Further Investigations on the Use of Camphor as an Enantiopure Starting Material in Natural Product Synthesis

by

MICHAEL KAY CHUNG WONG

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The University of British Columbia
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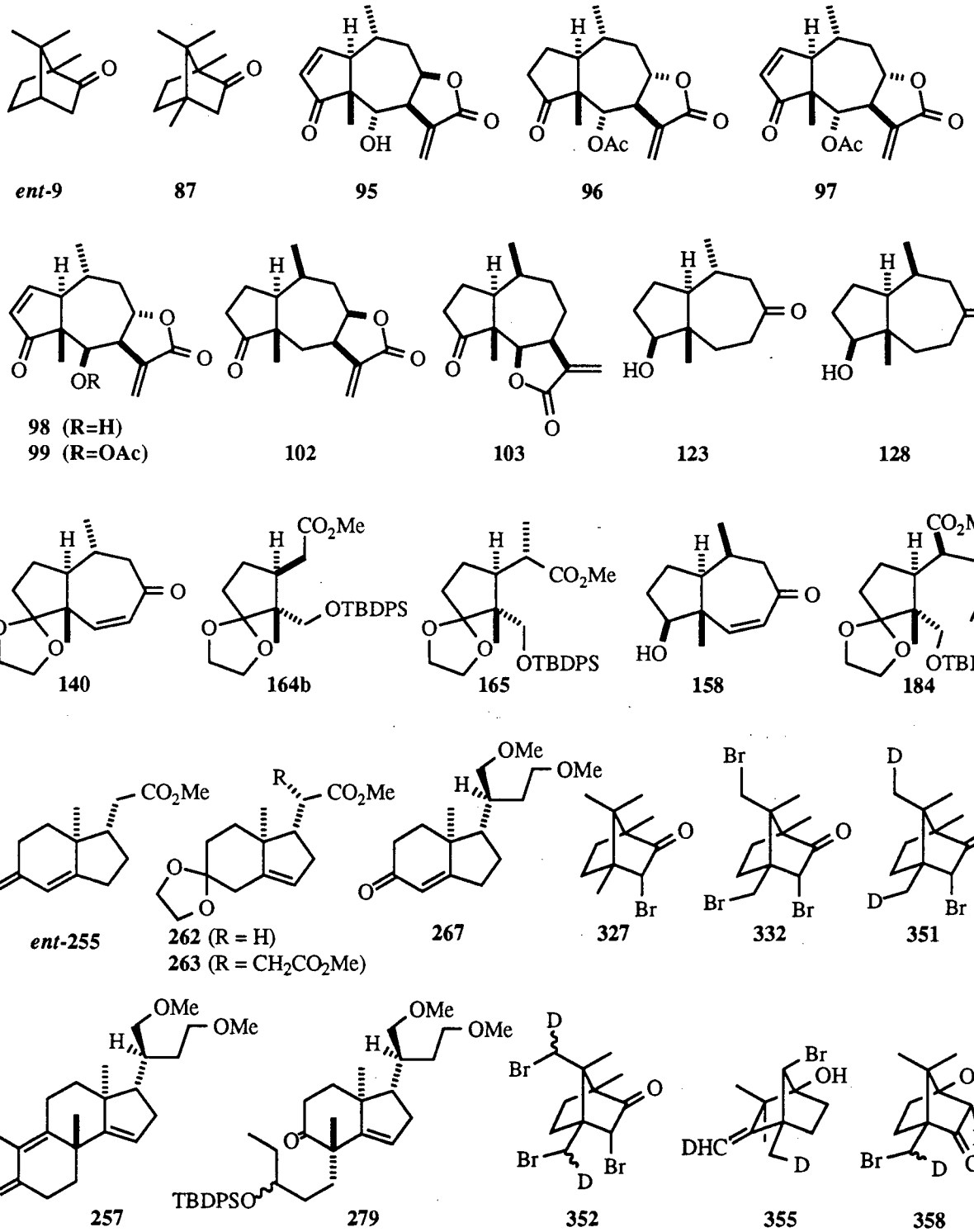
Abstract

The use of (–)-camphor (***ent*-9**) as an enantiopure intermediate in pseudoguaianolide and limonoid synthesis and further aspects of the chemistry of 4-methylcamphor (**87**) are presented in this thesis. First, the preparation of relay compounds ketal-enone **140**, hydroxy-ketone **123**, hydroxy-enone **158**, and hydroxy-ketone **128** represents a formal, enantiospecific synthesis of the helenanolides carpesiolin (**96**), helenalin (**95**), bigelovin (**97**), mexicanin I (**98**), and linifolin A (**99**) and the ambrosanolides damsin (**102**) and confertin (**103**). (–)-Camphor (***ent*-9**) was converted in nine steps to ketal-ester **164b**. Stereoselective alkylation of **164b** with methyl iodide yielded ketal-ester **165** that could be elaborated to the ketal-enone **140** in seven steps. Hydroxy-ketone **123** was obtained from **140** in a further three steps. Similarly, stereoselective alkylation of **164b** with allyl bromide yielded ketal-ester **184** that could be converted subsequently to hydroxy-enone **158** in nine steps. Finally, catalytic hydrogenation of **158** provided hydroxy-ketone **128**.

Secondly, as part of an enantiospecific synthetic approach to the limonoids, the tricyclic enone **257** was prepared. (–)-Camphor (***ent*-9**) was converted to the known bicyclic enone-ester (***ent*-255**) in ten steps. Alkylation of ketal-ester **262**, derived from ***ent*-255**, with methyl bromoacetate yielded ketal-diester **263**, which could be transformed into dimethoxy-enone **267** in three steps. Two successive alkylations of enone **267** yielded the β,γ-unsaturated enone **279**, and subsequent desilylation, oxidation, and aldol condensation steps provided the tricyclic enone **257**, which has potential as a BCD-intermediate for the synthesis of tetracyclic limonoids.

Finally, a proposed mechanism for the bromination of *endo*-3-bromo-4-methylcamphor (**327**) to yield *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) was evaluated using the corresponding deuterium-labelled analogue, *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**), as substrate. NMR spectroscopic evidence was used to identify the product resulting from the bromination of **351** as *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor

(**352**). Evidence supporting the proposed existence of unsaturated intermediates **355** and **358** in the bromination mechanism was also obtained.



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List of Abbreviations*

$[\alpha]_D^T$	-	specific rotation, recorded at the sodium D line (589 nm) at T °C
Ac	-	acetyl [–C(O)CH_3]
AIBN	-	azobis(isobutyronitrile)
Anal.	-	microanalysis
APT	-	attached proton test
aq.	-	aqueous
Bn	-	benzyl [$C_6H_5CH_2$–]
bp	-	boiling point
Bu *or* *n*-Bu	-	*normal*-butyl [$CH_3CH_2CH_2CH_2$–]
Bz	-	benzoyl [$C_6H_5C(O)$–]
c	-	concentration
calcd	-	calculated
COSY	-	correlation spectroscopy
Δ	-	unsaturation
δ	-	chemical shift
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	-	dicyclohexylcarbodiimide
DCI-MS	-	desorption chemical impact mass spectrometry or spectrum
DEAD	-	diethyl azodicarboxylate
DHP	-	dihydropyran
DIBAL	-	diisobutylaluminum hydride
DMAP	–	4-dimethylaminopyridine

* Abbreviations for chemical elements as well as SI and other units of measurement have been omitted from this list. Definitions of abbreviations and symbols used specifically for the description of nuclear magnetic resonance and infrared spectra are defined in the Experimental section of this thesis (*cf.* Chapter 5, page 122).

DME	-	1,2-dimethoxyethane
DMF	-	*N*,*N*-dimethylformamide
DMSO	-	dimethyl sulfoxide
e.e.	-	enantiomeric excess
EIMS	-	electron impact mass spectrometry *or* spectrum
ent	-	enantiomer of
eq	-	equivalents
Et	-	ethyl [CH_3CH_2–]
GLC	-	gas-liquid chromatography
HETCOR	-	heteronuclear correlation spectroscopy
hfc	-	3-(heptafluoropropylhydroxymethylene)-*d*-camphorato
HMDS	-	hexamethyldisilazide [$((CH_3)_3Si)_2N^-$]
HMPA	-	hexamethylphosphoramide
hν	-	light
i-Pr *or* Pr^i	-	isopropyl [$(CH_3)_2CH$–]
IR	-	infrared (spectroscopy)
J	-	coupling constant
LDA	-	lithium diisopropylamide
lit.	-	literature
M	-	parent mass (*mass spectra*) or molar, moles per liter (*concentration*)
m-CPBA	-	*meta*-chloroperbenzoic acid
m/z	-	mass-to-charge ratio
Me	-	methyl [CH_3–]
MEM	-	methoxyethoxymethyl [$CH_3OCH_2CH_2OCH_2$–]
mp	-	melting point
Ms	-	mesyl, methanesulfonyl [$-SO_2CH_3$]
n	-	normal (*nomenclature*)

NBS	-	*N*-bromosuccinimide
NMR	-	nuclear magnetic resonance (spectroscopy)
NOE	-	nuclear Overhauser effect
p	-	*para*
PCC	-	pyridinium chlorochromate
PDC	-	pyridinium dichromate
pet. ether	-	petroleum ether
Ph	-	phenyl [$-C_6H_5$]
ppm	-	parts per million
PPTS	-	pyridinium *para*-toluenesulfonate
r.t.	-	room temperature
R_f	-	retention factor *or* retardation factor
s-Bu *or* Bu^s	-	*secondary*-butyl [$CH_3CH_2C(CH_3)$–]
t-	-	*tertiary*-
t-Am	-	*tertiary*-amyl
t-Bu *or* Bu^t	-	*tertiary*-butyl [$(CH_3)_3C$–]
TBAF	-	tetrabutylammonium fluoride
TBAI	-	tetrabutylammonium iodide
TBDMS	-	*tertiary*-butyldimethylsilyl [$-Si(CH_3)_2(C(CH_3)_3)$]
TBDPS	-	*tertiary*-butyldiphenylsilyl [$-Si(C_6H_5)_2(C(CH_3)_3)$]
Tf	-	trifluoromethanesulfonyl [$-SO_2CF_3$]
THF	-	tetrahydrofuran
THP	-	tetrahydropyranyl
Thx	-	thexyl, *tertiary*-hexyl [$(CH_3)_2CH–C(CH_3)_2$–]
TLC	-	thin-layer chromatography
TMEDA	-	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
Ts *or* *p*-Ts	-	tosyl, *para*-toluenesulfonyl

Acknowledgments

Over the course of my graduate studies, I was privileged to have enjoyed the support of many faculty members, fellow graduate students, as well as friends from various undergraduate programs around the University. Unfortunately, space limitations force me to acknowledge, by name, only a subset of these people whom I consider to have made a significance difference to the outcome of my work.

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I extend my gratitude to Messrs. Adam Mezo, Lloyd MacKenzie, and Mark Rushton for voluntarily taking time from own work to proof-read parts of this thesis. The considerable effort and care they took as editors exceeded my expectations, and I very much appreciate their suggestions, ideas, and criticisms. I claim responsibility for any errors or deficiencies that remain.

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Last, but not least, I thank the staff of the NMR Laboratory, Mass Spectrometry Laboratory, Microanalysis Laboratory (Mr. Peter Borda), and Glass Shop (Mr. Steve Rak) for their ongoing assistance; the Chemistry Department for the award of a McDowell Fellowship and a travel grant, as well as for the grant of a Summer Sessional Lectureship to teach CHEM 230 at UBC (1995); the UBC Faculty of Graduate Studies for a travel grant; the Canadian Society for Chemistry for an Organic Division Student Award (1994); and Natural Sciences and Engineering Research Council (NSERC) for the award of a PGS-3 fellowship (1991–1993).

I dedicate this thesis to my parents,
John S.K. & Cynthia H.F. Wong,
with love and thanks for almost thirty years of
patience, guidance, and encouragement.

Chapter 1

Synthesis of Enantiopure Compounds and Use of Camphor as an Enantiopure Starting Material in Natural Product Synthesis

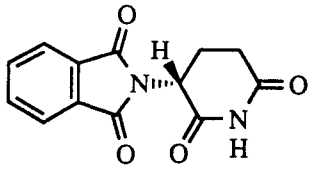
1. Synthesis of Enantiopure Compounds and Use of Camphor as an Enantiopure Starting Material in Natural Product Synthesis

(a) The Synthesis of Enantiopure Compounds

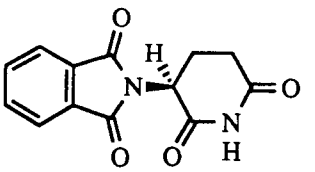
i. Introduction

In *Through the Looking Glass* (1872) by Lewis Carroll (1832-1898), Alice wonders about the nature of the world beyond her looking-glass.[1] As she is philosophizing, she asks her kitten, "How would you like to live in Looking-glass house, Kitty? I wonder if they'd give you milk in there? Perhaps Looking-glass milk isn't good to drink..." One may be tempted to ask whether Carroll, writing only 24 years after Louis Pasteur (1822-1895) demonstrated the separation of the enantiomers of sodium ammonium tartrate, was aware of the chemical implications of what Alice had just said! In Nature, the majority of natural compounds are biosynthesized in one of two enantiomeric forms, and it is generally recognized now that the two enantiomers of a compound can exhibit completely different biological activities.[2] Medicinal chemists often use the term 'eutomer' (from the Greek εὖ, 'good') to refer to the enantiomer of a drug that gives rise to the desired biological action and the term 'distomer' (alternative spelling: dystomer; from the Greek δυσ-, 'un-') to refer to the alternative enantiomer.[3]

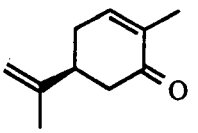
In addressing the topic of the biological activities of enantiomers one is often reminded of



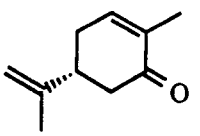
(*R*)-thalidomide (1)



(*S*)-thalidomide (*ent*-1)



(*S*)-(+)-carvone (2)



(*R*)-(–)-carvone (*ent*-2)

the tragic example provided by the drug thalidomide (**1**).[2a,3] Thalidomide (**1**), a bis(imide) bearing a single stereocenter, was commonly administered in the 1950s and early 1960s to pregnant women to combat the effects of morning sickness. Soon after, the high incidence of

births of infants with shortened or completely absent limbs prompted regulatory agencies around the world to discontinue the prescription of thalidomide (**1**). Meanwhile, it was found that although both the (*R*)- and (*S*)- enantiomers of thalidomide (**1**) possessed the desired sleep-inducing and hypnotic effects, (*S*)-thalidomide (***ent*-1**) exerted additional embryopathic and teratogenic effects.

A less severe illustration of enantiomeric compounds displaying different biological activities is provided by the monoterpenoids (*S*)-(+)-carvone (**2**) and (*R*)-(–)-carvone (***ent*-2**). Whereas (*S*)-(+)-carvone (**2**) tastes of caraway, (*R*)-(–)-carvone (***ent*-2**) tastes of spearmint,[2a] and suggests that our taste receptors are also chiral and can therefore distinguish between enantiomeric compounds.

The recognition that different enantiomers of compounds can exert different biological effects prompted the United States Food and Drug Administration to issue a policy statement in 1992[4] that encourages the production of drugs in enantiomerically pure form.[4,5] Furthermore, in cases where it would be more feasible to develop a drug as a racemate, drug companies would be required to demonstrate that the individual enantiomers were safe. As a result, "... [the drug manufacturers'] recognition of the chiral drug issue persuaded drug firms that were not already doing so [i.e. synthesizing enantiopure drugs] to start developing single enantiomers only."[4a] In fact, so important is the move toward enantiopure drug synthesis that the American Chemical Society publishes an annual feature article entitled "Chiral Drugs" in its newsmagazine *Chemical and Engineering News*.[4]

ii. Access to Enantiomerically Pure Compounds

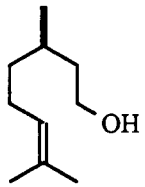
Access to enantiopure compounds[6] may be gained commonly in a number of ways. First, they may be isolated from natural sources. One must realize, however, that although it is commonly believed that many natural products can be isolated as pure enantiomers, there are a number of cases in which the isolated natural product is not enantiopure.[7] For example, commercially available (+)-α-pinene (**3**), (–)-α-pinene (***ent*-3**), and (–)-β-pinene (**4**), all derived

from natural sources, are only 92%, ~81%, and 92% enantiopure, respectively.[8] The enantiopurity of (*R*)-(+)-citronellol (**5**) ranges from 35–92%,[9a,b] while that of (*S*)-(–)-citronellol (***ent*-5**) is ~75–85%.[9c–f] More drastically, (1*S*, 5*R*)-karahana lactone (**6**),[7a] a constituent of the Japanese hop *Humulus lupulus*, is present in only 1.3% *e.e.* (*R*)-Dihydroactinidiolide (**7**),[7a] the

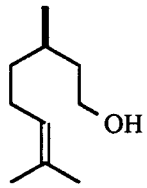
(+)-α-pinene (3)

(–)-α-pinene (*ent*-3)

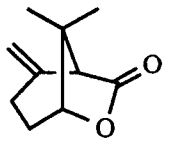
(–)-β-pinene (4)



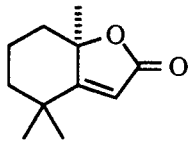
(*R*)-(+)-citronellol (5)



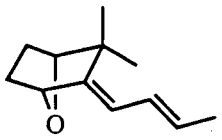
(*S*)-(–)-citronellol (*ent*-5)



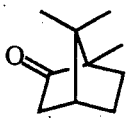
(1*S*, 5*R*)-karahana lactone (6)



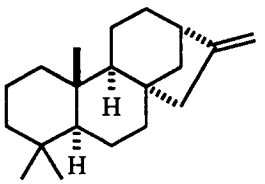
(*R*)-dihydroactinidiolide (7)



(2*S*, 5*R*)-2,5-epoxy-6,8-megastigmadiene (8)



(+)-camphor (9)



(+)-kaurene (10)

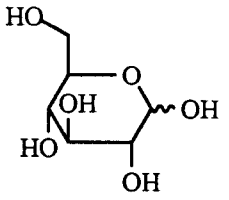
queen recognition pheromone of the red imported fire ant *Solenopsis invicta* Buren, can be isolated from tobacco leaves in 30% *e.e.*, while (2*S*, 5*R*)-2,5-epoxy-6,8-megastigmadiene (**8**),[7a] a constituent of *Osmanthus fragrans* Lourd, is present in 11% *e.e.* Thus, it is advisable that the enantiopurity of all isolated natural products be regarded with caution and where possible, checked by direct methods other than specific rotation. Furthermore, although some natural products are biosynthesized in both enantiomeric forms (e.g. camphor (**9**), carvone (**2**), α-pinene (**3**), and kaurene (**10**)),[7a] the majority of natural products are biosynthesized in only a single enantiomeric form. If one requires the "unnatural" enantiomer of such a compound, one must resort to the chemical synthesis of that enantiomer.[2b]

Secondly, enantiomerically pure compounds may be obtained through the resolution of a racemic mixture of compounds.[6a] Typically, this method involves the derivatization or complexation of the racemic compound with an enantiopure chiral auxiliary. The derivatives or complexes thus formed would be diastereomers that can be separated through conventional

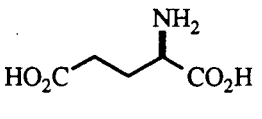
methods such as chromatography or crystallization. An illustration of this method can be found in a report by Mosher and co-workers,[10] in which they describe in detail the resolution of enantiomeric 2-phenyl-3-methylbutanoic acids by recrystallization of the diastereomeric salts formed with (*R*)-(+)-(1-phenylethyl)amine. Alternatively, the enantiomers themselves can be separated by chromatography in which a chiral stationary phase is used ('chiral chromatography').[11] The main disadvantages of resolution methods in general are that the maximum yield of the desired enantiomer can be no greater than 50%, and that the undesired enantiomer is often discarded. Furthermore, the resolution procedures, in practice, may be tedious due to the need for repeated recrystallization or chromatography, and if chiral chromatography is employed as the method of choice, the chiral column packing can be rather expensive. As well, if it is necessary to convert a racemic mixture into a mixture of diastereomers through derivatization with a chiral auxiliary, then at least two additional synthetic operations must be incorporated into the synthetic scheme: one step to introduce the chiral auxiliary, and another to remove it.

Thus, in view of the potential difficulties associated with resolution procedures, the possibility of synthesizing only one enantiomer of an optically active compound becomes attractive. Approaches toward the synthesis of enantiopure compounds fall into two broad categories. In the first, one uses an enantiopure, often structurally simple compound as a building block for the synthesis of the desired synthetic target.[6] If this building block is available in either enantiomeric form, then the possibility of synthesizing either enantiomer of the product exists, and the synthetic route is then termed 'enantiospecific.' Such enantiopure starting materials, which include sugars [e.g. D-glucose (**11**)],[12] terpenoids [e.g. carvone (**2**), camphor (**9**), and (+)-α-pinene (**3**)],[12b,13] α-amino acids [e.g. L-glutamic acid (**12**)],[12b,14] and alkaloids [e.g. (–)-ephedrine (**13**)],[12b] are often referred to collectively as the 'chiral pool.' Tabulations of commonly used chiral pool starting materials have been made,[6a] while other monographs and review articles illustrate how specific classes of chiral pool starting materials,

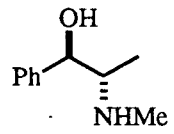
for example sugars[12a] and monoterpenoids,[13] have been used for the synthesis of specific natural products.



D-glucose (11)

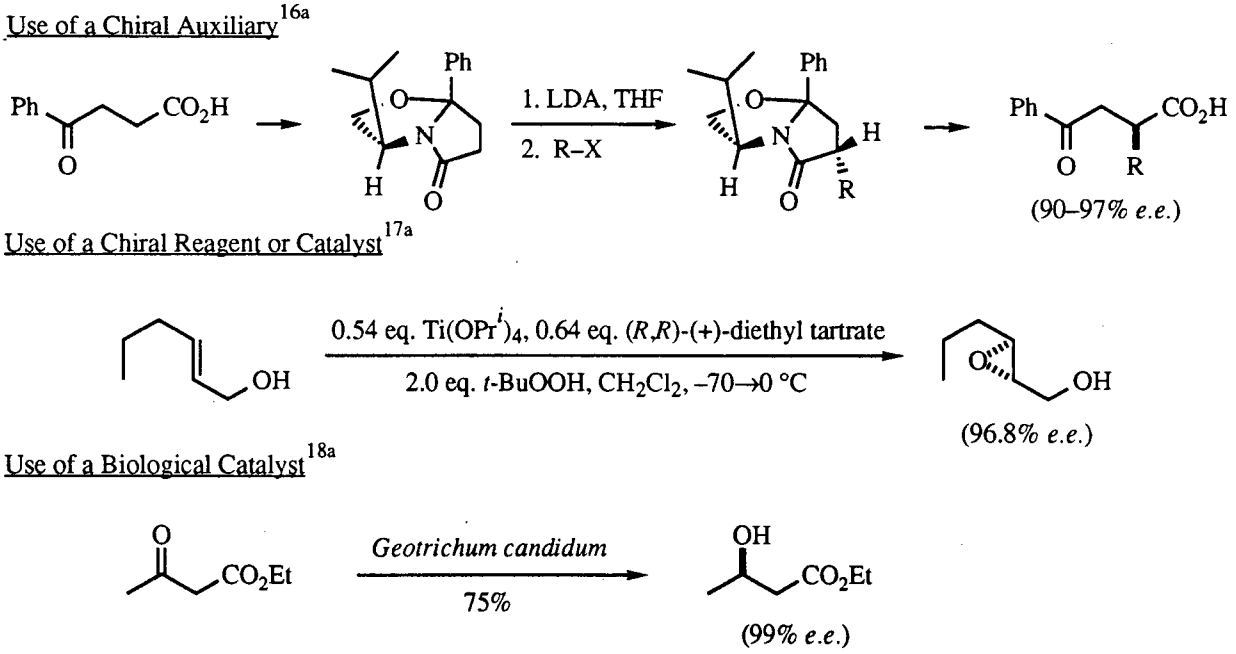


L-glutamic acid (12)



(–)-ephedrine (13)

The second major approach to synthesizing enantiopure compounds involves the conversion of a prochiral molecule to an enantiomerically enriched, or more preferably, enantiopure compound. This method is commonly known as 'asymmetric synthesis.'[15] One common asymmetric synthetic strategy involves the use of enantiopure chiral auxiliaries[16] that, when covalently bonded to a prochiral substrate, can bias the direction of approach of an external



Scheme 1.1. Examples of Common Asymmetric Synthetic Methods.

