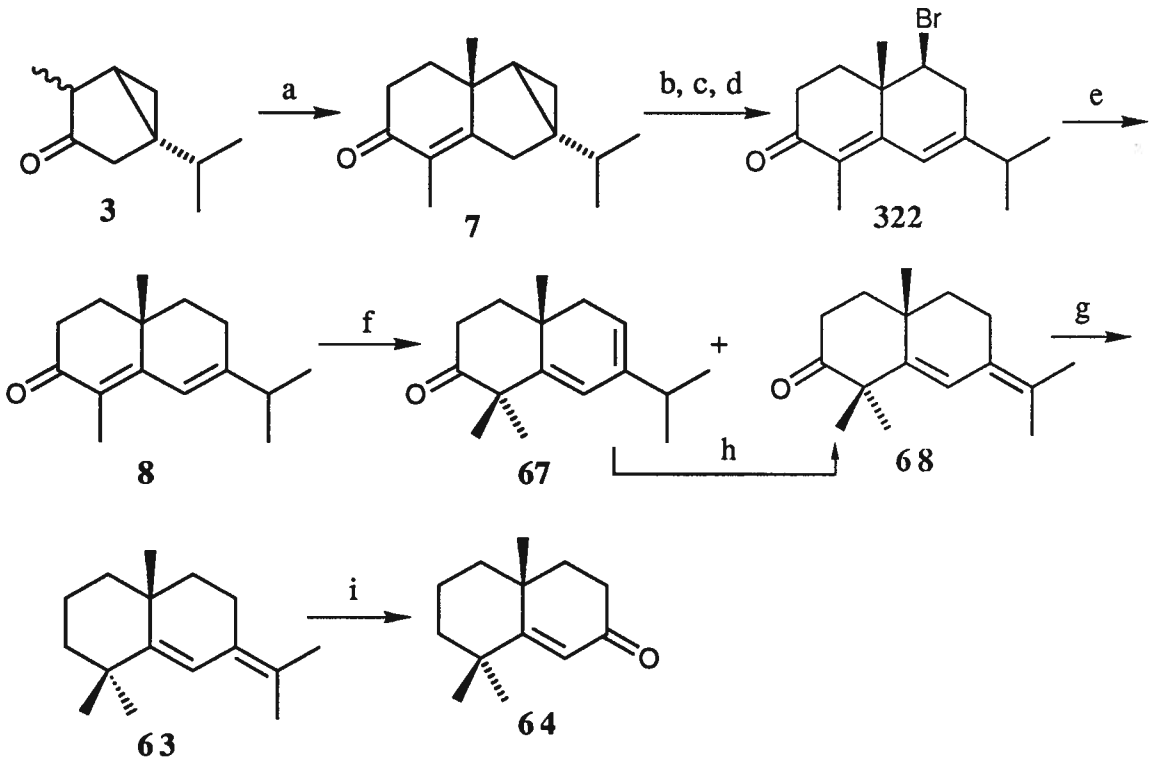
An enantioselective synthesis of (-)-polygodial (**2**) using (-)-carvone (**59**) as the building block was reported by de Groot et al.(Scheme 9)[33e]. Robinson annulation of **59** with MVK produced ketol **60** in 55% yield which was dehydrated to **61** in 87% yield. Dimethylation of **61** afforded **62** in 93%yield which was transformed to conjugated diene **63** by the Huang Minlon modification of Wolff-Kishner reaction reduction in 70% yield. Selective ozonolysis of diene **63** provided enone **64** which was then further reduced to enantiomerically pure **65** by lithium and ammonia in an overall yield of 70%. Since the racemic mixture of **65**, i.e., **26**, has been transformed to (±)-polygodial[32f] (Scheme 3), **65** can be converted into (-)-polygodial (**2**).



a) MVK, KOH, 0°C; b) KOH, CH_3OH, heating; c) CH_3I, KO^tBu; d) NH_2NH_2, KOH, 200°C; e) O_3; f) Li, NH_3.

Scheme 9 de Groot's Synthesis of (-)-Polygodial (**2**)

Another method to prepare enantiomerically pure **65** by using thujone as the chiral starting material was published recently by Kutney et al.[15] (Scheme 10). (+)-β-Cyperone (**8**) prepared from thujone (**3**)[13a] was methylated to a mixture of dienones **67** and **68** in 61% yield. The mixture was then converted into pure dienone **68** by iodine in refluxing hexane in 86% yield. Subsequent reduction of **68** produced diene **63** in 85% yield which was ozonolyzed to enone **64** following the previous conditions by de Groot et al. Compound **64** was further transformed into enantiomerically pure **65** by Birch reduction.



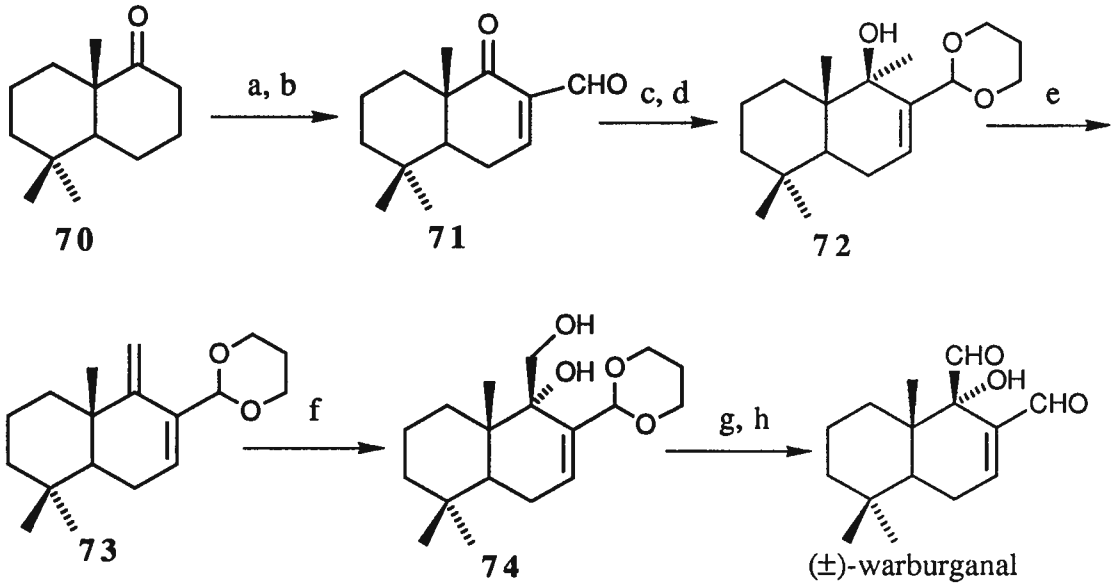
a) EVK, KOH, EtOH; b) H^+, $(CH_3)_2C(CH_2OH)_2$; c) $KMnO_4$; d) HBr (aq); e) Bu_3SnH; f) CH_3I, NaOMe, DMSO; g) I_2, hexane; h) KOH, NH_2NH_2, DEG; i) O_3.

Scheme 10 Kutney's Synthesis of (-)-Polygodial

2.1.2.(b). Warburganal

Two total syntheses of (±)-wargburganal were achieved starting from 5,5,8a-trimethyl-*trans*-fused-1-decalone (**70**). Scheme 11 shows the synthesis by Goldsmith et al[34g].

Formylation of **70** and subsequent dehydrogenation afforded the unsaturated keto-aldehyde **71** in high yield. Selective protection of the aldehyde group and the addition of methyllithium produced tertiary alcohol **72**, which was dehydrated using the Burgess reagent. Osmylation of diene **73** provided diol **74**. Oxidation, followed by hydrolysis of the acetal group afforded (±)-polygodial.

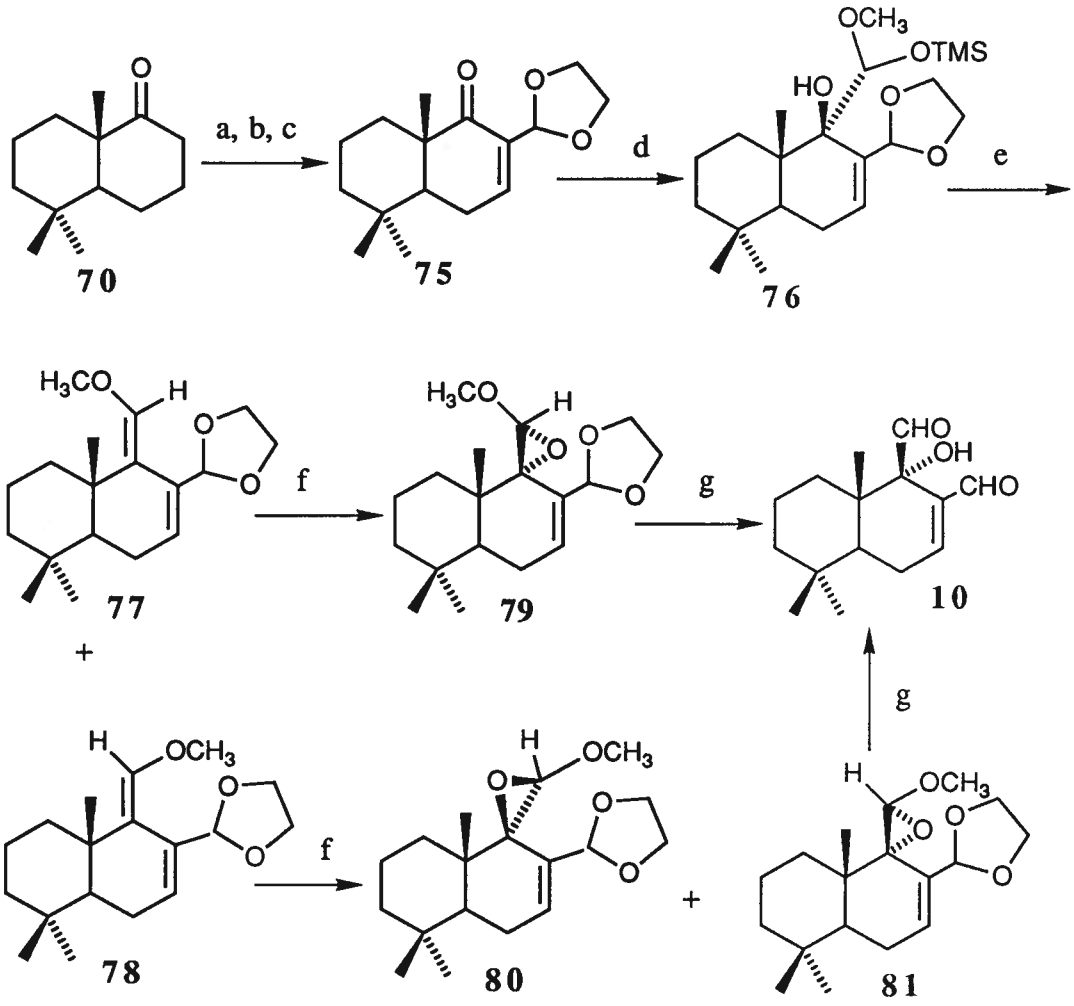


a) NaH, HCO_2Et; b) PhSeCl, Pyr./H_2O_2; c) H^+, $CH_2(CH_2OH)_2$; d) CH_3Li; e) $MeO_2CN\text{-}SO_3NEt_3$; f) OsO_4, Pyr.; g) DMSO, DCC; h) H^+, H_2O

Scheme 11 Goldsmith's Synthesis of (±)-Warburganal

Kende et al.[34h] reported the synthesis outlined in Scheme 12. Decalone **70** was converted into the selectively protected unsaturated ketone **75** by formylation, dehydrogenation with DDQ and reaction with 1,3-propanediol. The hindered carbonyl function in **75** did not react with several ylides, but addition of substituted organometallic reagents can be accomplished in good yield. Thus, addition of [methoxy(trimethylsilyl)-methyl]lithium gave a diastereomeric mixture of alcohols **76**, which underwent elimination of trimethylsilanol to afford a 1:3 mixture of (E) and (Z) enol ethers **77** and **78**. Epoxidation of the (E) isomer **77**

gave the α-epoxide **79**, which could be hydrolyzed under mild acidic condition to (±)-warburganal. Epoxidation of the (Z) isomer **78** yielded a 4:1 mixture of the β-and α-epoxides **80** and **81**, which were hydrolyzed to (±)-epiwarburganal and (±)-warburganal.



a) NaH, HCO_2Et; b) DDQ; c) H^+, $(CH_2OH)_2$; d) (MeO)(Me_3Si)CHLi; e) KH; f) *m*-CPBA; g)H^+, H_2O.

Scheme 12 Kende's Synthesis of (±)-Warburganal

Enantioselective synthesis of (-)-warburganal (**10**) has been accomplished by degradation of diterpenes, abietic acid (**82**)[35b] and royleanone (**86**)[35f], and triterpene **85**[35d]

and transformation of functionalized drimanes, drimenol (**33**)[35a], (+)-confertifoline (**83**)[35c], and diene **84**[35e] (Figure 5).

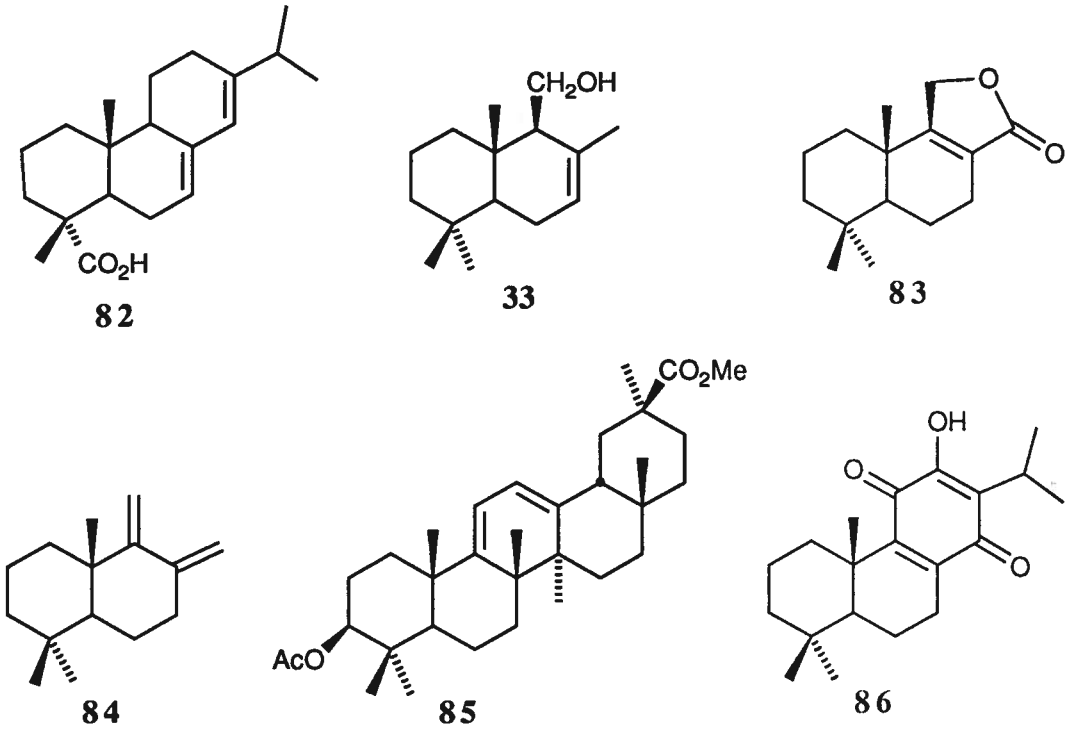
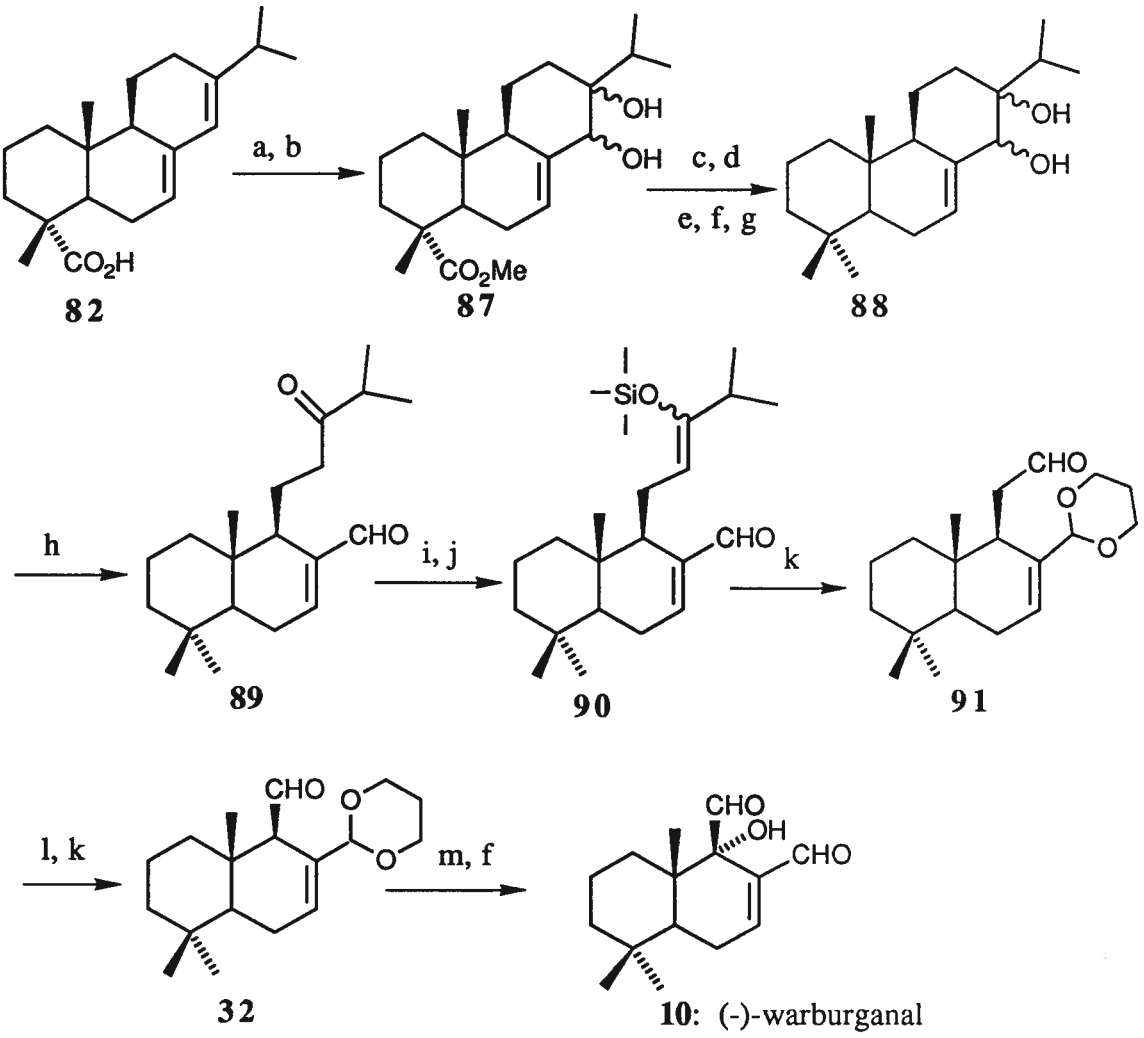


Figure 5 Chiral Starting Materials for the Synthesis of (-)-Warburganal (**10**)

The first synthesis[35b] of (-)-warburganal (**10**) from (-)-abietic acid (**82**) is outlined in Scheme 13. The regioselective osmylation of the double bond of the C ring of **82**, followed by esterification of the acid function, afforded a diastereomeric mixture of diols **87**. The ester group was transformed into a methyl group by the procedure indicated in the Scheme 13. The mixture of diols **88** was cleaved with $Pb(OAc)_4$ to give ketoaldehyde **89** and the aldehyde function was protected as its acetal. The regioselective formation of silylenol ether **90**, followed by ozonolysis gave aldehyde **91**. Compound **91** was subject to the silyl enol ether formation and ozonolysis again to provide aldehyde **32**. α-Hydroxylation of the aldehyde (**32**) and the removal of the protective group furnished (-)-warburganal (**10**).



a) OsO_4, Me_3NO; b) CH_2N_2; c) DHP, H^+; d) LAH; e) PCC; f) H^+, H_2O; g) NH_2NH_2, KOH; h) $Pb(Ac)_4$; i) H^+, $CH_2(CH_2OH)_2$; j) LDA, TMSCl, HMPA; k) O_3, Me_2S; l) LDA, TMSCl; m) LDA, MoO_5.

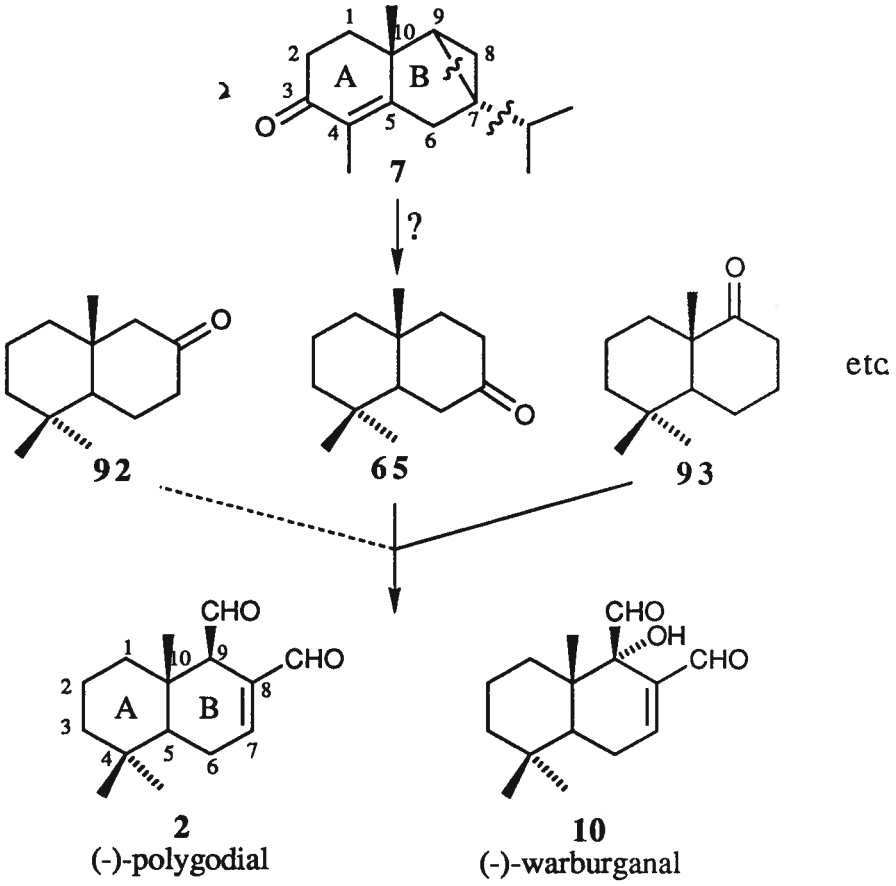
Scheme 13 Ohno's Synthesis of (-)-Warburganal (**10**)

2.2. Discussion

2.2.1. General Considerations about the Synthesis of (-) -Polygodial (2) and (-)-Warburganal (10) from Thujone (3)

As discussed in the Introduction, three published sequences, shown in Schemes 1, 9, and 10, to (±)-polygodial and (±)-warburganal utilized *trans*-fused decalones as their starting materials. The essential feature of these studies is to utilize the existing carbonyl groups in the decalones effectively for the introduction of all necessary carbons and functional groups required in the target molecule.

Therefore, we set as our first goal to convert the thujone-derived enone **7** into some enantiomerically pure, functionalized *trans*-decalones such as **65**, **92** and **93** (Scheme 14).



Scheme 14 The Overall Plan towards the Synthesis of (-)-Polygodial (2) and (-)-Warburganal (**10**)

Elaboration of enantiomerically pure decalones into (-)-polygodial (**2**) and (-)-warburganal (**10**) would be completed in a later stage.

In formulating our synthetic approach, we recognized two necessary and likely associated operations: the exclusion of the isopropyl side chain and the regioselective cleavage of the internal C-C bond (i.e., C7-C9 bond[£]) of the cyclopropyl group. There is no functional group nearby to be used to achieve these aims. Substantial chemistry is thus dictated.

2.2.2. Ozonation of Thujone and Its Derivatives

Ozonation of saturated hydrocarbons into alcohols and ketones by inserting oxygen into C-H bonds has been well-documented[38,39]. Usually tertiary carbons are preferentially attacked. However, the low solubility of ozone in organic solvents[40] (~0.1-0.3% by weight at -78°C) requires a long reaction time, leading to over-oxidation and poor selectivity. A practical improvement came from "dry ozonation" in which silica gel rather than organic solvents is used as the reaction medium[41]. At -78°C, the silica gel pre-adsorbed with the substrate (~1% by weight) was saturated with ozone; the mixture was then allowed to warm slowly to room temperature. Since silica gel adsorbs ozone efficiently at low temperature[42] (~4.5% by weight at -78°C), a complete oxidation of tertiary carbon-hydrogen bonds of cyclic hydrocarbons with high selectivity may be achieved under the reaction condition.

The selective "dry ozonation" of thujone at the tertiary carbon of the isopropyl side chain was first observed in our laboratories by Dr. K. Piotrowska in a study related to the preparation of steroid analogues[15]. Both ketol **94** (i.e., "thujonol") and dione **95** (i.e., "thujonone") were obtained in a ratio of 2 to 1, resembling the selectivity previously observed in the "dry ozonation" of isopropropyl cyclopropane[43]. However, the low overall conversion

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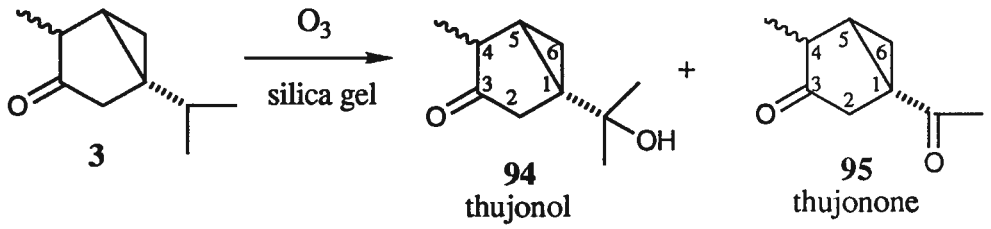
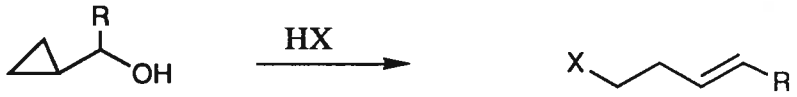
[£] Numbering for thujone-derived tricyclic intermediate **7** and latter related intermediates is kept similar to that for drimane sesquiterpenes such as (-)-polygidial (**2**) and (-)-warburganal (**10**) in order to provide facile comparison.

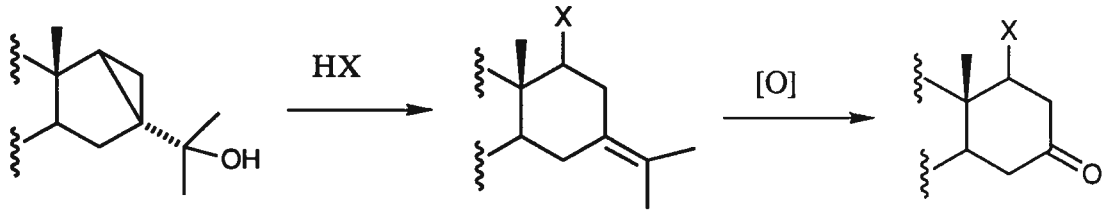
(~40%) and the inconvenience of handling a large amount of silica gel during scaling up* discouraged further exploration of this reaction.



The use of ozonation reaction in projected syntheses of *trans*-fused decalones was easily perceived. The ring cleavage of cyclopropylcarbinols by acids has been well-documented in the literature[44]. For example, treatment of cyclopropylcarbinols with aqueous hydrohalides generated homoallyic halides in good yields. If the ring cleavage of ozonation-



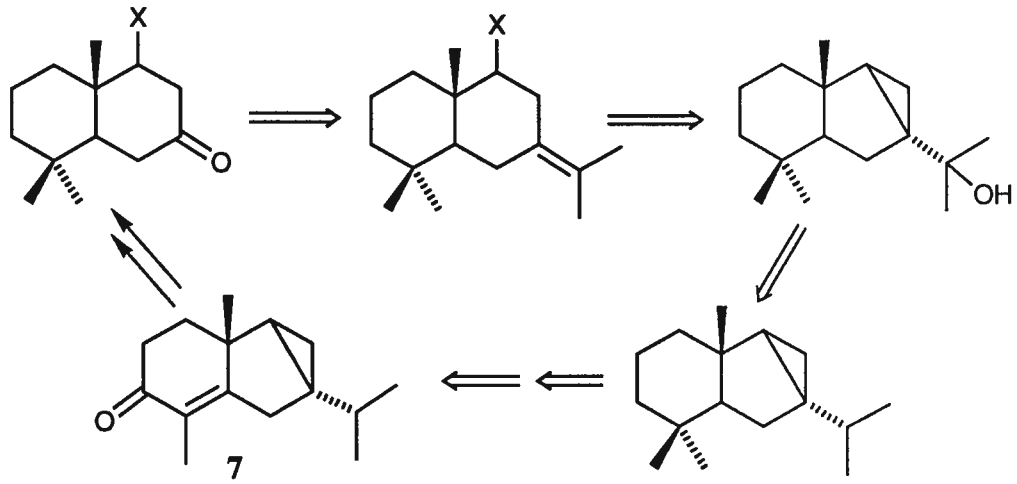
derived fused cyclopropylcarbinols occurred in the desired direction as shown in Scheme 15, the homoallylic halides produced would have an isopropylene side chain which could be oxidatively cleaved to provide a carbonyl group. In short, the ozonation of thujone and its derivatives could provide an entry to both required operations mentioned earlier (Scheme 14).



Scheme 15 A Perceived Sequence to Utilize Alcohols Derived from Ozonation of Thujone Derivatives

* The ratio of silica gel to substrate in weight is usually 100 to 1 in order to observe a complete reaction in terms of attack at the tertiary carbon-hydrogen bond of the cyclic hydrocarbon according to the original dry ozonation procedure[41].

In summary, the following synthetic pathway to a *trans*-fused decalone was thus envisaged (Scheme 16):



Scheme 16 An Ozonation Route to a *trans*-fused Decalone (Retrosynthetic Analysis)

Thus, efforts were directed to finding a better ozonation condition. Finally, the relatively neglected solution ozonation ("wet ozonation") was found to be satisfactory. The "wet ozonation" is easier to scale up (up to 30g scale), more reproducible, and easier to monitor. Complete conversion by wet ozonation can be easily achieved. A comparison of dry and wet ozonation of thujone (**3**) is shown in Table 1.

Table 1 Comparison of Dry and Wet Ozonation of Thujone

	Dry Ozonaton Method	Wet Ozonation Method
sample preparation	solvent evaporation of the slurry of silica gel in thujone-petroleum ether solution	dissolution of thujone in EtOAc
condition	8 hrs at -78°C, then warm up to r.t.	7 hrs at -25°C
workup	extraction with diethyl ether	water and sodium bicarbonate (aq.) extraction
conversion	43%	complete
yield	70%	65-70%
94:95	2:1	1.5:1

The mass spectrum of thujonol (**94**)* revealed the molecular ion peak at m/z 168 while the IR spectrum indicated intense absorption peaks at 3100-3700 and 1730 cm^{-1}, corresponding to the hydroxyl and carbonyl stretching absorptions. The ^{1}H-NMR spectrum displayed two methyl singlets& at δ 1.22 and 1.32 ppm corresponding to the two methyl groups of the isopropyl side chain and a methyl doublet& at δ 1.18 ppm (J=7.6 Hz) corresponding to the methyl group at C4. A one-proton broad singlet# at δ 1.60 ppm was assigned to the proton of the hydroxyl group.

The mass spectrum of thujonone (**94**) showed the molecular ion peak at m/z 152 while the IR spectrum revealed two intense absorption peaks at 1740 and 1685 cm^{-1}, corresponding to absorptions of the C3 carbonyl and the acetyl carbonyl groups. The ^{1}H-NMR spectrum indicated a methyl doublet at δ 1.22 ppm (J=8.4 Hz) and a methyl singlet at δ 2.09 ppm, correponding to the methyl at C4 and the methyl of the acetyl group respectively.

This selective ozonation was generally applicable to other thujone derivatives. For example, the ozonation of **99** and **102** has been applied in the syntheses of drimane antifeedant analogues[15,45] and rose oil fragrances[46]. The ozonation of **105** was explored in an attempted synthesis of steroid analogues[$] . Diketol **106** and trione **107** were obtained in 36% and 28% yield respectively. The mass spectrum of **106** showed the molecular ion peak at m/z 238 while the IR spectrum displayed the hydroxyl stretching absorption at 3450 cm^{-1} and the two carbonyl stretching absorptions at 1730, 1710 cm^{-1}. The ^{1}H-NMR spectrum of **106** revealed four methyl singlet signals at δ 1.00, 1.17, 1.33, 2.15 ppm. The mass spectrum of **107** indicated the molecular ion peak at m/z 222 while the IR spectrum showed three carbonyl

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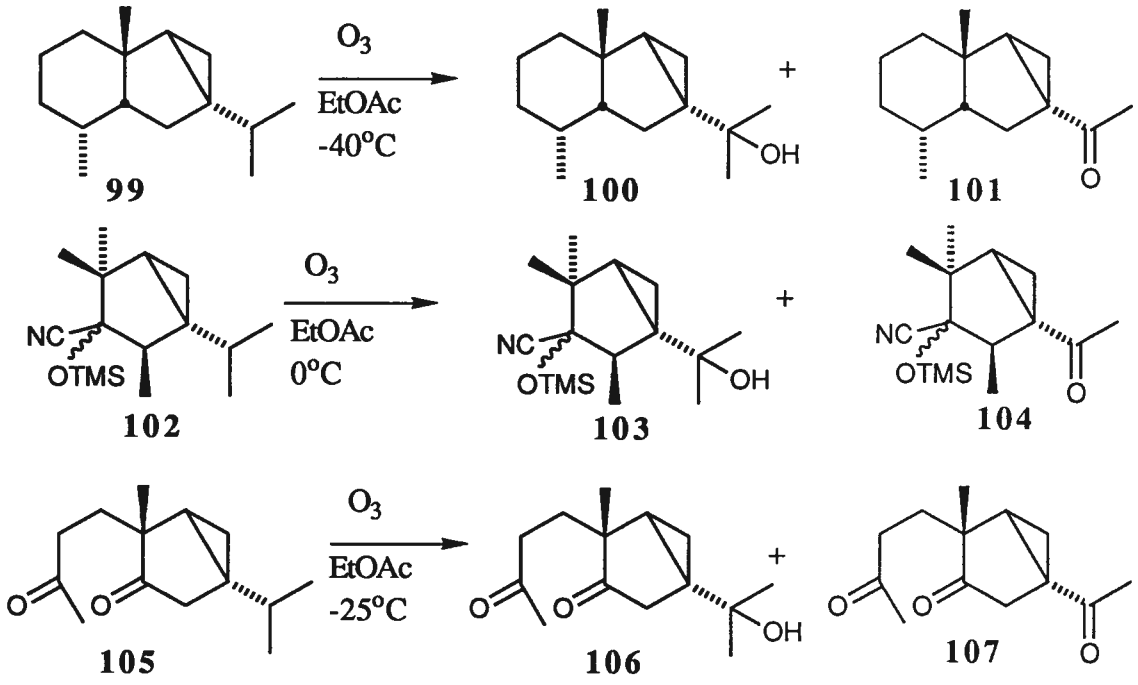
* Thujone used in this studies was a mixture of α and β diastereomers in a ratio of 10:1 as indicated from GC. Accordingly, thujonol and thujonone were mixtures of their α and β diastereomers in a similar ratio as analyzed from GC. All spectral data were recorded for these diastereomeric mixtures. The ^{1}H-NMR spectral data presented here should belong to α diastereomers only since signals of β diastereomers were hardly observable from the spectra.

& A methyl singlet is a singlet signal corresponding to a methyl group while a methyl doublet is a doublet signal corresponding to a methyl group.

A one-proton signal is a signal consisting of one proton. Accordingly, a signal consisting of m protons is called a m-proton signal.

$ This work carried out by this author is not described in this thesis.

absorption peaks at 1735, 1705, and 1685 cm^{-1} respectively. The ^1H-NMR spectrum of **107** revealed three methyl singlet signals at δ 1.04, 2.09, and 2.12 ppm.



Scheme 17 Generality of Selective Ozonation of Thujone Derivatives

A more detailed study on the ozonation of the *cis*-fused ketone **96**, prepared from enone **7** by catalytic hydrogenation, was carried out in order to find out factors influencing the wet ozonation reaction. The compound **96** was chosen since it was readily available (see the discussion on its preparation and stereochemistry in Section **2.2.3.**).

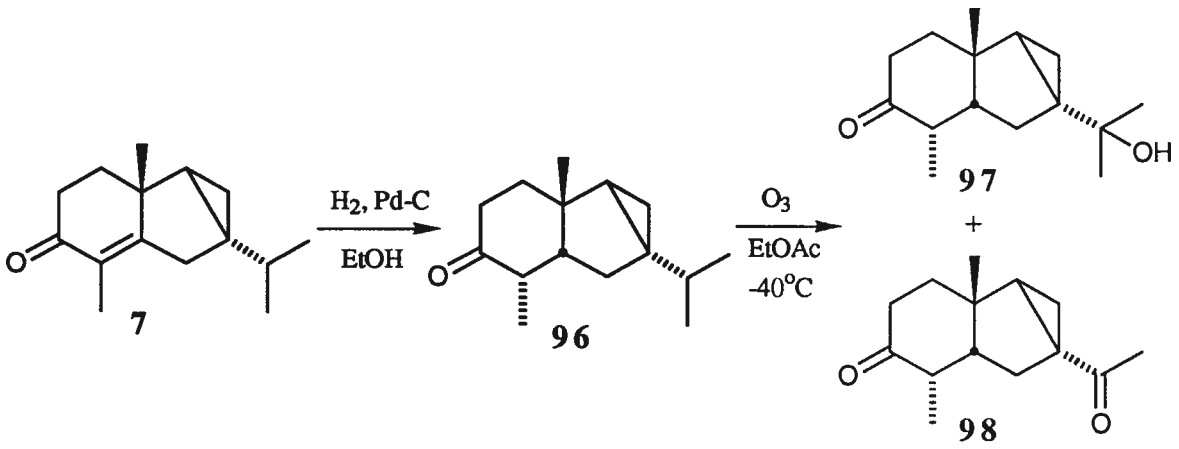


Table 2 The Wet Ozonation of **96** to **97** and **98**

Experiments[a]	#1	#2	#3	#4	#5
Solvent[b]	EtOAc	EtOAc	EtOAc	EtOAc	CH_2Cl_2
Temp. (°C)	-78	-40	-25	0	-40
Time(hrs)	7	7	5	3	7
%Recovery of **96**	90%	12%	0%	0%	10%
%Total Yield	70%	68%	62%	55%	50%
97:**98**[c]	1.55:1	1.50:1	1.40:1	1.20:1	1.00:1

a) 200 mg of **96** was used for every experiment; b) 50 ml of solvent was used for every experiment; c) the molar ratio of **97** and **98** was revealed by comparison of integrations at δ 0.35-0.70 ppm and δ 2.06 ppm of the mixture NMR spectrum; the signal at δ 0.35-0.70 ppm were due to two of the three cyclopropane protons in **97** while the signal at δ 2.06 ppm was from the three methyl protons of the acetyl group in **98**.

As shown in Table 2, when the temperature increased, the total yield of the two products and the ratio of **98** to **97** dropped down. Changing solvents from ethyl acetate to methylene chloride decreased the total yield as well as the ratio of **98** to **97**.

It is of interest to understand these results in terms of the mechanistic proposals of ozonation. For the insertion of oxygen into carbon-hydrogen bonds, a unified proposal was put forward by Hamilton et al.[47] According to this proposal (Figure 6), the transition state (**I**) can either convert to produce **ROH** and a singlet oxygen directly by path (2) or collapse to a

hydrotrioxide **ROOOH** which then decomposes to product **ROH** and a singlet oxygen by path (1) or degrades to a triplet oxygen, a hydroxyl radical, and an alkyl radical (**II**) which undergoes a chain reaction via an alkoxyl radical (**III**) to afford **ROH** by path (3). The occurrence of the different reaction paths depends on structural environments near the carbon-hydrogen bonds and the reaction conditions. Carbon-hydrogen bonds adjacent to heteroatoms, such as the α carbon-hydrogen bonds of alcohols, ethers, and amines, and the carbon-hydrogen bond of aldehyde groups favor path (1) because of the greater contribution of the resonant structure (**Ib**) to the transition state (**I**)[48a,b,c]. Clear evidence for hydrotrioxides has been obtained only with ozonation of alcohols, ethers, amines and aldehydes[48d]. Carbon-hydrogen bonds not activated by adjacent heteroatoms will go through path (2) to produce **ROH** directly in the liquid phase and at low temperature (<0°C) with the retention of configuration being usually observed[47]. In the vapor phase and at high temperature (>25°C), the radical-mediated path (3) becomes dominant[48e,f]. The mechanism of dry ozonation was presumed the same as that in liquid phase[40].

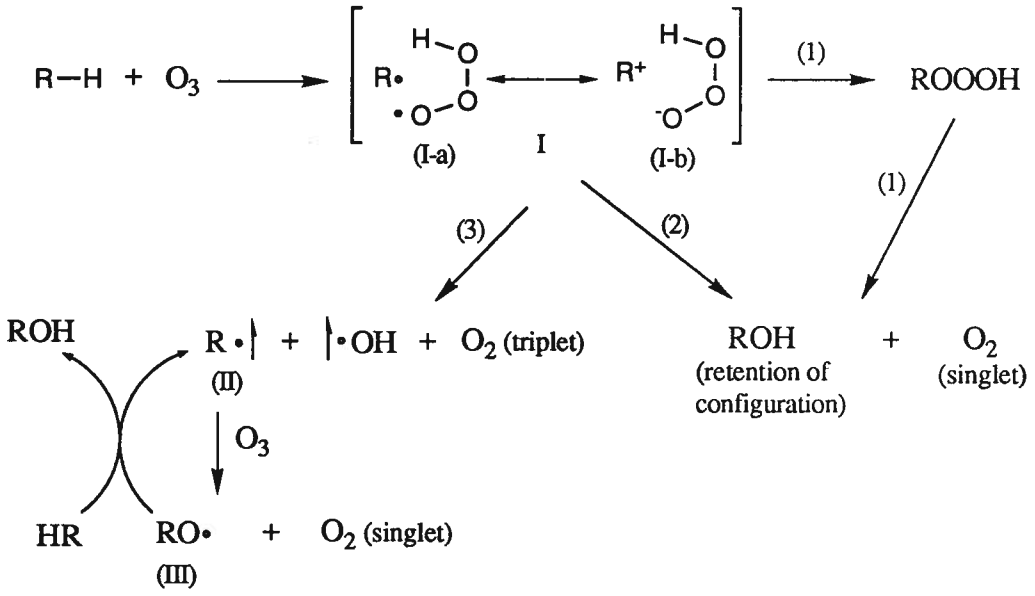


Figure 6 Oxygen Insertion into Carbon-Hydrogen Bonds

For the production of ketones from tertiary carbons through cleavage of C-C bonds, a similar insertion mechanism has been proposed for the liquid phase reactions (Figure 7)[43,49]. The transition state (**V**) was assumed to collapse into a trioxide by cleaving one carbon-carbon bond. The further decomposition of the trioxide provided a ketone and a hydroperoxide. The alternative mechanism, the fragmentation of alkoxyl radical (IV) generated from the oxygen insertion into the carbon-hydrogen bond following the Hamilton mechanism in Figure 6, was considered only possible at higher temperature (~25°C)[43].

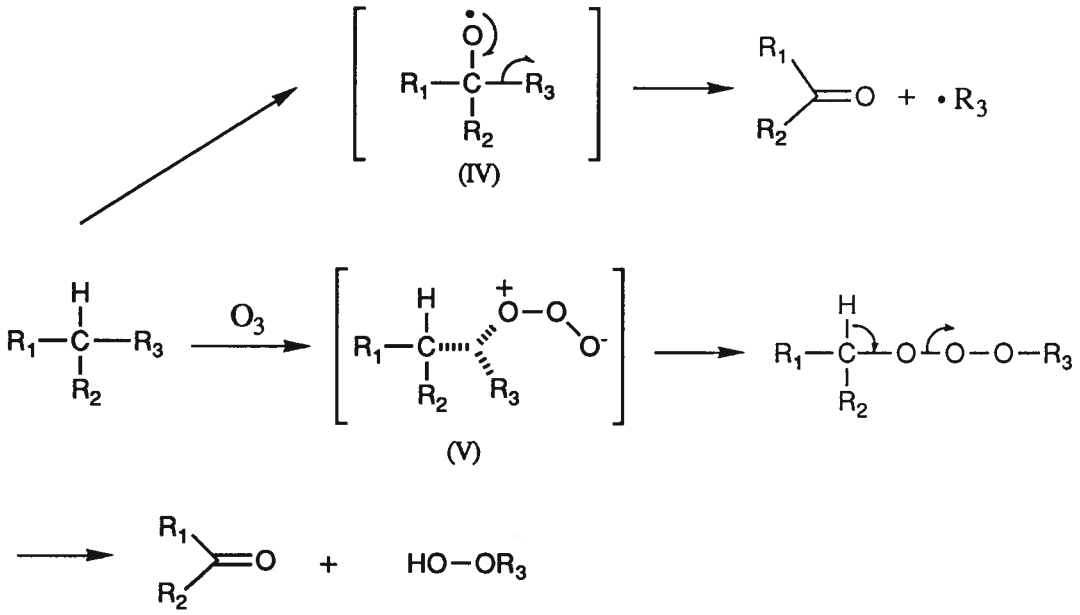
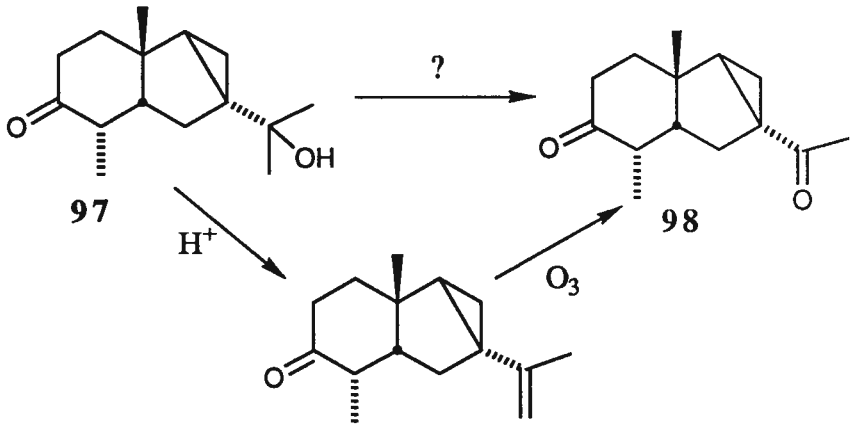


Figure 7 Oxygen Insertion into Carbon-Carbon Bonds

The selective ozonation of thujone (**3**) and its derivatives at the tertiary carbon-hydrogen bond of the isopropyl side chain is perhaps due to lower energies of transition states (**I**) in Figure 6 and (**V**) in Figure 7 resulting from the participation of the cyclopropyl group in these two transition states. The cyclopropyl group is known to stabilize neighboring positive charge in a way similar to an olefinic group[17a]. The oxidation of α-methylene groups of bicyclo[n.1.0]alkanes to carbonyl groups was also reported[50a].

Increase of temperature in the ozonation reaction appeared to encourage oxidation in other carbon-hydrogen and carbon-carbon bonds, therefore causing the total yield of **97** and **98** to drop. The accompanying increase of the overall reaction rate and the decrease of the **97**:**98** ratio seemed to follow the general relationship between the selectivity of two competative reactions and temperature[50b]. Changing solvents from ethyl acetate to methylene chloride had a dramatic effect on the total yield and the **97**:**98** ratio. This may reflect the participation of solvents in transition states (**I**) and (**V**).

Ketone **98** might be produced directly from alcohol **97**. To test this assumption, a solution of **97** in EtOAc was treated with ozone at -40°C for 7 hours. A new polar spot appeared on TLC plates. As revealed from the ^{1}H-NMR spectrum, this spot contained several compounds which were not characterized further. Apparently, ketone **98** was not directly generated from alcohol **97**. The fact that **97** and **98** were produced at an almost constant ratio of approximately 1.5:1 from the beginning to the end of the reaction, as indicated by GC analysis, supported this conclusion.



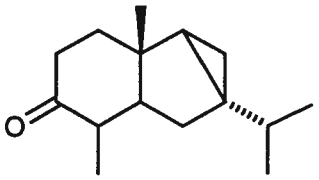
A small amount of olefin **108** could be isolated from the reaction. Its molecular ion peak appeared at m/z 218 in the mass spectrum while the IR absorptions of carbonyl and carbon-carbon double bonds were observed at 1710 and 1630 cm^{-1}. The ^{1}H-NMR spectrum showed a characteristic vinylic methyl singlet at δ 1.60 ppm and two overlapped one-proton

singlets at δ 4.65-4.80 ppm corresponding to the two olefinic protons. This result indicated that ketone **98** might be produced from **97** via the ozonolysis of the dehydration product **108**. The strong acidity accumulated during the reaction could promote the dehydration of **97** especially at higher temperature (see the following paragraph).

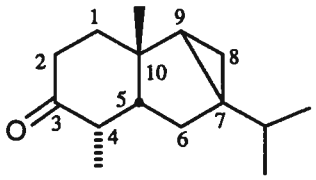
During our studies, a basic workup was found to be necessary to ensure that the alcohol product could be isolated intact; direct evaporation of the ethyl acetate mixture without neutralization with sodium bicarbonate aqueous solution led to serious decomposition of alcohols. A strong acidic medium was produced in the ozonation reaction; the water extract of the final reaction mixture had a pH value close to 1 . To test if the acidic by-products were formed from substrates or solvents, ozone was passed through blank solvents, ethyl acetate and methylene chloride, at -40°C for the same period of time as in the regular ozonation (i.e., 7 hours). Water extracts of the resulting solutions showed a similar strong acidity. It appeared that the acidic by-products were mainly generated by the oxidation of solvents or impurities present in them.

2.2.3. Stereochemistry of Hydrogenation of Thujone-derived Tricyclic Enones

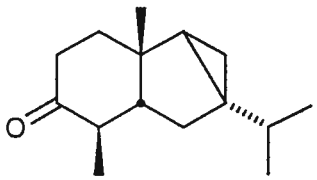
As shown in the Schemes 14 and 16 , a *trans*-fused A/B ring junction was needed in developing a sequence to (-)-polygodial (**2**). Therefore, we hoped the reduction of enone **7** (see Scheme 14) would provide a *trans*-fused tricyclic compound **110**.



110



96



109

Catalytic hydrogenation of enone **7** by 10% Pd-C in ethanol gave a major product **96** in 95% yield and a minor product **109** (2%) instead of the desired *trans*-fused ketone **110**. The minor product **109** (2%), the epimer of **96** at C4, was very labile. It epimerized to **96** completely in $CDCl_3$ at room temperature overnight. The ^{1}H-NMR spectrum of ketone **109** showed a two-proton multiplet at δ 0.30 ppm, three methyl doublets at δ 0.88 (J= Hz), 0.96 (J= Hz), 1.06 (J= Hz) ppm, a methyl singlet at δ 0.99 ppm, a two-proton multiplet at δ 2.00-2.30 ppm, and a one-proton multiplet at δ 2.45 ppm.

Ketone **96** had its molecular ion at m/z 220 in the mass spectrum. The carbonyl stretching frequency appeared at 1710 cm^{-1} in its IR spectrum while the ^{1}H-NMR spectrum revealed three methyl doublets at δ 0.85 (J=6.8 Hz), 0.91 (J=6.8 Hz), and 0.94 (7.2 Hz) ppm, a methyl singlet at δ 1.23 ppm, a triplet (1H, J=11.5 Hz) at δ 1.29 ppm, and one-proton multiplets at δ 1.34, 1.72, 2.15, 2.42, 2.58 ppm.

Assignment of protons in the ^{1}H-NMR spectrum of **96** was accomplished by the following experiments (Figure 8). Decoupling by irradiation at the δ 2.58 ppm signal caused the methyl doublet (J=7.2 Hz) at δ 0.94 ppm to collapse to a singlet and a simplification of a one-proton multiplet at δ 1.72 ppm. Thus, the methine proton at C4, the methyl at C4, and the methine proton at C5 were assigned to the signals at δ 2.58, 0.94, and 1.72 ppm respectively. The only methyl singlet at δ 1.23 ppm in the off-resonance spectrum was obviously from the methyl at C10. This C10 methyl signal was very close to a one-proton multiplet at δ 1.34 ppm and a one-proton triplet (J=11.5 Hz) at δ 1.29 ppm. Irradiation at δ 1.23 ppm, which actually affected the multiplet and the triplet simultaneously, led to the collapsing of two methyl doublets (both J=6.8 Hz) at δ 0.85 and 0.91 ppm and the simplification of the C5 proton multiplet. Therefore, the multiplet at δ 1.34 ppm must be from the methine proton in the isopropyl side chain and the triplet must be due to one of the methylene protons at C6. The methylene proton must be opposite to the C5 proton with regard to the cyclopentyl ring since the coupling constant (J=11.5 Hz) for the triplet was relatively large. The closeness of these proton signals and the complication of six possible conformational structures (two each from

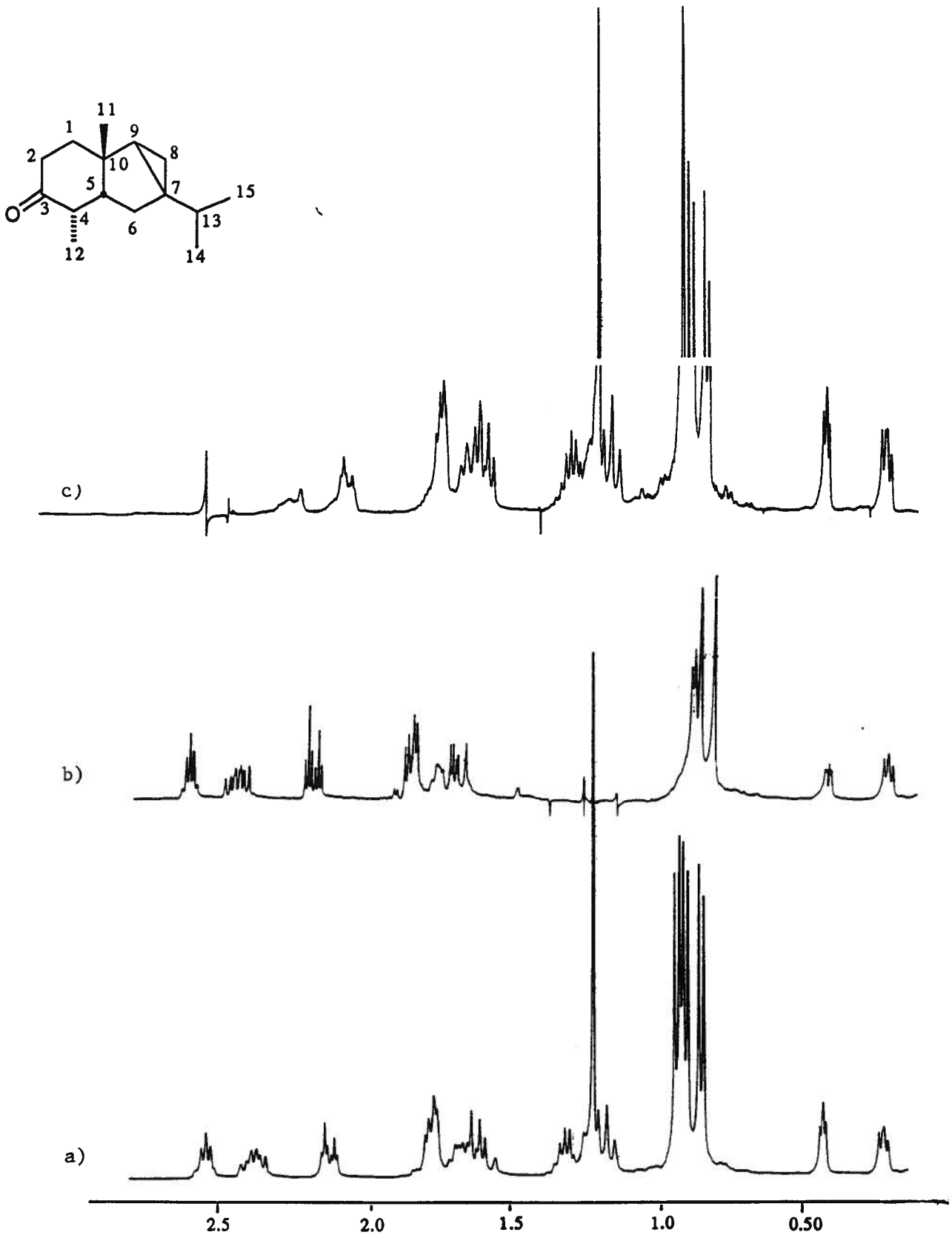


Figure 8 Decoupling Experiments on Ketone **96**

a) off resonance spectrum.
b) homonuclear spin decoupling at 1.23 ppm.
c) homonuclear spin decoupling at 2.58 ppm.

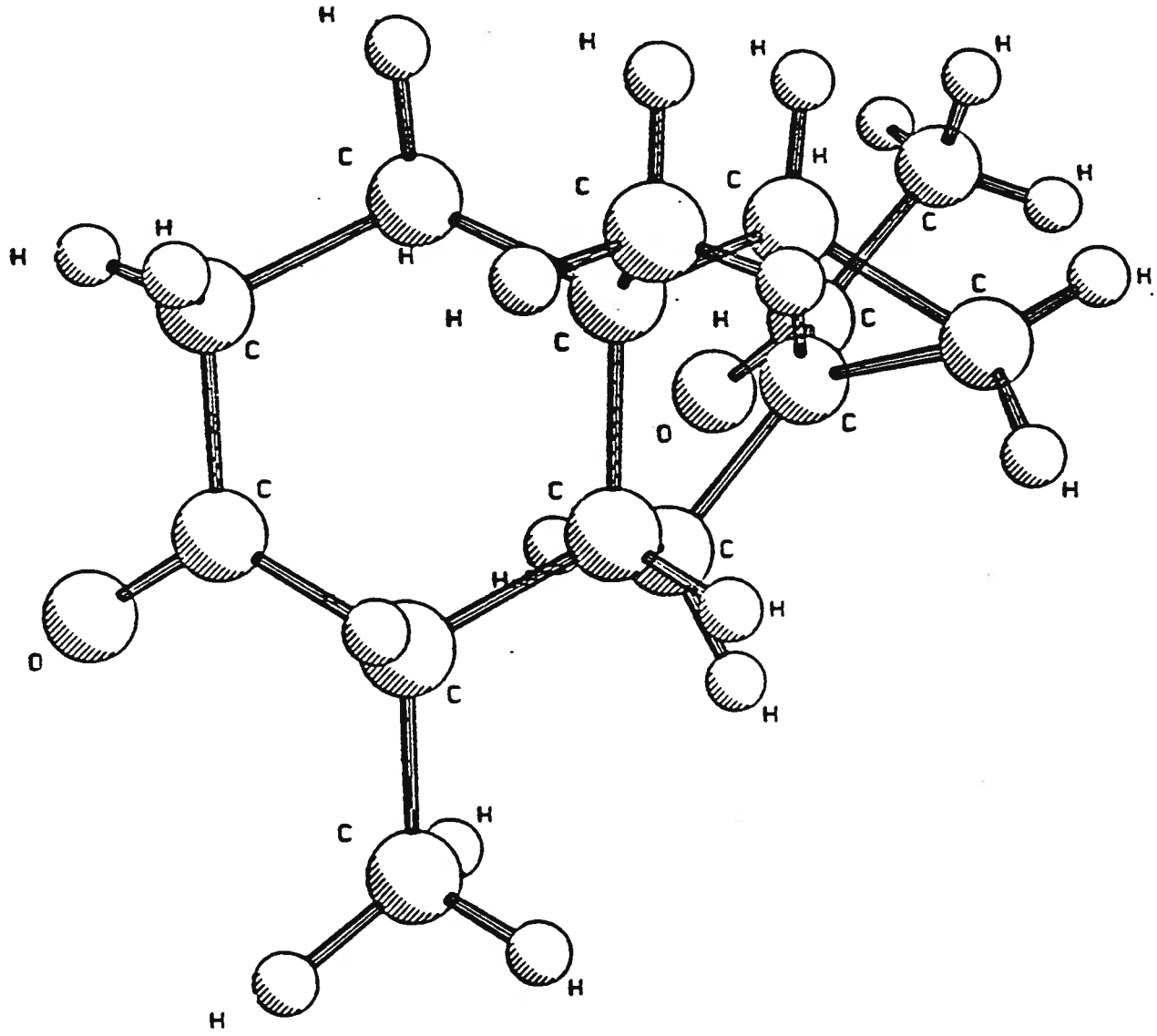


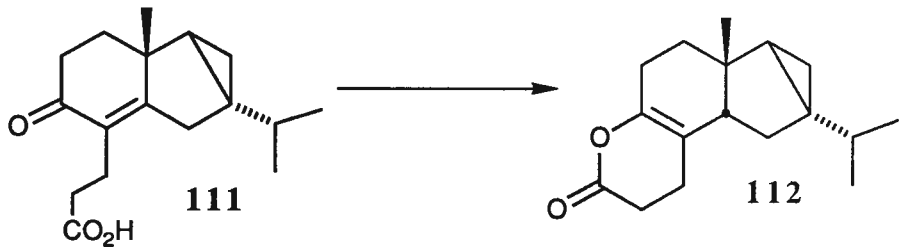
Figure 9 Single Crystal X-ray Structure of **98** (PLUTO Drawing[166a])

trans-fused **110**, *cis*-fused **96**, and *cis*-fused **109** to be considered in the analysis discouraged further NOE experiments in order to elucidate the stereochemistry of ketone **96**.

Fortunately, separation of ozonation products **97** and **98** (see p. 30) by column chromatography with a mixed solvent system (hexanes:methylene chloride:methanol=10:1:1) gave fractions containing **98** which crystalized readily upon slow evaporation of the solvent upon standing. The crystals were suitable for X-ray diffraction analysis. The crystals were also prepared from hexanes by Z. Gao in our laboratories and submitted for analysis[45]. The X-ray structure of **98** clearly showed an A/B*cis*-fused ring junction and an α-orientation of the methyl at C4 (Figure 9). The stereochemistry of **96** was thus established.

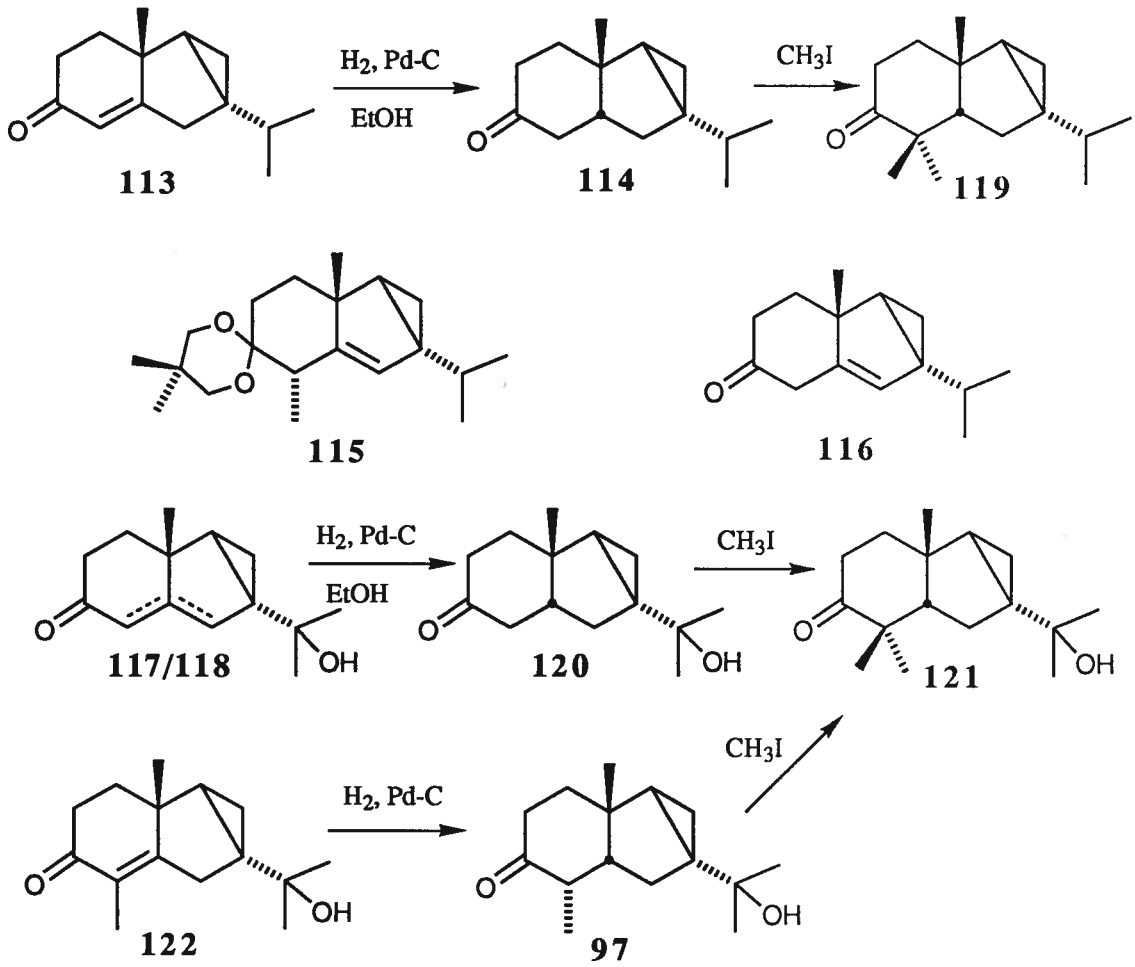
An attempt to obtain *trans*-fused compound **110** by Birch reduction using lithium and ammonia failed[45].

The similar phenomenon was observed in a previously published study related to steroid synthesis[14b]. Either catalytic or Birch reduction of **111**, followed by acetic anhydride treatment, gave the same *cis* -fused enol lactone **112**.



A range of enones were hydrogenated under catalytic conditions (Scheme 18). Reduction of the known compound **113**[13a] gave the *cis*-fused **114** in 90% yield. Its molecular ion peak in the mass spectrum appeared at m/z 206 while its carbonyl absorption was observed at 1710 cm^{-1}. The ^{1}NMR spectrum of **114** showed a one-proton doublet of doublets (J=4.8 and 8.0 Hz) at δ 0.23 ppm, a one-proton triplet (J=4.8 Hz) at δ 0.45 ppm, two methyl doublets at δ 0.86 (J=6.4 Hz) and 0.93 (J= 6.4 Hz) ppm, a methyl singlet at δ 1.20 ppm, a four-proton multiplet at δ 2.10-2.55. In order to establish the stereochemistry of 114, it was

subjected to methylation by treatment with potassium *t*-butoxide and iodomethane in *t*-butanol. The major product obtained in 70% yield was identical to the *cis*-fused ketone **119** prepared from the methylation of **96** (see p. 49) in all spectroscopic data. Thus, the *cis* fusion in **114** was confirmed. Two known compounds **115** and **116** with carbon-carbon double bonds at C5 and C6[13a] were hydrogenated. Complex product mixtures were obtained as indicated from GC chromatograms and ^{1}H-NMR spectra. The complication might be due to the cleavage of conjugated cyclopropyl groups.



Scheme 18 Attempted Catalytic Hydrogenation of Tricyclic Enones

A mixture of **117** and **118**, obtained from the pyrrolidine catalyzed aldol condensation of ozonation product **106** (Scheme 17), was reduced to the *cis* -fused ketol **120** in 70% yield.

The mass spectrum of **120** showed the molecular ion peak at m/z 222 while its IR spectrum indicated stretching absorptions of the hydroxyl and carbonyl groups at 3100-3700 and 1710 cm^{-1}. The ^1H-NMR spectrum displayed a one-proton doublet of doublets (J=4.0 and 5.4 Hz) at δ 0.44 ppm, a one-proton doublet of doublets of doublets (J=1.2, 5.4, and 8.6 Hz) at δ 0.63 ppm, three methyl singlets at δ 1.14, 1.21, and 1.25 ppm, a complex four-proton multiplet at δ 2.12-2.52 ppm. The *cis* A/B ring junction of **120** was established by correlating it with ketol **97** (p. 30) chemically. Thus, compound **120** was converted into a dimethylated compound in 60% yield by treatment with iodomethane and potassium *t*-butoxide in *t*-butanol. This compound was identical in all spectroscopic data to the *cis*-fused ketol **121**, prepared in 75% yield by treating **97** similarly. The comparison of their CD spectra* is shown in Figure 10.

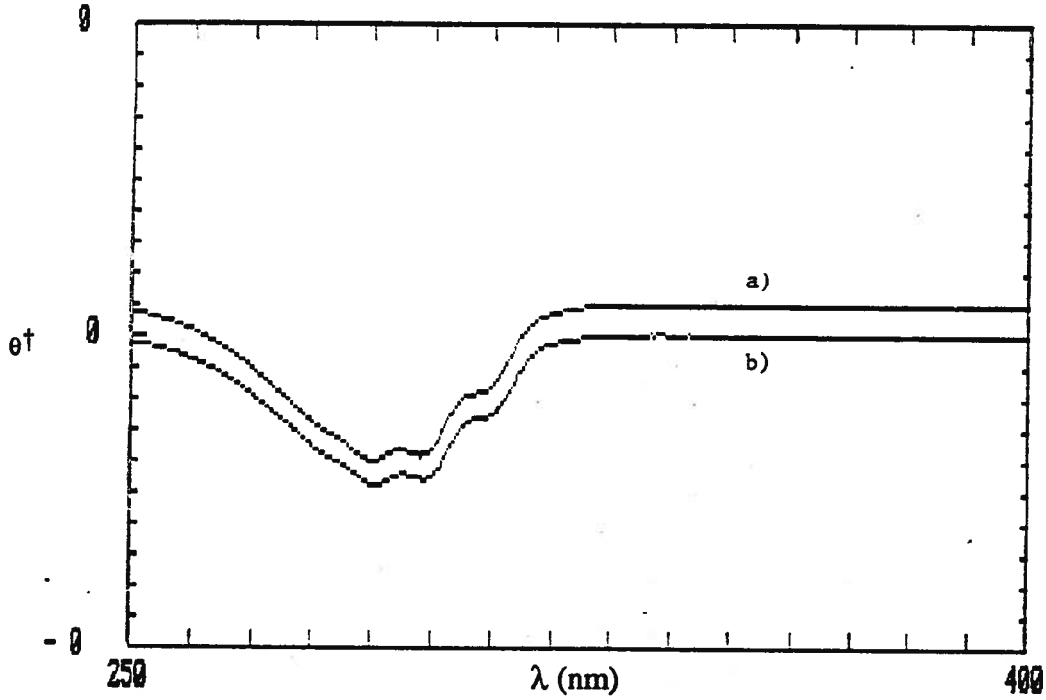


Figure 10 Comparison of CD Spectra of **121** Prepared from Two Different Routes

a) Ketol **121** prepared from **118**.
b) Ketol **121** prepared from **97**.

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* We are indebted to Dr. Ian Clark who gave us most helpful guidance in running the CD spectrometer.

† The observed ellipticity angle θ is expressed in a relative scale. Curve (a) is moved one devision up vertically in order to facilitate comparison. Since both measurements were made at 25°C in the same concentration (10.4 mg/ml), solvent (dioxane), and cell, there is no need to convert θ into molar ellipticity angle [θ] or molar circular dichroism Δε.

The mass spectrum of **121** showed the molecular ion peak at m/z 250 while the IR spectrum indicated the absorptions of the hydroxyl and carbonyl groups at 3100-3650 and 1705 cm^{-1}. The ^{1}H-NMR spectrum revealed a one-proton triplet (J=4.8 Hz) at δ 0.41 ppm, a one-proton doublet of doublets (J=4.8 Hz) at δ 0.58, five methyl singlets at δ 0.96, 1.12, 1.22, 1.24, and 1.34 ppm, two one-proton multiplets at δ 2.17 and 2.70 ppm.

The catalytic hydrogenation of **122**¶ (see Section **4.4.** for its stereochemistry), prepared from the Robinson annulation of thujonol (**94**) with ethyl vinyl ketone in 35% yield, produced a single compound **97** which was again identical to the ozonation product **97** previously obtained from **96**.

Difficulties encountered in the direct preparation of *trans*-fused compounds by hydrogenation can be understood from a different perspective. The easy access to the 6,5-fused enones and the need to generate a *trans*-fused C/D portion in steroid synthesis provided examples about reduction of these compounds. In fact, either catalytic hydrogenation[51] or Birch reduction[52] generally gave only or predominantly the *cis*-fused products. Our tricyclic enones derived from thujone (**3**) indeed behaved quite similarly. However, this outstanding problem has been remedied to some extent by recently developed hydroxyl-directed catalytic hydrogenation using homogeneous catalysts[53].

Unable to find a simple and efficient way to obtain *trans*-fused series of compounds directly, we decided that further effort in this direction would be terminated. The alternative, requiring two extra steps, was to carry on the sequence in the *cis*-fused series and to correct the stereochemistry at the ring junction in a later stage. From the point of view of preparing diverse types of analogues, the stereochemical correction alternative has its own advantage.

2.2.4. Acid Promoted Ring Cleavage of Thujone-derived Cyclopropylcarbinols

¶ The tertiary hydroxyl group of the isopropyl side chain of **122** may serve as a directing group for the desired direct α face hydrogenation, although not explored in present studies[53].

It is well known that cyclopropylcarbinols can be cleaved through the pathway as shown in Scheme 15. When the reaction is applied to a non-symmetrically substituted cyclopropylcarbinols with an achiral center at α position, two different compounds are expected to be generated, depending on which C-C bond is cleaved. In our specific system, we propose the following notation for the convenience of discussion: the endo-type cleavage will lead to a 6-membered ring homoallylic halide (X=halides); the exo-type 1 will result in formation of a 5-membered homoallylic halides (Figure 11). It is obvious that the endo-type cleavage is desirable for our purpose. The novel exo-type 2 cleavage is presented here in advance for the completeness of the notation and later discussion will indicate this mode of fragmentation (see section **2.2.7.**).