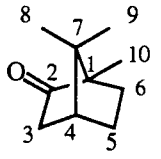
reagent. After the desired chemical transformation has taken place, the chiral auxiliary can be removed to yield an enantiopure or enantiomerically enriched product. Another strategy involves the development of chiral reagents or catalysts[17] that can differentiate the prochiral

groups or faces of the starting material. Alternatively, biological catalysts can also be used to effect the asymmetric transformation.[18] The tendency for different enantiomers to react at different rates with other chiral reagents, either biological or chemical, can also be exploited in asymmetric synthesis in a procedure known as 'kinetic resolution.'[19] Some representative examples of asymmetric synthetic strategies mentioned above are presented in Scheme 1.1.

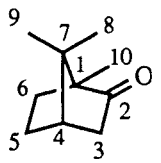
(b) Use of Camphor as an Enantiopure Starting Material in Natural Product Synthesis

i. Introduction

A 'chiral pool' monoterpenoid that is commonly used as a starting material for natural product synthesis is camphor (**9**). Camphor (**9**),[20a] known since antiquity, is a bridged bicyclic compound that occurs naturally in both enantiomeric forms as well as in racemic form. The more abundant (+)-camphor (**9**) can be isolated[20] from *Cinnamomum camphora* Nees, *Salvia officianalis* (sage), and *Santolina chamaecyparissus* (lavender), among others, while (–)-camphor



(+)-camphor
(9)



(–)-camphor
(*ent*-9)

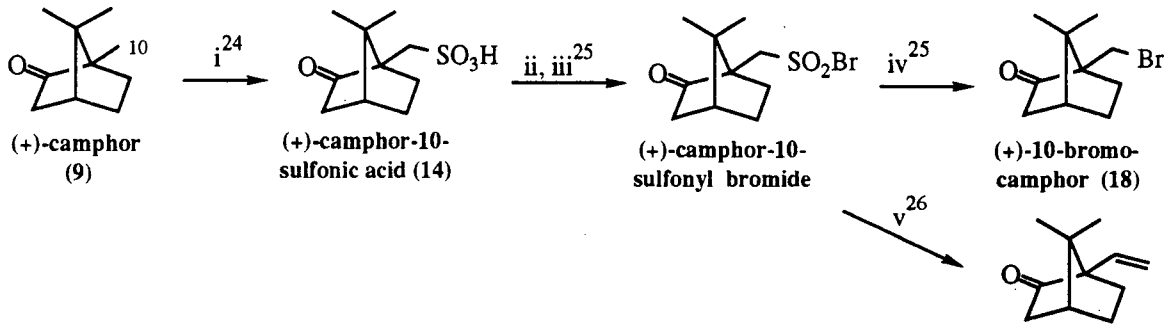
(***ent*-9**) can be isolated from *Artemesia tridentata*, *Rosemarinus officianalis* (rosemary), and *Blumea balsamifera*, among others. Camphor can be isolated in racemic form from *Chrysanthemum sinense* var. *japonicum*. In addition, camphor may be obtained through chemical synthesis.[21] Moreover, both enantiomers of camphor are commercially available, and Rautenstrauch and co-workers have determined recently that the enantiopurities of samples of (+)- and (–)-camphor from these sources (*e.g.* Aldrich Chemical Co.) are 99.6% and 98.3%, respectively.[22]

The numbering system that is most commonly used when referring to camphor is shown above, and will be employed throughout this thesis. For completeness, however, in the IUPAC

nomenclature system, camphor is named bornan-2-one and positions C(8) and C(9) are reversed. Furthermore, in the early literature (before ~1940) the C(3), C(8), C(9), and C(10) positions were designated as α, *cis*-π, *trans*-π, and ω (or β).

The versatility of (+)-camphor (**9**) and (–)-camphor (***ent*-9**) as enantiopure starting materials in natural product synthesis[13,23] is due to the fact that the camphor structure can be functionalized regioselectively at every available position, that is, at C(3), C(4), C(5), C(6), C(8), C(9), and C(10). Furthermore, cleavage of the C(1)–C(2), C(2)–C(3), and C(1)–C(7) bonds of suitably functionalized camphor derivatives provides a variety of intermediates that have potential in organic synthesis. It must be noted that both enantiomers of camphor have also been converted to derivatives that have found widespread use as chiral auxiliaries.[16b] Unfortunately, discussion of this topic is beyond the scope of this thesis. In the remainder of this chapter will be presented a brief survey of the key transformations of camphor (**9**) and its derivatives. A short presentation on the use of camphor (**9**) and its derivatives as an enantiopure starting material in natural product synthesis will also be given.

*ii. C(10) Substitution: Camphor-10-sulfonic Acid (**14**), etc.*

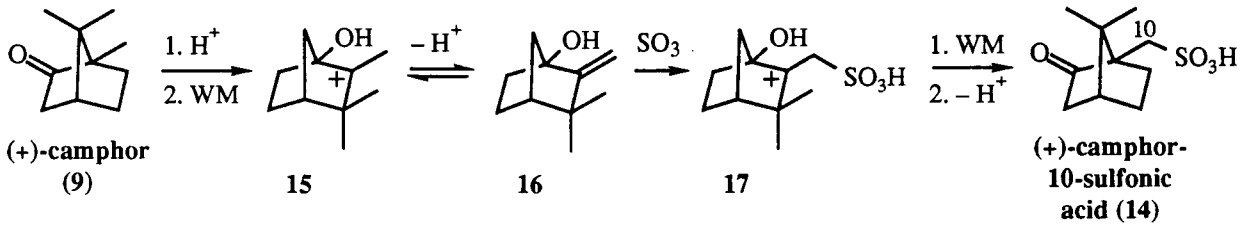


(i) H_2SO_4-Ac_2O (1:2) (ii) KOH, MeOH (iii) PBr_3 (iv) xylene, heat (v) Et_3N, CH_2N_2, Et_2O; 95°C.

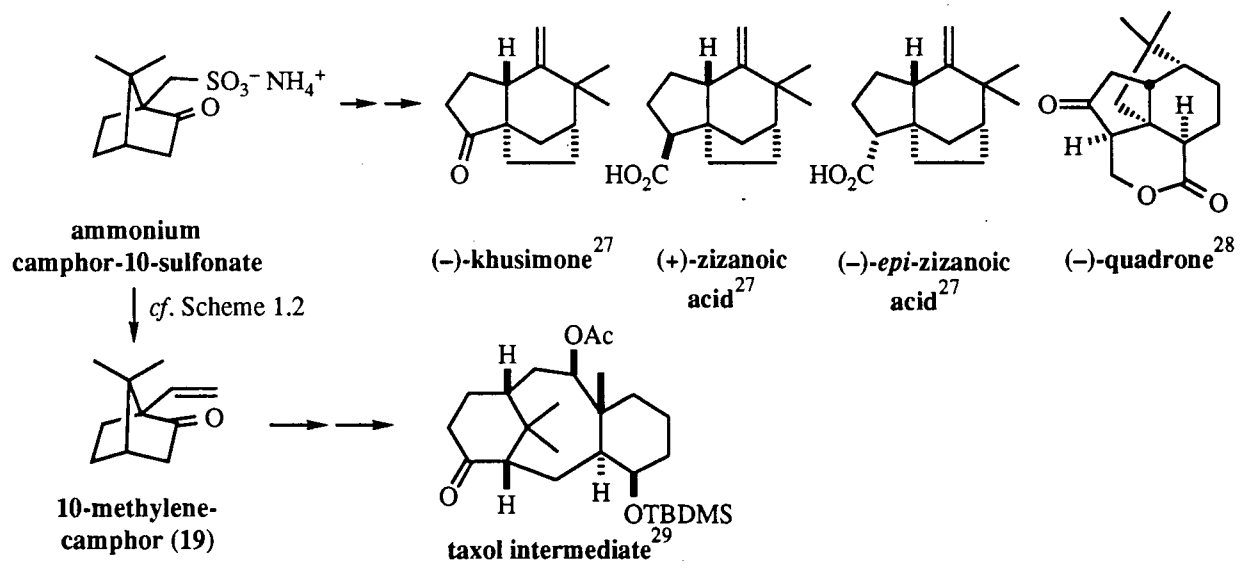
Scheme 1.2. Preparation of C(10)-Substituted Derivatives of Camphor.

Treatment of (+)-camphor (**9**) with sulfuric acid and acetic anhydride provides (+)-camphor-10-sulfonic acid (**14**; Scheme 1.2),[24] which is also commercially available. The mech-

anism (Scheme 1.3)[23] proposed for this transformation is typical of many of those that have been proposed for electrophilic substitution reactions (sulfonation or bromination) or acid-catalyzed rearrangements of camphor derivatives. Protonation of (+)-camphor (**9**) promotes a Wagner-Meerwein rearrangement to yield the tertiary carbocation **15**, which is in equilibrium with the exocyclic alkene **16**. Sulfonation of **16** by sulfur trioxide, generated *in situ* from sulfuric acid and acetic anhydride, yields **17**. A further Wagner-Meerwein rearrangement followed by deprotonation provides (+)-camphor-10-sulfonic acid (**14**).



Scheme 1.3. Mechanism for C(10) Sulfonation of Camphor.
[*WM = Wagner-Meerwein rearrangement*]

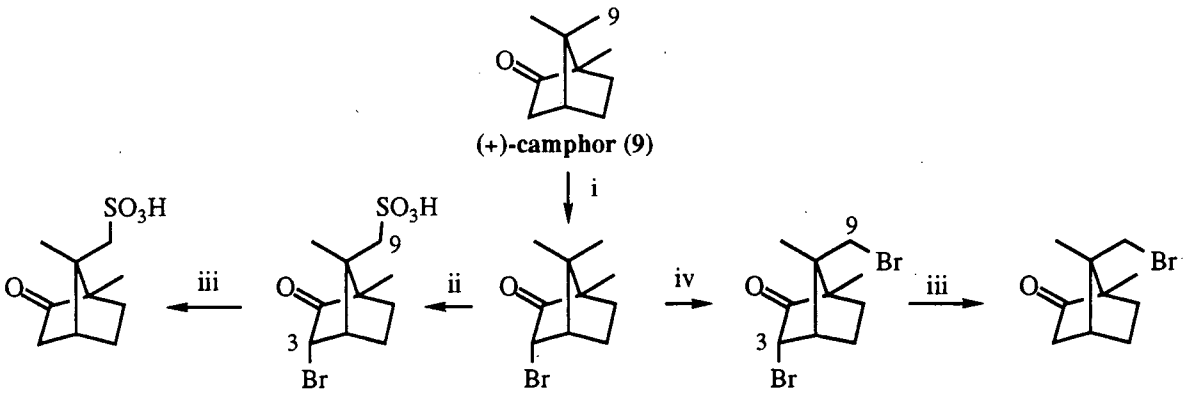


Scheme 1.4. Use of C(10)-Substituted Camphor Derivatives in Natural Product Synthesis.

(+)-Camphor-10-sulfonic acid (**14**) can also be converted to (+)-10-bromocamphor (**18**)[25] and 10-methylenecamphor (**19**),[26] as shown in Scheme 1.2. Scheme 1.4 illustrates the use of C(10)-substituted camphor derivatives in natural product synthesis.

iii. C(9) Substitution: Camphor-9-sulfonic Acid (23) and 9-Bromocamphor (24)

Treatment of (+)-camphor (**9**) with bromine in acetic acid yields (+)-*endo*-3-bromocamphor (**20**).[30] When **20** is treated with fuming sulfuric acid or chlorosulfonic acid, sulfonation at C(9) occurs to yield *endo*-3-bromocamphor-9-sulfonic acid (**21**).[23] Similarly, when **20** is treated with a mixture of bromine in chlorosulfonic acid, the product that is isolated is *endo*-3,9-dibromocamphor (**22**; Scheme 1.5).[31] Subsequent chemoselective reduction of the 3-bromo substituent of **21** and **22** yields camphor-9-sulfonic acid (**23**) and (+)-9-bromocamphor (**24**), respectively. It is interesting to note that direct sulfonation or bromination of (+)-camphor (**9**), that is, without proceeding via the 3-bromo derivative, results in the formation of an unequal mixture of enantiomeric camphor-9-sulfonic acids (**23** and ***ent*-23**) or 9-bromocamphors (**24** and ***ent*-24**), respectively.[23]

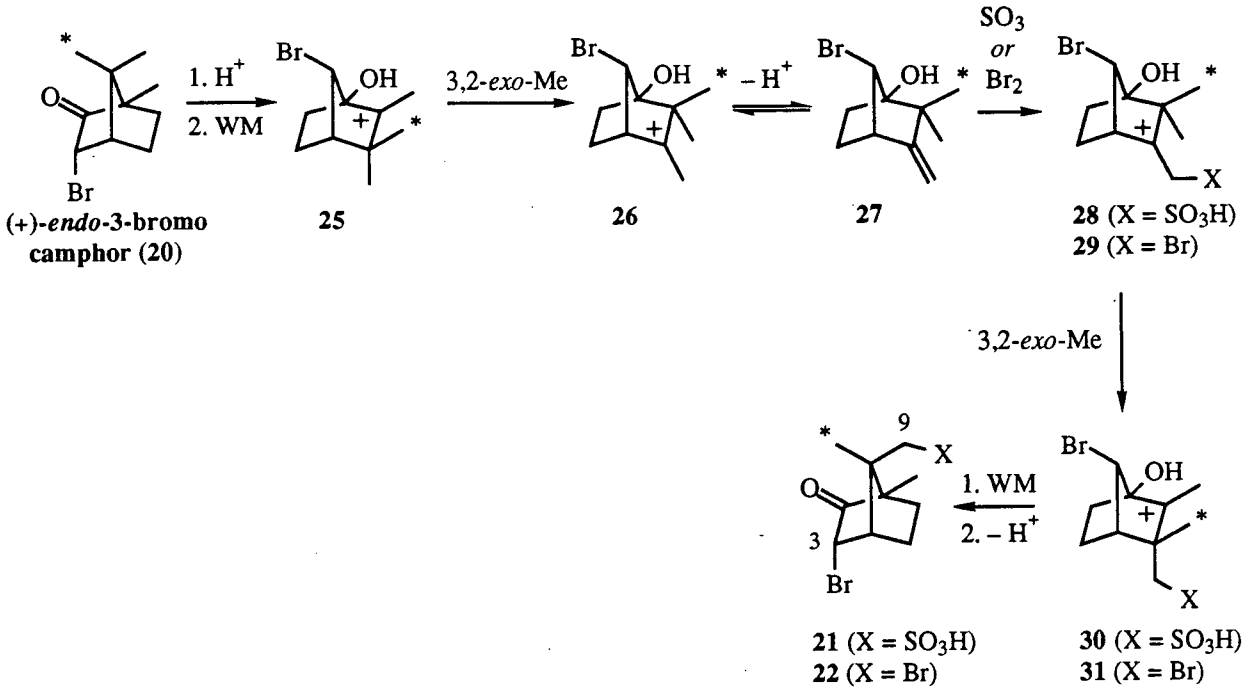


(i) Br_2, HOAc, 80 °C (ii) H_2SO_4, SO_3; *or* $ClSO_3H$ (iii) Zn, HOAc–Et_2O, 0 °C (iv) Br_2, $ClSO_3H$.

Scheme 1.5. Preparation of C(9)-Substituted Camphor Derivatives.

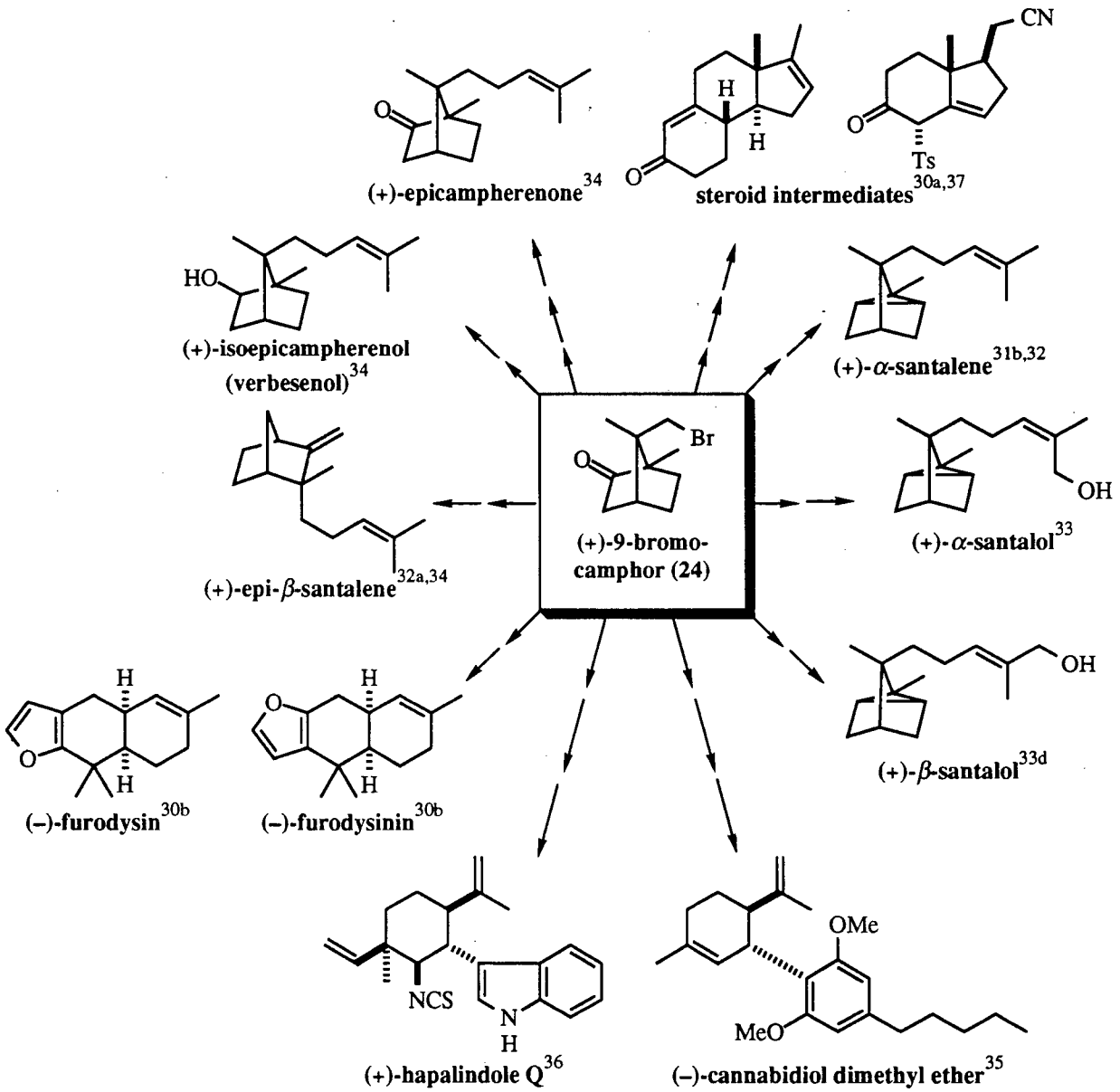
The proposed mechanism for C(9) sulfonation or bromination[23] is given in Scheme 1.6. Protonation of *endo*-3-bromocamphor (**20**) promotes a Wagner-Meerwein rearrangement and then *exo*-3,2-methyl shift to yield **26** which is in equilibrium with the exocyclic alkene **27**. Sulfonation or bromination of **27** yields tertiary carbocations **28** or **29**, respectively, which

undergo subsequent *exo*-3,2-methyl shift, Wagner-Meerwein rearrangement and proton loss to yield *endo*-3-bromocamphor-9-sulfonic acid (**21**) or *endo*-3,9-dibromocamphor (**22**), respectively.



Scheme 1.6. Mechanism of C(9) Sulfonation or Bromination of (+)-*endo*-3-Bromocamphor (**20**) [*WM = Wagner-Meerwein rearrangement; 3,2*-exo-*Me = 3,2*-exo-*methyl shift*]

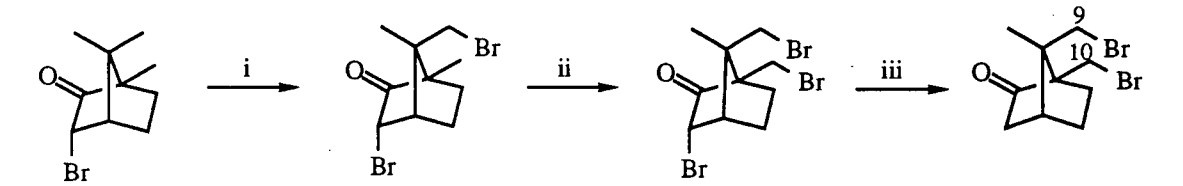
In general, 9-bromocamphor (**24**) has been used more extensively in natural product synthesis than the corresponding sulfonic acid derivative **23**. A selection of natural products that have been synthesized from 9-bromocamphor is presented in Scheme 1.7.



Scheme 1.7. Use of 9-Bromocamphor (**24**) in Natural Product Synthesis.

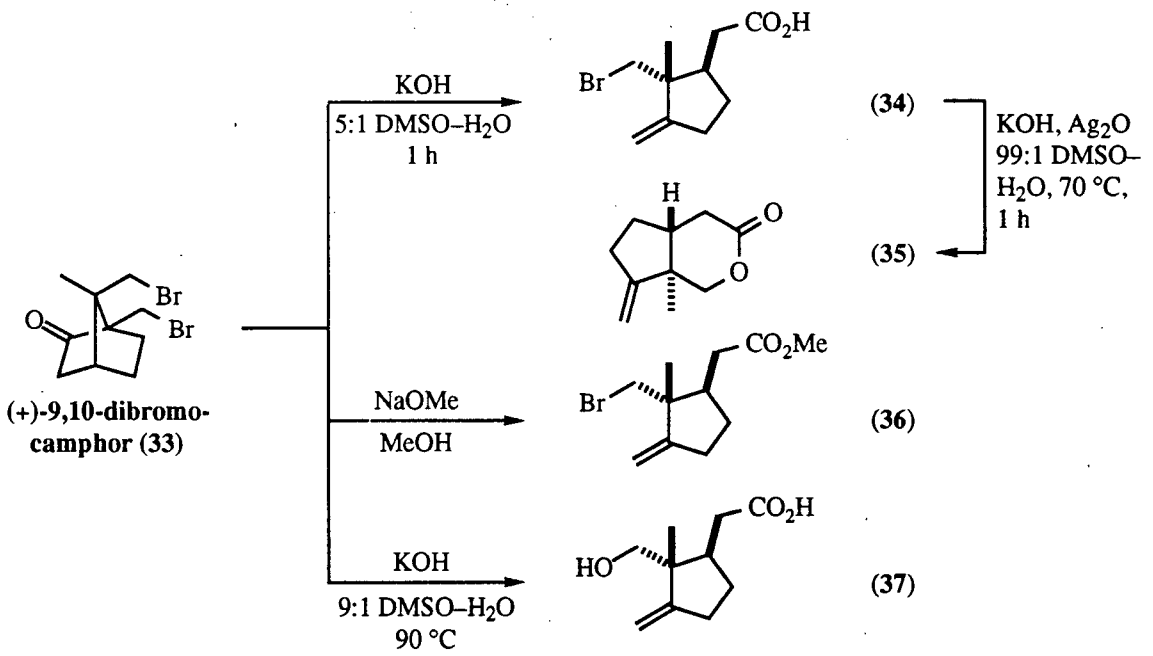
iv. C(9,10) Disubstitution: 9,10-Dibromocamphor (33) and Intermediates Derived from the Ring-Cleavage of 9,10-Dibromocamphor (33)

Prolonged treatment of (+)-*endo*-3,9-dibromocamphor (**22**) with bromine in chlorosulfonic acid yields (+)-3,9,10-tribromocamphor (**32**; Scheme 1.8). The reaction mechanism for C(10) bromination in this reaction is similar to that presented previously for C(10)-sulfonation (*cf.* Scheme 1.3). Chemoselective removal of the 3-bromo substituent using zinc dust in 1:1 acetic acid–diethyl ether provides (+)-9,10-dibromocamphor (**33**).[38,39]



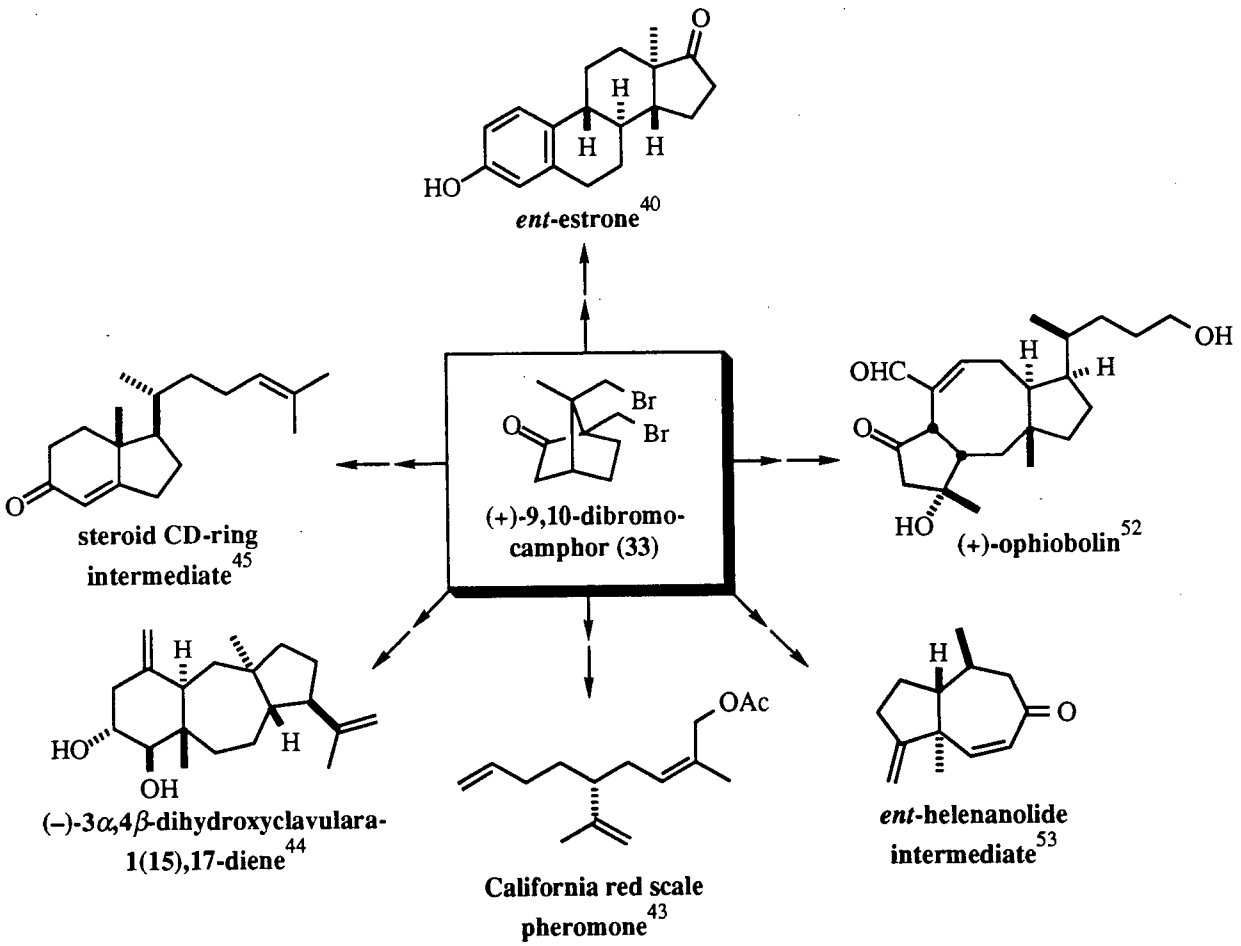
(i) Br_2, $ClSO_3H$, 5 h (ii) Br_2, $ClSO_3H$, 5–8 d (iii) Zn, 1:1 HOAc–Et_2O, 0 °C

Scheme 1.8. Preparation of (+)-9,10-Dibromocamphor (**33**).