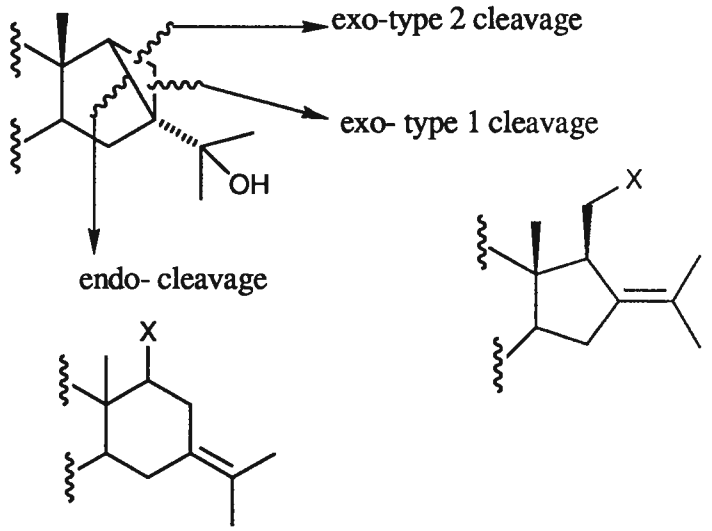
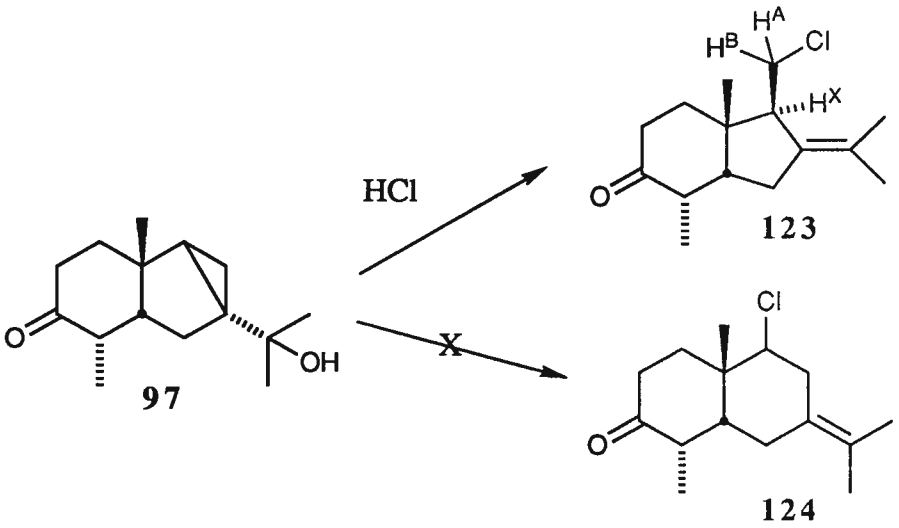


Figure 11 A Notation of Ring Cleavage Reactions

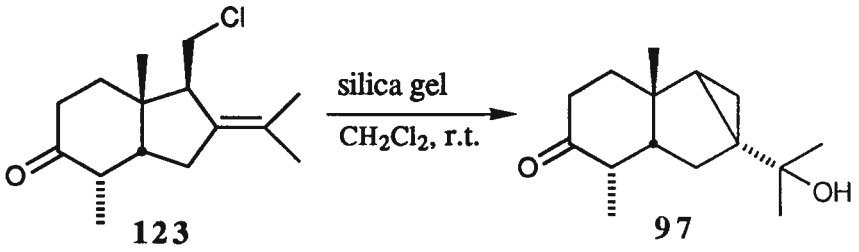
Treatment of the ketol **97** in either methylene chloride or diethyl ether with concentrated HBr solution (48%) gave a mixture of starting material and a less polar fraction which could not be identified by ^{1}H-NMR spectrum. The same result was obtained when the reaction was carried out with anhydrous $MgBr_2$ in refluxing ether[55]. It was considered that the complication might arise from the relatively weak C-Br bond of ring cleavage products and their consequent

decomposition. If this was the case, the corresponding chloro compounds may be stable enough to allow purification and characterization. In fact, treatment of **97** with concentrated HCl gave a stable major compound **123** rather than **124** in approximately 75% yield after column chromatographic purification.



In summary, compound **123** arises from the exo-type 1 cleavage. The IR spectrum of **123** showed the absence of an absorption corresponding to the hydroxyl stretching frequency. The parent ions at m/z 256 (0.6%) and 254 (2.2%) in the mass spectrum of **123** were consistent with two isotopic peaks ($C_{15}H_{23}O^{37}Cl$ and $C_{15}H_{23}O^{35}Cl$). The ^{1}H-NMR spectrum of **123** showed two methyl singlets in δ 1.71 and 1.60 ppm, indicating the presence of an isopropylidene group; a multiplet (octet) at δ 3.55 ppm, characteristic of the A/B portion of an ABX system, corresponded to the methylene attached to the chlorine.

The β orientation of the chloromethyl side chain was verified since a sample of the isolated product under stirring overnight in methylene chloride and silica gel regenerated the starting ketol **97** exclusively.



Whether the solvolysis reaction takes place stepwise through a cyclopropylcarbinyl cation or in a concerted manner through a SN2' like transition state has not been established (Figure 12). The regioselectivity is often explained by the SN2' mechanism involving stereoelectronic and steric factors. Considering the concerted mechanism, the rotation of the isopropyl side chain allows the hydroxyl to align antiparallel to either of the C-C bonds which may undergo cleavage. Inspection with molecular models revealed seemingly equal steric hindrance to these two alignments. Therefore, the hindrance to the incoming group, Cl^- in this case, is likely playing an important role. In the case of the stepwise mechanism, this factor seems to be able to differentiate endo- and exo-type 1 cleavage paths. In any event, the preference to this exo-type 1 cleavage is likely due to the more exposed and accessible nature of the methylene compared to the methine in the cyclopropyl ring.

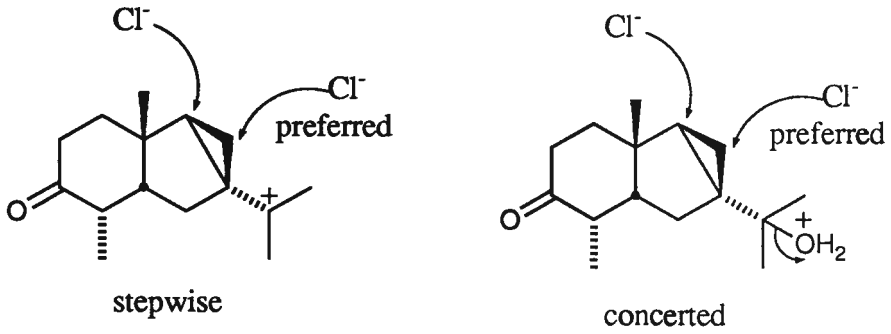
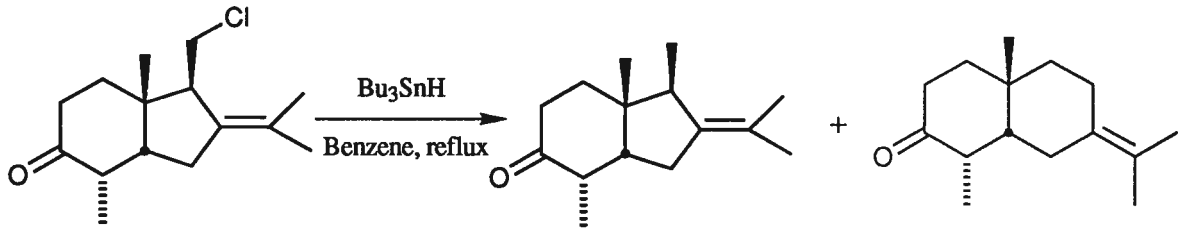


Figure 12 Rationalization of HCl Promoted Ring Cleavages

2.2.5. The Radical-mediated Rearrangement

Although the major product from concentrated HCl (aq.) treatment was initially determined to be the structure **123**, we felt that further evidence about this structure could be provided by a simple reduction. Reduction of **123** using tributyltin hydride as reducing agent was carried out with the expectation that the reduction product **125** would show a doublet corresponding to the newly generated methyl group in its ^{1}H-NMR spectrum. Surprisingly, in addition to the expected product **125** which showed an extra methyl doublet (J=7.2 Hz) at δ 0.92 ppm and absence of the two-proton multiplet at δ 3.5 ppm in **123**, another major product was isolated in 50% yield. Its ^{1}H-NMR spectrum showed a methyl doublet (J=6.4 Hz) at δ 1.02 ppm, a methyl singlet at δ 1.26 ppm, and two vinyl methyl singlets at δ 1.64 and 1.66 ppm. Thus, this major compound was assigned to be **126**. Its mass spectrum confirmed that it had a parent ion at m/z 254 corresponding to the molecular formula $C_{15}H_{24}O$ of **126**.



123 **125** **126**

Apparently, a ring expansion took place during the reduction. The following mechanism was proposed to rationalize this novel reaction (Figure 13).

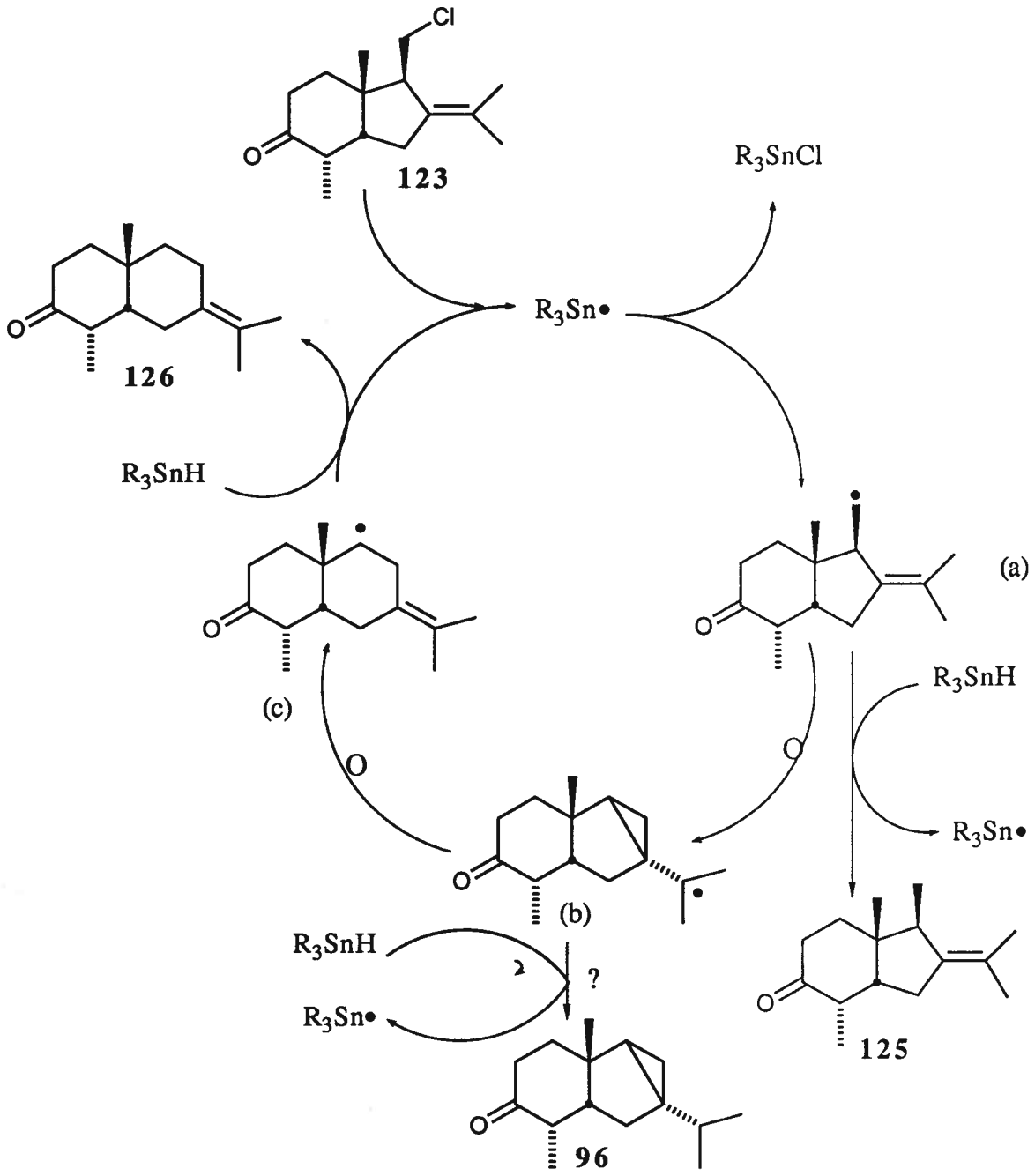


Figure 13 A Proposed Mechanism for the Novel Ring Expansion of **123**

In this mechanism, a cyclopropylcarbinyl radical (b) generated from cyclization of the initial radical (a) is postulated as the intermediate to the final ring-expanded radical (c). An alternative pathway could involve the apparent direct 1, 2-shift from (a) to (c). The thermodynamic driving force for the radical rearrangement from (a) to (c) is probably the

greater stability of the secondary radical (c) in comparison with the primary radical (a). The cyclization step from (a) to (b) is analogous to the cyclization of chloride **123** to **97** (p. 44). We were not able to isolate any compound **96**, a possible product resulting from the quenching of (b) during the reaction. A literature survey revealed that the postulation of a cyclopropyl carbinyl radical as an intermediate in the rearrangement of homoallylic radicals has been proposed[57a] and verified by product studies and labelling experiments[57b,c,d]. More recent studies are focusing on the quantitative aspect of this rearrangement[57f].

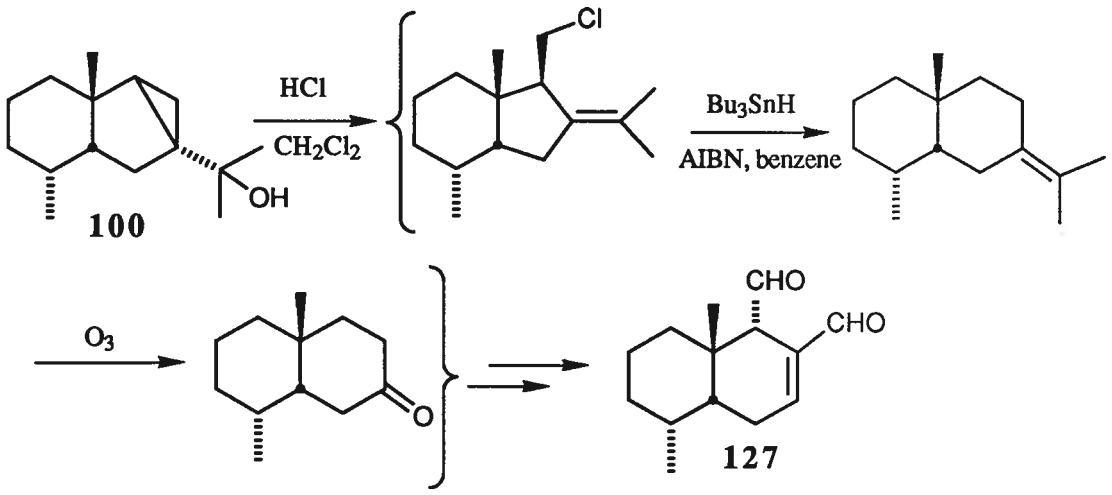
To improve the yield of the ring expansion product **126**, the direct quenching of radical (a) had to be suppressed. A longer life time for the initial radical (a) by decreasing the concentrations of both substrate **123** and reducing agent tributyltin hydride should allow it more likely to undergo a series of rearrangements and therefore improve the yield of **126**. In fact, further experiments verified this postulate (Table 3).

Table 3 Yield Optimization for Conversion of **123** to **126**[¥]

123	Bu_3SnH	AIBN	benzene	**126**:**125**	total yield
50.4 mg	82 µl	3.2 mg	20 ml	2.8:1	80%
50.4 mg	82 µl	3.2 mg	4.0 ml	2.4:1	74%

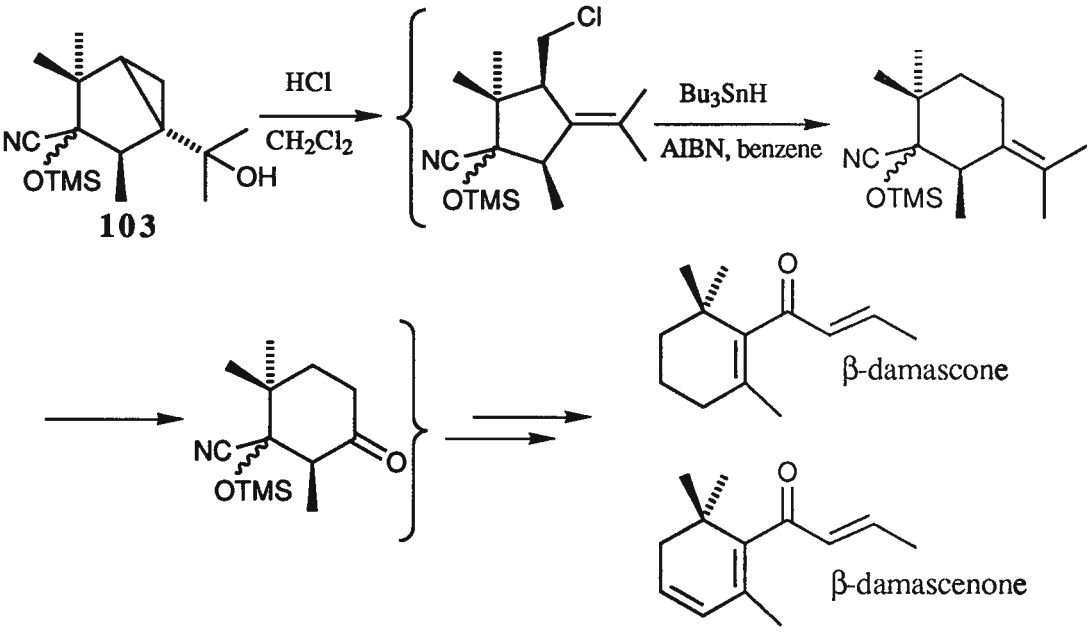
¥: Refluxing was continued for two days for both reactions.

In summary, despite the undesirable exo-type 1 cleavage to a hydroindane system in the acid-promoted ring cleavage reaction, the novel radical-mediated ring expansion provided us with a method to prepare the desired decalin system. Using the ozonation, acid-promoted ring cleavage, and radical-mediated ring expansion reactions as key steps, **127**, an analogue of (-)-polygodial (**2**), was prepared from thujone by Z. Gao[15,45]. (Scheme 19; see also Scheme 17 for preparation of **100** via ozonation).



Scheme 19 Gao's Synthesis of a (-)-Polygodial Analogue **127**

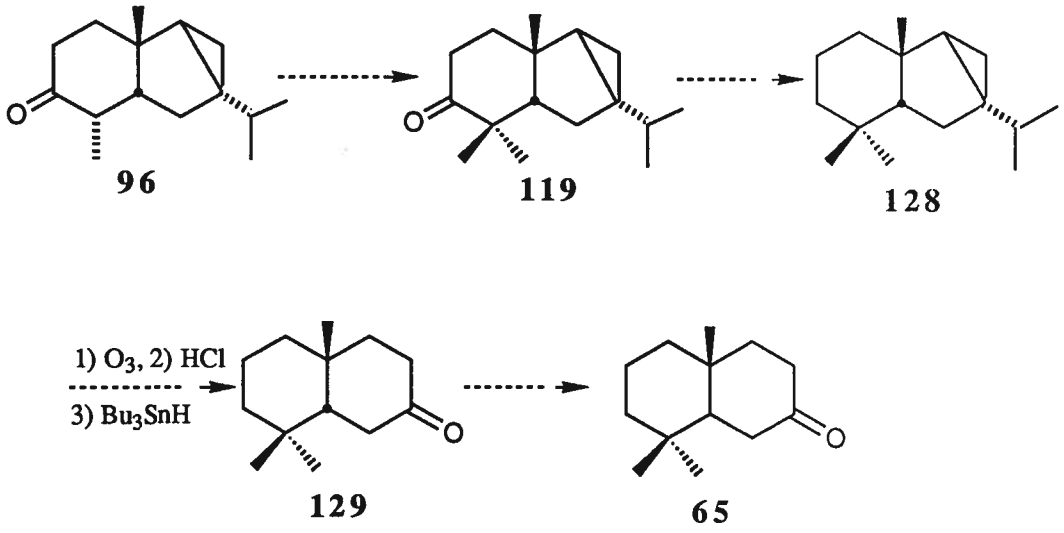
The same sequence was also successfully applied to the synthesis of the rose oil fragrances, β-damascone and β-damascenone, from thujone by Philip Gunning[46]. (Scheme 20; see also Scheme 17 for preparation of **103** via oznation).



Scheme 20 Gunning's Synthesis of Rose Oil Fragrances

2.2.6. Failure of the Radical-mediated Ring Expansion Reaction

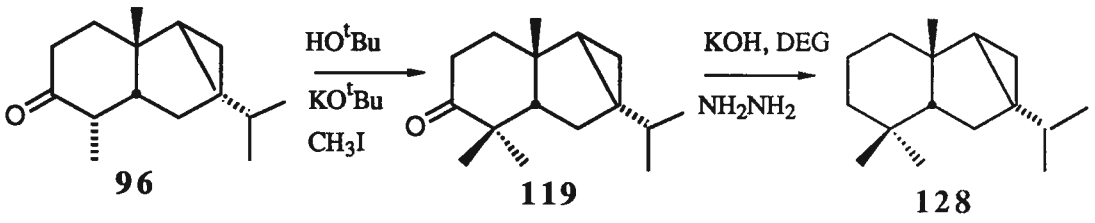
Having established the above sequence on the model compound **96**, we tried to apply it towards the synthesis of natural (-)-polygodial (**2**). The plan is shown in Scheme 21. A *cis*-fused alkane **128** would be derived from ketone **119** which could be obtained by methylation of **96**. Applying the established sequence to **128** would generate *cis*-fused decalone **129**, from which a stereochemical correction into A/B*trans*-fused decalone **26** would be carried out. The racemate of **26** (i.e., **65**) was used as a starting material in the synthesis of (±)-polygodial and (±)-warburgarnal by de Groot et al.(Scheme 3). During the course of our study, an enantioselective synthesis of **26** was completed by the same group from (-)-dihydrocarvone (Scheme 9).



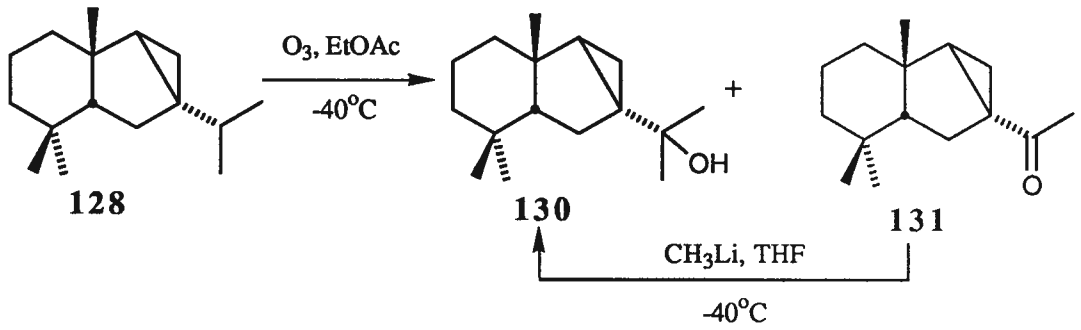
Scheme 21 A Revised Plan to an Enantiomerically Pure, *trans*-fused Decalone **65**

Following a standard method[58], *cis*-fused ketone **96** was refluxed with iodomethane and potassium *t*-butoxide in *t*-butanol to give the *gem*-dimethyl ketone **119** in 85% yield. The mass spectrum of **119** revealed the molecular ion peak at m/z=234. Its IR spectrum showed absorption peaks at 3060 cm^{-1}, characteristic of carbon-hydrogen stretching of the cyclopropyl

group, and 1700 cm^{-1}, corresponding to the carbonyl stretching frequency. Its ^{1}H-NMR spectrum showed two methyl doublets (δ 0.85 ppm, J=6.6 Hz; δ 0.90 ppm, J=6.6 Hz) corresponding to the two methyl groups at the isopropyl side chain. Three methyl singlets (δ 0.97 ppm, 1.22 ppm, 1.32 ppm) were observed which corresponded to the *gem*-dimethyl groups at C4 and the angular methyl at C10. A two-proton multiplet appeared at δ 2.15-2.70 ppm, corresponding to the methylene at C2.



Wolf-Kishner reduction[59] of **119** gave alkane **128** in 70% yield. The mass spectrum showed the molecular ion peak at m/z 220. Its IR spectrum was characterized by the absence of the carbonyl stretching absorption and an absorption peak at 3060 cm^{-1}, resulting from the stretching of carbon-hydrogen bonds in the cyclopropyl group. In the ^{1}H-NMR spectrum, no signals above δ 1.80 ppm were noted. Two one-proton multiplets at high field, one at δ 0.04 ppm (dd, J=4.5 and 7.5 Hz) and the other at δ 0.40 ppm (t, J=4.5 Hz) corresponded to two of the three protons in the cyclopropyl group.



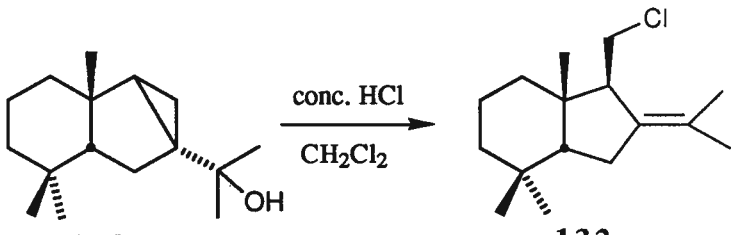
When alkane **128** was treated with ozone at -40°C in ethyl acetate for 8 hours, alcohol **130** and ketone **131** were obtained in 42% and 27% respectively. To obtain a maximal yield

of the alcohol, ketone **131** was treated with methyl lithium in THF at -40°C to give alcohol **130** in 70% yield. Therefore, the desired alcohol **130** was obtained in 61% overall yield from alkane **128**.

In the mass spectrum, alcohol **130** revealed its molecular ion peak at m/z 236 and a fragment ion peak at m/z 220 due to the dehydration of the parent molecule. Its IR spectrum was characterized by a broad hydroxyl stretching absorption near 3400 cm^{-1} and a carbon-hydrogen stretching absorption at 3060 cm^{-1} due to the C-H bonds in the cyclopropyl group. Its ^{1}H-NMR spectrum showed five methyl singlets at δ 0.72, 0.92,1.05, 1.10, and 1.19 ppm. There was a complex two-proton multiplet at high field δ 0.40-0.55 ppm due to two protons in the cyclopropyl group. The collapse of the two separate one-proton signals originally noted in the ^{1}H-NMR spectrum of **128** into this multiplet was probably due to the electronic effect of the newly introduced hydroxyl group at the isopropyl side chain.

The mass spectrum of ketone **131** showed a molecular ion peak at m/z 220. The IR spectrum had an intense absorption at 1675 cm^{-1} due to the carbonyl stretching frequency. This bathochromic shift when compared to usual saturated carbonyl absorptions (~ 1700 cm^{-1}) was the result of conjugation between the carbonyl and cyclopropyl groups[60] and this phenomenon was also observed in diketone **98**. The ^{1}H-NMR spectrum had four methyl singlets at δ 0.83, 1.00, 1.15, and 2.00 ppm. The methyl singlet at δ 2.00 ppm was apparently due to the methyl group at the methyl ketone side chain.

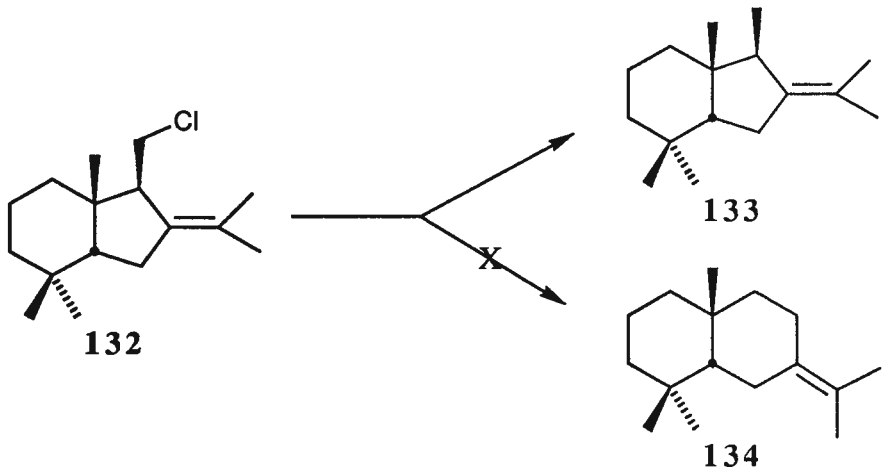
Treatment of alcohol **130** with concentrated hydrochloric acid in methylene chloride for 30 minutes produced homoallylic chloride **132** in 85% by the expected exo- type 1 cleavage.



130 **132**

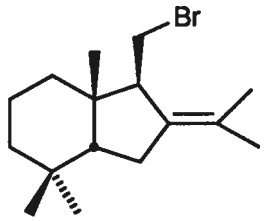
Compound **132** had a mass spectrum showing molecular peaks at m/z 256 (4.8%) and m/z 254 (14.8%) corresponding to two isotopic isomers $C_{16}H_{27}{}^{37}Cl$ and $C_{16}H_{27}{}^{35}Cl$. Its IR spectrum was devoid of O-H stretching absorption and the usual C-H stretching absorption from the cyclopropyl group due to the absence of both groups in this new compound. Its ^{1}H-NMR spectrum revealed five methyl singlets: three of them at higher field, δ 0.84, 1.04, and 1.22 ppm; two of them at lower field, δ 1.63 and 1.70 ppm, resulting from the two vinylic methyl groups of the isopropylene side chain. There was a two-proton octet at δ 3.40-3.75 ppm, corresponding to the methylene group carrying the chlorine function.

Using the condition previously established (Table 3), tributyltin hydride reduction of chloride **132** in refluxing benzene for 48 hours, generated in this instance only the simple reduction product **133** rather than the expected ring expansion product **134**. Compound **133** had a peak at m/z 220 corresponding to the molecular ion in the mass spectrum. Its ^{1}H-NMR spectrum showed five methyl singlets at δ 0.84, 0.87, 1.02, 1.58, 1.62 ppm and a methyl doublet at δ 1.05 ppm (J=6 Hz).



Changing the reducing agent to triphenyltin hydride and the solvent to toluene did not result in any significant change. We also treated alcohol **130** with concentrated hydrobromic acid in order to obtain a different substrate **135** for the radical-mediated ring expansion.

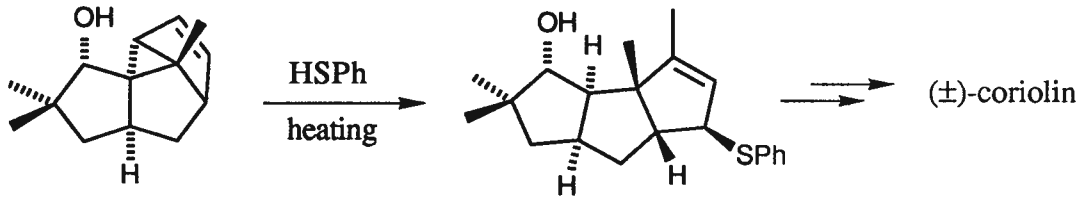
Unfortunately, a complex mixture was obtained after column chromatography. A direct tributyltin hydride treatment of the mixture from hydrobromic acid solvolysis without column separation produced compound **133** in addition to a large portion of an inseparatable mixture.



135

Therefore, the desired ring expansion for **132** had failed. Guided by the mechanistic proposal in Figure 13, we decided to approach the problem in a different way. According to this proposal, a cyclization to a cyclopropylcarbinyl radical (see (a) to (b) in Figure 13) from the initial primary radical was required before this cyclopropylcarbinyl radical opened to give the final radical (c), Figure 13). If, for some steric reason, the cyclization step did not take place, a simple reduction would be observed. On the other hand, if we could deliberately generate a cyclopropylcarbinyl radical centered at the tertiary carbon of the isopropyl side chain before opening the cyclopropane ring, the desired endo- type cleavage might be possible.

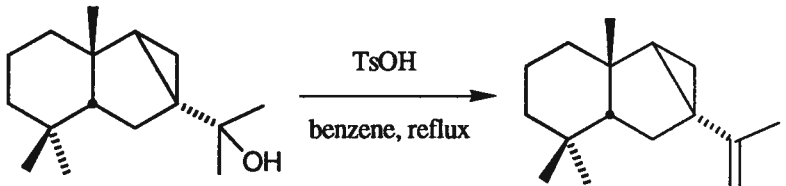
The way to generate such a cyclopropylcarbinyl radical from a vinylcyclopropane was reported by Wender et al. in the synthesis of (±)-coriolin[61a]. In their sequence, a regioselective cleavage of the vinylcylopropane in **136** (Scheme 22) was accomplished by thiophenol addition. In this reaction, thiophenol provided phenyl sulphuryl radical (PhS·)[61c] which then added to the double bond to generate a cyclopropylcarbinyl radical. The radical was selectively cleaved to produce intermediate **137**. Paquette et al. also used thiophenol to cleave vinylcyclopropanes[61b].



136 **137**

Scheme 22 Radical-initiated Selective Ring Cleavage of a Vinylcyclopropane **136**

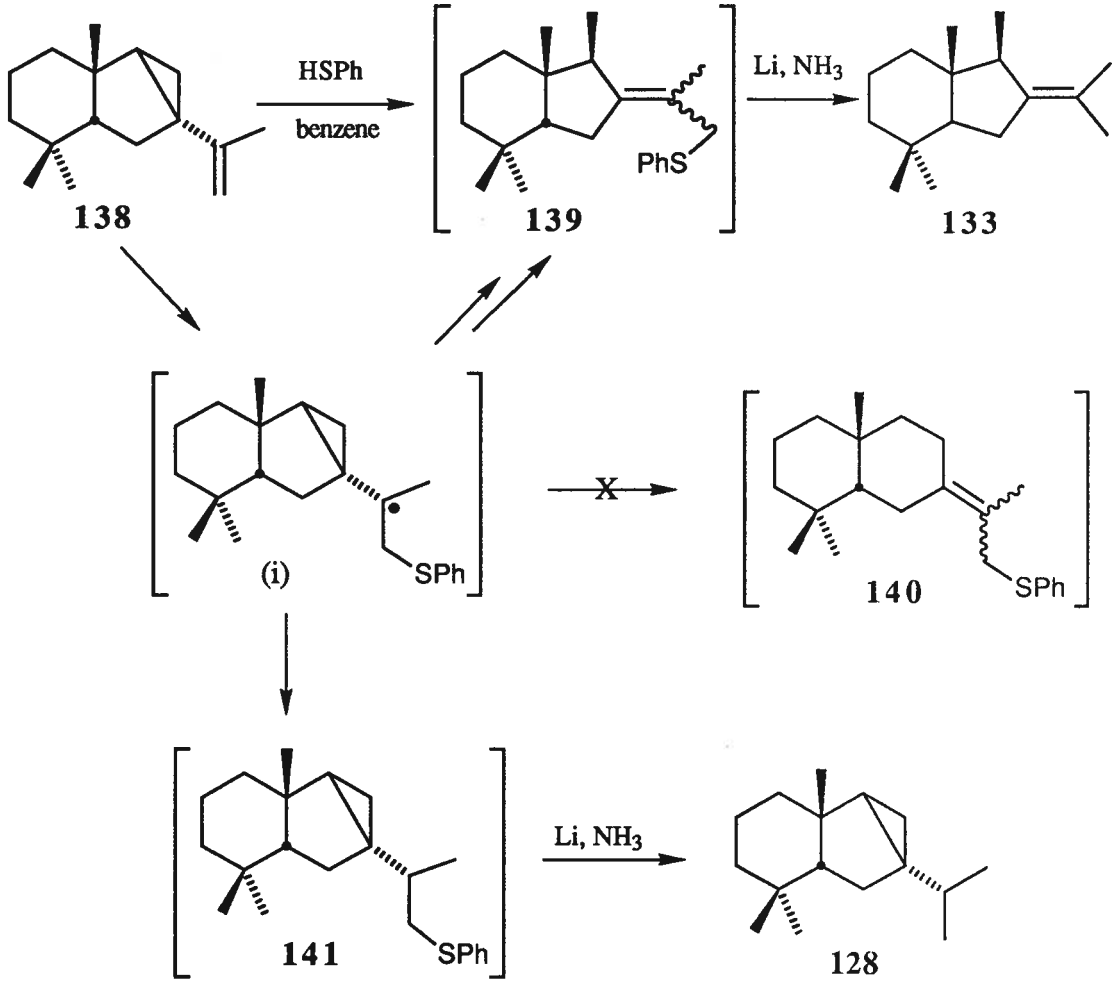
After refluxing alcohol **130** and a catalytic amount of pyridinium tosylate in benzene for 30 minutes, vinylcyclopropane **138** was separated in 95% yield. Its molecular ion at m/z 218 was revealed from the mass spectrum. The IR spectrum indicated the absence of O-H stretching absorption and a weak absorption peak at 1630 cm^{-1} due to the stretching of the terminal carbon-carbon double bond. Its ^{1}H-NMR spectrum showed two proton signals at high field due to the protons in the cyclopropyl group: one at δ 0.52 (dd, J=7.2 and 4.8 Hz) and the other at δ 0.68 ppm (t, J=4.8 Hz). Four methyl singlets appeared at δ 0.81, 1.00, 1.13, and 1.65 ppm; the latter signal at δ 1.65 ppm was due to the vinylic methyl group in the side chain. Two one-proton broad singlets at δ 4.65 and 4.85 ppm corresponded to the two terminal olefinic protons.



130 **138**

Refluxing of vinylcyclopropane **138** and thiophenol in benzene produced a rather complex inseparable mixture which may be expected in the form of four geometric isomers, two each of **139** and **140** (Scheme 23). The mixture was then subjected to lithium/ammonia hydrogenolysis at -33°C. In fact, column purification gave a colorless oil in 70% yield based on vinylcyclopropane **138**. The oil was composed of 70% **133** and 30% **128** as revealed by GC and ^{1}H-NMR comparison with pure samples of these two compounds. Apparently, the

deliberately generated cyclopropylcarbinyl radical (i) cleaved mainly in the exo-type 1 manner to give geometric isomers of **139**. The unexpected product **128** was probably derived from two diastereomers of **141**, which were produced by quenching radical (i) with thiophenol.



Scheme 23 Radical-initiated Ring Cleavage of Vinylcyclopropane **138**

Comparison of the radical-mediated ring expansion reaction of **123**, **132**, and the homoallylic chloride derived from **100** (see Scheme 17) revealed the dramatic effect induced by an extra methyl group in ring A. The radical-initiated ring cleavage reaction of vinylcyclopropane **138** by thiophenol indicated that a cyclopropylcarbinyl radical could not

necessarily guarantee the endo-type cleavage. This again indicated that the additional methyl group in ring A played an important role in determining the overall course of the reaction.

This subtle "methyl effect" could be rationalized in terms of the intermediate cyclopropylcarbinyl radical. The reaction of **132** with tributyltin hydride was assumed to involve a cyclopropylcarbinyl radical but the unidirectional cleavage of this radical in a way similar to the radical (i) in Scheme 23 resulted in the observed exo-type 1 cleavage product **133**. Inspection with molecular models revealed that *cis*-fused annulated thujone derivatives can have chair-chair and chair-boat conformations as shown in Figure 14. In the chair-chair conformation, the methyl group at C10 and the C4β substituent are equatorially oriented with respect to ring A; the plane C6-C5-C10 is below plane C6-C7-C9-C10, making the bicyclo[3.1.0]hexane portion chair-like. The major destabilizing factors are eclipsing interactions of the equatorial C6-H bond with the C7-C11 bond and the C1-C10 bond with the C9-H bond, and the non-bonded interaction between the isopropyl side chain and the axial methyl group at C4. In the chair-boat conformation, the methyl group at C10 and the C4β substituent are axially oriented; the plane C6-C5-C10 is above the plane C6-C7-C9-C10, making the bicyclo[3.1.0] hexane moiety boat-like. The eclipsing interactions are greatly diminished. The seemingly important non-bonded interaction between the axial methyl group at C10 and the axial C4β substituent is actually small because the flattening nature of plane C6-C5-C10-C9 (torsional angel <C6-C5-C10-C9 estimated ~ 25°)*[62] and the *cis* ring junction of the A and B rings leads to a spreading apart of these two groups[63]. In short, the chair-boat conformation is greatly preferred regardless if the C4β substituent is either hydrogen or methyl. This conclusion is well supported by the X-ray diffraction analysis of dione **98** (Figure 9) and compound **147** (Figure 15 and Appendix 1), the negative Cotton effect of Ketol **121** (Figure 10), and structural studies of substituted bicylo[3.1.0]hexanes[62]

* The estimation follows the average value provided by the studies on a series of bicylo[3.1.0] hexane compounds[62].

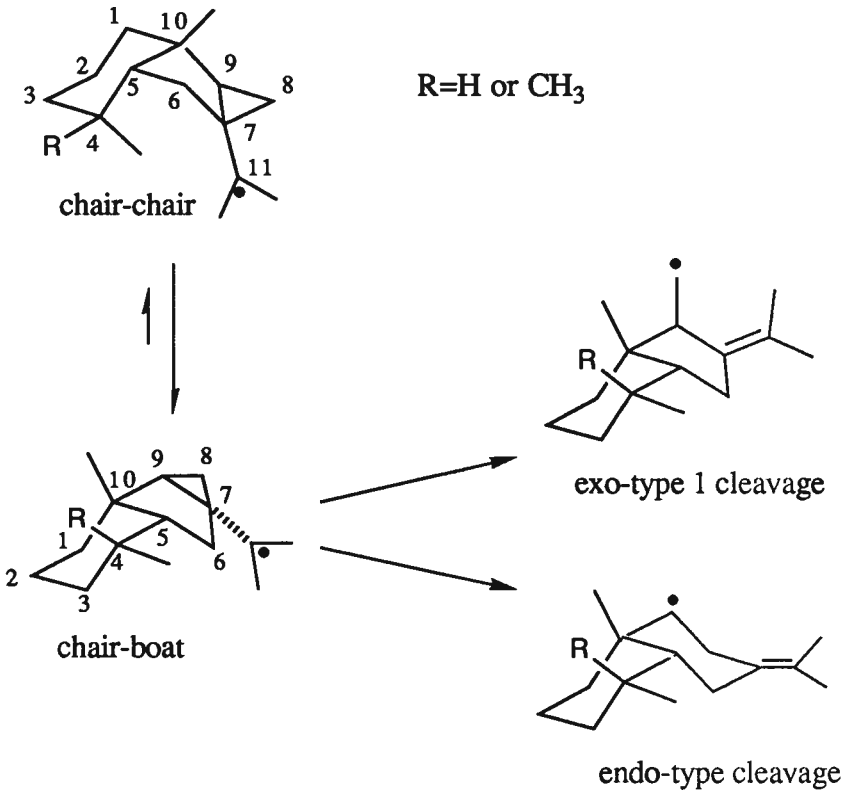


Figure 14 Rationalization of the "Methyl Effect"

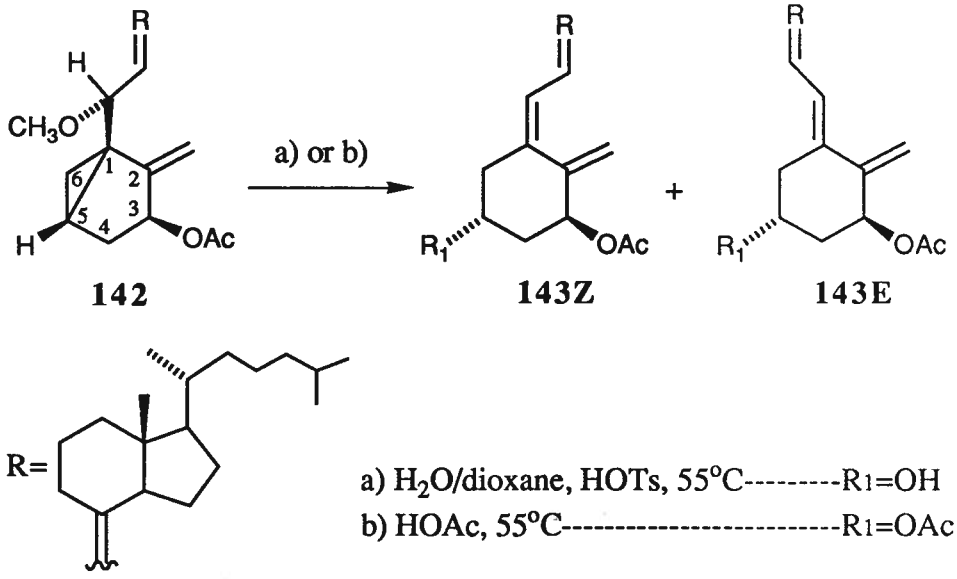
In the endo-type cleavage, the immediate product[64] from the active reactant chair-boat conformer should have a torsional angle <C6-C5-C10-C9 close to 55°# ; the methyl group at C10 and the substituent at C4β approaches each other during the cleavage, causing an increase in the energy of the transition state. If the substituent is methyl, the even greater increase in the transition state energy will probably forbid the endo-type cleavage from happening. In the exo-type 1 cleavage, the immediate product has a *cis*-fused hydroindene conformation. There should be little change in the <C6-C5-C10-C9$ and therefore the distance between the C10 methyl group and the C4β substituent. Thus, change from hydrogen to methyl for the C4β substituent will not cause much difference for this exo-type 1 pathway.

55° is the average value for the torsional angle of a saturated cyclohexane ring.

$ 30° is the average value for the torsional angle of a saturated cyclopentane ring.

2.2.7. Further Studies on the Acid-promoted Ring Cleavage of Cyclopropylcarbinols

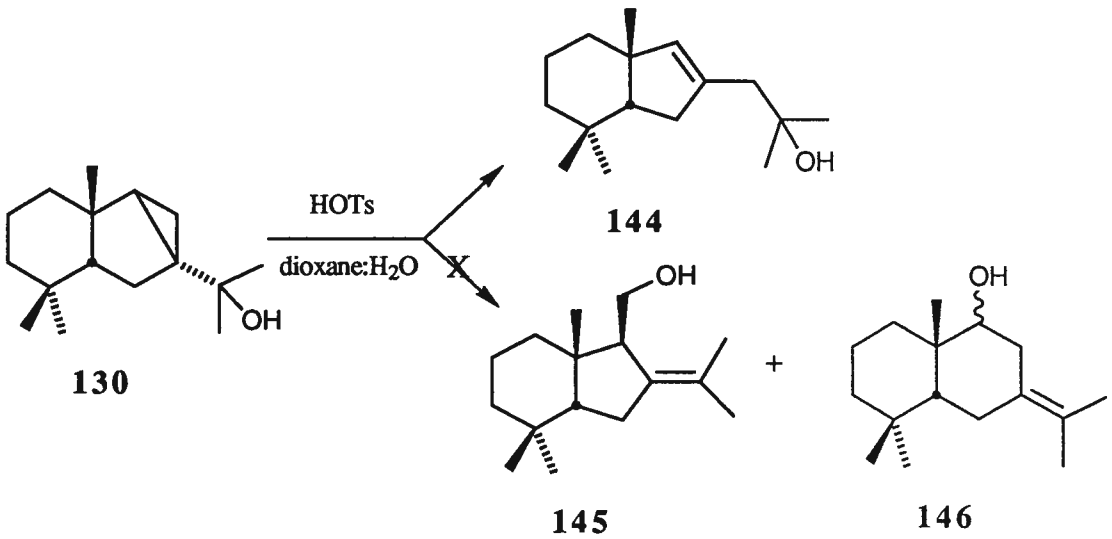
The unsuccessful efforts with the radical-mediated ring expansion and cleavage reactions required a return to studies on the acid-promoted ring cleavage reaction of thujone-derived cyclopropylcarbinols in greater detail. There are examples in the literature showing the use of other solvolysis conditions. In studies[65] on the preparation of vitamin D analogues, the conversion of compound **142** into the trienes **143Z** and **143E**, which are geometric isomers with regard to the newly formed double bond, was reported (Scheme 24). Obviously, compound **142** bears a close structural similarity to our thujone-derived cyclopropylcarbinols. The poor nucleophilicity of the attacking groups (e.g., H_2O and HOAc) in this set of conditions may allow the ring cleavage reaction to occur in a less synchronized mechanism in which the C-C bond cleavage occurs faster (see also Figure 12). The endo-type cleavage proceeds through a more stable transition state because the tertiary nature of C5 accommodates the partial charge developed better than the primary nature of C6. Therefore, the endo-type cleavage prevails.



Scheme 24 Precedents of the Endo-type Cleavage

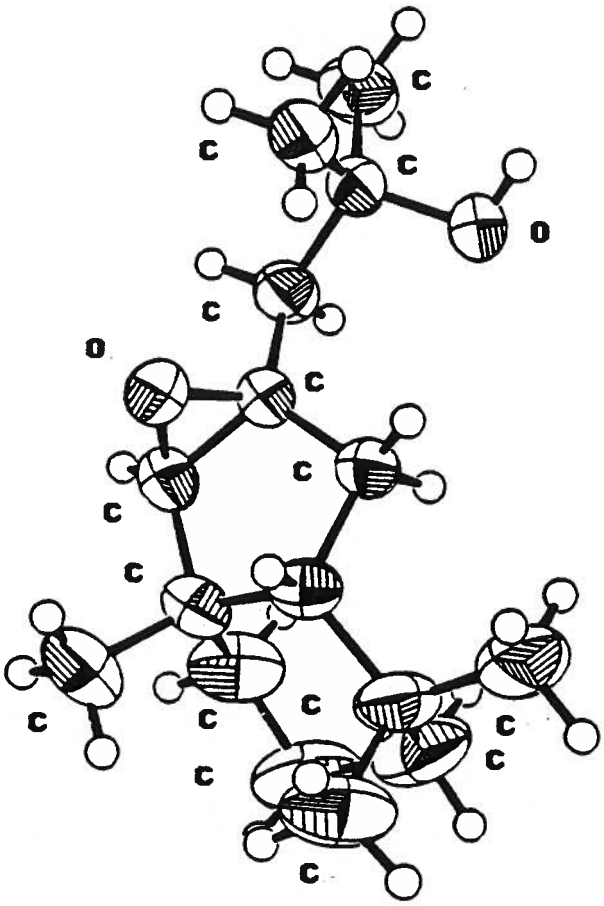
The orientation of the newly introduced group (OH or OAc) at C5 agrees well with concertedness of the nucleophilic attack and the C5-C1 bond cleavage.

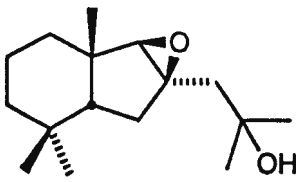
Treatment of **130** in dioxane:H_2O (1:1) with a catalytic amount of *p*-toluenesulfonic acid at 80°C for 1 hour generated a novel rearrangement product **144** in 85% yield rather than either of the ring cleavage products **145** and **146**. The absence of any signals at δ 3.0-4.0 ppm in the NMR spectrum clearly revealed the product obtained cannot be a primary or secondary alcohol. The homoallylic tertiary alcohol **144** was characterized by its mass, IR and ^{1}H-NMR spectra. Its mass spectrum indicated a peak at m/z 236 corresponding to the molecular ion and a fragment ion peak at m/z 218 due to loss of H_2O. The IR spectrum showed a broad absorption at 3100-3650 cm^{-1} corresponding to the hydroxyl stretching frequency while the ^{1}H-NMR spectrum contained five methyl singlets at δ 0.87, 1.01, 1.17, 1.21, and 1.22 ppm, a four-proton multiplet at δ 2.10-2.40 ppm corresponding to protons of two allylic methylene groups, and a one proton broad singlet at δ 5.33 ppm corresponding to the olefinic proton.



The most convincing evidence about the structure of **144** came from the X-ray diffraction analysis of its epoxide derivative **147**. Treatment of **144** with *m*-CPBA in

methylene chloride for one hour produced **147** in 90% yield, which was crystalized from methylene chloride. The structure of **147** established by X-ray analysis is shown in Figure 15 (See Appendix 1). The *cis* A/B ring junction in **147** and the β face epoxidation are revealed. The mass spectrum of **147** showed its molecular ion peak at m/z 252 and a fragment peak at m/z 234 due to the loss of H_2O. Its IR spectrum was characterized by a strong hydroxyl

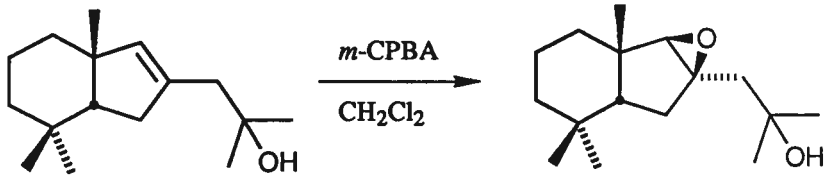




147

Figure 15 Single Crystal X-ray Structure of Epoxide **147** (ORTEP Drawing[166b])

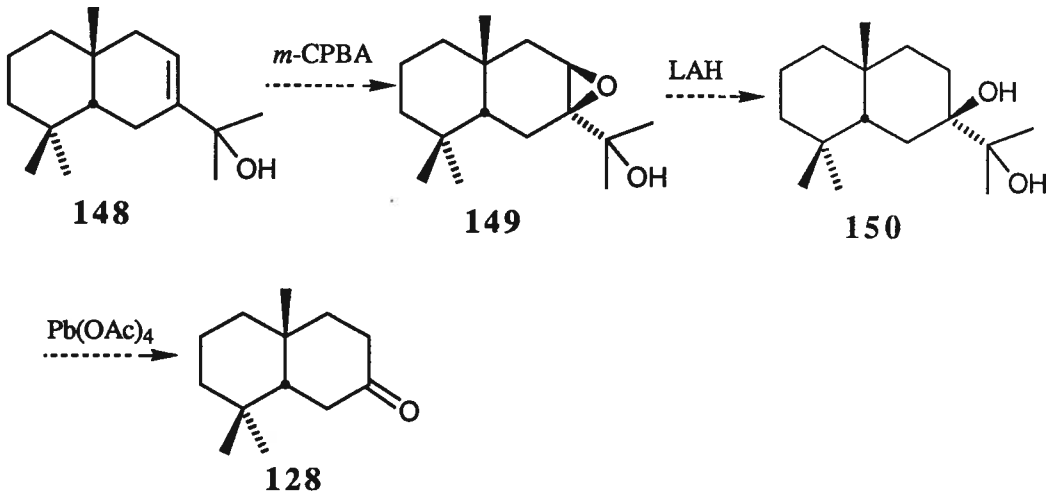
absorption at 3700 cm^{-1} ($CHCl_3$). The ^1H-NMR spectrum indicated a one-proton singlet at δ 2.85 ppm corresponding to the proton on the epoxide ring, and five methyl singlets at δ 0.80, 0.98, 1.20, 1.24, and 1.31 ppm.



144 **147**

Before the crystal structure of **147** was revealed by X-ray analysis, the allylic alcohol **148** was mistakenly assumed as the ring cleavage product, since the spectral data noted above could be consistent with such a proposal. Mechanistically, the formation of **148** from **130** via **146** by some familiar rearrangement steps was also perceivable.

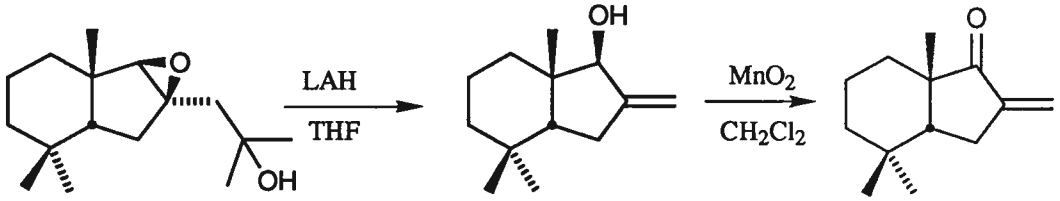
Based on the structure **148**, a sequence shown below was proposed to obtain the *cis*-fused decalone **128**. The epoxidation of **148** would generate **149**, which should give glycol **150** by hydride attack from the less substituted carbon upon lithium aluminium hydride treatment[66]. The latter would then be cleaved to **128** by lead tetraacetate.



148 **149** **150**

128

Therefore, epoxide **147**, mistaken as **148**, was treated with LAH in THF at 70°C for 2 hours. To our surprise, allylic alcohol **151** was obtained in almost quantitative yield. The mass spectrum showed its molecular ion peak at m/z 194, corresponding to a loss of an acetone molecule (m/z=58) from **147** or **148**. The IR spectrum displayed absorptions at 3100-3650, 3060, and 1650 cm^{-1} corresponding to hydroxyl, olefinic carbon-hydrogen, and carbon-carbon double bond stretching frequencies. The ^{1}H-NMR spectrum indicated only three methyl singlets at δ 0.82, 1.02, and 1.14 ppm, a complex two-proton multiplet at δ 2.20-2.60 ppm corresponding to the allylic methylene protons, a one-proton singlet at δ 3.80 ppm corresponding to the allyic tertiary proton α to the hydroxyl group, and two olefinic one-proton singlets at δ 5.06 and 5.21 ppm. The β orientation of the hydroxyl group was assigned based on a mechanistic argument shown in Figure 16.



147 **151** **152**

To confirm the structural assignment of **151**, it was subjected to allylic oxidation by manganese dioxide[67] in methylene chloride at room temperature for two days. The enone **152** was obtained in a 70% yield. The mass spectrum showed the molecular ion peak at m/z 192. Its UV spectrum in methanol displayed an intense absorption at 235 nm (log ε=4.0) and a weaker one at 278 nm (logε=2.5). The IR spectrum indicated a carbonyl absorption at 1710 cm^{-1}, and a carbon-carbon double bond absorption at 1635 cm^{-1}.

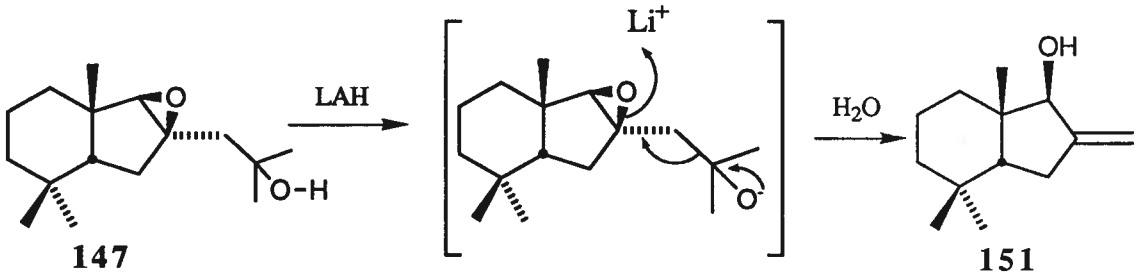


Figure 16 Mechanism of the Fragmentation of Epoxide **147**

We also treated **147**, still then mistaken as **148**, with "superhydride" (lithium triethylaluminium hydride) in order to see if the the desired reduction rather than the fragmentation would take place. However, the same compound **151** was obtained as the only product. This puzzling fragmentation is finally understood when the structure of **147** was elucidated by X-ray analysis. Since the epoxide ring is on the convex side of the carbon framework, the nucleophilic ring opening of the epoxide by hydride has to take place from the concave side. The unusually severe hindrance promotes the other pathway, that is, fragmentation. The deprotonation of the tertiary hydroxyl group with hydride is proposed to results in the intermediate alkoxide first and the latter then undergoes the fragmentation shown in Figure 16.

The novel rearrangement from **130** to **144** involved the insertion of the cyclopropane methylene into the position between the cyclopentyl ring and the isopropyl side chain. The cleavage of the carbon-carbon bond (i.e., the exo-type 2 cleavage, see the notation in Figure 11) in the original cyclopropyl ring was observed for the first time. The mechanism in Figure 17 is proposed to rationalize the reaction. Cyclopropylcarbinyl cation (i) is first formed by a proton-catalyzed elimination of the hydroxyl function in **130**. The 1,3-shift of the methylene can result in another cyclopropylcarbinyl cation (ii). Further cleavage of (ii) in a selective fashion to form a more stable homoallylic cation (iii) occurs and the latter, upon reaction with water, converts to **144**. The transformation between two cyclopropylcarbinyl cations in a

manner similar to that between (i) and (ii) was termed as a "cyclopropane sliding reaction" by H. Shirahama, who studied this type of transformation in greater detail with his system[68]. The mechanistic proposals involving this novel "sliding reaction" are scattered through the literature[69].

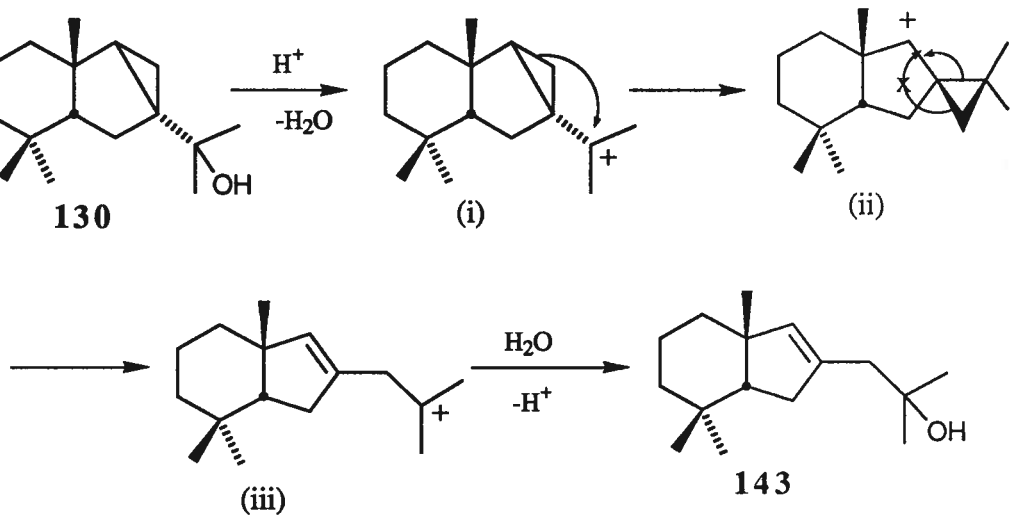


Figure 17 Mechanism of the "Cyclopropane Sliding Reaction"

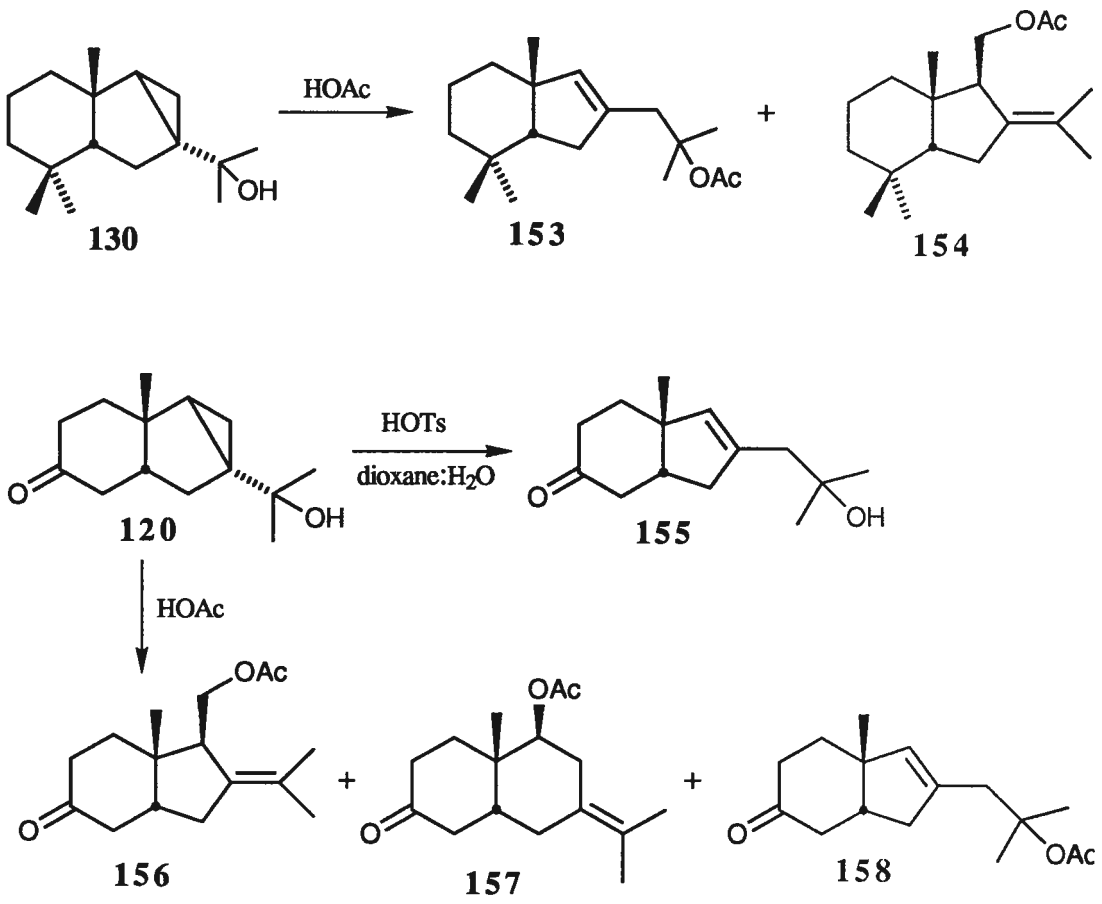
Treatment of **130** with acetic acid at 85°C for one hour produced the exo-type 2 cleavage product **153** in 60% yield in addition to the exo-type 1 cleavage product **154** in 6% yield. The competition of exo-type 1 cleavage is likely because **154** could only slowly convert to the cyclopropylcarbinyl cation (i) shown in Figure 17 once it is formed. The exo-type 1 product **145** could not be isolated in the previous reaction since it likely converts back to (i) rapidly under the acid catalysis.

The mass spectrum of **153** showed an intense fragment peak at m/z 218 due to the loss of an acetic acid molecule from the parent molecule (m/z=278). The chemical ionization mass spectrum using ammonia as carrier gas showed the protonated molecular ion ($M+H^+$) peak at m/z 279. The IR spectrum indicated carbonyl and carbon-carbon double bond stretching

absorptions at 1735 and 1650 cm^{-1} respectively. In the ^{1}H-NMR spectrum, six methyl singlets were observed at δ 0.85, 1.00, 1.15, 1.38, 1.45, and 1.97 ppm. The lowest field methyl singlet was due to the methyl protons of the acetate group. A complex multiplet at δ 2.02-2.62 ppm integrating for four protons was assigned to the two allylic methylene groups. There was a one-proton singlet at δ 5.26 ppm, corresponding to the olefinic proton.

The minor product **154** had its mass spectrum showing the molecular ion at m/z 278 and a fragment ion at m/z 218 due to loss of an acetic acid molecule. Its IR spectrum displayed a carbonyl stretching absorption at 1730 cm^{-1}. In the ^{1}H-NMR spectrum, six methyl singlets were observed at δ 0.85, 1.03, 1.14, 1.61, 1.69 and 2.01 ppm. The two singlets at δ 1.61 and 1.69 ppm were assigned to the two vinylic methyl groups of the isopropylidene group and the signal at δ 2.01 was clearly due to the methyl of the acetate group. A two-proton multiplet at δ 2.10-2.32 was due to the allylic methylene while a one-proton triplet (J=5.6 Hz) at δ 2.39 ppm was from the allylic methine proton. A two-proton multiplet at δ 3.92-4.25 ppm, which had a shape characteristic of the A/B portion of an ABX system, was assigned to the methylene attached to the acetate group.

To test the generality of the cyclopropane sliding reaction, ketol **120** was employed as substrate under the two conditions previously used (Scheme 25). The endo-type cleavage product **155** was obtained in 87% yield under *p*-toluenesulfonic acid catalysis in dioxane:water (1:1) mixture. It was characterized by its ion molecular peak at m/z 222 and IR absorptions at 3050-3650, 1700, and 1650 cm^{-1} due to hydroxyl, carbonyl, and carbon-carbon double bond stretching frequencies. Three methyl singlets, one at δ 1.20 ppm and two at δ 1.23 ppm, and an olefinic one-proton broad singlet at δ 5.20 ppm were observed in its ^{1}H-NMR spectrum.



Scheme 25 Generality of the Cyclopropane Sliding Reaction

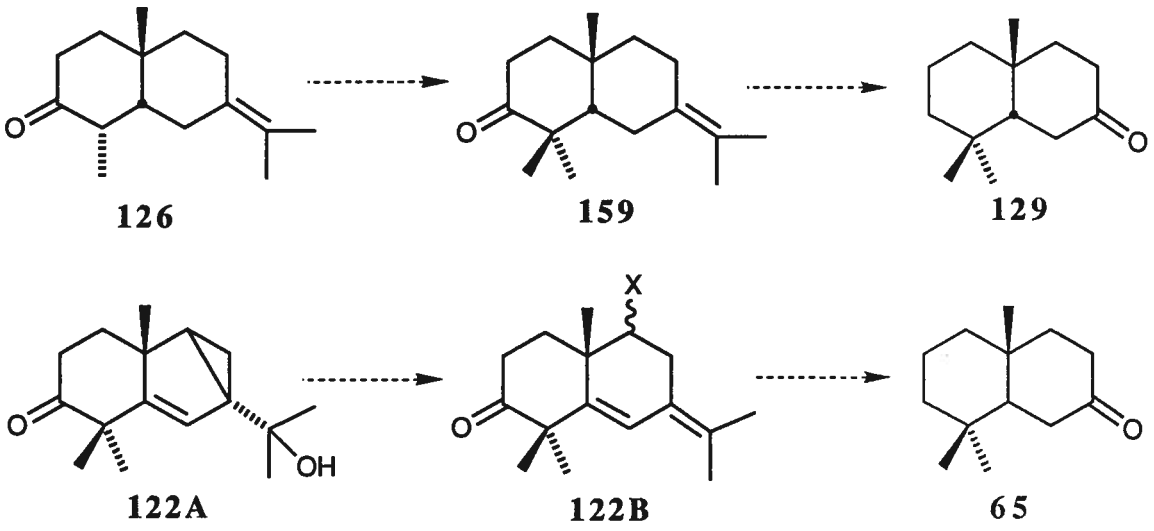
Treatment of **120** with acetic acid gave mainly the cleavage products **156** (56%, exo-type 1 cleavage) and **157** (14%, exo-type 2 cleavage). Although a very minor peak at δ 5.17 ppm in the ^{1}H-NMR spectrum of **156** indicated a probable presence of **158**, the very minor amount present prevented its isolation. Presumably, the faster rate of these more direct cleavage reactions and perhaps the higher stability of the acetate products, prevent the formation of a cyclopropylcarbinyl cation like (i) in Figure 17 and therefore the sliding reaction from taking place. The keto-acetate **156** was characterized by its molecular ion peak at m/z 264, carbonyl stretchings at 1735 and 1705 cm^{-1} in the IR spectrum, and a two-proton multiplet at δ 3.95-4.20 ppm corresponding to the methylene attached to the acetate group in the NMR spectrum. The electron impact mass spectrum of **157** revealed a fragment ion peak

at m/z 204 due to loss of a molecule of acetic acid; The chemical ionization mass spectrum using ammonia as carrier gas showed ($M+NH_4^+$) at m/z 282 and ($M+H^+$) at m/z 265. The IR spectrum exhibited a carbonyl stretching absorption at 1710 cm^{-1}. Two vinylic methyl singlets appeared at δ 1.65 ppm and 1.72 ppm. A methyl singlet at δ 2.10 ppm corresponding to the methyl of the acetate group and a one-proton doublet of doublets at δ 5.19 ppm (J=4.2 and 10.2 Hz) corresponding to the methine attached to the acetate group were observed. The acetoxyl group was assumed to have β-orietation, following the observed stereochemistry for the ring cleavage of related systems under similar conditions and the argument presented for this observation (Scheme 24).

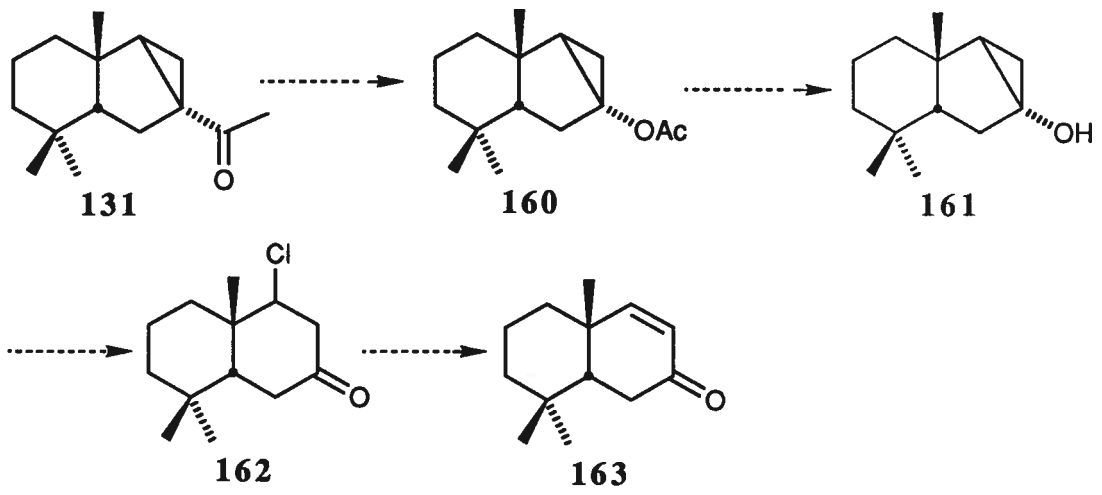
2.2.8. Baeyer-Villiger Oxidation of Cyclopropyl Ketones

Our other efforts on applying the alcohols derived from ozonation of thujone derivatives were to consider alternatives to the synthetic sequence shown in Scheme 21 by rearranging some steps involved. The successful radical-mediated ring expansion product **126** might be methylated to **159**, which could be then decarbonylated and ozonolyzed to give **129**. Unfortunately, methylation of **126** by KO^tBu and CH_3I in anhydrous *t*-butanol did not proceed at all at room temperature. Heating up the mixture gave a complex mixture. Although a protection of the methylene at C2 and the use of a strong base like LDA may eventually allow methylation proceed as desired, the added extra steps seemed to give very little advantage to such an effort. The other alternative sequence involved the use of **122A**, resulting from methylation of **122**. The mass spectrum of **122A** showed the molecular ion peak at m/z 248 while the IR spectrum indicated absorptions of the hydroxyl and carbonyl groups at 3100-3700 and 1705 cm^{-1}. The ^1H-NMR spectrum revealed a one-proton triplet at δ 0.44 ppm (J=4.4 Hz), a one-proton doublet of doublets at δ 1.04 ppm (J=4.4 and 8.0 Hz), five methyl singlets at δ 1.16, 1.19, 1.23, 1.26, and 1.28 ppm, two one-proton multiplets at δ 2.50 and 2.70 ppm, and a one-proton broad singlet at δ 5.62 ppm. Unfortunately, treatment of **122A** with hydrochloric acid in methylene chloride gave an intractable mixture rather than the desired

122B. The low yield (30%) of **122**, obtained from Robinson annulation of **94** with EVK, also discouraged further effort in this direction.



Therefore, the application of alcohols derived from ozonation of thujone derivatives to the synthesis of natural (-)-polygodial (**2**) had not met with any success. Our next consideration then to cyclopropyl ketones derived from ozonation, especially **131**. It was perceived that a Baeyer-Villiger reaction[71] would cleave the side chain in a regioselective manner to give **160** (Scheme 26). The preferential insertion of oxygen into the cyclopropyl group side during the Baeyer-Villiger reaction of methyl cyclopropyl ketone had been observed previously[70]. The cyclopropanol **161** from saponification of **160** would be cleaved via the internal carbon-carbon bond (i.e., endo-type 1 cleavage) by ferric chloride to generate the b-chloroketone **162**. It was recorded that the more substituted bonds of cyclopropanols were cleaved preferentially[73]. Subsequent elimination of HCl would afford enone **163** and the latter could be elaborated to intermediates **65** in Scheme 9 by standard methods, thereby completing a formal synthetic sequence to (-)-polygodial (**2**).



Scheme 26 Utilization of Cyclopropyl Ketone **131** via Baeyer-Villiger and Cyclopropanol Cleavage Reactions

For this purpose, compound **131** was treated with *m*-CPBA in methylene chloride at room temperature for 2 days to produce **160** in 79% yield based on the recovery of 46% starting material **131**. An optimization of the reaction was carried out according to Table 4. *p*-Toluenesulfonic acid had little catalytic effect on the *m*-CPBA oxidation reaction. Under refluxing conditions, the reaction appeared to accelerate at the beginning but slowed down quickly after a few hours and started to afford some unidentified by-products. When the concentration of the substrate was increased to 0.82 M, the reaction was quite complete after refluxing in methylene chloride for 12 hours and the yield of **160** was 82%. Although the use of trifluoroperacetic acid[70] improved the yield to as high as 94%, the reaction seemed not easily reproducible. This was likely due to the instability of trifluoroperacetic acid. Therefore, the preferred procedure for the preparation of **160** was to employ a high concentration of substrate **131** with *m*-CPBA as the oxidizing agent in refluxing methylene chloride.