Scheme 1.9. Base-Promoted Ring Cleavage of (+)-9,10-Dibromocamphor (**33**).[39]

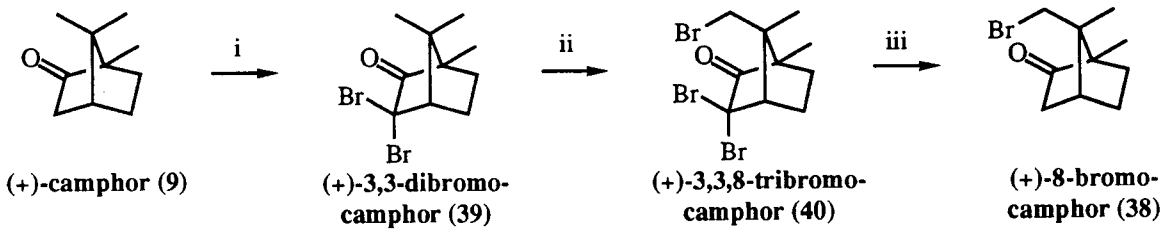
The considerable utility of 9,10-dibromocamphor (**33**) in synthesis derives from the presence of an α,α-disubstituted-β-bromocarbonyl unit, which promotes facile Grob fragmentation (Scheme 1.9) upon treatment with base (KOH or NaOMe) to yield bromo-acid **34**, bicyclic lactone **35**, bromo-ester **36**, or hydroxy-acid **37**.[39] The synthetic potential of these four derivatives **34** through **37** is illustrated in Scheme 1.10. Recent applications of (–)-9,10-dibromocamphor (***ent*-33**) in natural product synthesis are provided also in Chapters 2 and 3 of this thesis (*vide infra*).



Scheme 1.10. Use of (+)-9,10-Dibromocamphor (**33**) in Natural Product Synthesis.

v. C(8) Substitution: 8-Bromocamphor (38)

Of the various literature routes to 8-bromocamphor (**38**),[23] the most efficient involves the initial conversion of (+)-camphor (**9**) to (+)-3,3-dibromocamphor (**39**) using bromine (2–5 eq.) in acetic acid (Scheme 1.11). Further bromination of **39** using bromine in chlorosulfonic acid yields (+)-3,3,8-tribromocamphor (**40**). Chemoselective reduction of the C(3) *gem*-dibromo substituents with zinc dust in acetic acid affords enantiopure (+)-8-bromocamphor (**38**).[46]



(+)-camphor (9) **(+)-3,3-dibromo-camphor (39)** **(+)-3,3,8-tribromo-camphor (40)** **(+)-8-bromo-camphor (38)**

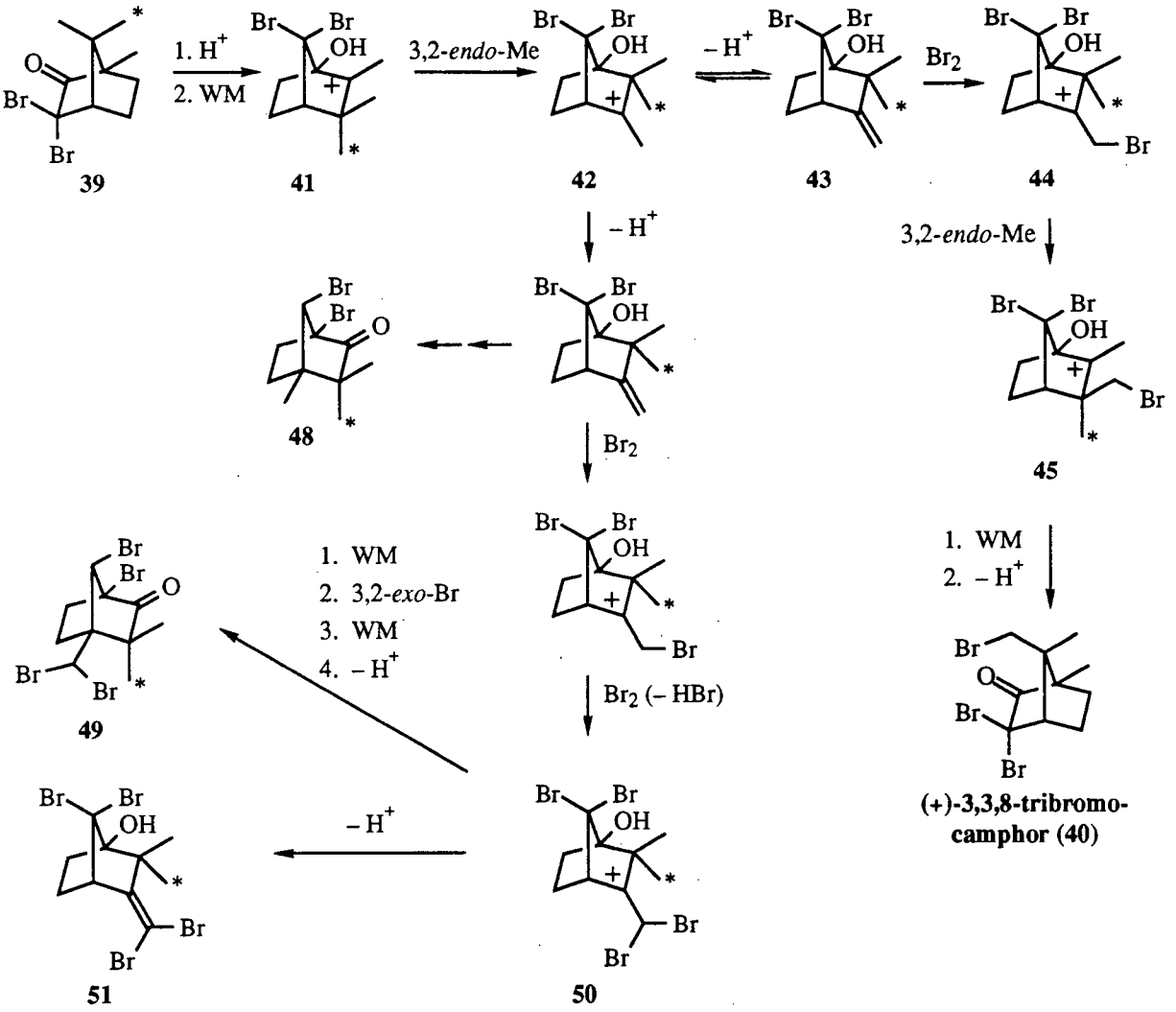
(i) Br_2, HOAc, 80 °C (ii) Br_2, $ClSO_3H$ (iii) Zn, HOAc.

Scheme 1.11. Preparation of (+)-8-Bromocamphor (**38**).

The proposed mechanism for the bromination of 3,3-dibromocamphor (**39**) is outlined in Scheme 1.12.[23] Protonation of 3,3-dibromocamphor (**39**) promotes Wagner-Meerwein rearrangement to yield the tertiary carbocation **41**. At this point, a 3,2-*endo*-methyl shift occurs to afford carbocation **42**, which is in equilibrium with the exocyclic alkene **43**. Bromination of **43** followed by successive 3,2-*endo*-methyl shift, Wagner-Meerwein rearrangement, and proton loss yields 3,3,8-tribromocamphor (**40**).

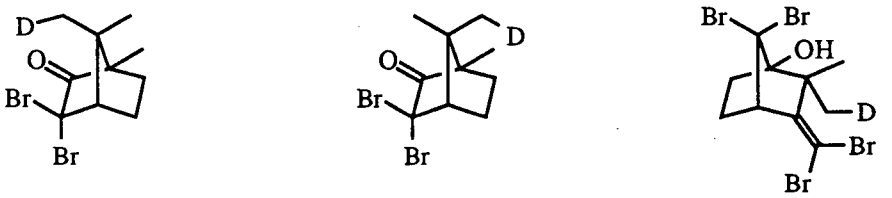
It is interesting to note that there is an almost exclusive preference for 3,2-*exo*-methyl shifts over 3,2-*endo*-methyl shifts in rearrangements involving bicyclo[2.2.1]heptyl carbocation intermediates.[47] Indeed it has been shown that in the absence of special structural features,[48] molecules tend to rearrange by circuitous routes[49] involving 3,2-*exo*-methyl shifts rather than simpler, more direct routes involving 3,2-*endo*-methyl shifts. However, experimental support for the proposed mechanism presented in Scheme 1.12 has been obtained through the results of comprehensive labelling studies. Investigations using 3,3-dibromo-8-deuteriocamphor (**46**) and

3,3-dibromo-9-deuteriocamphor (**47**)[46a,50] as starting materials have provided evidence that is completely consistent with the mechanism of C(8) bromination outlined in Scheme 1.12. In addition, we have isolated and characterized 1,7-dibromo-4-methylcamphenilone (**48**)[46c;d;51] and 1,7-dibromo-4-(bromomethyl)camphenilone (**49**; *cf.* Scheme 1.12),[46d,52] which are formed as by-products in the bromination of (+)-3,3-dibromocamphor (**39**). Recently, Antkowiak and



Scheme 1.12. Bromination of (+)-3,3-Dibromocamphor (**39**): Proposed Mechanism for the Formation of (+)-3,3,8-Tribromocamphor (**40**) and Accompanying By-products.
[*WM = Wagner-Meerwein rearrangement; 3,2*-endo-*Me = 3,2*-endo-*methyl shift; 3,2*-exo-*Br = 3,2*-exo-*bromide shift.*]

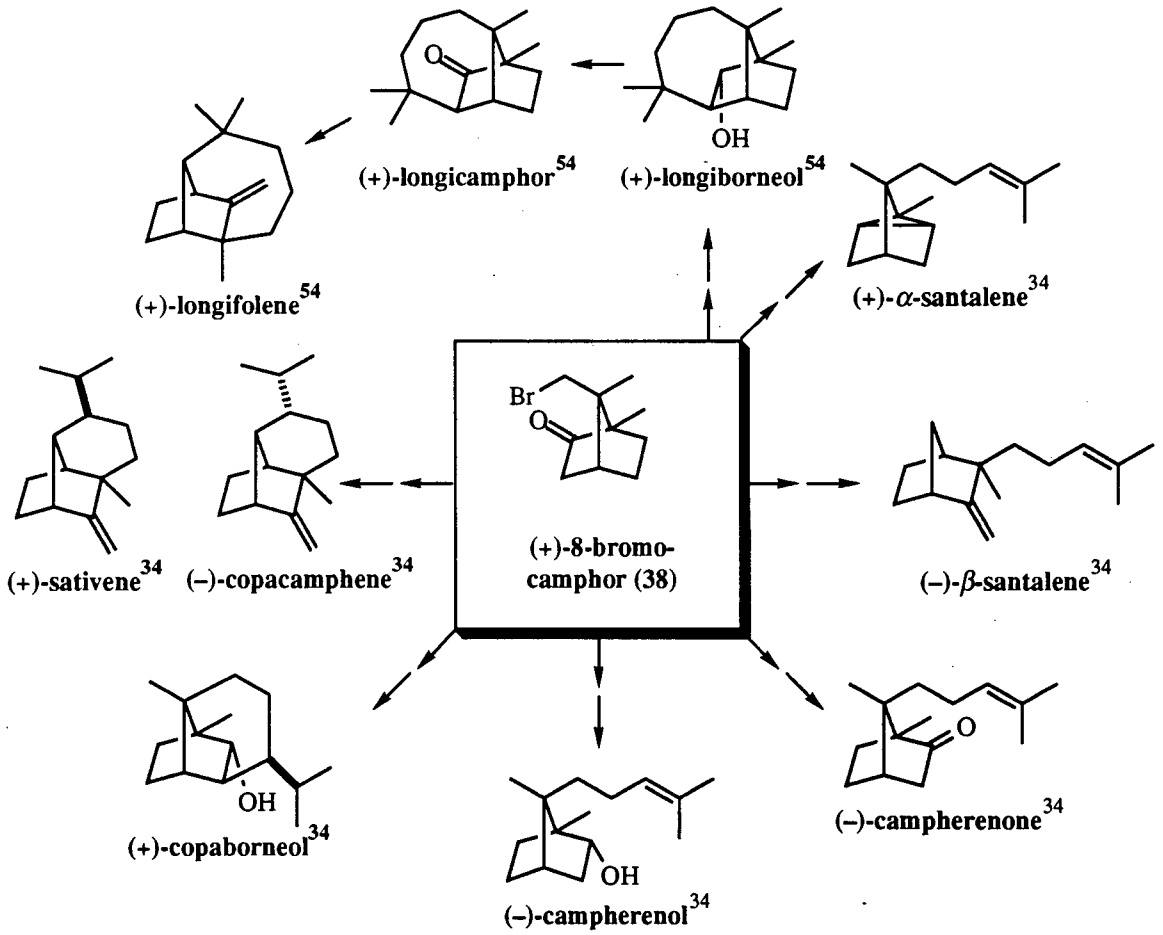
Antkowiak[53] re-investigated the bromination of 3,3-dibromocamphor (**39**) and isolated from the reaction mixture a minor by-product which they identified as the tetrabromo-alcohol **51**, presumably derived also from intermediate **50** (Scheme 1.12).



3,3-dibromo-8-deuterio-camphor (46)

3,3-dibromo-9-deuterio-camphor (47)

52

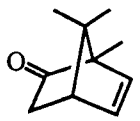


Scheme 1.13. Use of (+)-8-Bromocamphor (**38**) in Natural Product Synthesis.

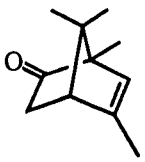
Furthermore, the use of 3,3-dibromo-9-deuteriocamphor (**47**) as an alternative bromination substrate led to the isolation of the deuterated tetrabromo-alcohol **52** (p. 17),[53] which provides additional support for the validity of the proposed mechanism as well as for the occurrence of a 3,2-*endo*-methyl shift during the bromination reaction. Finally, the application of 8-bromocamphor (**38**) to the synthesis of natural products is summarized in Scheme 1.13.

vi. C(5) Substitution: 5-Bromocamphor (53), 5-Ketobornyl Acetate (59) and 5-Ketoisobornyl Acetate (62)

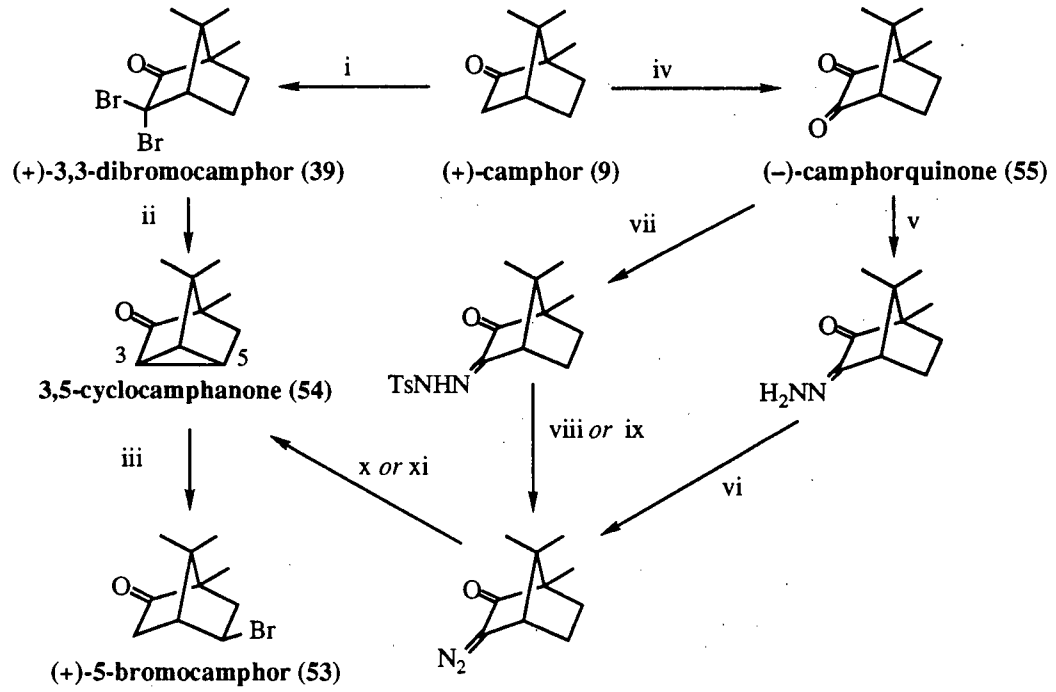
Among the several methods available[23] for the preparation of (+)-5-bromocamphor (**53**) from (+)-camphor (**9**; *cf.* Scheme 1.14), the most efficient and convenient[55] involves the initial conversion of (+)-camphor (**9**) to (+)-3,3-dibromocamphor (**39**) using bromine (2–5 eq.) in acetic acid. Treatment of (+)-3,3-dibromocamphor (**39**) with diethylzinc in refluxing benzene yields 3,5-cyclocamphanone (**54**), and subsequent reaction of **54** with hydrobromic acid in acetic acid yields (+)-5-bromocamphor (**53**). Our research group has demonstrated recently that 5-bromocamphor (**53**) can be converted also to (–)-5,6-dehydrocamphor (**56**)[56] and (–)-5-methyl-5,6-dehydrocamphor (**57**),[57] compounds that are envisioned to have considerable potential in terpenoid synthesis (*vide infra*).



(–)-5,6-dehydro-camphor (56)



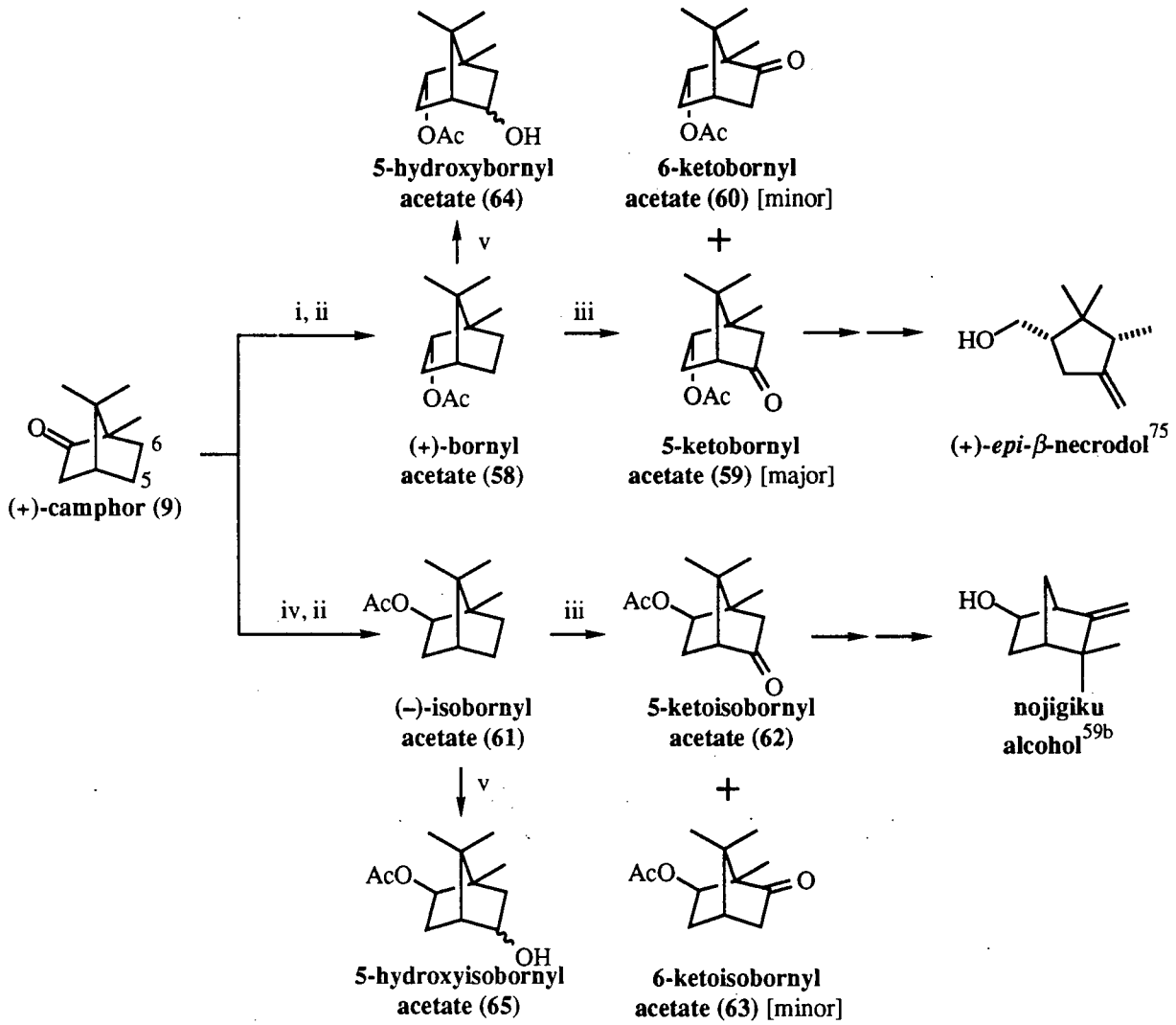
(–)-5-methyl-5,6-dehydrocamphor (57)



(i) Br_2, HOAc, reflux, 5 h (ii) Et_2Zn, C_6H_6, reflux, 24 h (iii) HBr (48%), HOAc, 65°C, 3 h (iv) SeO_2, Ac_2O (v) NH_2NH_2, EtOH (vi) HgO, C_6H_6, reflux, 8 h (vii) $TsNHNH_2$, HOAc (viii) NaOH, H_2O, pentane (ix) alumina (x) Cu, $(CH_2OH)_2$ (xi) $CF_3CF_2CF_2CO_2Ag$, THF.

Scheme 1.14. Preparation of (+)-5-Bromocamphor (**53**).

One can also introduce oxygen functionality into the C(5) position of camphor (**9**; Scheme 1.15). Direct oxidation of (+)-bornyl acetate (**58**)[57,58] with chromium(VI) oxide in acetic acid yields a mixture of 5-ketobornyl acetate (**59**) and 6-ketobornyl acetate (**60**), while similar oxidation of (–)-isobornyl acetate (**61**)[59] yields a 4:1 mixture of 5-ketoisobornyl acetate (**62**) and 6-ketoisobornyl acetate (**63**). In a related vein, C(5) hydroxylation of (+)-bornyl acetate (**58**) and (–)-isobornyl acetate (**61**) to yield 5-hydroxybornyl acetate (**64**) and 5-hydroxyisobornyl acetate (**65**), respectively, can also be effected microbiologically.[58g,60] Both 5-ketobornyl acetate (**59**) and 5-ketoisobornyl acetate (**62**) have been used in natural product synthesis, as illustrated in Scheme 1.15.

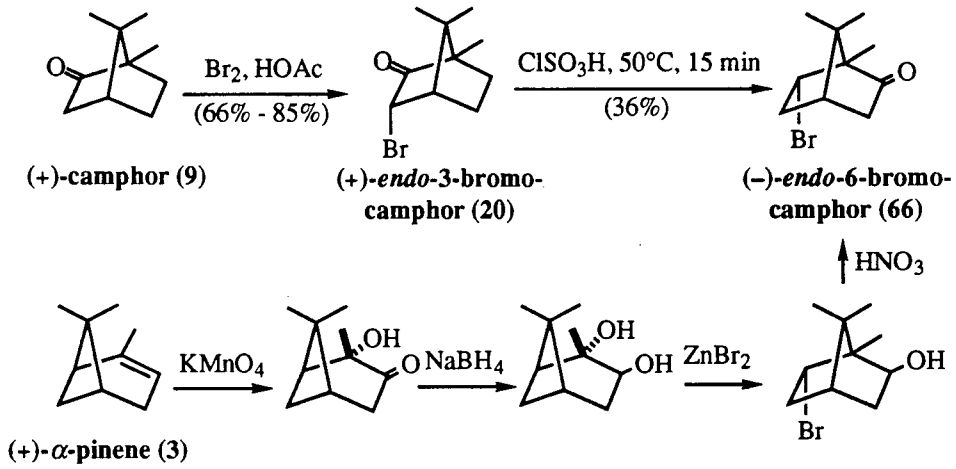


(i) Ca, NH_3 (ii) Ac_2O, C_5H_5N (iii) CrO_3, HOAc *or* CrO_3, Ac_2O, HOAc (iv) $LiAlH_4$, THF, 0 °C
(v) *Helminthosproium sativum* or *Fusarium culmorum.*

Scheme 1.15. Preparation and Use of C(5)-Oxygenated Camphor Derivatives in Natural Product Synthesis.

vii. C(6) Substitution: 6-Bromocamphor (66) and 5,6-Dehydrocamphor (56)

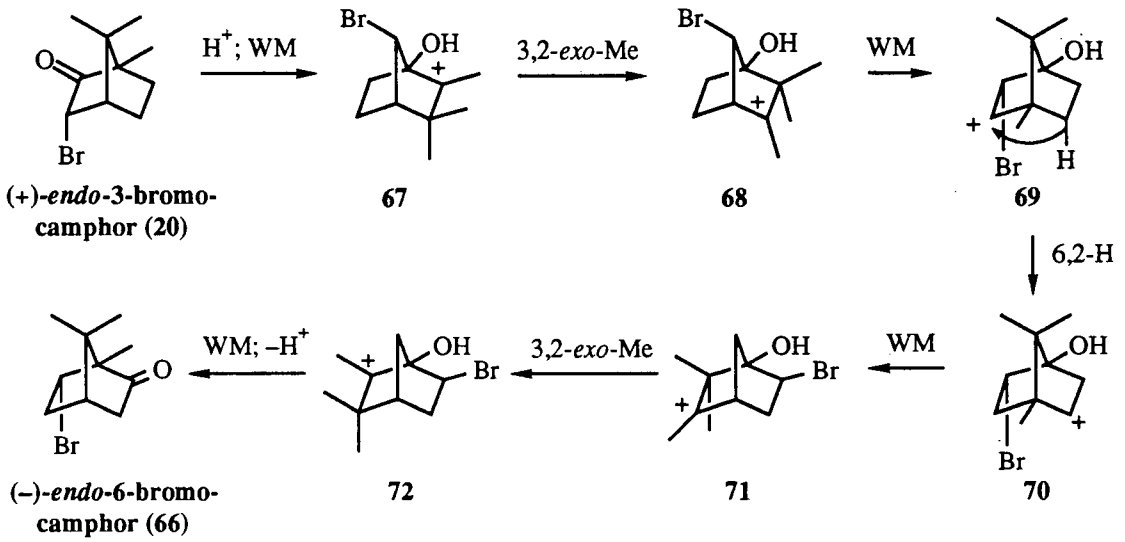
Two alternative methods[46a,61] for accessing (–)-*endo*-6-bromocamphor (**66**) are presented in Scheme 1.16. Of the two routes, the relatively low-yielding, acid-catalyzed rearrangement of (+)-*endo*-3-bromocamphor (**20**) to (–)-*endo*-6-bromocamphor (**66**)[46a] represents the most convenient method, and can also be carried out on relatively large scale (~120 g starting material) in the laboratory.



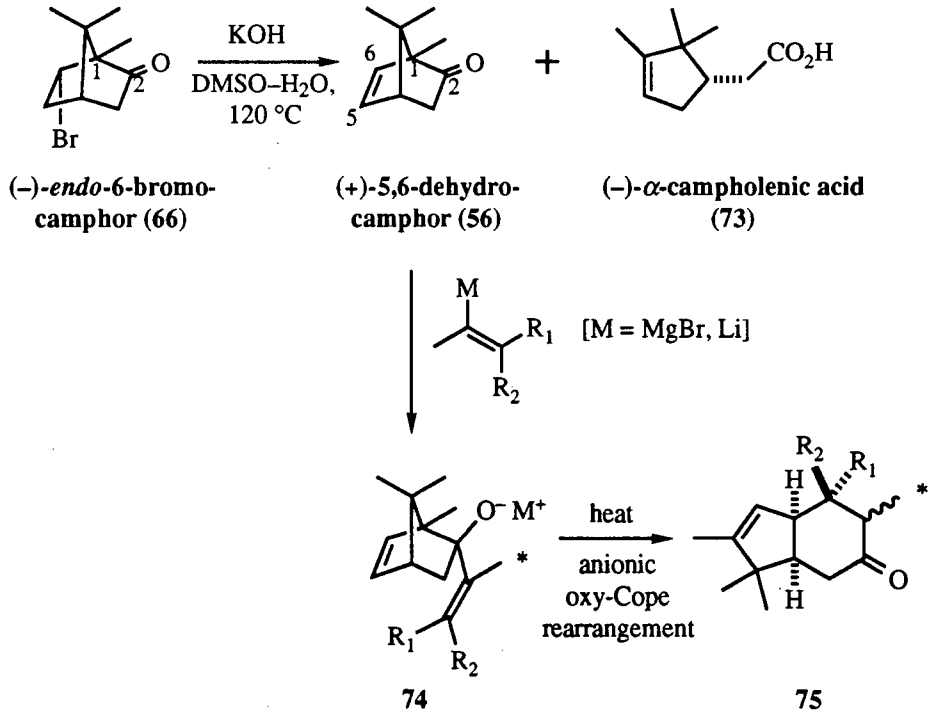
Scheme 1.16. Preparation of (–)-*endo*-6-Bromocamphor (**66**).

The mechanism that has been proposed to explain the acid-catalyzed rearrangement of (+)-*endo*-3-bromocamphor (**20**) is shown in Scheme 1.17, and like those presented in previous sections of this thesis, is thought to involve a series of skeletal rearrangements of the camphor structure. Protonation of **20** followed by a Wagner-Meerwein rearrangement yields the tertiary carbocation **67**. A 3,2-*exo*-methyl shift gives rise to an isomeric carbocation **68**, which undergoes a further Wagner-Meerwein rearrangement to yield the secondary carbocation **69**. A 6,2-hydride shift then occurs to afford the isomeric carbocation **70**. Finally, a sequence comprising a Wagner-Meerwein rearrangement, 3,2-*exo*-methyl shift, another Wagner-Meerwein rearrangement, and a final deprotonation step yields (–)-6-bromocamphor (**66**).

Dehydrobromination of (–)-6-bromocamphor (**66**) yields (+)-5,6-dehydrocamphor (**56**)[62] as well as a by-product, (–)-α–campholenic acid (**73**), that is derived from the cleavage of the C(1)–C(2) bond of (–)-6-bromocamphor (**66**; Scheme 1.18). The utility of 5,6-dehydrocamphor (**56**) as an intermediate in organic synthesis lies in the fact that addition of appropriate alkenyllithium or alkenyl Grignard reagents yields intermediates bearing a 1,5-diene sub-unit [*cf.* **74**] that can undergo subsequent anionic oxy-Cope rearrangement to yield substituted hydrindenones [*cf.* **75**].[62]

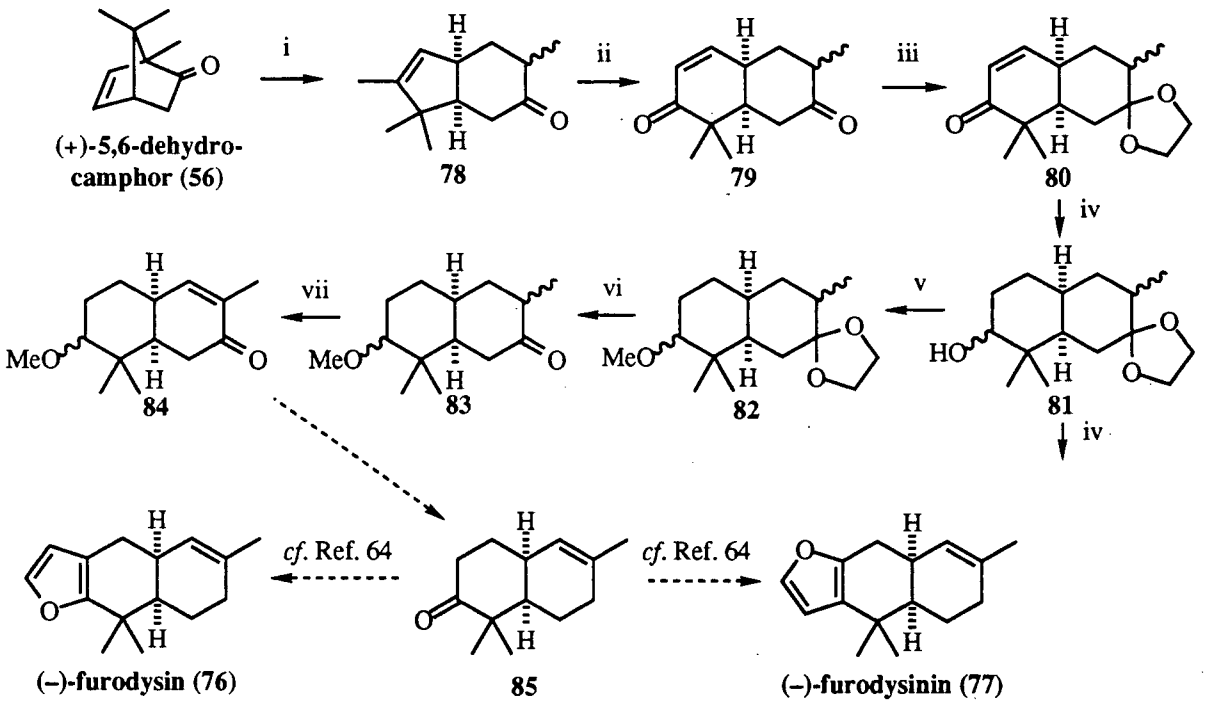


Scheme 1.17. Mechanism of the Acid-Catalyzed Rearrangement of (+)-*endo*-3-Bromocamphor (**20**) to (–)-*endo*-6-Bromocamphor (**66**) [*WM = Wagner-Meerwein rearrangement; 3,2*-exo-*Me 3,2*-exo-*methyl shift; 6,2-H = 6,2-hydride shift*].



Scheme 1.18. Preparation and Synthetic Potential of (+)-5,6-Dehydrocamphor (**56**).

The use of (+)-5,6-dehydrocamphor (**56**) in natural product synthesis is currently being evaluated in our laboratory. In a projected formal, enantiospecific synthesis[63] of the marine sesquiterpenoids furodysin (**76**) and furodysinin (**77**; Scheme 1.19), addition of isopropenylmagnesium bromide to (+)-5,6-dehydrocamphor (**56**) yields an alkoxy-1,5-diene intermediate that is not isolated but subjected to anionic oxy-Cope rearrangement to yield the diastereomeric hydrindenones **78**. Ozonolysis of **78** followed by intramolecular acid-catalyzed aldol condensation provided bicyclic keto-enones **79**. Chemoselective protection of the saturated

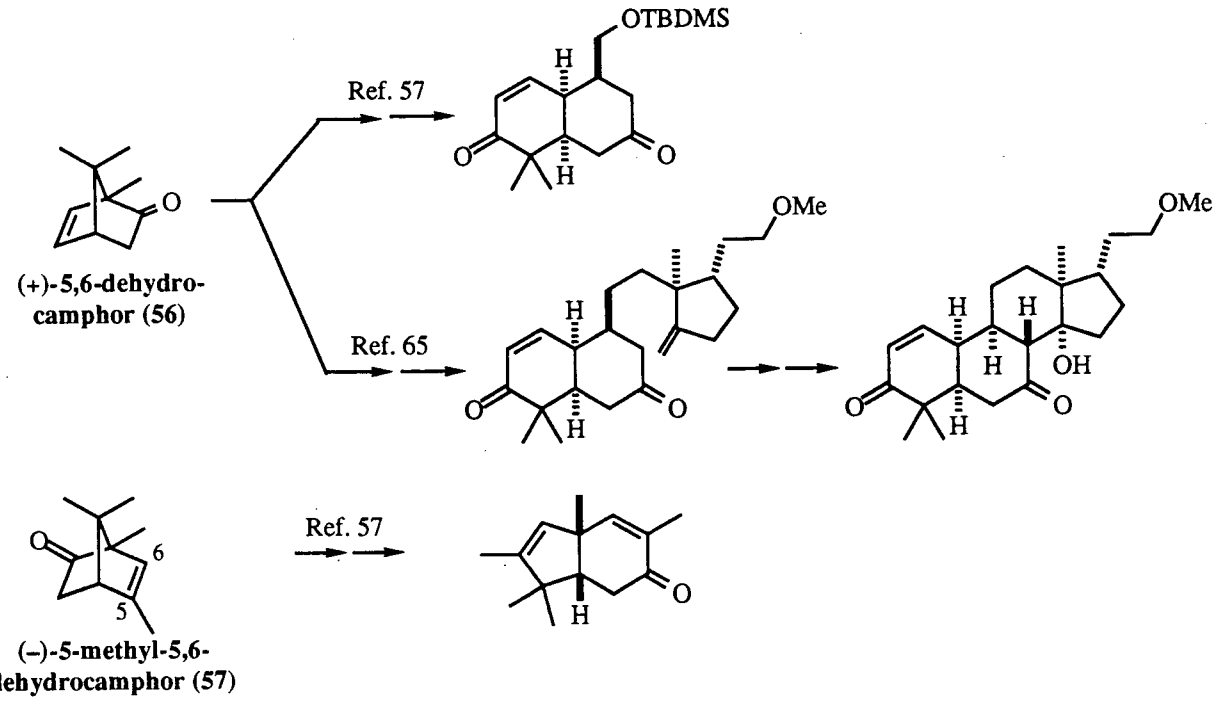


(i) $H_2C{=}C(CH_3)MgBr$, THF, 20 °C, 1.5 h; reflux, 5 h (ii) O_3, 1:1 CH_2Cl_2–MeOH; Zn, HOAc; *p*-TsOH, C_6H_6, reflux (iii) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux (iv) Li, NH_3, EtOH, THF (v) NaH, THF; CH_3I (vi) 1 M HCl, acetone (vii) $HN(SiMe_3)_2$, Me_3SiCl, LiI, CH_2Cl_2, 0 °C; PhSeCl, Et_2O, –78→0 °C; HOAc, H_2O_2, 0 °C→r.t.

Scheme 1.19. Money and Wong: Formal Synthetic Approach to (–)-Furodysin and (–)-Furodysinin.[63]

ketone functional group in **79** yielded the corresponding ketal-enones **80**, and subsequent lithium-liquid ammonia reduction of **80** gave the diastereomeric ketal-alcohols **81**. Protection of

the ketal-alcohols **81** as the corresponding methyl ethers **82** and ketal hydrolysis yielded the bicyclic ketones **83**, which were converted to the α,β–unsaturated ketones **84** ($HN(SiMe_3)_2$, Me_3SiI, Et_2O; PhSeCl; H_2O_2, HOAc). It is envisioned that deoxygenation at C(7) and functional group interconversion at C(4) should provide keto-alkene **85** which has already been converted to (±)-furodysin (**76**) and (±)-furodysinin (**77**) by Hirota and co-workers.[64] Other applications of 5,6-dehydrocamphor (**56**) and 5-methyl-5,6-dehydrocamphor (**57**) to terpenoid synthesis are illustrated in Scheme 1.20.[57,65]



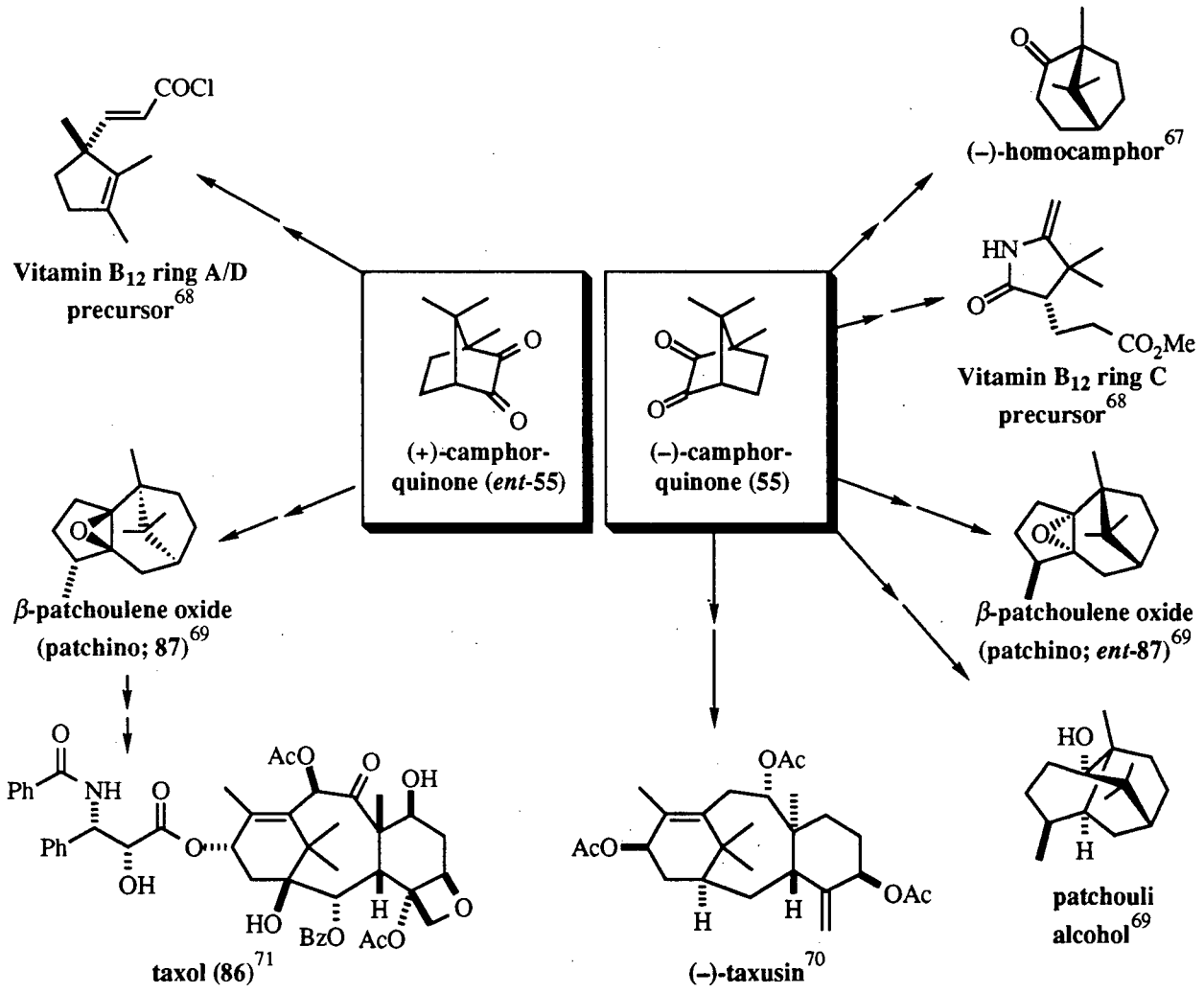
Scheme 1.20. Use of (+)-5,6-Dehydrocamphor (**56**) and (–)-5-Methyl-5,6-dehydrocamphor (**57**) in the Synthesis of Terpenoid Intermediates.

viii. C(3) Substitution: Camphorquinone (55)

The trivial conversions of (+)-camphor (**9**) to (+)-*endo*-3-bromocamphor (**20**) [Br_2 (1.1 eq.), HOAc, 80 °C] and (+)-3,3-dibromocamphor (**39**) [Br_2 (2–5 eq.), HOAc, 80 °C] have already been presented in Schemes 1.5 and 1.11, respectively, and will not be discussed further in this section. However, when (+)-camphor (**9**) is treated with excess selenium(IV) oxide in

refluxing acetic anhydride,[66] a tandem ene reaction–[2,3] sigmatropic rearrangement occurs to yield (–)-camphorquinone (**55**), a crystalline, bright yellow solid.

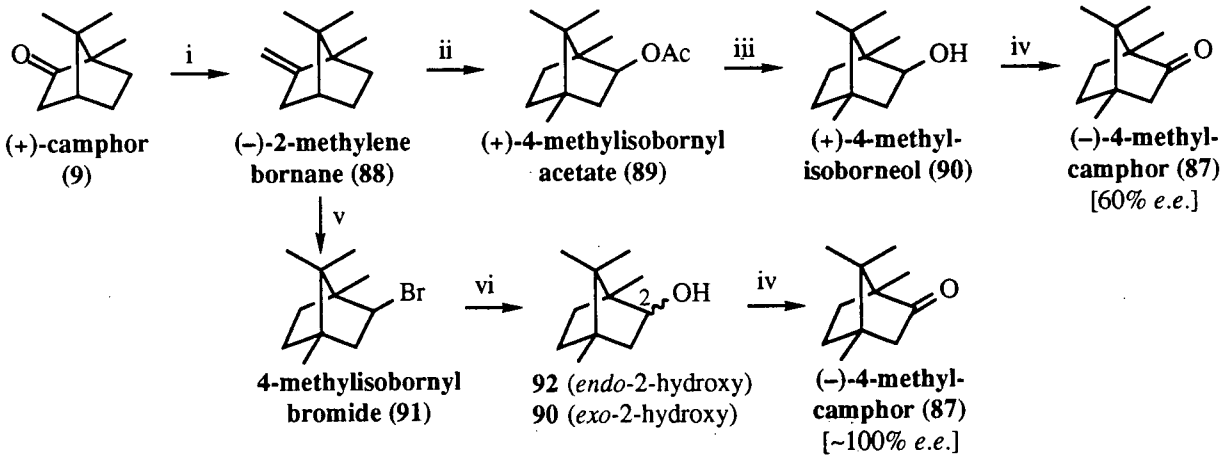
The use of camphorquinone (**55**) in natural product synthesis is summarized in Scheme 1.21. Of note, the enantiospecific total synthesis of taxol (**86**) by Holton and co-workers[71] employed β-patchoulene oxide (**87**),[69] derived from (+)-camphorquinone (***ent*-55**) and originally from (–)-camphor (***ent*-9**), as the starting material.