Table 4 The Optimization of Baeyer-Villiger Reaction of Ketone **131**

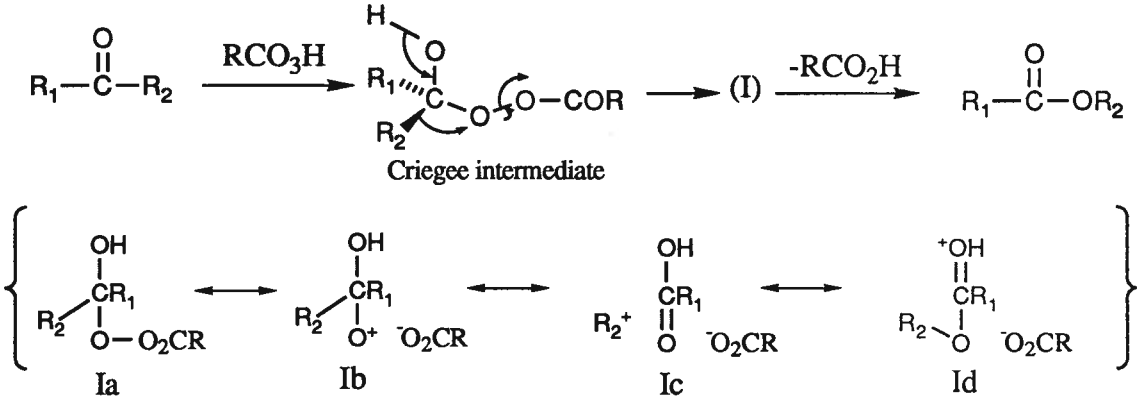
Experiment	1	2	3	4	5
131	176 mg	176 mg	176 mg	93 mg	1.80 g
Peracids¥	*m*-CPBA 346 mg (2.0 eqv.)	*m*-CPBA 346 mg (2.0 eqv.)	*m*-CPBA 346 mg (2.0 eqv.)	CF_3CO_3H 312 µl (2.7M) (2.0 eqv.)	*m*-CPBA 4.45 g (2.5 eqv.)
CH_2Cl_2	5.0 ml	5.0 ml	5.0 ml	2.0 ml 10 ml	
HOTs (mg)	0	39	0	0	0
Temp.	r.t.	r.t.	reflux	r.t.	reflux
Time (hrs)	48	48	24	48	12
% recovery of **131**	46	46	30	48	5
% yield of **160**	79	78	60	94	82%

¥: *m*-CPBA (80-85% pure) was used without further purification while CF_3CO_3H was prepared *in situ* according to ref. 70a.

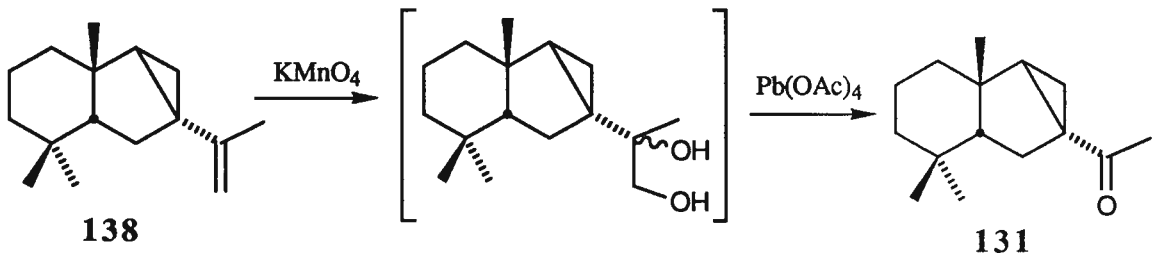
Acetate **160** had its mass spectrum showing the molecular ion peak at m/z 236. The IR spectrum had a carbonyl absorption at 1735 cm^{-1} while the ^1H-NMR spectrum displayed four methyl singlets at δ 0.80, 0.97, 1.05, and 2.10 ppm. The methyl singlet at δ 2.10 ppm was obviously due to the acetate group, which unambiguously demonstrated the insertion of oxygen into the position between the quaternary cyclopropyl carbon (C7) and and the carbonyl carbon.

According to the accepted mechanism of the Baeyer-Villiger reaction, a tetrahedral "Criegee intermediate" rearranges to ester products after it is formed by the peracid addition to the ketone carbonyl[72]. (I), the transition state of this rearrangement step, can be described by four resonance structures, Ia, Ib, Ic, and Id. The structure Ic implies that the preferred migration group will be the one that best accommodates a positive charge. Methyl cyclopropyl

ketone was unreactive to *m*-CPBA; only the much more reactive agent peroxytrifluoroacetic acid could make the oxygen insertion proceed to give cyclopropyl acetate[70b]. This is probably because the cyclopropyl group cannot accommodate a positive charge well. The smooth reaction of **131** with *m*-CPBA at room temperature shows that the transition state involved is likely stabilized by the fused cyclopentyl group, which can presumably stabilize a positive charge better than the cyclopropyl group..



As mentioned previously, ketone **131** was obtained in only 25% yield from the ozonation of alkane **128**. Therefore, a sequence was developed to convert alcohol **130** to ketone **131** in order to optimize the yield of **131**. Vinylcyclopropane **138**, prepared by dehydration of **130** (p. 54), was ozonized to **131** in only 60% yield. A two-step procedure, involving the treatment of **138** with potassium permanganate in 1:1 *t*-butanol:water and the subsequent oxidative cleavage of the non-purified crude mixture of diols by lead tetraacetate in benzene, was then developed. In this case, **131** was obtained in 83% yield from **130**. Thus, the overall yield of **131** from alkane **128** was improved to 65%.



2.2.9. Regioselective Ring Opening of the Cyclopropyl Alcohol 161

Regioselective ring opening of alkyl substituted cyclopropanols by ferric chloride has been studied extensively by DePuy[73]. The more substituted C-C bond is preferentially cleaved. The reaction (Figure 18) involves a cyclopropoxyl radical (i) which undergo a homolytic β scission of the more substituted C-C bond to give a carbinyl radical (ii). The subsequent abstraction of a chlorine from ferric chloride produces the β-chloroketone. This reaction was successfully applied to ring expansion of cyclic ketones via their derivatives 1-trimethylsilyloxybicyclo[n.1.0]alkanes[74]. More recently, a different reagent, iodosobenzene, was developed to effect the same ring expansion of cyclic ketones and lactones via similar derivatives[75].

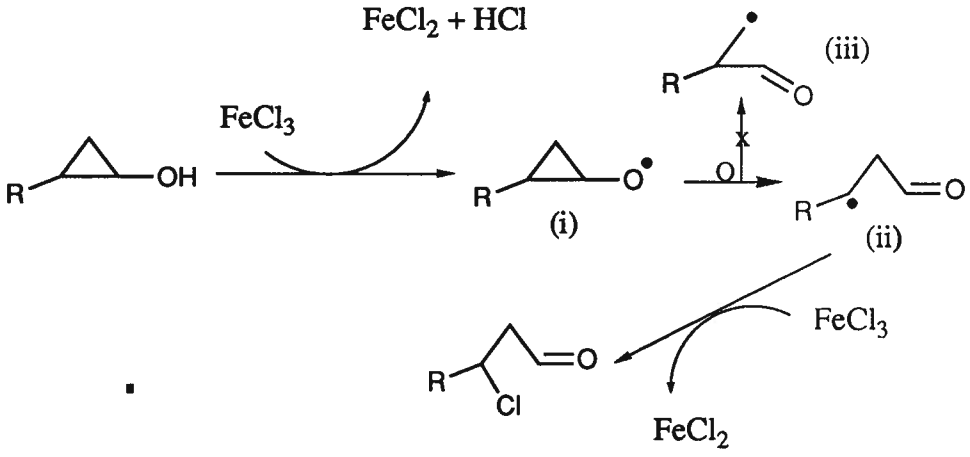


Figure 18 Regioselective Cleavage of Cyclopropanols

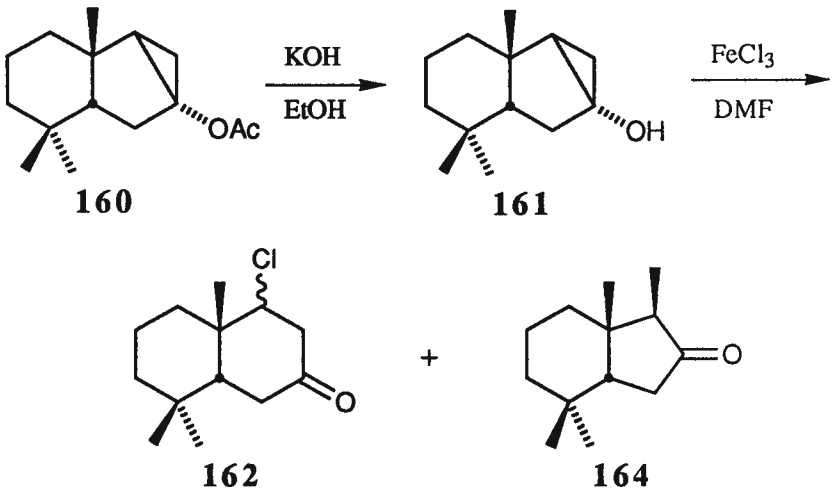
Saponification of **160** was carried out in dilute potassium hydroxide-ethanol solution for 30 minutes. The rather polar **161** was obtained in almost quantitative yield. The reaction had to be worked up immediately because **161** could be further converted into **164**. The mass spectrum of **161** indicated the molecular ion peak at m/z 194. Its IR spectrum showed the hydroxyl stretching frequency at 3050-3650 cm^{-1} and the absence of ester carbonyl absorption. The ^1H-NMR spectrum displayed three methyl singlets at δ 0.80, 0.96, and 1.01 ppm, a two-

proton multiplet at δ 1.98 ppm. The spectrum was contaminated by ketone **164** resulting from rapid decomposition of **161**.

The lability of cyclopropanol **161** dictated its immediate application to the next reaction. The mixture of anhydrous ferric chloride and **161** in anhydrous N,N-dimethylformamide were agitated under nitrogen at room temperature for 24 hours. The major product **162** was isolated in addition to a small amount of **164**.

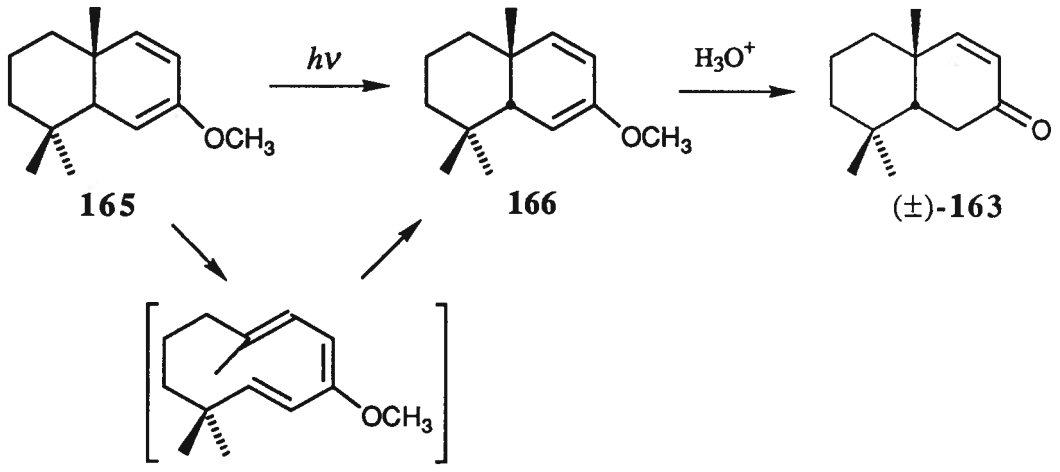
The β-chloroketone **162** had its mass spectrum showing molecular ion peaks at m/z 230 (0.2%) and 228 (0.6%) corresponding to formulas $C_{13}H_{21}O^{37}Cl$ and $C_{13}H_{21}O^{35}Cl$. Its IR spectrum displayed carbonyl stretching absorption at 1720 cm^{-1} while the ^{1}H-NMR spectrum indicated three methyl singlets at δ 0.76, 0.90, and 1.25 ppm, a complex four-proton multiplet at δ 2.10-3.00 ppm, and a one-proton doublet of doublets at δ 4.70 ppm (J=6.0 and 12 Hz) corresponding to the methine proton attached to the chlorine bearing carbon. The orientation of the chlorine function in **162** was uncertain.

The mass spectrum of **164** indicated the molecular ion peak at m/z 194 while the IR spectrum revealed the carbonyl absorption at 1725 cm^{-1}. The ^{1}H-NMR spectrum displayed two methyl singlets at δ 0.80 and 0.99 ppm, a methyl doublet at δ 0.93 ppm (J=7.2 Hz), a one-proton triplet at δ 1.77 ppm (J=8.0 Hz), a one-proton quartet at δ 2.06 ppm (J=7.2 Hz), and a complex one-proton multiplet at δ 2.15-2.35 ppm.

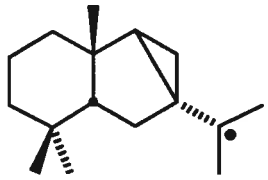


The β-chloroketone **162** underwent elimination of hydrogen chloride to give enone **163** easily even without addition of any base. The crude product from the above ring cleavage reaction was treated with sodium acetate in refluxing methanol for a few hours. The overall yield of **163** from acetate **160** was 80%, equivalent to a 93% yield for each step. The ketone **163** was a white solid with a m.p. of 64-66°C (literature value m.p. 68°C)[76]. The mass spectrum of **163** indicated its molecular ion peak at m/z 192. The IR spectrum showed an intense conjugated carbonyl stretching frequency at 1664 cm^{-1}. Three methyl singlets appeared at δ 0.77, 0.96, and 1.22 ppm in the ^{1}H-NMR spectrum. A complex two-proton multiplet at δ 2.50-2.80 ppm corresponded to the methylene α to of the carbonyl function. Two doublets at δ 5.95 and 6.27 ppm with a coupling constant, J=9.6 Hz were assigned to the two olefinic protons.

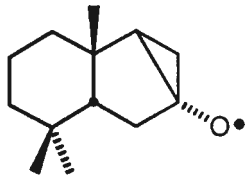
The racemate of **163** was prepared previously by an interesting photochemical epimerization[76]. The ether **165**, prepared from the *trans*-fused isomer of **163**, was irradiated to generate **166** which then, upon hydrolysis, afforded (±)-**163**. The transformation from **165** to **166** was mediated by an achiral triene and therefore the chirality of starting material **165** was lost completely during the reaction. In other words, this method is inherently not enantioselective.



The cyclopropylcarbinyl radical (i) and the cyclopropoxyl radical (ii) appears to have distinctly different cleavage pathways. Why are not the conformational factors previously considered in the cleavage of carbinyl radical (i) in Figure 14 playing any major role in the cleavage of the oxyl radical (ii).



carbinyl radical (i)



oxyl radical (ii)

A beautiful frontier molecular orbital (FMO) rationalization offered by Mariano and Bay[77] is adopted here (Figure 19). As we know, the SOMO of the oxygen-centered radical has much lower energy than that of the carbon-centered radical due to the greater electronegativity of oxygen. In general, the oxyl radical SOMO and the HOMO of a cyclopropane C-C bond are closer in energy than the SOMO-LUMO pair. Therefore, the SOMO-HOMO interaction contributes more to the stabilization of the transition state. A more alkyl substituted C-C bond has higher HOMO energy due to the electron donating nature of alkyl groups[78] and therefore has an enhanced SOMO-HOMO interaction. As a result, the more substituted C-C bond is preferentially cleaved. In the case of the oxyl radical (ii), such a SOMO-HOMO stabilizing interaction for the more substituted internal C-C bond overrides those unfavorable conformatiomal factors considered in the case of carbinyl radical (i) (Figure 14). Therefore, the endo-type cleavage is observed for the oxyl radical (ii). Using a similar argument, the kinetically controlled cleavage of cyclopropylcarbinyl radical (i) will go through the exo-type 1 pathway. The thermodynamically favorable endo-type cleavage cannot materialize even under the most favorable condition (i.e., high dilution and slow reaction rate) probably because of the great transition barrier present in this pathway (see Figure 14).

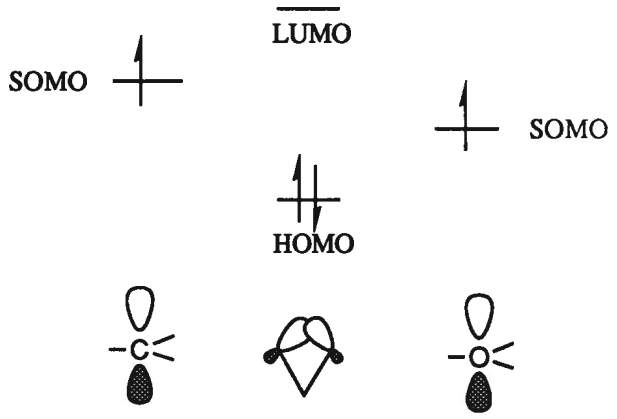
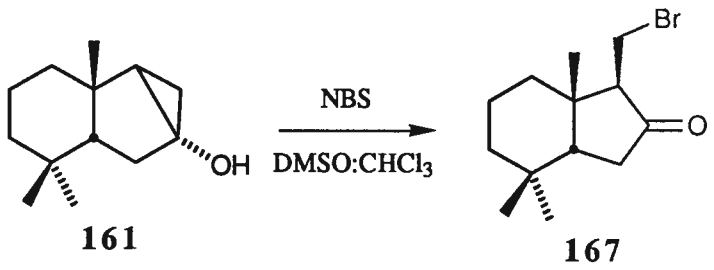


Figure 19 FMO Interactions of Carbinyl and Oxyl Radicals with Cyclopropane C-C Bonds

The preferential cleavage of the less substituted C-C bond in cyclopropanols by other reagents, which has a complementary regioselectivity to the ferric chloride reaction were also recorded[73]. We were curious to see if the exo-type 1 cleavage of the cyclopropanol **161**, which represents the cleavage of the less substituted C-C bond, could be effected by using similar conditions. Indeed, the β-bromoketone **167** was obtained in 60% yield after **161** was treated with NBS in DMSO:$CHCl_3$ (1:1) at room temperature. The mass spectrum of **167** revealed two isotopic molecular ion peaks at m/z 274 (2.4%) and 272 (2.5%) while the IR spectrum showed the carbonyl stretching absorption at 1730 cm^{-1}. The ^{1}H-NMR spectrum indicated three methyl singlets at δ 0.82, 1.00, and 1.14 ppm, a two-proton multiplet at δ 2.32 ppm, a triplet at δ 2.55 ppm (J=5.4 Hz), and a complex two-proton multiplet at δ 3.35-3.65 ppm.

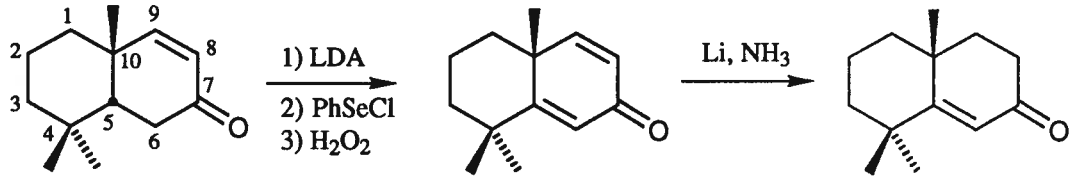


161 **167**

Therefore, the cyclopropyl ketone **131**, much less considered than the other ozonation-derived compound – cyclopropylcarbinol **130**, turned out to be the more versatile intermediate for further elaboration. The cyclopropanol group in **161** may give a better control of regioselective ring cleavages than the cyclopropylcarbinol group in **130**. In retrospect, we felt satisfied with what the ozonation method had brought us in terms of excluding the isopropyl side chain and controlling the regioselectivity of cyclopropane ring cleavage.

2.2.10. A Formal Enantioselective Synthesis of (-)-Polygodial (2) and (-)-Warburganal (10)

de Groot et al. have synthesized enantiomerically pure **64** from (-)-dihydrocarvone (Scheme 9)[33e]. Ketone **64** was then converted to natural (-)-polygodial (**2**) and (-)-warburganal (**10**) using a sequence previously developed (Scheme 3). Consequently, If the *cis*-fused enone **163** were transformed into enone **64**, a formal enantioselective synthesis of (-)-Polygodial (**2**) and (-)-warburganal (**10**) from thujone was at hand.



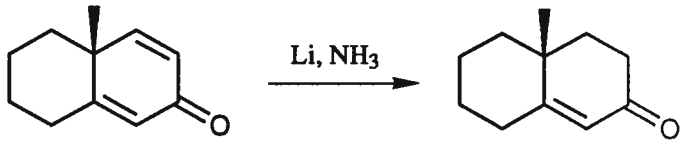
163 **168** **64**

Scheme 27 The Preparation of Enantiomerically Pure Enone **64** from **163**

To this end, LDA and phenylselenenyl chloride treatment of compound **163** in THF, followed by hydrogen peroxide oxidation, generated dienone **168** in very good yield (92%) (Scheme 27). Dienone **168**, in its mass spectrum, showed the molecular ion peak at m/z 190 while its UV spectrum displayed a broad absorption peak at λ 241 nm (log ε=4.0). The IR spectrum indicated a conjugated carbonyl stretching absorption at 1660 cm^{-1} and a weak C=C absorption at 1620 cm^{-1}. Three methyl singlets appeared at δ 1.22, 1.30, and 1.35 ppm in the

^{1}H-NMR spectrum. The olefinic proton at C8 was a doublet of doublets at δ 6.14 ppm due to the couplings with the proton at C9 (J=9.9 Hz) and with the proton at C6 (W coupling, J=0.2 Hz). The proton at C9 was a doublet at δ 6.25 ppm due to coupling with the the proton at C8 (J=9.9 Hz). The proton at C6 appeared as a doublet at δ 6.70 ppm (J=0.2 Hz) resulting from the above mentioned W coupling with the C8 proton.

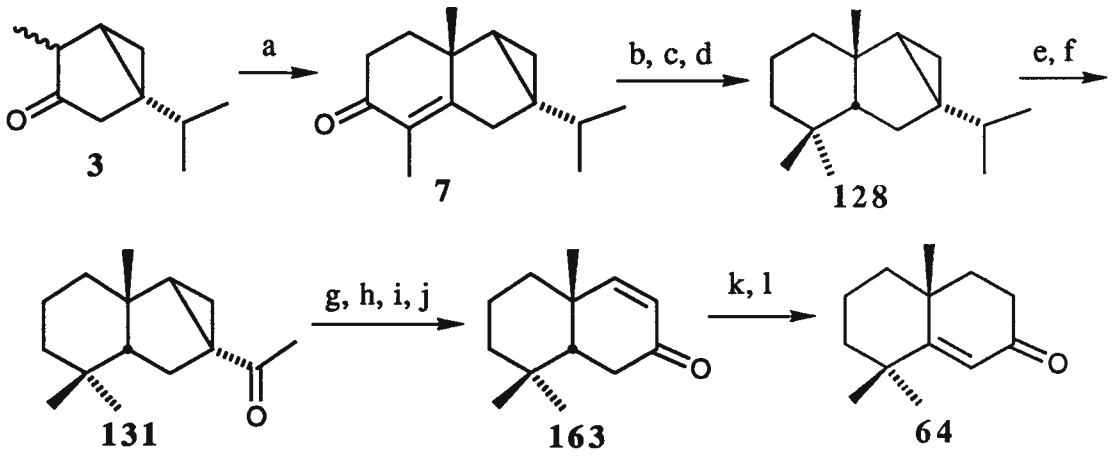
Birch reduction of dienone **168** without adding any proton donor gave the desired enone **64** in 70% yield. The specific rotation of compound **168** ($[\alpha]_D^{25}$=-100, c=1.00, $CHCl_3$) is in close agreement to the value reported by de Groot ($[\alpha]_D^{25}$=-105, c=1.0, $CHCl_3$)[33e]. This kind of selective reduction of the less substituted double bond of an analogous dienone **169** was observed previously[79]. Presumably the higher reduction potential



169 **170**

of the less substituted double bond led to a faster reaction. The spectroscopy data of **64** obtained by us was identical to that reported by de Groot[33e]. Thus, a formal synthetic sequence of (-)-polygodial (**2**) and (-)-warburganal (**10**) was completed.

The complete sequence from thujone (**3**) to enone **64** is summarized in the following scheme. This sequence consisting of 11 steps is considerably longer than the 5-step sequence developed by de Groot (Scheme 9). However, our sequence can be simplified by carrying out several continuous steps without purification of intermediates. Specifically, steps from b) to f), steps from g) to h), and steps from i) to j) have been performed in this manner. For the sake of completing a formal synthesis, we purposely intercepted enone **64** by conversion of enone **163**. Consequently, the A/B *cis* fusion became a complete handicap. In other words, the real strength of enone **163** as a chiral template and therefore thujone as a chiral building block could not be shown. As will be demonstrated in the synthesis of ambergris fragrances



a) EVK, KOH, EtOH; b) H_2, Pd-C; c) MeI, KO^{t}Bu, ^{t}BuOH; d) NH_2NH_2, KOH, DEG; e) O_3; f) $KMnO_4/Pb(OAc)_4$; g) *m*-CPBA; h) KOH, MeOH; i) $FeCl_3$, DMF; j) NaOAc, MeOH; k) LDA, $PhSeCl/H_2O_2$; l) Li, NH_3.

(Chapter 3), the direct application of the *cis*-fused enone **163** as a chiral template is much more advantageous*.

Ketone **171**, which was an intermediate used in the preparation of a (-)-polygodial analogue (Scheme 17), was converted to **173** and **174** using a similar dehydrogenation-reduction sequence. Dienone **172** was obtained in 80% yield by treatment of **161** with DDQ in refluxing dioxane[80]. This product was characterized by its molecular ion peak at m/z 176 in the mass spectrum, a conjugated carbonyl and carbon-carbon double bond absorptions at 1650 and 1620 cm^{-1} in the IR spectrum as well as typical ^{1}H-NMR signals. In the latter spectrum, a methyl doublet at δ 1.14 ppm (J=6 Hz), a methyl singlet at δ 1.27 ppm, a one-proton septet (J=6 Hz) corresponding to the methine proton at C4, a singlet at δ 6.11 ppm corresponding to the olefinic proton at C6, a doublet at δ 6.21 ppm (J=9.0 Hz) corresponding to the olefinic proton at C8, and another doublet at δ 6.78 ppm (J=9.0 Hz) corresponding to the proton at C9 were observed.

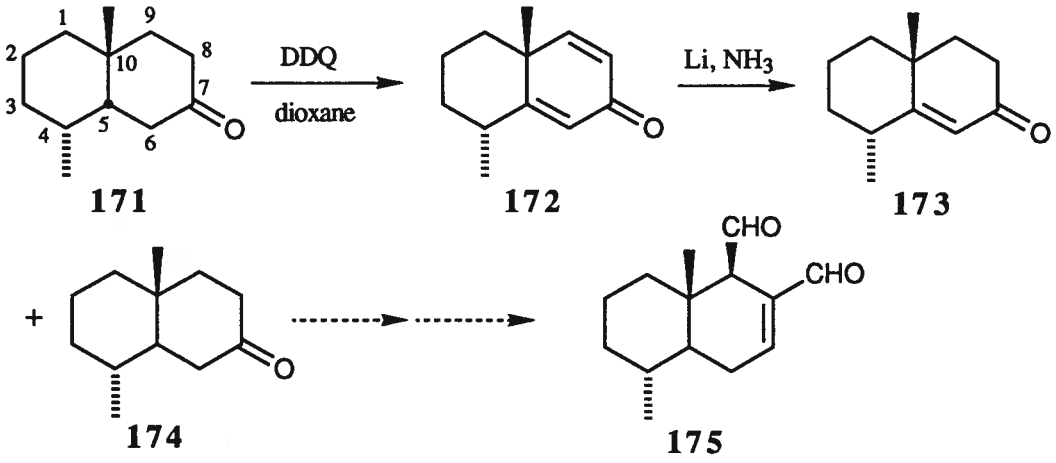
Birch reduction of **172** gave both enone **173** (42%) and the saturated ketone **174** (25%). The double reduction of **172** was probably due to the presence of a trace amount of

* Following the synthetic plan presented there (Section **3.2.1.**), one may also envisage a new route to (-)-polygodial and (-)-warburganal, starting with the *cis*-fused enone **163**.

water which could protonate the enolate of **173**, generated in the initial reduction of the less substituted carbon-carbon double bond, to produce **173** *in situ.* The further reduction of **173** yielded **174.**

The mass spectrum of **173** indicated the molecular ion peak at m/z 178. The IR spectrum showed a conjugated carbonyl stretching absorption at 1660 cm^{-1} and a carbon-carbon double bond stretching absorption at 1610 cm^{-1}. The NMR spectrum displayed a methyl doublet at δ 1.06 (J=6 Hz), a methyl singlet at δ 1.25 ppm, a complex three-proton multiplet corresponding to the allylic C4 proton and the methylene group α to the carbonyl function, and one singlet for the olefinic proton at δ 5.79 ppm.

The saturated ketone **174** had a specific rotation $[\alpha]_D^{25}$=-39.7 (c=1.00, CHCl3), which is in good agreement with the reported value ($[\alpha]_D^{25}$=-39.0, c=1.0, $CHCl_3$)[80]. Its mass spectrum showed the molecular ion peak at m/z 180. In the IR spectrum, the carbonyl stretching absorption appeared at 1702 cm^{-1}. The ^{1}H-NMR spectrum indicated a methyl doublet (J=6 Hz) at δ 0.81 ppm, a methyl singlet at δ 1.05 ppm, and a complex four-proton multiplet at δ 2.00-2.55 ppm corresponding to the two methylene groups α to the carbonyl group.



Scheme 28 A Possible Sequence to a New (-)-Polygodial Analogue

Transformation of **173** and **174** into another (-)-polygodial analogue **175** using a sequence similar to that developed by de Groot (Scheme 3) can be perceived (Scheme 28).

2.3. Experimental

2.3.1. General

Solvents as provided from the Chemistry Store were used for chromatography without further purification. Petroleum ether refers to the fraction boiling in the range of 30-60°C. Anhydrous diethyl ether, tetrahydrofuran, and benzene were prepared by distillation from a mixture containing sodium and benzophenone. Anhydrous methylene chloride, chloroform, and *n*-pentane were prepared by distillation from phosphorus pentoxide. Anhydrous isopropylamine, HMPA, DMF and DMSO were prepared by distillation from calcium hydride and stored in the presence of molecular seives (3 Å) under nitrogen. Anhydrous methanol and ethanol were distilled from magnesium.

Commercial reagents were purified, when necessary, by procedures described in Perrin and Perrin[162]. *n*-Butyllithium, LDA, and vinylmagnesium bromide solutions were standardized by titration against *sec*-butanol in benzene using 1,10-phenanthroline as indicator under nitrogen[165]. Borane in THF and L-Selectride were standardized by measuring hydrogen released from their reaction with 1:1 glycerol:water solution[130]. Thujone was distilled from Western red cedar leaf oil which was generously donated by Intrinsic Research and Development Incorporated.

Syringes and needles were oven-dried at 120°C for a minimum of 4 hours and stored in a desiccator. Unless stated otherwise, all reactions were carried out under a positive pressure of dry nitrogen. Reactions at -78°C, -40°C, -25°C, and 0°C were performed with dry ice/ acetone, dry ice/acetonitrile, dry ice/carbon tetrachloride, and ice/water cooling baths respectively. Air-sensitive materials were transferred inside a glove bag filled with nitrogen during weighing. All glassware was assembled under nitrogen immediately after being oven-dried. Alternatively, it was flame-dried with nitrogen flowing through the reaction setup.

Reactions were monitored by thin layer chromatography (TLC) and/or gas chromatography (GC). Analytical TLC was carried out on aluminium-backed silica gel plates

(Merck Silica Gel 60 F_{254}). Visualization was realized by ultraviolet light and/or by heating after spraying with 10% ammonium molybodate in 10% sulfuric acid. Gas chromatography was performed on a Hewlett-Packard 5890A gas chromatograph, using a flame ionization detector and a 14.5 m x 0.252 mm fused silica capillary column coated with cyanopropyl-phenyl silicone gum (DB 1701). Unless otherwise stated, all reaction products were purified by "flash chromatography" using silica gel (230-400 mesh) supplied by E. Merck Co. with air pressure to obtain a suitable flow[163].

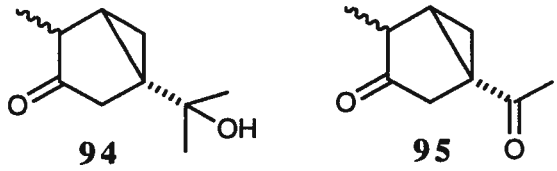
Melting points were measured using a Kofler block melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 automatic polarimeter in chloroform solution using a quartz cell of 10 cm path length with the concentration (in g/100 ml) given in brackets. The ultraviolet spectra were recorded on Cary 15 or Perkin-Elmer Lambda 4B UV/VIS spectrometers using quartz cells of 1 cm path length. The infrared spectra were recorded on Perkin-Elmer 710, 710B, and 1710 spectrometers in chloroform solution using NaCl cells of 0.1 mm path length or as thin film using NaCl plates. The ^{1}H-NMR spectra were obtained from Bruker WH-400, AE-200 or Varain XL-300 spectrometers with duteriochloroform as solvent and the chemical shifts are reported in the delta (δ) scale in ppm relative to tetramethylsilane. The ^{13}C spectra were taken on Bruker AE-200, or XL-300 spectrometers and chemical shifts are reported in the delta (δ) scale in ppm relative to tetramethylsilane. The low and high resolution mass spectra were recorded on AEI-MS-9 or KRATOS-MS-50 spectrometers using the electron impact ionization method while the chemical ionization mass spectra were recorded on a Delsi Nermag R10-1 OC spectrometer using ammonia as carrier gas. CD spectra were recorded on a JASCO J-20 automatic recording spectropolarimeter. Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia. Previously known compounds, some by-products or unstable intermediates may not have elemental analysis. Single Crystal X-ray structure determinations were performed by Dr. S. Rettig on a Rigaku AFC6S or Enraf-Nonius CAD4-F diffractometers.

All compounds are named in accordance with IUPAC and CA rules. For compounds of the tricyclo[4.4.0.0^{7,9}]decane skeleton (i.e., the cyclopra[*a*]indene skeleton), their von Baeyer names are also included in order to facilitate comparison with other similar compounds previously prepared and named by our group. However, the numbering system employed in all Introduction and Discussion sections follows the normal conventions of terpenoid and steroid literature in order to have convenient comparison with natural products and with themselves.

2.3.2. Ozonation: thujone (3) to thujonol (94) and thujonone (95)

[1**R**-(1α,4α/β,5α)] 1-(1-hydroxyl-1-methylethyl)-4-methyl-bicyclo[3.1.0]hexan-3-one (**94**)

[1**R**-(1α,4α/β,5α)] 1-acetyl-4-methyl-bicyclo[3.1.0]hexan-3-one (**95**)



94 **95**

Thujone (**3**) (10.00 g, 65.8 mmol) dissolved in EtOAc (500 ml) was subjected to a stream of ozone-oxygen at -25°C for 10 hours. After the ozonizer was turned off, the gas flow was allowed to continue for 15 minutes to remove the residual ozone. After addition of dimethyl sulfide (5 ml), the reaction mixture was warmed to room temperature with stirring for 15 minutes, washed with water (100 ml) and saturated sodium bicarbonate solution (2X50 ml), and dried over magnesium sulfate. Solvent evaporation *in vacuo* gave an oil which was chromatographed using a mixture of isopropanol:hexanes (3:7) to afford compound **94** (4.70 g, 47%) and **95** (2.32 g, 23%).

The physical properties of **94** are as follows* :

IR (film) νmax.: 3100-3700 (O-H stretching), 1730 (C=O stretching).

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* All spectral data were taken from spectra of the mixture containing α and β diastereomers at a ratio of 10:1 as analyzed by GC. The ^{1}H-NMR spectral signals should be those of the major α diastereomer since they can be

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.11(1H, t, J=4.8 Hz), 1.13 (1H, m), 1.18(3H, d, J=7.6 Hz), 1.22 (3H, s), 1.32 (3H, s), 1.35 (1H, dd, J=4.0 and 8.0 Hz), 1.60 (1H, bs), 2.19 (1H, d, J=16.4 Hz), 2.29 (1H, q, J=7.6 Hz), 2.79 (1H, dm, J=16.4 Hz).

MS m/z: 168 (M^+, 10.0%), 150 (4.0%), 107 (69.5), 43 (100.0%). High resolution mass measurement: calculated for $C_{10}H_{16}O$: 168.1150; found: 168.1146.

The physical properties of **95** are as follows*:

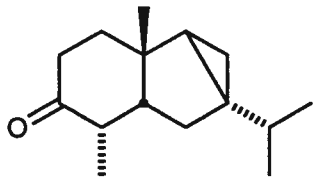
IR (film) $\nu_{max.}$: 1740 (C=O stretching), 1685 (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75 (1H, t, J=4.8), 1.22 (3H, d, J=8.4 Hz), 1.86-1.98 (2H, m), 2.09 (3H, s), 2.30-2.4 1(2H, m), 3.25 (1H, m).

MS m/z: 152 (M^+, 35.0%), 137 (11.0%), 124 (32.0%), 109 (100.0%). High resolution mass measurement: calculated for $C_9H_{12}O$: 152.0837; found:. 152.0839.

2.3.3. Catalytic Hydrogenation: enone 7 to ketone 96

[1a**S**-(1aα,1bβ,5α,5aβ,6aα)] 1a,1b,2,3,5,5a,6,6a-Octahydro-1b,5-dimethyl-6a-(1-methylethyl)cycloprop[*a*] inden-4(1*H*)-one (**96**) or [1**R**,2**S**,6**S**,7**S**,9**R**] 2,6-Dimethyl-9-(1-methylethyl)tricyclo [4.4.0.0^{7,9}.]decan-3-one (**96**)



96

Enone **7** (62.00 g, 282 mmol) was dissolved in ethanol (500 ml). 10% palladium-charcoal catalyst (1.50 g) was added. The mixture was vigorously stirred under 1 atm H_2 for 8 hours and filtered through a thick Celite cake. Evaporation of ethanol gave **96** as a colorless oil (62.06 g, 99.1%).

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readily recognized from the integrations. The signals of the minor β diastereomer were hardly observable from the spectrum. See footnote at p. 28.

The physical properties of **96** are as follows:

$[\alpha]_D^{25}$=+61.5 (c=1.00, $CHCl_3$).

IR (film) νmax.: 3050 (C-H stretching of the cyclopropyl group), 1710 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.20 (1H, J=4.8 and 8.0 Hz), 0.42 (1H, t, J=4.8 Hz), 0.85 (3H, d, J=6.8 Hz), 0.87-1.00 {7H, including 0.91 (3H, d, J=6.8 Hz) and 0.94 (3H, d, J=7.2 Hz)}, 1.10-1.40{5H, m, including 1.24 (3H, s)}, 1.45-1.90 (4H, m), 2.15 (1H, m), 2.42 (1H, m), 2.58 (1H, m).

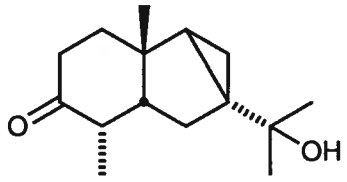
MS m/z: 220 (M^+, 8.0%), 205 (5.1%), 159 (%), 93 (75.2%), 86 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{24}O$: 220.1821; found:. 220.1815.

Elemental analysis: calculated for $C_{15}H_{24}O$: C 81.76, H 10.98; found: C 81.67, H 11.00

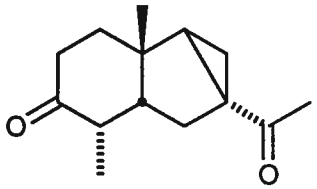
2.3.4. Ozonation: ketone 96 to ketol 97 and dione 98

[1a**R**-(1aα,1bβ,5α,5aβ,6aα)] 1a,1b,2,3,5,5a,6,6a-Octahydro-6a-(1-hydroxyl-1-methylethyl)-Cycloprop[*a*]indene-4(1*H*)-one (**97**) or [1**R**,2**S**,6**S**,7**R**,9**S**] 2,6-Dimethyl-9-(1-hydroxyl-1-methylethyl)tricyclo[4.4.0.$0^{7,9}$.]decan-3-one (**97**)

[[1a**R**-(1aα,1bβ,5α,5aβ,6aα)] 6a-Acetyl-1a,1b,2,3,5,5a,6,6a-octahydro-1,5-dimethyl-cycloprop[*a*]indene-4(1*H*)-one (**98**) or [1**R**,2**S**,6**S**,7**R**,9**S**] 9-Acetyl-2,6-dimethyltricyclo [4.4.0.$0^{7,9}$.]decan-3-one (**98**)



97



98

Method A:

Ketone **96** (1.03 g, 4.68 mmol) in EtOAc (100 ml) was cooled to -40°C. A stream of ozone-oxygen was passed for 10 hours. The oxygen flow continued for another 15 minutes to

remove residual ozone. After dimethyl sulfide (1.0 ml) was added, the mixture was warmed slowly to room temperature with stirring, washed with water (50 ml), saturated sodium bicarbonate solution (2X50 ml), and brine (30 ml), dried palladium. Solvent evaporation gave an oil which was chromatographed with isopropanol:hexanes (1:10) to give compounds **97** (0.42 g, 40%) and **98** (0.27 g, 28%) in a total yield 68% in addition to starting material **96** (0.06 g, 6%).

Method B:

Compound **122** (100 mg, o.427 mmol) in ethanol (10 ml) was treated with 10% palladium-charcoal catalyst (10 mg) and stirred under 1 atm hydrogen for 1 hour. Filtration of the reaction mixture and concentration of the filtrate gave compound **97** (95 mg, 95%) as an oil.

The physical properties of **97** are as follows:

m.p.: 45-47°C.

$[\alpha]_D^{25}$=+1.36X10^2 (c=1.00, $CHCl_3$).

IR (film) $\nu_{max.}$: 3000-3650 (O-H stretching), 3050 (C-H stretching of the cyclopropyl group), 1710 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.42 (1H, t, J=4.4), 0.62 (1H, dd, J=4.4 and 8.0), 0.95 (3H, d, J=6.4), 1.10-1.35 {10H, including 1.15(3H, s), 1.23 (3H, s) and 1.26 (3H, s)}, 1.41(1H, m), 1.59(1H, bs), 1.65-1.95 (4H, m), 2.21 (1H, m), 2.44 (1H, m), 2.61 (1H, m).

MS m/z: 236 (M^+, 2.3%), 218 (17.8%), 203(10.7%), 178 (35.4%), 161 (24.5%), 147 (26.0%0,133 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{24}O_2$: 236.1776; found:. 236.1778.

The physical properties of **98** are as follows:

m.p.: 100-102°C.

$[\alpha]_D^{25}$=+1.72X10^2 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3020 (C-H stretching of the cyclopropyl group), 1713 (C=O stretching), 1680 (conjugated C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.99 (3H, d, J=7.2), 1.05 (1H, t, J=6.0), 1.31 (3H, s), 1.38 (1H, dd, J=6.0 and 8.8), 1.65-2.02 (8H, m), 2.06 (3H, s), 2.17 (1H, m), 2.44 (1H, m), 2.62 (1H, m).

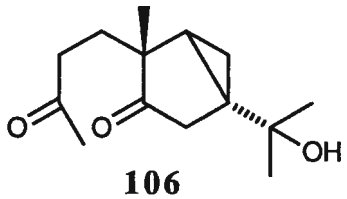
MS m/z: 220 (M^+, 15.3%), 205 (3.2%), 192 (5.1%), 177 (10.4%), 43 (100.0%). High resolution mass measurement: calculated for $C_{14}H_{22}O_2$: 220.1463; found:. 220.1461.

Elemental Analysis: calculated for $C_{14}H_{22}O_2$: C 76.33, H 9.15; found: C 76.28, H 9.13.

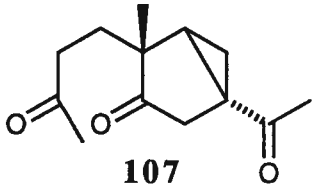
2.3.5. Ozonation: dione 105 to hydroxydione 106 and trione 107

[1**R**-(1α,4α,5α)] 1-(1-Hydroxyl-1-methylethyl)-4-methyl-4-(3-oxobutyl)-bicyclo[3.1.0]hexan-3-one (**106**)

[1**R**-(1α,4α,5α)] 1-Acetyl-4-methyl-4-(3-oxobutyl)-bicyclo[3.1.0]hexan-3-one (**107**)



106



107

Diketone **105** (1.00 g, 4.50 mmol) in ethyl acetate (100 ml) was cooled to -25°C and passed with a stream of ozone-oxygen for 10 hours. After the continuation of oxygen flow for another 15 minutes, the mixture was treated with dimethyl sulfide (1.0 ml) and warmed slowly to room temperature. Washing with water and saturated sodium bicarbonate solution and evaporation of solvent gave an oil which was chromatographed with a mixed solvent system isopropanol:hexanes (3:7) to give **106** (0.39 g, 36%) and **107** (0.28 g, 28%).

Compound **106** was also prepared from ketol **94** in the following way:

The solution of thujonol **94** (52 mg, 0.31 mmol) in toluene (5.0 ml) was mixed with distilled water (5.0 ml), methyl vinyl ketone (77 µl, 0.93 mmol), potassium hydroxide (93 mg, ~80% pure, 1.3 mmol), and tetrabutylammonium iodide (28 mg, 0.076 mmol) under nitrogen. This mixture was stirred for 10 hours at room temperature. After the mixture was saturated with sodium chloride, the organic layer was separated and concentrated to give a yellowish oil. Column chromatography of this oil afforded compound **106** (45 mg, 62%).

The physical properties of **106** are as follows:

$[\alpha]_D^{25}$=-44.7 (c=1.09, $CHCl_3$).

IR (film) $\nu_{max.}$: 3450 (O-H stretching), 1730, 1710 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.00 (1H, m), 0.96 (1H, m), 1.00 (3H, s), 1.17 (3H, s), 1.33 (3H, s), 1.41 (1H, dd, J=4.2 and 8.4 Hz), 1.59 (1H, bs), 1.77 (2H, m), 2.10-2.25 {4H, including 2.15 (3H, s)}, 2.51 (2H, m), 2.97 (1H, m).

MS m/z: 238 (M^+, 0.2%), 220 (4.0%), 202 (1.4%), 43 (100.0%). High resolution mass measurement: calculated for $C_{14}H_{22}O_3$: 238.1569; found: 238.1568.

The physical properties of **107** are as follows:

$[\alpha]_D^{25}$=+15.5 (c=1.03, $CHCl_3$).

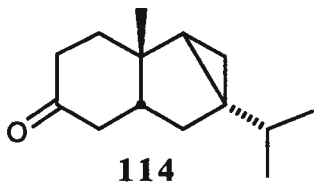
IR (film) $\nu_{max.}$: 1735 (cyclopentanone C=O stretching), 1705 (aliphatic C=O stretching), 1680 (conjugated C=O stretching).cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.62 (1H, t, J=5.6 Hz), 1.04 (3H, s), 1.70-1.90 (3H, m), 2.03 (1H, dd, J=5.6 and 8.6 Hz), 2.09 (3H, s), 2.12 (3H, s), 2.30-2.45 (3H, m), 3.30 (1H, dd, J=2.4 and 19.0 Hz).

MS m/z: 222 (M^+, 11.6%), 207 (1.7%), 179 (11.9%), 164 (100.0%). High resolution mass measurement: calculated for $C_{13}H_{18}O_3$: 222.1256; found: 222.1261.

2.3.6. Catalytic Hydrogenation: enone 113 to ketone 114

[1aS-(1aα,1bβ,5aβ,6aα)] 1a,1b,2,3,5,5a,6,6a-Octahydro-1b-methyl-6a-(1-methylethyl)-cycloprop[*a*]inden-4(1*H*)-one (**114**) or [1**R**,6**S**,7**S**,9**R**] 6-Methyl-9-(1-methylethyl)tricyclo [4.4.0.$0^{7,9}$.]decan-3-one (**114**)



114

Enone **113** (0.45 g, 2.2 mmol) in methylene chloride (20 ml) was treated with 5% palladium-charcoal (0.76 g) at room temperature. The mixture was stirred under 1 atm hydrogen for 12 hours, filtered, and concentrated *in vacuo*. Ketone **114** was obtained in 90% yield (0.41 g).

The physical properties of **114** are as follows:

IR (film) $\nu_{max.}$: 3040 (C-H stretching), 1710 (C=O stretching) cm^{-1}.

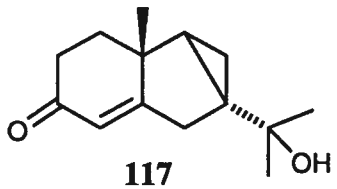
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.23 (1H, dd, J=4.8 and 8.0 Hz), 0.45 (1H, t, J=4.8 Hz), 0.80-0.99 {7H, m, including 0.86 (3H, d, J=6.4 Hz), 0.93 (3H, d, J=6.4 Hz)}, 1.20 (3H, s), 1.25-1.50 (2H, m), 1.60-1.95 (4H, m), 2.10-2.25 (2H, m), 2.30-2.55 (2H, m).

MS m/z: 206 (M^+, 23.4%), 191 (6.3%), 188 (10.6%), 173 (16.7%), 163 (38.6%), 93 (100.0%).

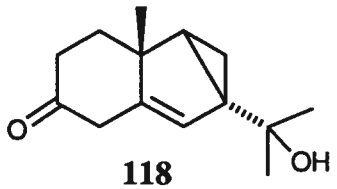
2.3.7. Aldol Condensation: hydroxydione 106 to hydroxyenones 117 and 118

[1a**R**-(1aα,1bβ,5aβ,6aα)] 1a,1b,2,3,6,6a-Hexahydro-6a-(1-hydroxyl-1-methylethyl)-1b-methyl-cycloprop[*a*]inden-4(1*H*)-one (**117**) or [6**R**,7**R**,9**R**] 9-(1-Hydroxyl-1-methylethyl-6-methyl)tricyclo [4.4.0.$0^{7,9}$.]dec-1(10)-en-3-one (**117**)

[1a**R**-(1aα,1bβ,5aβ,6aα)] 1a,1b,2,3,5,6a-Hexahydro-6a-(1-hydroxyl-1-methylethyl)-1b-methyl--cycloprop[*a*]inden-4(1*H*)-one (**118**) or [6**R**,7**S**,9**R**] 9-(1-Hydroxyl-1-methylethyl)-6-methyltricyclo [4.4.0.$0^{7,9}$.]dec-1(10)-en-3-one (**118**)



117



118

Compound **106** (1.94 g, 8.15 mmol) in benzene (50 ml) was treated with pyrrolidine (0.82 ml, 9.8 mmol) and refluxed for 5 hours with a dean-stark trap . Concentration *in vacuo* gave a brown viscous oil which was chromatographed with ethyl acetate:hexanes mixture (1:1, v/v) to provide **117** (0.54 g, 30%) and **118** (0.79 g, 44%) in a total yield 74%.

The physical properties of **117** are as follows:

$[\alpha]_D^{25}$=+119 (c=1.00, $CHCl_3$).

UV (MeOH, c=20.0 mg/l) $\lambda_{max.}$: 234 nm (log ε=4.211).

IR (film) $\nu_{max.}$: 3420 (O-H stretching), 3050 (C-H stretchings of cyclopropyl group), 1655 (conjugated C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.80 (1H, J=4.4 Hz), 1.12 (3H, s), 1.20 (6H, s), 1.32 (1H, dd, J=4.4 and 8.8 Hz), 2.00-2.85 (6H, m), 5.60 (1H, bs).

MS m/z: 220 (M^+, 0.8%), 202 (9.1%), 57 (34.7%), 43 (100.0%) High resolution mass measurement: calculated for $C_{14}H_{20}O_2$: 220.1463; found: 220.1464.

The physical properties of **118** are as follows:

m.p.=70-71°C.

$[\alpha]_D^{25}$=+61 (c=0.58, $CHCl_3$).

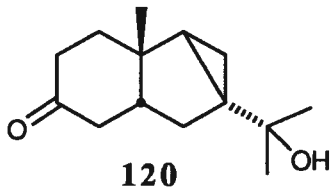
IR ($CHCl_3$) $\nu_{max.}$: 3450 (O-H stretching), 1702 (C=O stretching), 1642 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.34 (1H, t, J=4.4 Hz), 1.06 (1H, dd, J=4.4 and 8.2 Hz), 1.19 (3H, s), 1.25 (3H, s), 1.27 (3H, s), 1.50-1.70 (2H, m), 1.87 (1H, m), 2.35-2.65 (2H, m), 2.80-3.10 (2H, m), 5.53 (1H, d, J=1.2 Hz).

MS m/z: 220 (M^+, 3.5%), 202 (23.3%), 187 (15.0%), 43 (100.0%). High resolution mass measurement: calculated for $C_{14}H_{20}O_2$: 220.1463; found: 220.1471.

2.3.8. Catalytic Hydrogenation: hydroxyenones 117 and 118 to ketol 120

[1a**R**-(1aα,2β,5aβ,6aα)] 1a,1b,2,3,5,5a6,6a-Octahydro-6a-(1-hydroxyl-1-methylethyl)-1b-methylcycloprop[*a*]inden-4(1*H*)-one (**120**) or [1**R**,6**S**,7**R**,9**S**] 9-(1-Hydroxyl-1-methylethyl)-9-methyltricyclo [4.4.0.$0^{7,9}$.]decan-3-one (**120**)



120

To enones **117** and **118** (536 mg, 2.44 mmol) in ethanol (20 ml) solution was added 10% palladium on charcoal catalyst (130.3 mg). The mixture was then stirred under 1 atm hydrogen (1 atm) for 1.2 hours. After the mixture was filtered through a layer of Celite and washed with additional ethanol (20 ml), the solution was concentrated *in vacuo*. Column chromatography of the crude oil with hexanes:ethyl acetate (1:1) gave ketol **120** (519 mg, 96.0%).

The physical properties of **120** are as follows:

$[\alpha]_D^{25}$=+61.8 (c=1.00, $CHCl_3$).

IR (film) $\nu_{max.}$: 3100-3700 (O-H stretching), 1710 (C=O stretching) cm^{-1}.

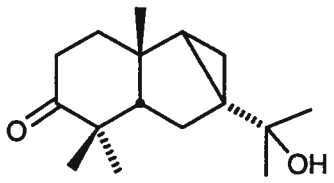
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.44 (1H, dd, J=4.0 and 5.4 Hz), 0.63 (1H, ddd, J=1.2, 5.4, and 8.6 Hz), 1.06 (1H, bs), 1.10-1.30 {(10H, m, including 1.14 (3H, s), 1.21 (3H, s)

and 1.25 (3H, s)}, 1.63 (1H, m), 1.72-1.92 (4H, m), 2.12-2.25 (2H, m), 2.35-2.52 (2H, m).

MS m/z: 222 (M^+, 1.4%), 204 (16.9%), 189 (13.5%), 133 (74.9%), 59 (100.0%). High resolution mass measurement: calculated for $C_{14}H_{22}O_2$: 222.1620; found:. 222.1618.

2.3.9. Methylation: ketol 97 and 120 to ketol 121

[1a**R**-(1aα,1bβ,5aβ,6aα)] 1a,1b,2,3,5,5a,6,6a-Octahydro-6a-(1-hydroxyl-1-methylethyl)-1b,5,5,trimethyl-cycloprop[*a*]inden-4(1*H*)-one (**121**) or [1**S**,6**R**,7**R**,9**R**] 9-(1-Hydroxyl-1-methylethyl)-2,2,6-trimethyltricyclo [4.4.0.$0^{7,9}$.]decan-3-one (**121**)



121

Method A:

To the solution of ketol **120** (50 mg, 0.23 mmol) in anhydrous *t*-butanol (2.0 ml) was added potassium *t*-butoxide (174 mg, 1.42 mmol) and iodomethane (85 µl, 1.4 mmol). The mixture was then refluxed under nitrogen for 2 hours, cooled, and quenched with water (10 ml). Extraction with diethyl ether (2X10 ml), drying with magnesium sulfate, and evaporation of solvent *in vacuo* gave an oil which was chromatographed to afford **121** (33 mg, 62%).

Method B:

Ketol **97** (48 mg, 0.20 mmol) in *t*-butanol (2.0 ml) was treated with potassium *t*-butoxide (124 mg, 1.01 mmol) and iodomethane (65 µl, 1.0 mmol) under nitrogen. The mixture was refluxed for 1.5 hours, cooled down, and quenched with water (10 ml). Extraction with diethyl ether (2X10 ml), drying with magnesium sulfate, and evaporation of

ether *in vacuo* provided an oil which was chromatographed with ethyl acetate:hexanes mixture (3:7, v/v) to give **121** (41 mg, 81%).

The physical properties of **121** are as follows:

$[\alpha]_D^{25}$=-19.2 (c=0.0832, dioxane).

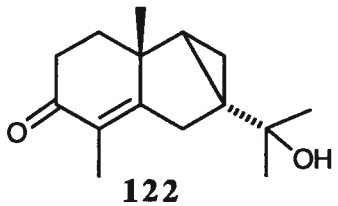
IR $\nu_{max.}$ (film): 3100-3650 (O-H stretching), 1705 (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.41 (1H, dd, J=4.8 Hz), 0.58 (1H, dd, J=4.8 and 7.8 Hz), 1.05-1.40 {18H, m, including 0.96 (3H, s), 1.12 (3H, s), 1.22 (3H, s) , 1.24 (3H, s) and 1.34 (3H, s)}, 1.46-1.62 (2H, m), 1.75-1.90 (2H, m), 2.17 (1H, m), 2.70 (1H, m).

MS m/z: 250 (M^+, 1.7%), 235 (9.4%), 232 (3.7%), 217 (6.4%), 192 (30.5%), 177 (18.1%), 133 (47.1%), 59 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{26}O_2$: 250.1934; found: 250.1936.

2.3.10. Robinson Annulation: thujonol (94) to hydroxyenone 122

[1a**R**-(1aα,1bβ,6aα)] 1a,1b,2,3,6,6a-Hexahydro-6a-(1-hydroxyl-1-methylethyl)-1b,5-dimethyl-cycloprop[*a*]inden-4(1*H*)-one (**122**) or [6**R**,7**R**,9**R**] 9-(1-hydroxyl-1-methylethyl)-2,6-dimethyltricyclo [4.4.0.0^{7,9}.]dec-1(2)-en-3-one (**122**)



122

To 1-dimethylaminopentan-2-one~iodomethane salt (2.84 g, 9.44 mmol) in ethanol (80 ml) was added the solution of ketol **94** (1.43 g, 8.51 mmol) in ethanol (20 ml). After potassium hydroxide (0.92 g, ~80% pure, 13 mmol) was added, the mixture was refluxed under nitrogen for 3 hours. Concentration of the reaction mixture *in vacuo* gave a yellow oil

which was chromatographed using ethyl acetate:hexanes mixture (1:1, v/v) to provide compound **122** as a colorless oil (636 mg, 32%).

The physical properties of **122** are as follows:

$[\alpha]_D^{25}$=+90.3 (c=2.03, $CHCl_3$).

UV (MeOH, c=40.6 mg/l) $\lambda_{max.}$: 248 nm (logε=4.04).

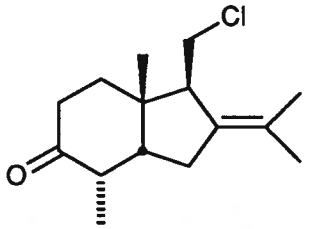
IR (film) $\nu_{max.}$: 3200-3600 (O-H stretching), 1645 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.76 (1H, t, J=4.7 Hz), 1.11 (3H, s), 1.20 (6H, s), 1.67 (3H, s) ppm.

MS m/z: 234 (M^+, 1.2%), 216 (31.5%), 201 (48.0%), 173 (34.7%), 59 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{22}O_2$: 234.1619; found: 234.1613.

2.3.11. Cyclopropane Ring Opening Reaction: ketol 97 to chloroketone 123

[1**R**-(1α,3aα,4β,7aα)] 3,3a,4,6,7,7a-Hexahydro-1-chloromethyl-4,7a-dimethyl-2(1*H*)-(1-methylethylidene)-5*H*-inden-5-one (**123**)



123

Ketol **97** (78 mg, 0.33 mmol) in methylene chloride (5.0 ml) was stirred with concentrated hydrochloric acid (5.0 ml) at room temperature for 30 minutes. Water (20 ml) was added to quench the reaction. After methylene chloride extraction (2X10 ml), drying over magnesium sulfate, and evaporation of solvent *in vacuo*, the crude product was chromatographed with ethyl acetate:hexanes mixture (1:8, v/v) to afford the starting ketol **97** (15 mg, 19%) and chloride **123** (51 mg, 74%).

The physical properties of **123** are as follows:

$[\alpha]_D^{25}$=+1.4X10^2 (c=0.50, $CHCl_3$).

IR $\nu_{max.}$ (film): 1700, 1641 cm^{-1}.

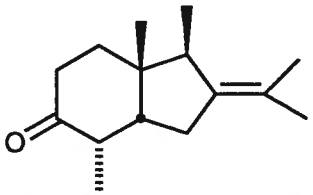
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, d, J=7.0 Hz), 1.05 (1H, m), 1.24 (1H, m), 1.44 (3H, s), 1.58-1.80 {7H, including 1.60 (3H, s) and 1.71 (3H, s)}, 2.10 (6H,m), 3.45-3.65 (2H, m).

MS m/z: 256/254 (M^+, 0.6%/2.2%), 239 (0.5%), 218 (34.6%), 203 (18.4%), 133 (85.0%), 41 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{23}O^{35}Cl$: 254.1437, found: 254.1437; calculated for $C_{15}H_{23}O^{37}Cl$: 256.1408, found: 256.1412.

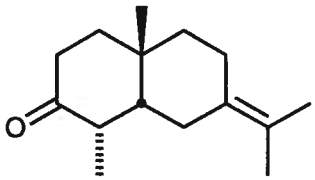
2.3.12. Radical-mediated Rearrangement: chloroketone 123 to enones 125 and 126

[1**R**-(1α,3aα,4β,7aα)] 3,3a,4,6,7,7a-Hexahydro-1,4,7a-trimethyl-2(1*H*)-(1-methyl-ethylidene)-5*H*-inden-5-one (**125**)

[1**S**-(1α,4aβ,8aβ)] 4,4a,5,6,8,8a-Hexahydro-1,4a-dimethyl-7(3*H*)-(1-methylethylidene)-naphthalen-2(1*H*)-one (**126**)



125



126

Chloride **123** (50.4 mg, 0.198 mmol) in benzene (20 ml) was treated with tributyltin hydride (82 μl, 0.30 mmol, 1.5 eqv.) and AIBN (3.2 mg, 0.019 mmol, 0.10 eqv.) under nitrogen. This mixture was then refluxed for 2 days. Concentration *in vacuo* gave the crude product which was chromatographed with ethyl acetate:hexanes mixture (1:8) to afford **126**

(19.9 mg) and **125** (7.1 mg) in a total yield 80%, based on the recovery of chloride **123** (12.0 mg).

The physical properties of **126** are as follows:

m. p.=85°C.

$[\alpha]_D^{25}$=-23.9 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ ($CHCl_3$): 1700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90-2.00 {17H, m, including 1.02 (3H, d, J=), 1.26 (3H, s), 1.64 (3H, s) and 1.66 (3H, s)}, 2.20-2.65 (6H, m), 2.93 (1H, m).

MS m/z: 220 (M^+, 44.4%), 203 (8.2%), 187 (8.7%), 148 (47.3%), 135 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{24}O$: 220.1827; found:. 220.1822.

The physical properties of **125** are as follows:

$[\alpha]_D^{25}$=+35 (c=0.94, $CHCl_3$).

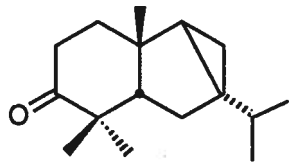
IR $\nu_{max.}$ (film): 1710 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.80-2.00{ 18H, m, including 0.92 (3H, d, J=), 0.99 (3H, d, J=), 1.22 (3H, s), 1.54 (3H, s), 1.64 (3H, s)}, 2.10 (4H, m), 2.50 (1H, m), 2.57 (1H, m).

MS m/z: 220 (M^+, 23.5%), 205 (8.2%), 187 (4.9%), 175 (11.4%), 163 (50.3%), 135 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{24}O$: 220.1827; found: 220.1822.

2.3.13. Methylation: ketone 96 to ketone 119

[1a**S**-(1aα,1bβ,5aβ,6aα)] 1a,1b,2,3,5,5a,6,6a-Octahydro-1b,5,5-trimethyl-6a-(1-methylethyl)-cycloprop[*a*]inden-4(1H)-one (**119**) or [1**S**,6**R**,7**S**,9**S**] 2,2,6-triimethyl-9-(1-methylethyl)tricyclo [4.4.0.$0^{7,9}$.]decan-3-one (**119**)



119

To the solution of ketone **96** (62.0 g, 0.282 mol) in anhydrous *t*-butanol (700 ml) was added potassium *t*-butoxide (130.5 g, 1.07 mol) slowly under nitrogen. Iodomethane (66.6 ml, 1.07 mol) was added in a dropwise manner with stirring to ensure a gentle reflux. Upon finishing the addition, refluxing continued for 30 minutes. The mixture was cooled down, quenched with water (700 ml), extracted with petroleum ether (3X500 ml). evaporation of solvent gave an oil which was chromatographed to provide the methylated ketone **119** (55.1 g, 84%).

The physical properties of **119** are as follows:

$[\alpha]^{25}_{365nm}$=+14.0 (c=0.993, $CHCl_3$); $[\alpha]^{25}_{D}$=0.00 (c=0.993, $CHCl_3$).

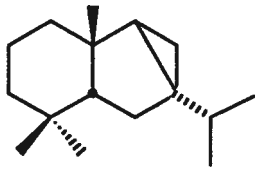
IR $\nu_{max.}$ (film): 3060, 1700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.18 (1H, dd, J=4.0 and 8.0 Hz), 0.40 (1H, t, J=4.0 Hz), 0.80-0.88 {4H, m, including 0.85 (3H, d, J=7.2 Hz)}, 0.90 (3H, d, J=7.2 Hz), 0.97 (3H, s), 1.22 (3H, s), 1.25-1.50 {6H, m, including 1.32 (3H, s)}, 1.65-1.90 (3H, m), 215 (1H, td, J=4.4 and 15.2 Hz), 2.70 (1H, m).

MS m/z: 234 (M, 55.8%), 219 (14.3%), 201 (22.0%), 191 (29.9%), 173 (51.1%), 43 (100.0%). High resolution mass measurement calculated for $C_{16}H_{26}O$: 234.1983; found: 234.1986.

2.3.14. Wolf-Kishner-Huang Minlon Reaction: ketone 119 to alkane 128

[1a**S**-(1aα,1bβ,5aβ,6aα)] Decahydro-1b,5,5-trimethyl-6a-(1-methylethyl)-cycloprop[*a*]indene (**128**) or [1**R**,6**S**,7**S**,9**R**] 9-(1-Methylethyl)-2,2,6-trimethyltricyclo [4.4.0.0^{7,9}.]decane (**128**)



128

Ketone **119** (42.0 g, 180 mmol) in diethylene glycol (300 ml) was treated with potassium hydroxide (37.0 g, ~80% pure, 528 mmol) and hydrazine monohydrate (26.8 ml, 552 mmol). The mixture was heated at 100°C for 1.5 hours under nitrogen. The temperature was then raised to 220°C to distill away water and excess hydrazine. Refluxing continued at 210°C for 4 hours. The mixture was cooled down, diluted with water (1 l), and extracted with petroleum ether (3X600 ml). Evaporation of the solvent gave a brown oil which was chromatographed with petroleum ether through a short column gave **128** as a colorless oil (24.50 g, 62%).

The physical properties of **128** are as follows:

$[\alpha]_D^{25}$=+42.5 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3060 cm^{-1}.

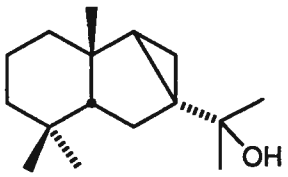
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.04 (1H, dd, J=4.6 and 8.4 Hz), 0.40 (1H, t, J=4.6 Hz), 0.72-0.82 {4H, including 0.78 (3H, s)}, 0.82-1.65 {22H, including 0.88 (3H, d, J=7.2 Hz), 0.95 (3H, d, J=7.2 Hz), 0.98 (3H, s) and 1.07 (3H, s)}.

MS m/z: 220 (M^+, 3.4%), 205 (10.3%), 177 (45.5%), 109 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{28}$: 220.2191; found: 220.2198.

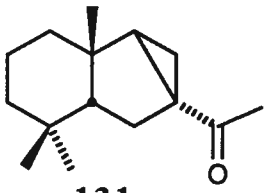
2.3.15. Ozonation: alkane 128 to alcohol 130 and ketone 131

[1a**R**-(1aα,2aβ,5aβ,6aα)] Decahydro-α-hydroxy-α,α,1b,5,5-pentamethylcycloprop[*a*] inden -6a-methanol (**130**) or [1**R**,6**S**,7**R**,9**S**] 9-(1-Hydroxyl-1-methylethyl)-2,2,6-trimethyltricyclo [4.4.0.$0^{7,9}$.]decane (**130**)

[1aR-(1aα,2aβ,5aβ,6aα)] 6a-Acetyl-decahydro-1b,5,5-trimethylcycloprop[*a*]indene (**131**) or [1R,6S,7R,9S] 9-Acetyl-2,2,6-trimethyltricyclo [4.4.0.$0^{7,9}$.] decan-3-one (**131**)



130



131

Compound **128** (4.50 g, 20.4 mmol) in ethyl acetate (500 ml) was cooled to -40°C. A stream of ozone in oxygen (90 volts, flow rate 9.1 ml/sec) was passed for 6.5 hours. The oxygen flow continued to pass the solution till the blue color disappeared. Dimethyl sulfide (1.0 ml) was added and the mixture was warmed slowly to room temperature with stirring. After washed with water and saturated sodium bicarbonate solution, the mixture was dried with magnesium sulfate. Solvent evaporation gave an oil which was chromatographed to afford compounds **130** (2.01 g, 42%) and **131** (1.23 g, 27%) in a total yield 69%.

The physical properties of **130** are as follows:

$[\alpha]_D^{25}$=+49.2 (c=0.995, $CHCl_3$).

IR $\nu_{max.}$ (film): 3 400 (O-H stretching), 3060 (C-H stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.40-0.55 (2H, m), 0.72 (3H, s), 0.80-1.90 {23H, including 0.92 (3H, s), 1.05 (3H, s), 1.10 (3H, s) and 1.19 (3H, s)}.

MS m/z: 236 (M^+, 1.0%), 218 (35.8%), 203 (26.9%), 178 (41.3%), 163 (59.5%), 59 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{28}O$: 236.2140; found: 236.2140.

Elemental analysis: calc. for $C_{16}H_{28}O$: C 81.29, H 11.94; found: C 81.23, H 12.00.

The physical properties of **131** are as follows:

$[\alpha]_D^{25}$=+82 (c=0.24, $CHCl_3$).

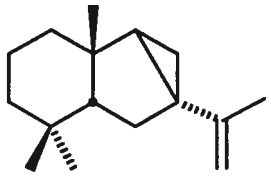
IR $\nu_{max.}$ (film): 1675 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, s), 1.00 (3H, s), 1.05 (1H, m), 1.10-1.70 {12H, m, including 1.15 (3H, s)}, 1.80 (1H, dd, J=4.0 and 12.0 Hz), 2.00 (3H, s), 2.20 (1H, t, J=12.0 Hz).

MS m/z: 220 (M^+, 33.6%), 205 (16.5%), 177 (17.0%), 109 (33.9%), 43 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{24}O$: 220.1827; found: 220.1825.

2.3.16. Dehydration: alcohol 130 to alkene 138

[1a**R**-(1aα,1bβ,5aβ,6aα)] Decahydro-1b,5,5-trimethyl-6a-(1-methylethenyl)-cycloprop[*a*] indene (**138**) or [1**R**,6**S**,7**R**,9**S**] 9-(1-methylethenyl)-2,2,6-trimethyltricyclo [4.4.0.$0^{7,9}$.] decane (**138**)



138

To the alcohol **130** (171 mg, 0.724 mmol) in benzene (15.0 ml) solution was added pyridinium tosylate (28 mg, 0.11 mmol, 0.15 eqv.). The mixture was refluxed with a Dean-Stark trap on for 15 minutes. After the reaction mixture was washed with saturated sodium bicarbonate solution (10 ml), the organic layer was separated and concentrated in *vacuo*. Column chromatograghy by ethyl acetate:hexanes mixture (8:1, v/v) gave the vinyl cyclopropane **138** (127 mg, 91%) and the starting alcohol **130** (20.0 mg, 11.7%).

The physical properties of **138** are as follows:

$[\alpha]_D^{25}$=+87.9 (c=1.09, $CHCl_3$).

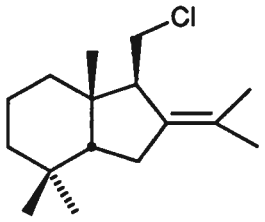
IR $\nu_{max.}$ (film): 3075, 1650 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.52 (1H, dd, J=4.8 and 8.8 Hz), 0.68 (1H, t, J=4.8 Hz), 0.81 (3H, s), 1.00 (3H, s), 1.02-1.58 {11H, m, including 1.13 (3H, s)}, 1.65 (3H, s), 1.70-1.92 (2H, m), 4.65-4.85 (2H, two broad singlets).

MS m/z: 218 (M^+, 26.5%), 203 (23.2%), 189 (4.2%), 175 (20.9%), 147 (31.3%), 147 (51.3%), 109 (100.0%). High resolution mass measurement calculated for $C_{16}H_{26}$: 218.2035; found: 218.2030.

2.3.17. Cyclopropane Ring Opening Reaction: alcohol 130 to chloride 132

[1R-(1α,3aα,7aβ)] 3a,4,5,6,7,7a-Hexahydro-1-chloromethyl-2(3*H*)-(1-methylethylidene)-4,4,7a-trimethyl-1*H*-indene (**132**)



132

Alcohol **130** (100 mg, 0.420 mmol) in methylene chloride (5.0 ml) was stirred with concentrated hydrochloric acid (5.0 ml) at room temperature for 30 minutes. Separation and concentration of the methylene layer gave the crude product which was chromatographed with ethyl acetate:hexanes (1:8, v/v) to afford **132** as a colorless oil (92 mg, 85%).

The physical properties of **132** are as follows:

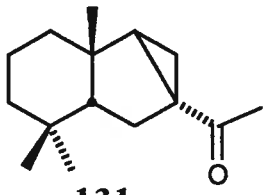
$[\alpha]_D^{25}$=+33.5 (c=1.00, $CHCl_3$).

IR νmax (film): 2910 (C-H stretching).

^{1}H-NMR (400 MHz, CDCl3) δ: 0.75-1.85 {22H, m, including 0.84 (3H, s), 1.04 (3H, s), 1.22 (3H, s), 1.63 (3H, s) and 1.70 (3H, s), 2.04-2.55 (3H, m), 3.40-3.75 (2H, m).

MS m/z: 256/254 (M^+, 4.8/14.8%), 241 (12.8%), 239 (37.6%), 203 (96.4%), 109 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{27}{}^{37}Cl$: 256.1772, found: 256.1763; calculated for $C_{16}H_{27}{}^{35}Cl$: 254.1801, found: 254.1801.

2.3.18. Ozonolysis: alkene 138 to ketone 131



131

Method A:

To a solution of vinylcyclopropane **138** (200 mg, 0.917 mmol) in a mixture solvent *t*-BuOH:water (9.0 ml, 2:1, v/v) was added potassium permanganate (436 mg, 2.76 mmol) at room temperature; the dark purple solution was stirred first at room temperature for 40 minutes.and then at 40°C for 10 minutes. Afterwards, the mixture was diluted with water (20.0 ml) and extracted with ethyl acetate (2x25ml). The combined extract was washed with brine (10 ml) and concentrated *in vacuo*.

The oil obtained above was then dissolved in methanol (10 ml) and treated with $Pb(OAc)_4$ (313 mg, 0.706 mmol) for 1 hour at room temperature. After concentration *in vacuo*, the crude product was column chromatographed using ethyl acetate:hexanes mixture (1:8, v/v) to give the starting vinylcyclopropane **138** (4.1 mg, 2.0%) and ketone **131** (180 mg, 91% based on recovery).