Scheme 1.21. Use of (+)- and (–)-Camphorquinone in Natural Product Synthesis.

ix. C(4) Substitution: 4-Methylcamphor (87)

Several research groups have reported synthetic routes to 4-methylcamphor (**87**).[23a] However, in none of these reports was the enantiopurity of the final product ascertained. Our studies on the acid-catalyzed rearrangement of 2-methylenebornane (**88**) [H_2SO_4, HOAc] culminated in a new synthesis[72] of (–)-4-methylcamphor (**87**) from enantiopure (+)-camphor (**9**; Scheme 1.22, top). As part of the same project, the enantiopurity of the synthesized (–)-4-methylcamphor (**87**) was determined by a NMR method employing a chiral lanthanide shift reagent. Although the specific rotation of our sample of **87** compared favorably with those quoted in the literature, the results of our NMR study suggested that our sample of (–)-4-methylcamphor (**87**), *as well as those obtained through the alternative literature methods*, was only 60% enantiopure! However, recent work in our laboratory has resulted in the development



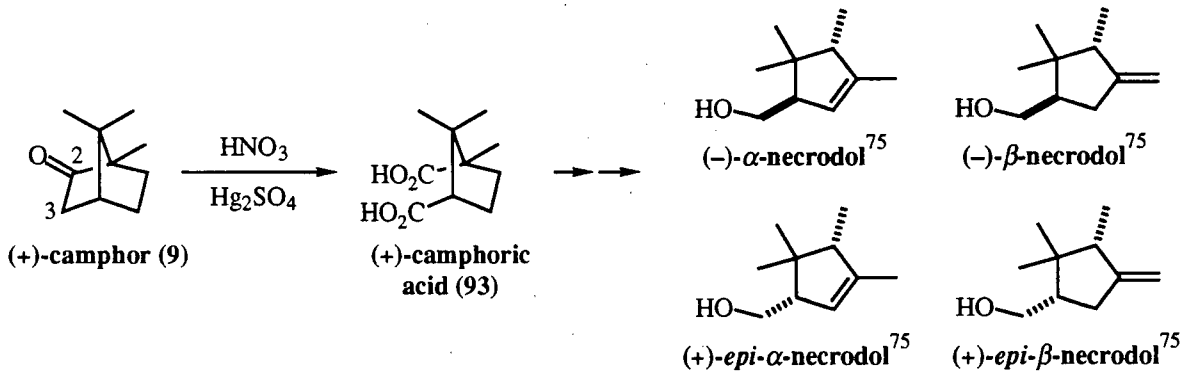
(i) $CH_3PPh_3^+Br^-$, BuLi, THF, reflux (ii) H_2SO_4, HOAc (iii) $LiAlH_4$, THF, 0 °C; H_2O (iv) CrO_3, aq. H_2SO_4, acetone, 0 °C (v) HBr, HOAc (vi) Mg, THF, 0 °C; O_2; H_3O^+.

Scheme 1.22. Preparation of (–)-4-Methylcamphor (**87**) from (+)-Camphor.[72,73]

of an improved route[73] that yields enantiopure (–)-4-methylcamphor (**87**; Scheme 1.22, bottom). A more detailed discussion of the enantiopurity and substitution chemistry of 4-methylcamphor (**87**) will be presented in Chapter 4 of this thesis.

x. Cleavage of the C(2)–C(3) Bond of Camphor

Oxidative cleavage of the C(2)–C(3) bond of (+)-camphor with nitric acid in the presence of mercury(II) sulfate[74] results in the formation of the monocyclic (+)-camphoric acid (**93**; Scheme 1.23). In addition, both enantiomers of camphoric acid (**93**) are commercially available, and Meinwald's recent synthesis of α-necrodol, β-necrodol, *epi*-α-necrodol, and *epi*-β–necrodol (Scheme 1.23)[75] serves to exemplify the use of camphoric acid (**93**) in natural product synthesis.



(+)-camphor (9) **(+)-camphoric acid (93)** **(–)-α-necrodol**[75] **(–)-β-necrodol**[75] **(+)-*epi*-α-necrodol**[75] **(+)-*epi*-β-necrodol**[75]

Scheme 1.23. Cleavage of the C(2)–C(3) Bond of Camphor; Use of Camphoric Acid (**93**) in Natural Product Synthesis.

In 1902, the British chemists Armstrong and Lowry remarked,[76] "No substance known to us suffers rearrangement of its parts and undergoes a complete change of type more readily than does camphor..." Now, in 1996, in view of what is known about the transformations of camphor, the modern chemist can still find reason to agree with Armstrong and Lowry. The preceding discussion was intended both as a cursory introduction to the fascinating chemistry of camphor and an exhibition of the variety of natural products into which the camphor structure has been successfully transformed. The interested reader can find more detailed and specialized treatments of these topics in recent reviews or monographs.[13,23] In the following chapters are described the results of some of our most recent investigations on the use of (–)-camphor (***ent*-9**) as an enantiopure starting material in pseudoguaianolide (Chapter 2) and limonoid (Chapter 3) synthesis, and on aspects of the unusual chemistry of 4-methylcamphor (**87**) and its derivatives (Chapter 4).

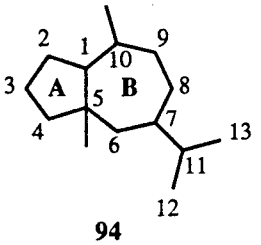
Chapter 2

A Formal, Enantiospecific Synthesis of Pseudoguaianolides

2. A Formal, Enantiospecific Synthesis of Pseudoguaianolides[120]

(a) Introduction

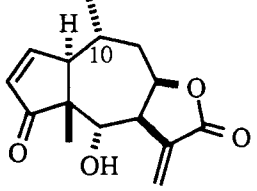
The pseudoguaianolides[77] are a relatively large group of tricyclic sesquiterpenoid lactones that have been isolated from plants of the Compositae family, which are found generally in the southern United States and Central America. The basic pseudoguaiane skeleton and num-



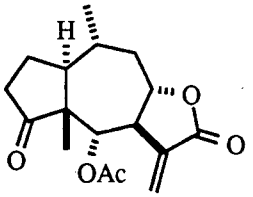
94

bering system is given in structure **94**. A common structural feature in many pseudoguaianolides (*cf.* Scheme 2.1) is a trans-fused bicyclic 5/7-ring system to which is fused a third ring that forms an α-methylene-γ-lactone unit. This family of compounds is further divided into two categories on the basis of the orientation of the C(10)-methyl group. Compounds (*cf.* Scheme 2.1) in which the C(10)-methyl group adopts an α-orientation are classified as helenanolides

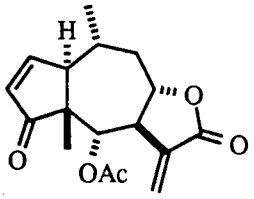
Helenanolides



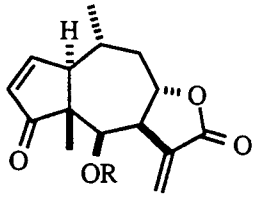
95: helenalin



96: carpesiolin

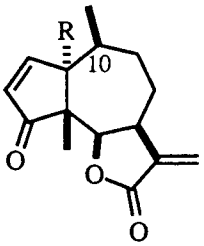


97: bigelovin

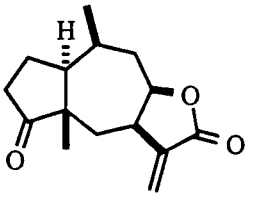


98: mexicanin I (R=H)
99: linifolin A (R=OAc)

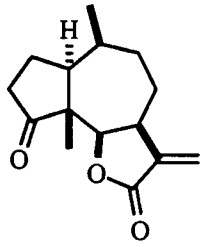
Ambrosanolides



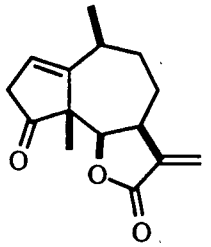
100: ambrosin (R = H)
101: parthenin (R = OH)



102: confertin



103: damsin



104: neoambrosin

Scheme 2.1. Structures of Representative Pseudoguaianolides

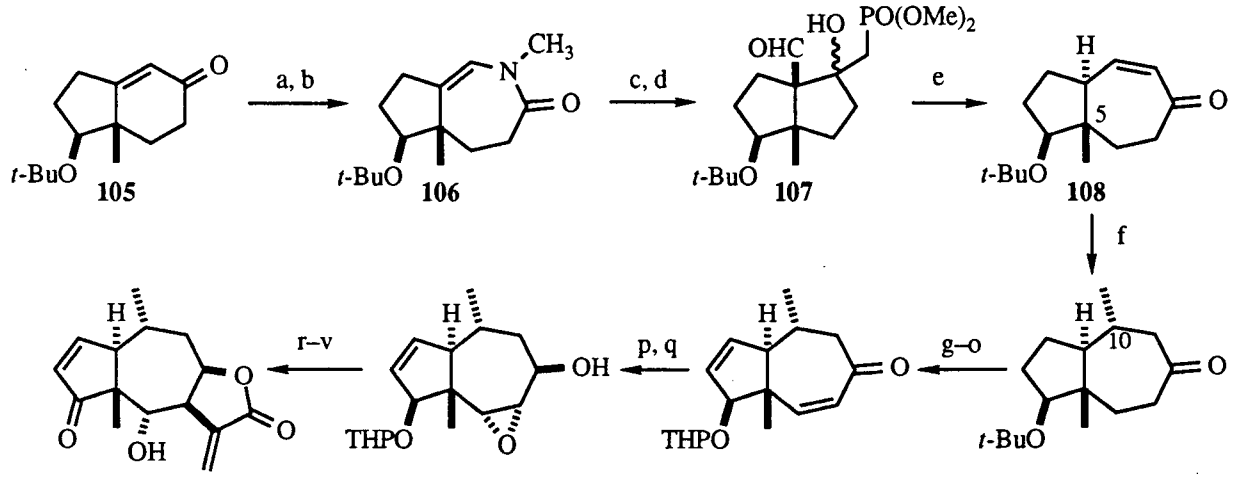
(after helenalin (**95**)) while compounds (*cf.* Scheme 2.1) in which the same methyl group adopts a β-orientation are classified as ambrosanolides (after ambrosin (**100**)).

(b) Previous Synthetic Routes to Pseudoguaianolides

Much work has been done to investigate the biological activity of members of the pseudoguaianolide family.[78] The cytotoxicity and anti-neoplastic activity of helenalin (**95**), for example, is attributed to the presence of the α-methylene-γ-lactone and ring A α,β–unsaturated cyclopentenone moieties in the molecule.[78] It has been discovered, generally, that many pseudoguaianolides display anti-inflammatory, cytotoxic, anti-leukemic, anti-tumor, anti-bacterial, dermatological, or insect antifeedant properties.[78] Consequently, much attention has been directed towards the total or partial synthesis of these compounds.[79–88] Present space limitations do not permit a comprehensive examination of the synthetic work done on this class of compounds. Fortunately, much of this work has already been reviewed.[79] Thus, for illustrative purposes, only a small subset of these syntheses will be highlighted.

In 1979, Roberts and Schlessinger reported a synthesis of (±)-helenalin (**95**)[81] from bicyclic enone **105** (Scheme 2.2). Bicyclic enone **105** was converted to the lactam **106** via a Beckman rearrangement reaction. Ring contraction of lactam **106** gave hydroxy-aldehyde **107**. Subsequent treatment of **107** with base promoted a retro-aldol/aldol reaction sequence that provided the hydrazulenone **108**. Conjugate addition of methylmagnesium bromide to enone **108** occurred from the face of the enone opposite the C(5) methyl group to afford ketone **109**. At this point the newly introduced stereocenter at C(10) had the correct (10*R*) configuration required for the synthesis of helenalin. Standard functional group manipulations were used to convert ketone **109** to dienone **110**. Addition of dilithioacetate to epoxide **111**, derived from **110**, followed by lactonization, α-methylenation, and oxidation completed the synthesis of (±)-helenalin (**95**).

The above synthesis of (±)-helenalin (**95**) served also to lay the foundation for syntheses of the ambrosanolides (±)-confertin (**102**) and (±)-damsin (**103**) by Quallich and Schlessinger.[82]

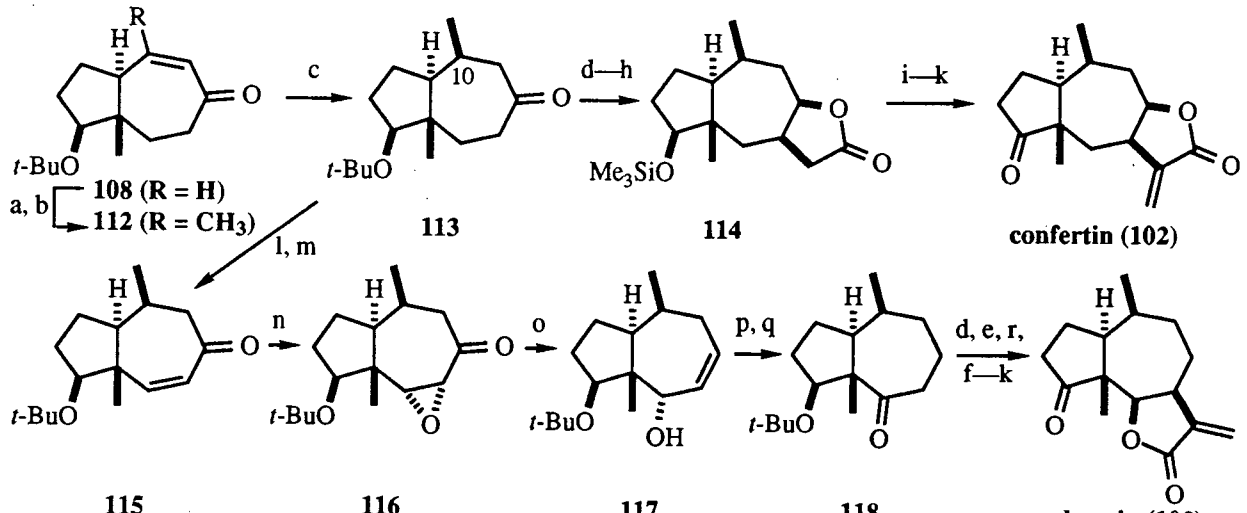


(a) $CH_3NHOH{\cdot}HCl$, C_5H_5N, 40 °C (b) *p*-TsCl, C_5H_5N (c) $LiCH_2PO(OMe)_2$, THF, –78 °C (d) NaOAc, HOAc, H_2O, Et_2O, 0 °C (e) *t*-BuOH, *t*-BuOK (f) CH_3MgBr, CuI, Me_2S, Et_2O, 0 °C (g) HCl, MeOH, 0 °C (h) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, 90 °C (i) PCC, NaOAc, CH_2Cl_2 (j) NaH, PhSSPh, DME, 45 °C; *m*-CPBA, CH_2Cl_2, 0 °C; $P(OMe)_3$, $PhCH_3$, 110 °C (k) DIBAL, $PhCH_3$, –40 °C (l) HCl, MeOH, 0 °C (m) DHP, *p*-TsOH, CH_2Cl_2, 0 °C (n) LiHMDS, Me_3SiCl, THF, –78 °C (o) $Pd(OAc)_2$, CH_3CN (p) NaOH, H_2O_2, MeOH, 40 °C (q) *i*-Bu_3Al, $PhCH_3$, 0 °C (r) $LiCH_2CO_2Li$, THF, HMPA, 50 °C; 6 N HCl (s) Me_3SiCl, Et_3N, THF (t) magnesium methoxycarbonate, 140 °C (u) 30% CH_2O, Et_2NH (v) MnO_2, $CHCl_3$, 45 °C

Scheme 2.2. Roberts and Schlessinger: Total Synthesis of (±)-Helenalin (**95**).[81]

Hydrazulenone **108**, which had been converted to (±)-helenalin (**95**) as described above, served as the starting point in the confertin synthesis (Scheme 2.3). Conjugate addition of lithium dimethylcuprate to **108** followed by a Saegusa reaction yielded enone **112**. Hydrogenation of enone **112** over a rhodium catalyst resulted in delivery of the elements of dihydrogen from the face of the enone opposite the C(5) methyl group to give ketone **113** with the correct (10*S*) ambrosanolide configuration. Alkylation of **113** with *t*-butyl iodoacetate, followed by installation of the α-methylene-γ-lactone unit yielded (±)-confertin (**102**).

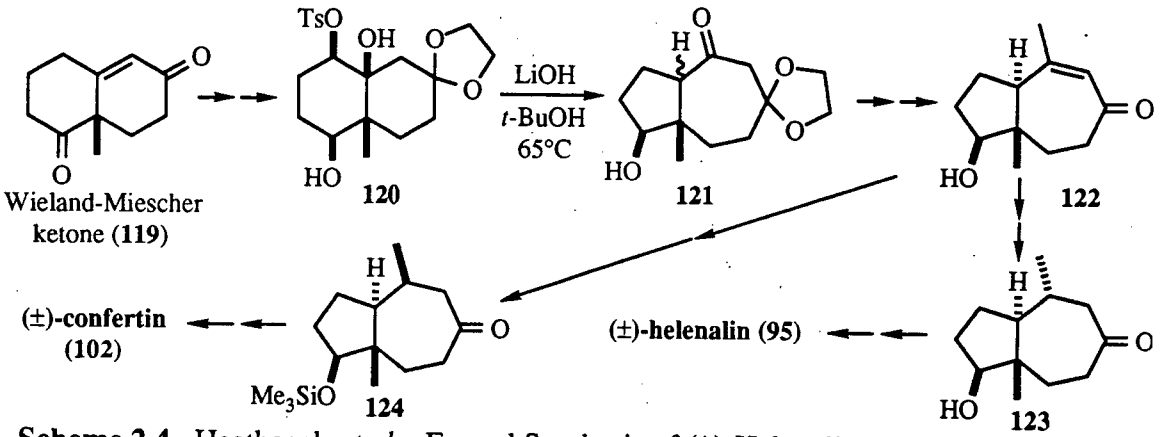
On the other hand, conversion of **113** to (±)-damsin (**103**) (Scheme 2.3)[82] required a 1,3-ketone transposition sequence. To this end, ketone **113** was converted to enone **115** via a Saegusa reaction and then to epoxy-ketone **116**. Application of the Wharton rearrangement afforded the allylic alcohol **117**. After transformation of **117** to ketone **118** through standard means, the remainder of the damsin synthesis was carried out in a manner analogous to that of the synthesis of (±)-confertin (**102**) described above (Scheme 2.3).[82]



(a) Me_2CuLi, THF, 0 °C; Me_3SiCl, Et_3N (b) $Pd(OAc)_2$, CH_3CN (c) H_2, Rh-Al_2O_3, EtOH (d) LiHMDS, t-BuO_2C-CH_2I, TMEDA, THF, –78 °C (e) Ac_2O, $HClO_4$, EtOAc, 0 °C (f) H_2, Rh-Al_2O_3, EtOH, 500 psi (g) KOH, MeOH, H_2O (h) Me_3SiCl, C_5H_5N (i) magnesium methoxycarbonate, 140 °C (j) 30% CH_2O, Et_2NH (k) Jones oxidation (l) LiHMDS, THF; Me_3SiCl, Et_3N, –78 °C (m) $Pd(OAc)_2$, CH_3CN (n) NaOH, H_2O_2, MeOH, H_2O (o) N_2H_4, HOAc, MeOH, Et_2O, 0 °C (p) H_2, Rh-Al_2O_3, Et_2O (q) Jones oxidation (r) Ac_2O, NaOAc, 140 °C.

Scheme 2.3. Quallich and Schlessinger: Total Synthesis of (±)-Confertin and (±)-Damsin.[82]

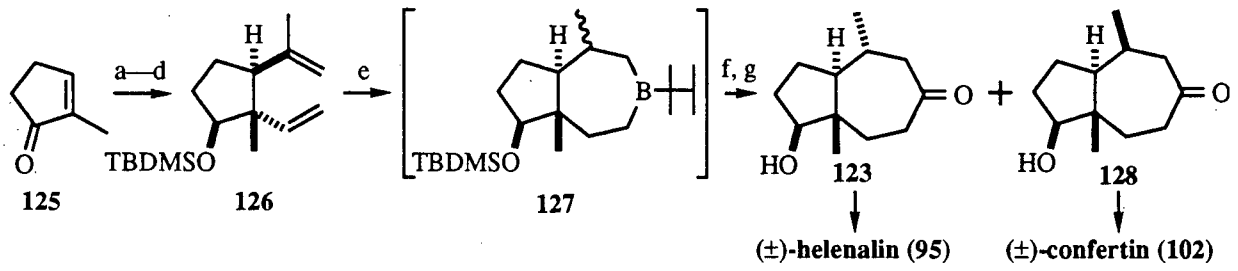
Heathcock and co-workers have completed a formal synthesis of (±)-helenalin (**95**; Scheme 2.4)[83] in which the Wieland-Miescher ketone (**119**) was used as the starting material. The synthetic route features a pinacol-pinacolone type rearrangement of a bicyclo[4.4.0]decanol **120** to a bicyclo[4.3.0]decanone **121** *en route* to the relay compound hydroxy-ketone **123**. The *t*-butyl ether of **123** had been converted previously to (±)-helenalin (**95**) by Roberts and Schlessinger,[81] as already outlined (Scheme 2.2).



Scheme 2.4. Heathcock *et al.*: Formal Synthesis of (±)-Helenalin; Total Synthesis of (±)-Confertin.[83]

Hydroxy-enone **122** was employed by Heathcock and co-workers also as an entry point into a total synthesis of (±)-confertin (**102**) (Scheme 2.4).[83] Derivatization of hydroxy-enone **122**, followed by alkylation with methyl bromoacetate allowed for the subsequent introduction of the α-methylene-γ-lactone unit of confertin (**102**).

Welch and Bryson employed a boron-mediated annulation reaction as the key step in their synthesis of (±)-confertin (**102**) and (±)-helenalin (**95**) (Scheme 2.5).[84] Conversion of 2-methyl-2-cyclopenten-1-one (**125**) to the silyloxy-diene **126** followed by boron-mediated annulation with thexylborane and desilylation yielded an 30:70 epimeric mixture of ketones **123** and **128**, respectively. The major epimer **128** was a relay compound in a formal synthesis of (±)-confertin (**102**) while the minor epimer **123** was a relay compound for the synthesis of (±)-helenalin (**95**). It was found that the stereoselectivity of the annulation reaction could be reversed if bromoborane were used in place of thexylborane. Under the bromoborane conditions the synthesis yielded a 77:23 mixture of the epimeric hydroxy-ketones **123** and **128**, respectively.

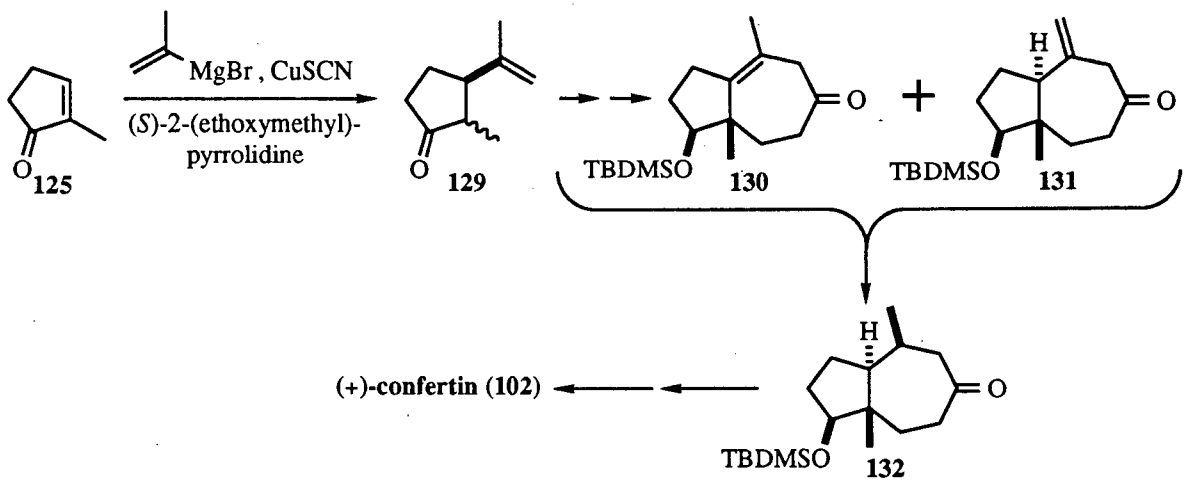


(a) $H_2C{=}C(CH_3)MgBr$, CuI, THF; $PhSeCH_2CHO$ (b) MsCl, Et_3N, CH_2Cl_2 (c) KBu_3BH, THF; NaOH, H_2O_2
(d) TBDMS-Cl, *i*-Pr_2NEt, DMF (e) Thx–BH_2, THF (**123/128** = 30:70) or $BrBH_2$, THF; (**123/128** = 77:23)
(f) NaCN; Tf_2O; NaOH, H_2O_2 (g) HF, CH_3CN; separation of epimers.