Method B:

A stream of ozone was passed through a solution of vinylcyclopropane **138** (117 mg, 0.536 mmol) in methylene chloride (5.0 ml) at -40°C for 30 minutes. After the addition of dimethyl sulfide (2.0 ml), the mixture was warmed up slowly and then stirred at room

temperature for two days. Concentration of the reaction mixture *in vacuo* gave a crude product which was chromatograghed with ethyl acetate:hexanes mixture (1:8, v/v) to provide ketone **131** (73 mg, 62%).

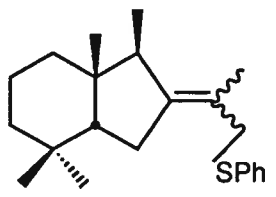
2.3.19. Nucleophilic Addition by MeLi: ketone 131 to alcohol 130

To compound **131** (91 mg, 0.41 mmol) in anhydrous THF (2.0 ml) was added methyl lithium (1.40 M, THF) in a dropwise manner at -40°C with bipyridyl as the indicator till an orange color was observed persistently. The mixture was warmed to room temperature, stirred for an additional 60 minutes, quenched with water (15 ml), and extracted with diethyl ether (2X15 ml). The ether solution was dried over magnesium sulfate. Solvent evaporation gave an oil which was chromatographed with ethyl acetate:hexanes mixture (1:8, v/v) to provide alcohol **130** as a colorless oil.(65.5 mg, 75% based on recovery of starting material) and the starting compound **131** (9.1 mg, 10%).

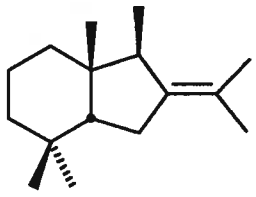
2.3.20. Conversion of 138 to 133 via 139

[1**R**-(1α,3aα,7aα)] 3a,4,5,6,7,7a-Hexahydro-1,4,4,7a-tetramethyl-2(3*H*)-(1-methyl ethylidene)-1*H*-indene (**133**)

[1**R**-(1α,3aα,7aα)] 3a,4,5,6,7,7a-Hexahydro-1,4,4,7a-tetramethyl-2-(1-(phenylthiomethyl)ethylidene-1*H*-indene (**139**)



139



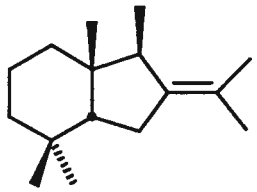
133

The mixture of vinylcyclopropane **138** (50.5 mg, 0.23 mmol) and thiophenol (50 µl, 0.49 mmol, 2.0 eqv.) in benzene (2.0 ml) was refluxed for 24 hours under nitrogen. This mixture was concentrated and chromatographed to give the starting vinyl cyclopropane

mixture was concentrated and chromatographed to give the starting vinyl cyclopropane **138** (10.1 mg, 20%) and and a polar fraction containing **139** (mg).

The concentrated polar fraction was dissolved in THF (2.0 ml). To this solution was distilled ammonia (~3 ml) under nitrogen. Small pieces of lithium were added with stirring till a dark blue color persisted. The reaction mixture was then treated with ammonium chloride, filtered, and concentrated to provide a crude product. The crude product was purified by column chromatography to afford a mixture (28 mg, 69%) containing **133** and **128** (2.3:1) as indicated by GC.

2.3.21. Reduction by Bu_3SnH: chloride 132 to alkene 133



133

Homoallylic chloride **132** (50.2 mg, 0.197) in benzene (19 ml) was treated with tributyltin hydride (66 µl, 0.24 mmol, 1.2 eqv.) and AIBN (3.2 mg, 0.19 mmol, 0.15 eqv.) under nitrogen. The mixture was refluxed for 2 days. Evaporation of the solvent gave an oil which was then chromatographed with hexanes to give hydrocarbon **133** as a colorless oil (30 mg, 69%).

The physical properties of **133** are as follows:

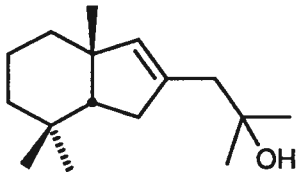
IR (film) $\nu_{max.}$: 2950 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.84 (3H, s), 0.87 (3H, s), 1.02 (3H, s), 1.05 (3H, d), 1.58 (3H, s), 1.62 (3H, s), 2.04-2.35 (3H, m).

MS m/z: 220 (M^+, 23.1%), 205 (77.6%), 177 (30.6%), 41 (100.0).

2.3.22. Cyclopropane Sliding Reaction: alcohol 130 to alcohol 144

[3aS-(3aα,7aα)] 3a,4,5,6,7,7a-Hexahydro-α,α,3a,7,7-pentamethyl-1*H*-indene-2-ethanol (**144**)



144

To the solution of alcohol **130** (80 mg, 0.34 mmol) in a dioxane:water mixture solvent (4.00 ml, 1:1, v/v) was added *p*-toluentsulfonic acid hydrate (20 mg, 0.10 mmol, 0.30 eqv.). The mixture was heated at 85°C for 1 hour and cooled to room temperature. Water (10 ml) was added and methylene chloride (2x10 ml) was used to extract the aqueous solution. The methylene solution was washed with brine (10 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:8, v/v) gave homoallylic alcohol **144** (70 mg, 87%).

The physical properties of **144** are as follows:

$[\alpha]_D^{25}$=+45.2 (c=1.00, $CHCl_3$).

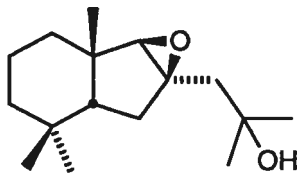
IR $\nu_{max.}$ (film): 3100-3650 (OH stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88(3H, s), 1.02(3H, s), 1.07-1.70{18H, m, including 1.18 (3H, s), 1.21 (3H, s) and 1.22 (3H, s)}, 2.05-2.45 (4H, m), 5.33 (1H, bs)

MS m/z: 236 (M^+, 0.1%), 218 (1.6%), 203 (5.0%), 178 (7.1%), 163 (100.0%), 135 (21.1%). High resolution mass measurement: calculated for $C_{16}H_{28}O$: 236.2140; found: 236.2145.

2.3.23. Epoxidation: alcohol 144 to epoxyalcohol 147

[2R-(2α,3α,3aα,7aα)] 2,3,3a,4,5,6,7,7a-Octahydro-α,α,3a,7,7-pentamethyl-1*H*-2,3-epoxyindene-2-ethanol (**147**)



147

To a solution of alcohol **144** (172 mg, 0.729 mmol) in chloroform (5.0 ml) was added *m*-CPBA (243 mg, ~80% pure, 1.1 mmol, 1.5 eqv.). The mixture was stirred at room temperature for 1 hour. After addition of methylene chloride (5.0 ml) and washing with sodium bicarbonate solution (10 ml, 10%), the mixture was dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography of the crude product with ethyl acetate:hexanes mixture (2:8, v/v) gave epoxide **147** (159 mg, 87%).

The physical properties of **147** are as follows:

m.p.: 82-84°C.

$[\alpha]_D^{25}$=+56.7 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film):3700 (O-H stretching).

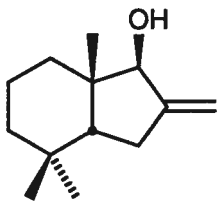
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70-1.70 {24H, m, including 0.80 (3H, s), 0.98 (3H, s), 1.20 (3H, s), 1.24 (3H, s) and 1.31 (3H, s)}, 1.75-2.02 (2H, m), 2.04-2.15 (1H, dd, J=7.2 and 13.6 Hz), 2.85 (1H, s).

MS m/z: 252 (M^+, 0.2%), 234 (4.1%), 219 (6.9%), 194 (17.9%), 179 (19.8%), 161 (19.3%), 123 (100.0%), 109 (90.4%). High resolution mass measurement: calculated for $C_{16}H_{28}O_2$: 252.2089; found: 252.2088.

Elemental Analysis: calculated for $C_{16}H_{28}O_2$: C 76.14, H 11.18; found: C 76.14, H 1.05.

2.3.24. Reductive Fragmentation by LAH: epoxyalcohol 147 to allylic Alcohol 151

[1S-(1α,3aα,7aα)] 3a,4,5,6,7,7a-Hexahydro-4,4,7-trimethyl-2(3*H*)-methylene-1*H*-inden-1-ol (**151**)



151

Epoxide **147** (30.3 mg, 0.583 mmol) in anhydrous THF (1.0 ml) was added in a dropwise manner to a slurry of LAH (18.4 mg) in THF (1.0 ml) under nitrogen. The mixture was then heated at about 70°C (bath temperature) for 2 hours. After cooling to room temperature, ethanol (5.0 ml) was added and stirring continued for 10 minutes. Subsequently, water (15 ml) was added and the resulting mixture was extracted with ethyl acetate (2X10 ml). The ethyl acetate solution was dried over magnesium sulfate and concentrated *in vacuo*.. Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:8, v/v) gave allylic alcohol **151** (20 mg, 87%)

The physical properties of **151** are as follows:

$[\alpha]_D^{25}$=+5.4 (c=1.00, $CHCl_3$).

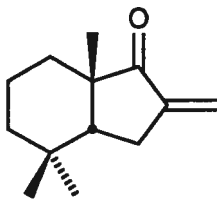
IR $\nu_{max.}$ (film): 3100-3650 (O-H stretching), 3060 (C-H stretching, olefinic), 1650 (C=C stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, s), 1.02 (3H, s), 1.05-1.72 {13H, m, including 1.14 (3H, s)}, 1.78 (1H, t, J=8.8), 2.20-2.60 (2H, m).

MS m/z: 194 (M^+,13.1 %), 179 (21.6%), 161 (13.0%), 123 (100.0%), 109 (85.5%). High resolution mass measurement: calculated for $C_{13}H_{22}O$: 194.1670; found: 194.1661.

2.3.25. Allylic Oxidation by MnO_2: homoallylic alcohol 151 to enone 152

[3a**R**-(3aα,7aα)] 3a,4,5,6,7,7a-Hexahydro-4,4,7a-trimethyl-2(3*H*)-methylene-1*H*-inden-1-one (**152**)



152

Allylic alcohol **151** (29 mg, 0.15 mmol) in methylene chloride (2.0 ml) was treated with manganese dioxide (65 mg, 0.75 mmol). The slurry was stirred at room temperature for 72 hours. After Filtering of the slurry and washing with methylene chloride (10 ml), the methylene chloride solution was concentrated *in vacuo* . Column chromatography of the crude product gave enone **152** (8.0 mg, 67% based on recovery)and starting allylic alcohol **151** (17 mg, 59% recovery).

The physical properties of **152** are as follows:

$[\alpha]_D^{25}$=+57 (c=0.58, $CHCl_3$).

UV (MeOH, c=23 mg/l) $\lambda_{max.}$: 235 nm (log ε=4.0), 278 (log ε=2.5).

IR $\nu_{max.}$ (film): 1710 (C=O stretching), 1635 (C=C stretching) cm^{-1}.

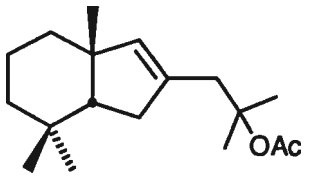
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75-1.70 {16H, m, including 0.85 (3H, s), 1.07 (3H, s) and 1.22 (3H, s)}, 2.35-2.65 (2H, m), 5.37 (3H, bs), 6.07 (3H, bs).

MS m/z: 192 (M^+, 49.9%), 177 (20.3%), 149 (28.9%), 123 (80.7%), 68 (100.0%). High resolution mass measurement: calculated for $C_{13}H_{20}O$: 192.1514; found: 192.1515.

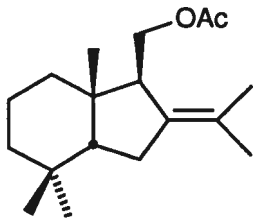
2.3.26. Cyclopropane Sliding Reaction: alcohol 130 to acetates 153 and 154

[1a**S**-(3aα,7aα)] 3a,4,5,6,7,7a-Hexahydro-α,α,3a,7,7-pentamethyl-1*H*-indene-2-ethyl acetate (**153**)

[1**R**-(1α,3aα,7aα)] 1,3,3a,4,5,6,7,7a-Octahydro-4,4,7a-trimethyl-2*H*-indene-1-methyl acetate (**154**)



153



154

A solution of alcohol **130** (60 mg, 0.26 mmol) in acetic acid (2.5 ml) was heated at 65°C for 2 hours. After cooling to room temperature, methylene chloride (10 ml) was added and the mixture was extracted with 10% sodium bicarbonate solution (10 ml). The methylene chloride solution was dried over magnesium sulfate and concentrated *in vacuo* . Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:25, v/v) yielded acetate **153** (41 mg, 60% based on recovery), acetate **154** (4.0 mg, 6% based on recovery), starting alcohol **130** (2.9 mg, 5%) and vinyl cyclopropane **138** (3.1 mg, 6% based on recovery).

The physical properties of **153** are as follows:

$[\alpha]_D^{25}$=+41.7 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 1735 (C=O stretching), 1650 (C=C stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, s), 1.00 (3H, s), 1.03-1.60 {16H, including 1.15 (3H, s), 1.38 (3H, s) and 1.45 (3H, s)}, 1.97 (3H, s), 2.02-2.35 (2H, m), 2.39-2.62 (2H, AB type, J=7.2 Hz), 5.2 6(1H, s).

MS m/z: 218 (M - HOAc, 37.0%), 203 (100.0%), 175 (16.7%), 147 (21.5%). High resolution mass measurement: calculated for $C_{16}H_{26}$ ($C_{18}H_{30}O_2$ - HOAc): 218.2034; found: 218.2030. Chemical ionization (NH_3 as carrier gas): 279 ($M+H^+$), 219, 203.

The physical properties of **154** are as follows:

$[\alpha]_D^{25}$=+63 (c=0.20, $CHCl_3$).

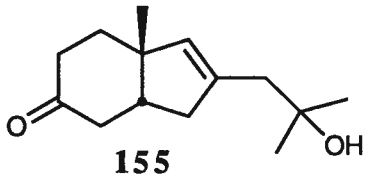
IR $\nu_{max.}$ (film): 1730 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75-1.80 {22H, m, including 0.85(3H, s), 1.03 (3H, s), 1.14 (3H, s), 1.61 (3H, s) and 1.69 (3H, s)}, 2.01 (3H, s), 2.10-2.32 (2H, m), 2.39 (1H, t, J=5.6 Hz)

MS m/z: 278 (M^+, 0.3%), 218 (26.0%), 203 (100.0%). High resolution mass measurement: calculated for $C_{18}H_{30}O_2$: 278.2246; found: 278.2248.

2.3.27. Cyclopropane Sliding Reaction: ketol 117 to ketol 155

[3a**R**-(3aα,7aα)] 3,3a,4,6,7,7a-Hexahydro-2-(2-hydroxyl-2-methylpropyl)-7a-methyl-5*H*-inden-5-one (**155**)



155

To the solution of ketol **117** (82 mg, 0.37 mmol) in a dioxane :water mixture solvent (4.00 ml, 1:1, v/v) was added *p*-toluenesulfonic acid hydrate (22 mg, 0.11 mmol, 0.30 eqv.). The mixture was heated at 85°C for 3.8 hours. After cooling to room temperature, the mixture was diluted with water (10 ml) and extracted with methylene chloride (2x10.0 ml). The methylene solution was extracted with brine (10 ml), dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography of the crude mixture with ethyl acetate:hexanes mixture (2:8, v/v) gave product **155** (72 mg, 87%).

The physical properties of **155** are as follows:

$[\alpha]_D^{25}$=+111 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3050-3650 (O-H stretching), 1700 (C=O stretching), 1650 (C=C stretching).

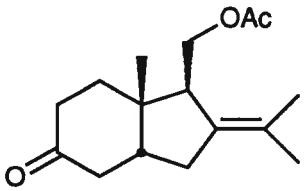
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10-1.90 {13H, m, including 1.20 (3H, s) and 1.23 (6H, two singlets)}, 1.95-2.60 (7H, m), 2.75 (1H, dd, J=8.8 and 17 Hz), 5.20 (1H, bs).

MS m/z: 222 (M^+, 2.8%), 204 (13.6%), 189 (10.0%), 147 (100.0%), 133 (34.6%), 106 (47.4%). High resolution mass measurement: calculated for $C_{14}H_{22}O_2$: 222.1620; found: 222.1618.

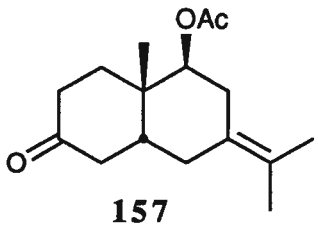
2.3.28. HOAc Promoted Ring Opening: ketol 117 to ketoacetates 156 and 157

[1**R**-(1α,3aα,7aα)] 1-Acetoxymethyl-3,3a,4,6,7,7a-hexahydro-7a-methyl-2(1*H*)-(1-methylethylidene)-5*H*-inden-5-one (**156**)

[4a**S**-(4aα,5α,8aα)] 5-Acetoxyl-3,4,4a,5,8,8a-hexahydro-4a-methyl-7(6*H*)-(1-methyl ethylidene)-naphthalen-2(1*H*)-one (**157**)



156



157

A solution of alcohol **117** (65.2 mg, 0.294 mmol) in acetic acid (2.5 ml) was heated at 85°C for 2 hours. After cooling to room temperature, methylene chloride (10 ml) was added and the mixture was extracted with 10% sodium bicarbonate solution (10 ml). The methylene chloride solution was dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography of the crude product with hexanes : ethyl acetate (1:8, v/v) yielded acetate **156** (44 mg, 56%) and acetate **157** (11 mg, 14%).

The physical properties of **156** are as follows:

$[\alpha]_D^{25}$=+63.0 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 1735 (C=O stretching of the acetate group), 1705 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, s), 1.50-1.85 {8H, m, including 1.59 (3H, s) and 1.70 (3H, s)}, 1.92 (1H, m), 2.06 (3H, s), 2.10-2.60 (7H, m), 3.95-4.20 (2H, m).

MS m/z: 264 (M^+, 0.1%), 204 (23.6%), 189 (13.2%), 147 (100.0%), 134 (85.1%), 119 (44.4%). High resolution mass measurement: calculated for $C_{16}H_{24}O_3$: 264.1725; found: 264.1720.

The physical properties of **157** are as follows:

$[\alpha]_D^{25}$=+30 (c=0.66, $CHCl_3$).

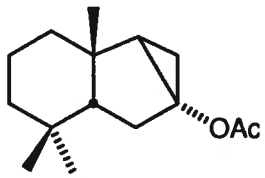
IR $\nu_{max.}$ (film): 1710 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.17 (3H, s), 1.40-1.80 {8H, m, including 1.65 (3H, s), and 1.72 (3H, s)}, 1.90-2.80 {12H, m, including 2.10(3H, s)}, 5.19 (1H, dd, J= 4.2 and 10.2 Hz).

MS m/z: 204 (M-HOAc, 43.5 %), 189 (19.2%), 147 (91.9%), 133 (100.0%), 119 (54.4%), 105 (51.2%). High resolution mass measurement calculated for $C_{14}H_{20}O$ (M-HOAc): 204.1514; found: .204.1508. Chemical ionization (NH_3): 282 ($M+NH_4^+$), 265 ($M+H^+$), 222 ($M-HOAc+NH_4^+$), 205 ($M-HOAc+H^+$).

2.2.29. Baeyer-Villiger Reaction: ketone 131 to acetate 160

[1a**R**-(1aα,ibβ,5aβ,6aα)] Decahydro-1b,5,5-trimethylcycloprop[*a*]inden-6a-yl acetate (**160**) or [1**R**,6**S**,7**R**,9**S**] 9-Acetoxyl-2,2,6-trimethyltricyclo [4.4.0.0^{7,9}.]decane (**160**)



160

To the solution of ketone **131** (1.80 g, 8.18 mmol) in methylene chloride (10.0 ml) was added *m*-CPBA (4.45 g, 80-85% pure, 2.1 mmol, 2.5 eqv.). The above mixture was refluxed for 12 hours during which a milky thick slurry was observed. After cooling to room temperature, methylene chloride (50 ml) was added and the mixture was washed with 10% rapidly solution (50 ml). The organic layer was separated, washed with brine (20 ml), dried

with magnesium sulfate, and concentrated *in vacuo*. Column chromatography of the crude product gave acetate **160** (1.50 g, 82% based on starting material recovery) and starting ketone **131** (0.09 g).

The physical properties of **160** are as follows:

$[\alpha]_D^{25}$=+36.7 (c=0.995, $CHCl_3$).

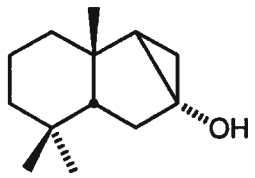
IR $\nu_{max.}$ (film): 3050 (C-H stretching), 1735 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70 (1H, m), 0.80 (3H, s), 0.90-1.02 {4H, m, including 0.97 (3H, s)}, 1.05 (3H, s), 1.10-1.70 (8H, m), 1.90-2.10 {4H, including 2.10 (3H, s)}, 2.23 (1H, dd, J=8.0 and 12.0 Hz).

MS m/z: 236 (M^+, 1.1%), 221 (19.0%), 194 (21.5%), 179 (22.2%), 109 (100,0%). High resolution mass measurement: calculated for $C_{15}H_{24}O_2$: 236.1776; found:. 236.1774.

2.3.30. Saponification: acetate 160 to cyclopropanol 161

[1a**R**-(1aα,1bβ,5aβ,6aα)] Decahydro-1b,5,5-trimethylcycloprop[*a*]inden-6a-ol (**161**) or [1**R**,6**S**,7**R**,9**S**] 2,2,6-Trimethyltricyclo [4.4.0.0^{7,9}.] decan-9-ol (**161**)



161

Acetate **160** (589 mg, 2.50 mmol) was dissolved in ethanol (20 ml) at room temperature. To this solution was added grounded potassium hydroxide (230 mg, ~80% pure, 3.28 mmol) under nitrogen. The resulting mixture was stirred for 30 minutes, diluted with water (20 ml), and extracted with methylene chloride (2X20 ml). The methylene chloride solution was dried over magnesium sulfate, concentrated to provide alcohol **161** as an oil (490 mg, 100%).

The physical properties of **161** are as follows:

$[\alpha]_D^{25}$=+34.5 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3050-3650 cm^{-1}.

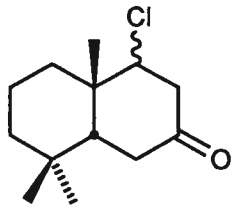
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.80 (3H, s), 0.96 (3H, s), 1.01 (3H, s), 1.98 (2H, m).

MS m/z: 194 (M^+, 3.2%), 179 (4.6%), 124 (28.8%), 109 (100.0%), 81 (22.6%). High resolution mass measurement: calculated for $C_{13}H_{22}O$: 194.1672; found:.194.1665.

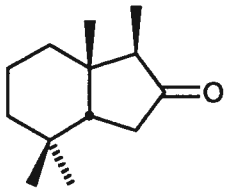
2.3.31. Cyclopropane Ring Opening Reaction by $FeCl_3$: cyclopropanol 157 to β-chloroketone 162

[4a**S**-(4aα,8aα)] 4-Chloro-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethylnaphthalen-2(1*H*)-one (**162**)

[1**R**-(1α,3aα,7aα)] 1,3,3a,4,5,6,7,7a-Octahydro-1,4,4,7a-tetramethyl-2*H*-inden-2-one (**164**)



162



164

The alcohol **161** (490 mg, 2.53 mmol) obtained from above was dissolved in anhydrous DMF (12.5 ml) under nitrogen and cooled to 0°C. Dry ferric chloride (1.03 g, 6.35 mmol) was added to this solution. After stirring for 1 hour, the resulting brown mixture was warmed up to room temperature and remained stirred for 24 hours. Addition of 1 M hydrochloric acid (20 ml), extraction with diethyl ether (2X20 ml), and drying over magnesium sulfate was followed by concentration to give the crude product containing **162** and **164** which was subject to elimination in the next step without separation.

The physical properties of **162** are as follows:

IR νmax. (film): 1720 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.76 (3H, s), 0.90 (3H, s), 1.25 (3H, s), 2.10-3.00 (4H, m), 4.70 (1H, dd, J=6.0 and 12.0 Hz).

MS m/z: 228/230 (M^+, 0.6%/0.2%), 206 (1.0%), 193 (7.5%), 43 (100.0%). High resolution mass measurement: calculated for $C_{13}H_{21}O^{37}Cl$: 230.1251, found: 230.1223; calculated $C_{13}H_{21}O^{35}Cl$: 228.1281, found: 228.1276.

The physical properties of **164** are as follows:

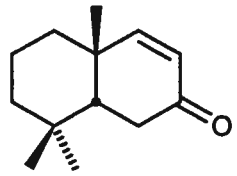
IR (film) $\nu_{max.}$: 1725 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.84 (3H, s), 0.91 (3H, s), 1.17 (3H, s), 1.24 (3H, s), 1.74 (1H, t, J=10.6 Hz), 2.00 (1H, q, J=7.2 Hz), 2.04-2.35 (2H, m).

MS m/z: 194 (M^+, 3.2%), 124 (28.8%), 109 (100.0%), 81 (22.6%).

2.3.32. Dehydrochlorination: β-chloroketone 162 to enone 163

[4a**R**-(4aα,8α)] 4a,5,6,7,8,8a-Hexahydro-4a,8,8-trimethylnaphthalen-2(1*H*)-one (**163**)



163

The above crude product containing β-chloro-ketone **162** was dissolved in a saturated sodium acetate methanol solution (10 ml). This mixture was refluxed for 3 hours and concentrated *in vacuo*. Purification by column chromatography with ethyl acetate: hexanes (2:8) gave enone **163** (384 mg, 80% from acetate **160**) and ketone **164** (24 mg, 5%).

The physical properties of **163** are as follows:

m.p.: 64-66°C.

$[\alpha]_D^{25}$=+47.6 (c=1.00 , $CHCl_3$).

UV (MeOH, c=20.0 mg/l) $\lambda_{max.}$: 235 nm (log ε=3.842).

IR nmax. (film): 1664 cm^{-1} (C=O stretching).

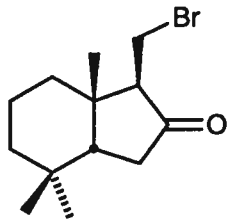
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.77 (3H, s), 0.96 (3H, s), 1.22 (3H, s), 1.22 (3H, s), 1.27-1.75 (7H, m), 2.50-2.80 (2H, m), 5.95 (1H, d, J=9.6 Hz), 6.27 (1H, d, J=9.6 Hz).

MS m/z: 192 (M^+, 13.3%), 150 (45.1%), 69 (100.0%). High resolution mass measurement: calculated for $C_{13}H_{20}O$: 192.1514; found: 192.1518.

Elemental Analysis: calculated for $C_{13}H_{20}O$: C 81.20, H 10.50; found: C 81.13, H 10.48.

2.3.33. Ring Opening Reaction by NBS: cyclopropanol 161 to β-bromoketone 167

[1**R**-(1α,3aα,7aα)] 1-Bromomethyl-1,3,3a,4,5,6,7,7a-octahydro-4,4,7a-trimethyl-2*H*-inden-2-one (**167**)



167

Cyclopropanol **161** (12.8 mg, 0.066 mmol) in dimethylsulfoxide:chloroform (4.0 ml, 1:1, v/v) mixture solvent was stirred with NBS (23.5 mg, 0.132 mmol, 2.0 eqv.) at room temperature for 3 hours. Water (5 ml) was added and methylene chloride (10 ml) was used to extract the aqueous solution. Magnesium sulfate drying and concentration *in vacuo* resulted in an oil which was chromatographed with ethyl acetate:hexanes mixture (2:8, v/v) to afford β-ketobromide **167** (6.3 mg, 60%) and cyclopropanol **161** (5.3 mg).

The physical properties of **167** are as follows:

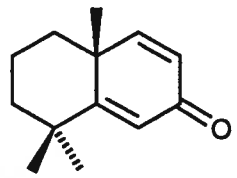
IR (film) νmax.: 1730 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, s), 1.00 (3H, s), 1.14 (3H, s), 1.91 (1H, t, J=9.0 Hz), 2.32 (2H, m), 2.55 (1H, t, J=5.4 Hz), 3.35-3.65 (2H, m).

MS m/z: 274/272 (M^+, 2.4% /2.5%), 193 (71.2%), 175 (16.1%), 109 (100.0%).

2.3.34. Dehydrogenation: enone 163 to dienone 168

[4a**R**] 5,6,7,8-Tetrahydro-4a,8,8-trimethylnaphthalen-2(4a*H*)-one (**168**)



168

The solution of 0.42 M LDA (1.84 ml) in *n*-pentane was concentrated to a viscous mixture and cooled to -78°C. To this mixture was added THF (1.0 ml) and introduced the solution of **163** (135 mg, 0.703 mmol) in THF (1.5 ml) in a dropwise manner under nitrogen protection. After stirring for 1 hour, phenylselenenyl chloride (183 mg, 0.844 mmol, 1.2 eqv.) in anhydrous THF (0.50 ml) was added rapidly. The reaction mixture was warmed to room temperature, stirred for another 1 hour, and treated with 30% hydrogen peroxide (0.72 ml). After stirring for 5 hours, saturated sodium carbonate (aq., 5 ml) and diethyl ether (5 ml) were added. The organic layer was separated, washed with brine, dried over magnesium sulfate, concentrated *in vacuo* to afford the crude product. The crude product was purified by column chromatography using ethyl acetate:hexanes mixture (2:8, v/v) to provide dienone **168** (111 mg, 92% based on recovery of starting material) and the starting enone **163** (13 mg).

The physical properties of **168** are as follows:

$[\alpha]_D^{25}$=+57.3 (c=1.00, $CHCl_3$).

UV (MeOH, c=20 mg/l) $\lambda_{max.}$: 241 nm (log ε=4.00).

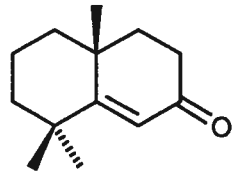
IR $\nu_{max.}$ (film): 1660 (C=O stretching), 1620 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.15-2.10 {15H, m, including 1.22 (3H, s), 1.30 (3H, s), 1.35 (3H, s)}, 6.14 (1H, dd, J=0.2 and 9.9 Hz), 6.25 (1H, d, J=0.2 Hz), 6.70 (1H, d, J=9.9 Hz).

MS m/z: 190 (M^+, 6.1%), 175 (12.0%), 147 (9.9%), 41 (21.2%). High resolution mass measurement: calculated for $C_{13}H_{18}O$: 190.1357; found: 190.1358.

2.3.35. Birch Reduction: dienone 168 to enone 64

[4a**R**] 4,4a,5,6,7,8-Hexahydro-4a,8,8-trimethylnaphthalen-2(3*H*)-one (**64**)



64

To the solution of dienone **168** (85.9 mg, 0.452 mmol) in anhydrous THF (2.0 ml) was distilled ammonia (4 ml) from sodium under nitrogen. Small pieces of lithium were added for 30 minutes until a dark blue color persisted. After stirring was continued for 30 minutes, ammonium chloride powder was added to remove excess lithium. Evaporation of ammonia and THF gave a yellowish oil which upon column chromatography produced the desired enone **64** (58.0 mg, 74.2%) and the starting dienone **168** (8.5 mg).

The physical properties of **64** are as follows:

$[\alpha]_D^{25}$=-100 (c=1.00, $CHCl_3$).

UV (MeOH, c=20.0 mg/l) λ_{max} : 242 nm (log ε=4.10).

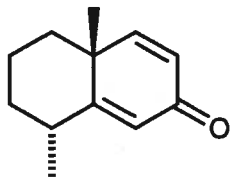
IR ν_{max} (film): 1665 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.14 (3H, s), 1.19 (3H, s), 1.34 (3H, s), 1.40-2.00 (8H, m), 2.38 (1H, m), 2.59 (1H, m), 5.96 (1H, s).

MS m/z: 192 (M^+, 100.0%), 177 (30.7%), 164 (12.8%), 149 (37.0%). High resolution mass measurement: calculated for $C_{13}H_{20}O$: 192.1514; found: 192.1512.

2.3.36. Dehydrogenation: ketone 171 to dienone 172

[4a**R**-(1α,8β)] 5,6,7,8-Tetrahydro-4a,8-dimethylnaphthalen-2(4a*H*)-one (**172**)



172

The mixture of ketone **171** (2.64 g, 14.7 mmol) and DDQ (7.41 g, 32.2 mmol, 2.2 eqv.) in dioxane (50 ml) was refluxed under nitrogen for 24 hours. Evaporation of the solvent *in vacuo* gave a brown oil which was purified by column chromatography with ethyl acetate:hexanes mixture (2:8, v/v) to provide dienone **172** in 80% yield (1.65 g) and the starting material 0.53 g.

The physical properties of **172** are as follows:

IR (film) $\nu_{max.}$: 1650 (C=O stretching), 1620 (C=C stretching) cm^{-1}.

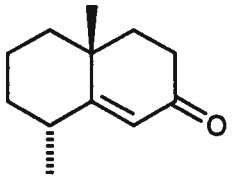
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.95-1.45 {8H, m, including 1.14 (3H, d, J=6.0 Hz) 1.27 (3H, s)}, 1.65-2.10 (4H, m), 2.51 (1H, septet, J=6.0 Hz), 6.11 (1H, s), 6.21 (1H, d, J=9.0 Hz), 6.78 (1H, d, J=9.0 Hz).

MS m/z: 176 (M^+, 5.1%), 161 (3.1%), 149 (16.2%), 43 (100.0%). High resolution mass measurement: calculated for $C_{12}H_{16}O$: 176.1201; found: 176.1198.

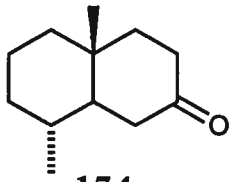
2.3.37. Birch Reduction: dienone 172 to enone 173 and ketone 174

[4a**R**-(1α,8β)] 4,4a,5,6,7,8-Hexahydro-4a,8-dimethylnaphthalen-2(3*H*)-one (**173**)

[4a**R**-(1α,8β)] 3,4,4a,5,6,7,8,8a-Octahydro-4a,8-dimethylnaphthalen-2(1*H*)-one (**174**)



173



174

To a solution of dienone **172** (200 mg, 1.14 mmol) in anhydrous diethyl ether (3.0 ml) was distilled anhydrous ammonia (~4 ml) from sodium. Small pieces of lithium were added under nitrogen for 30 minutes until a steady dark blue was observed. This solution was stirred at -33°C for another 30 minutes, quenched with ammonium chloride powder, warmed to room temperature. Concentration of the mixture *in vacuo* gave the crude product which was chromatographed with ethyl acetate:hexanes mixture (2:8, v/v) to provide enone **173** (75 mg, 42%), ketone **174** (45 mg, 25%), and the starting material **171** (21 mg).

The physical properties of **173** are as follows:

$[\alpha]_D^{25}$=-193 (c=1.03, $CHCl_3$).

UV (EtOH, c=10.3 mg/l) $\lambda_{max.}$: 240 nm (log ε=4.025)

IR (film) $\nu_{max.}$: 3052 (olefinic C-H stretching), 1660 (C=O stretching), 1610 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, s), 1.15 (1H, m), 1.25 (3H, s), 1.38 (1H, m), 1.55-2.00 (6H, m), 2.25 (3H, m), 5.79 (1H, s).

MS m/z: 178 (M^+, 76.0%), 162 (25.8%), 150 (54.7%), 79 (100.0%). High resolution mass measurement: calculated for $C_{12}H_{18}O$: 178.1357 ; found: 178.1354.

The physical properties of **174** are as follows:

$[\alpha]_D^{25}$=-39.7 (c=0.985, $CHCl_3$).

IR (film) $\nu_{max.}$: 1702 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.81 (3H, d, J=6.0 Hz), 0.93 (1H, m), 1.05 (3H, s), 1.12 (1H, m), 1.30-1.80 (8H, m), 2.00 (1H, t, J=14 Hz), 2.25-2.55 (3H, m).

MS m/z: 180 (M^+, 50.1%), 165 (9.3%), 109 (100.0%). High resolution mass measurement: calculated for $C_{12}H_{20}O$: 180.1514; found: 180.1517.

Chapter 3. The Synthesis of Ambergris Fragrances

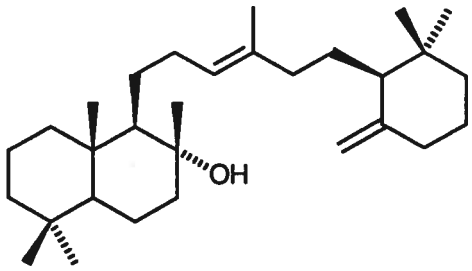
3.1. Introduction

3.1.1. Ambergris Fragrances

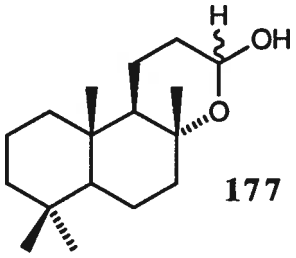
Ambergris is one of the most valuable animal perfumes, like civet, musk, and castoreum[81]. Its outstanding fragrance and mysterious effects of its odor account for man's familiarity with this material since long before the Christian era in all great civilizations. It is a metabolic product of the sperm whale (*Physeter macrocephalus* L.), which accumulates as concretions in the gut of the animal. After the concretion leaves the animal body, an aging process takes place over time, as a result of the action of sunlight and oxygen when floating in waves. During this process, the strong stecoraceous indole of fecal note and the waxy constituency disappear. At the same time, a complex yet balanced fragrance that is composed of a series of notes and subnotes, develops gradually to give a harmonious character[82].

The major constituent of ambergris is an odorless triterpene alcohol (-)-ambrein (**176**)[83] which is responsible for the generation of odoriferous compounds **177-184**[84] found in the steam volatile fraction (Figure 20). It can be presumed that the tricyclic compounds **177**, **178**, and (-)-Ambrox®* (**179**) are derived from the bicyclic part of (-)-ambrein (**176**), while the smaller fragments **180-184** are from the monocyclic part of the molecule. Ambrinol (**181**) and (+)-dihydro-γ–ionone (**180**) are structurally related and in fact a racemate of **181** can be formed stereoselectively from the racemate of **180** in 70% yield by an intramolecular Prins reaction with Bronsted or Lewis acids as catalysts[85]. The facile formation of (+)-ambreinolide (**185**) and (+)-dihydro-γ-ionone (**180**) during oxidation of **176** with permanganate supports this structural correlation[86].

*Ambrox® is a registered trade name of Firmenich SA. Systematic name of (-)-Ambrox® (**179**): [3aR-(3aα,5aβ,9aα,9bβ)]-dodacahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan.



(-)-ambrein (**176**)



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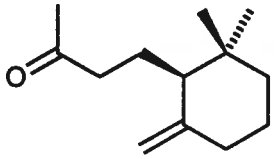

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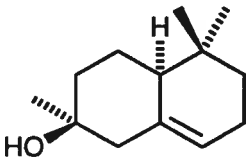
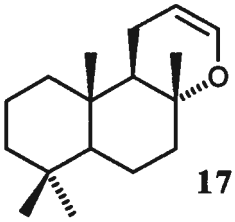


181



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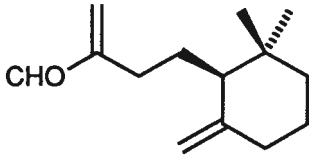

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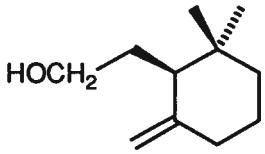

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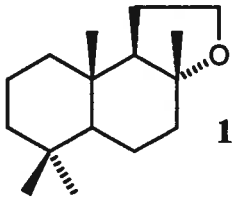

179

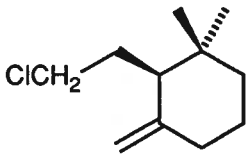

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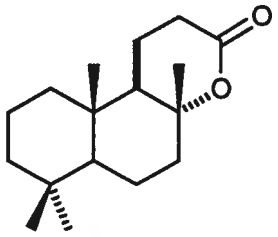
Figure 20 The Constituents of Ambergris

According to one hypothesis[81b], (-)-ambrein (**176**) is degraded by autooxidation during the aging process. Singlet oxygen may be considered as an active agent while copper ions from haemocyanin may function as a catalyst in this degradation. Porphyrins, known to be efficient photosensitizers, have been identified in ambergris[87a]. This theory is supported by

a photooxygenation experiment in which (-)-ambrein (**176**) was converted to compounds **178**, **180**, **181**, and **182** by the cleavage of its allylic hydroperoxide[87b].



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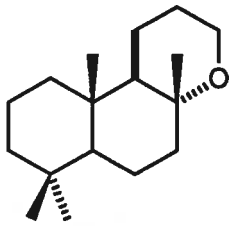
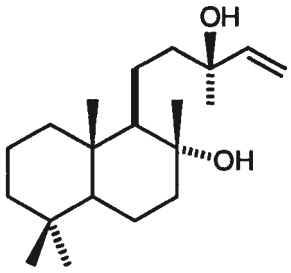


186



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Ambergris is disappearing from the world market due to excessive whale hunting. In addition, the continued increase in the pollution of coasts makes it more difficult to find prime-quality material which is more and more rarely washed ashore. In the future, the perfume industry must meet its needs for the natural product with a synthetic equivalent. The racemic form of α-ambrinol (**181**), possessing an exceptionally strong odor of damp earth with a crude civet subnote, is the only naturally occurring amber odorant for which a fully synthetic equivalent is used commercially. In 1950, it was established that the amber-like odor (woody nature) of the enol ether **178** was retained in its hydrogenation product, ambraoxide (**186**)[88]. The following search for adequate odorants resulted in the discovery of (-)-Ambrox®*, a degradation product of easily accessible sclareol (**187**); a breakthrough was then achieved in the commercial production of tricyclic amber odorants of woody nature in the late 1950's[89]. The mixture of (-)-Ambrox® (**179**) and (+)-*iso*-Ambrox® (**189**) in the form of the base Fixateur 404 (trade name of Firmenich) has been available in perfumery for more than 30 years.

*The identification of (-)-Ambrox® (**179**) from ambergris is a much later event[84b].

3.1.2. Structure and Activity Relationship of Ambergris Fragrances

With (-)-Ambrox® (**179**) as a model compound, a large number of compounds have been prepared for the correlation of structure and odor relationship. For example, the stable A/B *trans*-fused[90a] and *cis*-fused[91] diastereomers of (-)-Ambrox® (**179**) have been prepared and their odor quality and strength have been evaluated* (Figure 21). The difference in the odors of (-)-Ambrox® (**179**) and (+)-Ambrox® (**188**) is rather small. (+)-Ambrox® (**188**) with its higher threshold value (2.4 ppb) and accentuated woody note lacks the strong and warm animal note of its enantiomer **179** (threshold value 0.3 ppb). Therefore, (+)-Ambrox® has been called "poor man's ambrox" by perfumers. The exotic, spicy undertone in (+)-Ambrox® (**188**) disappears in its racemate, for which a threshold concentration of 0.5 ppb was measured. (+)-*Iso*-Ambrox® (**189**) has a threshold value of 34 ppb which is more than a hundred times weaker than its model compound **179**, showing the importance of an axial methyl at C8 for the receptor event. Surprisingly, (-)-9-*epi*-Ambrox® (**190**) possesses the strongest odor and the lowest threshold concentration of 0.15 ppb; it lacks slightly the rich and complex bouquet of **179**. The diastereomer **191** is unlikely to exist because the *trans* fusion would force the B ring into a highly strained boat-like conformation. Among the A/B *cis*-fused series, only racemic diastereomers were evaluated*. Only diastereomer **192** has an odor quality comparable to the prototype (-)-Ambrox® (**179**); it has a threshold value of 11 ppb which is 20 times higher than that of racemic Ambrox®. Racemic diastereomers **193**, **194**, and **195** are very weak odorants and almost devoid of any ambergris odor.

*A comparison of these racemic diastereomers with **179** seems permissible since there is only a small difference in the odor of (-)-ambrox® (**179**) and (+)-ambrox® (**188**). The organoleptic evaluation was carried out using a threshold concentration method[90b].

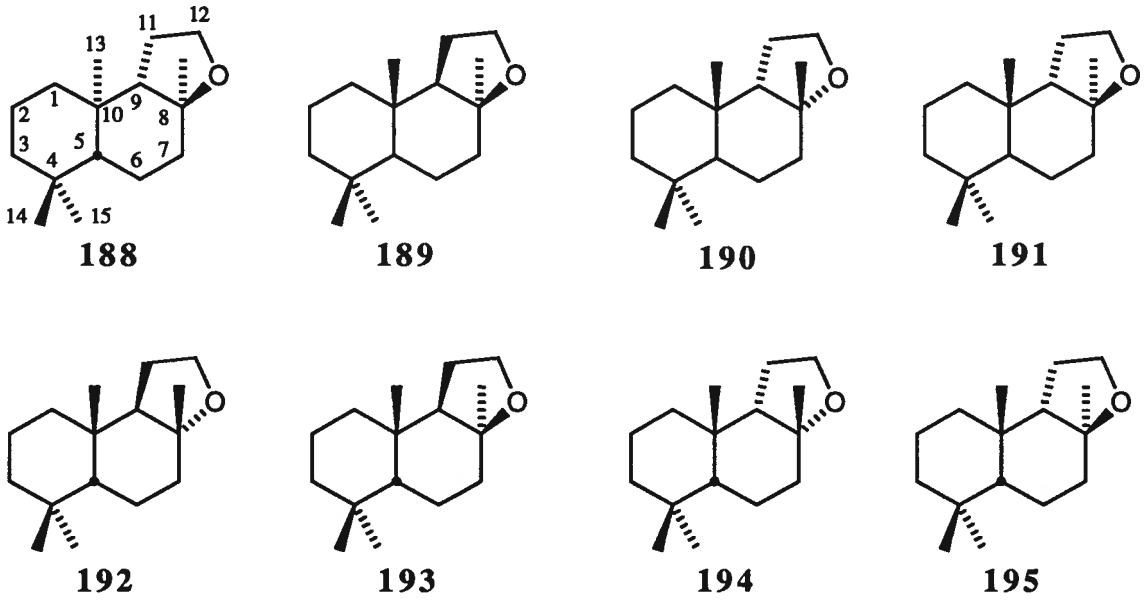


Figure 21 Stereoisomers of (-)-Ambrox®

The significance of the *gem*-dimethyl groups at C4 for the ambergris odor sensation was assessed (Figure 22)[90]. Both nor-methyl Ambrox® **196** and **197** have the Ambrox® note although **196** with an axial methyl at C4 (threshold value 1.4 ppm) has a greater strength than **197** with an equatorial methyl at C4 (threshold value 3 ppm). (±)-Dinor-Ambrox® **198** without *gem*-dimethyl group possesses the same woody character of Ambrox® and a dominant earthy odor reminiscent of a freshly plowed earth; it has a threshold value 2.4 ppm. Therefore, the *gem*-dimethyl group at ring A has considerable influence on the quality and strength although their presence is not an absolute necessity for the ambergris sensation.

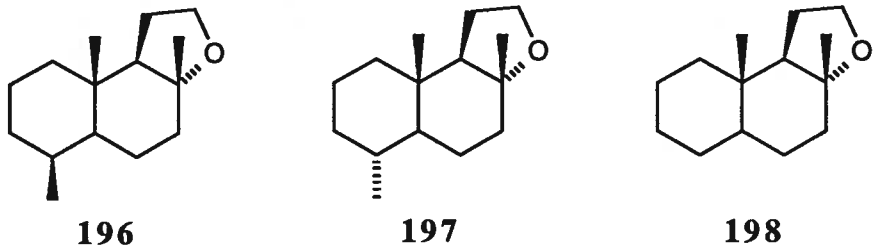


Figure 22 The Effect of the *gem*-Dimethyl Groups on the Ambergris Odor Activity

Based on a large number of analogues assessed, Ohloff[92] proposed a qualitative "triaxial rule of odor sensation" to summarize the minimal structural requirements for a compound to have ambergris odor activity: 5, 8, 10-triaxial arrangement of the substituents R', R", and Ra in the *trans*-fused decalin ring system is the geometric requirement for a molecule in order to exhibit an ambergris type odor (Figure 23). The compound must possess an oxygen-containing group, the incorporation of which into the R', R", or Ra substituents is advantageous but not indispensable. Based on this rule, it is speculated that the specific site of the human olfactory receptor system reacts with the stimulating substance by an intermolecular three-point interaction in three dimensional space. Therefore, the related *cis*-fused decalyl derivatives, for obvious conformational reasons, do not in general fulfill the stereochemical requirements for odorants with ambergris-like properties.

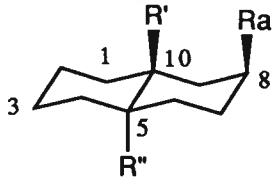
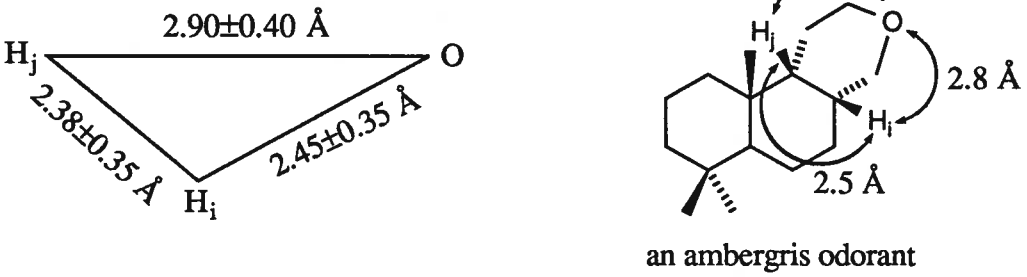


Figure 23 Triaxial Rule of Ambergris Odor Sensation

More recently, a so-called "ambergris triangle" rule was established by analyzing both electronic structures and stereochemical features of substituted decalin compounds[93]. According to this rule, an odorous compound should contain an "ambergris triangle" of certain dimensions formed by a carbon-attached oxygen atom (O) and two carbon-attached hydrogen



an ambergris odorant

Figure 24 The Ambergris Triangle Rule

atoms (H_i and H_j) making major contribution to the LUMO of this compound (Figure 24). Typically, H_i and H_j are allylic, tertiary, or axial. A specific example is given in Figure 24. According to this group of authors, the interaction between the active odorous molecule and the receptor is molecular orbital controlled.

However, as indicated by Winter[94a], many inactive compounds also fulfil the general structural conditions postulated as being necessary for ambergris-type activity. He explored an approach using the concepts of oriented profile and steric accessibility of the functional group, focussing on a quantitative estimation of the degree of interaction between the polar (hydrogen bond acceptor, e.g., oxygen) part of an odorant molecule and the hypothetical hydrogen bond donor group (e.g., hydroxyl) on the receptor site[94b]. The accessible polar surface area, a measure of the steric accessibility, was calculated for each structure after optimization by molecular mechanics calculations. A lower limit of accessibility necessary for activity was found to 6 Å. So far, only a limited range of molecules have been tested by this approach.

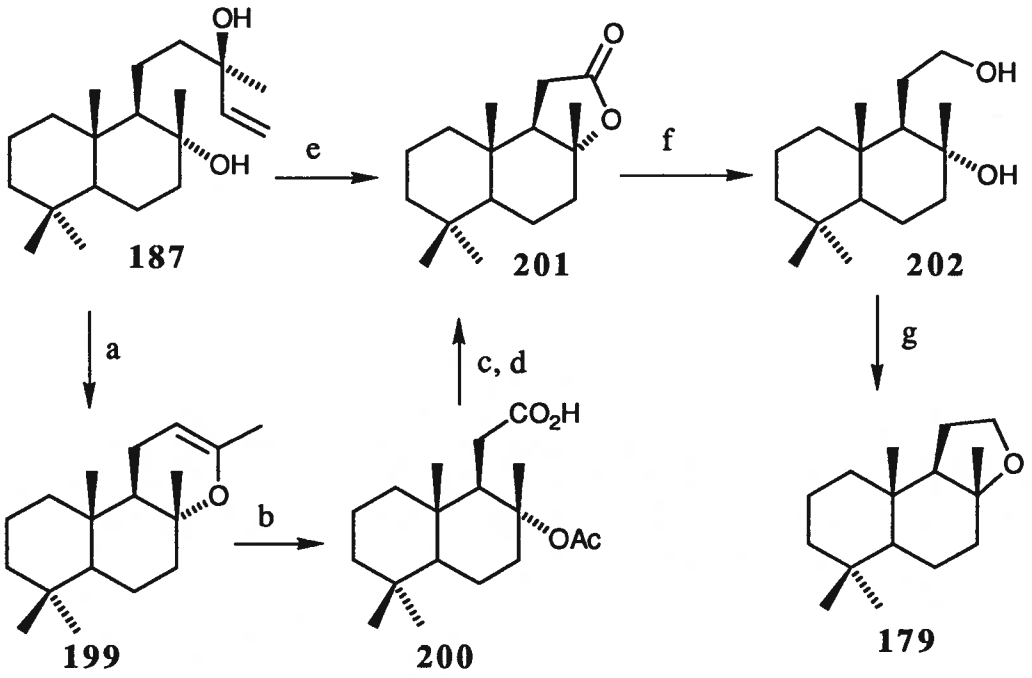
The precise nature of the ambergris odorant and the receptor interaction is essentially a speculation. Each model reveals certain truth since each can make certain successful predictions. More precise models of greater power in the quantitative prediction are likely to evolve in the future as chemists get more acquainted with ever more sophisticated computational technology. In addition, very recent exciting progress has been made in the isolation of human olfactory receptors[95]. Studies of receptor structures and the nature of active sites will enhance our understanding of the sense of smell as a whole as well as the ambergris olfaction.

3.1.3. Synthesis of Ambrox®

Many synthetic sequences leading to (-)-Ambrox® (**179**) and its racemate have appeared in the past few years, which reflects the reduction in available natural sources and the increasing market demand for ambergris fragrances. Most enantioselective syntheses involve

the use of naturally derived diterpenes or sesquiterpenes as starting material. A brief summary of the more typical synthetic sequences is presented below.

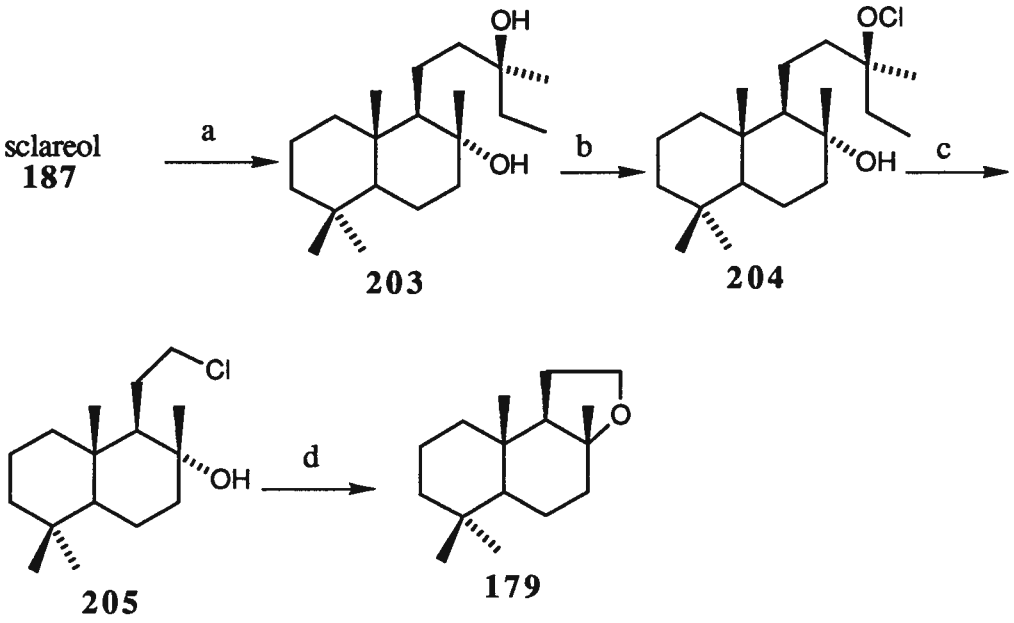
The commercial production[96a,b] of (-)-Ambrox® (**179**) is based on procedures developed by Hinder and Stoll in 1950[96c,d] (Scheme 29). These procedures involved degradation of natural sclareol (**187**), the principal source of which is clary sage (*salvia sclarea* L.). Direct treatment of sclareol (**187**) with chromium trioxide gave lactone **201**[96c]. An alternative way[96d] of obtaining **201** consisted of a sequence of reactions: the conversion of **187** into sclareol oxide (**199**) by potassium permanganate, ozonolysis of **199** to yield the acetoxy acid **200**, and the cyclization of **200** to lactone **201**. LAH reduction of lactone **201** generated diol **202** which was then cyclized to (-)-Ambrox® (**179**) employing a catalytic amount of of β-naphthalene sulfonic acid. Usually, (+)-*iso*-Ambrox® (**189**) was generated as a minor by-product.



a) $KMnO_4$; b) O_3, heating; c) KOH, then HCl; d) 150°C, vacuum; e) CrO_3, AcOH; f) LAH, Et_2O; g) β-naphthalenesulfonic acid

Scheme 29 Stoll and Hinder's Synthesis of (-)-Ambrox® from Sclareol (**187**)

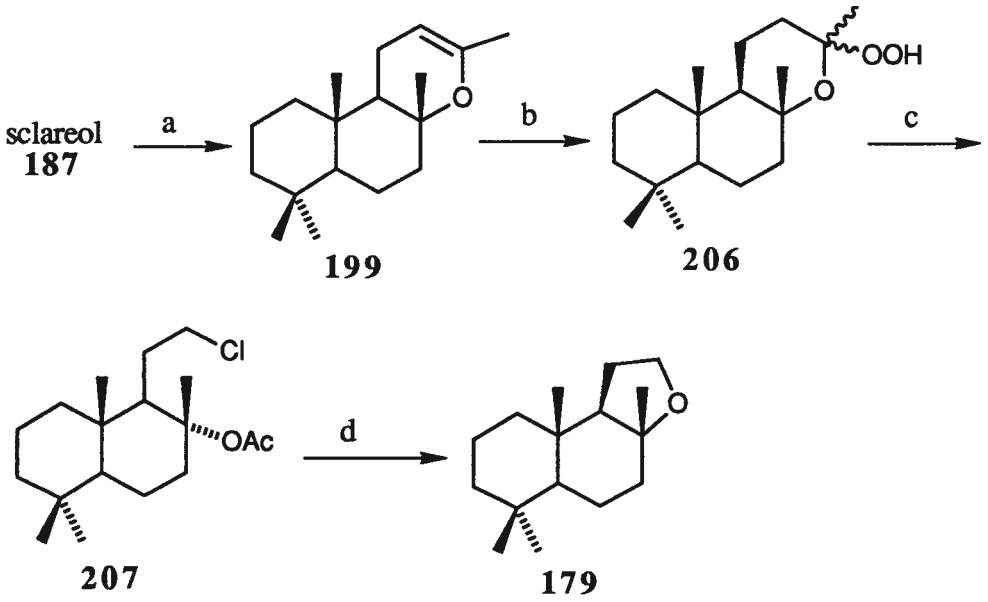
A short sequence using sclareol (**187**) as starting material was reported by Naf et al.[97] (Scheme 30) Catalytic hydrogenation of sclareol (**187**) gave dihydrosclareol (**203**) in good yield. The reduction of this double bond was necessary to ensure a regioselective cleavage in the next step. The diol **203** in carbon tetrachloride was then treated with aqueous sodium hypochlorite to provide hypochlorite **204** which was then decomposed to chloride **205** via an alkoxyl radical fragmentation mechanism. The cyclization of **205** by means of sodium hydride in THF afforded (-)-Ambrox® (**179**). The overall yield from sclareol (**187**) was 11-12%.



a) 5% Pd-C, H_2, EtOH; b) aq. NaOCl, CCl_4; c) 30-35°C, 3h; d) NaH, THF, 3h, reflux

Scheme 30 Naf's Synthesis of (-)-Ambrox® from Sclareol

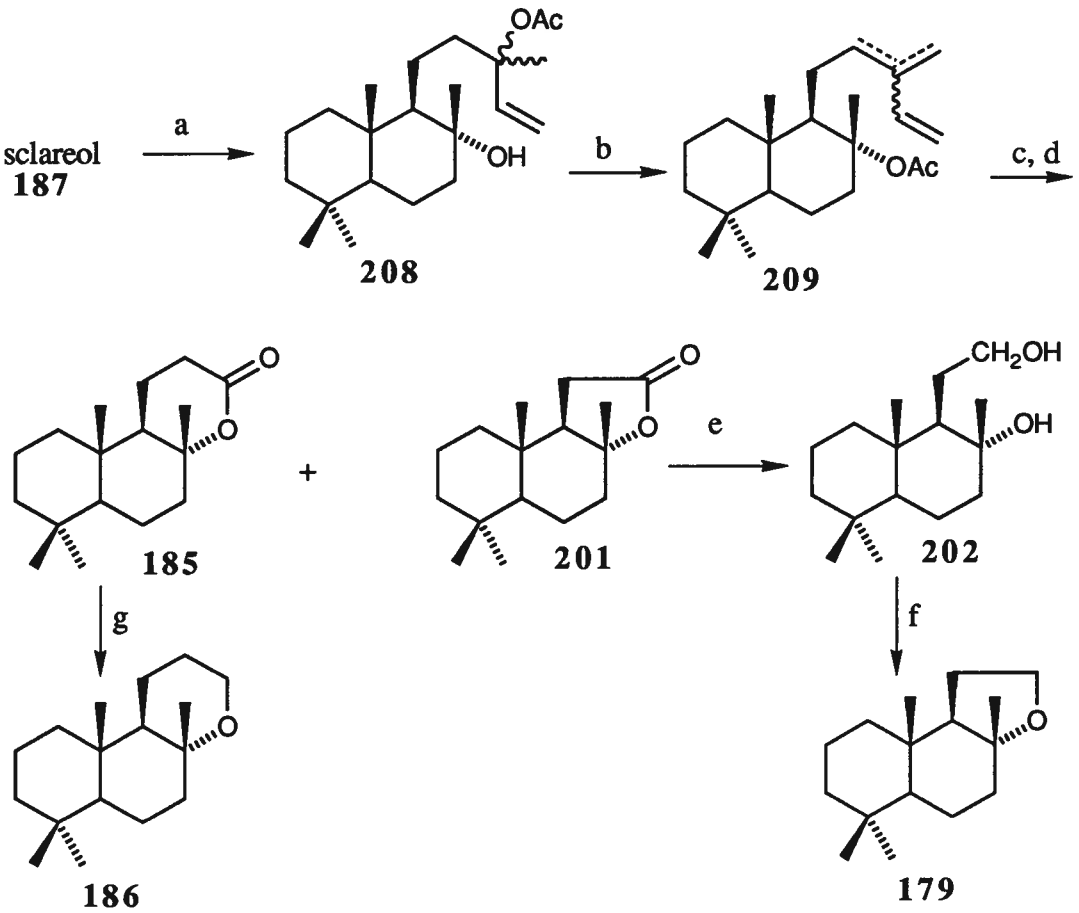
A similar sequence from sclareol (**187**) based on the fragmentation of an alkoxyl radical was also reported by Christenson[98a] (Scheme 31). Sclareol oxide (**199**), previously prepared from sclareol (**187**)[98b], was treated with hydrogen peroxide to produce a diastereomeric hydroperoxide mixture (**206**). Reaction of **206** with ferrous chloride and a catalytic amount of cupric chloride provided a bifunctional compound **207** which was then hydrolyzed to (-)-Ambrox® (**179**). The overall yield from sclareol (**187**) was 34%.



a) $KMnO_4$; b) H_2O_2, HOAc; c) $FeCl_2$, $CuCl_2$ (cat.); d) KOH, ^iPrOH, H_2O

Scheme 31 Christenson's Synthesis of (-)-Ambrox® from Sclareol

The fourth sequence towards (-)-Ambrox® (**179**) using sclareol (**187**) as starting material was reported by I. C. Coste-Manere et al.[99] (Scheme 32). Sclareol was acetylated to afford **208** which was then converted, in quantitative yield, to diene **209** by treatment with a catalytic amount of palladium acetate in quantitative yield. Reaction of **209** with potassium permanganate generated a mixture of ambreinolide (**185**) and sclareolide (**201**) (3:2) in an overall yield of 80%. LAH reduction of **185** and subsequent cyclization by *p*-toluenesulfonyl chloride provided ambraoxide (**186**). Similar treatment of **201** furnished (-)-Ambrox® (**179**).



a) Ac_2O; b) $Pd(Ac)_2$ /dioxane, 100°C/15min, 100%; c) LAH, Et_2O/H^+, 2h, 96%; d) $KMnO_4$, 24hr, 80%; e) LAH/THF, 25°C/3hr, 98%; f) $TsCl/CH_2Cl_2$, 25°C, 90%; g) LAH, Et_2O/H^+; TsCl, 2hr, 90%

Scheme 32 Coste-Manere's Synthesis of (-)-Ambrox® from Sclareol

Several other diterpenes (Figure 25), abietic acid (**82**)[100], manoyl oxide (**211**)[101], and methyl labdanolate (**212**)[102], were also degraded into (-)-Ambrox® (**179**).

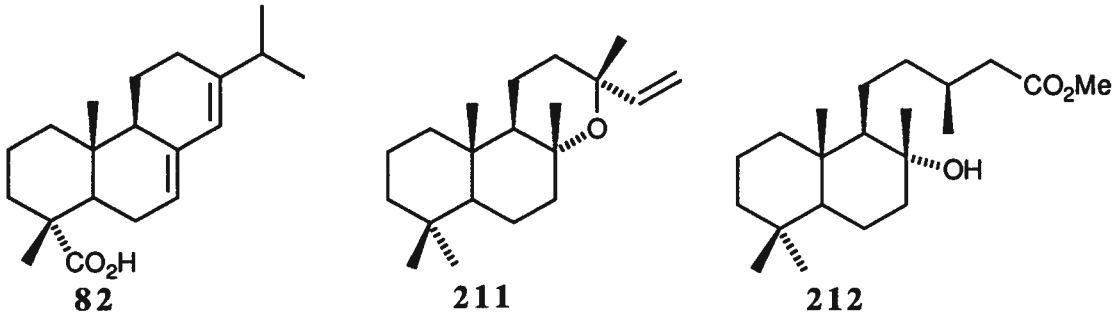
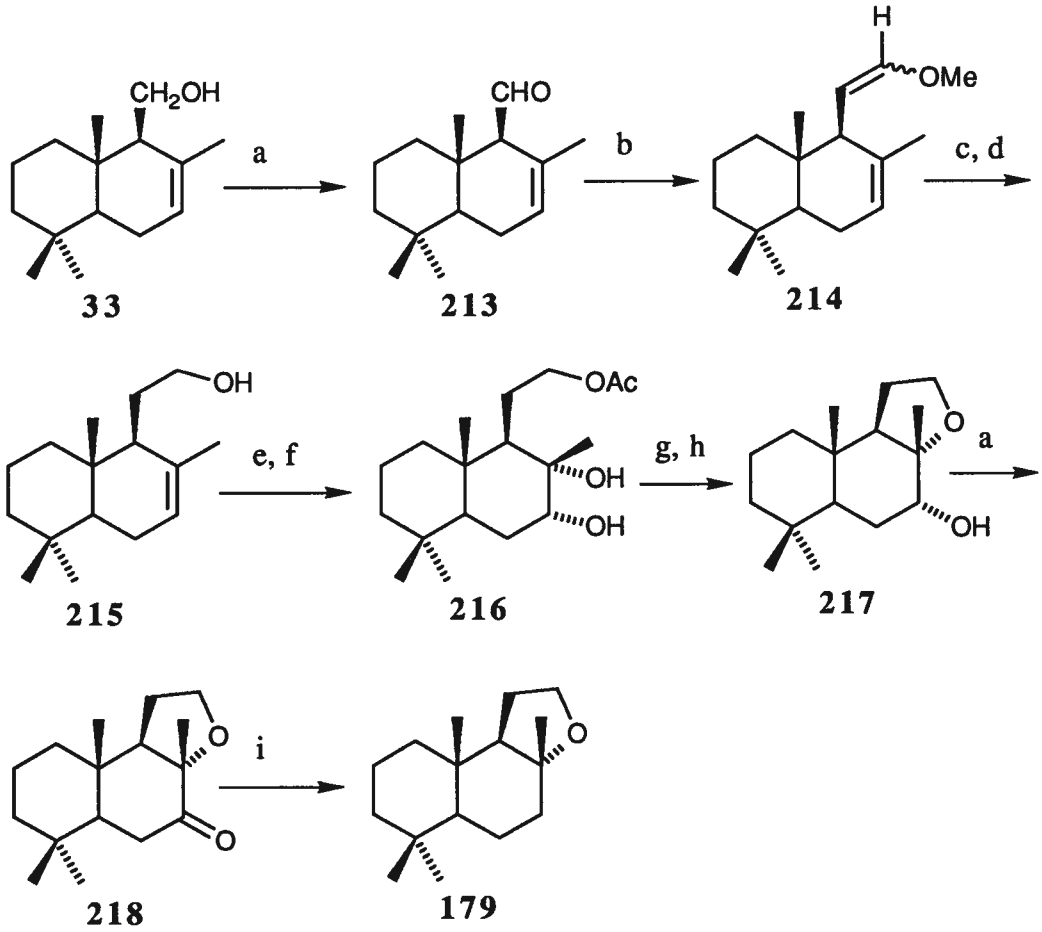


Figure 25 Several Other Diterpene Starting Materials for (-)-Ambrox® Synthesis

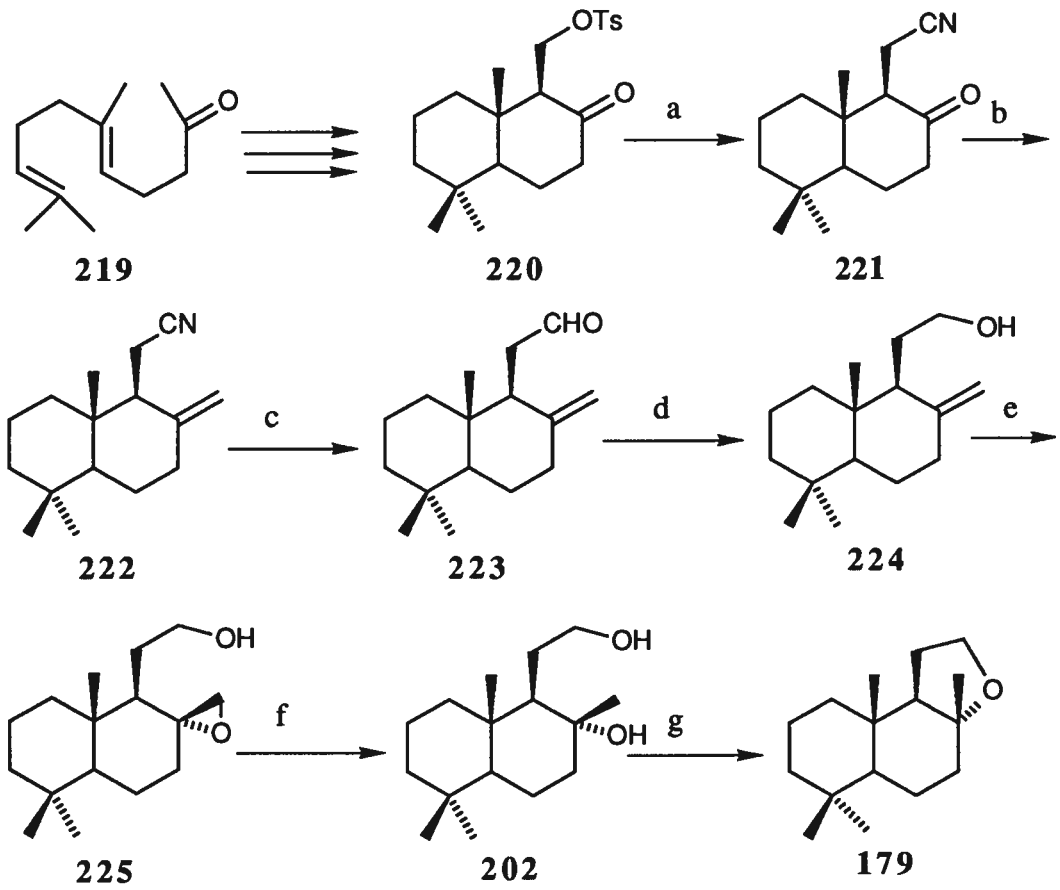
M. J. Cortes et al.[103] (Scheme 33) reported the conversion of the sesquiterpene (-)-drimenol (**33**) into (-)-Ambrox® (**179**). Oxidation of **33** by pyridinium chlorochromate resulted in aldehyde **213** which was homologated to enol ether **214**. Hydrolysis of **214** and the following LAH reduction provided alcohol **215**. Protection of the hydroxyl group in **215** as acetate and subsequent dihydroxylation afforded **216** which was then cyclized into furan **217**. Oxidation of **217** led to ketone **218** which was further reduced into (-)-Ambrox® (**179**). The overall yield of (-)-Ambrox® (**179**) from (-)-drimenol (**33**) was 19%. Notably, the ether linkage α to the carbonyl group in **218** survived during the Wolf-Kishner reduction.



a) PCC, CH_2Cl_2; b) $Ph_3P{=}CH(OMe)$; c) H_3O^+; d) LAH; e) Ac_2O, Pyr.;f) OsO_4; g) NaOH, H_2O; h) $MeSO_2Cl$, Pyr.; i) KOH, DEG, NH_2NH_2

Scheme 33 Cortes' Synthesis of (-)-Ambrox® from (-)-Drimenol (**33**)

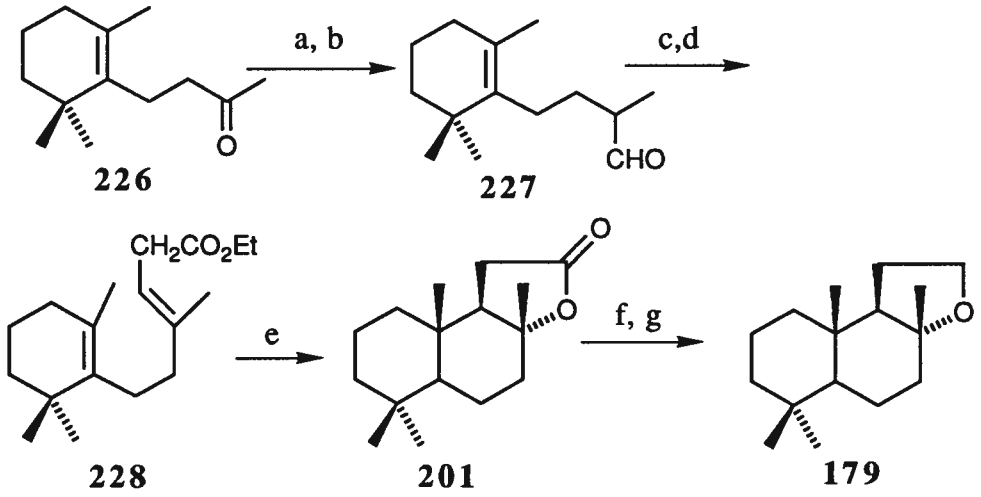
Mori et al.[104a] (Scheme 34) developed an enantionselective synthesis of (-)-Ambrox® (**179**) from geranylacetone (**219**). Enantiomerically pure tosylate **220** was previously prepared from **219** by the same group[104b]. The substitution of the tosyl group in **220** gave nitrile **221** which was treated with a Wittig reagent to give the methylene nitrile **222**. This nitrile was reduced with DIBAL to provide **223** and further reduction with sodium borohydride yielded alcohol **224**. Stereoselective epoxidation of **224** resulted in **225**. Reduction of **225** with LAH generated diol **202** which was then cyclized to (-)-Ambrox® (**179**). The overall yield of **179** from geranylacetone (**219**) was 2.2% in 15 steps.



a) NaCN, DMSO; b) $Ph_3{=}CH_2$, DME; c) DIBAL; d) $NaBH_4$, MeOH; e) m-CPBA, CH_2Cl_2; f) $LiAlH_4$, THF; g) TsCl, C_5H_5N

Scheme 34 Mori's Synthesis of (-)-Ambrox® from Geranylacetone (**219**)

The first synthesis of racemic Ambrox® was reported by Matsui et al.[105] (Scheme 35) Darzen's condensation of dihydro-β-ionone (**226**) with ethyl chloroacetate and decarboxylation of the resulting glycidic acid with a catalytic amount of sodium acetate gave an aldehyde **227**. Treatment of **227** with malonic acid and subsequent ethylation by titanium tetrachloride in ethanol afforded ethyl *trans*-β-monocyclohomofarnesate (**228**). The cyclization of **228** by means of trifluoroacetic acid yielded tricyclic sclareolide (**201**). Reduction of this lactone and subsequent ring closure furnished (±)-Ambrox®. The overall yield of (±)-Ambrox® from dihydro-β-ionone (**226**) was 4.9%.