Scheme 2.5. Welch and Bryson: Formal Synthesis of (±)-Helenalin and (±)-Confertin.[84]

Quinkert and co-workers have published an enantioselective synthesis of (+)-confertin[85] (**102**) (Scheme 2.6) starting from 2-methyl-2-cyclopenten-1-one (**125**). Treatment of **125** with the organocuprate reagent derived from copper(I) thiocyanate, isopropenyllithium (2 eq.) and (*S*)-2-(ethoxymethyl)pyrrolidine resulted in the enantioselective conjugate addition of an isopropenyl group to **125** to afford an epimeric mixture of ketones **129** (88% *e.e.*). Ketones **129** were converted in several steps to a mixture of bicyclic silyloxy-enones **130** and **131**, and

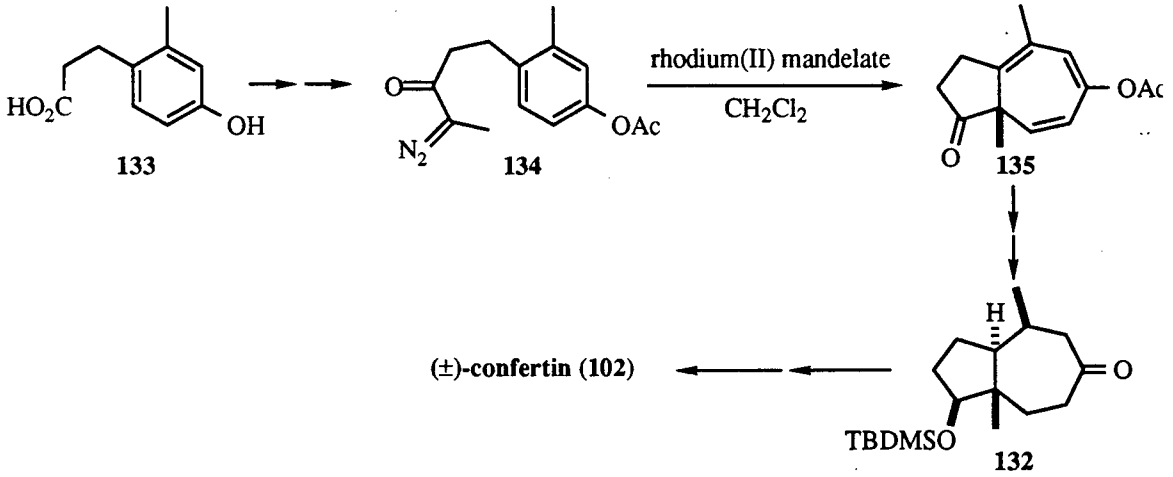
ultimately to silyloxy-ketone **132**. Because the *t*-butyl analogue (**113**) of silyloxy-ketone **132** had been converted previously to confertin (**102**; *cf.* Scheme 2.3),[82] the route by Quinkert and co-workers[85] constitutes a formal synthesis of (+)-confertin (**102**).



Scheme 2.6. Quinkert *et al.*: Formal, Enantioselective Synthesis of (+)-Confertin.[85]

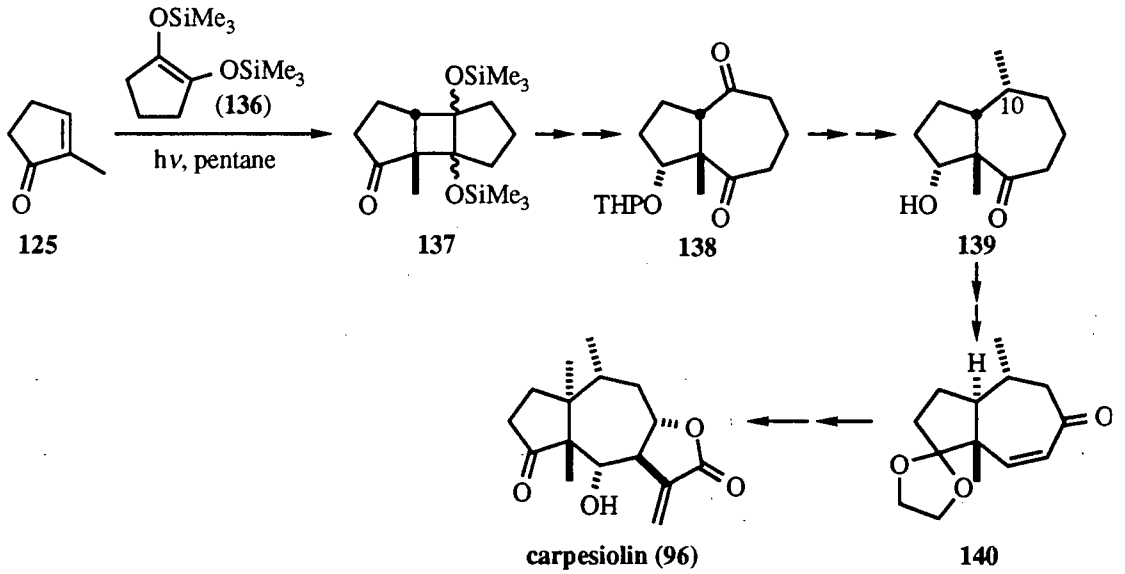
A further synthesis of (±)-confertin (**102**) is that reported by Kennedy and McKervey (Scheme 2.7).[86] The key step in this synthesis is a rhodium-mediated cyclization of the α–diazoketone **134**, derived from the dihydrocinnamic acid derivative **133**. The resulting acetoxy-ketone **135** was transformed into the bicyclic *t*-butyldimethylsilyloxy-ketone **132** using conventional methods. *t*-Butyldimethylsilyloxy-ketone **132** had already been converted into confertin (**102**) by Quinkert and co-workers (*cf.* Scheme 2.6);[85] thus, the route reported by Kennedy and McKervey constitutes a formal synthesis of (±)-confertin (**102**).[86]

Vandewalle and co-workers carried out the photocycloaddition of 2-methyl-2-cyclopenten-1-one (**125**) to 1,2-bis(trimethylsilyloxy)cyclopent-1-ene (**136**) as the initial step in their synthesis of the helenanolide (±)-carpesiolin (**96**; Scheme 2.8).[87] Subsequent desilylation, diol cleavage, and protection of the A-ring hydroxyl group as a tetrahydropyranyl ether provided

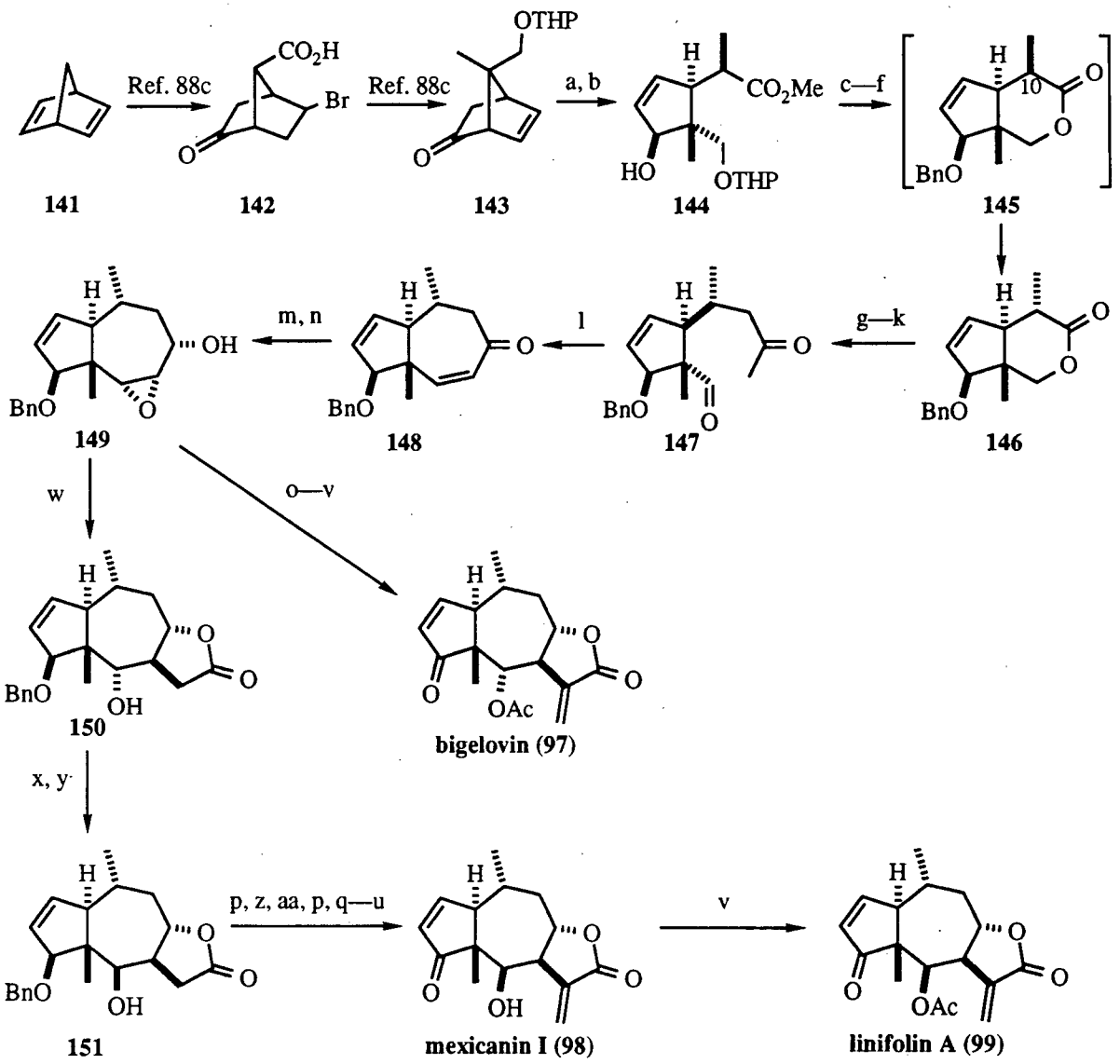


Scheme 2.7. Kennedy and McKervey: Formal Synthesis of (±)-Confertin.[86]

the bicyclic diketone **138.** Regioselective methylenation of **138**, followed by tetrahydropyranyl ether hydrolysis and catalytic hydrogenation yielded the hydroxy-ketone **139** in which the desired (10*R*) ambrosanolide stereochemistry was now present. Conversion of **139** to ketal-enone **140** followed by installation of the α–methylene-γ-lactone unit completed the synthesis of (±)-carpesiolin (**96**).[87]



Scheme 2.8. Vandewalle *et al.*: Total Synthesis of (±)-Carpesiolin.[87]



(a) LDA, THF, 0 °C; CH_3I, 0—20 °C (b) NaOH, H_2O_2, 1:1 MeOH-H_2O, 0 °C (c) NaH, THF, HMPA; $PhCH_2Br$, Bu_4NI (d) *p*-TsOH, MeOH, 0 °C (e) KOH, EtOH; H_3O^+ (f) *p*-TsCl, DBU, $PhCH_3$, reflux (g) DIBAL, $PhCH_3$, –78 °C (h) $MeOCH_2PPh_3^+ Cl^-$, *t*-AmONa, C_6H_6 (i) 1 N HCl (j) CH_3Li, Et_2O, –20—>0 °C (k) PCC, NaOAc, CH_2Cl_2 (l) 5% KOH, MeOH; *p*-TsOH, C_6H_6, reflux (m) $LiAlH_4$, THF, 0 °C (n) *m*-CPBA, CH_2Cl_2 (o) $LiCH_2CO_2Li$, DME, 43—>55 °C; Li, NH_3 (p) DHP, *p*-TsOH, CH_2Cl_2, 0 °C—>r.t. (q) LDA, THF, –78 °C; CH_2O, –25 °C (r) MsCl, C_5H_5N, 0 °C (s) DBU, C_6H_6 (t) H_2O, HOAc (2:3) (u) MnO_2, CH_2Cl_2–C_6H_6 (v) Ac_2O, DMAP, C_5H_5N (w) $LiCH_2CO_2Li$, DME, 43—>55 °C (x) Jones reagent (y) $NaBH_4$, EtOH, 0 °C (z) KOH, DME; Li, NH_3; NH_4Cl (aa) DCC, CH_2Cl_2.

Scheme 2.9. Grieco *et al.*: Total Synthesis of (±)-Bigelovin, (±)-Mexicanin I, and (±)-Linifolin A.[88]

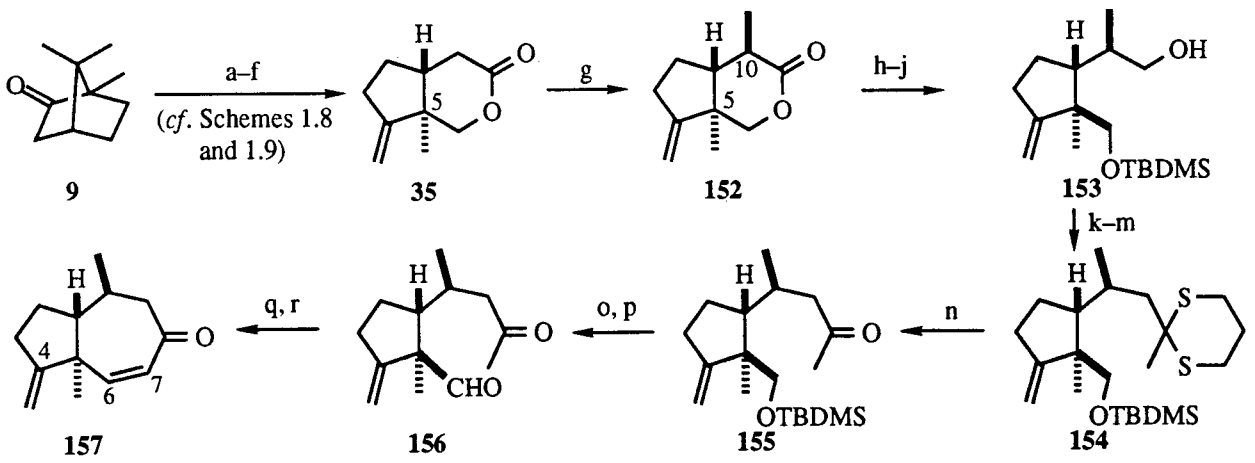
The synthesis of the helenanolides (±)-bigelovin (**97**), (±)-mexicanin I (**98**), and (±)-linifolin A (**99**) by Grieco and co-workers is summarized in Scheme 2.9. Norbornadiene (**141**) was converted in four steps to the bromo-keto-acid **142** and in a further seven steps to the bicyclic ketone **143**. Subsequent alkylation of **143** with methyl iodide followed by Baeyer-Villiger oxidation and esterification yielded hydroxy-ester **144**. Hydroxy-ester **144** was transformed presumably into benzyloxy-lactone **145** but as a result of the lactonization reaction conditions, further epimerization of the C(10) methyl group (pseudoguaianolide numbering) in **145** occurred to yield the diastereomeric benzyloxy-lactone **146** in which the correct (10*S*) configuration required for helenanolide synthesis is present. Subsequent elaboration of **146** to the keto-aldehyde **147** permitted the aldol ring closure of **147** to provide the bicyclic enone **148**. It is relevant to note at this point that the tetrahydropyranyl ether analogue of **148** was an intermediate in Roberts and Schlessinger's synthesis of (±)-helenalin (**95**; *cf.* Scheme 2.2).[81]

Enone **148** was converted to the epoxy-alcohol **149**. Addition of dilithioacetate followed by lactonization yielded the tricyclic hydroxy-lactone **150** which was converted to (±)-bigelovin (**97**) via a route similar to those presented above (*cf.* Schemes 2.2 and 2.3). On the other hand, epimerization of the C(6)-hydroxyl group in **150** via an oxidation-reduction sequence, followed by introduction of the exocyclic methylene group and functional group manipulations made possible the synthesis of the helenanolides (±)-mexicanin I (**98**) and (±)-linifolin (**99**) by a method (Scheme 2.9) similar to that followed above for the bigelovin (**97**) synthesis.[88]

An examination of the synthetic schemes presented above reveals that all the syntheses except for Quinkert's synthesis of (+)-confertin (**102**; Scheme 2.6)[85] yield racemic products. In fact, the recent report of the enantiospecific synthesis of (–)-neoambrosin (**104**), (–)-parthenin (**103**), and (+)-dihydroisoparthenin by Asaoka and co-workers[80t] represents only the second enantioselective or enantiospecific synthesis of pseudoguaianolides. The paucity of synthetic routes to enantiopure pseudoguaianolides prompted our research group to devise a new enantiospecific route (Scheme 2.10) to the *ent*-helenanolides from (+)-camphor (**9**). Previously, we have demonstrated that (+)-9,10-dibromocamphor (**33**),[38] derived from (+)-camphor (**9**; *cf.*

Scheme 1.8), can undergo facile ring cleavage to yield a variety of cyclopentanoid derivatives, including the bicyclic lactone **35** (*cf.* Scheme 1.9).[39] In noting the structural similarity between lactone **35** and the A ring of the pseudoguaianolides, and that the relative configurations of the two stereocenters in lactone **35** are the same as those present at C(1) and C(5) of most pseudoguaianolides, we considered lactone **35** to be a potential intermediate in our projected synthesis of the *ent*-helenanolides (*cf.* Scheme 2.10).[42]

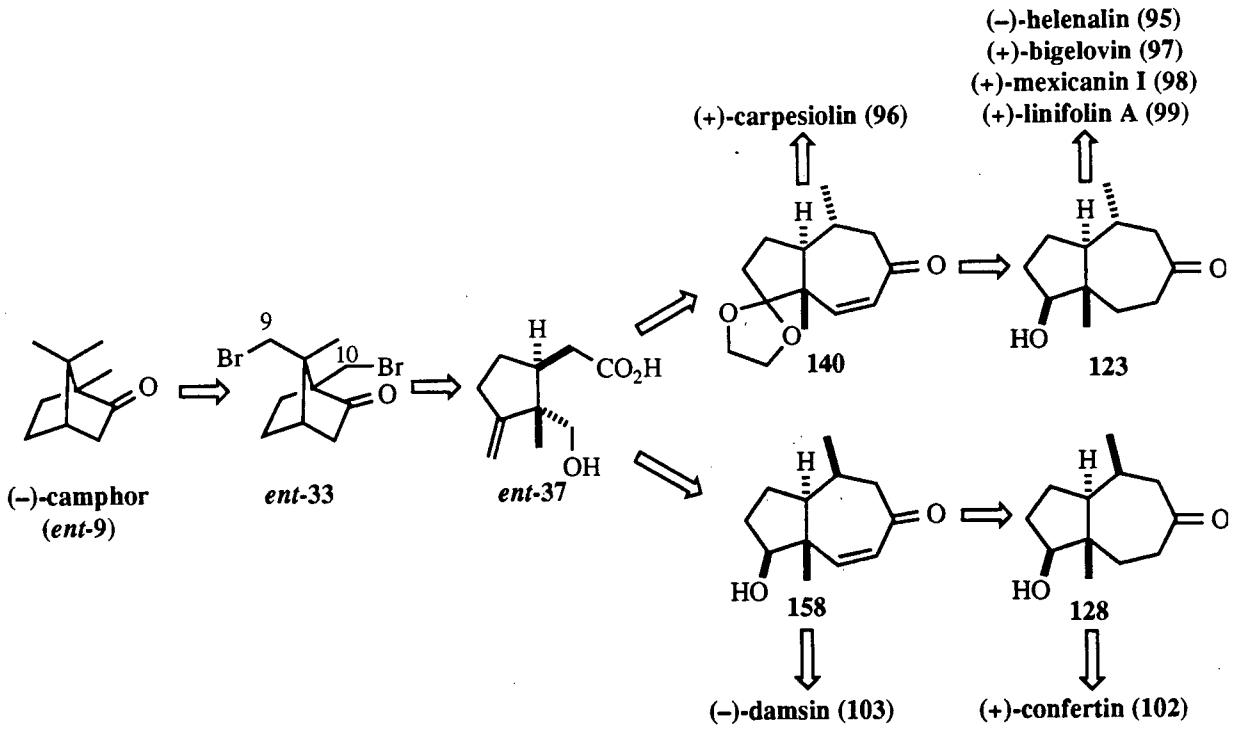
In the event, alkylation of lactone **35** with methyl iodide occurred stereoselectively from the face opposite the C(5) methyl group to yield lactone **152**. Transesterification of lactone **152** with methanol, followed by protection of the primary alcohol group as the corresponding *t*-butyldimethylsilyl ether and reduction of the methyl ester group yielded alcohol **153**. Conversion of alcohol **153** to the corresponding iodide followed by alkylation with 2-lithio-2-methyl-1,3-dithiane yielded the dithiane derivative **154**. Hydrolysis of the thioketal group in **154** yielded silyloxy-ketone **155**. Subsequent hydrolysis of the silyl protective group and oxidation of the resulting primary alcohol group afforded keto-aldehyde **156**, and intramolecular aldol condensation yielded the bicyclic dienone **157**.



(a) Br_2, HOAc, 80 °C (b) Br_2, $ClSO_3H$, 5 h (c) Br_2, $ClSO_3H$, 5–8 d (d) Zn, 1:1 HOAc–Et_2O, 0 °C (e) KOH, 5:1 DMSO–H_2O, 1 h (f) KOH, Ag_2O, 99:1 DMSO–H_2O, 70 °C, 1 h (g) LDA, THF, –78 °C; CH_3I, –78 °C →r.t. (h) MeOH, conc. H_2SO_4 (i) TBDMS-Cl, DMAP, CH_2Cl_2 (j) $LiAlH_4$, THF, 0 °C (k) MsCl, Et_3N, CH_2Cl_2 (l) NaI, HMPA (m) 2-lithio-2-methyl-1,3-dithiane, THF (n) CH_3I, $CaCO_3$, CH_3CN–H_2O, 80 °C (o) TBAF, THF (p) PDC, CH_2Cl_2 (q) KOH, MeOH (r) MsCl, Et_3N, DMAP, CH_2Cl_2; DBU.

Scheme 2.10. Money *et al.*: An Enantiospecific Synthetic Approach to the Helenanolides.[42]

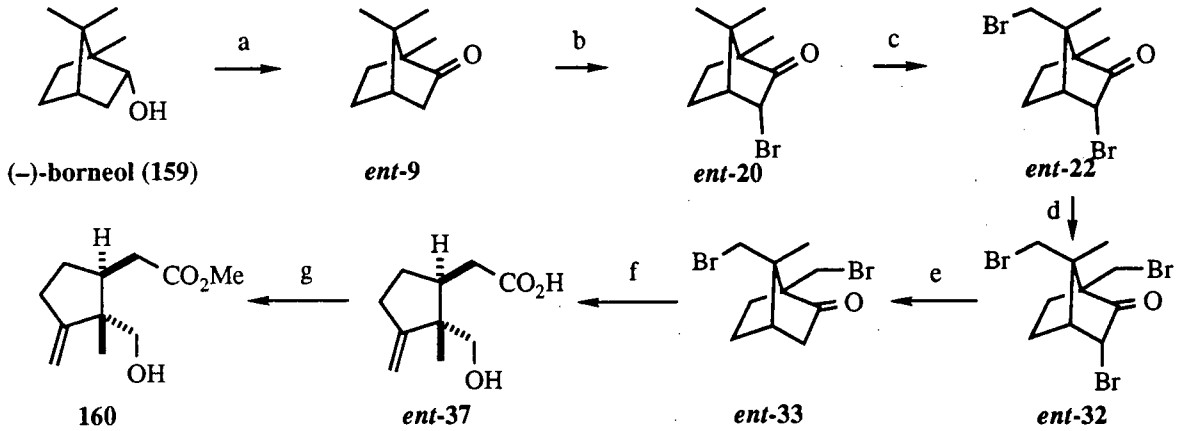
Examination of the pseudoguaianolide structures in Scheme 2.1 reveals that all examples bear a carbonyl group at C(4). In retrospect, the utility of dienone **157** in pseudoguaianolide synthesis is limited because it is difficult to introduce oxygen functionality at C(4) selectively. For example, ozonolysis of **157** would lead to oxidative cleavage of not only the exocyclic methylene group at C(4), but also the C(6)–C(7) double bond. Consequently, we revised our synthetic strategy by proposing an alternate route that could provide access to not only the helenanolides, but also the ambrosanolides. Instead of employing lactone **35** as an intermediate in our revised route, we chose to exploit the synthetic potential of hydroxy-acid ***ent*-37**,[39] derived from (–)-9,10-dibromocamphor (***ent*-33**) and in turn, from (–)-camphor (***ent*-9**). We envisioned that by converting hydroxy-acid ***ent*-37** subsequently to ketal-enone **140**, hydroxy-enone **158**, hydroxy-ketone **123** and hydroxy-ketone **128**, a formal, enantiospecific synthesis of the helenanolides (+)-carpesiolin (**96**),[87] (–)-helenalin (**95**),[81,83] (+)-bigelovin (**97**),[88] (+)-mexicanin I (**98**),[88] and (+)-linifolin A (**99**),[88] and the ambrosanolides (+)-confertin (**102**)[82] and (–)-damsin (**103**)[82] would be achieved. Our results in this area are summarized in the following section.