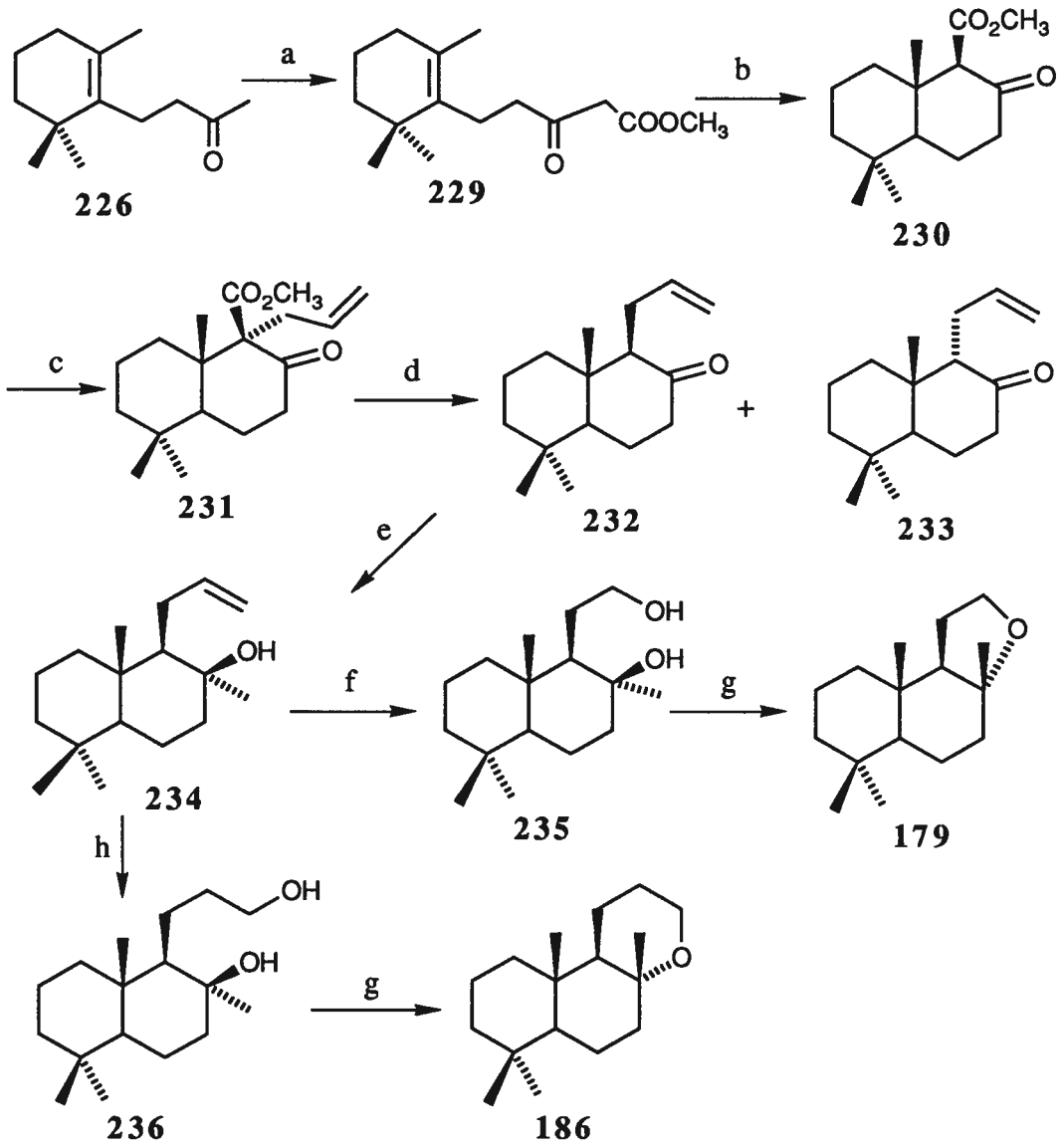


a) $ClCHCO_2Et$, NaOEt; b) NaOAc, 200°C; c) $CH_2(COOH)_2$, Et_3N; d) $TiCl_4$, EtOH; e) CF_3COOH; f) $NaAlH_2(OCH_2CH_2OCH_3)_2$; g) TsCl, Pyr.

Scheme 35 Matsui's Synthesis of (±)-Ambrox® from Dihydro-β-ionone (**226**)

The second racemic synthesis of Ambrox® by Buchi and Wuest[106] also started with dihydro-β-ionone (**226**) (Scheme 36). Condensation of **226** with dimethyl carbonate gave the monocyclic β-ketoester **229** which was cyclized to the bicyclic β-ketoester **230** using stannic chloride as catalyst. The O-allylation of **230** provided an allyl ether which was heated in xylene to afford **231**. Demethoxycarbonylation led to a mixture of **232** and **233** (6:1). The addition of MeMgI to **232**, the ozonolysis of the resulting alcohol **234**, and the subsequent treatment with sodium borohydride afforded diol **235**. The cyclization of this diol with a

catalytic amount of *p*-toluenesulfonic acid in nitromethane furnished (±)-Ambrox® as major product. The hydroboration of **234** yielded a diol **236** which was cyclized to (±)-ambraoxide (**186**). The overall yields of (±)-Ambrox® and (±)-ambraoxide from dihydro-β-ionone (**226**) were 9.0% and 5.4% respectively.



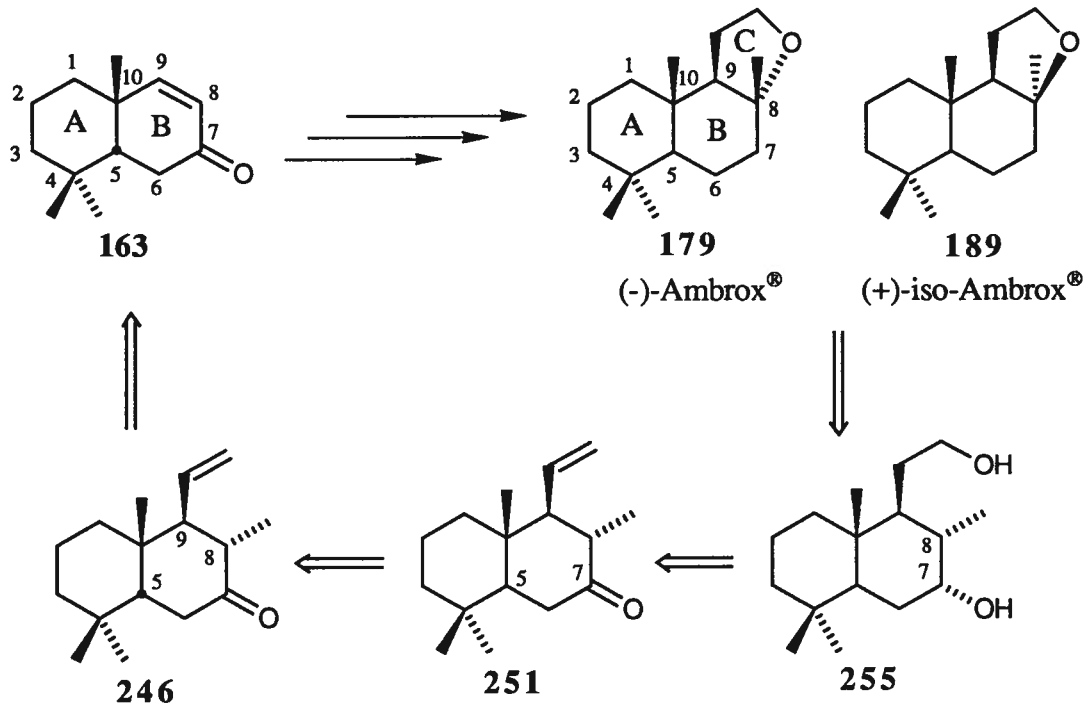
a) $(CH_3O)_2CO$, NaH, DMF, 20°C; b) $SnCl_4$, CH_2Cl_2, 5-20°C; c) allyl bromide, NaH, DMF; d) $CaCl_2$, DMSO; e) MeMgI; f) O_3, MeOH/$NaBH_4$; g) *p*-TsOH, CH_3NO_2 ; h) BH_3-THF/ OH^-, H_2O_2

Scheme 36 Buchi and Wuest's Synthesis of (±)-Ambrox® from Dihydro-β-ionone (**226**)

3.2. Discussion

3.2.1. Retrosynthetic Analysis for Synthesis of (-)-Ambrox® (179) from Enone 163

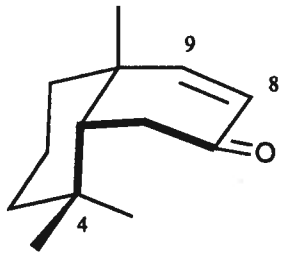
After the completion of the formal sequence to (-)-polygodial (**2**), we turned our attention to (-)-Ambrox® (**179**), the synthesis of which from thujone was vigorously pursued in our laboratories. (-)-Ambrox® may be considered as a homo-drimane sesquiterpene. The synthetic sequence we perceived is shown in Scheme 37.



Scheme 37 Retrosynthetic Analysis for Synthesis of (-)-Ambrox®

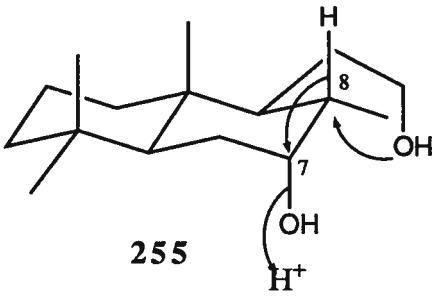
The *cis*-fused enone **163** was a promising starting material: the convex β face and the steric hindrance from the axial methyl at C4 in the ring A of the major conformer (non-steroidal) should ensure a favorable conjugate addition (e.g., by a vinyl anion equivalent) from the β face of the ring B segment thereby, generating a chiral center C9 of the same configuration as that in the (-)-Ambrox® (**179**). The conjugate addition might provide a good

opportunity of introducing a methyl group into C8 regioselectively, by trapping the enolate produced in the addition reaction with methylating reagents like iodomethane. The *cis*-fused γ,δ-enone **246** thus obtained would undergo a stereochemical correction step at C5 to its epimer, the *trans*-fused γ,δ-enone **251**.

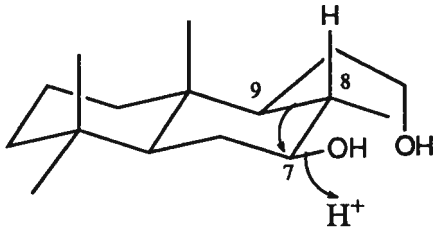


the major conformer of **163**

We also envisaged that the furan ring C of (-)-Ambrox® (**179**) or (+)-*iso*-Ambrox® (**189**) may be formed by an acid catalyzed cyclization of the *trans*-fused 1,5-diol **255** which would be prepared by stereoselectuive reduction of **251** and subsequent hydroboration. Compound **251** was expected to possess the conformation as drawn below. An axial orientation of the secondary hydroxyl group at C7 would be necessary to ensure a facile migration of the axial hydride from the vicinal tertiary carbon C8. Alternatively, an equatorial orientation of the secondary hydroxyl group would probably lead to some skeletal rearrangement as shown.



255



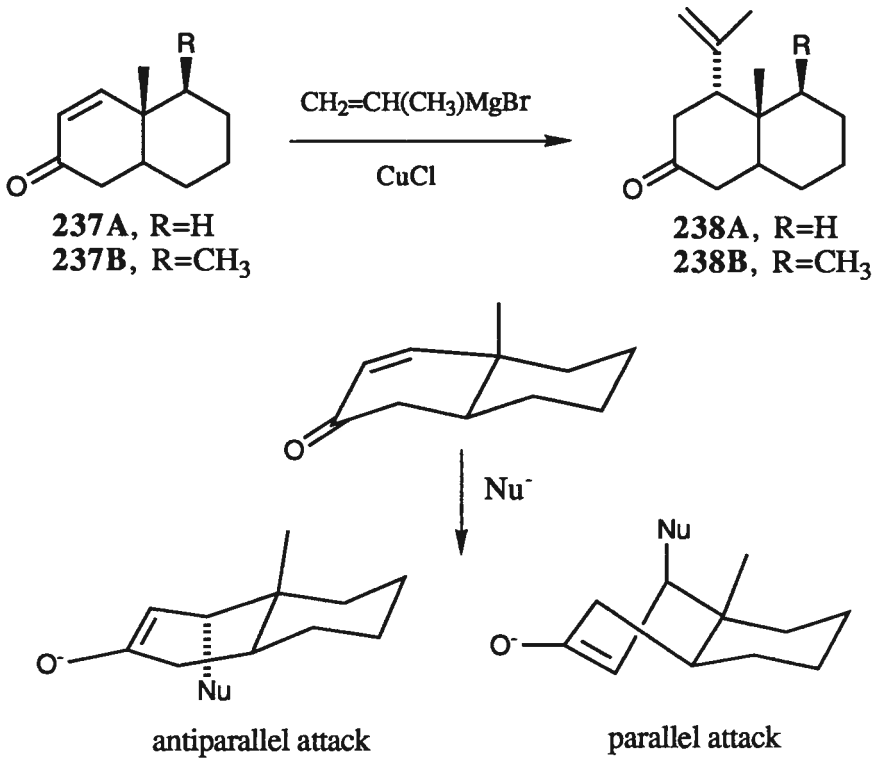
260

3.2.2. Studies on Conjugate Addition to Enone 163 and Subsequent Methylation of 245

To complete the synthesis of (-)-Ambrox® (**179**) as planned above, a diastereoselective conjugate addition to enone **163** from the β face was necessary. Conjugate addition to enones by organocopper reagents has been most widely used in organic synthesis[107]. The stereochemistry of such conjugate addition to octalones analogous to **163** was first examined.

Cuprous chloride-catalyzed addition of (2-propenyl) magnesium bromide to *trans*-fused octalones **237A** and **237B** (Scheme 38), gave exclusively the products **238A** and **238B** respectively, resulting from the α face attack[108]. This facial preference can be explained in the following manner[109]: the incoming group has to be perpendicular to the enone plane in order to have maximal orbital overlap during the progress of the reaction and therefore a minimal transition state energy (stereoelectronic requirement); as a result, the antiparallel attack* from the α face would go through a half-chair (chair-like) transition state while the parallel attack* from the β face will involve a skew-boat (boat-like) transition state. The highly strained skew-boat transition state would require much higher activation energy and therefore the antiparallel attack from the α face prevailed.

* An antiparallel attack to a carbon-carbon double bond of a cyclohexene ring is defined as the attack antiparallel to the neighboring pseudoaxial group while a parallel attack as the attack parallel to the neighboring pseudoaxial group.



237A, R=H
237B, R=CH_3

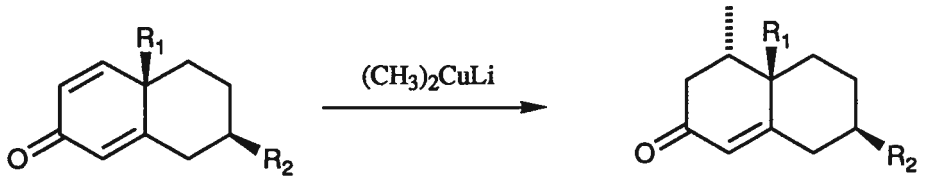
238A, R=H
238B, R=CH_3

antiparallel attack

parallel attack

Scheme 38 Conjugate Addition of Organocopper Reagents to *trans*-Fused Octalones

Even for cross-conjugated dienones **239A**, **239B**, and **239B** (Scheme 39), the α face attack still predominated[110].

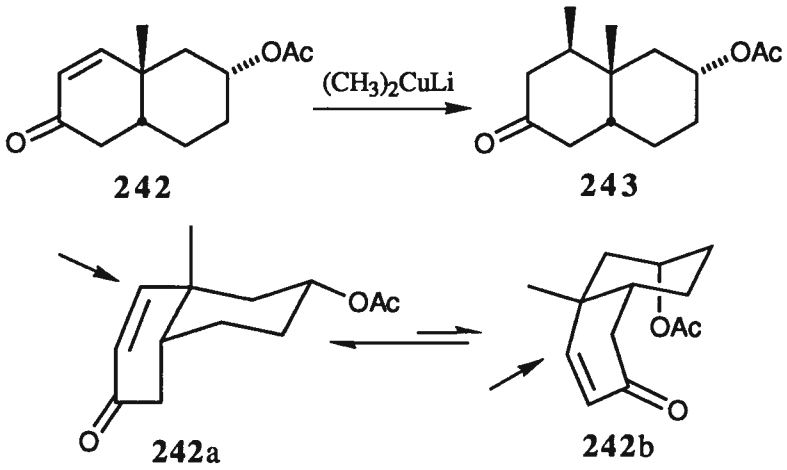


239A, R_1=CH_3, R_2=H
239B, R_1=CO_2CH_3, R_2=H
239C, R1=CH_3, R_2=–C(=CH_2)CH_3

240A, R_1=CH_3, R_2=H
240B, R_1=CO_2CH_3, R_2=H
240C, R1=CH_3, R_2=-C(CH_2)CH_3

Scheme 39 Conjugate Addition of Organocopper Reagents to Cross-conjugated Dienones

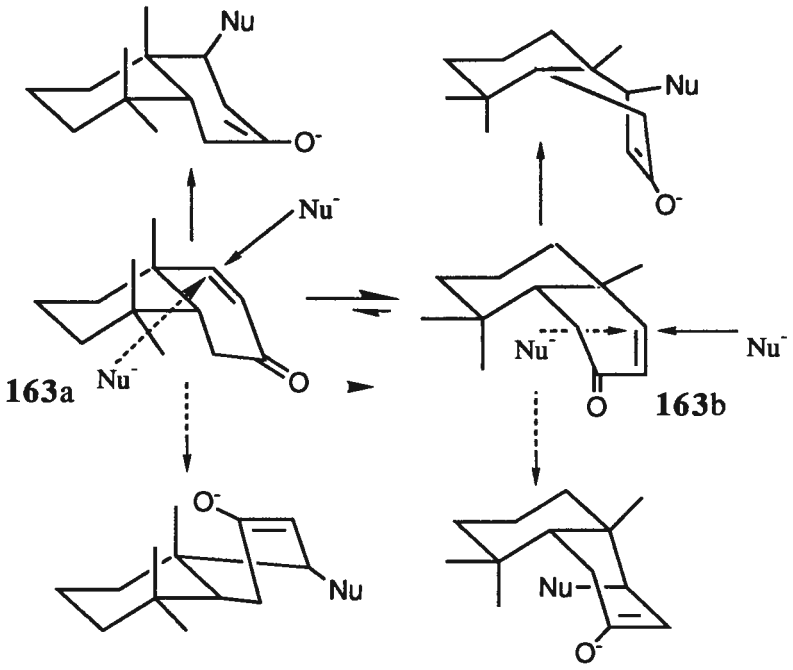
In the case of *cis*-fused octalone **242** (Scheme 40), only the product **243** resulting from β face attack was obtained by lithium dimethylcuprate addition[111]. Since octalone **242** does not have a rigid conformation, a consideration of all its conformers is necessary to understand this reverse facial stereoselectivity. For the steroid-like conformer **239**a, which should be more stable, the parallel attack from the α face is especially disfavored because of the highly hindered concave geometry of the α face and the skew-boat transition state involved. For the non-steroid-like conformer **239**b, the antiparallel attack from the α face is effectively blocked by the concave face and the axial acetoxyl grouping which remains in the approaching path of the reagent, despite that the transition state of this antiparalell attack has a half-chair conformation. In the event, the β face attack was the reaction path observed.



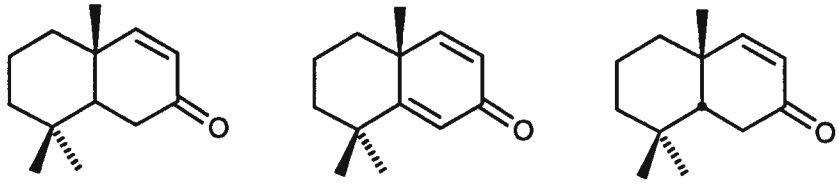
Scheme 40 Conjugate Addition of Organocopper Reagents to a *cis*-Fused Octalone

Using the same argument, we concluded that β face attack of the *cis*-fused enone **163** would be the favored mode. It is expected that **163** may exist in a conformational equilibria between **163**a and **163**b. In contrast to **242**, the non-steroid-like conformer (i.e., **163**b) is more stable than the steroid-like conformer (i.e., **163**a). The β face attack at **163**a is favored over the α face attack since it represents an antiparalle which requires a half-chair transition state rather than the less favorable skew-boat essential for the α face attack. The β face attack

at **163b** is expected as preferred because the severe steric hindrance from the axial methyl at C4 of ring A and the concave geometry of α face would block the α face antiparallel attack.



The use of the *trans*-fused enone **244** and dienone **165** (Figure 26), which were derivable from **160**[112], would probably produce α face addition compounds. Thus, these two compounds were very unlikely to be the backup or alternative intermediates towards the synthesis of (-)-Ambrox® (**179**).

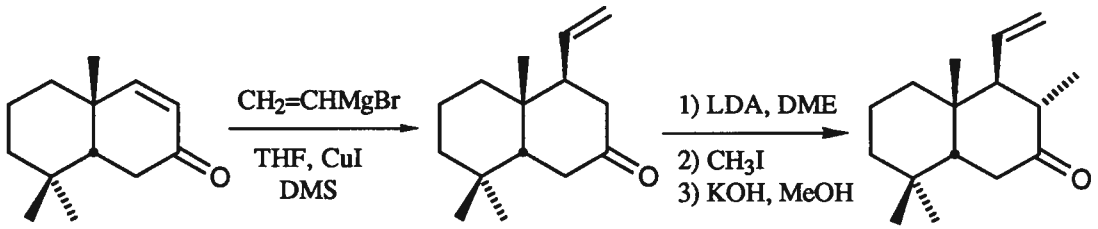


244 **168** **163**

Figure 26 Potential Candidate Intermediates for the Stereoselective Conjugate Addition

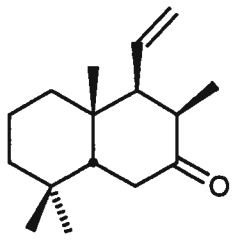
Experimentally, conjugate addition of **163** with 2.0 equivalents of vinyl magnesium bromide and a catalytic amount of cuprous iodide in dimethyl sulfide:THF (1:5, v/v) solution

gave the β face addition product **245** in 70% yield, the stereochemistry of which was confirmed by the ^{1}H-NMR spectrum of the methylation product **246** (see Figures 27 and 28 and the corresponding discussion). The absence of dimethyl sulfide[113] or the use of cuprous bromide as catalyst led to decrease in yields, likely due to the formation of competing 1,2-addition by-products. Some polar by-products were often observed in the reaction. γ,δ-Enone **245** had its mass spectrum showing the molecular ion peak at m/z 220 while its IR spectrum indicated absorptions at 1710 and 1635 cm^{-1}, corresponding to the presence of the carbonyl group and the terminal carbon-carbon double bond. Its ^{1}H-NMR spectrum displayed three methyl singlets at δ 0.90, 0.95, and 1.09 ppm, a complex five-proton multiplet at δ 2.25-3.10 ppm corresponding to the two methylene groups α to the carbonyl group and the tertiary allylic proton, and a three-proton multiplet at δ 4.95-5.80 ppm corresponding to the three olefinic protons in the terminal carbon-carbon double bond.



163 **245** **246**

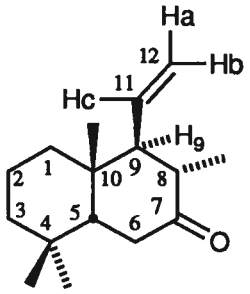
After γ,δ-enone **245** was treated with LDA in DME[114] initially at -78°C for 30 minutes, the mixture was warmed to approximately 45°C. Iodomethane (5.0 eqv.) was added rapidly to the mixture. Compound **246** together with its minor epimer **247** (6:1) was isolated



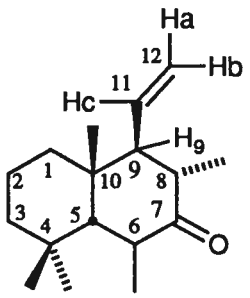
247

in 60-70% yield. Since these two epimers were not separable, a basic treatment with potassium hydroxide in methanol was performed to convert the epimeric mixture into the more stable compound **246** (~97% pure by GC). When THF was used as the solvent for the methylation reaction, a very large recovery (>60%) of starting material was observed presumably because the sluggishness of the methylation reaction led to a quick equilibration of the initially generated enolate with the methylation products through proton exchange[115]. The use of DME as a solvent to improve the alkylation reaction has been reported[116]. The improvement can be rationalized as follows: the bidentate chelation of DME causes the equilibration of the enolate mixture in the direction of the monomer which is more reactive and the alkylation reaction is thus accelerated[115,117]. The mass spectrum of **246** revealed the molecular ion peak at m/z 234. Its IR spectrum indicated an olefinic C-H stretching absorption at 3060 cm^{-1}, a carbonyl stretching absorption at 1700 cm^{-1}, and a carbon-carbon double bond stretching absorption at 1630 cm^{-1}. Its ^{1}H-NMR spectrum in $CDCl_3$ displayed three methyl singlets at δ 0.82, 0.94, and 1.14 ppm and one methyl doublet (J=6 Hz) at δ 1.04 ppm. There were a one-proton multiplet at δ 2.30 ppm and a complex three-proton multiplet at δ 2.40-2.70 ppm, corresponding to the allylic proton at C9 and three protons α to the carbonyl group. The olefinic signal at δ 5.01 ppm appeared as a doublet of doublets of doublets (J=17.0, 1.8, and 0.5 Hz). This signal was assigned to Hb since the resonance of Hb was expected to have a large J value (~15-20 Hz), due to coupling with Hc which was *trans* to Hb, and two small J values due to coupling with Ha and H9. Thus, the three J value were tentatively assigned as J (H_b,H_c)=17.0 Hz, J (H_a,H_b)=1.8 Hz, and J (H_b,H_9)=0.5 Hz. The olefinic proton signal at δ 5.14 ppm appeared as a doublet of doublets (J=10.2 and 1.8 Hz). This signal was assigned to Ha since the resonance of Ha should have a J value at 8-12 Hz, due to coupling with Hc which was *cis* to Ha, and a small J value of 1.8 Hz due to coupling with Hb. Thus, we obtained J (H_a,H_c)=10.2 Hz. The olefinic proton signal at δ 5.55 appeared as a doublet of triplets (J=17.0 and 10.2 Hz). It was assigned to Hc since the resonance of Hc was expected to appear at lower field and should show J values of 17.0 and 10.2 Hz. Thus, we obtained J (H_c,H_9)=J

(H_a,H_c)=10.2 Hz. The large coupling constant between Hc and H9 (J=10.2 Hz) indicated a near coplanarity of the C9-H9 and C11-Hc bonds. In the nonsteroid-like conformer **246a**, the vinyl side chain is drawn as shown in order to portray this situation and to indicate minimal interactions with neighboring groups, as revealed from molecular models.

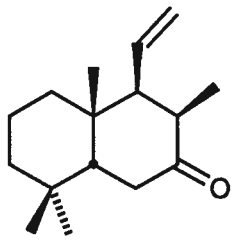


246



248

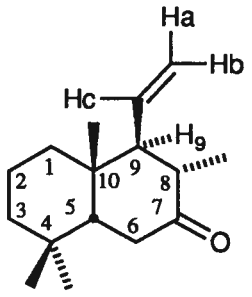
The epimer **247,** generated as a minor product together with **246** during the methylation of **245,** was not characterized by spectroscopy since its separation from **246** was very difficult. However, a partially enriched sample (50% by GC) obtained from the methylation in THF was converted into **246** (97% pure by GC) by treatment of the mixture with a dilute KOH-methanol solution. The existence of **247** was then indirectly confirmed.



247

To confirm the stereoselectivity of the conjugate addition reaction and the regioselectivity of the methylation reaction, a detailed ^{1}H-NMR spectrum analysis of **246** was conducted (Figure 27). The ^{1}H-NMR spectrum in deuteriated benzene[118] afforded a clear resolution of the four proton signals at δ 2.20-2.70 ppm previously observed in the spectrum taken in

deuteriated chloroform. Decoupling by irradiation at δ 5.75 ppm (Hc signal) caused a one-proton triplet (J=10.2 Hz) at δ 2.42 ppm to collapse into a doublet (J=10.2 Hz) in addition to the collapsing of the Ha signal at δ 4.94 ppm and Hb at δ 4.82 ppm into two broad singlets. Therefore, the triplet signal at δ 2.42 ppm was clearly due to the allylic proton (H9) which apparently coupled only with Hc and one neighboring axial proton (J=10.2 Hz). Thus, the methylation of **245** must have taken place at C8 rather than at C6. The methylation at C6 would have produced **248** which should have a more complex signal (doublet of doublets or triplet) for the allylic proton (H9) if irradiation at the Hc signal had occurred. The only methyl doublet signal in the $CDCl_3$ spectrum appeared at δ 1.15 (J=5.1 Hz) was assigned to the methyl group at C8. A one-proton mutiplet, consisting of six lines of equal spacing (5.1 Hz) and an intensity ratio 1:3:4:4:3:1, appeared at δ 1.90 ppm in the C_6D_6 spectrum and at δ 2.28 ppm $CDCl_3$ respectively. The splitting pattern of this signal was indeed a doublet of quartets with J=10.2 Hz for the doublet coupling and J=5.1 Hz for the quartet coupling. Thus, this signal was assigned to the α methine proton at C8.



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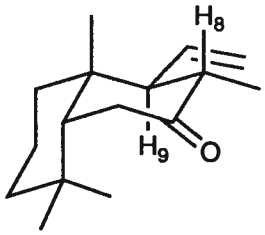
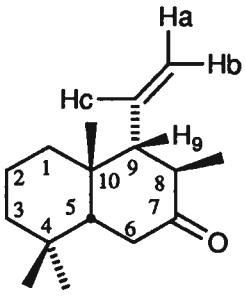
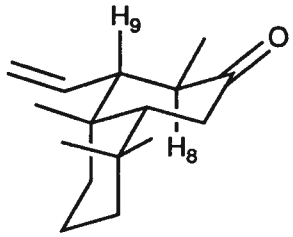


246a



249



249a

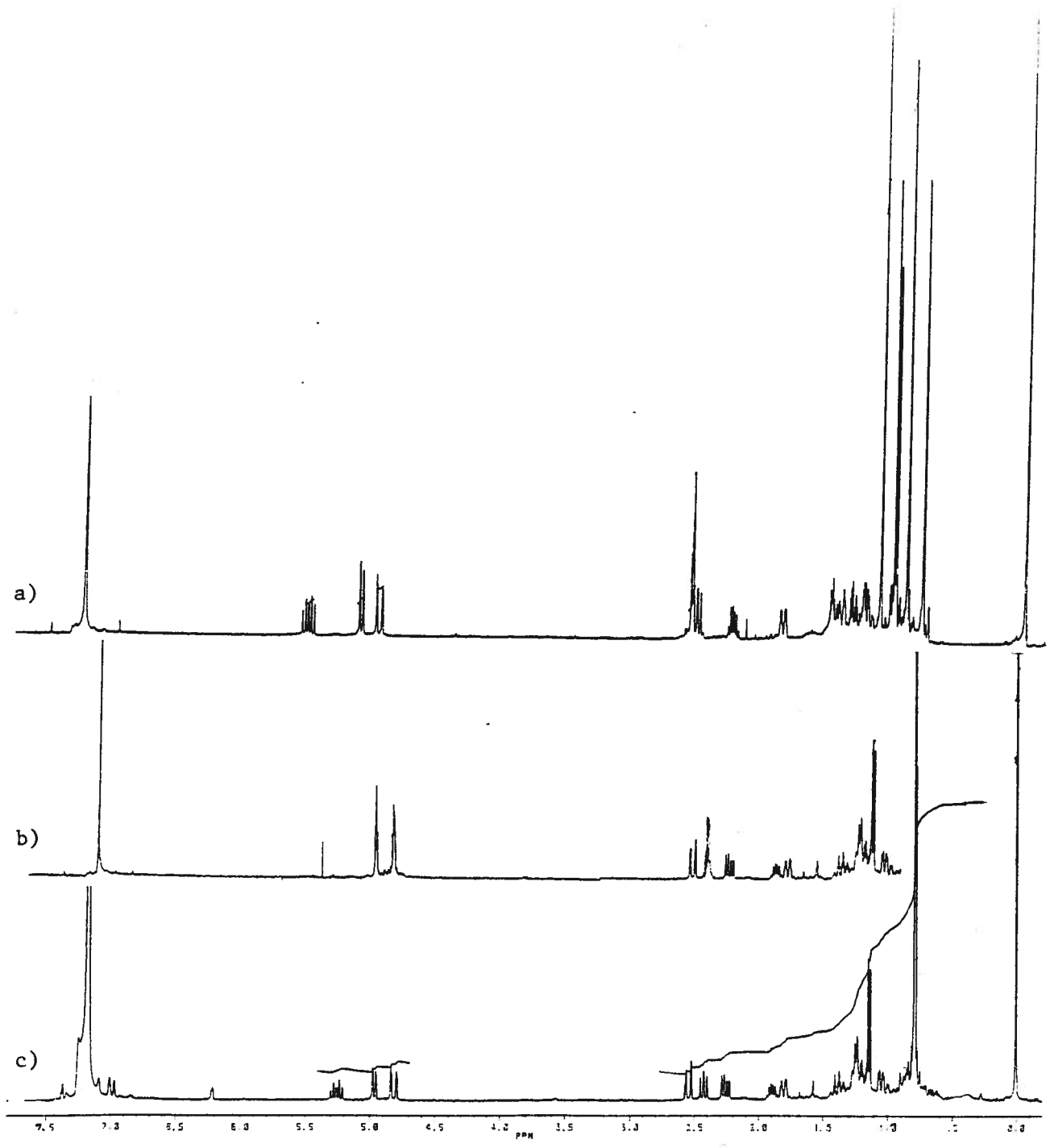


Figure 27 Decoupling Experiments of **246**
a) the ^{1}H-NMR off-resonance spectrum in $CDCl_3$.
b) proton-proton homonuclear decoupling at 5.75 ppm (C_6D_6).
c) the ^{1}H-NMR off-resonance spectrum in C_6D_6.

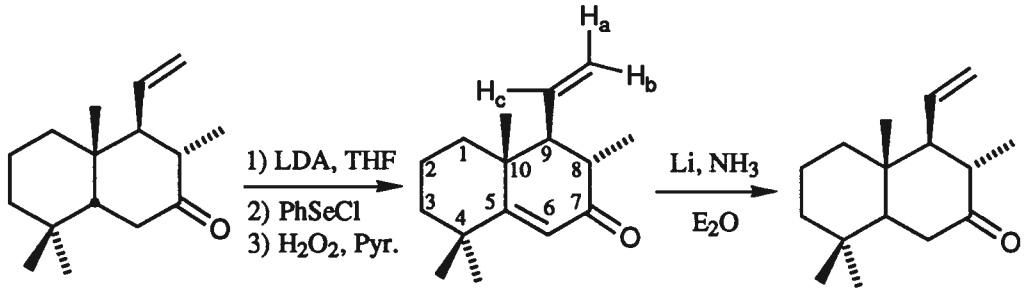
In fact, the structure **249**a (a conformer of compound **249** which had reverse configurations at C8 and C9 with regard to **246**) could also account for the result of decoupling experiments, especially the large coupling constant between Hc and H1 (J (H_c,H1)=10.2 Hz) due to the diaxial orientation of these two protons. Therefore, to eliminate further doubt about the stereochemistry of **246**, NOE difference experiments were carried out. Unfortunately, this effort did not prove to be productive. The crowdedness of signals in the aliphatic proton region in both $CDCl_3$ and C_6D_6 spectra caused the interpretation of NOE difference experiments very difficult. However, important evidence was later obtained from compound **251**, the epimer of **246** (see section **3.2.3.**).

To obtain **246** more effectively, we had tried to carry out an "one-pot reaction" by quenching the enolate generated in the conjugate addition with iodomethane. The one-pot operation would eliminate intermediate isolation and could be an efficient way to ensure the desired regioselective methylation[119]. However, the one pot operation proved to be very sluggish and produced mostly by-products in addition to compound **246** (10%) and **245** (10%). Attempts to improve the reaction by changing solvents (Et_2O, THF, DME), temperature, and using HMPA as additive failed. Since the conjugate addition worked well to produce **245** in good yield, the methylation step must be responsible for the sluggishness of this one-pot operation. The slowness of the methlyation reaction under the experimental conditions could lead to the proton exchange between the initially formed enolate from the conjugate addition reaction and the methylation product **246**. The enolate of **246** thus generated would be then further methylated. O-methylation of enolates might be also responsible for some by-reactions.

3.2.3. Conversion of *cis*-fused γ,δ-enone 246 to *trans*-fused γ,δ-251

The stereochemical conversion of the A/B *cis* fusion in compound **246** to the desired A/B *trans* fusion in **251** was realized through a two-step sequence: the introduction of a

double bond to give **250** and a stereoselective reduction of **250** to produce the *trans*-fused compound **251**.



246 **250** **251**

Slow addition of **246** dissolved in THF solution to a lithium diisopropylamide-THF solution at -78°C under nitrogen was followed by a rapid injection of a phenylselenenyl chloride-THF mixture. After stirring 1 hour at room temperature, THF was evaporated *in vacuo*. Methylene chloride, pyridine, and hydrogen peroxide were added and the resulting mixture was stirred overnight. Dienone **250** was then isolated in 65% yield based on a 25% recovery of starting material. The mass spectrum of **250** indicated a molecular ion peak at m/z 232. The UV spectrum showed maximal absorptions at 242 nm (log ε=3.96) and 383 nm (log ε=3.46) corresponding to π-π^* and n-π^* transition absorptions of the enone moiety. The IR spectrum displayed an olefinic carbon-hydrogen stretching absorption at 3060 cm^{-1}, a conjugated carbonyl stretching absorption at 1660 cm^{-1}, and a carbon-carbon double bond stretching absorption at 1630 cm^{-1}. The ^{1}H-NMR spectrum revealed a methyl doublet (J=5.1 Hz) at δ 1.07 ppm and three methyl singlets at δ 1.17, 1.22, 1.25 ppm. A triplet (J=10.2 Hz) at δ 2.12 ppm and a multiplet at δ 2.40 ppm, consisting of six equally-spaced (5.1 Hz) lines which had an intensity ratio 1:3:4:4:3:1, were assigned to the allylic proton at C9 and the methine proton at C8 (dq, J=10.2 and 5.1 Hz). Four olefinic protons at δ 5.05 (dd, J=17.0 and 1.8 Hz), 5.18 (dd, J=10.2 and 1.8 Hz), 5.64 (dt, J=17.0 and 10.2 Hz), and 6.00 (s) ppm, were attributed to Hb, Ha, Hc, and H6.

To reduce the large recovery of starting material and improve the yield of dehydrogenation, different conditions were applied[120]. One-phase elimination of the phenylselenide oxide by direct H_2O_2 (30%) addition to the phenylselenide prepared in THF or DME (dimethoxylethane) led to a even greater recovery of starting material (50%) and a lower yield of **250** (50% based on recovery). Another one-phase elimination of phenylselenide oxide by transferring the phenylselenide into a sodium periodate solution in methanol-H_2O (1:1) mixture resulted in the formation of a new compound of unknown structure (25% based on recovery) in addition to **250** (40% based on recovery) and the recovered starting material (25%).

TLC monitoring of the reaction showed that little starting material **246** was left after the introduction of phenylselenenyl chloride and the newly generated phenylselenides appeared as two UV active spots of apparenly different intensities. Attempts to separate these two spots by silica gel chromatography failed as only the starting material **246** was isolated. Apparently, the selenides were very labile. In fact, even leaving the phenylselenides in THF-H_2O mixture overnight regenerated the starting material **246** as exclusive product.

It was expected that the phenylselenylation of **246** would produce two diastereomers (iv) and (v), resulting from the attacks on α and β faces of the enolate of **246** (Figure 28). The β face attack of phenylselenenyl chloride on the dominant conformer (i) of the enolate has the advantage of going through a less strained half-chair transition state (ii) but suffers the steric hindrance from the angular methyl group. The α face attack has to go through a strained skew-boat transition state (iii) and suffers the hindrance from the *gem*-dimethyl groups in ring A[121]. Therefore, the β face attack has some advantage overall. As we know, the [2,3] sigmatropic elimination of selenoxides goes through a *syn*-coplanar transition state[122]. Therefore, only the selenoxide derived from (iv) will undergo elimination to afford **250** while the selenoxide from (iv) will likely decompose back to the starting material **246**.

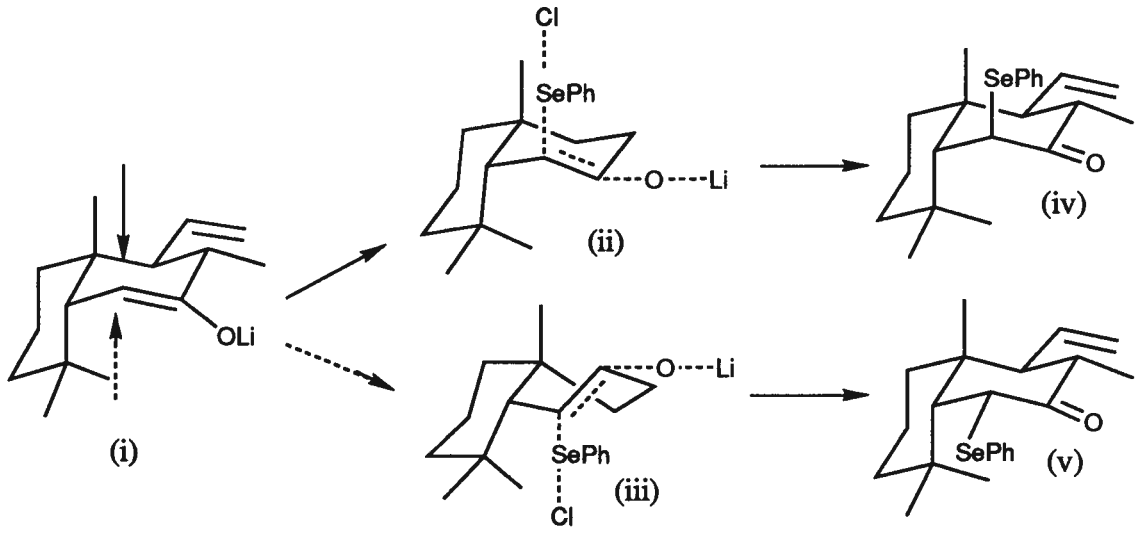
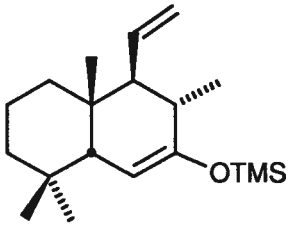


Figure 28 Stereochemistry of Phenylselenenylation of **246**

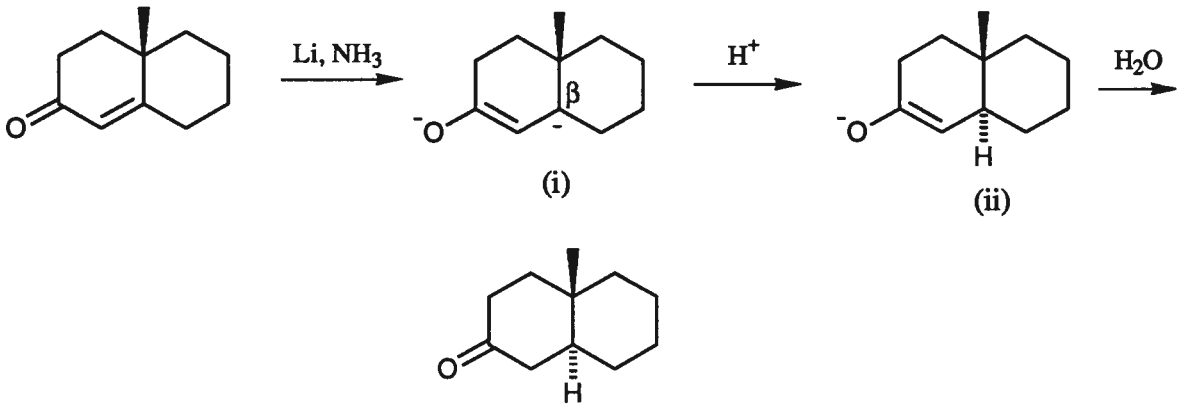
In another attempt, the trimethylsilyl enolether **252** was prepared by reaction of **246** with LDA and trimethylsilyl chloride in THF and subsequent treatment with different oxidizing agents, DDQ[123a,b,c], palladium (II) acetate[123d], and trityl fluoroborate (ie., triphenylcarbenium tetrafluoroborate)[123b]. None of these treatments gave any new product.



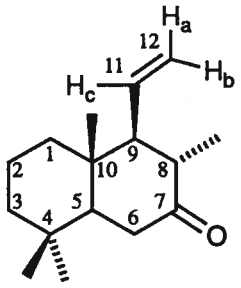
252

The stereochemistry of Birch reduction on octalones has been well studied[124] and theories to rationalize the data have been forwarded[125,126]. For simple octalones, the *trans*-fused products were frequently obtained. It is assumed that the reduction goes through a dianion intermediate (i). The protonation of (i) at the β position produces enolate (ii) which is then hydrolyzed to give the saturated product. Thus, the stereochemistry of the final product is decided by the protonation step of dianion (i). Stork et al.[125] assumed the dianion (i) has a

tetrahedral β carbon while Robinson[126] instead proposed that the β carbon is trigonal. The importance of orbital overlap in the transition state of the transformation between (i) and (ii) was recognized by both groups.



Treatment of **250** in anhydrous ether:ammonia (1:2) employing a slightly excessive lithium for one hour and quenching the resulting mixture by ammonium chloride, afforded **251** in 90% yield. The GC retention times of the epimers **246** and **251** were very different from each other. The mass spectrum of **251** showed its molecular ion peak at m/z 234 while the IR spectrum indicated the carbonyl stretching absorption at 1706 cm^{-1}. The ^{1}H-NMR spectrum in $CDCl_3$ displayed three methyl singlets at δ 0.88, 0.90, and 1.09 ppm, a methyl doublet (J=6.0 Hz) at δ 0.93 ppm, a four-proton multiplet at δ 2.00-2.50 ppm, and three olefinic protons at δ

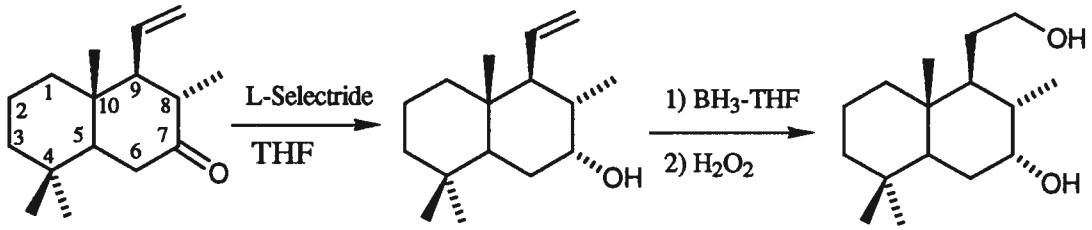


248

4.98 ppm (dd, J=16.8 and 1.6 Hz), 5.12 ppm (dd, J=10.0 and 1.6 Hz), and 5.56 ppm (dt, J=16.8 and 10.0 Hz). As in the case of **246**, these three olefinic signals were assigned to Hb at C12, Ha at C12, and Hc at C11 respectively. The large coupling constant (J=12.0 Hz) between the H9 and H8 was again observed from the H9 signal (δ 1.96 ppm, t, J=12.0 Hz) in the ^{1}H-NMR spectrum (C_6D_6), which proved beyond any doubt that the diequatorial orientation of vinyl group at C9 and methyl group at C8 in **251**. Therefore, the diequatorial orientation of these two groups in the structure **246**a were further confirmed. The structure **249**a can now be firmly excluded since its corresponding *trans*-fused product would have these two groups diaxially oriented.

3.2.4. Synthesis of Diol 255 from *trans*-Fused γ,δ-Enone 251

As stated earlier, an axial secondary hydroxyl group at C7 in the diol **255** was required for the cyclization to occur in a desired manner.



251 **253** **255**

To this end, γ,δ-enone **251** was treated with L-Selectride (i.e., lithium tri-*sec* -butylborohydride) in THF at -78°C. The axial alcohol **253** was isolated in nearly quantitative yield. The mass spectrum indicated the molecular ion peak at m/z 236 and a fragment ion at m/z 218 due to the loss of a water molecule. The IR spectrum showed a broad intense hydroxyl stretching absorption near 3450 cm^{-1} and a carbon-carbon double bond stretching absorption at 1630 cm^{-1}. The ^{1}H-NMR spectrum revealed a quartet (J=3.0 Hz) at δ 3.92 ppm corresponding to the α proton of the axial hydroxyl group and three one-proton multiplets at δ

4.94 (dd, J=17.2 and 2.4 Hz), 5.02 (dd, J=10.4 and 2.4 Hz), and 5.52 (dt, J=17.2 and 10.4 Hz) ppm. The fact that the α proton of the newly introduced secondary hydroxyl appeared as a quartet at δ 3.92 ppm with a small coupling constant (J=3.0 Hz) confirmed its equatorial orientation. As shown in Figure 29, an equatorial proton at C7 in compound **253** is expected to couple nearly equally with the vicinal axial protons (Hax at C8 and Hax at C6) and the equatorial proton (Heq) at C6 because of the close dihedral angles, <Heq(7)-C7-C8-Hax(8), <Heq(7)-C7-C6-Hax(6), and <Heq(7)-C7-C6-Heq(6)[127]. Therefore, a quartet with a small coupling constant is expected for an equatorial proton at C7. Instead, an axial proton at C7 in compound **254** would couple nearly equally with the axial protons at C6 and C8 but differently to the equatorial proton at C6. A doublet of triplets with $J_{ax,eq}$ ~ 3 Hz and $J_{ax,ax}$ ~ 10Hz would be expected for this axial proton at C7.

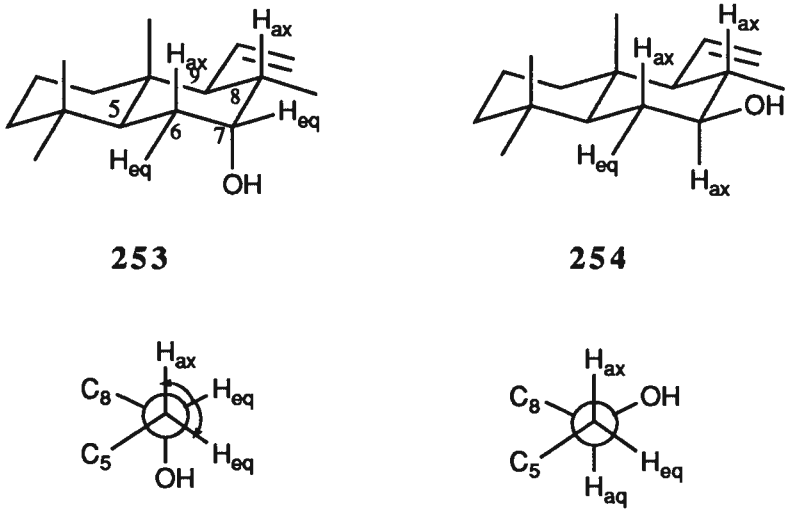
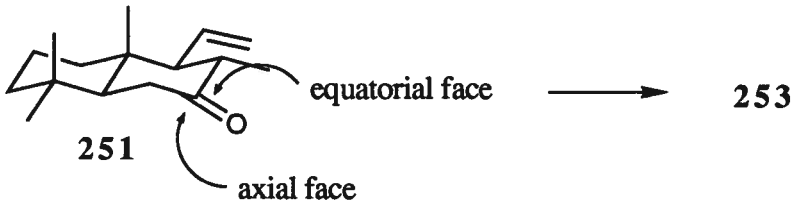


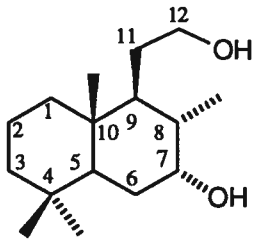
Figure 29 Structural Analysis of Stereoselective Reduction Product **253**

The stereochemical outcome of the reaction between cyclic ketones and various hydrides has been frequently reviewed[128]. For highly hindered hydride reagents like lithium tri-*sec*-butylborohydride[129a] and lithium tris(*trans*-2-methylcyclopentyl)borohydride[129b], the product from the less hindered face attack is usually expected. The most remarkable feature of these hindered hydride reagents lies in their ability to deliver the hydride almost exclusively in

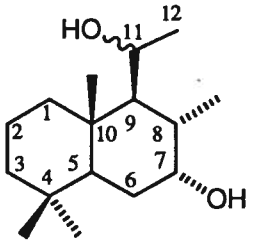
an equatorial manner, even in the absence of any other nearby differentiating groups in the cyclohexanone ring, to give an axial alcohol. Therefore, we could predict with confidence that lithium tri-*sec*-butylborohydride reduction of **251** would produce the axial alcohol **253**. This is indeed the case.



The hydroboration of **253** with borane in THF, followed by basic hydrogen peroxide workup, produced mainly the 1,5-diol **255** (70%) in addition to a minor 1,4-diol **256** (10%). Diol **255** had its mass spectrum showing the molecular ion peak at m/z 254 and two fragment ions at m/z 236 and 218 corresponding to loss of one and two water molecules from the parent molecular ion. The ^{1}H-NMR spectrum revealed two overlapping methyl singlets at δ 0.82 ppm, one methyl singlet at δ 0.85ppm, a methyl doublet at δ 0.98 (J =6.0 Hz), a one-proton multiplet (dt, J=7.2 and 9.6 Hz) at δ 3.50, a one-proton multiplet at δ 3.62 ppm (J=5.6 and 9.6 Hz), and a quartet (J=3.0 Hz) at δ 3.85 ppm corresponding to the α hydrogen attached to the secondary hydroxyl group at C7. The two one-proton multiplets at δ 3.50 and 3.62 ppm were due to the methylene group attached to the newly created primary hydroxyl group. Therefore, the hydroboration reaction of **253** proceeded regioselectively according to the general rule that the hydroxyl group is preferentially situated at the less substituted end of a double bond in hydroboration reaction[130].



255

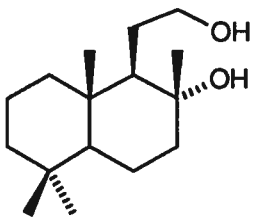


256

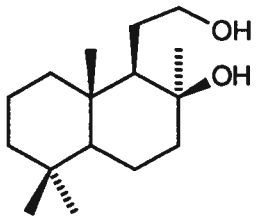
The minor product **256** appeared to be a mixture of two diastereomers with a ratio of 4:1, as indicated in the ^{1}H-NMR spectrum. These two diastereomers were difficult to separate by column chromatography. The mass spectrum of the mixture revealed a molecular ion peak at m/z 254. The IR spectrum showed an intense hydroxyl absorption at 3400 cm^{-1}. In the ^{1}H-NMR spectrum, the minor diastereomer had a broad singlet at δ 3.77 ppm corresponding to H7 and a quartet (J=8.0 Hz) at δ 4.12 ppm corresponding to the α proton at C11 while the major isomer had a broad singlet at δ 3.87 ppm corresponding to H7 and a quartet (J=8.0 Hz) at δ 4.21 ppm corresponding to the α proton at C11 in the ^{1}H-NMR spectrum. Further assignment of the stereochemistry at C11 to these two diastereomers was not possible based on the above obtained data.

3.2.5. Cyclization of Diol 255 to (-)-Ambrox® (179)

As shown in the Introduction, most of the synthetic sequences to natural or racemic Ambrox® involved a cyclization of a 1,4-difunctional (at C8 and C12) intermediate to form the tetrahydrofuran ring. Cyclizations of the the 1,4-diol **199** by β-naphthalenesulfonic acid in toluene[96] or *p*-toluenesulfonyl chloride in pyridine[99,104] and the epimeric 1,4-diol **232** by *p*-toluenesulfonic acid in nitromethane[106] are of more direct relevance to our designed cyclization of diol **255** (Figure 30).



202



235

Figure 30 1,4-Diols Utilized for Acid Catalyzed Cyclization to (-)-Ambrox®

It is assumed[106] that these cyclization reactions catalyzed by acids proceed through a tertiary carbocation (i) which is formed by elimination of the tertiary hydroxyl group at C2

(Figure 31). The α face attack by the primary hydroxyl is kinetically preferred to the β face attack because the latter would be subjected to steric hindrance from the angular methyl group in the transition state (iii). Thus, Ambrox® (**179**) is preferentially produced through a lower energy transition state (ii). However, *iso*-Ambrox® (**189**) resulting from the β face attack will become the major product under prolonged treatment and can actually be obtained from Ambrox® (**179**) under the same condition[96]. This reflects that (+)-*iso*-Ambrox® (**189**) with a *cis*-fused tetrahydrofuan ring is thermodynamically more stable.

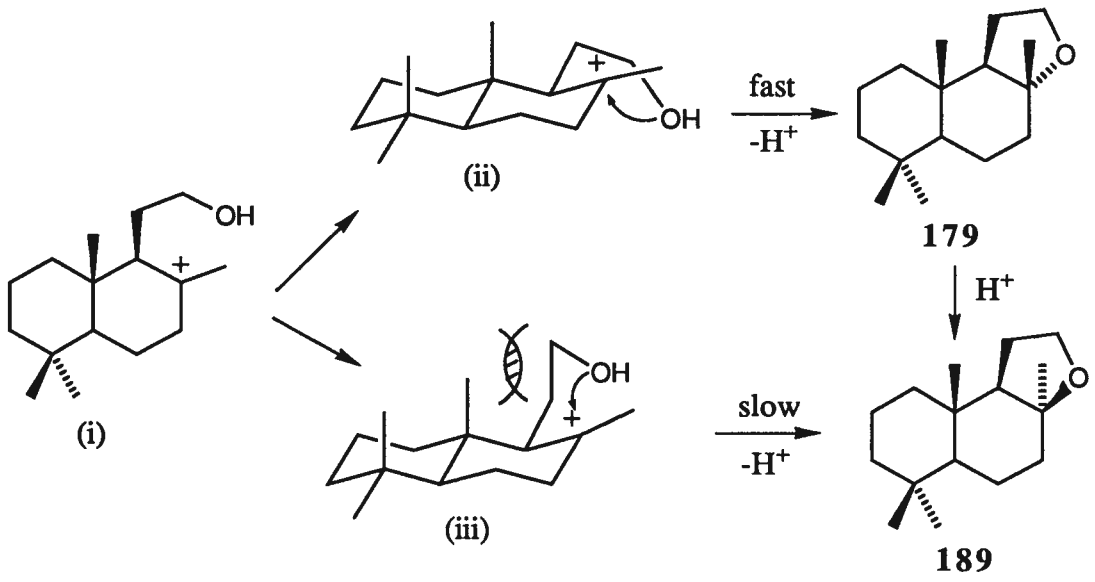
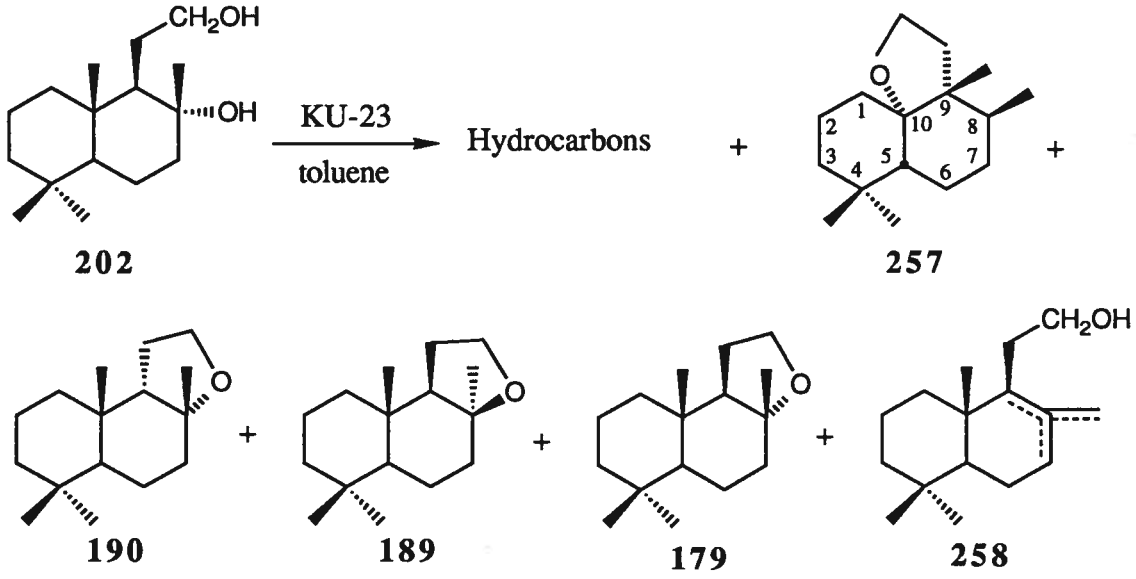


Figure 31 Mechanistic Analysis of Cationic Cyclizations of **202** and **235**

Under even more dramatic condition, i.e., boiling toluene with a cation-exchange resin "KU-23"* as catalyst[131a], (-)-Ambrox® (**179**), initially formed from diol **202**, was rapidly converted to a hydrocarbon mixture of unidentified structures (60%) and a new tetrahydrofuran

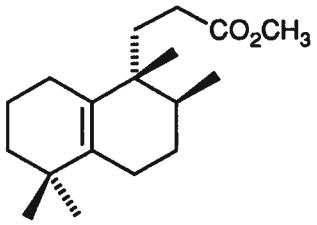
* The Chemical Abstract registry number for KU-23 is [9049-63-2]. This resin was first recorded in Chemical Abstract in 1966 (CA 65: 15600a). Regretfully, we have no access to the corresponding original article[131b] by Soviet chemists. Later reports on the application of KU-23 contain no specific information about its preparation and structural characterization. Since KU-2, another cation exchange resin, is a sulfonated copolymer of styrene and divinyl benzene[131c] (CA 55: 27959i) and KU-21, also a cation exchange resin, is a modification of KU-2 containing additional hydroxyl and carboxyl groups[131d] (CA 55: 4819g), KU-23 is probably a modification of KU-2, i.e., a modified sulfonated copolymer of styrene and divinyl benzene.

257 of a rearranged bicyclofarnesane skeleton (32%) in addition to a small amount of *epi*-Ambrox® (**190**) and *iso*-Ambrox® (**189**) (Scheme 41). This resulting dehydration product of definite chemical composition was called "ionoxide". It was claimed that the 'ionoxide' had a very distinct musk-ambergris odor and a very high rating as a perfume. On the whole, the smell of "ionoxide" was determined by the tricyclic compound **258**, which had a strong musk odor, reminiscent of the odor of muscone. At lower temperature (90°C), the major products were detected to be Ambrox® (**179**), (+)-*iso*-Ambrox® (**189**) and a mixture of unsaturated alcohols **259** as shown in Scheme 41.



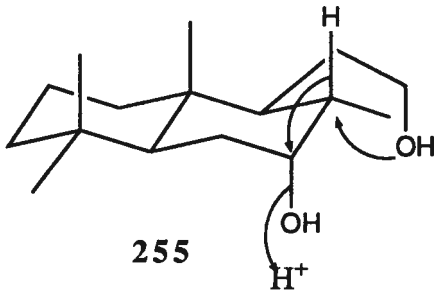
Scheme 41 The Formulation of "Ionoxide"

The gross structure and stereochemistry of **257** was established[131a] by a chemical correlation with the known compound **259**. The configurational reversal at C5 is especially noteworthy.

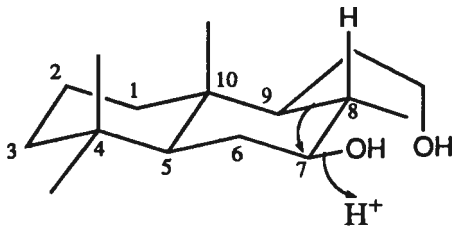


259

The choice of diol **255** as the substrate to be cyclized to (-)-Ambrox® (**179**) has been briefly justified in Section **3.2.1**. Diol **260**, the epimer of **255**, has an equatorial hydroxyl group at C7 and therefore it is very likely to undergo a skeletal rearrangement (ring contraction), as indicated below, when treated with acids*.

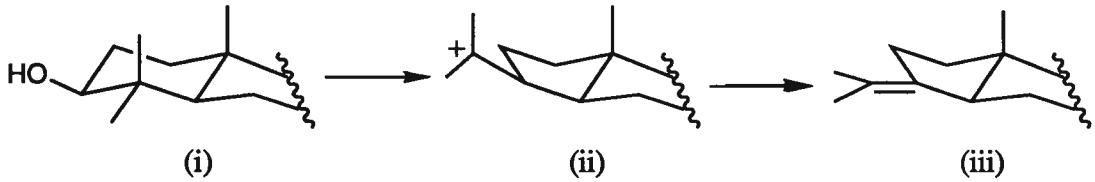


255

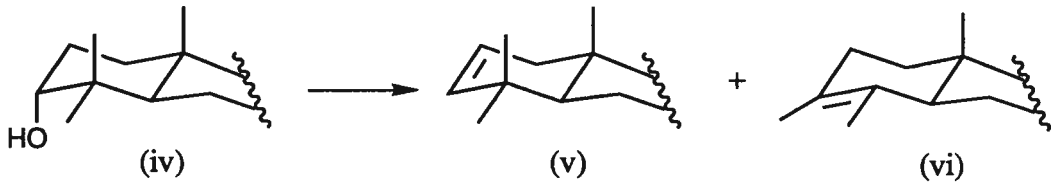


260

It is well known that 3β-hydroxy-triterpenoids, e.g., (i), undergo ring A contraction to give isopropylidene derivatives of partial formula (iii) via carbocation (ii) when treated with acids[132,133]. This rearrangement is of diagnostic value, since 3α-hydroxytriterpenoids (iv), when treated under the same conditions, yield principally products of partial structures (v) and (vi) due to a simple 1,2-elimination and a methyl migration. It is assumed that the four centers involved in the migration or elimination should adopt an anti co-planar conformation.



(i) (ii) (iii)



(iv) (v) (vi)

* It should be noted that no precedent for the cyclization of a 1,5-diol into a tetrahydrofuran could be found in the literature.

The cyclization of **255** was effected under different conditions, as is summarized in Table 5. Treatment of **255** with *p*-toluenesulfonic acid (2.0 eqv.) in nitromethane at 80°C for 2 hours gave (-)-Ambrox® (**179**) (31%), (+)-*iso*-Ambrox® (**189**) (30%), a mixture of alcohols **261** (15%), and a mixture of hydrocarbons. All spectroscopic data of **179**, **189** were consistent with those recorded in literature. The yield of **179** increased to 48% and the production of (+)-*iso*-Ambrox® (**189**) decreased to 15% by using toluene as the solvent.

The melting point and specific rotation $[\alpha]_D^{25}$ of the obtained (-)-Ambrox® were measured to be 74-76°C and -25.1 (c=1.00, $CHCl_3$). They agree well with the reported values [m.p. 77-77.5°C; $[\alpha]_D^{20}$=-24.7 (c=1.0, $CHCl_3$)][90]. The IR, ^{1}H-NMR, and mass spectroscopic data are identical with those recorded in the literature[90].

The melting point and specific rotation $[\alpha]_D^{25}$ of the obtained (+)-*iso*-Ambrox® were measured to be 57-59°C and +7.3 (c=1.00, $CHCl_3$). They agree well with the reported values [m.p. 60-60.5°C; $[\alpha]_D^{20}$=+7.5 (c=1.0, $CHCl_3$)][90]. The IR, ^{1}H-NMR, and mass spectroscopic data are identical with those recorded in the literature[90].

The mixture of alcohols **261** contained a few compounds, as shown the gas chromatogram and the complex ^{1}H-NMR spectrum. This mixture could not be further purified by column chromatography. It displayed a hydroxyl stretching absorption at 3450 cm^{-1} in the mass spectrum and a molecular ion peak at m/z 220 in the mass spectrum. Thus, this mixture was probably composed of monodehydrated compounds from diol **255**.

The non-polar hydrocarbon mixture was obtained from the earliest fractions from column chromatography. It contained several compounds, as revealed from the gas chromatogram. The IR spectrum indicated no hydroxyl stretching absorption while the mass spectrum showed a molecular ion peak at m/z 218. Thus, this mixture must be a doubly dehydrated product of diol **255**. The ^{1}H-NMR spectrum displayed poorly resolved aliphatic proton signals at δ 0.60-2.65 ppm and olefinic proton signals at δ 5.00-5.60 ppm. It could not be further separated.

Under a more dramatic condition (CH_3NO_2, 100°C, 3.0 eqv. HOTs), the cyclization produced compound **257**, the principal component of "ionoxide", in 34% yield and (+)-*iso*-Ambrox® (**189**) in 19% yield. The specific rotation $[\alpha]_D^{25}$ of compound **257** was +37.1 (c=1.00, $CHCl_3$), which is in good agreement with the reported value ($[\alpha]_D^{18}$=+39.1, c= 6.7, $CHCl_3$)[131a]. Its other spectroscopic data, including IR, ^{1}H-NMR, and MS spectra are consistent with those reported[131a]. Similar to what was reported by Vlad et al.[131a], a hydrocarbon mixture was isolated in large amount (41%) from this reaction.

Table 5 Cyclization of the 1,5-Diol **255** under Different Conditions

Conditions	Composition of dehydration products, %				
	179	**189**	**257**	**261**	hydrocarbons
HOTs (2.0 eqv.), CH_3NO_2 80°C, 2 hrs	31	30	--	15	22
HOTs (2.0 eqv.), Toluene 80°C, 2 hrs	48	10	--	15	8
HOTs (3.0 eqv.), CH_3NO_2 100°C, 0.5 hrs	--	19	34	--	40

No significant difference was observed when *p*-toluenesulfonic acid was replaced with β-naphthalenesulfonic acid.

Non-protonic, poorly ionizing solvents, i.e., nitromethane and toluene, were used for our cyclization of the 1,5-diol-**255**. These two solvents have been employed previously in the cyclization of 1,4-diols to (-)-Ambrox® (**179**)[96,106,131]. The yield of 1,2-elimination (dehydration) by-products **258** (Scheme 41) was minimized by using these solvents. Presumably, mainly ion pairs rather than free carbocations are involved under these conditions[134]. The loss of β protons has to take place from the same side of the leaving group

Presumably, mainly ion pairs rather than free carbocations are involved under these conditions[134]. The loss of β protons has to take place from the same side of the leaving group (i.e., H_2O) which, instead of the solvent, acts as the base. Such a stereochemical requirement reduces the possibilities of 1,2-eliminations in rigid *trans*-fused decalone systems. If highly ionizing solvents were used, free planar carbocations would be formed and therefore the loss of β protons would occur from either the same or the opposite side of the leaving group.

The mechanism for the formation of **257** from (+)-*iso*-Ambrox® (**189**)[131] as well as from our 1,5-diol **255** is proposed (Figure 32). The consecutive 1,2-shifts of peripheral axial hydrogens and the angular methyl group as indicated may produce an olefin **261** which has two conformers **262** (i) and **262** (ii). Cyclization of the more stable conformer (ii) via an intramolecular anti addition produces **257**, the principal component of "ionoxide".

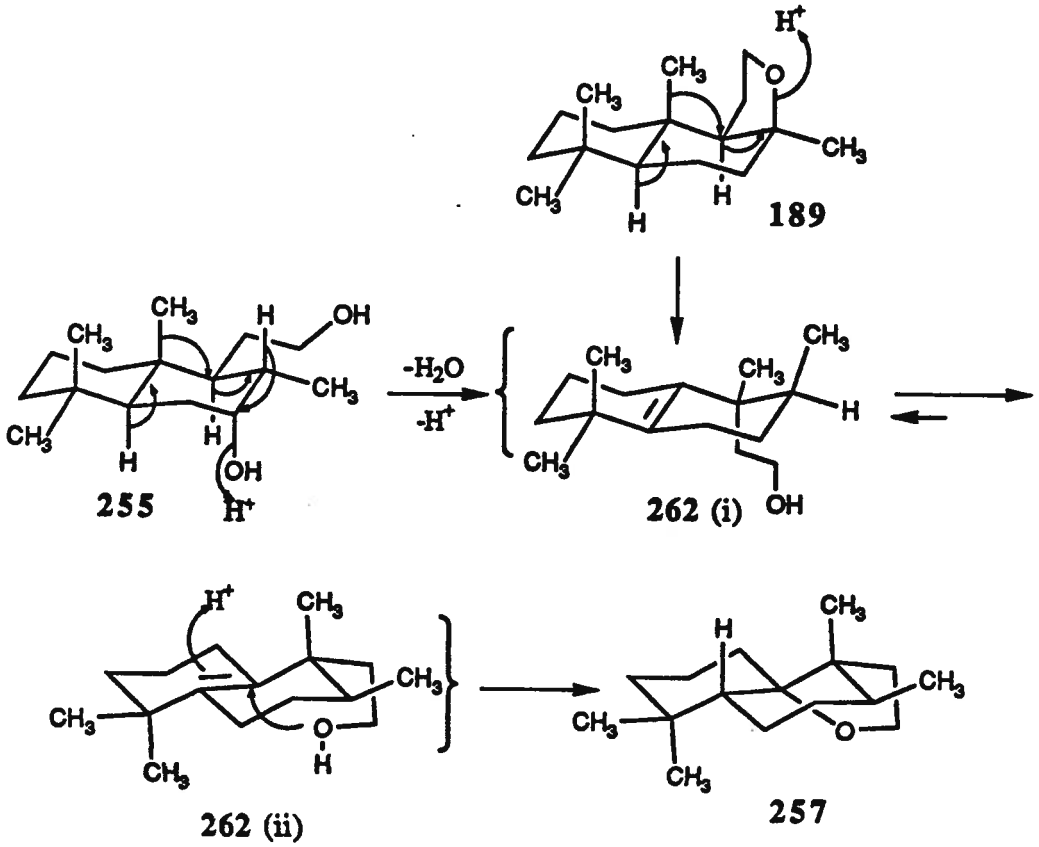


Figure 32 Mechanism for the Formation of **257**

the triterpenoid 3-β-friedelanol (**263**) was transformed into 13 (18)-oleanene (**264**) by acid catalysis[135]. Presumably, the carbocation (i) (Figure 33) generated from **263** undergoes six stereoelectronically controlled 1,2-shifts as shown to afford the carbocation (ii). The loss of a proton results in 13 (18)-oleanene **264**.

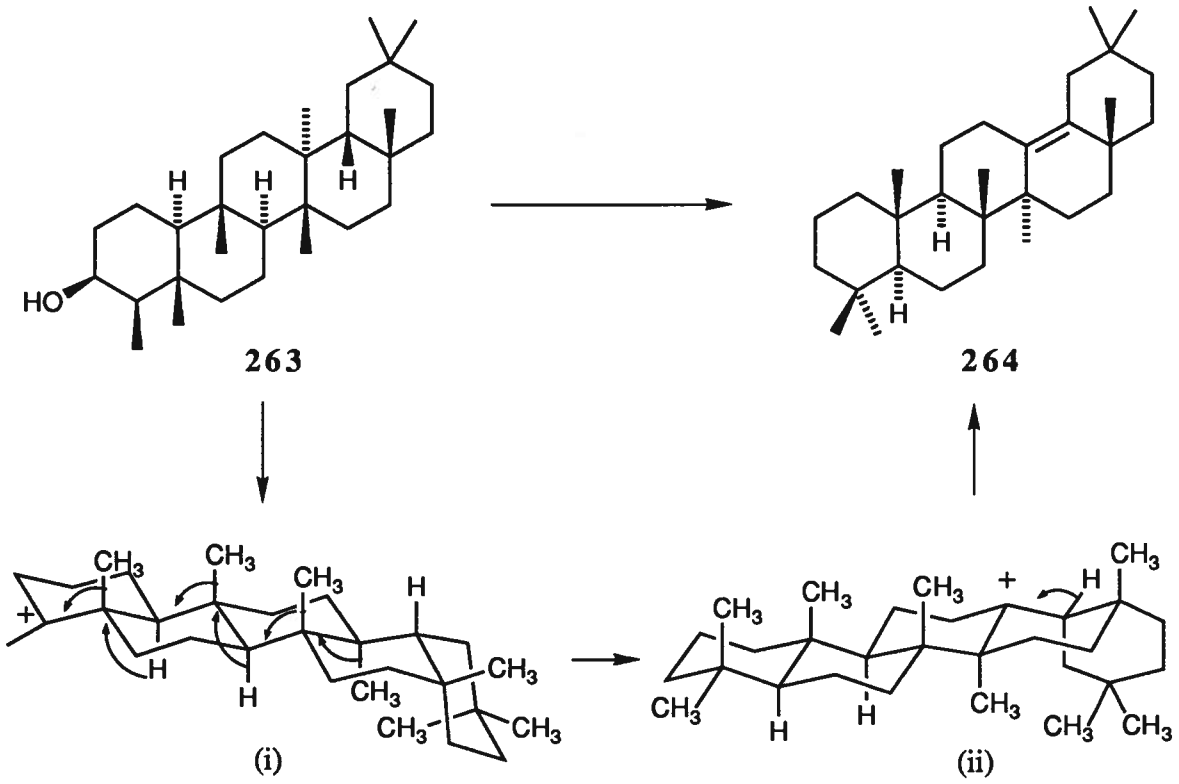
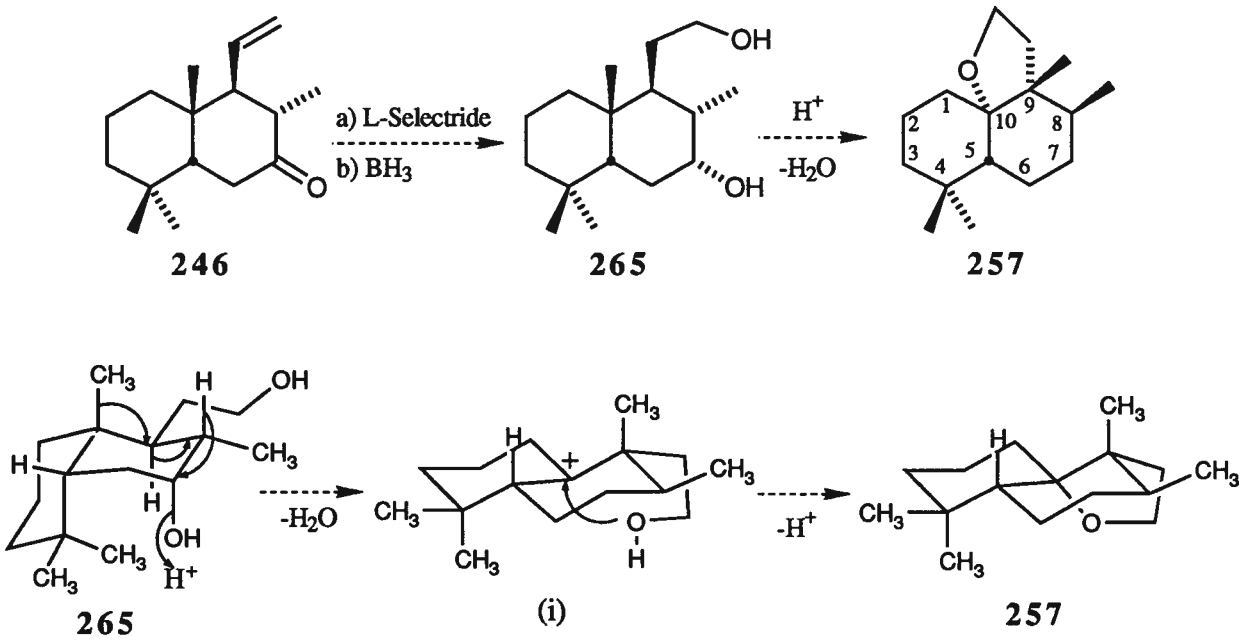


Figure 33 The Conversion of 3-β-Friedelanol (**263**) into 13 (18)-Oleanene (**264**)

In conclusion, we have succeeded in synthesizing (-)-Ambrox® (**179**) enantio-selectively from the thujone-derived enone **163** in seven steps in an overall yield of 9.5%. Moreover, a novel synthesis of **257**, the principal component of "ionoxide", was discovered. The successful strategy should be applicable to the synthesis of other ambergris fragrances, which will be discussed in the next section.

3.3. Future Developments

The synthesis of (-)-Ambrox® (**179**) dictates the preparation of its precursor **255** (Scheme 37). During the preparation of **255** from enone **163**, two steps, i.e., **246** to **250** and **250** to **251** (Section **3.2.3.**) are required in order to reverse the configuration at C5. However, for the direct synthesis of **257** (i.e., the principal component of "ionoxide") from enone **163**, it is unnecessary to have these two steps, since the configuration at C5 of compound **257** is the same as that of **163**. Thus, a shorter route is perceived, as shown in Scheme 42.

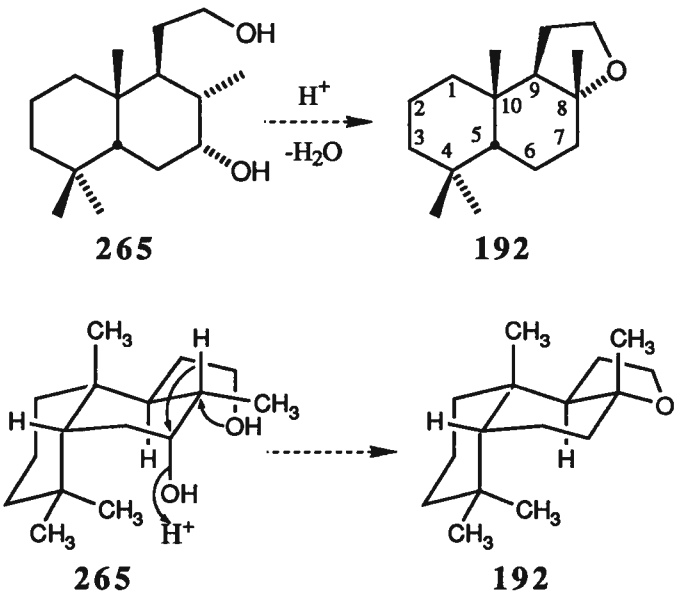


Scheme 42 A Possible Shorter Route to Compound **257**

cis-Fused Ketone **246**, prepared in two steps from **163** (Section **3.2.3.**), might be subjected to L-Selectride reduction and hydroboration to give the *cis*-fused diol **265**. An acid-catalyzed cyclization of **265** could then provide **257**. Mechanistically, a series of consecutive 1,2-shifts of peripheral axial groups in **265** would first generate the tertiary carbocation (i). The subsequent ring closure of (i) should afford the desired product **257**.

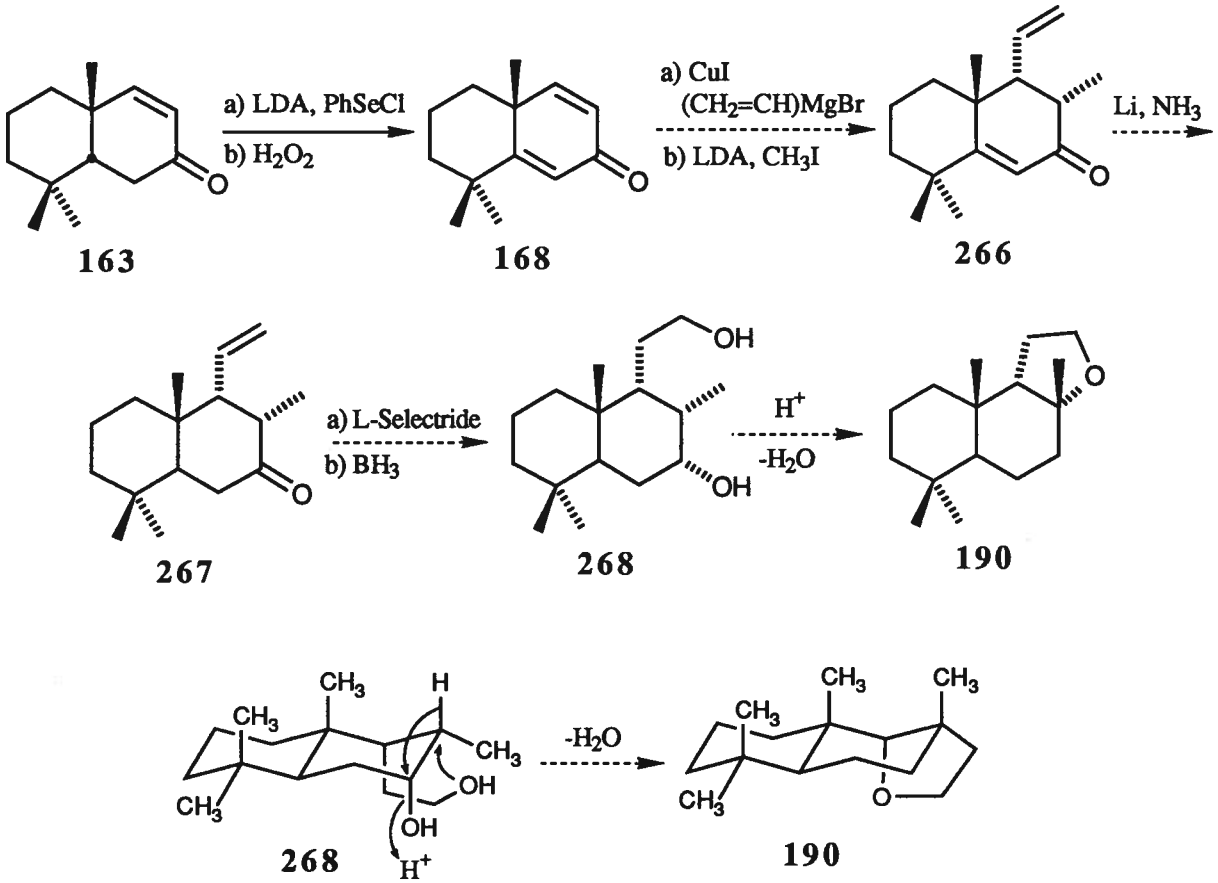
The developed strategy (Scheme 37) to the synthesis of (-)-Ambrox® (**179**) may be further extended to the synthesis of other diastereomers possessing significant odoriferous properties, for example, the *cis*-fused isomer **189** and (-)-*epi*-Ambrox® (**187**).

The diol **265**, if prepared as outlined in Scheme 42, would be cyclized to afford **192** under mild acid catalysis (Scheme 43). Functioning as the reactive species, the stable conformer of **265** could follow the reaction path as envisaged to yield the desired **192** stereoselectively.



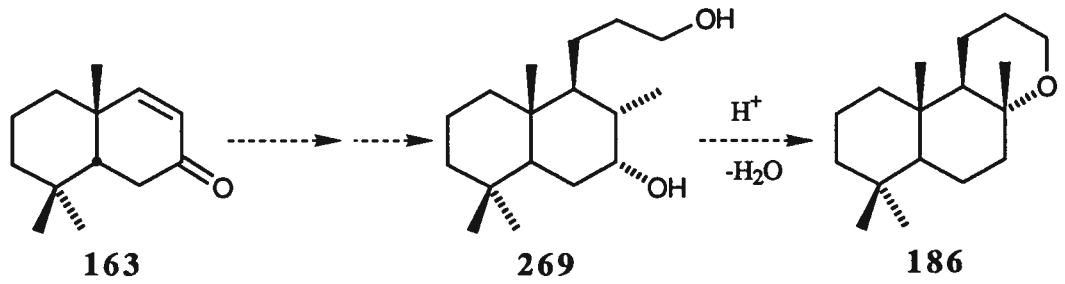
Scheme 43 A Possible Synthesis of Compound **192**

To synthesize (-)-*epi*-Ambrox® (**190**), dienone **168**, prepared previously from **163** (Section **2.2.9.**), would be converted to **266** by a cuprous iodide-catalyzed conjugate addition and a subsequent methylation (Scheme 44). According to the argument presented in Section **3.2.2.**(Scheme 39), the α face attack in the conjugate addition reaction is expected to be dominant. Birch reduction of compound **266** could generate the *trans*-fused ketone **267**, which might undergo L-Selectride reduction and hydroboration to provide diol **268**. The stereoselective cyclization of this diol by acid catalysis, following the reaction path as shown, could finally lead to the (-)-*epi*-Ambrox® (**190**).



Scheme 44 A Possible Synthesis of (-)-*epi*-Ambrox (**190**)

In replacing vinylmagnesium bromide with allylmagnesium bromide in the conjugate addition step, it should be possible to obtain the 1,6-diol **269** from enone **160**, by using the same strategy (Scheme 37). The acid-catalyzed cyclization of **269** would then furnish another ambergris odorant: ambraoxide (**186**), the homologue of (-)-Ambrox® (**179**) (Scheme 45).



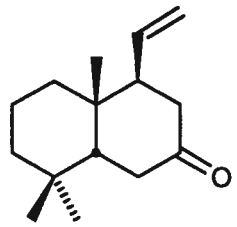
Scheme 45 A Possible Synthesis of Ambraoxide (**186**)

3.4. Experimental

See Section **2.3.1.** for General experimental.

3.4.1. Conjugate Addition: α,β-enone 163 to *cis*-fused γ,δ-enone 245

[4**R**-(4α,4aα,8aα)] 4-Ethenyl-3,4,4a,5,6,7,8,8a-octahydro-4a,8,8-trimethylnaphthalen-2(1*H*)-one (**245**)



245

To a solution of enone **163** (718 mg, 3.74 mmol) in anhydrous THF (20.0 ml), cuprous iodide (112 mg, 0.59 mmol, 0.15 eqv.) and dimethyl sulfide (5.0 ml) were introduced under a nitrogen atmosphere. This mixture was cooled to 0°C and 0.66 M vinylmagnesium bromide in THF solution (8.2 ml, 5.41 mmol, 1.4 eqv.) was added in a dropwise manner over a period of 1 hour. After the mixture was warmed to room temperature and stirred for another 1 hour, saturated sodium chloride (20 ml) was introduced to quench the excess vinylmagnesium bromide. The organic layer was separated; the aqueous layer was extracted with diethyl ether (10 ml). The combined organic solution was dried over magnesium sulfate and concentrated *in vacuo* to give a crude oil which was then chromatographed to provide enone **245** in 70% yield (576 mg).

The physical properties of **245** are as follows:

$[\alpha]_D^{25}$=+22.2 (c=1.00, $CHCl_3$).

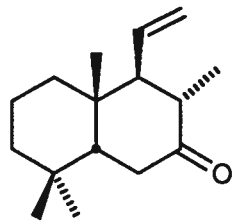
IR $\nu_{max.}$ (film): 3065(C-H stretch , olefinic), 1710(C=O stretch), 1635(C=C stretch).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.80-1.70 {14H, including 0.90 (3H, s), 0.95 (3H, s) and 1.09 (3H, s)}, 1.90 (1H, m), 2.25-3.10 (5H, m), 4.95-5.15 (2H, m), 5.70 (1H, m).

MS m/z: 220 (M^+, 15.6%), 205 (4.0%), 123 (67.8%), 43 (100.0%). High resolution mass measurement: calculated for $C_{15}H_{24}O$: 220.1828; found:. 220.1831.

3.4.2. Methylation by LDA and Iodomethane: *cis*-fused γ,δ-enone 245 to *cis*-fused γ,δ-enone 246

[3S-(3α,4β,4aβ,8aβ)] 4-Ethenyl-3,4,4a,5,6,7,8,8a-octahydro-3,4a,8,8-tetramethylnaphthalen-2(1*H*)-one (**246**)



246

A LDA / *n*-pentane solution (0.68 M, 2.6 ml, 1.77 mmol) was concentrated to remove *n*-pentane. The resulting white viscous mixture was cooled to -40°C, to which anhydrous dimethoxyethane (1.0 ml) was then added under nitrogen. Enone **245** (350 mg, 1.59 mmol) in dimethoxyethane (3.5 ml) was introduced to the LDA solution in a dropwise manner over a period of 1 hour. This enolate solution was warmed rapidly to 50°C and freshly distilled iodomethane (0.40 ml, 6.42 mmol) was added rapidly. The resulting turbid yellowish mixture was stirred at 50°C for 30 minutes and quenched with a solution of potassium hydroxide (100 mg) in methanol (10 ml). After stirring for 30 minutes, the reaction mixture was concentrated *in vacuo* to give the crude product which was chromatographed with ethyl acetate:hexanes (1:8, v/v) to afford **246** (207 mg, 65% based on recovery of **245**) and the starting enone **245** (53 mg, 15%).

The physical properties of **246** are as follows:

$[\alpha]_D^{25}$=+29.3 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3060 (C-H stretching, olefinic), 1700 (C=O stretching), 1630 (C=C

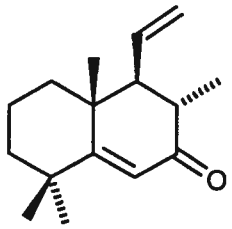
stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70-1.60 {18H, m, including 0.82 (3H, s), 0.94 (3H, s) and 1.04 (3H, d, J=6.4 Hz), 1.14 (3H, s)}, 1.90 (1H, m), 2.30 (1H, m), 2.45-2.70 (3H, m), 4.95-5.20 (2H, m), 5.55(1H, m).

MS m/z: 234 (M^+, 1.7%), 219 (0.5%), 167 (35.7%), 149 (100.0%).

3.4.3. Dehydrogenation by PhSeCl/H_2O_2: *cis*-fused γ,δ-enone 246 to dienone 250

[3S-(3α,4β,4aβ,8aβ)] 4-Ethenyl-4,4a,5,6,7,8-hexahydro-3,4a,8,8-tetramethylnaphthalen-2(3*H*)-one (**250**)



250

A LDA solution in *n*-pentane (0.50 M, 2.30 ml, 1.15 mmol) was concentrated *in vacuo* to remove *n*-pentane. The viscous mixture was cooled to -40°C and THF (1.0 ml) was then added under nitrogen. The solution of **246** (250 mg, 1.07 mmol) in THF (3.0 ml) was added in a dropwise manner with stirring over a 45 minute period. The resulting mixture was warmed to room temperature and phenylselenyl chloride (212 mg, 1.10 mmol) was introduced. Stirring at room temperature was continued for 1.5 hours before addition of pyridine (0.50 ml), methylene chloride (5.0 ml), and hydrogen peroxide (0.50 ml of 30% H_2O_2 in 3.0 ml of water). The two-phase mixture was stirred at room temperature for 5 hours and separated. The aqueous layer was extracted with methylene chloride (5.0 ml). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to yield a crude product. Purification by column chromatography with ethyl acetate:hexanes (1:8, v/v) afforded dienone

250 (134 mg, 62% based on recovery of starting material) and the starting material **246** (31 mg).

The physical properties of **250** are as follows:

$[\alpha]_D^{25}$=-4.2 (c=1.00, $CHCl_3$).

UV (MeOH, c=40.0 m g/l) $\lambda_{max.}$: 242 nm (log ε=3.96).

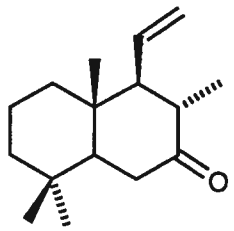
IR $\nu_{max.}$ (film): 3060 (olefinic C-H stretching), 1665 (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.80-1.90 {18H, m, including 1.07 (3H, d, J=5.1 Hz), 1.17 (3H, s), 1.22 (3H, s) and 1.25 (3H, s}, 2.12 (1H, t, J=10.2 Hz), 2.40 (1H, m), 5.00-5.25 (2H, m), 5.69 (1H, m), 6.00 (1H, s).

MS m/z: 232 (M^+, 21.2 %), 217 (17.2%), 189 (2.7%), 178 (7.7%), 164 (100.0%), 149 (48.7%), 121 (14.9%). High resolution mass measurement calculated for $C_{16}H_{24}O$: 232.1827; found: .232.1829.

3.4.4. Birch Reduction: dienone 250 to *trans*-fused γ,δ-enone 251

[3S-(3α,4β,4aβ,8aα)] 4-Ethenyl-3,4,4a,5,6,7,8,8a-octahydro-3,4a,8,8-tetramethylnaphthalen-2(1*H*)-one (**251**)



251

To a solution of dienone **250** (300 mg, 1.29 mmol) in anhydrous THF (2.0 ml), anhydrous ammonia (4 ml) was distilled from sodium under a nitrogen atmosphere. Small pieces of lithium were added slowly over a 30 minute period until a persistent dark blue color remained. After stirring for 1 hour at -33°C, ammonium chloride powder was introduced to

quench excess lithium. Evaporation of ammonia and THF gave a yellowish oil which was chromatographed to afford the *trans*-fused decalone **251** (268 mg, 90%).

The physical properties of **251** are as follows:

$[\alpha]_D^{25}$=-8.38 (c=2.40, $CHCl_3$).

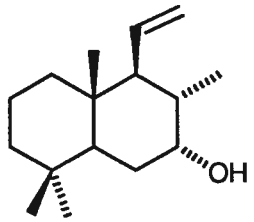
IR $\nu_{max.}$ (film): 3060 (C-H stretching, olefinic), 1706 (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75-1.80 {19H, m, including 0.88 (3H, s), 0.90 (3H, s), 0.97 (3H, d J=6.0 Hz), and 1.09 (3H, s)}, 2.00-2.50 (4H, m), 4.98 (1H, dd, J=1.6 and 16.8 Hz), 5.12 (1H, dd, J=1.6 and 10.0 Hz), 5.56 (1H, dt, J=10.0 and 16.8 Hz)

MS m/z: 234 (M^+, 33.8%), 219 (8.8%), 203 (0.3%), 137 (10.8%), 123 (100.0%), 109 (19.2%). High resolution mass measurement calculated for $C_{16}H_{26}O$: 236.2140; found: 236.2097.

3.4.5. Reduction by L-Selectride: *trans*-fused γ,δ-enone 251 to alcohol 253

[2**R**-(2α,3α,4β,4aβ,8aα)] 4-Ethenyl-decahydro-3,4a,8,8-tetramethylnaphthalen-2-ol (**250**)



253

The *trans*-fused ketone **251** (250 mg, 1.07 mmol) in anhydrous THF (2.0 ml) was added in a dropwise manner to L-Selectride (0.72 M, 3.0 ml, THF) at -78°C for 30 minutes. The solution was stirred for 1.5 hour, warmed to 0°C, and stirred for an additional 1 hour. Aqueous sodium hydroxide solution (3.0 ml, 3 M) and aqueous 30% hydrogen peroxide (3.0 ml) were then introduced. The resulting mixture was stirred 30 minutes, saturated with potassium carbonate, and separated. The aqueous layer was further extracted with diethyl ether (2X10 ml). The organic solutions were combined and concentrated *in vacuo*. Purification by

column chromatography with ethyl acetate:hexanes (2:8, v/v) gave alcohol **253** (240 mg, 95%).

The physical properties of **253** are as follows:

$[\alpha]_D^{25}$=-40.9 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3450 (O-H stretching), 3060 (C-H stretching, olefinic), 1630 (C=C stretching).

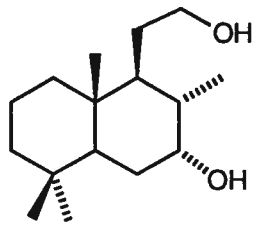
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70-1.85 {24H, m, including }, 3.92 (1H, q, J=3.0 Hz), 4.94 (1H, dd, J=2.4 and 17.2 Hz), 5.02 (1H, dd, J=2.4 and 10.4 Hz), 5.52 (1H, td, J=10.4 and 17.2 Hz).

MS m/z: 236 (M^+, 2.4%), 218 (2.1%), 203 (4.5%), 123 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{28}O$: 236.1240; found: 236.2136.

Elemental Analysis: calculated for $C_{16}H_{28}O$: C 81.29, H 11.09; found: C 81.22, H 11.11

3.4.6. Hydroboration: alcohol 253 to 1,5-diol 255

[1S-(1α,2β,3β,4β,4aβ,8aα)] Decahydro-3-hydroxyl- 2,5,5,8a--tetramethylnaphthalene-1-ethanol (**255**)



255

To a cooled solution (0°C) of alcohol **253** (300 mg, 1.27 mmol) in THF (2.0 ml) was added borane in THF solution (7.0 ml, 0.56 M) in a dropwise manner under nitrogen over a period of 30 minutes. The solution was warmed to room temperature and then stirred for 1.5 hours. After water (1.0 ml), aqueous sodium hydroxide (3.0 ml, 3M), and aqueous hydrogen

peroxide (3.0 ml, 30%) were introduced, the resulting mixture was stirred overnight, saturated with sodium chloride, and separated. The aqueous layer was further extracted with diethyl ether (10 ml). The organic solutions were combined, dried over magnesium sulfate, and concetrated *in vacuo* to give the crude product. The crude product was chromatographed with ethyl acetate: methanol:hexanes (1:1:2, v/v/v) to afford diol **255** in 71% yield (229 mg).

The physical properties of **255** are as follows:

m.p.: 128-130°C.

$[\alpha]_D^{25}$=-16.9 (c=1.00, $CHCl_3$).

IR $\nu_{max.}$ (film): 3400 (O-H stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70-1.80 {27H, m, including 0.82 (6H, two overlapped singlets), 0.86 (3H, s), and 0.98 (3H, d, J=6.0 Hz)}, 3.50 (1H, dt, J=7.2 and 9.6 Hz), 3.62 (1H, dt, J=5.6 and 9.6), 3.85 (1H, q, J=3.0 Hz).

MS m/z: 236 (M^+-H_2O, 6.6%), 221 (6.5%), 191 (16.9%), 177 (6.0%), 167 (18.9%), 138 (62.2%), 123 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{30}O_2$: 254.2236; found: .254.2241.

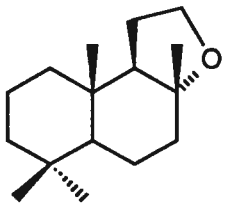
Elemental Analysis: calculated for $C_{16}H_{30}O_2$: C 75.53, H 11.89; found: C 75.75, H 12.00.

3.4.7. Cyclization: 1,5-Diol 255 to 179, 189, and 257

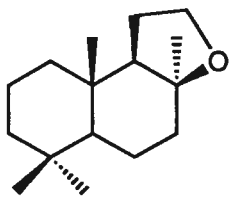
[3a**R**-(3aα,5aβ,9aα,9bβ)] Dodecahydro-3a,6,6,9a-tetramethyl-1*H*-naphtho[2,1-b]furan (**179**)

[3a**S**-(3aα,5aα,9aβ,9bα)] Dodecahydro-3a,6,6,9a-tetramethyl-1*H*-naphtho[2,1-b]furan (**189**)

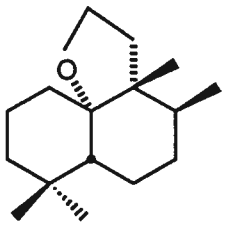
[3a**R**-(3aα,4α,6aα,10a**S***)] Dodecahydro-3a,4,7,7-tetramethyl-2*H*-naphtho[8a,1-b]furan (**257**)



179



189



257

Procedure #1:

Diol **255** (20 mg, 0.079 mmol) in anhydrous toluene (2.0 ml) was treated with *p*-toluenesulfonic acid (27 mg, 0.16 mmol, 2.0 eqv.) under a nitrogen atmosphere. This solution was then heated at 80°C for 2 hours. The resulting mixture was transferred by diethyl ether (10 ml) to a separatory funnel, washed with saturated sodium carbonate solution, dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography with hexanes, ethyl acetate:hexanes (1:50, v/v), ethyl acetate:hexanes (1:20, v/v), and ethyl acetate:hexanes (1:8, v/v) consecutively gave a mixture of hydrocarbons (1.4 mg, 8%), (+)-*iso*-Ambrox® (**189**) (1.9 mg, 10%), (-)-Ambrox® (**179**) (8.9 mg, 48%), and a mixture of alcohols **258** (2.8 mg, 15%).

Procedure #2:

Diol **255** (20 mg, 0.079 mmol) in nitromethane (2.0 ml) was treated with *p*-toluenesulfonic acid (40 mg, 0.23 mmol, 3.0 eqv.) under a nitrogen atmosphere. The solution was then heated at 100°C for 30 minutes. After a workup similar to that in the procedure #1, the crude product was chromatographed with hexanes and ethyl acetate:hexanes (1:50, v/v) to give a mixture of hydrocarbons (7.0 mg, 40%), the ionoxide principal **257** (6.4 mg, 34%), and (+)-*iso*-Ambrox® (**189**) (3.5 mg, 19%).

The physical properties of **179** are as follows:

m.p.=74-76°C.

$[\alpha]_D^{25}$=-25.1 (c=1.00, $CHCl_3$).

IR ($CHCl_3$) $\nu_{max.}$: 1455, 1380, 1000, 975 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, s), 0.84 (3H, s), 0.88 (3H, s), 1.09 (3H, s), 3.83 (1H, q, J=8.0 Hz), 3.92 (1H, m).

MS m/z: 236 (M^+, 3.4%), 221 (100.0%), 205 (6.8%), 177 (3.8%), 137 (40.2%), 97 (37.5%), 84 (23.8%), 81 (20.3%), 69 (20.4%), 59 (22.8%), 55 (18.8%), 43 (20.6%). High resolution mass measurement: calculated for $C_{16}H_{28}O$: 236.2140; found: 236.2139.

The physical properties of **189** are as follows:

m.p.=57-59°C.

$[\alpha]_D^{25}$=+7.4 (c=1.00, $CHCl_3$).

IR ($CHCl_3$) νmax.: 1450, 1375, 1070, 1035 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, s), 0.89 (3H, s), 0.90 (3H, s), 1.06 (3H, s), 3.70 (q, J=8.0 Hz), 3.80 (1H, dt, J=3 and 8.0 Hz).

MS m/z: 236 (M^+, 0.0%), 221 (M^+-CH_3, 100.0%), 177 (1.7%), 137 (21.3%), 109 (7.9%), 97 (33.0%), 84 (31.6%), 69 (21.5%), 55 (34.0%), 47 (7.5%), 43 (49.8%). High resolution mass measurement: calculated for $C_{15}H_{25}O$ (M^+-CH_3): 221.1905; found: 221.1906. Chemical ionization MS using methane as carrier gas: 251 ($M+CH_5^+$), 237 ($M+H^+$).

The physical properties of **257** are as follows:

$[\alpha]_D^{25}$=+37.1 (c=1.00, $CHCl_3$).

IR (film) νmax.: 1455, 1370, 1040, 1025 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.81 (3H, s), 0.83 (3H, d, J=6.6 Hz), 0.87 (3H, s), 0.94 (3H, s), 3.70 (1H, dt, J=2 and 8.0 Hz), 3.81 (1H, q, J=9 Hz). ^{1}H-NMR (400 MHz, CCl_4) δ: 0.80 (3H, s), 0.82 (3H, d, J=6.6 Hz), 0.87 (3H, s), 0.92 (3H, s), 3.67 (1H, dt, J=2 and 8.0 Hz), 3.76 (1H, q, J=8.0 Hz).

MS m/z: 236 (M^+, 7.7%), 221 (7.0%), 194 (13.7%), 193 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{28}O$: 236.2140; found: 236.2146.

Chapter 4 Exploratory Studies of Different Strategies to Develop Thujone as a Chiral Building Block

The synthetic strategy described in the previous two chapters focussed primarily on the cleavage of the isopropyl side chain of thujone as an important operation, to afford eventually target molecules like (-)-polygodial (**2**) and (-)-Ambrox® (**179**). A direct result of such a strategy is that the synthesized target molecule always incorporates seven of the ten carbon atoms in the starting thujone molecule. A question is then raised: is it possible to develop other strategies which incorporate different number of carbon atoms into these target molecules? If developed, each of such new strategies would be characteristic of its own carbon incorporation, providing novel entries into various natural products. A closely related issue is that, in principle, for a given strategy which incorporates a certain number of carbons, there can be various methods which integrate the same number of carbon atoms into target molecules, depending on how the starting structure is incorporated or how and where some parts of the starting structure are removed during the incorporation.

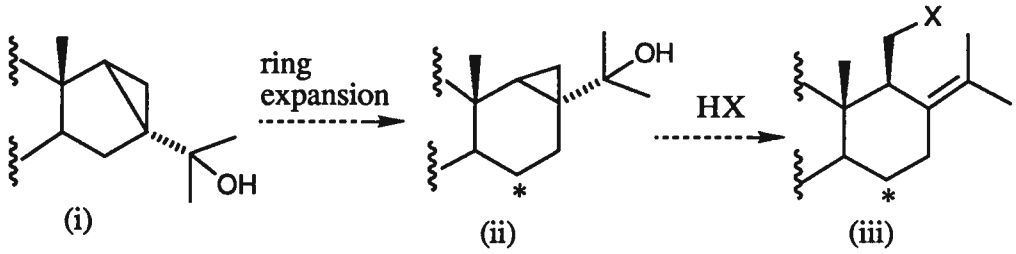
With these general considerations in mind, we decided to integrate the isopropyl side chain of thujone into target molecules as much as possible, rather than to cleave the isopropyl side chain completely as in the previous studies. Thus, strategies of different degrees of carbon incorporation can be developed. This chapter summarizes some exploratory studies in this direction. For the purpose of presentation, strategies incorporating seven, nine, and ten carbons are called C7, C9, and C10 strategies respectively.

4.1. Studies on "Homothujone" and Its Derivatives: a new C7 strategy

As shown in Section **2.2.4.** and **2.2.7.**, previously synthesized thujone-derived cyclopropylcarbinols of the general skeleton (i) (Scheme 46) usually undergo acid-promoted ring cleavage reactions through exo-type 1 and exo-type 2 cleavage pathways, rather than the endo-type cleavage pathway to provide the desired cyclohexane ring (Figure 11). It was

hypothesized that the preferred exo-type 1 cleavage was due to the exposed nature of the methylene in the cyclopropyl ring, towards the incipient nucleophiles (Figure 12).

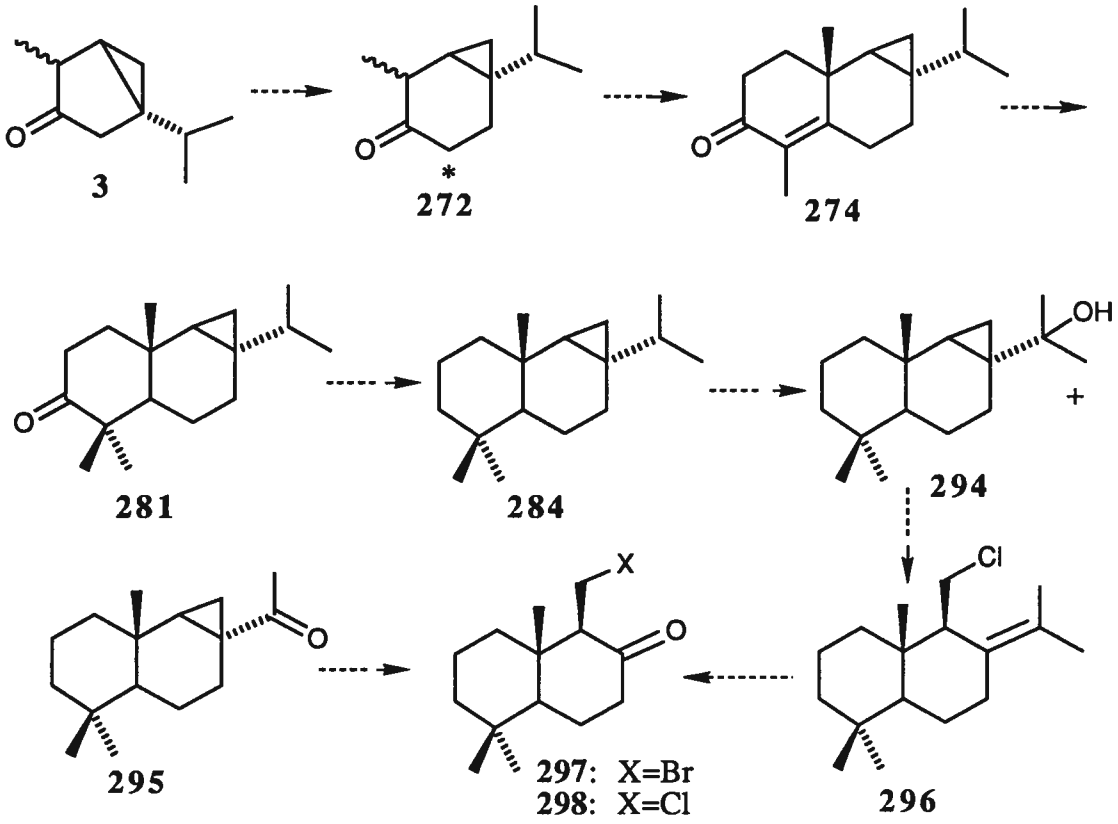
If the bicylo[3.1.0]hexane system (i) could be expanded to the bicyclo[4.1.0]heptane system (ii) in a regioselective manner shown in Scheme 46, the homoallylic halide (iii) with a desired cyclohexane ring would become the "logical product" due to the preferred exo-type 1 cleavage. With a versatile homoallylic halide group, (iii) may be readily elaborated into (-)-polygodial (**2**) and (-)-Ambrox® (**179**).



Scheme 46 The Potential of a Regioselective Ring Expansion Reaction

This ring expansion reaction had not been considered in our earlier studies nor in other laboratories in which other avenues of thujone chemistry had been developed. Therefore, its evaluation would also make a fundamental contribution to thujone chemistry.

Scheme 47 shows the overall plan in which this strategy may afford alternative syntheses of (-)-polygodial (**2**) and (-)-Ambrox® (**179**). Ring expansion of thujone may be expected to generate a "homothujone" (**272**) which could be then converted to enone **274**. Birch reduction followed by enolate trapping should produce a *trans*-fused ketone **281** which would be reduced to hydrocarbon **284**. Ozonation should then form both alcohol **294** and ketone **295**. Exo-type 1 cleavage of alcohol **294** would result in homoallylic chloride **296** and the latter could be ozonized to a β-chloro-ketone **298** while the ketone **295** could be converted to β-bromoketone **297** using *m*-CPBA and NBS as described in Section **2.2.8.**.Versatile functional groups in both **297** and **298** would allow them to be readily converted to either (-)-polygodial (**2**) or (-)-Ambrox® (**179**).



Scheme 47 "Homothujone" Strategy for Syntheses of Various Natural Products

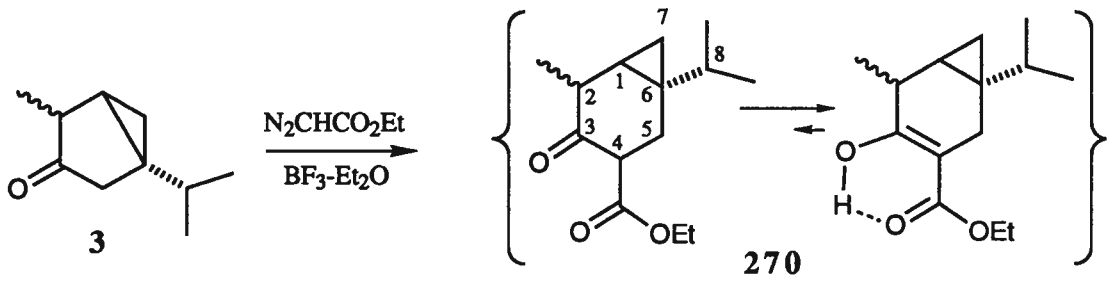
The apparent advantage of the homothujone strategy is that the *trans* A/B ring fusion could be possibly realized by Birch reduction directly, rather than through a tedious stereochemical correction sequence from the A/B *cis*-fused systems obtained earlier. As a new C7 strategy, the homothujone strategy incorporates seven of the original ten carbon atoms present in thujone into potential target molecules in a novel way.

4.1.1. Regioselective Ring Expansion of Thujone

The desired regioselective ring expansion of thujone was accomplished by treating thujone with ethyl diazoacetate and boron trifluoride etherate under nitrogen at room temperature[137]. The β-ketoester **270**[$], which existed mainly in its enol form, was isolated in

[$] Because thujone in use was a mixture of α-thujone and β-thujone (10:1), the product **270** was a mixture of two diastereomers in a similar ratio, as revealed by GC. No attempt was made to separate these two diastereomers. The ^{1}H-NMR spectral data presented here represent the characterization of the major α

70% yield. The mass spectrum of **270** showed a molecular ion at m/z 238. The UV spectrum indicated an absorption band at 258 nm (log ε=3.980) while the IR spectrum displayed a broad hydroxyl absorption at 3370 cm^{-1}, an intense conjugated ester carbonyl stretching absorption at 1655 cm^{-1}, and a weak carbon-carbon double bond stretching absorption at 1615 cm^{-1}. The



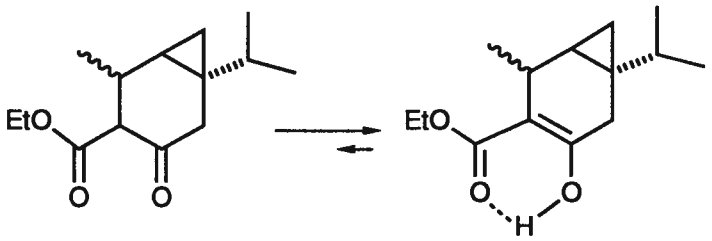
presence of an intense UV absorption and the lack of any non-conjugated carbonyl absorption demonstrated domination of the enol form in compound **270**[138]. The ^{1}H-NMR spectrum revealed three separate one-proton signals at high field δ 0.30 (dd, J=4.4 and 8.8 Hz), 0.39 (t, J=4.4 Hz), and 0.68 (dd, J=4.4 and 8.8 Hz), corresponding to the three protons in the cyclopropane ring. Two methyl doublets (J=5.6 and 4.4 Hz), corresponding to the two methyl groups at the isopropyl side chain, overlapped at δ 0.98 ppm. There were a one-proton multiplet at δ 1.03 ppm corresponding to the methine proton at C8, a methyl doublet (J=7.2 Hz) at δ 1.24 ppm corresponding to the methyl at C2, and a methyl triplet (J=6.8 Hz) at δ 1.31 ppm corresponding to the methyl of the ethyl ester group. A two-proton signal of AB type at δ 2.25-2.57 ppm (J=16 Hz) was assigned to the methylene at C5 while a quartet (J=7.2 Hz) at δ 2.64 ppm was due to the methine at C2. The J coupling constant between the methine protons at C1 and C2 was zero!. A two-proton multiplet at δ 4.21 ppm corresponded to the methylene in the ethyl ester group and a very low field singlet signal at δ 12.24 ppm was due to the hydroxyl proton in the enol form of **270**.

The spectroscopic data presented above could not differentiate the enol form of **270**

---

diastereomer while other spectroscopic data are the gross properties of the diastereomeric mixture. This situation remains the same for homothujone **272**.

from that of **271**, which would be the product of carbon insertion from the more substituted side of carbonyl function in thujone. Crucial evidence was obtained, however, from the next step, i.e., the decarboxylation of the β-keto ester.



271

Treatment produced **272**# in 95% yield[139]. The mass spectrum of **272** showed its molecular ion at m/z 166 while the IR spectrum indicated a carbonyl absorption at 1700 cm^{-1}. It is expected that **272** would have its three α protons (to the carbonyl group) in the region between δ 2.00 ppm and δ 3.00 ppm in the ^{1}H-NMR spectrum whereas **273** available from **271** would reveal four protons in this region. To our surprise, **272** contained four protons in this region: two at δ 2.10 ppm (m), one at δ 2.35 ppm (m), and one at δ 2.47 ppm (dt, J=3.0 and 8.0 Hz). A series of decoupling experiments were performed to clarify the situation (Figure 34). Irradiation of the one-proton signal at high field (δ 0.72 ppm), which was assigned to one of the three cyclopropane protons, caused the multiplet at δ 2.47 ppm to collapse into a quartet (J=8.0 Hz) in addition to the simplification of the complex two-proton signal at high field (δ 0.50 ppm), which was assigned to the two remaining cyclopropane protons. Irradiation of the signal at δ 0.50 ppm resulted in only the collapse of the signal at δ 0.72 ppm. Thus, the signal at δ 0.72 ppm was clearly due to the C1 proton while the signal at δ 2.47 ppm was assigned to the methine proton at C2. Irradiation of the methyl doublet resonance (J=8.0 Hz) at δ 1.22

The product **272** was a mixture of α and β diastereomers (10:1), as indicated by GC. The ^{1}H-NMR data described here represent the characterization of the major α diastereomer while other spectroscopic data are the gross properties of the diastereomeric mixture. See also the footnote at p. 178.

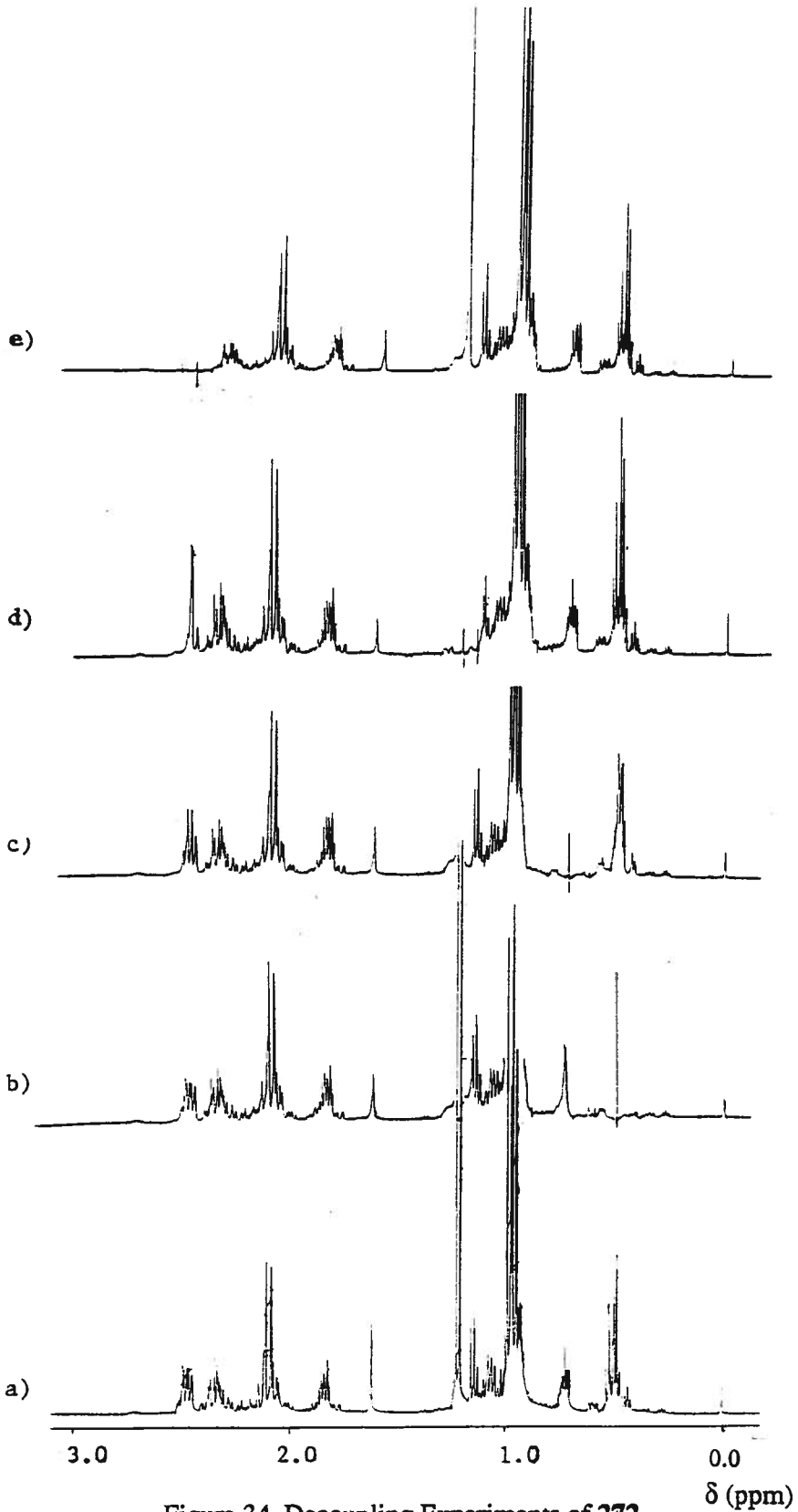
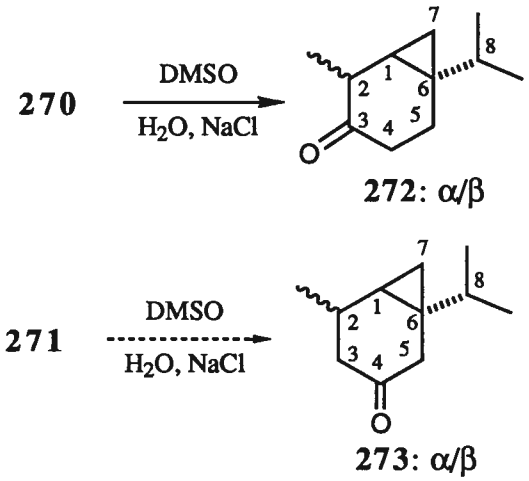


Figure 34 Decoupling Experiments of **272**

a) off-resonance spectrum.
b) proton-proton homonuclear decoupling at 0.50 ppm.
c) proton-proton homonuclear decoupling at 0.72 ppm.
d) proton-proton homonuclear decoupling at 1.22 ppm.
e) proton-proton homonuclear decoupling at 2.47 ppm.

ppm led to the collapse of the C2 proton signal into a doublet (J=3.0 Hz) and irradiation at δ 2.47 ppm transformed the methyl doublet signal at δ 1.22 ppm into a singlet and the C1 proton signal at δ 0.72 ppm into a doublet of doublets (J=4.8 and 8.8 Hz), further confirming the assignment. The fact that the C2 proton was coupled only to the C1 proton and and the methyl protons at δ 1.22 ppm suggested the correct structural assignment to **272** and thus **270**. The proton at C2 of **273** would have coupled to the C3 protons in addition to the methyl protons and the C1 proton. Seemingly, one of the methylene protons at C5 of **272** had an unusually high chemical shift between δ 2.00 to 2.70 ppm.



It is noteworthy that the coupling between the C1 proton and the C2 proton in compound **272** (J=3.0 Hz) was rather different from that in **270** (J=0 Hz). This can be explained when one considers the possible conformations of these two compounds (Figure 35). The enol form of compound **270α*** can have two boat-like conformers **270a** and **270b**. Conformer **261b** is less stable because of the repulsion between the axial methyl at C2 and the axial hydrogen at C5. Inspection of models reveals a dihedral angel <H1-C1-C2-H2 close to 90° in conformer **261a** which possesses an equatorial methyl group at C2. Therefore, the coupling constant between H1 and H2 is expected to be small. Among the two half-chair

* As indicated in the footnotes at p. 178 and p. 180, the ^{1}H-NMR data thus far described for **270** and **272** represent their α diastereomers only.

conformers of **272α***, **272b** with an axial methyl group is considered more stable because it is devoid of the C2-methyl bond and the C1-H1 bond eclipsing interaction present in **272a** and the flat nature of the plane involving C2-C1-C6-C5 also greatly reduces the repulsion between the axial methyl at C2 and the axial proton at C4 in **272b**. The dihedral angle <H1-C1-C2-H2 is approximately 30° and therefore a larger coupling constant between H1 and H2 is expected.

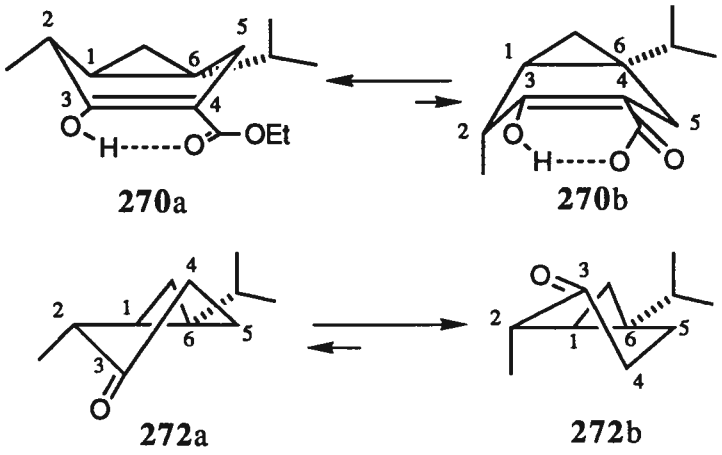


Figure 35 Conformational Analysis of **270α** and **272α**;

The insertion reaction of a ketone by ethyl diazoacetate usually take place from the less substituted or less bulky side. The formation of the reactive conformer shown in Figure 36 is presumably faster than other possible conformers due to minimal gauche steric repulsions[140]. Assuming that the subsequent migration is a faster process than the internal rotation about the carbon-carbon bond, the insertion from the less substituted side becomes the dominant product.

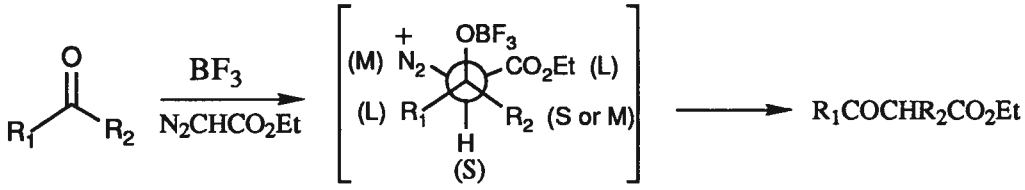
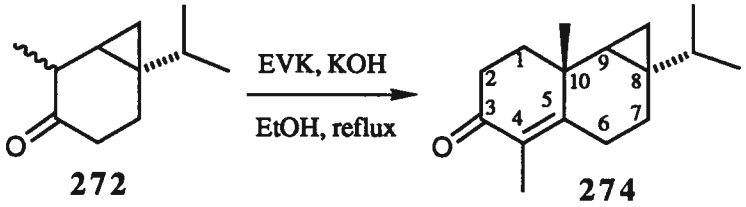


Figure 36 Explanation for Regioselectivity of the Carbon Insertion Reaction

4.1.2. Stereoselective Robinson Annulation of Homothujone (272)

The Robinson annulation of homothujone (**272**) was carried out by refluxing the starting material with potassium hydroxide and the salt of 1-diethylamino-3-pentanone and one equivalent iodomethane in ethanol. Enone **274** as shown was isolated in 70% yield.

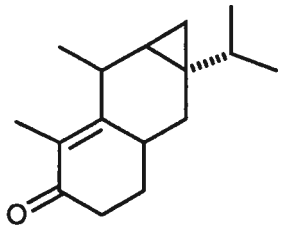


272 **274**

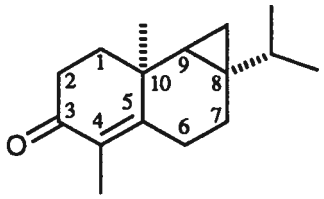
The mass spectrum of **274** indicated the molecular ion at m/z 232 corresponding to the formula $C_{16}H_{24}O$. The UV spectrum showed an intense absorption band at 250 nm (log ε=4.133) corresponding to the π to π^* transition in the enone chromophore. The IR spectrum displayed a conjugated carbonyl absorption at 1660 cm^{-1}. The ^{1}H-NMR spectrum was fairly well resolved. Three low field one-proton signals at δ 0.30 (dd, J=4.8 and 9.6 Hz), 0.50 (dd, J=4.8 and 9.6 Hz), and 0.66 ppm (t, J=4.8 Hz) were assigned to the cyclopropane protons. Two methyl doublets (both J=7.2 Hz) at δ 0.90 and 0.93 ppm were due to the two methyl groups of the isopropyl side chain while a neighboring multiplet at δ 0.95 was assigned to the methine proton of the side chain. Two methyl singlets at δ 1.16 and 1.74 ppm corresponded to the angular methyl (at C10) and the vinylic methyl (at C4) protons respectively. Three multiplets at δ 1.58 (2H), 1.82 (1H), and 1.93 ppm (1H) were assigned to the methylene protons at C1 and C7 while two other lower field multiplets at δ 2.12 ppm (1H, dt, J=5.2 and 14.0 Hz) and at δ 2.35-2.70 ppm (3H) were due to the four methylene protons at C2 and C6.

The structure of **274** was further confirmed by a series of NMR experiments. The structure **275**, which might possibly be formed by the EVK Robinson annulation from the less substituted side of the carbonyl group, is inconsistent with the fact that only two methyl doublets were observed in the spectrum of the isolated product **274**. However, the structure

276, which was possibly generated from the β face attack of the more substituted side, could accommodate all the spectroscopic data so far obtained. More evidence was needed to differentiate **274** and **276**.

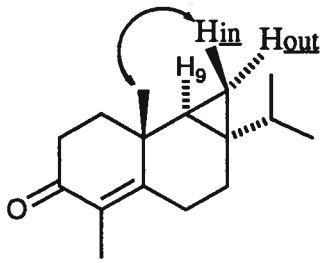


274

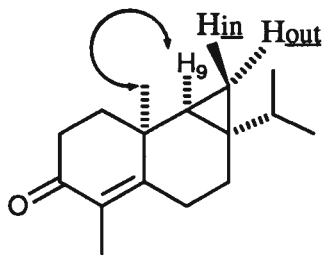


276

Inspection of molecular models reveals that the angular methyl groups at C10 have different spatial relationships with the three cyclopropane protons in the diastereomers **274** and **276**. In the case of **274**, the angular methyl is relatively close to the cyclopropane methylene proton directed into the concave face of the bicyclo[4.1.0]heptane moiety (i.e., H_{in}) but distant from the cyclopropane methine proton (i.e., H9) and the other methylene proton which is directed away from the concave face of the bicyclo[4.1.0]heptane moiety (i.e., H_{out}). For **276**, the angular methyl is relatively close to H9 but distant from both methylene protons H_{in} and H_{out}. Thus, if the the angular methyl is irradiated, a positive NOE enhancement for H_{in} will indicate the presence of **274** while a positive enhancement for H9 will suggest the existence of **276**.



274



276

Fortunately, the ^{1}H-NMR spectrum was fairly well resolved. The methyl singlet signal at δ 1.22 ppm, previously assigned to the angular methyl, was well separated from nearby signals and the three cyclopropane proton signals at high field were also well separated from each other. From a large number of recorded spectra of substituted cyclopropanes, it is generally observed that, in any designated cyclopropane, the magnitude of the vicinal coupling constant for *cis* protons (protons on the same side of a cyclyopropane plane, e.g., H9 and H_{out}) is always larger than that for *trans* protons (e.g., H9 and H_{in})[141]. Since each of the three coupling constants in the AMX system, composed by the three cyclopropane protons of **274** or **276**, had to be either 4.8 Hz or 9.6 Hz , the coupling constant between H9 and H_{out} [J ($H9,H_{out}$)] and the coupling constant between H9 and H_{in} [J ($H9,H_{in}$)] should have values 9.6 Hz and 4.8 Hz respectively, in order to satisfy the relationship: J ($H9,H_{out}$) > J ($H9,H_{in}$). J (H_{out},H_{in}) had to be 4.8 Hz to produce a triplet of J=4.8 Hz observed in the spectrum and this triplet signal was due to H_{in}. Otherwise, if J (H_{out},H_{in}) were 9.6 Hz, a triplet of J=9.6 Hz would have been observed and this triplet would have been due to H_{out}. Thus, the consideration of magnitude for coupling constants enabled us to assign the triplet (J=4.8 Hz) at δ 0.66 ppm to H_{in} but the two doublet of doublets signals at δ 0.30 and 0.50 ppm cannot be assigned further.

A two dimensional ^{1}H-^{13}C heteronuclear correlation spectrum (2D-HETCOR, Figure 37) further confirmed the assignment. The proton (doublet of doublets) at δ 0.50 ppm correlated intensely with a tertiary carbon at δ 33.00 ppm but weakly with a secondary carbon at δ 12.60 ppm. Both the proton (triplet) at δ 0.66 pm and the proton (doublet of doublets) at δ 0.30 ppm correlated intensely with the secondary carbon at δ 12.60 ppm but not with the tertiary carbon at δ 33.00 ppm. This suggested that the proton (doublet of doublets) at δ 0.50 ppm was due to H9 and the quartet proton at δ 0.30 ppm was due to H_{out}.

The determination of substitution of the above mentioned carbons was facilitated by an APT (Attached Proton Test) experiment (Figure 38). The carbon at δ 12.60 ppm was assigned as secondary since it was very intense in the off-resonance spectrum and did not invert its

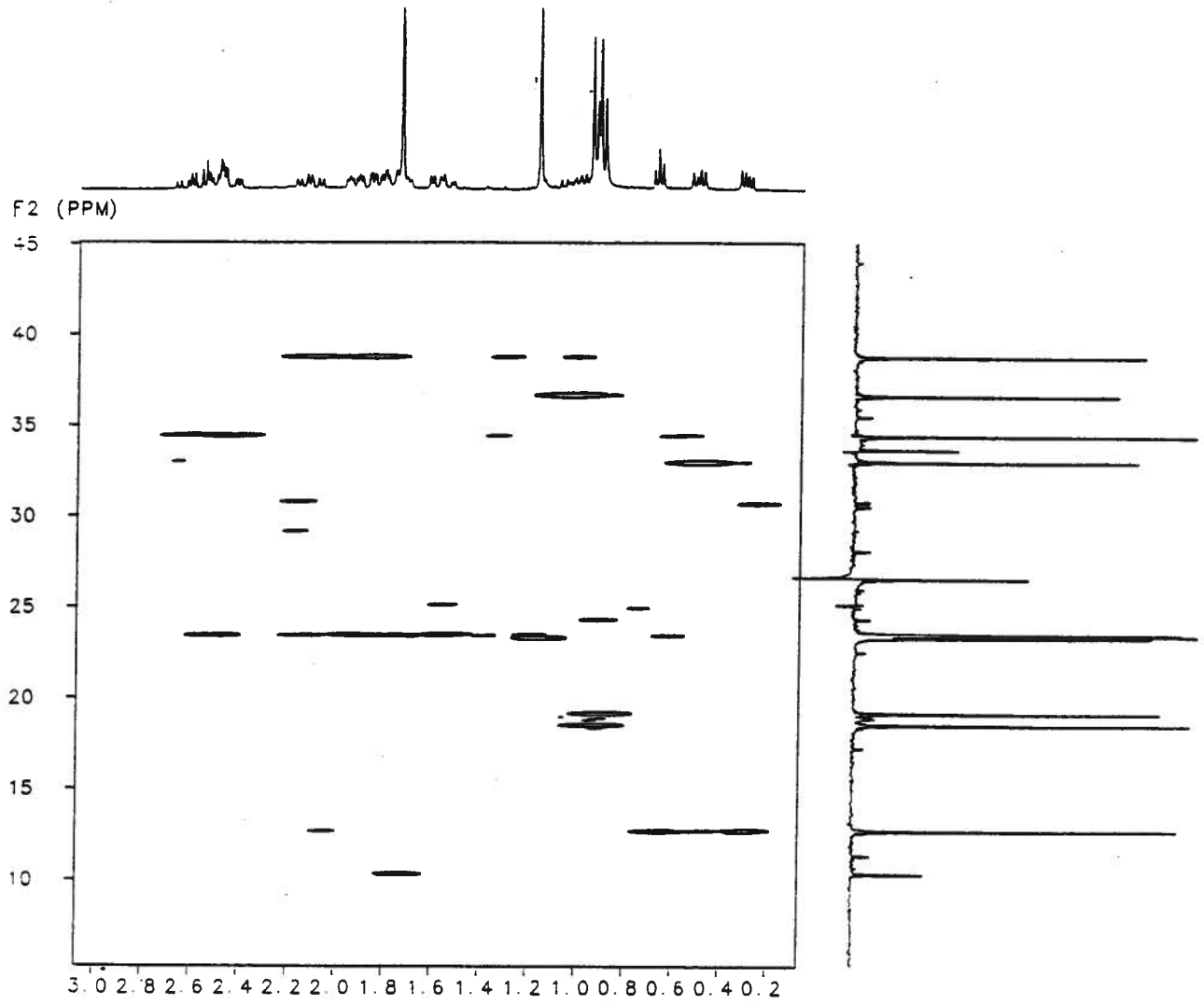


Figure 37 2D-HETCOR spectrum of **274**

a) H (0.30 ppm) ---C (12.60 ppm).
b) H (0.66 ppm) ---C (12.60 ppm).
c) H (0.50 ppm) ---C (33.00 ppm).

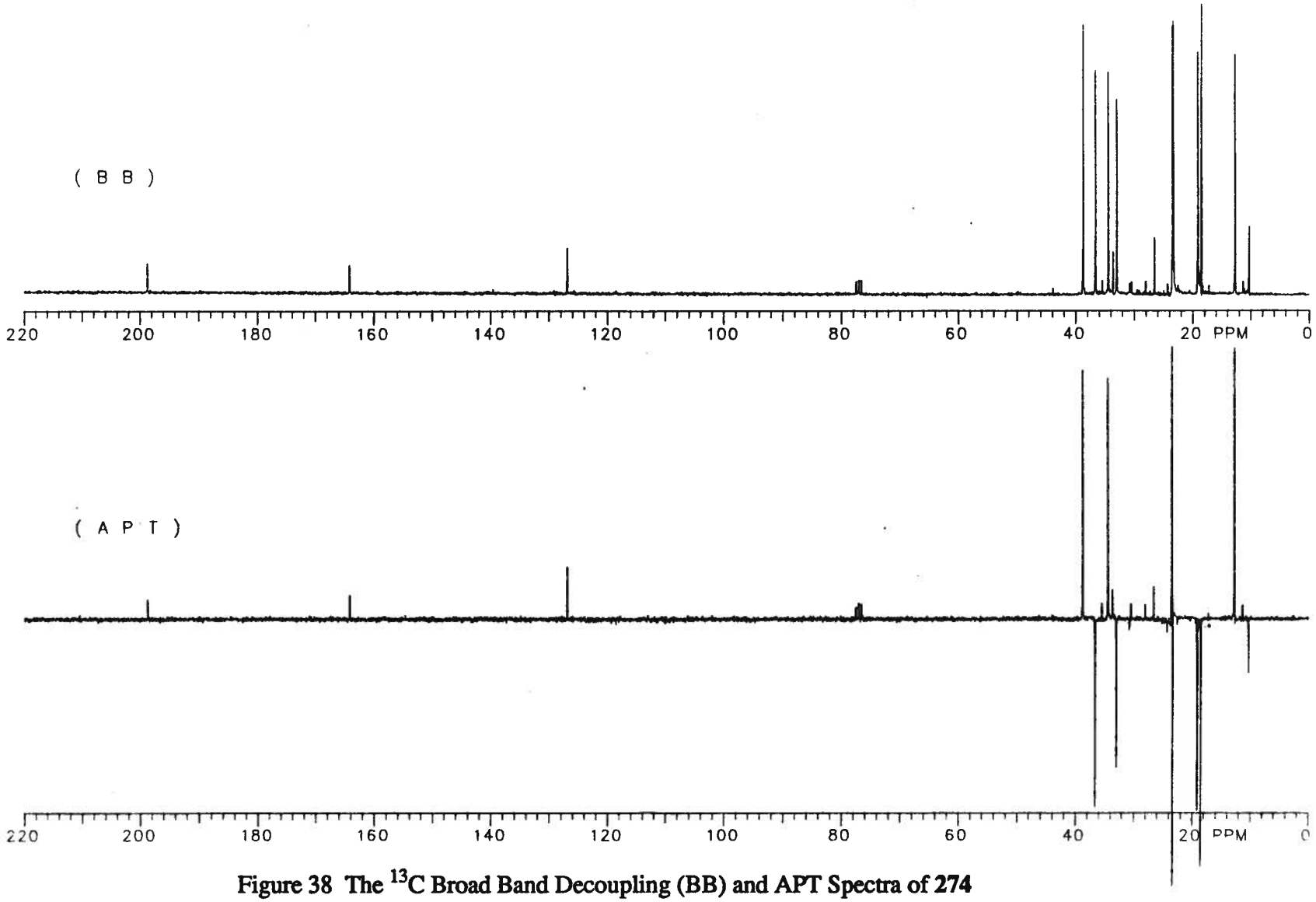


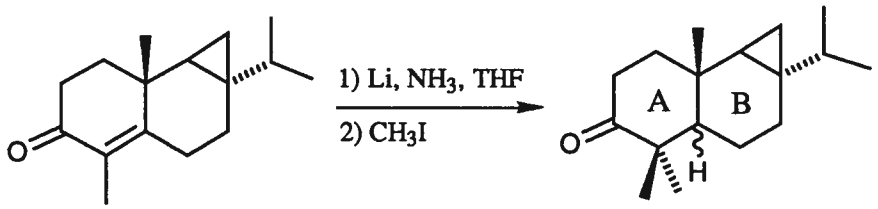
Figure 38 The ^{13}C Broad Band Decoupling (BB) and APT Spectra of **274**

phase in the APT spectrum. Among the six carbons of inverse phase (which can be either primary or tertiary carbons) in the APT spectrum, four of them were sorted out as primary carbons since they had low chemical shifts in the ^{13}C spectrum (δ: 10.35, 18.55, and 19.20 ppm). As shown from the HETCOR spectrum, these four carbons also correlated well with four methyl singlets in the ^{1}H-NMR spectrum. Thus, the other two carbons at δ 33.00 and 36.65 ppm must be tertiary carbons.

NOE experiments[143] were then carried out on compound **274** (Figure 39). Irradiation at the angular methyl signal at δ 1.22 ppm resulted in a 4.0% enhancement of H_{in} at δ 0.66 ppm but no enhancement of either H9 or H_{out}. Therefore, the stereochemistry of **274** was finally confirmed. Irradiation of H_{in} at δ 0.66 ppm did not give a clear enhancement of the angular methyl signal but did cause a 10% enhancement of H_{out} and a negative enhancement of H9.

4.1.3. Attempted Generation of the *trans*-Fused Hydrocarbon 284

Having obtained the desired intermediate **274** in good overall yield from thujone, it was appropriate to evaluate some chemistry with this compound. Birch reduction of **274**, followed by iodomethane addition to trap the generated enolate[144], gave the *gem*-dimethylated ketone **277** in low yield (15%). Attempts to improve this reaction by addition of proton donors (i.e., water and t-butanol) during the Birch reduction step, quenching of excess lithium with isoprene, and removal of ammonia prior to iodomethane addition proved to be infertile. The by-products were relatively non-polar and difficult to separate from each other. Simple reduction of **274** and polymethylation of **274** and **277** might be responsible for their generation.



274 **277**

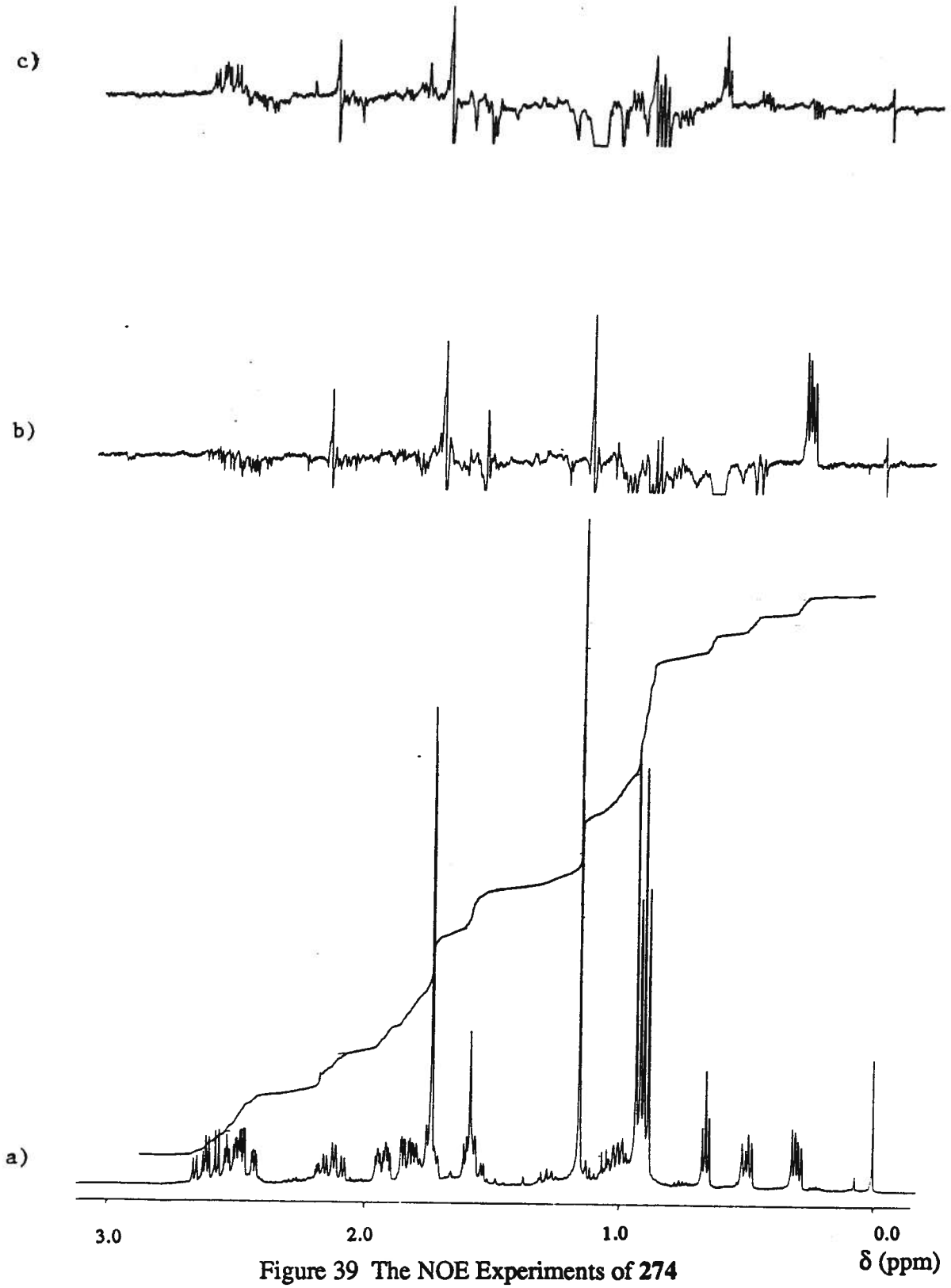
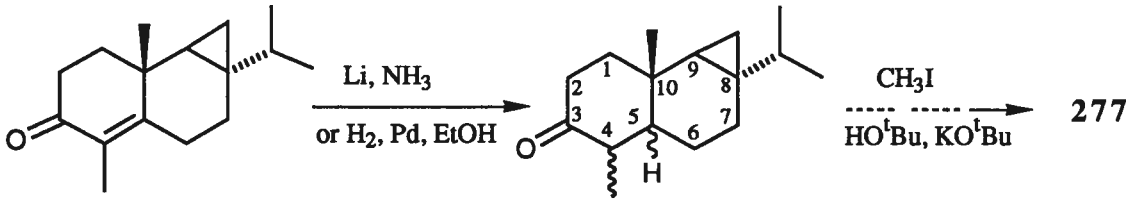


Figure 39 The NOE Experiments of **274**

a) off-resonance spectrum.
b) irradiation at 0.62 ppm.
c) irradiation at 1.22 ppm.