Scheme 2.11. Proposed Formal, Enantiospecific Syntheses of Helenanolides and Ambrosanolides Using Camphor as an Enantiopure Starting Material.

(c) An Enantiospecific Synthesis of Helenanolides

Structural considerations (*cf.* Scheme 2.10) suggested that we choose (–)-camphor (***ent*-9**) as our starting material. Although (–)-camphor (***ent*-9**) is commercially available, it is about five times more expensive than (+)-camphor (**9**). For this reason we prefer to prepare (–)-camphor (***ent*-9**) from the less expensive, commercially available (–)-borneol (**159**) instead (*cf.* Scheme 2.12). Thus, (–)-borneol (**159**) was oxidized using Jones reagent (CrO_3, aqueous H_2SO_4, acetone) at 0 °C to provide (–)-camphor (***ent*-9**) in excellent yield (>95%).[89]



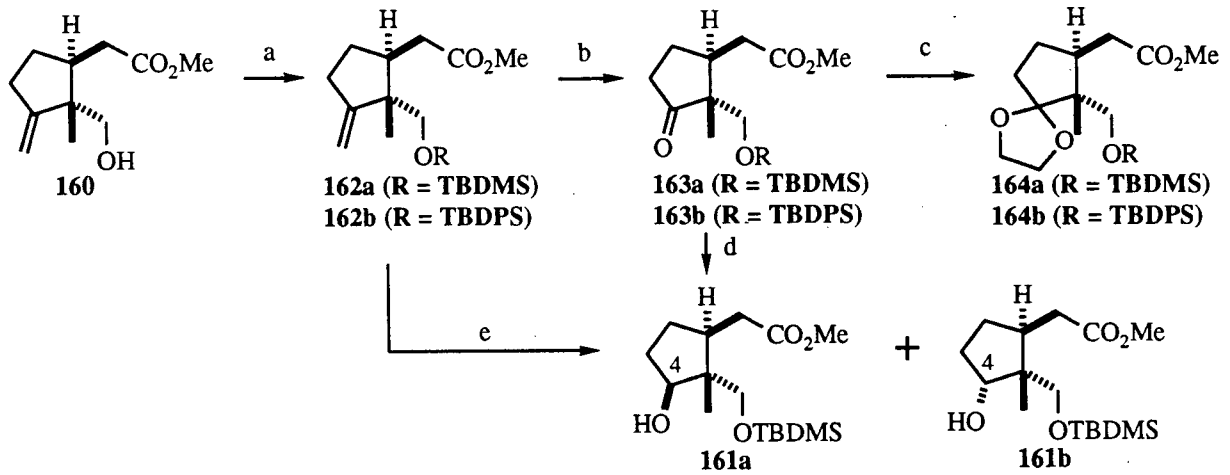
(a) CrO_3, aq. H_2SO_4, acetone, 0 °C [97%] (b) Br_2, HOAc, 80 °C [71%] (c) Br_2, $ClSO_3H$, 5 h [65%] (d) Br_2, $ClSO_3H$, 5–8 d (e) Zn, 1:1 Et_2O–HOAc, 0 °C [65% from ***ent*-22**] (f) KOH, 9:1 DMSO–H_2O, 90 °C [90%] (g) K_2CO_3, DMF; CH_3I [95%].

Scheme 2.12. Conversion of (–)-Borneol to (–)-Hydroxy-ester **160**.[38,39]

Treatment of (–)-camphor (***ent*-9**) with one equivalent of bromine in glacial acetic acid at 80 °C afforded (–)-*endo*-3-bromocamphor (***ent*-20**) in 82% yield. Subsequent reaction of ***ent*-20** with bromine in chlorosulfonic acid for 5 h yielded (–)-*endo*-3,9-dibromocamphor (***ent*-22**), which was purified by recrystallization from 1:1 methanol–dichloromethane. The purified dibromocamphor ***ent*-22** was converted to (–)-*endo*-3,9,10-tribromocamphor (***ent*-32**) through further reaction with bromine in chlorosulfonic acid for five to eight days. Chemoselective debromination of ***ent*-32** with zinc powder in 1:1 HOAc–Et_2O gave (–)-9,10-dibromocamphor (***ent*-33**). Base-promoted ring cleavage of ***ent*-33** (KOH, 9:1 DMSO–H_2O) yielded the cyclopentanoid hydroxy-acid ***ent*-37**,[38,39] and subsequent esterification (K_2CO_3, DMF; CH_3I)

yielded (–)-hydroxy-ester **160**.[39] The spectroscopic properties of hydroxy-ester **160** were identical with those reported previously in the literature.[39,45]

Originally it was planned at this point to convert **160** to the hydroxy-ester **161a** (*cf.* Scheme 2.13). Protection of the C(4) hydroxyl group of **161a** as the corresponding *t*-butyl ether would then provide a potentially useful intermediate for pseudoguaianolide synthesis. With this goal in mind, the hydroxy-ester **160** was converted to the corresponding *t*-butyldimethylsilyl[90] ether **162a** using *t*-butyldimethylsilyl chloride and imidazole in dry DMF. Subsequent ozonolytic cleavage (O_3, 1:1 CH_2Cl_2–CH_3OH, –78 °C; Me_2S) of the exocyclic methylene group in **162a** yielded keto-ester **163a**.



(a) TBDMS-Cl or TBDPS-Cl, imidazole, DMF [>95%] (b) O_3, 1:1 CH_2Cl_2–MeOH, –78 °C; Me_2S, –78 °C → r.t. [92%] (c) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux [92%] (d) $NaBH_4$, MeOH or $LiAl(OBu^t)_3H$, THF (e) O_3, 1:1 CH_2Cl_2–MeOH, –78 °C; $NaBH_4$, –78 °C → r.t.

Scheme 2.13. Conversion of (–)-Hydroxy-ester **160** to (–)-Ketal-ester **164b**.

We then explored the possibility of carrying out a chemo- and stereoselective reduction[91] of the keto group of **163a** (*cf.* p. 224). However, treatment of keto-ester **163a** with sodium borohydride in methanol at 0 °C yielded a 3:1 mixture of diastereomeric alcohols **161a** and **161b**, respectively. When the same reaction was conducted at a lower temperature, no significant improvement in stereoselectivity was observed. Moreover, the reaction rate was greatly reduced at lower temperatures. A procedure involving the use of a more bulky reducing agent, lithium tri(*t*-butoxy)aluminum hydride,[91a] did not offer any significant improvement to the

stereoselectivity of the reduction. The direct conversion of alkene **162a** to hydroxy-esters **161a** and **161b** (4:1; *cf.* Scheme 2.13 and p. 222)[91b,c] was likewise unattractive. The low stereoselectivity encountered at such an early stage of the synthesis, coupled with the fact that the diastereomeric alcohols **161a** and **161b** could be separated only after much difficulty prompted us to postpone the reduction step to a later stage of the synthesis.

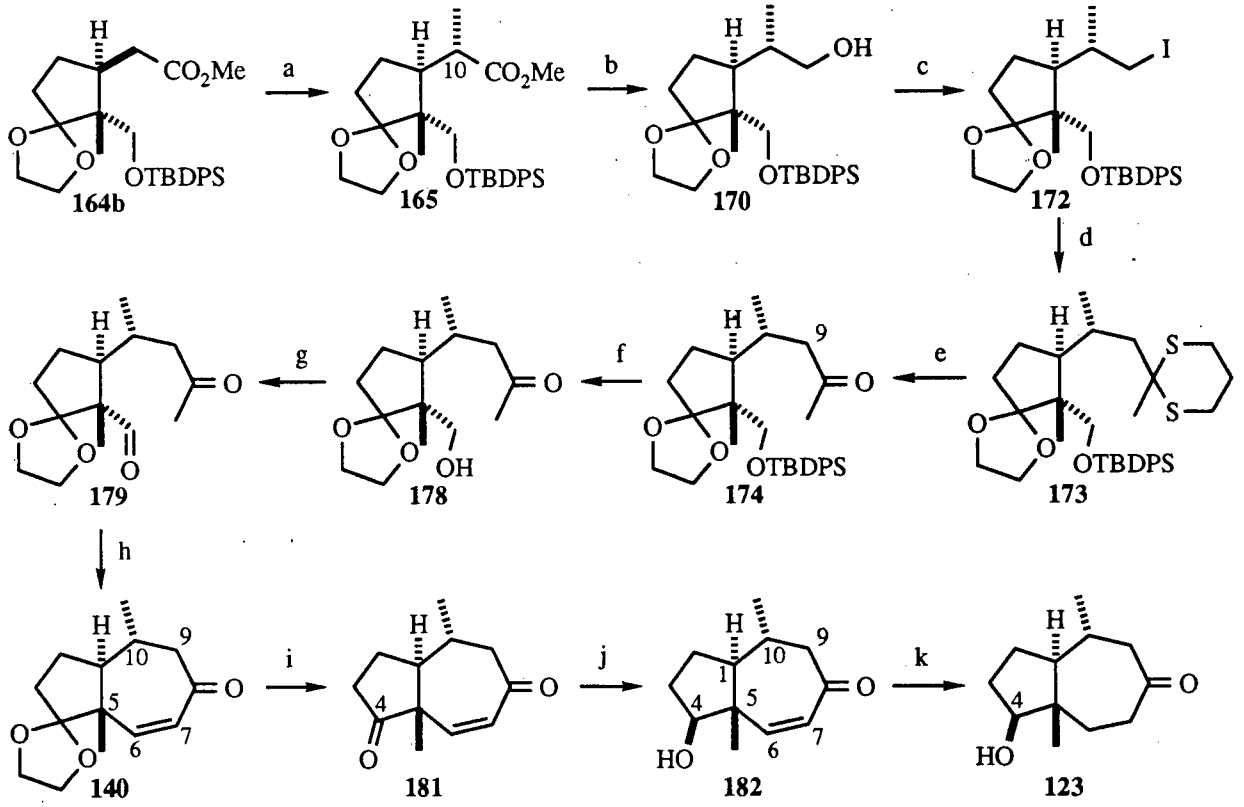
After revising our synthetic plan in the light of the above results, we chose to convert the keto-ester **163a** (Scheme 2.13) to the corresponding ketal-ester **164a** instead. Disappointingly, attempts to effect ketal formation [($HOCH_2CH_2OH$, *p*-TsOH, benzene, reflux),[92a] ($HOCH_2CH_2OH$, PPTS, benzene, reflux)[92b,c] or ($HOCH_2CH_2OH$, Me_3SiCl)[92d]] resulted only in cleavage of the silyl protective group or recovery of starting material **163a**. Moreover, with the *p*-TsOH conditions, prolonged reaction times led to transesterification of the methyl ester group with ethylene glycol.

The apparent lability of the silyl protective group of keto-ester **163a** prompted us to consider the more robust *t*-butyldiphenylsilyl group[93] as an alternative hydroxyl protective group. Thus, hydroxy-ester **160** was converted to the corresponding TBDPS ether **162b** with *t*-butyldiphenylsilyl chloride and imidazole in DMF. Ozonolysis of **162b** followed by reductive work-up with dimethyl sulfide yielded the keto-ester **163b**. Conversion of the keto-ester **163b** to ketal-ester **164b** occurred readily, in 92% yield, upon treatment with excess ethylene glycol, *p*-toluenesulfonic acid in refluxing benzene.[92a]

The identity of ketal-ester **164b** was confirmed by its spectroscopic characteristics. Noteworthy in the infrared spectrum is the presence of a sharp, strong absorption at 1739 cm^{-1} that can be assigned to the stretching of the ester carbonyl group in **164b**. Furthermore, two weak bands at 3072 and 3055 cm^{-1}, representing aromatic C–H stretches, as well as a weak band at 1589 cm^{-1}, representing an aromatic C=C stretch, support the presence of a TBDPS protective group in **164b**.

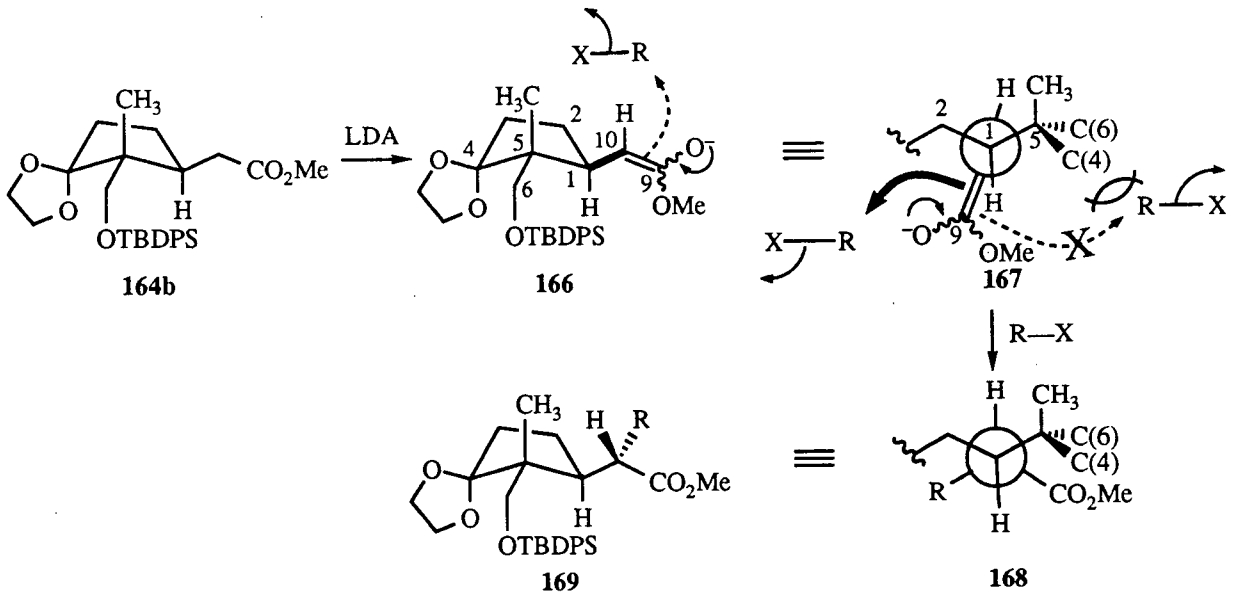
In the 400 MHz ^1H NMR spectrum a multiplet at 3.72–3.84 ppm, representing protons in the –O$\underline{CH_2}C\underline{H_2}$O– unit, provides evidence that the desired ethylene ketal protective group has

been introduced successfully into the molecule. The integrity of the silyl protective group is apparent from the signals at 7.67–7.76 (m, 4H), 7.32–7.46 (m, 6H), and 1.06 (s, 9H) ppm. Furthermore, the three-proton singlet at 3.62 ppm can be assigned to the protons of the methoxycarbonyl (–CO_2Me) moiety. These data support the fact that the product obtained through this step of the synthetic sequence is in fact the desired ketal-ester **164b**. Furthermore, ^{13}C NMR, APT, COSY (*cf.* Table 5.2, p. 130), HETCOR (*cf.* Table 5.3, p. 131) and mass spectral data are also consistent with those expected for **164b**.



(a) LDA, THF, –78 °C; CH_3I, –78 °C—>r.t. [95%] (b) $LiAlH_4$, THF, 0°C [96%] (c) I_2, PPh_3, imidazole, Et_2O–CH_3CN (5:3) [85%] (d) 2-methyl-1,3-dithiane, BuLi, THF, –25 °C [85%] (e) $Hg(ClO_4)_2$, $CaCO_3$, H_2O, THF [93%] (f) TBAF, THF, reflux [90%] (g) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78°C—>r.t [95%] (h) 10% KOH, MeOH; MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; DBU [82%] (i) 1 M HCl, Me_2CO [90%] (j) $NaBH_4$, MeOH, –10 °C [85%] (k) H_2, Pd-C, EtOH [95%]

Scheme 2.14. Conversion of (–)-Ketal-Ester **164b** to the Helenanolide Relay Compounds (–)-Ketal-enone **140** and Hydroxy-Ketone **123**.



Scheme 2.15. Stereoselective Alkylation of an Ester Bearing a Stereocenter at the β Position.

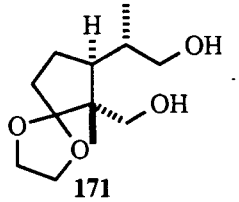
We envisioned that the ketal-ester **164b** could serve as a common intermediate in our projected routes to the helenanolides and ambrosanolides. In the helenanolide series (*cf.* Scheme 2.14), treatment of ketal-ester **164b** with LDA in THF at –78 °C followed by addition of methyl iodide resulted in the stereoselective[94] formation of alkylated ester **165**. As far as could be determined by 400 MHz ^{1}H NMR, GLC, and TLC, only one diastereomer was produced as a result of this alkylation reaction.

The excellent stereoselectivity[94] with which this alkylation occurred was not surprising. Similar stereoselectivity had been observed previously by us[45,140] and others[94] in ester alkylation reactions in which there is a stereocenter at the β-position; Evans[94b] has coined the term 'extra-annular chirality transfer' to describe this phenomenon. A rationale (*cf.* Scheme 2.15) has been proposed to explain the stereselective alkylation. It is presumed[94] that the enolate **166** formed when ketal-ester **164b** is treated with LDA adopts a preferred conformation in which allylic strain between the oxide or methoxy group at C(9) and the groups at C(1) is minimized.[94b] In such a preferred conformation (*cf.* **167**), the smallest group at C(1), namely the proton, eclipses[94c] or is slightly staggered[94a,c] from the enolate double bond (*cf.* **167**).

Alkylation occurs from the most accessible face of the enolate (*cf.* **167** → **168**) to yield the ester **168** (≡ **169**) with the indicated C(10) configuration (Scheme 2.15).[94]

Attempts to confirm the predicted configuration at C(10) of **165** by means of NOE difference spectroscopy (*cf.* Table 5.4, p. 133) were not successful. The proximity of the C(10)-methyl proton signal (1.08 ppm) to that of the *t*-butyl group (1.04 ppm) in the 400 MHz ^{1}H NMR spectrum did not permit selective irradiation of the former even when low decoupler power was used. Furthermore, although it was possible to irradiate the H(10) signal selectively, the results of the NOE experiment could not be interpreted with certainty. Based on our previous experience with this stereoselective alkylation reaction we assumed for now that the correct C(10) stereochemistry, as depicted in structure **165** (Scheme 2.14), had been obtained. We elected to postpone the NOE experiment to a later, more convenient stage of the synthesis.

Reduction of ester **165** with lithium aluminum hydride in THF provided ketal-alcohol **170** in 96% yield. It was important to keep the reaction temperature at or below 0 °C. When the reaction mixture was allowed to warm to room temperature after the addition of **165** to $LiAlH_4$ was complete, a significant amount of the ketal-diol **171** resulting from cleavage of the silyl pro-

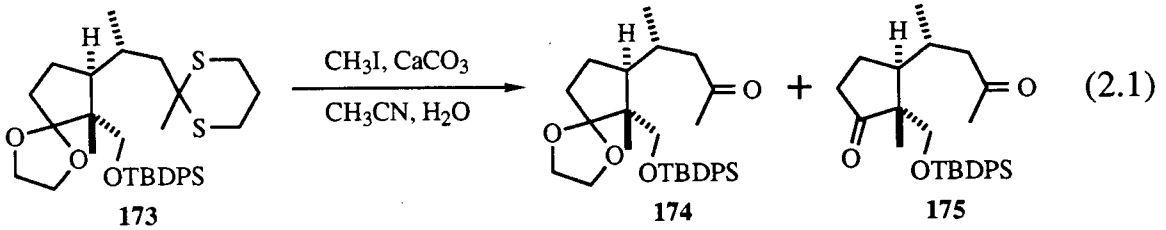


171

tective group was isolated. This observation is consistent with results reported recently by Corey and Jones[95] who have documented the ability of DIBAL to cleave silyl ethers.

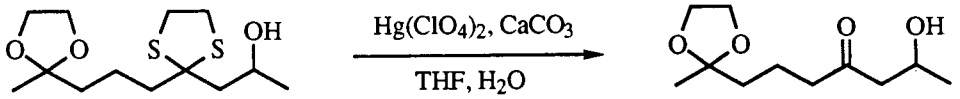
Conversion of alcohol **170** to the corresponding iodide **172** was accomplished uneventfully by reaction with I_2, PPh_3, imidazole in 5:3 diethyl ether–acetonitrile.[96] Addition of iodide **172** to a solution of 2-lithio-2-methyl-1,3-dithiane[97] in THF at –25 °C, generated by dropwise addition of butyllithium to a solution of 2-methyl-1,3-dithiane at –25 °C, yielded the ketal-dithiane **173** as a viscous, colourless oil in ~85% yield.

Chemoselective hydrolysis of the thioketal in **173** was attempted initially using a ten-fold excess of methyl iodide and powdered calcium carbonate in aqueous acetonitrile.[42,98] The calcium carbonate was added in order to neutralize any hydriodic acid that would be formed during the course of the reaction. However, analysis of the reaction mixture by TLC revealed the presence of two compounds, later separated and identified as the desired methyl ketone **174** and the diketone **175** (Equation 2.1). Attempts to minimize the formation of the undesired diketone **175** by increasing the amount of calcium carbonate or decreasing the amount of methyl iodide used were not successful.



173 **174** **175** (2.1)

Fortunately we were able to uncover an alternative procedure that was reported by Bernardi and Ghiringhelli,[99] who were able to hydrolyze selectively the thioketal in **176** (*cf.* Equation 2.2) using mercury(II) perchlorate and calcium carbonate in aqueous THF to yield the hydroxy-ketone **177**. In this case, the purpose of the calcium carbonate is to neutralize any perchloric acid that is formed over the course of the reaction.



176 **177** (2.2)

Following this procedure, an aqueous solution of mercury(II) perchlorate trihydrate (1.5 eq) was added over 5 min to a suspension of ketal-dithiane **173** (1 eq) and calcium carbonate (2.0 eq). The reaction was complete after only 5 min and gratifyingly, only one product was detected by TLC. Ultimately the desired methyl ketone **174** was isolated in excellent (93%) yield.

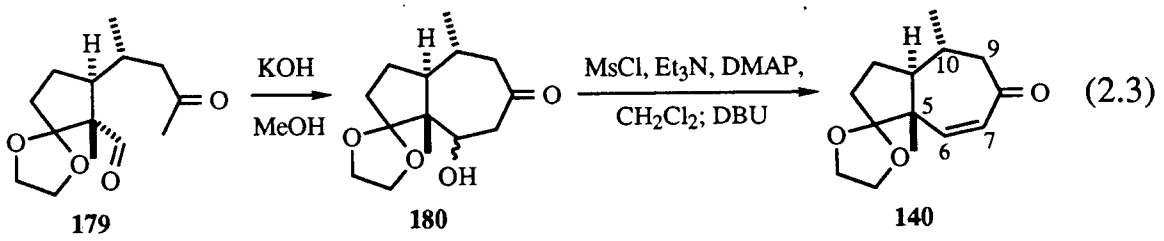
The identity of methyl ketone **174** was confirmed by its spectral characteristics. In the 400 MHz ^{1}H NMR spectrum, the signal at 1.97 ppm (s, 3H) supports the presence of a

–C(O)C<u>H</u>$_3$ fragment. Likewise the one-proton multiplets at 2.05–2.17 ppm and 2.61–2.71 ppm can be assigned to the diastereotopic protons at C(9). The ^{13}C NMR spectrum shows a signal at 208.9 ppm that can be assigned to the carbonyl carbon of **174**, and the infrared spectrum shows a carbonyl stretching absorption at 1717 cm^{-1}.

The removal of the TBDPS protective group[93] of **174** was now attempted. However, when the methyl ketone **174** was treated with a 1 M solution of tetrabutylammonium fluoride (TBAF; 2 eq) in THF and stirred at room temperature for 24 h, no reaction occurred. Likewise, treatment of **174** with ~2 M NaOH in 1:1 EtOH–H_2O[93] resulted only in recovery of starting material. It was found later that when five equivalents of TBAF were used and the reaction was conducted at reflux the deprotection could be accomplished in only 3 h. The success of the procedure was evident after inspection of the infrared spectrum of the product alcohol **178**. The medium-intensity absorption at 3533 cm^{-1} supports the presence of a hydroxyl group in the product. Likewise the disappearance of signals found previously in the spectra of **174**, namely those at 3072 and 3042 cm^{-1} (aromatic C–H stretch) and 1590 cm^{-1} (aromatic C=C stretch) is consistent with the loss of the TBDPS group.