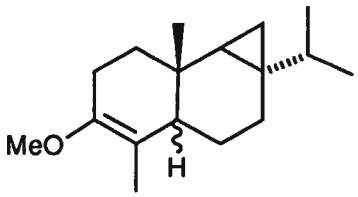
The mass spectrum of **277** revealed the molecular ion peak at m/z 248 while the IR spectrum indicated a carbonyl absorption at 1703 cm^{-1}. The relatively complex ^{1}H-NMR spectrum could be analyzed in support of structure **277**. Two multiplets appearing at δ 0.08 ppm (1H) and at δ 0.35 (2H), corresponded to the three cyclopropane protons. A triplet (J=2.4 Hz) at δ 0.85 ppm consisted of six protons, probably due to the overlapping of two doublets of the methyl groups of the isopropyl group. Three methyl singlets at δ 1.03, 1.21, and 1.22 ppm and two multiplets at δ 2.30 ppm (2H) and 2.62 ppm (1H) were also observed. The A/B ring junction was assumed to be *trans*, in accord with the expected stereochemistry of Birch reduction (see Chapter 3, Section **3.1.3.**) although insufficient evidence is available to be certain. The poorly resolved ^{1}H-NMR spectrum discouraged attempts to use NOE experiments to elucidate the nature of A/B ring junction at this stage.

An alternative route to **277** was perceived. Reduction of **274** by lithium and ammonia produced a mixture of two compounds **278** and **279** in a ratio of 4:1. Because these two compounds were not convertible by reaction with potassium hydroxide in methanol, they were assumed to be two diastereomers of opposite A/B ring fusion with the major isomer **278** presumed to possess the *trans* ring fusion as in compound **277**. These two compounds were difficult to separate by column chromatography. The mass spectrum of the mixture (**278** and **279**) indicated a molecular ion at m/z 236.while the IR spectrum showed a carbonyl absorption at 1700 cm^{-1}. Catalytic hydrogenation of **274** with 5% Pd-C at room temperature in ethanol generated **278** and **279** in a ratio of 6:1. Thus, the ^{1}H-NMR spectrum of this mixture could reveal some characteristic signals of **278**. Two multiplets appeared at δ 0.09 ppm (1H, t, J=5.2 Hz) and 0.40 ppm (2H, m), corresponding to the three cyclopropane protons. Three methyl doublets at δ 0.85 ppm (J=6.0 Hz), 0.88 ppm (J=6.0 Hz), and 0.93 ppm (J=8.0 Hz) corresponded to the two methyl groups of the isopropyl side chain and the methyl group at C4. The angular methyl appeared at δ 1.35 ppm as a singlet.



274 278/279

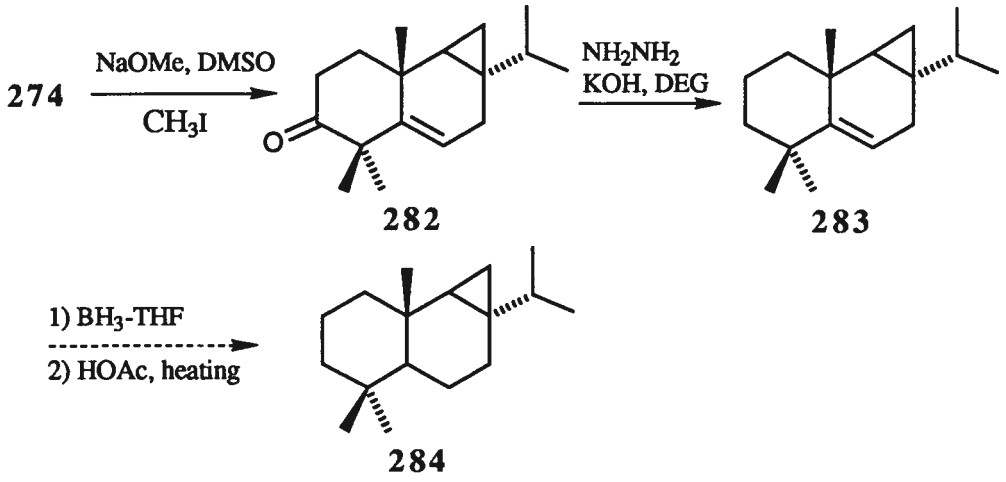
Refluxing the reduction mixture containing **278** and **279** with iodomethane and potassium *t*-butoxide in anhydrous *t*-butanol under nitrogen resulted in a mixture which did not contain **277**, as indicated by GC. No further attempt was made to elucidate this mixture. The reaction carried out at room temperature gave only recovered starting material.



280

Treatment of the mixture of **278** and **279** (6:1) with sodium methoxide and iodomethane produced **280** in 54% yield. This compound was characterized by a molecular ion peak at m/z 248 in its mass spectrum, a carbon-carbon double bond stretching absorption at 1680 cm^{-1} in its IR spectrum, and two methyl singlets at δ 1.57 and 3.50 ppm, corresponding to the vinylic methyl and the methoxyl methyl in the ^{1}H-NMR spectrum. The A/B ring junction of **280** was assumed to be *trans*, the same as that of **278** and **277**.

At this point, an alternative sequence to the A/B *trans-fused* hydrocarbon **273**, which was based on the rearrangement of the original sequence as shown in Scheme 47, was considered. The order of steps involved in this new sequence (Scheme 48) would be methylation, decarbonylation, hydrogenation; whereas the original sequence would have steps in a different order: hydrogenation, methylation, decarbonylation.

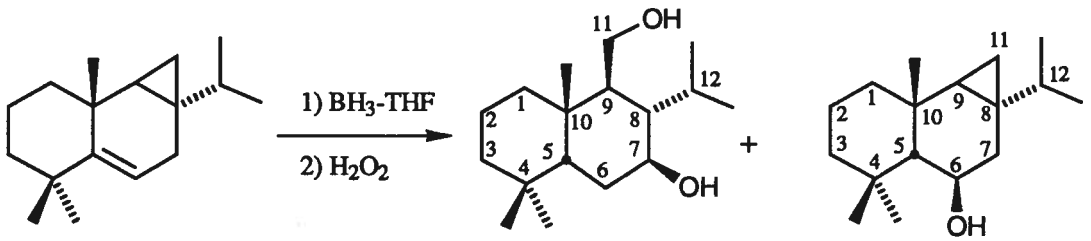


Scheme 48 An Alternative Sequence to Hydrocarbon **284**

Enone **274** was first methylated to **282** in 60% yield using sodium methoxide in DMSO[145]. The mass spectrum of **282** showed its molecular ion at m/z 246 while the IR spectrum displayed a carbonyl absorption at 1700 cm^{-1}. The ^{1}H-NMR spectrum revealed three methyl singlets at δ 1.01, 1.18, and 1.20 ppm, corresponding to the angular methyl group and the two geminal methyl groups, and a one-proton triplet (J=4.0 Hz) at δ 5.42 ppm corresponding to the olefinic proton.

Decarbonylation of **282** utilizing the Wolf-Kishner-Huang Minlon conditions proceeded smoothly to give **283** in 67% yield. The mass spectrum of **283** revealed the molecular ion peak at m/z 232 while the IR spectrum indicated the absence of carbonyl absorption. The ^{1}H-NMR spectrum showed three one-proton multiplets at δ 0.14, 0.36, and 0.50 ppm, corresponding to the three cyclopropane protons, and a one-proton triplet (J=4.0 Hz) at δ 5.30 ppm corresponding to the olefinic proton.

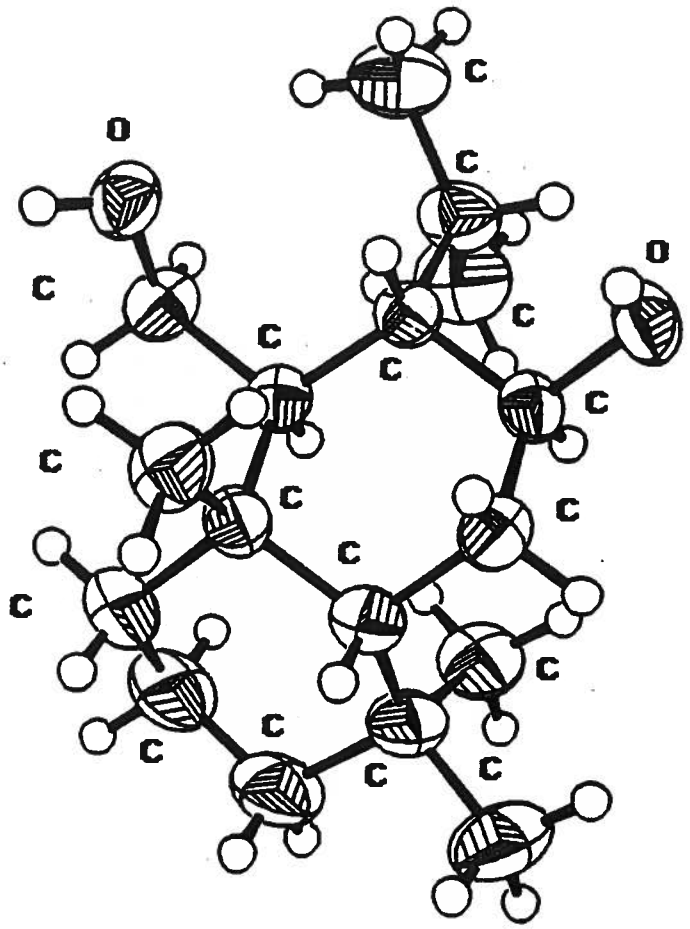
Treatment of carbon-carbon double bonds by borane to form organoboranes which are then decomposed with acetic acid to produce saturated C-C bonds is a useful indirect method of carbon-carbon double bond reduction[146]. However, such a treatment of **283** generated a complex mixture which was composed of several compounds as detected by GC and the ^{1}H-NMR spectrum.

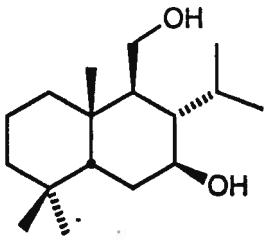


283 **285** **286**

To understand the complication, an oxidative treatment of the intermediate organoboranes by basic hydrogen peroxide was carried out. Diol **285** and alcohol **286** were isolated in 39% and 29% yield respectively. The mass spectrum of **285** had its molecular ion peak at m/z 268 while the IR spectrum indicated an intense hydroxyl absorption near 3500 cm^{-1}. The ^{1}H-NMR spectrum showed three methyl singlets at δ 0.96, 0.98, 1.00 ppm and two methyl doublets at δ 1.01 ppm (J=7.0 Hz) and 1.15 ppm (J=7.0 Hz). Two multiplets appearing at δ 3.72 ppm (2H) and 4.04 ppm (1H) corresponded to the the methylene and methine protons attached to C11 and C7. An X-ray structure of **285** (crystalized from methylene chloride) is shown in Figure 40 (see also Appendix 2). The *cis* A/B ring fusion is clearly indicated.

Alcohol **286** had its molecular ion peak at m/z 250 in the mass spectrum and an hydroxyl absorption at 3450 cm^{-1} in the IR spectrum. The ^{1}H-NMR spectrum indicated three multiplets at δ 0.14, 0.45, and 0.64 ppm, corresponding to the three cyclopropane protons. Two methyl doublets appeared at δ 0.85 ppm (J=6.0 Hz) and 0.90 ppm (J=6.0 Hz) while three methyl singlets were observed at δ 0.98, 1.10, and 1.16 ppm. A doublet of doublets at δ 2.14 ppm (1H, J=5.2 and 7.4 Hz) was probably due to one of the methylene protons at C7 which was neighboring to the cyclopropane ring). A one-proton complex multiplet at δ 3.87 ppm was assigned to the proton at C6. By analogy to structure **285** and the following mechanistic explanation, the ring fusion of **286** was presumed to be *cis* and the hydroxyl should have β orientation.



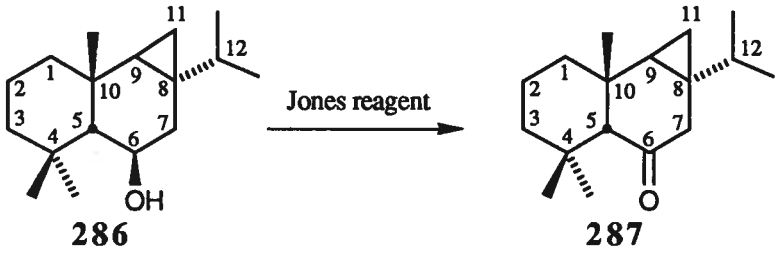


285

Figure 40 Single Crystal X-ray Structure of **285** (ORTEP Drawing)

The oxidation of **286** by Jones reagent produced ketone **287** in 80% yield. Compound **287** was characterized by its molecular ion peak at m/z 248 in the mass spectrum, a non-conjugated carbonyl absorption at 1700 cm^{-1} in the IR spectrum, and a two-proton signal

of strongly coupled AB type at δ 2.29 ppm corresponding to the two methylene protons at C7 in the ^{1}H-NMR spectrum.



286 **287**

The formation of **285** and **286** can be rationalized as follows (Figure 41). The hydroboration of the carbon-carbon double bond in **283** probably takes place from the β face to generate the *cis*-fused organoborane (i) which undergoes a direct oxidation to yield alcohol **286**. Isomerization of (i) may afford another organoborane (ii) which rearranges to the third

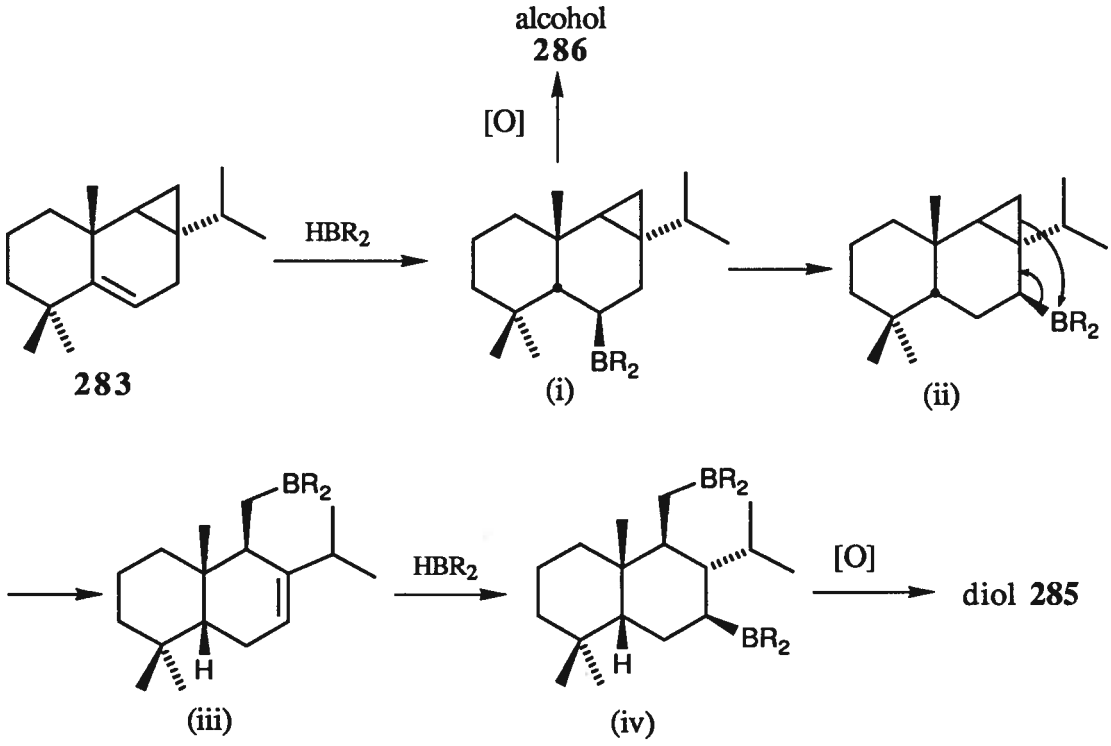
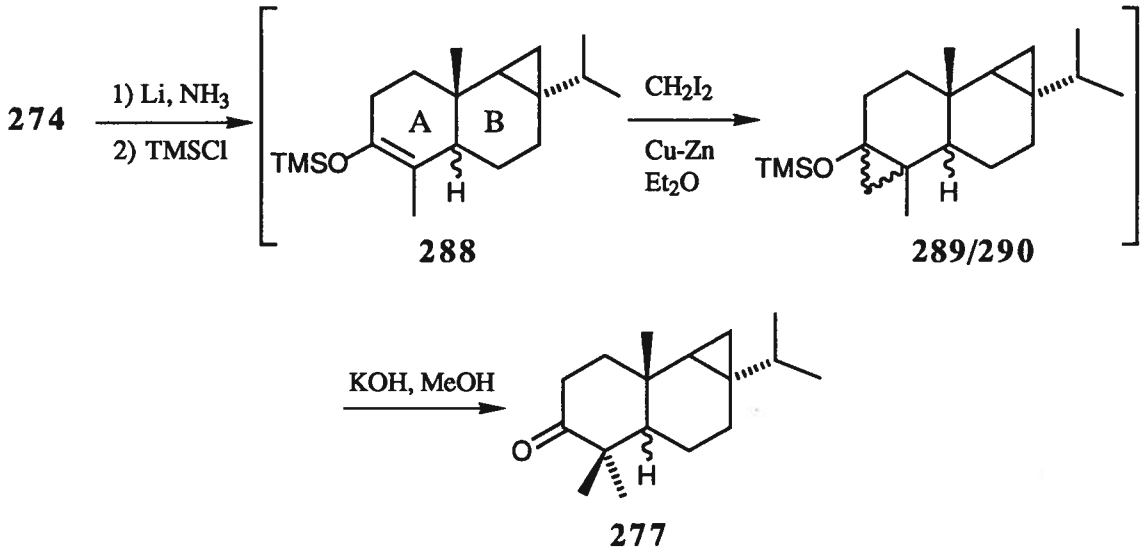


Figure 41 Novel Cyclopropane Ring Cleavage in the Hydroboration of **283**

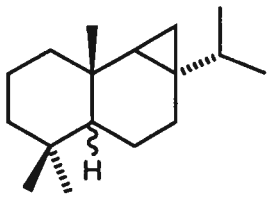
organoborane (iii) via a novel cyclopropane ring cleavage. A stereoselective hydoboration of (iii) provides the fourth organoborane intermediate (iv) and a two-fold oxidation of the latter results in the isolated diol **285**. Cleavage of vinyl cyclopropanes has been previously observed[147] but usually a drastic condition is required. Notably, the cleavage reaction of **283** took place at room temperature. After all, the complication of this indirect reduction was due to the unexpected conversions occurring during the hydroboration step.



Scheme 49 An Alternative Route to Ketone **277**

In a last attempt to improve the yield of **277**, the sequence in Scheme 49 was considered and put into experimental test. Trimethylsilyl enol ether **288** was prepared by trapping the enolate generated in the Birch reduction of **274** with trimethylsilyl chloride[148]. The crude product thus obtained was then converted into a mixture of trimethylsilyl cyclopropyl ethers (**289/290**) using the Simmons-Smith reaction[149,150,151]. This mixture probably contained two diastereomers **289** and **290** which had the newly created cyclopropyl ring α and β oriented since TLC indicated more than two spots. The crude product from Simmons-Smith reaction was hydrolyzed in warm potassium hydroxide-methanol solution[150,151]. A major compound isolated was identified as **277** by comparing its MS, IR,

NMR data with **277** previously obtained in the Stork enolate trapping reaction. The nature of A/B ring junction in **288, 289,** and **299** was uncertain although tentatively assumed to be *trans* as for **277**. The overall yield of **277** from **274** was 45% .

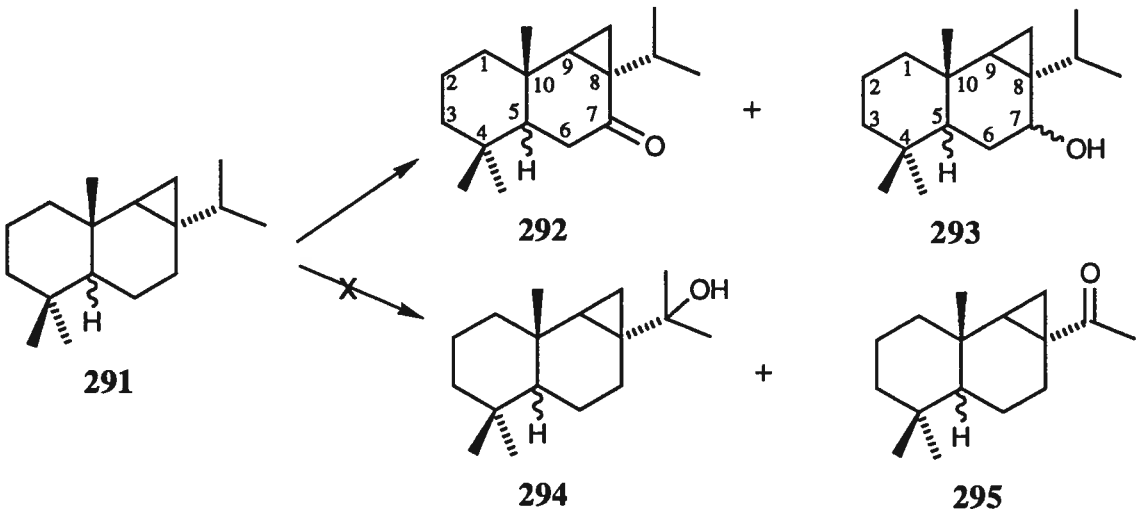


291

The reduction of **277** by the Wolf-Kishner-Huang Minlon method gave hydrocarbon **291** in 70% yield. The mass spectrum of **291** indicated the molecular ion at m/z 234 while the IR spectrum showed the absence of carbonyl absorption. The ^{1}H-NMR spectrum revealed two multiplets at δ 0.07 ppm (1H) and 0.40 ppm (2H), corresponding to the three cyclopropane protons. A triplet (6H, J=2.5 Hz) and three methyl singlets appeared at δ 0.84 ppm, 1.10, 1.20, and 1.22 pm respectively.

4.1.4. Ozonation of 291

Ozonation of hydrocarbon **291** in ethyl acetate, as before, resulted in the isolation of ketone **292** (35%) and alcohol **293** (5%) instead of the expected compounds **294** and **295**.



291 **292** **293** **294** **295**

Ketone **292** in its mass spectrum revealed a molecular ion at m/z 248 and its IR spectrum displayed a conjugated carbonyl absorption at 1665 cm^{-1}. Its ^1H-NMR spectrum indicated two methyl doublets at δ 0.84 ppm (J=6.6 Hz) and 0.94 ppm (J=6.6 Hz), corresponding to the two methyl groups of the isopropyl side chain, and three methyl singlets at δ 0.78, 1.11, and 1.30 ppm. A one-proton septet (J=6.6 Hz) corresponding to the methine proton in the isopropyl side chain appeared at δ 1.84 ppm. A multiplet containing two protons at δ 2.00-2.30 ppm corresponded to the two methylene protons at C6. An attempt to prepare suitable crystals for X-ray diffraction analysis of the solid **292** was not successful. The mass spectrum of alcohol **281** showed the molecular ion peak at m/z 250 and its IR spectrum revealed a broad absorption band near 3405 cm^{-1} which corresponded to hydroxyl stretching absorption. Its ^1H-NMR spectrum indicated two multiplets at δ 0.13 ppm (1H) and 0.45 ppm (2H), corresponding to the three cyclopropane protons, and two methyl doublets at δ 0.89 and 0.98 ppm, corresponding to the two methyl groups of the isopropyl side chain. Three methyl singlets appeared at δ 0.86, 1.10, 1.20 while a multiplet (1H) at δ 4.16 ppm corresponded to the proton at C8, the hydroxyl bearing carbon. The orientation of the hydroxyl group was not determined.

It is surprising that the previously noted selective ozonation of thujone derivatives could not be applied to the homothujone derivative **291**. The reasons for this reactivity change are unknown. Generally, a cyclohexane ring is more puckering than a cyclopentane. This may allow one of carbon-hydrogen bonds at C7 properly oriented towards the cyclopropane ring in **291**. This orientation may then facilitate the participation of the cyclopropyl group in the ozone insertion into this particular carbon-hydrogen bond*. The unusual reactivity of the carbon-hydrogen bonds of the methylene neighboring to the cyclopropane ring in homothujone derivatives was assumed to be general, which discouraged further pursuit of the homothujone strategy at that time. Since the oxidation of cyclopropylmethylene to cyclopropylketone has

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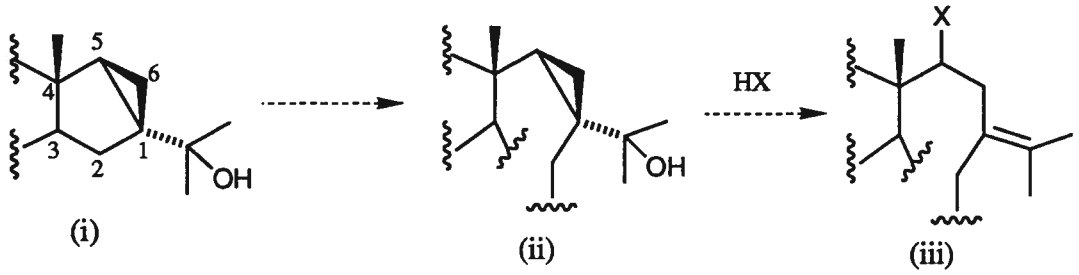
* For discussion on the mechanism of ozone insertion into carbon-hydrogen bonds, see Section **2.2.2.**

been observed by other oxidizing reagents[152], the oxidation of homothujone derivatives may find application in a way complementary to the ozonation of thujone derivatives in the future.

4.2. Studies on Utilizing the C2-C3 Bond Cleavage Products: a C9 strategy

Cyclopropylcarbinol of the general structure (ii) was considered as potentially useful intermediate in the thujone chemistry (Scheme 50). They might be available from thujone-derived cyclopropylcarbinol (i) by cleavage of the C2-C3 bond. Because the relief of the cyclopentane ring constraint, this *seco*-(C2-C3) cyclopropylcarbinol could possibly undergo acid-promoted ring opening via the cleavage of C1-C5 bond (endo type cleavage), rather than the cleavages of C1-C6 and C5-C-6 bonds (exo-type 1 and exo-type 2) usually observed for (i).

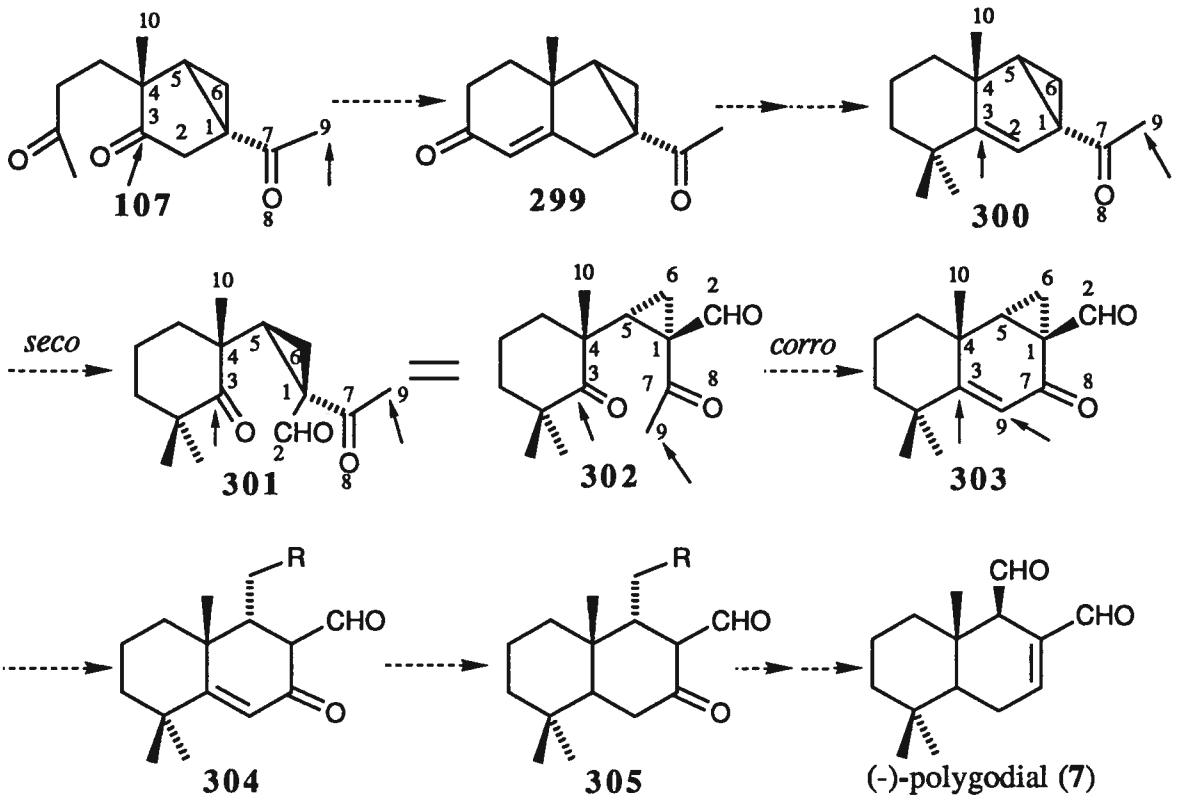


Scheme 50 Ring Cleavage of *seco*-(C2-C3) Cyclopropylcarbinols

A more attractive sequence leading to syntheses of (-)-polygodial (**7**) and its analogues involved the utilization of a *seco*-(C2-C3) intermediate (Scheme 51). Trione **107**, which could not find a ready application like its congener **106***, might undergo aldol condensation to afford enone **299** which would subsequently be methylated and selectively reduced to **300**. An oxidative cleavage of the C2-C3 bond should produce trione **301** which could be then recyclized to **303**. The *seco*-(C2-C3) compound **301** was considered equivalent to **302**. Conjugate addition of geminally diactivated cyclopropane **303**[153] would then generate

* Both **106** and **107** were derived from ozonation (Section **2.2.2.**, Scheme 17) Compound **106** was used in the studies on synthesis of steroid analogues from thujone, which is not described in this thesis.

compound **304** and the latter could then be reduced to the *trans*-fused decalone **305** by Birch reduction. Application of **305** in the syntheses of (-)-polygodial (**7**) and its analogues can be readily perceived.

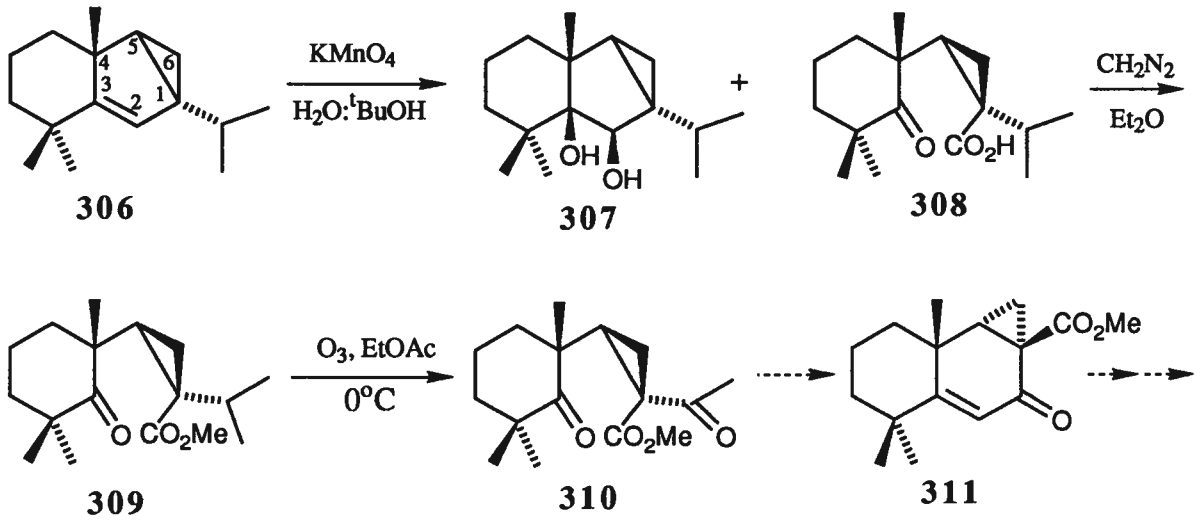


Scheme 51 A Novel Sequence to (-)-Polygodial (**7**);

This novel sequence belongs to C9 strategy in which nine of the ten carbons in thujone is incorporated into the target molecule (-)-polygodial (**7**). The cleavage of the C2-C3 bond and the following cyclization are interesting from the structural point of view and they are termed *seco* (from *seco* -thujone) and *corro* (from *corre* lation or connection of two seemingly distant carbons C3 and C9[#]) operations. These two operations reveal an inherent topology or connectivity of the thujone carbon skeleton. The direct creation of a *trans* A/B ring fusion and the use of a electrophilic cyclopropane are quite appealing from the chemical point of view.

[#] The numbering for the structural segment derived from thujone is kept the same as that for thujone to facilitate analysis.

Experimentally, the cyclization of **107** turned out to be a difficult reaction to perform. Treatment of **107** with pyrrolidine in refluxing benzene produced a rather complex mixture. Thus, no further attempt was made to carry out the above sequence. Fortunately, Dr. Dominik Guggisberg obtained ketoacid **308** as a by-product in the preparation of diol **307** from olefin **306***. A similar sequence to that in Scheme 51 was perceived starting with **308** (Scheme 52).



Scheme 52 The Utilization of a *seco*-(C2-C3) Intermediate **308**

Thus, methylation of ketocarboxylic acid **308** with diazomethane in diethyl ether gave ketoester **309** in 95% yield[154]. had The mass spectrum of compound **309** showed the molecular ion at m/z 280 corresponding to the molecular formula $C_{17}H_{28}O_3$ while Its IR spectrum revealed absorptions at 1710 cm^{-1} and 1685 cm^{-1} corresponding to the stretching absorptions of the conjugated ester carbonyl and the carbonyl in the cyclohexane ring. Two methyl doublets at δ 0.67 ppm (J=7.2 Hz) and 0.92 ppm (J=7.2 Hz) corresponding to the two methyl groups of the isopropyl side chain and three methyl singlets at δ 1.11, 1.13, and 1.20 ppm were observed in the ^{1}H-NMR spectrum. A methyl singlet at δ 3.65 corresponded to the methyl of the methoxycarbonyl group.

* I am grateful to Dr. Dominik Guggisberg for providing a sample of compound **308**.

The ozonation of **309** in ethyl acetate at 0°C generated **310** in 45% yield. The tertiary alcohol **312** (Scheme 53) was not isolated. Probably it was rapidly dehydrated to a terminal olefin at 0°C; the latter was then ozonized to **310** (see Section **2.2.2.**). Diketoester **310** had its mass spectrum showing the molecular ion at m/z 280 ppm and the IR spectrum showing carbonyl stretching absorptions at 1710 cm^{-1} and 1690 cm^{-1}. The ^{1}H-NMR spectrum indicated a methyl singlet at δ 1.08 ppm, an overlap of two methyl singlets as a broad singlet at δ 1.10 ppm, a methyl singlet at δ 2.28 ppm corresponding to the methyl of the acetyl group, and a methyl singlet at δ 3.76 ppm corresponding to the methyl of the methoxycarbonyl group.

LDA treatment of **310** in THF resulted in only recovery of the starting material. Instead, pyrrolidine treatment in refluxing benzene resulted in a messy mixture which was not analyzed further.

At this stage, we realized that a mistake had been made. Compound **301** is not equivalent to **302** at all (Scheme 51) but actually identical to **313** (Figure 42). Therefore, the cyclization of **301** and **310** would not produce **303** and **311** as drawn in Scheme 51 and 52 but highly stained compounds **314** and **315** (Figure 42) which have *trans*-fused bicyclo[4.1.0]heptane moieties[16].

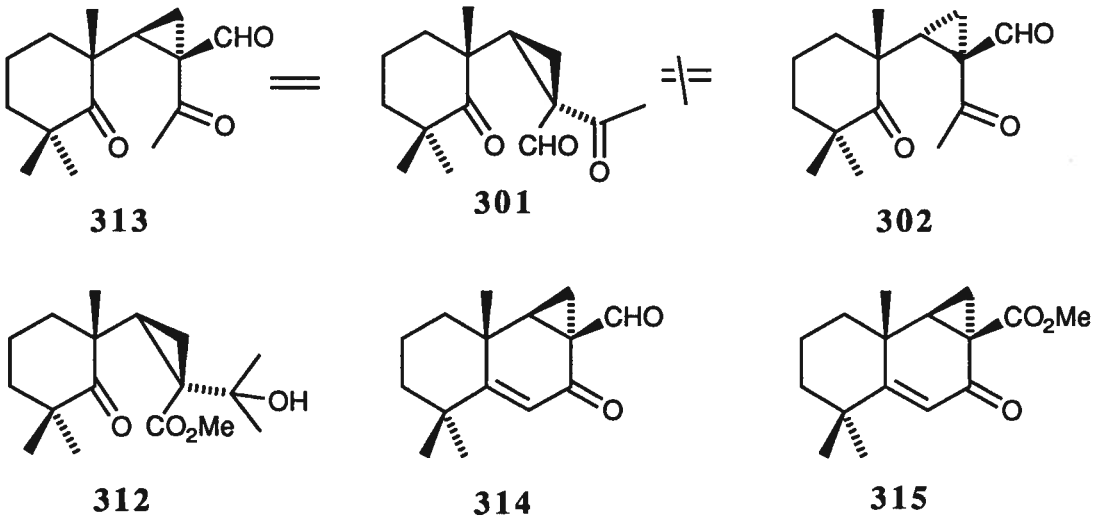
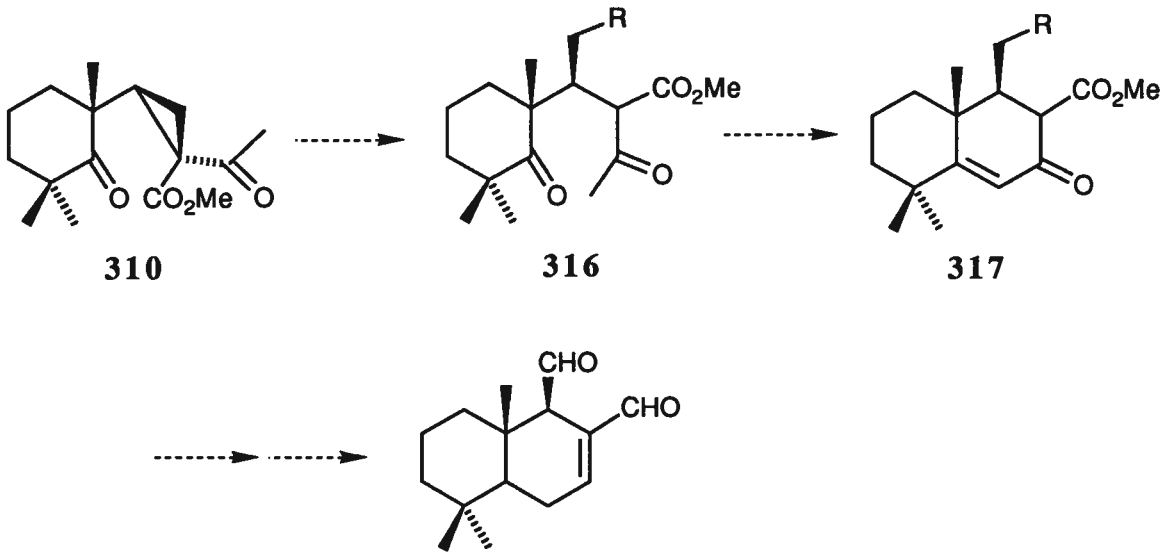


Figure 42 A Structural Misperception for **301**

With this consideration in mind, a new sequence was devised as shown in Scheme 53. A selective conjugate addition of the geminally diactivated cyclopropane **308** from the less substituted carbon[155] would generate **316** which could be cyclized to the highly functionalized octalone **317**. The further elaboration of **317** to (-)-polygodial (**7**) can be readily envisaged. This new sequence has the advantages stated for that in Scheme 51 and is no doubt a worthwhile undertaking in the future.



310 **316** **317**

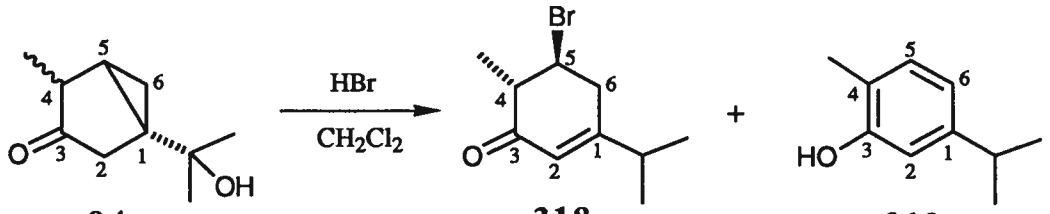
(-)-polygodial (**7**)

Scheme 53 The Final "*seco*/*corro*" C9 Strategy to the Synthesis of (-)-Polygodial (**7**);

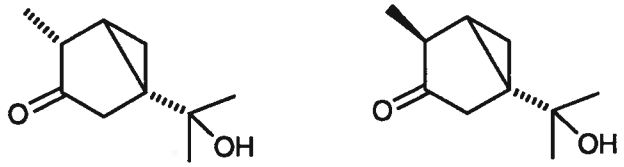
4.3. A Formal Synthesis of (+)-β-Cyperone: a C10 strategy

Thujonol (**94**)* as prepared earlier (Section **2.2.2.**) was treated with concentrated hydrobromic acid in methylene chloride at room temperature for two hours. Enone **318** and phenol **319** were isolated in 85% and 10% yield respectively.

* "Thujonol" was a mixture of α and β diastereomers in a ratio of 10:1. See the footnote at p. 28.



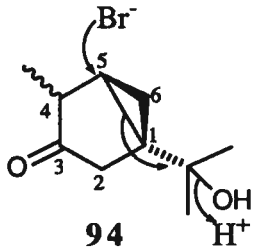
The specific rotation $[\alpha]_{25}^{D}$ of **318** was measured to be +42 (c=0.29, $CHCl_3$). The UV spectrum displayed a broad absorption peak maximal at λ 234.3 nm (logε=3.95, CH_3OH, c=20 mg/l), corresponding to the π to π* transition of the enone chromophore. The mass spectrum indicated the molecular ion peaks at m/z 232 and 230 (intensity ratio = 1:1), corresponding to two isotopic parent ions of formulas $C_{10}H_{15}O^{81}Br$ and $C_{10}H_{15}O^{79}Br$. The IR spectrum showed an intense conjugated carbonyl absorption at 1670 cm^{-1} and a weak carbon-carbon double bond absorption at 1630 cm^{-1}. The ^{1}H-NMR spectrum was well resolved. An apparent doublet at δ 1.11 ppm (J=6.8 Hz), corresponding to the two methyl groups of the isopropyl side chain. A methyl doublet at δ 1.34 ppm (J=7.1 Hz) corresponded to the methyl at C4. A septet at δ 2.43 ppm (1H), a multiplet at δ 2.55 ppm (1H), and another multiplet at δ 2.92 ppm (2H) were assigned to the methine proton of the isopropyl side chain, the methine proton at C4, and the two methylene protons at C6. A doublet of triplets signal at δ 4.19 ppm (J=4.4 and 10.2 Hz) was due to the methine proton at C5 (i.e., the bromine bearing carbon) while a broad singlet at δ 5.97 ppm was clearly due to the olefinic proton at C2.



α diastereomer of **94** β diastereomer of **94**

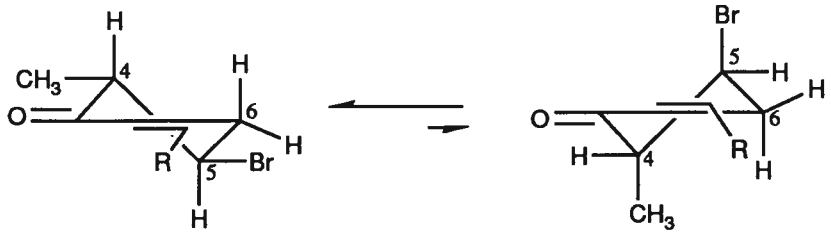
Since the α diastereomer of thujonol (**94**) was the predominant component (~90%) of

the starting material*, it was reasonable to assume that the major ring cleavage product **318** (85%) had the configuration at C4 as shown. The configuration at C5 was assigned as shown by analogy with the observed nucleophilic attack on C5 from the back side of the cleaving C1-C5 bond during the acid promoted ring cleavage of an analogous cyclopropylcarbinol .



94

These two configurational assignments were supported by the ^{1}H-NMR spectral data. As indicated above, the methine proton at C5 appeared as doublet of triplets at δ 4.19 ppm with J=4.4 for doublet and J=10.2 Hz for triplet. This can be well understood from the conformational analysis of **318**. As shown below, compound **318** have two half-chair-like conformer **318**a and **318**b. Conformer **318**a is the predominant one since it has both the methyl group at C4 and the bromo group at C5 equatorially oriented. The gross ^{1}H-NMR spectrum can be approximately represented by conformer **318**a. The axial proton at C5 of **318**a should couple with two axial protons at C4 and C6 nearly equally (J≈8-13 Hz) and with the equatorial proton at C6 relatively weakly (J≈3-5 Hz). We may predict with confidence that the methine proton at C5 will appear as a triplet splitting into three doublets with J values in



318a **318**b

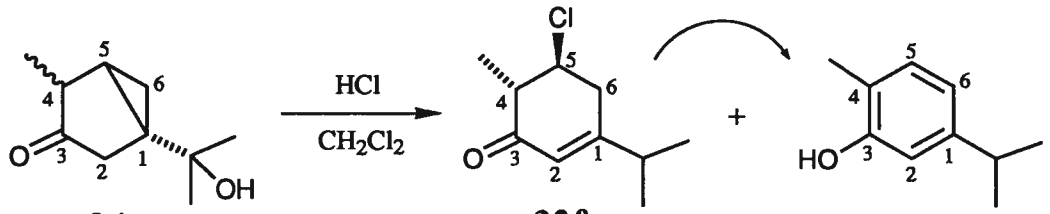
R=–CH(CH$_3$)$_2$

* See footnotes at page 28 and 204.

ranges just indicated. This is indeed the case. In fact, except the enantiomer of **318**, no other diastereomer of **318** can explain the particular splitting pattern of the signal at δ 4.19 ppm.

Phenol **319** is known as carvacrol[164]. The mass spectrum of **319** indicated the molecular ion peak at m/z 150, consistent with the formula $C_{10}H_{14}O$. The IR spectrum showed an intense hydroxyl absorption at 3300 cm^{-1}. The ^1H-NMR spectrum was exceedingly simple. An apparent doublet at δ 1.22 ppm (6H, J=7.2 Hz) was assigned to the two methyl groups of the isopropyl side chain. A methyl singlet at δ 2.20 was due to the methyl group at C4 while a one-proton septet was assigned to the methine proton of the isopropyl side chain. A broad one-proton singlet at δ 3.96 ppm corresponded to the hydroxyl proton. Three olefinic proton signals at δ 6.65 (1H, d, J=1.8 Hz), 6.73 (1H, dd, J=7.5 and 1.8 Hz), and 7.04 (1H, d, J=7.5 Hz) corresponded to protons at C2, C6 and C5 respectively.

When thujonol (**94**) was treated with concentrated hydrochloric acid at room temperature, chloro-enone **320** and carvacrol (**319**) were isolated in 45% and 40% yield respectively.



94 **320** **319**

The mass spectrum of compound **320** revealed molecular ion peaks at m/z 188 and 186 (intensity ratio ≈1:3), corresponding to two isotopic parent ions of formulas $C_{10}H_{15}O^{37}Cl$ and $C_{10}H_{15}O^{35}Cl$. The IR spectrum indicated an intense conjugated carbonyl stretching absorption at 1675 cm^{-1} and a weak carbon-carbon double bond absorption at 1630 cm^{-1}. This chloro-enone was rather unstable and the obtained ^1H-NMR spectrum always contained extra signals due to the presence of carvacrol (**319**). However, a "difference spectrum" between the "contaminated spectrum" and the spectrum of **319** revealed all signals of **320** clearly. In fact, this "difference spectrum" of **320** was very similar to the spectrum of **318**. An apparent

doublet at δ 1.09 ppm (6H, J=7.2 Hz) was due to the two methyl groups of the isopropyl side chain while a methyl doublet at δ 1.30 ppm was assigned to the methyl group at C4. A septet at δ 2.43 ppm (1H), a multiplet at δ 2.54 ppm (1H), and another multiplet at δ 2.78 ppm (2H) were further assigned to the methine proton of the isopropyl group, the methine proton at C4, and the two methylene protons at C6. A doublet of triplet signal at δ 4.06 ppm (1H, J=4.4 and 9.8 Hz) corresponded to the methine proton at C5 (i.e., the chlorine bearing carbon) while a broad singlet at δ 5.95 ppm (1H) was due to the olefinic proton at C2. Based on the analysis of the splitting pattern of the C5 methine proton signal in a way similar to that for **318**, the stereochemistry of **320** was determined to be as shown.

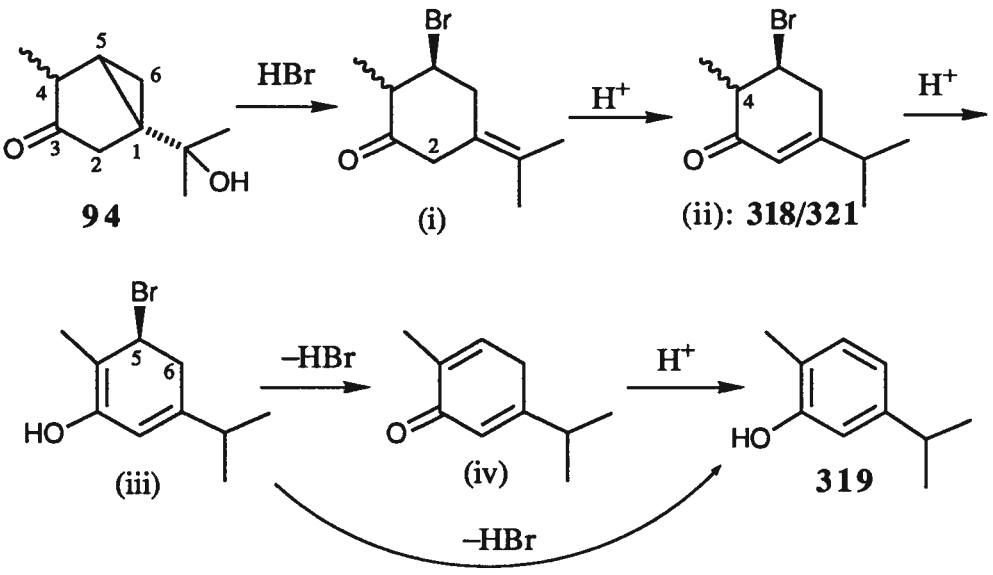
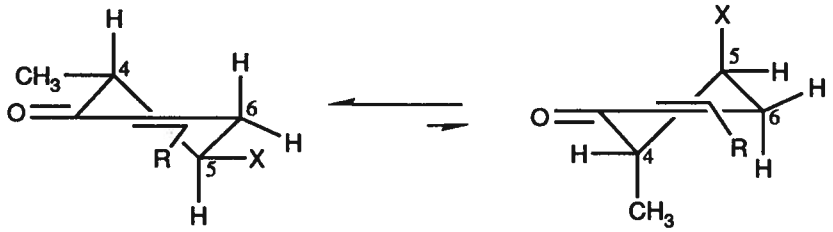


Figure 43 The Endo-type Cleavage Mechanism for the Formation of **318** and **319**

The mechanism in Figure 43 was proposed to explain the formation of **318** and **319**. The HBr promoted ring opening through the C1-C5 bond cleavage (i.e., the endo-type cleavage) produces (i) which undergoes a double bond migration to give the more stable isomer (ii), i.e., **318** and its C4 epimer **321**. The acid catalyzed enolization of (ii) generates dienol (iii) and the latter may lose a HBr molecule either through a 1,2-elimination to yield **319** directly or through a 1,4-elimination to afford dienone (iv) first and then **319** later.

It is noted above that chloroenone **320**, although structurally similar to bromoenone **318**, was much less stable. It decomposed into carvacrol (**319**) in deuteriated chloroform at room temperature. This instability may account for the fact that more carvacrol (**319**) was isolated from the HCl promoted ring cleavage of thujonol (**94**). Both **318**a and **320**a, the major half-chair-like conformers of **318** and **320**, are suitable for acid catalyzed enolization since they all have axial protons at C4.

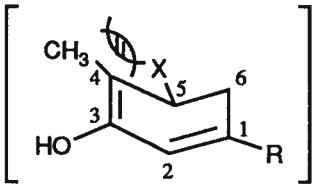


X=Br, **318**a
X=Cl, **320**a

X=Br, **318**b
X=Cl, **320**b

R=–$CH(CH_3)_2$

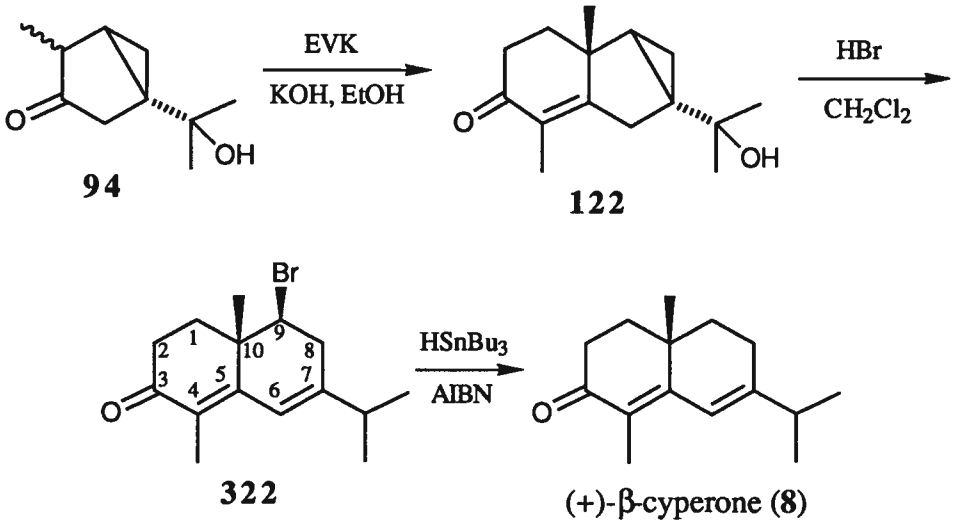
However, the formation of enol from **318**a is likely to be more difficult because of the greater steric interaction (allylic strain) between the more bulky equatorial bromine at C5 and the methyl at C4 during the enolization. The relative ease of enolization for **320**a allows the following dehydrobromination to take place (Figure 43) and carvacrol (**319**) is thus more readily converted from **320**.



X=Br, Cl
R=–$CH(CH_3)_2$

The endo-type cleavage pathway during the acid promoted ring opening of another thujone-derived cyclopropylcarbinol was again observed (Scheme 54). Hydroxyenone **122**,

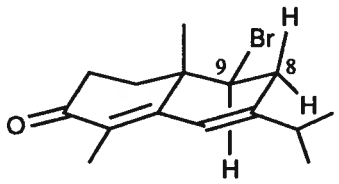
previously obtained from Robinson annulation of thujonol (**94**) with EVK in 35% yield (Section **2.2.3.**), was treated with hydrobromic acid in methylene chloride. Bromo-dienone **322** was isolated in 91% yield. Compound **322** has been previously reduced to (+)-β-cyperone (**8**) by tributyltin hydride in an earlier synthesis of (+)-β-cyperone from thujone[13a]. Thus, a new sequence to (+)-β-cyperone was completed in four steps using ozonation of thujone, Robinson annulation of thujonol (**94**), ring opening of **122**, and radical-mediated reduction of **322**. The new sequence incorporates all the ten carbons of thujone into the target molecule (+)-β-cyperone (**8**). This synthesis provides an example of C10 strategy.



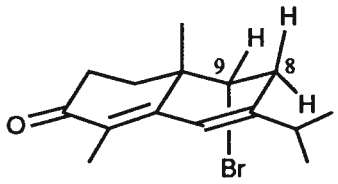
Scheme 54 A Formal Synthesis of (+)-β-Cyperone (**8**)

The specific rotation $[\alpha]_{25}^{D}$ of **322** was measured to be +420 (c=1.00, $CHCl_3$), which is in good agreement with the reported value +430 (c=1.0, $CHCl_3$)[13a]. The UV spectrum displayed an intense absorption peak maximal at λ 293 nm (log ε=4.40, MeOH). Thus, a conjugation among the carbonyl group, the C4-C5 double bond, and the C6-C7 double bond was suggested. The mass spectrum indicated molecular ion peaks at m/z 298 and 296 (intensity ratio ≈ 1:1), corresponding to two isotopic parent ions of formulas $C_{15}H_{21}O^{81}Br$ and $C_{15}H_{21}O^{79}Br$. The IR spectrum revealed a intense conjugated carbonyl absorption at

1660 cm^{-1} and a weak carbon-carbon double bond absorption at 1620 cm^{-1}. The ^1H-NMR spectrum showed an apparent doublet at δ 1.12 ppm (6H, J=6.0 Hz), corresponding to the two methyl groups of the isopropyl side chain, and two methyl singlets at δ 1.17 and 1.86 ppm, corresponding to the angular methyl group at C10 and the vinylic methyl group at C4. A one-proton doublet of doublets signal at δ 4.14 (J=6.0 and 10.0) was assigned to the methine proton at the bromine bearing carbon (C9) while a one-proton singlet at δ 6.31 ppm was clearly due to the olefinic proton at C6. The particular splitting pattern of the signal at δ 4.14 ppm allowed the assignment of the configuration at C9. The molecular model of **322** revealed a rather rigid conformation in order to accommodate the full conjugation of the three double bonds. The axial proton at C9 would couple with the axial proton at C8 (usually, J=8-13 Hz) and the equatorial proton at C8 (usually, J=3-5 Hz) quite differently and a doublet of doublets with J values in regions just indicated should be expected for the C9 proton signal. This prediction is quite close to what was observed. Compound **323**, the epimer of **322** with the bromine at C9 α oriented, would show the C9 proton signal as a triplet with J=3-5 Hz or a doublet of doublets with both J=3-5 Hz. The slightly larger J value for the coupling between the C9 axial proton and the C8 equatorial proton in **322** (J=6.0 Hz), than normally observed for the coupling between an axial proton and an equatorial proton, is probably due to some geometric distortion.



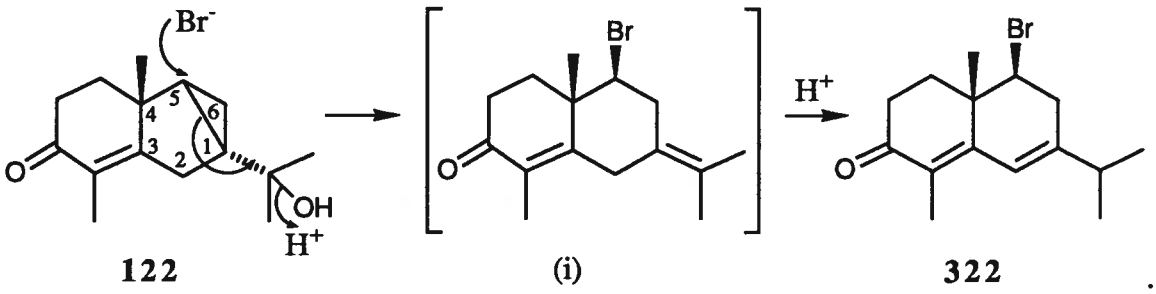
322



323

The mechanism shown in Figure 44 was proposed to rationalize the formation of **322** from **122**, which is similar to what was proposed for the formation of **318** from thujonol (**94**) (Figure 43). The nucleophilic ring opening generates an unstable intermediate (i) which then

rearranges to the more stable dienone **322** with a fully conjugated dienone system. The ring opening reaction proceeds through the cleavage of C1-C5 bond* , i.e., the endo-type cleavage. The bromide anion attacks on the C5 from the backside of the cleaving C1-C5 bond, leaving the β orientation of the bromo group in (i) and thus **322**.

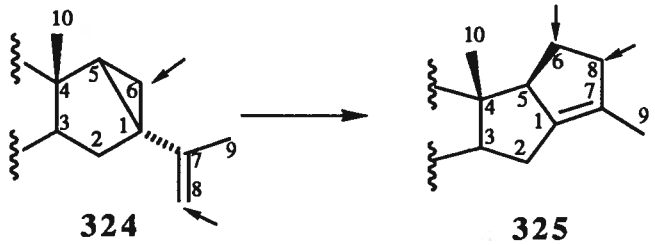


122 (i) **322**

Figure 44 The Ring Opening reaction of **122** via the Endo-type Cleavage Pathway

It is speculated that the interaction of the double bond exo to the bicyclo[3.1.0]hexane and the C1-C5 bond in hydroxyenone **122** and thujonol (**94**) leads to the weakening of C1-C5 and eventually its facile cleavage under acidic conditions.

A possible new way of incorporating all the ten carbons into target molecules is shown in Scheme 55. Rearrangement of vinylcyclopropanes of general structure **324** available from ozonation of thujone derivatives may provide useful intermediates of general structure **325** to synthesis of polyquinanes which possess a bicylo[3.3.0]octane unit. It also serves as one way to correlate two "distant carbons": C6 and C8.

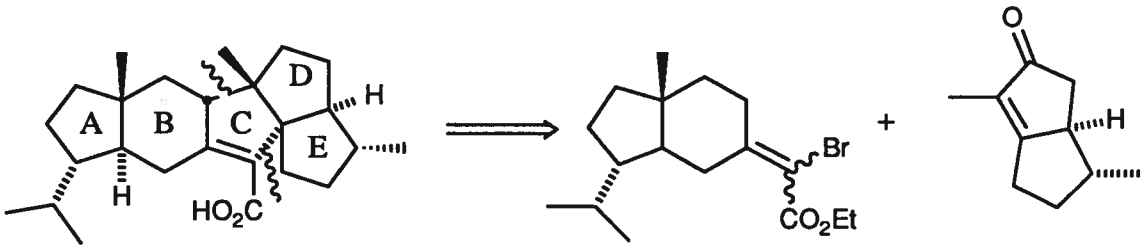


324 **325**

Scheme 55 A Potential New C10 Strategy

* In order to facilitate the comparison with the ring opening of thujonol **94**, the numbering of those carbons in the bicyclo[3.1.0]hexane moiety in **120** is, at this point, kept the same as that in thujonol (**94**).

A few polyquinanes containing such a dimethylated bicyclo[3.3.0]octane unit are known, for example, (-)-retigeranic acid **304**. In a recent total synthesis of **304**, a chiral starting material **305** of the dimethylated bicylo[3.3.0]octane unit was incorporated into the target molecule[157] (Figure 45).



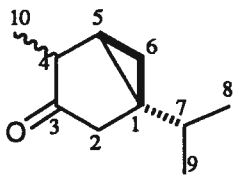
326 **327** **328**

Figure 45 Incorporation of a Dimethylated Bicylo[3.3.0]octane unit

4.4. Concluding Remarks: prospect of thujone chemistry

The abstract of this thesis summarizes the highlights on applying the ozonation methodology into specific directions of investigation. Solutions to some remaining problems in these directions are suggested along the presentation while some possible extensions of the present work are also discussed. It remains to present some reflections on the subject of thujone chemistry as a whole.

The enrichment of thujone chemistry and the enhancement of its versatility as a chiral starting material for the synthesis of biologically active natural products depend largely on the accumulation of fundamental knowledge about this unique entity in structurally diverse environments.



The ozonation of thujone and its derivatives allowed a novel functionalization of these molecules and opened the door to apply the cyclopropane chemistry on a different level in the last few years. This kind of carbon-hydrogen bond functionalization may be realized through other more recently developed reagents[159b], for example, dioxyrane[159a] and should be explored in the future. Functionalization of other positions in the thujone framework should be considered too.

Ring expansion or contraction of thujone may provide interesting new avenues of thujone chemistry with regard to cyclopropane ring opening control and carbocyclic ring incorporation.

The Robinson annulation of thujone is regioselective and stereoselective due to the substitution pattern of the thujone frame work and the particular geometry of the bicyclo[3.1.0]hexane unit. Annulations of opposite or complementary regioselectivity and stereoselectivity will enhance the versatility of thujone as a chiral building block. The 6-membered ring annulation may be changed to annulations forming other ring sizes, for example, 5-membered and 4-membered rings when suitable new target molecules are chosen. Bridged and spiral annulations should be subjected to similar studies when needed.

The degree of carbon incorporation may guide the planning in a more thorough and systematic manner. The *seco* and *corro* operations reveal an inherent connectivity of the thujone skeleton and allow novel chemistry to unfold. This may provide some novel solutions to difficult problems, for example, the direct creation of 6,6-A/B *trans* ring fusion. Abstraction of such formal operations from synthetic studies is intellectually inspiring and may find applications somewhere else*.

As stated in Section **1.1.** of Chapter 1 (General Introduction), the often tedious and lengthy process to prepare an intermediate, the racemate of which could be synthesized in a simple manner, is a serious drawback of using chiral building block. To avoid this problem,

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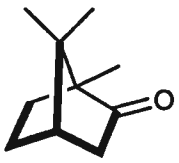
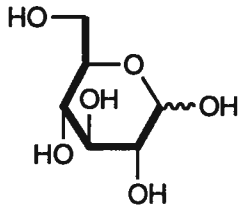
* For relevant discussion on general problem solving techniques, see ref. 156, under "Can you use the result?".

such simple intermediates possibly derived from chiral building blocks should not be considered favorably. Highly functionalized intermediates, like functionalized cyclopropanes, cyclopentanes, cyclohexanes, and bicyclo systems like decalones, indenone, pentalenones are to be chosen as sub-goals early in the planning stage.

There are other versatile chiral starting materials in use, for example, camphor and D-glucose. Applications of D-glucose and other simple sugars have been numerous and provide the major basis for a systematic analysis of some synthetic problems, the so-called "chiron" approach[160]. Since sugars are highly functionalized molecules, the application of them frequently requires the removal of functional groups, a feature contrasting very much to



camphor



D-glucose (pyranose)

the application of terpenes as starting materials. The camphor has been established as a very versatile chiral starting material*[161]. Comparison of thujone and the camphor chemistry will reveal some important elements responsible for their own effectiveness as chiral building block. The cross fertilization from the chemistry of camphor and other monoterpenes will certainly stimulate the chemistry of thujone.

Different from camphor, thujone has not been employed as a chiral auxiliary so far. The diastereomeric impurity of thujone and unavailability of its enantiomer can attenuate its usefulness in this regard. However, derivatization of the diastereomeric mixture by converting the C4 chiral center into a trigonal center or into a quartery center may provide diastereomerically pure thujone derivatives useful as chiral auxiliaries.

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* We would like to thank Dr. T. Money for providing his newest review on this subject for our reference.

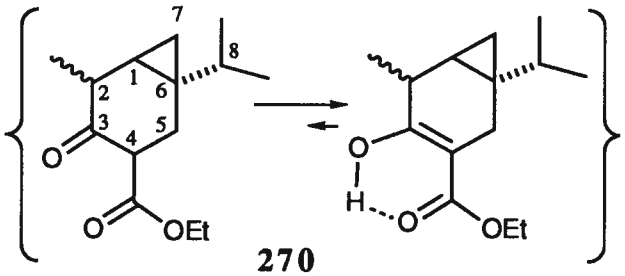
4.5. Experimental

See Section 2.3.1. for General experimental.

4.5.1. Ring Expansion: thujone (3) to ketoester 270

[1**R**-(1α,2α/β,6α)] 4-Ethoxycarbonyl-2-methyl-6-(1-methylethyl)bicyclo[4.1.0]heptan-3-one (**270**, the ketoester form)

[1**R**-(1α,2α/β,6α)] 4-Ethoxycarbonyl-2-methyl-6-(1-methylethyl)bicyclo[4.1.0]hept-3-ene-3-ol (**270**, the enolester form)



270

To a cooled solution (0°C) of thujone (**3**) (3.04 g, 20.0 mmol) and boron trifluoride etherate (4.26 g, 30.0 mmol) in anhydrous diethyl ether (25 ml), ethyl diazoacetate (3.42 g, 30.0 mmol) in anhydrous diethyl ether (5 ml) was added dropwise over a period of 30 minutes. The resulting solution was stirred under nitrogen at room temperature overnight, made basic with saturated aqueous sodium carbonate solution, and extracted with diethyl ether. The diethyl ether solution was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography of the crude product with ethyl acetate:hexanes (1:30, v/v) mixture produced β-ketoester **270** in 70% yield (3.34 g).

The physical properties of **270** are as follows*:

UV (MeOH, c=20.4 mg/l) $\lambda_{max.}$: 258 nm (log ε=3.980).

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* All data were taken from spectra of the mixture of α and β diastereomers (9:1 from GC). The ^{1}H-NMR spectral signals should be those of the predominant α diastereomer since these signals can be easily selected by comparing the integrations. The ^{1}H-NMR spectral signals of the minor β diastereomer were hardly observable from the spectrum. See foots at p. 178 and 180.

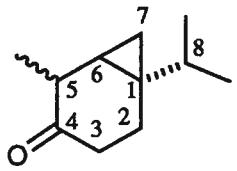
IR (film) νmax.: 3370 (O-H stretching), 1655(C=O stretching), 1615 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.30 (1H, dd, J=4.4 and 8.8 Hz), 0.39 (1H, t, J=4.4 Hz), 0.68 (1H, dd, J=4.4 and 8.8 Hz), 0.98 (6H, two overlapped doublets, J=5.6 and 4.4 Hz), 1.03 (1H, m), 1.24 (3H, d, J=7.2 Hz), 1.31 (3H, t, J=6.8 Hz), 2.25-2.57 (2H, AB type, J=16 Hz), 2.64 (1H, q, J=7.2 Hz), 4.21 (2H, m), 12.24 (1H, s).

MS m/z: 238 (M^+, 35.0%), 192 (79.7%), 177 (66.4%), 149 (100.0%). High resolution mass measurement calculated for $C_{14}H_{22}O_3$: 238.1569; found: 238.1570.

4.5.2. Decarboxylation: ketoester 270 to homothujone (272)

[1**R**-(1α,2α/β,6α)] 2-Methyl-6-(1-methylethyl)bicyclo[4.1.0]heptan-3-one (**272**)



272

To ketoester **270** (2.70 g, 11.3 mmol) in DMSO (20 ml) was added sodium chloride (1.20 g, 20.9 mmol) and water (1.0 ml). The resulting mixture was refluxed at 140°C for 4 hours, cooled down, diluted with water (40 ml), and extracted with diethyl ether (3X25 ml). The ether solution was dried over magnesium sulfate and concentrated *in vacuo* to give a crude product which was chromatographed with ethyl acetate:hexanes (1:8, v/v) mixture. Homothujone **272** was obtained in 96% yield (1.80 g).

The physical properties of **272** are as follows*:

IR (film) νmax.: 3060, 1700 cm^{-1}.

^{1}H-NMR (400 MHz, CDCl3) δ: 0.50 (2H, m), 0.72 (1H, m), 0.95 (3H, d, J=6.4 Hz), 0.98

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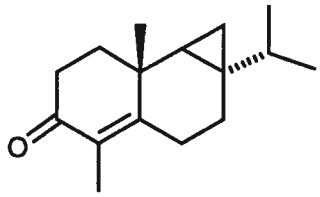
* All data were taken from spectra of the mixture of α and β diastereomers (9:1 from GC). The ^{1}H-NMR spectral signals should be those of the predominant α diastereomer since these signals can be easily selected by comparing the integrations. The ^{1}H-NMR spectral signals of the minor β diastereomer were hardly observable from the spectrum. See also foots at p. 178 and 180.

(3H, d, J=6.4 Hz), 1.06 (1H, m), 1.22 (3H, d, J=8.0 Hz), 1.84 (1H, m), 2.10 (2H, m), 2.35 (1H, m), 2.47 (1H, m).

MS m/z: 166 (M^+, 18.3%), 123 (29.7%), 109 (58.0%), 96 (91.2%), 41 (100.0%). High resolution mass measurement calculated for $C_{11}H_{18}O$: 166.1358; found: 166.1360.

4.5.3. Robinson Annulation: homothujone (272) to enone 274

[1a**R**-(1aα,7aβ,7bα)] 1,1a,2,3,6,7,7a,7b-Octahydro-4,7a-dimethyl-1a-(1-methylethyl)-5*H*-cyclopropa[*a*]naphthalen-5-one (**274**)



274

Homothujone **272** (341 mg, 2.05 mmol) was mixed with 1-diethylamino-3-pentanone-iodomethane salt (675 mg, 2.26 mmol) in anhydrous ethanol (20 ml) under an atmosphere of nitrogen. After the addition of potassium hydroxide (184 mg, ~80% putre, 2.57 mmol), the reaction mixture was heated to reflux for 1 hour, cooled down, and diluted with water (30 ml). Petroleum ether (2X20 ml) was used to extract the above aqueous mixture. Concentration of the combined petroleum ether solution *in vacuo* furnished an oil which was chromatographed to provide **274** in 70% yield (332 mg).

The physical properties of **274** are as follows:

$[\alpha]_D^{25}$=+1.94X10^2 (c=1.00, $CHCl_3$).

UV (MeOH, c=20.0 mg/l) $\lambda_{max.}$: 250 nm ((log ε=4.133).

IR (film) $\nu_{max.}$: 3060, 1660, 1620 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.30 (1H, dd, J=4.8 and 9.6 Hz), 0.50 (1H, dd, J=4.8 and 9.6 Hz), 0.66 (1H, t, J=4.8 Hz), 0.90 (3H, d, J=7.2 Hz), 0.93 (3H, d, J=7.2 Hz), 1.01 (1H,

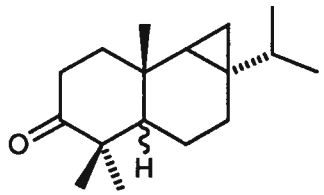
m), 1.16 (3H, s), 1.58 (2H, m), 1.74 (3H, s), 1.82 (1H, m), 1.93 (1H, m), 2.12 (1H, dt, J=5.2 and 14.0 Hz), 2.35-2.70 (3H, m).

MS m/z: 232 (M^+, 57.2%), 217 (18.3%), 189 (60.1%), 161 (100.0%). High resolution mass measurement calculated for $C_{16}H_{24}O$: 232.1827; found: 232.2819.

Elemental analysis: calc. for $C_{16}H_{24}O$: C 82.70, H 10.41; found: 82.58, H 10.44.

4.5.4. Birch Reduction-CH_3I Trapping and Birch Reduction-TMSCl Trapping-Simmons-Smith Reaction-Hydrolysis Sequences: enone 274 to ketone 277

[1aR-(1α,7aβ,7bα)] Decahydro-4,4,7a-trimethyl-1a-(1-methylethyl)-5*H*-cyclopropa[*a*] naphthalen-5-one (**277**)



277

Method A:

Ammonia was distilled from sodium to a flask charged with enone **274** (419 mg, 1.81 mmol) under nitrogen. Pieces of lithium metal (13.8 mg, 1.99 mmol, 1.1 eqv.) were added and the resulting dark purple solution was stirred at -33°C for 1 hour before iodomethane (1.3 ml) and anhydrous diethyl ether (5.0 ml) were introduced. The dry ice-acetone condenser was removed to allow ammonia to evaporate. The reaction mixture was stirred overnight and transferred to a separatory funnel containing water (15 ml) and ether (20 ml). The ether layer was separated, washed with brine (10 ml), dried over magnesium sulfate. Evaporation of diethyl ether *in vacuo* resulted in a yellowish oil which was chromatographed first with ethyl acetate:hexanes (1:15, v/v) and then benzene to furnish ketone **277** in 15% yield (63 mg).

Method B:

Ammonia (~20 ml) was distilled from sodium to a solution of enone **274** (1.10 g, 4.74 mmol) in anhydrous ether (10 ml) under nitrogen. Lithium (35 mg, 4.98 mmol,1.05 eqv.) was added. The dark purple mixture was stirred for 1.5 hours at -33°C before freshly distilled trimethylsilyl chloride (1.20 ml, 2.0 eqv.) was injected. The resulting yellowish solution was warmed to room temperature and stirred for 1 hour. Evaporation of ammonia and ether gave a yellowish crude oil.

Anhydrous ether (10.0 ml) was introduced to the above crude product. Half of the solution (~5.0 ml) thus prepared was transferred to a new dry flask. Zinc-copper couple (powder, 314 mg) and distilled diiodomethane (0.80 ml) were added and the greyish mixture was refluxed overnight. Filtration through a layer of Celite afforded an ether solution which was condensed to a colorless oil.

This oil was then dissolved in methanol (10 ml). After introduction of potassium hydroxide (100 mg, ~80% pure, 1.78 mmol), the solution was refluxed 1 hour and cooled down. Evaporation of solvent *in vacuo* and repeated column chromatography with ethyl acetate:hexanes (1:8, v/v) mixture yielded **277** in 45% (262 mg).

The physical properties of **277** are as follows:

$[\alpha]_D^{25}$=-8.3 (c=0.42, $CHCl_3$).

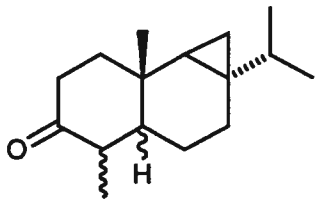
IR (film) $\nu_{max.}$: 1703 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.08 (1H, m), 0.35 (2H, m), 0.70-1.55 {20H, including 0.85 (6H, t, J=2.4 Hz), 1.04 (3H, s), 1.21 (3H, s), 1.22 (3H, s)}, 1.70 (1H, m), 1.85 (1H, m), 2.30 (2H, m), 2.62 (1H, m).

MS m/z: 248 (M^+, 18.6%), 230 (12.0%), 205 (27.2%), 41 (100.0%). High resolution mass measurement calculated for $C_{17}H_{28}O$: 248.2140; found: 248.2135.

4.5.5. Catalytic Hydrogenation: enone 274 to ketone 278

[1aR-(1α,7aβ,7bα)] Decahydro-4,7a-dimethyl-1a-(1-methylethyl)-5*H*-cyclopropa[*a*] naphthalen-5-one (**278**)



278

Method A:

Ammonia (5 ml) was distilled from sodium to a flask containing **274** (151 mg, 0.500 mmol) in anhydrous ether (3.0 ml) under an atmosphere of nitrogen. While the flask was kept at -33°C, small pieces of lithium were added slowly for about 1 hour until a blue color persisted. After further stirring for 30 minutes, ammonium chloride was added to destroy excess lithium and ammonia was evaporated during warming up to room temperature. Concentration of the reaction mixture gave an oil which was chromatographed with ethyl acetate:hexanes (1:8, v/v) mixture to give a mixture of **278** and **279** (124 mg, 82%) of at a ratio 4.3:1 as indicated by GC.

Method B:

The solution of enone **274** (368 mg, 1.59 mmol) in ethanol (15.9 ml) was mixed with 10% palladium-charcoal catalyst (85 mg). The mixture was charged with 1 atm hydrogen at room temperature and stirred for 2 hours. Filtration through a layer of Celite gave a colorless solution which was then concentrated *in vacuo*. A mixture of **278** and **279** at a ratio 6:1 as shown from GC were thus obtained (350 mg, 95% yield) .

The physical properties of **278** are as follows:*

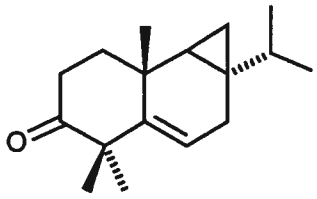
IR (film) $\nu_{max.}$: 1705 cm^{-1} (C=O stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.09 (1H, t, J=5.2 Hz), 0.40 (2H, m), 0.85 (3H, d, J=6.0 Hz), 0.88 (3H, d, J=6.0 Hz), 0.93 (3H, J=8.0 Hz), 1.45 (3H, s), 1.73 (1H, m), 1.87 (1H, m), 2.24 (2H, m), 2.50 (1H, m), 2.89 (1H, m).

MS m/z: 234 (M^+, 30.6%), 219 (16.3%), 191 (20.2%), 41 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{26}O$: 234.1984; found: 234.1980.

4.5.6. Methylation: α,β-enone 274 to β,γ-enone 282

[1aS-(1α,7aβ,7bα)] 1,1a,2,4,6,7,7a,7b-Octahydro-4,4,7a-trimethyl-1a-(1-methylethyl)-5*H*-cyclopropa[*a*]naphthalen-5-one (**282**)



282

To the solution of enone **274** (109 mg, 0.470 mmol) in anhydrous DMSO (5.0 ml) was added sodium methoxide (55 mg, 1.0 mmol, 2.1 eqv.) under nitrogen. After the mixture was stirred for 5 hours, iodomethane (100 µl, 1.61 mmol, 4.0 eqv.) was injected. Stirring continued for another 3 hours. The reaction mixture was poured to a funnel containing 20 ml water. The aqueous mixture was extracted with hexanes (2X15ml). After drying over magnesium sulfate, evaporation of solvent *in vacuo*, and chromatography with ethyl

* All data were taken for the spectra of the mixture. The ^{1}H-NMR spectral signals were those of the predominant diastereomer **278** since they can be easily selected by comparing the integrations while the ^{1}H-NMR spectral signals of **279** were difficult to observe from the spectrum. See also footnotes at p. 178 and 180.

acetate:hexanes (1:8, v/v) mixture, ketone **282** was obtained (62 mg, 60 % yield based on 10% recovery of starting material).

The physical properties of **282** are as follows:

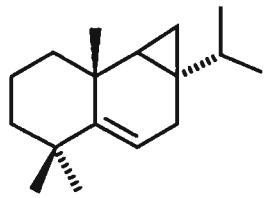
IR (film) $\nu_{max.}$: 1700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.20 (1H, t, J=4.0 Hz), 0.39 (1H, dd, J=4.0 and 10.0 Hz), 0.58 (1H, dd, J=4.0 and 10.0 Hz), 0.80-1.40 {16 H, m, including 0.94 (6H, d, J=6.0 Hz), 1.01 (3H, s), 1.18 (3H, s), 1.20 (3H, s)}, 1.84 (1H, m), 1.98 (1H, m), 2.14-2.35 (2H, m), 2.38-2.65 (2H, m), 5.41 (1H, t, J=4.0 Hz).

MS m/z: 246 (M^+, 36.4%), 231 (42.1%), 218 (5.9%), 203 (50.2%), 105 (100.0%).

4.5.7. Wolf-Kishner-Huang Minlon Reaction: β,γ-enone 282 to alkene 283

[1aS-(1α,7aβ,7bα)] 1a,2,4,5,6,7,7a,7b-Octahydro-4,4,7a-trimethyl-1a-(1-methylethyl)-1*H*-cyclopropa[*a*]naphthalene (**283**)



283

To the mixture of ketone **282** (500 mg, 2.03 mmol) in diethylene glycol (10 ml) was added potassium hydroxide (422 mg, ~80% pure, 6.02 mmol) and hydrazine hydrate (300 μl, 6.18 mmol) under nitrogen. After refluxing at 100-150°C for 1 hour, water and excess hydrazine hydrate were distilled away through a Dean-Stark trap until the temperature reached 250°C. Further refluxing at 200°C continued for 4 hours. The reaction mixture was then cooled to room temperature and and diluted with water (20 ml). The aqueous mixture was extracted with petroleum ether (3X10 ml). Evaporation of solvent *in vacuo* and column chromatograghy with petroleum ether afforded **283** (316 mg, 67%).

The physical properties of **283** are as follows:

IR (film) $\nu_{max.}$: 3050 cm^{-1} (C-H stretching).

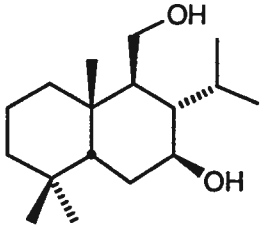
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.15 (1H, m), 0.40 (2H, m), 0.87 (6H, d, J=6.0 Hz), 1.05 (3H, s), 1.09 (3H, s), 1.16 (3H, S), 5.30 (1H, t, J=4.0 H).

MS m/z: 232 (M^+, 53.4%), 217 (39.3%), 204 (6.7 %), 189 (62.1%), 105 (100.0%).

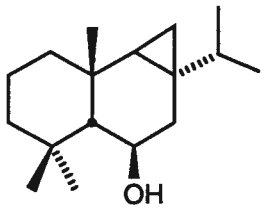
4.5.8. Hydroboration: alkene 283 to diol 285 and alcohol 286

[1S-(1α,2β,3α,4aα,8aα)] Decahydro-3-hydroxy-5,5,8a-trimethyl-2-(1-methylethyl) naphthalenemethanol (**285**)

[1aS-(1α,3β,3aβ,7aβ,7bα)] Decahydro-4,4,7a-Trimethyl-1a-(1-methylethyl)-3*H*-cyclopropa[*a*]naphthalen-3-ol (**286**)



285



286

To the solution of **283** (100 mg, 0.43 mmol) in THF (5.0 ml) at 0°C under nitrogen was added borane (0.35 M in THF, 1.0 ml) in a dropwise manner. The resulting mixture was stirred for 5 hours at room temperature and cooled to 0°C again. Aqueous sodium hydroxide solution (3.0 M, 1.0 ml) and hydrogen peroxide solution (aq., 30%, 1.0 ml) were added slowly. The resulting two-phased mixture was warmed to room temperature, stirred for 2 hours, and saturated with sodium chloride. The THF layer was separated and the aqueous layer was extracted with ether (5 ml). The organic layers were combined and concentrated *in vacuo*. Column chromatography of the crude product with ethyl acetate:hexanes mixture (1:8 first and then 3:7, v/v) generated **285** (45 mg, 39%) and **286** (31 mg, 29%).

The physical properties of **285** are as follows:

m.p.=136-138°C.

$[\alpha]_D^{25}$=+23 (c=0.84, $CHCl_3$).

IR (film) νmax.: 3500 (O-H stretching) cm^{-1}.

^{1}H-NMR (400 MHz, CDCl3) δ: 0.90-1.80 {26H, 0.96 (3H, s), 0.98 (3H, s), 1.00 (3H, s), 1.01 (3H, d, J=7.0), 1.15 (3H, d, J=7.0)}, 1.97 (2H, m), 2.18 (1H, m), 3.72 (2H, m), 4.04 (1H, m).

MS m/z: 250 (M^+-H_2O, 1.2%), 235 (3.1%), 232 (1.7%), 123 (100%). High resolution mass measurement calculated for $C_{17}H_{32}O_2$. 268.2402; found: 268.2215. Chemical ionization MS (using NH_3 as carrier gas) m/z: 286 ($M+NH_4^+$), 269 ($M+H^+$).

Elemental Analysis: calculated for $C_{17}H_{32}O_2$: C 76.06, H 12.02; found: C 76.26, H 12.02.

The physical properties of **286** are as follows:

$[\alpha]_D^{25}$=+13 (c=0.50, $CHCl_3$).

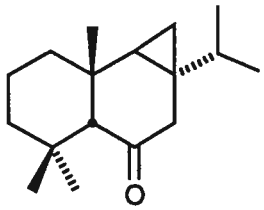
IR (film) νmax.: 3400 (O-H stretching), 3060 (cyclopropane C-H stretching) cm^{-1}.

^{1}H-NMR (400 MHz, CDCl3) δ: 0.14 (1H, dd, J=4.4 and 8.8 Hz), 0.45 (1H, dd, J=4.4 and 8.8 Hz), 0.64 (1H, t, J=4.4 Hz), 0.85 (3H, d, J=6.0 Hz), 0.90 (3H, d, J=6.0 Hz), 0.98 (3H, s), 1.10 (3H, s), 1.16 (3H, s), 2.14 (1H, dd, J=7.5 and 15.0), 3.87 (1H, m).

MS m/z: 250 (M^+, 2.1%), 232 (10.5%), 217 (12.8%), 207 (10.6%), 109 (100.0%). High resolution mass measurement: calculated for $C_{17}H_{30}O$: 250.2297; found: 250.2307.

4.5.9. Oxidation by Jones Reagent: alcohol 286 to ketone 287

[1aS-(1α,3aβ,7aβ,7bα)] Decahydro-4,4,7a-trimethyl-1a-(1-methylethyl)-3*H*-cyclopropa[*a*] naphthalen-3-one (**287**)



287

To the solution of alcohol **286** (20 mg, 0.080 mmol) in acetone (2.5 ml) was added Jones reagent (12M CrO_3 in concentrated sulfuric acid) in a dropwise manner until the mixture changed to a steady orange color. Water (10 ml) was added and the aqueous mixture was extracted with hexanes (2X5 ml). Evaporation of solvent *in vacuo* and column chromatography with ethyl acetate:hexanes (1:8, v/v) mixture afforded **287** (16 mg, 80%).

The physical properties of **287** are as follows:

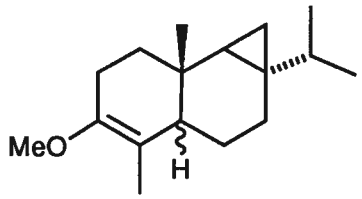
IR (film) $\nu_{max.}$: 1700 cm^{-1}.

^{1}H-NMR (400 MHz, C_6D_6) δ: 0.18 (2H, m), 0.53 (1H, m), 0.65 (3H, d, J=7.2 Hz), 0.90 (3H, d, J=7.2 Hz), 0.97 (3H, s), 1.01 (3H, s), 1.19 (3H, s), 2.29 (2H, AB type, J=16.0 Hz).

MS m/z: 248 (M^+, 10.6 %), 233 (2.8%), 205 (5.2%), 177 (9.6%), 109 (100.0%).

4.5.10. O-Methylation: ketone 278/279 to methyl enol ether 280

[1a**R**-(1α,7aβ,7bα)] 1a,2,3,3a,6,7,7a,7b-Octahydro-4,7a-dimethyl-1a-(1-methylethyl)-5-methoxyl-1*H*-cyclopropra[*a*]naphthalene (**280**)



280

Ketone **278/279** (6:1, 200 mg, 0.855 mmol), obtained from palladium-charcoal catalyzed hydrogenation of **274**, was treated with sodium hydride (70 mg, 2.0 eqv., 60% in mineral oil) in anhydrous DMSO (5.0 ml) under nitrogen at room temperature for 1 hour. Freshly distilled iodomethane (106 µl, 1.71 mmol, 2.0 eqv.) was added rapidly and the resulting mixture was stirred for another 1 hour. The reaction mixture was then poured to water (20 ml) and the aqueous mixture was extracted with hexanes (2X15ml). Evaporation of

hexanes *in vacuo* and column chromatography with ethyl acetate:hexanes (1:8, v/v) mixture gave **280** (91 mg, 54% based on recovery of starting material) and starting material **278/279** (42 mg).

The physical properties of **280** are as follows:

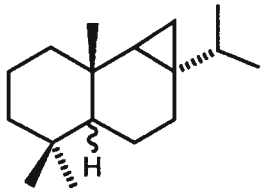
IR (film) $\nu_{max.}$: 3050, 1680 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.08 (1H, m), 0.30 (2H, m), 0.70-1.70 {(22H, m, including 0.87 (6H, t, J=6.0 Hz), 0.95 (3H, s), 1.60 (3H, s)}, 3.47 (3H, s).

MS m/z: 248 (M^+, 40.2%), 233 (8.4%), 216 (2.9%), 137 (90.2%), 41 (100.0%).

4.5.11. Wolf-Kishner-Huang Minlon Reaction: ketone 277 to Alkane 291

[1a**R**-(1α,7aβ,7bα)] Decadydro-4,4,7a-trimethyl-1a-(1-methylethyl)-1*H*-cyclopropa[*a*] naphthalene (**291**)



291

Ketone **277** (250 mg, 1.01 mmol) in diethylene glycol (20 ml) was treated with potassium hydroxide (370 mg, 5.28 mmol) and hydrazine monohydrate (270 µl, 5.56 mmol). The mixture was heated at 100-150°C for 1.5 hours under nitrogen. The temperature was then gradually raised up to 220°C to distill away water and excess hydrazine over a period of 1.5 hours. Refluxing continued at 210°C for 4 hours. The mixture was cooled down, diluted with water, and extracted with petroleum ether (3X20 ml). Evaporation of the solvent *in vacuo* gave a brown oil which was chromatographed with petroleum ether through a short column to yield **291** as a colorless oil (175 mg, 75%).

The physical properties of **291** are as follows:

IR (film) $\nu_{max.}$: 3050 (cyclopropane C-H stretching) cm^{-1}.

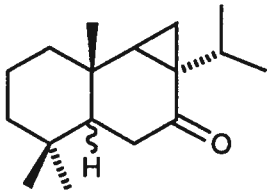
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.07 (1H, m), 0.40 (2H, m), 0.84 (6H, t, J=3.0 Hz), 1.10 (3H, s), 1.20 (3H, s), 1.22 (3H, s).

MS m/z: 234 (M^+, 2.7%), 219 (4.5%), 191 (11.0%), 43 (100.0%). High resolution mass measurement: calculated for $C_{17}H_{30}$: 234.2348; found: 234.2358.

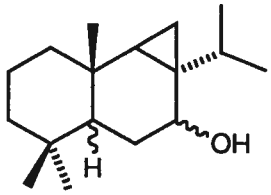
4.5.12. Ozonation: alkane 291 to ketone 292 and alcohol 293

[1aS-(1α,7aβ,7bα)] 1,1a,3,3a,4,5,6,7,7a,7b-Decahydro-4,4,7a-trimethyl-1a-(1-methylethyl) -2*H*-cyclopropra[*a*]naphthalen-2-one (**292**)

[1aS-(1α,7aβ,7bα)] 1,1a,3,3a,4,5,6,7,7a,7b-Decahydro-4,4,7a-trimethyl-1a-(1-methylethyl) -2*H*-cyclopropra[*a*]naphthalen-2-ol (**293**)



292



293

A stream of ozone-oxygen gas was passed through the solution of **291** (200 mg, 0.855 mmol) in ethyl acetate (10.0 ml) at -40°C for 7 hours. Oxygen was passed through the solution for 15 minutes to remove the residual ozone in the solution. The reaction mixture was then treated with dimethyl sulfide (0.5 ml), extracted with water (10 ml), and 10% aqueous sodium bicarbonate solution (10 ml). Removal of solvent *in vacuo* and chromatography of the crude product with ethyl acetate:hexanes (2:8, v/v) mixture provided ketone **292** (74 mg, 35%) and alcohol **293** (10 mg, 5%).

The physical properties of **292** are as follows:

IR (film) $\nu_{max.}$: 1665 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75-1.35 {23H, m, including 0.78 (3H, s), 0.84 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=6.6 Hz), 1.11 (3H, s), 1.30 (3H, s)}, 1.47 (1H, m), 1.63 (1H,

m), 1.84 (1H, septet, J=6.6 Hz), 2.00-2.30 (2H, m).

MS m/z: 248 (M^+, 18.4%), 233 (15.2%), 205 (23.2%), 177 (42.3%), 41 (100.0%). High resolution mass measurement: calculated for $C_{17}H_{28}O$: 248.2140; found: 248.2135.

The physical properties of **293** are as follows:

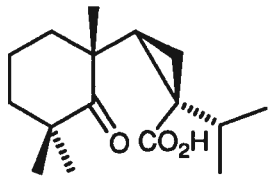
IR (film) νmax.: 3405 cm^{-1} (O-H stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.13 (1H, m), 0.45 (2H, m), 0.86 (3H, s), 0.89 (3H, d, J=6.0 Hz), 0.98 (3H, d, J=6.0 Hz), 1.10 (3H, s), 1.20 (3H, s), 4.16 (1H, m).

MS m/z: 250(M^+, 0.8%), 232 (5.3%), 217 (4.5%), 43 (100.0%). High resolution mass measurement: calculated for $C_{17}H_{30}O$: 250.2297; found: 250.2301.

4.5.13. Ketoacid 308

[1**S**,2**R**,1'(2)**R**] 2-(2'-oxo-1',3',3'-trimethylcyclohexyl)cyclopropaneformic acid (**308**)



308

The physical properties of **308**, which was provided by Dr. Dominik Guggisberg are as follows:

m.p.: 88-90°C.

$[\alpha]_D^{25}$=-4.9 (c=1.00, $CHCl_3$).

IR (film) νmax.: 2300-3650 (O-H stretching), 1685 (C=O stretching), 1645 (carboxylic acid group's C=O stretching) cm^{-1}.

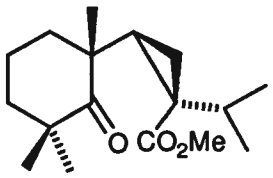
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.62 (1H, dd, J=5.6 and 8.8 Hz), 0.85-1.30 {19H, including 0.93 (1H, t, J=8.8)}, 1.60-1.95 (6H, m).

MS m/z: 266 (M^+, 21.0%), 251 (4.9%), 238 (3.0%), 220 (15.0%), 205 (10.8%), 195

(3.3%), 109 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{26}O_3$: 266.1881; found: 266.1874.

4.5.14. Methylation by Diazomethane: ketoacid 308 to ketoester 309

[2**R**,1'(2)**R**,2'(2)**S**] 2-[2-(1-Methylethyl))-2-(methoxycarbonyl)]cyclopropyl-2,6,6,-trimethylcyclohexanone (**309**)



309

To the solution of **308** (500 mg, 1.88 mmol) in anhydrous diethyl ether (10.0 ml) at 0°C was added 0.35M diazomethane-diethyl ether solution (6.0 ml, 2.1 mmol) in a dropwise manner. The resulting mixture was stirred at room temperature for 2 hours. Solvent removal *in vacuo* and column chromatography with diethyl ether:hexanes (2:8, v/v) yielded ketoester **309** (501 mg, 95% yield).

The physical properties of **309** are as follows:

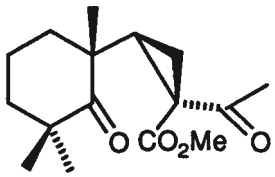
IR (film) νmax. 2960 (C-H stretching), 1710 (C=O stretching), 1685 (C=O stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.67 (1H, dd, J=4.8 and 9.6 Hz), 0.92 (3H, d, J=7.2 Hz), 1.07 (3H, d, J=7.2 Hz), 1.11 (3H, s), 1.13 (3H, s), 1.17-1.82 {12H, m, including 1.20 (3H, s)}, 3.65 (3H, s).

MS m/z: 280 (M^+, 13.1%), 265 (2.3%), 248 (3.7%), 233 (2.4%), 220 (14.9%), 205 (10.0%), 177 (11.8%), 69 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{26}O_3$: 280.2038; found: 280.2035.

4.5.15. Ozonation: ketoester 309 to compound 310

[2**R**,1'(2)**R**,2'(2)**R**] 2-[2-Acetyl-2-(methoxycarbonyl)]cyclopropyl-2,6,6,-trimethylcyclohexanone (**310**)



310

The solution of ketoester **309** (241 mg, 0.861 mmol) in ethyl acetate (20 ml) was cooled to 0°C and passed with ozone-oxygen stream through a gas dispersion tube for 6 hours. The stream of oxygen was passed for 15 minutes to remove excess ozone. Dimethyl sulfide (0.5 ml) was added and the resulting mixture was stirred for 10 minutes at room temperature, extracted with water (10 ml), 10% aqueous sodium bicarbonate solution (2X10 ml), dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:ether 8:2, v/v) to give **310** (63 mg, 45% based on recovery of starting material) in addition to the starting material **309** (101 mg, 42%).

The physical properties of **310** are as follows:

IR (film) $\nu_{max.}$: 1725, 1690 cm^{-1}.

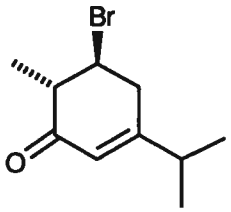
^{1}H-NMR (400 MHz, CDCl3) δ: 1.08 (3H, s), 1.10 (6H, bs), 1.34 (1H, dd, J=4.7 and 9.0 Hz), 1.50-2.05 (9H, m), 2.10 (1H, t, J=9.0 Hz), 2.28 (3H, s), 3.76 (3H, s).

MS m/z: 280 (M^+, 0.5%), 262 (2.9%), 252 (4.8%), 43 (100.0%). High resolution mass measurement: calculated for $C_{16}H_{24}O_4$: 280.1675; found: 280.1675.

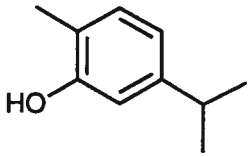
4.5.16. Cyclopropane Ring Opening Reaction: thujonol (94) to bromoenone 318 and carvacrol (319)

[2R,3S] 3-Bromo-2-methyl-5-(1-methylethyl)cyclohex-5-en-1-one (**318**)

2-Methyl-5-(1-methylethyl)phenol (**319**)



318



319

Thujonol (**94**) (600 mg, 3.57 mmol) in methylene chloride (25 ml) was stirred with concentrated 48% hydrobromic acid (25 ml) for 1.5 hours at room temperature. The organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography using ethyl acetate:hexanes (1:15, v/v) mixture to provide bromoenone **318** (700 mg, 85%) and carvacrol (**319**) (51 mg, 10%).

The physical properties of **318** are as follows:

$[\alpha]_D^{25}$=+42 (c=0.29, $CHCl_3$).

UV (MeOH, c=20 mg/l) $\lambda_{max.}$: 234 nm (log ε=3.95)

IR (film) $\nu_{max.}$: 1670 (C=O stretching), 1630 (C=C stretching).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.11 (6H, d, J=6.8 Hz), 1.34 (3H, d, J=7.1 Hz), 2.43 (1H, septet, J=6.8 Hz), 2.55 (1H, m), 4.19 (1H, dt, J=4.4 and 10.2 Hz), 5.97 (1H, bs).

MS m/z: 232/230 (M^+, 1.1%/1.3%), 151 (100.0%), 135 (33.6%), 123 (60.2%). High resolution mass measurement: calculated for $C_{10}H_{15}O^{81}Br$ and $C_{15}H_{15}O^{79}Br$: 232.0287 and 230.0130; found: 232.0280 and 230.0116.

The physical properties of **319** are as follows:

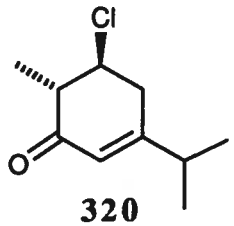
IR (film) $\nu_{max.}$: 3400 (O-H stretching) cm^{-1}.

^{1}H-NMR (400 MHz, CDCl3) δ: 1.22 (6H, d, J=6.6 Hz), 2.21 (3H, s), 2.82 (1H, septet, J=6.6 Hz), 3.96 (1H, bs), 6.66 (1H, d, J=1.8 Hz), 6.72 (1H, dd, J=1.8 and 7.1), 7.04 (1H, d, J=7.1 Hz).

MS m/z: 150 (M^+, 35.5%), 135 (100.0%), 107 (15.6%). High resolution mass measurement: calculated for $C_{10}H_{14}O$: 150.1045; found: 150.1051.

4.5.17. Cyclopropane Ring Opening Reaction: thujonol (94) to chloroenone 320 and carvacrol (319)

[2R,3S] 3-Chloro-2-methyl-5-(1-methylethyl)cyclohex-5-en-1-one (**320**)



320

Thujonol (**94**) (500 mg, 2.98 mmol) was treated with concentrated 35~36% hydrochloric acid (25 ml) in methylene chloride (25 ml) at room temperature for 1.5 hours. The methylene chloride solution was separated, dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography with ethyl acetate:hexanes (1:20, v/v) provide chloro-enone **320** (252 mg, 45%) and carvacrol (**319**) (177 mg, 40%).

The physical properties of **320** are as follows:

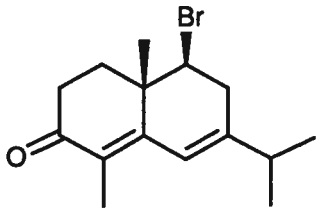
IR (film) $\nu_{max.}$: 1675 (C=O stretching), 1630 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.09 (6H, d, J=7.2 Hz), 1.30 (3H, d, J=7.8 Hz), 2.43 (1H, septet, J=7.2 Hz), 2.54 (1H, m), 2.78 (2H, m), 4.06 (1H, dt, J=4.4 and 9.8 Hz), 5.95 (1H, bs) ppm.

MS m/z: 188/186 (M^+, 5.8%/19.1%), 151 (100.0%), 135 (15.9%).

4.5.18. Cyclopropane Ring Opening Reaction: hydroxyenone 122 to bromodienone 322

[4a*S*-(4aα,5α)] 5-Bromo-2,3,3a,4,5,6-hexahydro-1,4a-dimethyl-(1-methylethyl) naphthalen-2(3*H*)-one (**322**)



322

Hydroxyl-enone **122** (39 mg, 0.17 mmol) in methylene chloride (5 ml) was stirred with concentrated 48% hydrobromic acid (5 ml) at room temperature for 3 hours. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (5 ml). The combined methylene chloride solution was dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography of the crude product afforded bromo-dienone **322** (45 mg, 91%).

The physical properties of **322** are as follows:

$[\alpha]_D^{25}$=+420 (c=1.00, $CHCl_3$).

UV (MeOH, c=20 mg/l) $\lambda_{max.}$: 293 nm (log ε=4.40)

IR (film) $\nu_{max.}$: 1660 (C=O stretching), 1620 (C=C stretching) cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12 (6H, d, J=6.0 Hz), 1.17 (3H, s), 1.86 (3H, s), 2.00-2.90 (7H, m), 4.14 (1H, dd, J=6.0 and 10.0 Hz), 6.31 (1H, s).

MS m/z: 298/296 (M^+, 80.0%/88.5%), 217 (100.0%), 175 (56.3%). High resolution mass measurement: calculated for $C_{15}H_{21}O^{79}Br$: 296.0775; found: 296.0768.

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Appendix 1. X-ray Structure Report on Epoxide 147

A. Crystal Data

Empirical Formula	$C_{16}H_{28}O_2$
Formula Weight	252.40
Crystal Color, Habit	colorless, prism
Crystal Dimensions (mm)	0.300 X 0.400 X 0.500
Crystal System	monoclinic
No. Reflections Used for Unit Cell Determination (2θ range)	25 (100.7 - 109.0°)
Omega Scan Peak Width at Half-height	0.37
Lattice Parameters:	
	a = 6.767 (1)Å
	b = 9.616 (1)Å
	c = 12.205 (1)Å
	β = 98.84 (1)°
	V = 784.7 (2)Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.068 g/cm^3
F_{000}	280
$\mu_{(CuK\alpha)}$	4.97 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	CuKα (λ = 1.54178 Å)
Temperature	21°C
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 6.0 mm vertical

Crystal to Detector Distance	285 mm
Scan Type	ω-2θ
Scan Rate	32.0°/min (in omega) (8 rescans)
Scan Width	(1.15 + 0.20 tanθ)°
$2\theta_{max}$	154.6°
No. of Reflections Measured	Total: 1929 Unique: 1776 (R_{int} = .035)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.82 - 1.00) Secondary Extinction (coefficient: 0.70718E-04)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.04
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>4.00σ(I))	1656
No. Variables	167
Reflection/Parameter Ratio	9.92
Residuals: R; R_w	0.045; 0.067
Goodness of Fit Indicator	2.83
Max Shift/Error in Final Cycle	0.01
Maximum Peak in Final Diff. Map	0.24 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-0.12 $e^-/Å^3$

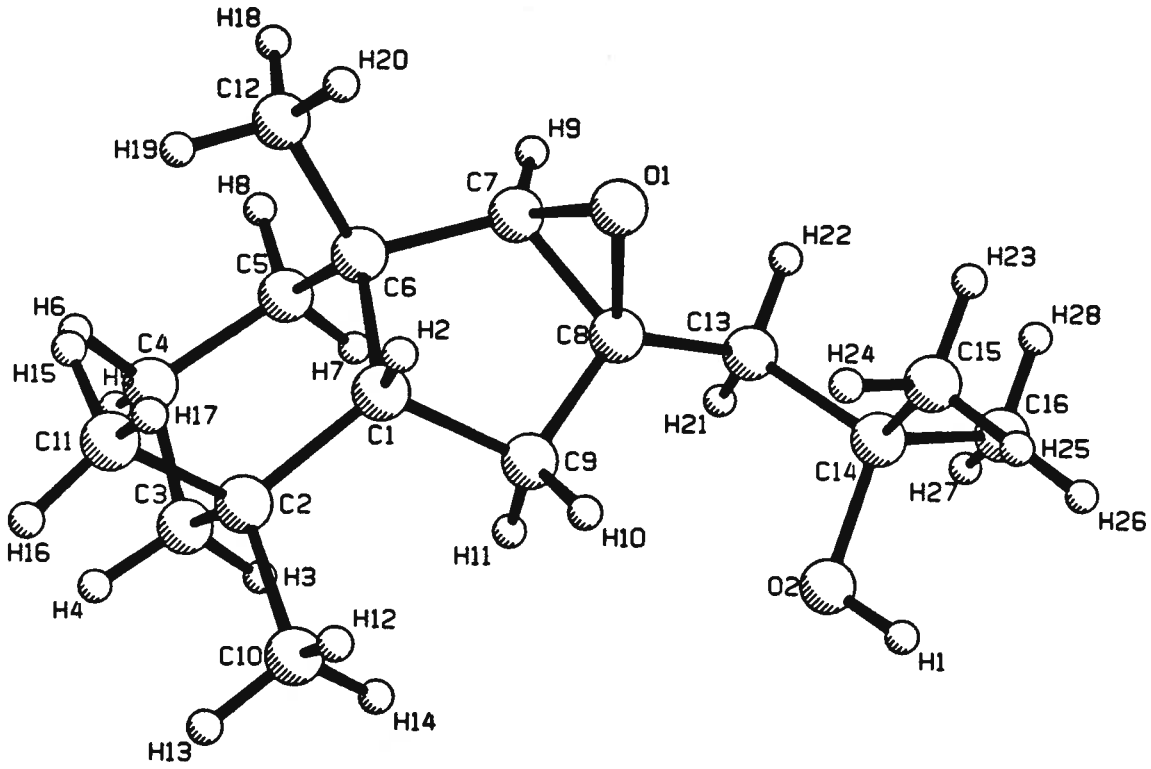

Figure 46 Single Crystal X-Ray Structure of Epoxide 147 (PLUTO Drawing)*

* The numbering of carbon atoms here is different from that used in the Discussion (Section 2.2.7.).

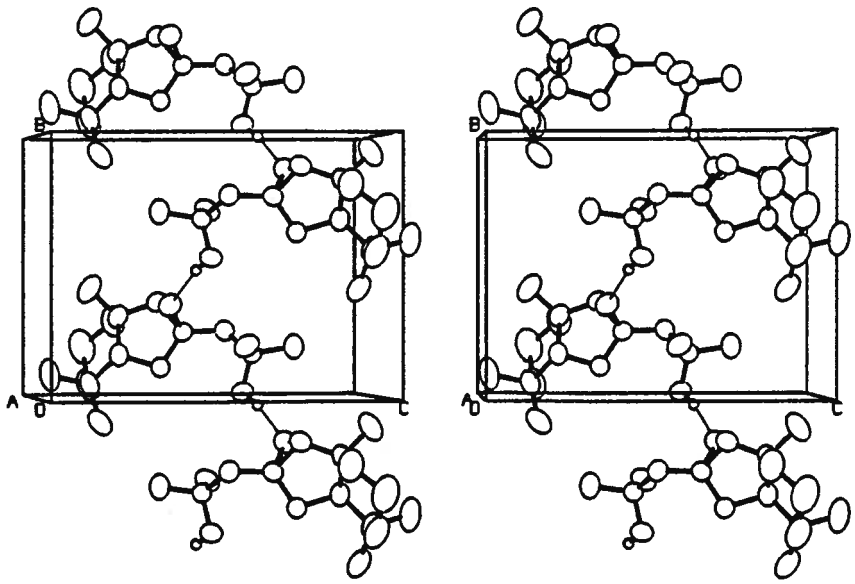

Figure 47 The Unit Cell Structure of Epoxide **147** (Packing Diagram)

Table 6 Final Atomic Coordinates (fractional) and B_{eq} ($Å^2$) of Epoxide **147**

atom	x	y	z	B_{eq}
O(1)	0.1042(3)	0.3562	0.3502(2)	5.46(7)
O(2)	0.1848(3)	0.0318(3)	0.5658(1)	5.04(7)
C(1)	0.2368(3)	0.1703(3)	0.2154(1)	4.00(7)
C(2)	0.3048(4)	0.0589(4)	0.1368(2)	5.5(1)
C(3)	0.5313(5)	0.0506(5)	0.1542(3)	7.7(2)
C(4)	0.6307(4)	0.1929(6)	0.1443(3)	7.9(2)
C(5)	0.5753(3)	0.2917(5)	0.2316(2)	6.6(1)
C(6)	0.3497(3)	0.3117(3)	0.2235(2)	4.56(8)
C(7)	0.3116(3)	0.3663(3)	0.3346(2)	4.81(8)
C(8)	0.2487(3)	0.2547(3)	0.4026(2)	3.87(6)
C(9)	0.2407(3)	0.1229(3)	0.3363(2)	4.23(7)
C(10)	0.2170(8)	-0.0818(5)	0.1588(3)	9.3(2)
C(11)	0.2282(5)	0.0955(6)	0.0149(2)	7.6(2)
C(12)	0.2684(6)	0.4159(5)	0.1330(3)	7.7(2)
C(13)	0.2878(4)	0.2592(3)	0.5272(2)	4.67(8)
C(14)	0.1451(4)	0.1742(3)	0.5876(2)	4.41(8)
C(15)	-0.0724(4)	0.2082(4)	0.5470(2)	5.7(1)
C(16)	0.1953(5)	0.1997(4)	0.7123(2)	6.7(1)

Table 7 Hydrogen Atom Coordinates (fractional) and B_{iso} ($Å^2$) of Epoxide **147**

atom	x	y	z	B_{iso}
H(1)	0.100(4)	-0.016(4)	0.599(3)	5.3(6)
H(2)	0.0969	0.1913	0.1864	4.8
H(3)	0.5773	0.0131	0.2284	9.2
H(4)	0.5719	-0.0120	0.0984	9.2
H(5)	0.7762	0.1813	0.1549	9.5
H(6)	0.5850	0.2316	0.0705	9.5
H(7)	0.6273	0.2543	0.3050	7.9
H(8)	0.6370	0.3823	0.2223	7.9
H(9)	0.3944	0.4422	0.3702	5.8
H(10)	0.1198	0.0699	0.3437	5.1
H(11)	0.3589	0.0655	0.3608	5.1
H(12)	0.0707	-0.0758	0.1462	11.2
H(13)	0.2601	-0.1512	0.1085	11.2
H(14)	0.2635	-0.1094	0.2357	11.2
H(15)	0.2920	0.1816	-0.0047	9.1
H(16)	0.2610	0.0198	-0.0330	9.1
H(17)	0.0829	0.1084	0.0048	9.1
H(18)	0.3456	0.5024	0.1438	9.3
H(19)	0.2798	0.3767	0.0601	9.3
H(20)	0.1276	0.4355	0.1371	9.3
H(21)	0.4236	0.2244	0.5513	5.6
H(22)	0.2794	0.3565	0.5499	5.6
H(23)	-0.0979	0.3058	0.5631	6.9
H(24)	-0.1022	0.1924	0.4669	6.9
H(25)	-0.1578	0.1483	0.5848	6.9
H(26)	0.1112	0.1403	0.7513	8.1
H(27)	0.3364	0.1778	0.7374	8.1
H(28)	0.1705	0.2975	0.7282	8.1

Table 8 Bond Lengths (Å) of Epoxide **147**
with Estimated Standard Deviations in Parentheses

atom	atom	distance	atom	atom	distance
O(1)	C(7)	1.448(3)	C(4)	C(5)	1.517(5)
O(1)	C(8)	1.459(3)	C(5)	C(6)	1.527(3)
O(2)	C(14)	1.428(3)	C(6)	C(7)	1.513(3)
C(1)	C(2)	1.554(3)	C(6)	C(12)	1.530(4)
C(1)	C(6)	1.555(3)	C(7)	C(8)	1.460(3)
C(1)	C(9)	1.541(3)	C(8)	C(9)	1.500(3)
C(2)	C(3)	1.517(4)	C(8)	C(13)	1.503(3)
C(2)	C(10)	1.519(5)	C(13)	C(14)	1.537(3)
C(2)	C(11)	1.539(4)	C(14)	C(15)	1.515(4)
C(3)	C(4)	1.537(7)	C(14)	C(16)	1.527(3)

Table 9 Bond Angles (deg) of Epoxide **147**
with Estimated Standard Deviations in Parentheses

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	O(1)	C(8)	60.3(1)	C(7)	C(6)	C(12)	109.1(2)
C(2)	C(1)	C(6)	116.9(2)	O(1)	C(7)	C(6)	113.4(2)
C(2)	C(1)	C(9)	115.1(2)	O(1)	C(7)	C(8)	60.2(1)
C(6)	C(1)	C(9)	105.2(2)	C(6)	C(7)	C(8)	111.0(2)
C(1)	C(2)	C(3)	109.8(2)	O(1)	C(8)	C(7)	59.5(1)
C(1)	C(2)	C(10)	110.1(2)	O(1)	C(8)	C(9)	111.3(2)
C(1)	C(2)	C(11)	110.6(3)	O(1)	C(8)	C(13)	115.2(2)
C(3)	C(2)	C(10)	110.0(3)	C(7)	C(8)	C(9)	107.7(2)
C(3)	C(2)	C(11)	109.3(2)	C(7)	C(8)	C(13)	122.2(2)
C(10)	C(2)	C(11)	107.0(3)	C(9)	C(8)	C(13)	123.8(2)
C(2)	C(3)	C(4)	112.8(3)	C(1)	C(9)	C(8)	105.1(2)
C(3)	C(4)	C(5)	110.1(2)	C(8)	C(13)	C(14)	116.4(2)
C(4)	C(5)	C(6)	112.7(2)	O(2)	C(14)	C(13)	105.7(2)
C(1)	C(6)	C(5)	111.8(2)	O(2)	C(14)	C(15)	110.3(2)
C(1)	C(6)	C(7)	102.2(2)	O(2)	C(14)	C(16)	108.7(2)
C(1)	C(6)	C(12)	114.1(2)	C(13)	C(14)	C(15)	112.3(2)
C(5)	C(6)	C(7)	107.0(2)	C(13)	C(14)	C(16)	109.4(2)
C(5)	C(6)	C(12)	112.0(2)	C(15)	C(14)	C(16)	110.3(2)

Table 10 Torsional or Conformational Angles (deg) of Epoxide **147**

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O(1)	C(7)	C(6)	C(1)	-47.1(2)	C(1)	C(2)	C(10)	H(13)	180
O(1)	C(7)	C(6)	C(5)	-164.7(2)	C(1)	C(2)	C(10)	H(14)	-60
O(1)	C(7)	C(6)	C(12)	74.0(3)	C(1)	C(2)	C(11)	H(15)	66
O(1)	C(7)	C(8)	C(9)	104.7(2)	C(1)	C(2)	C(11)	H(16)	-174
O(1)	C(7)	C(8)	C(13)	-102.3(2)	C(1)	C(2)	C(11)	H(17)	-54
O(1)	C(8)	C(7)	C(6)	-105.6(2)	C(1)	C(6)	C(5)	C(4)	48.9(3)
O(1)	C(8)	C(7)	H(9)	109	C(1)	C(6)	C(5)	H(7)	-72
O(1)	C(8)	C(9)	C(1)	46.1(2)	C(1)	C(6)	C(5)	H(8)	169
O(1)	C(8)	C(9)	H(10)	-73	C(1)	C(6)	C(7)	C(8)	18.4(2)
O(1)	C(8)	C(9)	H(11)	165	C(1)	C(6)	C(7)	H(9)	164
O(1)	C(8)	C(13)	C(14)	86.4(2)	C(1)	C(6)	C(12)	H(18)	179
O(1)	C(8)	C(13)	H(21)	-153	C(1)	C(6)	C(12)	H(19)	-61
O(1)	C(8)	C(13)	H(22)	-35	C(1)	C(6)	C(12)	H(20)	59
O(2)	C(14)	C(13)	C(8)	67.7(3)	C(1)	C(9)	C(8)	C(7)	-17.3(2)
O(2)	C(14)	C(13)	H(21)	-53	C(1)	C(9)	C(8)	C(13)	-169.8(2)
O(2)	C(14)	C(13)	H(22)	-171	C(2)	C(1)	C(6)	C(5)	-43.3(3)
O(2)	C(14)	C(15)	H(23)	179	C(2)	C(1)	C(6)	C(7)	-157.4(2)
O(2)	C(14)	C(15)	H(24)	-61	C(2)	C(1)	C(6)	C(12)	85.0(3)
O(2)	C(14)	C(15)	H(25)	59	C(2)	C(1)	C(9)	C(8)	158.8(2)
O(2)	C(14)	C(16)	H(26)	-61	C(2)	C(1)	C(9)	H(10)	-82
O(2)	C(14)	C(16)	H(27)	59	C(2)	C(1)	C(9)	H(11)	39
O(2)	C(14)	C(16)	H(28)	179	C(2)	C(3)	C(4)	C(5)	60.9(4)
C(1)	C(2)	C(3)	C(4)	-53.1(3)	C(2)	C(3)	C(4)	H(5)	-179
C(1)	C(2)	C(3)	H(3)	67	C(2)	C(3)	C(4)	H(6)	-59
C(1)	C(2)	C(3)	H(4)	-174	C(3)	C(2)	C(1)	C(6)	45.2(3)
C(1)	C(2)	C(10)	H(12)	60	C(3)	C(2)	C(1)	C(9)	-79.1(3)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Table 10 Torsional or Conformational Angles (deg) of Epoxide **147** (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
C(9)	C(1)	C(2)	C(10)	42.2(3)	C(13)	C(14)	O(2)	H(1)	-178(2)
C(9)	C(1)	C(2)	C(11)	160.2(2)	C(13)	C(14)	C(15)	H(23)	-63
C(9)	C(1)	C(6)	C(12)	-145.9(2)	C(13)	C(14)	C(15)	H(24)	57
C(9)	C(8)	C(7)	H(9)	-146	C(13)	C(14)	C(15)	H(25)	177
C(9)	C(8)	C(13)	C(14)	-56.5(3)	C(13)	C(14)	C(16)	H(26)	-176
C(9)	C(8)	C(13)	H(21)	64	C(13)	C(14)	C(16)	H(27)	-56
C(9)	C(8)	C(13)	H(22)	-178	C(13)	C(14)	C(16)	H(28)	64
C(10)	C(2)	C(1)	H(2)	-75	C(15)	C(14)	O(2)	H(1)	-57(2)
C(10)	C(2)	C(3)	H(3)	-54	C(15)	C(14)	C(13)	H(21)	-174
C(10)	C(2)	C(3)	H(4)	65	C(15)	C(14)	C(13)	H(22)	68
C(10)	C(2)	C(11)	H(15)	-175	C(15)	C(14)	C(16)	H(26)	60
C(10)	C(2)	C(11)	H(16)	-55	C(15)	C(14)	C(16)	H(27)	-180
C(10)	C(2)	C(11)	H(17)	65	C(15)	C(14)	C(16)	H(28)	-60
C(11)	C(2)	C(1)	H(2)	43	C(16)	C(14)	O(2)	H(1)	64(2)
C(11)	C(2)	C(3)	H(3)	-171	C(16)	C(14)	C(13)	H(21)	64
C(11)	C(2)	C(3)	H(4)	-52	C(16)	C(14)	C(13)	H(22)	-54
C(11)	C(2)	C(10)	H(12)	-61	C(16)	C(14)	C(15)	H(23)	59
C(11)	C(2)	C(10)	H(13)	59	C(16)	C(14)	C(15)	H(24)	179
C(11)	C(2)	C(10)	H(14)	179	C(16)	C(14)	C(15)	H(25)	-61
C(12)	C(6)	C(1)	H(2)	-33	H(2)	C(1)	C(9)	H(10)	35
C(12)	C(6)	C(5)	H(7)	159	H(2)	C(1)	C(9)	H(11)	157
C(12)	C(6)	C(5)	H(8)	40	H(3)	C(3)	C(4)	H(5)	61
C(12)	C(6)	C(7)	H(9)	-75	H(3)	C(3)	C(4)	H(6)	-180
C(13)	C(8)	C(7)	H(9)	7	H(4)	C(3)	C(4)	H(5)	-58
C(13)	C(8)	C(9)	H(10)	71	H(4)	C(3)	C(4)	H(6)	61
C(13)	C(8)	C(9)	H(11)	-50	H(5)	C(4)	C(5)	H(7)	-57

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Table 10 Torsional or Conformational Angles (deg) of Epoxide **147** (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
C(3)	C(2)	C(1)	H(2)	164	C(6)	C(1)	C(9)	H(10)	148
C(3)	C(2)	C(10)	H(12)	-179	C(6)	C(1)	C(9)	H(11)	-91
C(3)	C(2)	C(10)	H(13)	-59	C(6)	C(5)	C(4)	H(5)	-178
C(3)	C(2)	C(10)	H(14)	61	C(6)	C(5)	C(4)	H(6)	62
C(3)	C(2)	C(11)	H(15)	-55	C(6)	C(7)	O(1)	C(8)	101.7(2)
C(3)	C(2)	C(11)	H(16)	65	C(6)	C(7)	C(8)	C(9)	-0.9(2)
C(3)	C(2)	C(11)	H(17)	-175	C(6)	C(7)	C(8)	C(13)	152.0(2)
C(3)	C(4)	C(5)	C(6)	-57.9(4)	C(7)	O(1)	C(8)	C(9)	-98.6(2)
C(3)	C(4)	C(5)	H(7)	63	C(7)	O(1)	C(8)	C(13)	113.9(2)
C(3)	C(4)	C(5)	H(8)	-178	C(7)	C(6)	C(1)	C(9)	-28.3(2)
C(4)	C(3)	C(2)	C(10)	-174.5(3)	C(7)	C(6)	C(1)	H(2)	84
C(4)	C(3)	C(2)	C(11)	68.3(4)	C(7)	C(6)	C(5)	H(7)	39
C(4)	C(5)	C(6)	C(7)	160.0(3)	C(7)	C(6)	C(5)	H(8)	-80
C(4)	C(5)	C(6)	C(12)	-80.5(4)	C(7)	C(6)	C(12)	H(18)	66
C(5)	C(4)	C(3)	H(3)	-60	C(7)	C(6)	C(12)	H(19)	-174
C(5)	C(4)	C(3)	H(4)	-179	C(7)	C(6)	C(12)	H(20)	-54
C(5)	C(6)	C(1)	C(9)	85.8(2)	C(7)	C(8)	C(9)	H(10)	-137
C(5)	C(6)	C(1)	H(2)	-162	C(7)	C(8)	C(9)	H(11)	102
C(5)	C(6)	C(7)	C(8)	-99.1(2)	C(7)	C(8)	C(13)	C(14)	154.9(2)
C(5)	C(6)	C(7)	H(9)	46	C(7)	C(8)	C(13)	H(21)	-84
C(5)	C(6)	C(12)	H(18)	-52	C(7)	C(8)	C(13)	H(22)	34
C(5)	C(6)	C(12)	H(19)	68	C(8)	O(1)	C(7)	H(9)	-109
C(5)	C(6)	C(12)	H(20)	-172	C(8)	C(7)	C(6)	C(12)	139.5(3)
C(6)	C(1)	C(2)	C(10)	166.5(3)	C(8)	C(9)	C(1)	H(2)	-84
C(6)	C(1)	C(2)	C(11)	-75.5(2)	C(8)	C(13)	C(14)	C(15)	-52.6(3)
C(6)	C(1)	C(9)	C(8)	28.6(2)	C(8)	C(13)	C(14)	C(16)	-175.4(2)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Table 10 Torsional or Conformational Angles (deg) of Epoxide **147** (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
H(5)	C(4)	C(5)	H(8)	62					
H(6)	C(4)	C(5)	H(7)	-177					
H(6)	C(4)	C(5)	H(8)	-58					

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Appendix 2. X-ray Structure Report on Diol 285

A. Crystal Data

Empirical Formula	$C_{17}H_{32}O_2$
Formula Weight	268.44
Crystal Color, Habit	colorless, needle
Crystal Dimensions (mm)	0.120 X 0.180 X 0.480
Crystal System	orthorhombic
No. Reflections Used for Unit Cell Determination (2θ range)	25 (57.4 - 81.8°)
Omega Scan Peak Width at Half-height	0.37
Lattice Parameters:	
	a = 10.730 (2)Å b = 20.411 (2)Å c = 7.484 (1)Å
	V = 1639.0 (3)Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.088 g/cm^3
F_{000}	600
$\mu_{(CuK\alpha)}$	4.97 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	CuKα (λ = 1.54178 Å)
Temperature	21°C
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal 6.0 mm vertical
Crystal to Detector Distance	285 mm

Scan Type	ω-2θ
Scan Rate	16.0°/min (in omega) (8 rescans)
Scan Width	(0.94 + 0.20 tanθ)°
$2\theta_{max}$	155.0°
No. of Reflections Measured	Total: 1921
Corrections	Lorentz-polarization Absorption (trans. factors: 0.92 - 1.07) Secondary Extinction (coefficient: 0.26140E-04)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.025
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1570
No. Variables	181
Reflection/Parameter Ratio	8.67
Residuals: R; R_w	0.036; 0.047
Goodness of Fit Indicator	1.93
Max Shift/Error in Final Cycle	0.002
Maximum Peak in Final Diff. Map	0.18 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-0.11 $e^-/Å^3$

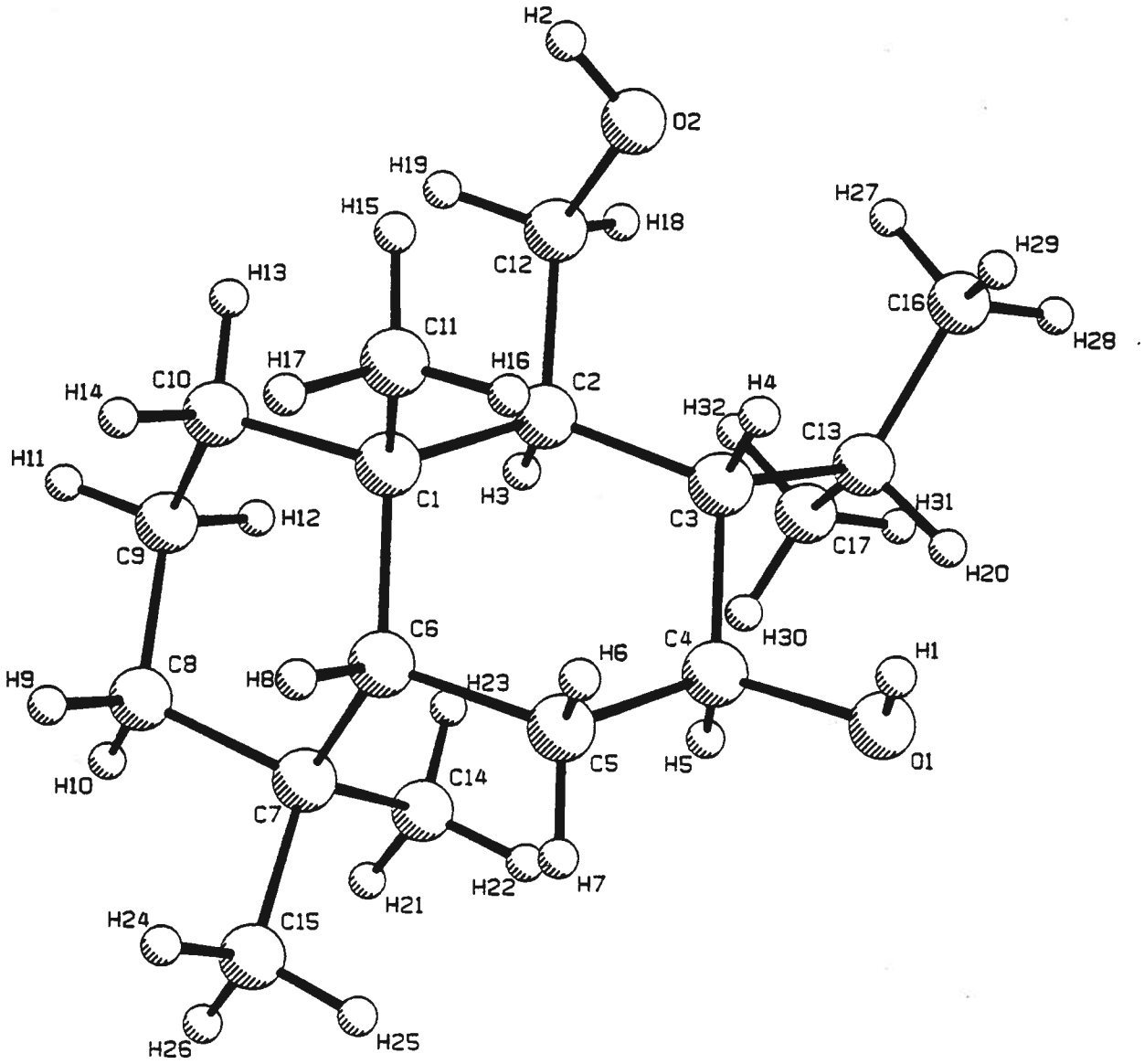

Figure 48 Single Crystal X-ray Structure of Diol **285** (PLUTO Drawing)*

* The numbering of carbon atoms here is different from that used in the Discussion (Section 4.1.3.).

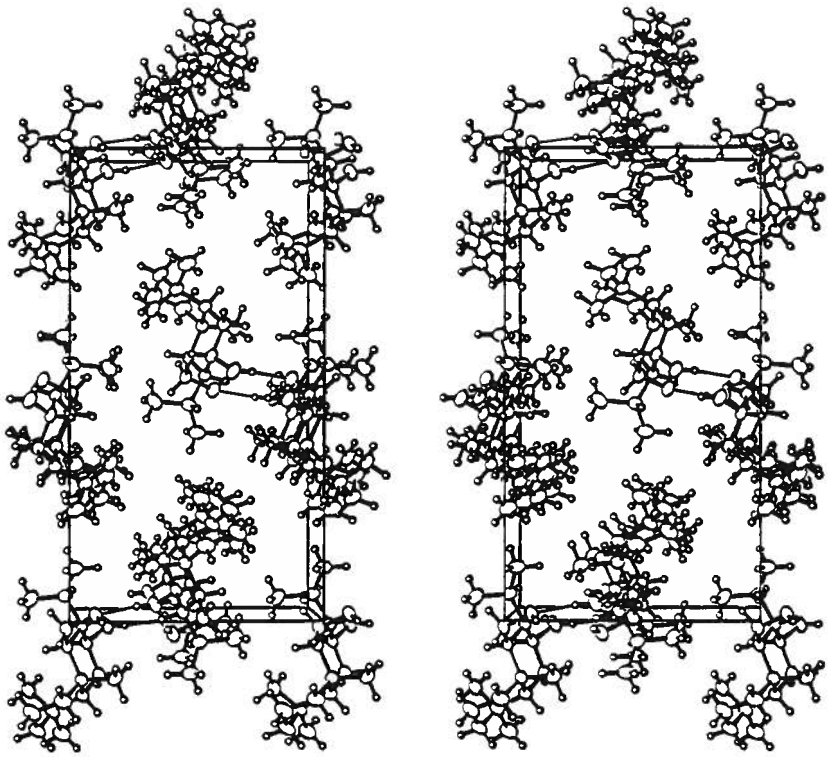

Figure 49 The Unit Cell Structure of Diol **285** (Packing Diagram)

Table 11 Final Atomic Coordinates (fractional) and B_{eq} ($Å^2$) of Diol 285

atom	x	y	z	B_{eq}
O(1)	0.3431(2)	0.47048(9)	0.7356(2)	4.39(7)
O(2)	0.3951(1)	0.51200(9)	0.0739(2)	4.28(7)
C(1)	0.4487(2)	0.3707(1)	0.2595(3)	3.66(9)
C(2)	0.5054(2)	0.4402(1)	0.2899(3)	3.27(8)
C(3)	0.4447(2)	0.4791(1)	0.4452(3)	3.35(8)
C(4)	0.4255(2)	0.4375(1)	0.6131(3)	3.49(8)
C(5)	0.3754(2)	0.3697(1)	0.5802(3)	3.82(9)
C(6)	0.4429(2)	0.3302(1)	0.4364(3)	3.8(1)
C(7)	0.5628(2)	0.2940(1)	0.5021(4)	4.5(1)
C(8)	0.6244(3)	0.2597(1)	0.3415(5)	6.0(1)
C(9)	0.6465(3)	0.3047(2)	0.1864(4)	6.4(2)
C(10)	0.5229(3)	0.3310(1)	0.1208(4)	5.6(1)
C(11)	0.3155(2)	0.3759(1)	0.1845(4)	4.8(1)
C(12)	0.5111(2)	0.4819(1)	0.1214(3)	4.1(1)
C(13)	0.5125(2)	0.5433(1)	0.5005(4)	4.9(1)
C(14)	0.6601(2)	0.3372(1)	0.5965(4)	5.4(1)
C(15)	0.5242(3)	0.2405(1)	0.6344(5)	6.7(2)
C(16)	0.4755(3)	0.6043(1)	0.3994(5)	6.5(1)
C(17)	0.6530(3)	0.5358(2)	0.5186(5)	6.6(2)

$*B_{eq} = (8/3)\pi^2 \Sigma\Sigma U_{ij} a_i * a_j * (a_i \cdot a_j)$

Table 12 Hydrogen Atom Coordinates (fractional) and B_{iso} ($Å^2$) of Diol **285**

atom	x	y	z	B_{iso}
H(1)	0.269(3)	0.472(1)	0.694(4)	6.2(7)
H(2)	0.372(3)	0.500(2)	-0.029(4)	5.9(8)
H(3)	0.5922	0.4329	0.3256	3.9
H(4)	0.3616	0.4920	0.4041	4.0
H(5)	0.5066	0.4329	0.6720	4.2
H(6)	0.2879	0.3738	0.5445	4.6
H(7)	0.3808	0.3452	0.6925	4.6
H(8)	0.3848	0.2946	0.4087	4.6
H(9)	0.5700	0.2240	0.3022	7.2
H(10)	0.7047	0.2418	0.3800	7.2
H(11)	0.6876	0.2806	0.0898	7.7
H(12)	0.6996	0.3413	0.2242	7.7
H(13)	0.5390	0.3594	0.0178	6.7
H(14)	0.4716	0.2938	0.0834	6.7
H(15)	0.3172	0.3999	0.0711	5.8
H(16)	0.2626	0.3993	0.2701	5.8
H(17)	0.2820	0.3319	0.1646	5.8
H(18)	0.5729	0.5166	0.1401	4.9
H(19)	0.5376	0.4540	0.0221	4.9
H(20)	0.4838	0.5514	0.6228	5.9
H(21)	0.7295	0.3098	0.6375	6.5
H(22)	0.6215	0.3589	0.6993	6.5
H(23)	0.6913	0.3703	0.5128	6.5
H(24)	0.4663	0.2102	0.5759	8.0

Table 12 Hydrogen Atom Coordinates (fractional) and B_{iso} ($Å^2$) of Diol 285 (cont.)

atom	x	y	z	B_{iso}
H(25)	0.4832	0.2606	0.7379	8.0
H(26)	0.5982	0.2165	0.6741	8.0
H(27)	0.5116	0.6029	0.2791	7.8
H(28)	0.5064	0.6430	0.4628	7.8
H(29)	0.3844	0.6064	0.3905	7.8
H(30)	0.6718	0.4953	0.5840	8.0
H(31)	0.6869	0.5733	0.5840	8.0
H(32)	0.6908	0.5337	0.3995	8.0

Table 13 Bond Lengths (Å) of Diol 285
with Estimated Standard Deviations in Parentheses

atom	atom	distance	atom	atom	distance
O(1)	C(4)	1.440(2)	C(4)	C(5)	1.505(3)
O(2)	C(12)	1.432(3)	C(5)	C(6)	1.527(3)
C(1)	C(2)	1.560(3)	C(6)	C(7)	1.563(3)
C(1)	C(6)	1.562(3)	C(7)	C(8)	1.540(4)
C(1)	C(10)	1.539(3)	C(7)	C(14)	1.538(4)
C(1)	C(11)	1.539(3)	C(7)	C(15)	1.532(4)
C(2)	C(3)	1.552(3)	C(8)	C(9)	1.500(4)
C(2)	C(12)	1.523(3)	C(9)	C(10)	1.512(5)
C(3)	C(4)	1.531(3)	C(13)	C(16)	1.510(4)
C(3)	C(13)	1.553(3)	C(13)	C(17)	1.522(4)

Table 14 Bond Angles (deg) of Diol 285
with Estimated Standard Deviations in Parentheses

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	C(1)	C(6)	111.9(2)	C(1)	C(6)	C(5)	109.7(2)
C(2)	C(1)	C(10)	112.0(2)	C(1)	C(6)	C(7)	119.0(2)
C(2)	C(1)	C(11)	110.6(2)	C(5)	C(6)	C(7)	114.7(2)
C(6)	C(1)	C(10)	108.3(2)	C(6)	C(7)	C(8)	108.8(2)
C(6)	C(1)	C(11)	108.0(2)	C(6)	C(7)	C(14)	115.6(2)
C(10)	C(1)	C(11)	105.7(2)	C(6)	C(7)	C(15)	108.5(2)
C(1)	C(2)	C(3)	114.3(2)	C(8)	C(7)	C(14)	109.1(2)
C(1)	C(2)	C(12)	113.8(2)	C(8)	C(7)	C(15)	107.2(2)
C(3)	C(2)	C(12)	110.5(2)	C(14)	C(7)	C(15)	107.2(2)
C(2)	C(3)	C(4)	112.8(2)	C(7)	C(8)	C(9)	113.2(2)
C(2)	C(3)	C(13)	115.8(2)	C(8)	C(9)	C(10)	109.3(3)
C(4)	C(3)	C(13)	108.2(2)	C(1)	C(10)	C(9)	114.9(2)
O(1)	C(4)	C(3)	110.2(2)	O(2)	C(12)	C(2)	114.2(2)
O(1)	C(4)	C(5)	108.4(2)	C(3)	C(13)	C(16)	116.0(2)
C(3)	C(4)	C(5)	115.1(2)	C(3)	C(13)	C(17)	113.8(2)
C(4)	C(5)	C(6)	115.6(2)	C(16)	C(13)	C(17)	112.8(2)

Table 15 Torsional or Conformational Angles (deg) of Diol 285

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O(1)	C(4)	C(3)	C(2)	-166.2(2)	C(2)	C(1)	C(10)	C(9)	74.5(3)
O(1)	C(4)	C(3)	C(13)	64.4(2)	C(2)	C(1)	C(10)	H(13)	-46
O(1)	C(4)	C(3)	H(4)	-50	C(2)	C(1)	C(10)	H(14)	-165
O(1)	C(4)	C(5)	C(6)	173.2(2)	C(2)	C(1)	C(11)	H(15)	59
O(1)	C(4)	C(5)	H(6)	52	C(2)	C(1)	C(11)	H(16)	-61
O(1)	C(4)	C(5)	H(7)	-66	C(2)	C(1)	C(11)	H(17)	179
O(2)	C(12)	C(2)	C(1)	79.5(2)	C(2)	C(3)	C(4)	C(5)	-43.2(2)
O(2)	C(12)	C(2)	C(3)	-50.6(2)	C(2)	C(3)	C(4)	H(5)	77
O(2)	C(12)	C(2)	H(3)	-165	C(2)	C(3)	C(13)	C(16)	87.6(3)
C(1)	C(2)	C(3)	C(4)	44.7(2)	C(2)	C(3)	C(13)	C(17)	-45.7(3)
C(1)	C(2)	C(3)	C(13)	170.1(2)	C(2)	C(3)	C(13)	H(20)	-159
C(1)	C(2)	C(3)	H(4)	-72	C(2)	C(12)	O(2)	H(2)	-121(2)
C(1)	C(2)	C(12)	H(18)	-160	C(3)	C(2)	C(1)	C(6)	-50.9(2)
C(1)	C(2)	C(12)	H(19)	-41	C(3)	C(2)	C(1)	C(10)	-172.7(2)
C(1)	C(6)	C(5)	C(4)	-53.3(2)	C(3)	C(2)	C(1)	C(11)	69.7(2)
C(1)	C(6)	C(5)	H(6)	68	C(3)	C(2)	C(12)	H(18)	70
C(1)	C(6)	C(5)	H(7)	-174	C(3)	C(2)	C(12)	H(19)	-171
C(1)	C(6)	C(7)	C(8)	-44.2(3)	C(3)	C(4)	O(1)	H(1)	69(2)
C(1)	C(6)	C(7)	C(14)	79.0(3)	C(3)	C(4)	C(5)	C(6)	49.3(2)
C(1)	C(6)	C(7)	C(15)	-160.6(2)	C(3)	C(4)	C(5)	H(6)	-72
C(1)	C(10)	C(9)	C(8)	60.5(3)	C(3)	C(4)	C(5)	H(7)	170
C(1)	C(10)	C(9)	H(11)	-179	C(3)	C(13)	C(16)	H(27)	-74
C(1)	C(10)	C(9)	H(12)	-59	C(3)	C(13)	C(16)	H(28)	166
C(2)	C(1)	C(6)	C(5)	53.2(2)	C(3)	C(13)	C(16)	H(29)	46
C(2)	C(1)	C(6)	C(7)	-81.6(2)	C(3)	C(13)	C(17)	H(30)	-45
C(2)	C(1)	C(6)	H(8)	164	C(3)	C(13)	C(17)	H(31)	-165

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Table 15 Torsional or Conformational Angles (deg) of Diol **285** (cont.)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
C(3)	C(13)	C(17)	H(32)	75	C(6)	C(7)	C(8)	H(9)	-68
C(4)	C(3)	C(2)	C(12)	174.6(2)	C(6)	C(7)	C(8)	H(10)	173
C(4)	C(3)	C(2)	H(3)	-71	C(6)	C(7)	C(14)	H(21)	177
C(4)	C(3)	C(13)	C(16)	-144.7(2)	C(6)	C(7)	C(14)	H(22)	57
C(4)	C(3)	C(13)	C(17)	82.0(3)	C(6)	C(7)	C(14)	H(23)	-63
C(4)	C(3)	C(13)	H(20)	-31	C(6)	C(7)	C(15)	H(24)	58
C(4)	C(5)	C(6)	C(7)	83.6(2)	C(6)	C(7)	C(15)	H(25)	-62
C(4)	C(5)	C(6)	H(8)	-164	C(6)	C(7)	C(15)	H(26)	178
C(5)	C(4)	O(1)	H(1)	-58(2)	C(7)	C(6)	C(1)	C(10)	42.3(3)
C(5)	C(4)	C(3)	C(13)	-172.6(2)	C(7)	C(6)	C(1)	C(11)	156.4(2)
C(5)	C(4)	C(3)	H(4)	73	C(7)	C(6)	C(5)	H(6)	-155
C(5)	C(6)	C(1)	C(10)	177.2(2)	C(7)	C(6)	C(5)	H(7)	-37
C(5)	C(6)	C(1)	C(11)	-68.8(2)	C(7)	C(8)	C(9)	C(10)	-61.5(3)
C(5)	C(6)	C(7)	C(8)	-176.9(2)	C(7)	C(8)	C(9)	H(11)	179
C(5)	C(6)	C(7)	C(14)	-53.7(3)	C(7)	C(8)	C(9)	H(12)	58
C(5)	C(6)	C(7)	C(15)	66.7(3)	C(8)	C(7)	C(6)	H(8)	71
C(6)	C(1)	C(2)	C(12)	-179.1(2)	C(8)	C(7)	C(14)	H(21)	-60
C(6)	C(1)	C(2)	H(3)	65	C(8)	C(7)	C(14)	H(22)	-180
C(6)	C(1)	C(10)	C(9)	-49.4(3)	C(8)	C(7)	C(14)	H(23)	60
C(6)	C(1)	C(10)	H(13)	-170	C(8)	C(7)	C(15)	H(24)	-59
C(6)	C(1)	C(10)	H(14)	71	C(8)	C(7)	C(15)	H(25)	-179
C(6)	C(1)	C(11)	H(15)	-178	C(8)	C(7)	C(15)	H(26)	61
C(6)	C(1)	C(11)	H(16)	62	C(8)	C(9)	C(10)	H(13)	-179
C(6)	C(1)	C(11)	H(17)	-58	C(8)	C(9)	C(10)	H(14)	-60
C(6)	C(5)	C(4)	H(5)	-71	C(9)	C(8)	C(7)	C(14)	-74.5(3)
C(6)	C(7)	C(8)	C(9)	52.5(3)	C(9)	C(8)	C(7)	C(15)	169.7(2)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Table 15 Torsional or Conformational Angles (deg) of Diol **285** (cont.)

(1)	(2)	(3)	(4)	angle
C(9)	C(10)	C(1)	C(11)	-164.9(2)
C(10)	C(1)	C(2)	C(12)	59.1(2)
C(10)	C(1)	C(2)	H(3)	-57
C(10)	C(1)	C(6)	H(8)	-72
C(10)	C(1)	C(11)	H(15)	-62
C(10)	C(1)	C(11)	H(16)	178
C(10)	C(1)	C(11)	H(17)	58
C(10)	C(9)	C(8)	H(9)	59
C(10)	C(9)	C(8)	H(10)	178
C(11)	C(1)	C(2)	C(12)	-58.6(2)
C(11)	C(1)	C(2)	H(3)	-174
C(11)	C(1)	C(6)	H(8)	42
C(11)	C(1)	C(10)	H(13)	74
C(11)	C(1)	C(10)	H(14)	-44
C(12)	C(2)	C(3)	C(13)	-60.0(2)
C(12)	C(2)	C(3)	H(4)	58
C(13)	C(3)	C(2)	H(3)	54
C(13)	C(3)	C(4)	H(5)	-53
C(14)	C(7)	C(6)	H(8)	-166
C(14)	C(7)	C(8)	H(9)	165
C(14)	C(7)	C(8)	H(10)	46
C(14)	C(7)	C(15)	H(24)	-176
C(14)	C(7)	C(15)	H(25)	64
C(14)	C(7)	C(15)	H(26)	-56
C(15)	C(7)	C(6)	H(8)	-46
C(15)	C(7)	C(8)	H(9)	49
C(15)	C(7)	C(8)	H(10)	-70
C(15)	C(7)	C(14)	H(21)	56
C(15)	C(7)	C(14)	H(22)	-64
C(15)	C(7)	C(14)	H(23)	176
C(16)	C(13)	C(3)	H(4)	-31
C(16)	C(13)	C(17)	H(30)	-179
C(16)	C(13)	C(17)	H(31)	61
C(16)	C(13)	C(17)	H(32)	-59
C(17)	C(13)	C(3)	H(4)	-164
C(17)	C(13)	C(16)	H(27)	59
C(17)	C(13)	C(16)	H(28)	-61
C(17)	C(13)	C(16)	H(29)	179
H(1)	O(1)	C(4)	H(5)	-174
H(2)	O(2)	C(12)	H(18)	118
H(2)	O(2)	C(12)	H(19)	0
H(3)	C(2)	C(3)	H(4)	172
H(3)	C(2)	C(12)	H(18)	-44
H(3)	C(2)	C(12)	H(19)	75
H(4)	C(3)	C(4)	H(5)	-167
H(4)	C(3)	C(13)	H(20)	83
H(5)	C(4)	C(5)	H(6)	168
H(5)	C(4)	C(5)	H(7)	50
H(6)	C(5)	C(6)	H(8)	-43
H(7)	C(5)	C(6)	H(8)	75
H(9)	C(8)	C(9)	H(11)	-61
H(9)	C(8)	C(9)	H(12)	179

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Table 15 Torsional or Conformational Angles (deg) of Diol **285** (cont.)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
H(10)	C(8)	C(9)	H(11)	58					
H(10)	C(8)	C(9)	H(12)	-62					
H(11)	C(9)	C(10)	H(13)	-59					
H(11)	C(9)	C(10)	H(14)	60					
H(12)	C(9)	C(10)	H(13)	61					
H(12)	C(9)	C(10)	H(14)	180					
H(20)	C(13)	C(16)	H(27)	172					
H(20)	C(13)	C(16)	H(28)	52					
H(20)	C(13)	C(16)	H(29)	-68					
H(20)	C(13)	C(17)	H(30)	68					
H(20)	C(13)	C(17)	H(31)	-52					
H(20)	C(13)	C(17)	H(32)	-172					

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.