Subsequently, subjection of hydroxy-ketone **178** to Swern oxidation conditions[100] led to the formation of keto-aldehyde **179**. Of note, the infrared spectrum of **179** showed a weak absorption at 2735 cm^{-1} which is characteristic[101] of an aldehydic C–H stretch and a strong absorption at 1715 cm^{-1} (carbonyl stretch). In the ^{1}H NMR spectrum, the diagnostic singlet at 9.72 ppm (s, 1H) is indicative of an aldehyde proton (–C<u>H</u>O) resonance.

Treatment of keto-aldehyde **179** with 10% aqueous potassium hydroxide (3 eq) in methanol[42] at room temperature resulted in an intramolecular aldol reaction to yield a single product that was suggested by TLC analysis to be more polar than the starting material. The infrared spectrum of this crude product exhibited a broad O–H stretching absorption at 3519 cm^{-1} and a strong carbonyl stretching band at 1697 cm^{-1} suggesting that the product that had formed was the hydroxy-ketone **180** (Equation 2.3).



179 **180** **140** (2.3)

The hydroxy-ketone intermediate **180** was not characterized or purified further, but was converted directly to the corresponding mesylate via standard conditions (MsCl, DMAP, Et_3N, CH_2Cl_2). The progress of the reaction was monitored by TLC, and it was found that the hydroxy-ketone **180** was converted completely to the corresponding mesylate after 1.5 h. At this point, DBU was added to the reaction mixture in order to promote dehydromesylation to afford the desired ketal-enone **140**.

With the successful preparation of ketal-enone **140** we have achieved the first formal, enantiospecific synthesis of the helenanolide (+)-carpesiolin (**96**), as Vandewalle and co-workers[87] have already reported (*cf.* Scheme 2.6) the conversion of ketal-enone **140** to carpesiolin (**96**). The spectral data that we obtained for ketal-enone is in agreement with those reported previously by Vandewalle and co-workers.[87] As expected, the infrared spectrum of **140** showed absorptions at 1672 cm^{-1} (carbonyl stretch) and 1626 cm^{-1} (C=C stretch), both of which support the presence of an α,β-unsaturated carbonyl unit in ketal-enone **140**.

In the ^1H NMR spectrum, the doublet at δ 6.40 ppm can be assigned to H(6) while the doublet of doublets at δ 5.91 ppm can be assigned to H(7). The additional multiplicity in the latter signal is due to long-range coupling of H(7) with H(9). The four protons of the ketal moiety of **140** give rise to a multiplet at 3.86–4.04 ppm.

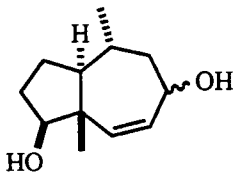
At this juncture, an attempt was made to confirm the *anti* relationship of the C(5) and C(10) methyl groups in **140** by means of a difference NOE experiment (*cf.* Table 5.7, p. 143). Originally, it was hoped that irradiation of the H(10) signal would give rise to enhancement of the intensity of the C(5) methyl signal; however, the H(10) signal formed part of the multiplet at 1.89–2.06 ppm in the 400 MHz ^1H NMR spectrum, and selective irradiation of H(10) was not

possible. Irradiation of the C(5) methyl signal at 1.12 ppm led to enhancement of signals at 1.89–2.06 ppm [H(10), H(1), and H(3)], 1.72–1.86 ppm [H(2) and H(3)], and 1.36–1.46 [H(2)], but not the C(10) methyl signal at 1.01 ppm. Likewise, irradiation of the C(10) methyl signal did not lead to enhancement of the C(5) methyl signal. However, we are aware that the absence of an NOE between the C(5) and C(10) methyl groups does not necessarily imply that the two methyl groups are far apart from each other. Despite this reservation, we argue that in view of the fact that an NOE *is* observed between the C(5) and C(10) methyl groups of the epimeric ketal-enone **200** (see pp. 60–61), which differs from ketal-enone **140** *only in the C(10) configuration*, the absence of an NOE between the C(5) and C(10) methyl groups of **140** suggests that the C(10) methyl group of **140** must bear the alternative, namely α configuration.

Noteworthy in the 75 MHz ^{13}C NMR spectrum are the signals at δ 203.4, 148.4, and 130.5 ppm, which can be assigned to C(8), C(6), and C(7), respectively. The chemical shifts of these signals are consistent with those expected for the –C̲H=C̲H–C̲(O)– unit of an α,β-unsaturated carbonyl system. Other signals in the ^{13}C NMR spectrum were assigned with the help of a HETCOR spectrum (*cf.* Table 5.9, p. 144). Additionally, the APT and COSY (*cf.* Table 5.8, p. 144), and mass spectra were also consistent with those expected for **140**.

We recognized that it was possible to convert (–)-ketal-enone **140** further to hydroxy-ketone **123**, the racemic form of which was an intermediate (*cf.* Schemes 2.2 and 2.9) in total syntheses of (±)-helenalin (**95**),[83,84] (±)-bigelovin (**97**),[88] (±)-mexicanin I (**98**),[88] and (±)-linifolin A (**99**)[88] by various workers. To this end, ketal-enone **140** was converted to the enedione **181** with 1 M HCl in acetone.[102] In addition to the α,β-unsaturated carbonyl band at 1672 cm^{-1} of the infrared spectrum, another peak is present at 1742 cm^{-1}. This latter peak, arising from the stretching of the C(4) carbonyl group, falls in the range expected for a five-membered ring ketone carbonyl stretch. The ^{13}C NMR spectrum of **181** exhibits two signals, at δ 217.2 and 202.3 ppm, which can be assigned to the carbonyl and α,β-unsaturated carbonyl carbons, respectively.

At this stage it was anticipated that it would be possible to effect a chemoselective reduction[103] of the saturated carbonyl group owing to the reduced electrophilicity of the α,β-unsaturated carbonyl carbon. Thus, treatment of an ethanolic solution of enedione **181** at –10 °C



183

with sodium borohydride[103] led to the formation of (–)-hydroxy-enone **182** in 85% yield. Less than 5% of the enediol **183** was isolated.

An infrared absorption at 3363 cm^{-1} supports the presence of the newly introduced hydroxyl group while one at 1687 cm^{-1} indicates the presence of an α,β-unsaturated carbonyl group. In the 400 MHz ^1H NMR spectrum, the multiplet at δ 3.58–3.64 ppm can be assigned to the H(4) proton while a broad singlet at 1.62 ppm that exchanges with D_2O can be assigned to the hydroxyl proton. That the α,β-unsaturated carbonyl has not been reduced by $NaBH_4$ is indicated by the presence of the two vinyl proton signals at 6.62 ppm (d, J = 11.6 Hz, 1H) and 5.91 (dd, J = 11.6, 1.5 Hz). The chemical shifts of these two signals are in the ranges expected for vinyl protons of α,β-unsaturated carbonyl systems. Further evidence that the reduction was chemoselective is given by the ^{13}C NMR spectrum, which shows a carbonyl carbon signal at δ 202.9 ppm.

An attempt was made to confirm the configuration of the newly introduced stereocenter at C(4) using a difference NOE experiment. Irradiation of the H(4) proton [3.58–3.64 (m, 1H)] resulted in enhancement of the signals at 6.62 ppm (representing H(6)), 1.99–2.09 ppm ($H(3_A)$), 1.82–1.98 ppm (H(10) and $H(2_A)$, collectively), 1.62 ppm (–O<u>H</u>), and 1.34–1.58 (H(1), $H(3_B)$, and $H(2_B)$, collectively). However, no enhancement of the singlet at 1.03 ppm, representing the C(5) methyl protons, was observed. Unfortunately, due to the proximity of the C(5)- and C(10)-methyl signals at 1.03 and 1.00 ppm, respectively, it was not possible to irradiate the former

signal selectively. Likewise, the presence of various overlapping multiplets in the spectrum prevented further unambiguous NOE determinations from being made.

Although the absence of an NOE between H(4) and the C(5) methyl protons does not necessarily provide conclusive evidence to support the configurational assignment at C(4), we have assigned the β-stereochemistry to the C(4) hydroxyl group in **182** on the basis of analogous[103] stereoselective sodium borohydride reductions. In any case, the exact stereochemistry at C(4) in hydroxy-enone **182** is not crucial to its subsequent use in helenanolide synthesis, as there is a carbonyl group at C(4) of all the helenanolides under consideration (*cf.* Scheme 2.1).

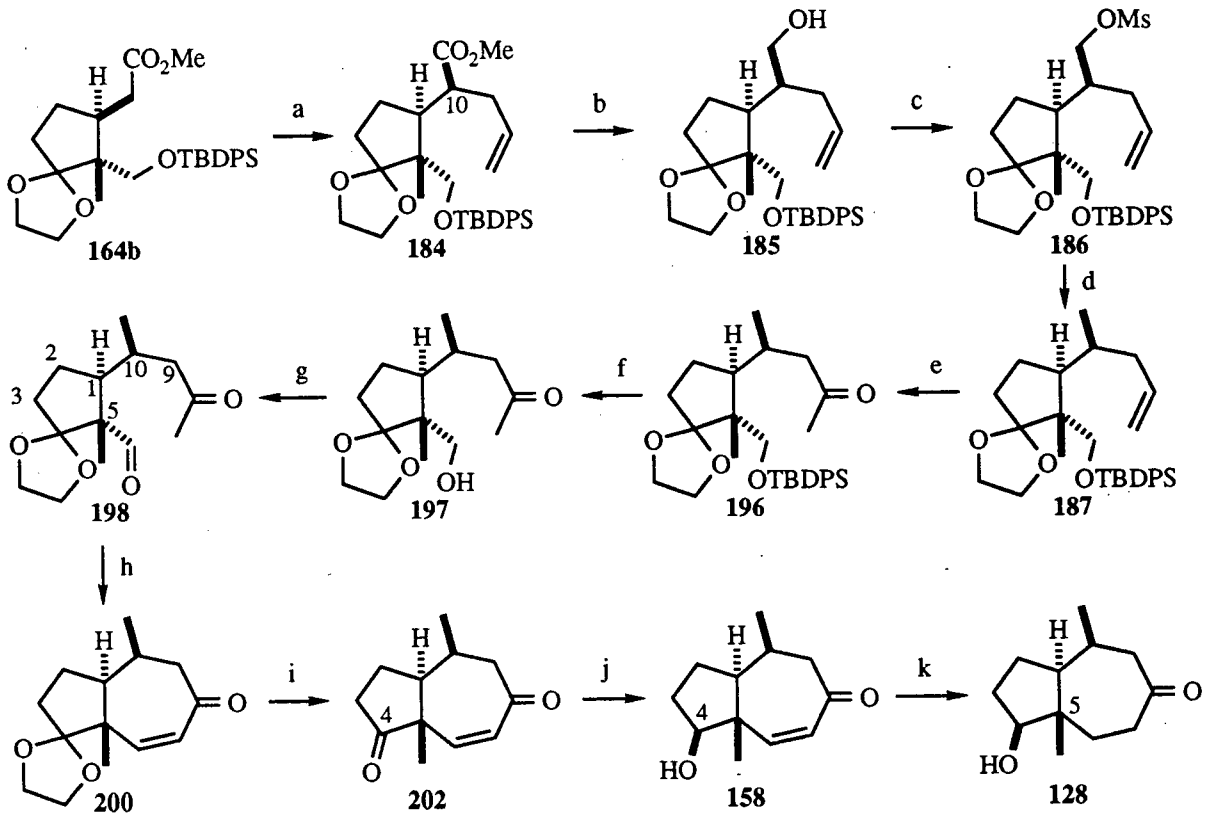
Finally, catalytic hydrogenation of (–)-hydroxy-enone **182** (H_2, 10% Pd-C, EtOH) led to the formation of hydroxy-ketone **123**. As expected, the infrared spectrum of (–)-hydroxy-ketone **123** exhibits a hydroxyl stretching vibration at 3420 cm^{-1}. The carbonyl stretching vibration that was present at 1687 cm^{-1} in the infrared spectrum of the starting (–)-hydroxy-enone (**182**) now shifts to 1695 cm^{-1}. Most notable in the 400 MHz ^1H NMR spectrum is the absence of peaks between 4.5–7.0 ppm, supporting the fact that there are no vinyl protons in **123**. The multiplet at 3.60–3.66 ppm can be assigned to the C(4) proton, which is deshielded by the presence of the geminal, C(4)-hydroxyl group. The 75 MHz ^{13}C NMR, APT, and mass spectral data, also, are consistent with those expected for (–)-hydroxy-ketone **123**.

Racemic hydroxy-ketone **123** and its tetrahydropyranyl ether derivative have been converted previously to the bicyclic dienone **110** and in turn, to (±)-helenalin (**95**) (*cf.* Scheme 2.2) by Roberts and Schlessinger.[82] Likewise, the benzyl analogue of **110** has been converted to (±)-bigelovin (**97**),[88] (±)-mexicanin I (**98**),[88] and (±)-linifolin A (**99**)[88] by Grieco and co-workers (*cf.* Schemes 2.2 and 2.9). Our enantiospecific synthesis of (–)-hydroxy-ketone **123** from (–)-camphor (***ent*-9**) therefore constitutes the first formal synthesis of (–)-helenalin (**95**), (+)-bigelovin (**97**), (+)-mexicanin I (**98**), and (+)-linifolin A (**99**). It follows that the enantiomers of these natural products could be prepared if (+)-camphor (**9**) were used as the starting material instead.

(d) An Enantiospecific Synthesis of Ambrosanolides

The versatility of our synthetic route to pseudoguaianolides is demonstrated by the fact that the same (–)-ketal-ester **164b** that was used in our helenanolide synthesis (*cf.* Scheme 2.14) can serve as an intermediate in a proposed route to the ambrosanolides as well. Access to the ambrosanolide series was gained through a reaction sequence (*cf.* Scheme 2.16) that starts with the stereoselective alkylation of (–)-ketal-ester **164b** with allyl bromide to obtain ester **184**. Once again, as far as could be determined by 400 MHz ^{1}H NMR spectroscopy, GLC, and TLC, only one diastereomer was formed through this alkylation reaction. The rationale for the high (>99%) diastereoselectivity[94] has already been addressed (*cf.* Scheme 2.15). As in the helenanolide case, because of difficulties in irradiating protons whose chemical shifts were close together, determination of the C(10) configuration by NOE difference spectroscopy (*cf.* Table 5.11, p. 150) was postponed to a later stage of the project. Drawing on our previous experience with the stereoselective alkylation reaction, it was assumed for now that the C(10) configuration was the same as that predicted (*cf.* Scheme 2.15), and represented by structure **184** in Scheme 2.16.

Treatment of ester **184** with lithium aluminum hydride at 0 °C provided ketal-alcohol **185** in excellent (~95%) yield. As before (*cf.* conversion of **165** to **170**, Scheme 2.14, p. 43) the reduction reaction could not be carried out chemoselectively at room temperature because of a competing desilylation reaction. Mesylation of **185** using the standard procedure (MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C)[42] yielded ketal-mesylate **186**. Subsequent reductive removal[104] of the



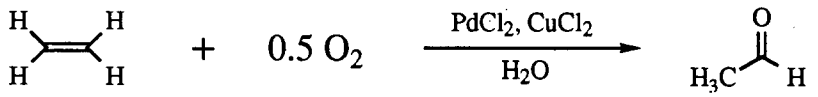
(a) LDA, THF, –78 °C; $H_2C{=}CHCH_2Br$, –78 °C—>r.t. [95%] (b) $LiAlH_4$, THF, 0 °C [96%] (c) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C [97%] (d) $LiEt_3BH$, THF; 3 M NaOH, 30% H_2O_2 [88%] (e) $PdCl_2$, CuCl, O_2, DMF–H_2O (9:1) [91%] (f) TBAF, THF, reflux [90%] (g) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78 °C—>r.t [95%] (h) 10% KOH, MeOH, 12–16 days; MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; DBU [70%] (i) 1 M HCl, Me_2CO [90%] (j) $NaBH_4$, MeOH, –10 °C [87%] (k) H_2, Pd-C, EtOH [93%].

Scheme 2.16. Conversion of (–)-Ketal-Ester **164b** to the Ambrosanolide Relay Compounds Hydroxy-Enone **158** and Hydroxy-Ketone **128**.

mesyloxy group with two equivalents of lithium triethylborohydride (SuperHydride®) solution in THF followed by oxidative work-up (NaOH, H_2O_2) yielded the ketal-alkene **187**. It has been suggested by Holder and Matturro[104] that the second equivalent of $LiEt_3BH$ is necessary in this reaction because the triethylborane that is formed after initial reaction of the mesylate **186** with $LiEt_3BH$ reacts with a further equivalent of $LiEt_3BH$ to yield an unreactive complex with stoichiometry $Et_6B_2H^-\ Li^+$.[104] Regardless, this deoxygenation reaction proceeded in high yield to afford the ketal-alkene **187** with a presumed (10*S*) configuration.

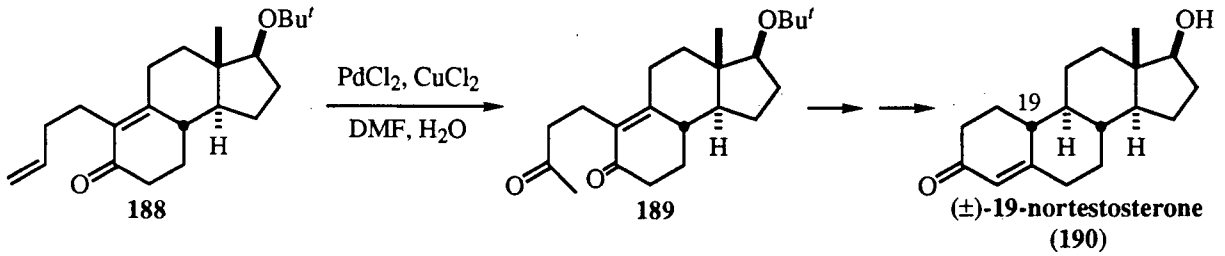
Conversion of the terminal alkene moiety in **187** to a methyl ketone group was accomplished by application of the Wacker oxidation.[105] Although the Wacker process

(Equation 2.4) was developed originally in 1958 as an industrial process for converting ethylene to acetaldehyde,[106] the reaction has found considerable utility in the hands of synthetic chemists.



(2.4)

In one example (Scheme 2.17) drawn from a synthesis of (+)-19-nortestosterone by Tsuji and co-workers,[107] subjection of the enone **188** to Wacker oxidation conditions yielded the keto-enone **189** which was converted to (+)-19-nortestosterone (**190**) in two more steps.



188 **189** **(±)-19-nortestosterone (190)**

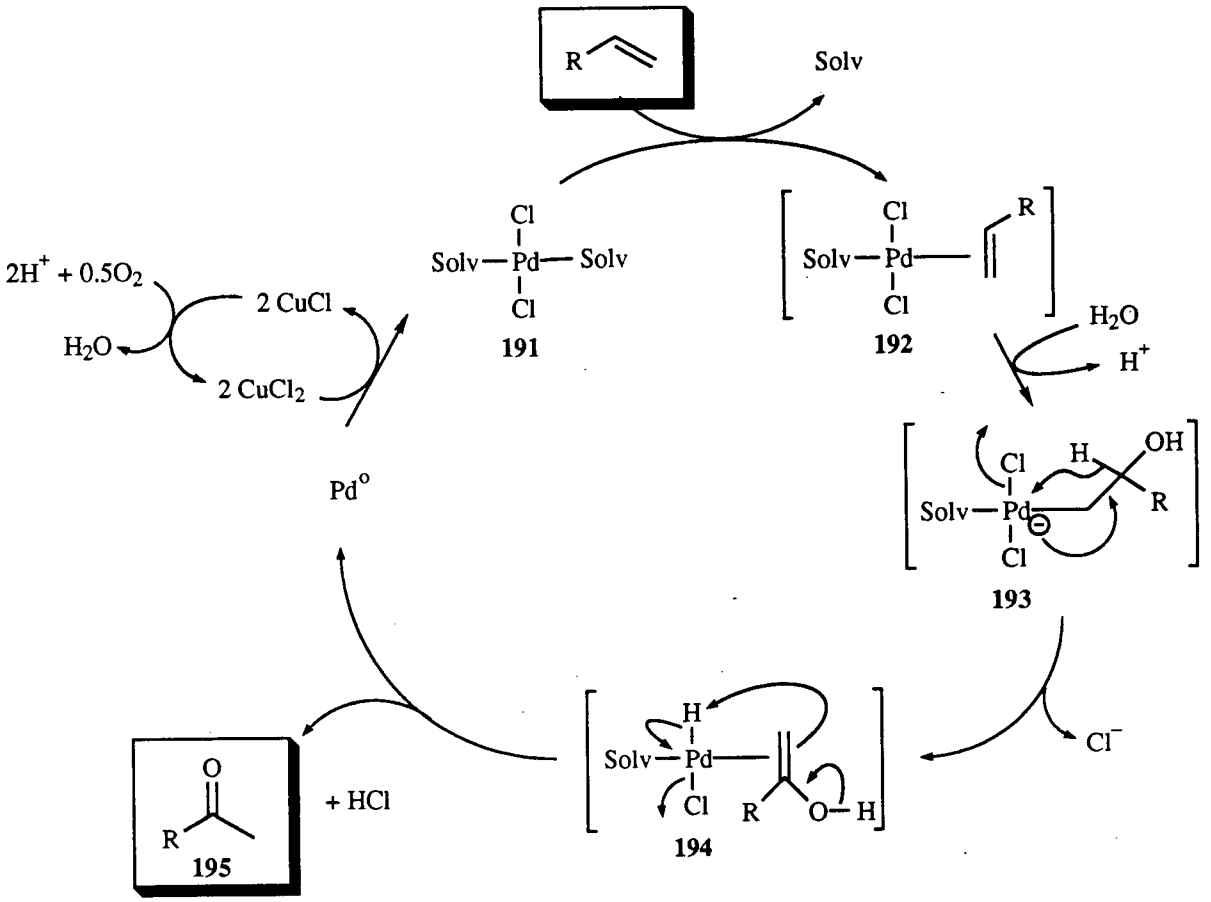
Scheme 2.17. Synthetic Utility of the Wacker Oxidation. Tsuji *et al.*: Total synthesis of (±)-19-Nortestosterone (**190**).[107]

Although the exact mechanism of the Wacker oxidation is still debatable, a catalytic cycle has been proposed (*cf.* Scheme 2.18)[108] in which initially the palladium(II) salt **191** coordinates with the terminal olefin to give an (η^2-olefin)palladium(II) complex **192**. Attack of water at the more substituted position of the olefin yields a σ-(hydroxyalkyl)palladium complex **193**. Subsequent β-hydride elimination occurs to provide the coordinated (η^2-enol)palladium complex **194**, which decomposes to yield the methyl ketone **195**, HCl, and palladium metal.

The palladium metal thus formed can be re-oxidized to palladium(II) using a suitable oxidant. One such oxidant that is commonly used is copper(II) chloride. The reactions that are operative in the re-oxidation process are presented in Scheme 2.18. In practice, copper(I) chloride is initially oxidized with oxygen gas* to yield copper(II) chloride. Although one could start with the copper(II) salt directly, it has been reported, however, that the use of the copper(II)

*So that the nomenclature throughout this thesis remains consistent, the molecule O_2 is named 'oxygen' rather than 'dioxygen.' It is recognized, however, that the latter name is preferred in the inorganic and organometallic literature.

salt can lead to chlorination of the carbonyl compound formed from the Wacker reaction.[105a] Copper(II) chloride reacts with palladium(0) metal to yield the palladium(II) salt, and in the process, copper(II) chloride is converted back to copper(I) chloride.



Scheme 2.18. Proposed Mechanism of the Wacker Oxidation [N.B. Solv = solvent].[108]

In our synthesis of the ambrosanolides, a solution of ketal-alkene **187** (1 eq) in 9:1 DMF–H_2O was added to a suspension of $PdCl_2$ (0.2 eq) and CuCl (1 eq) in 7:1 DMF–H_2O, and the reaction mixture was stirred under an oxygen atmosphere. The product, methyl ketone **196**, was isolated in ~85% yield. Spectroscopic data obtained for the Wacker oxidation product are consistent with those expected for silyloxy-ketone **196**. The infrared spectrum shows a strong absorption at 1716 cm^{-1} while the ^{13}C NMR spectrum exhibits a signal at δ 209.0 ppm, both of

which support the presence of a carbonyl group in **196**. Furthermore, a singlet at δ 2.09 ppm of the ^{1}H NMR spectrum of the product is diagnostic of a C$\underline{H}_3$C(O)- subunit.

From this point on it was planned to complete the synthesis according to a plan similar to that outlined earlier in our helenanolide synthesis. Silyloxy-ketone **196** was subjected to the same desilylation conditions that had been worked out for the corresponding aldol reaction in the helenanolide series (namely the conversion of **174** to **178**, Scheme 2.14). Thus, reaction of silyloxy-ketone **196** with TBAF (5–10 eq) at reflux afforded hydroxy-ketone **197** in 95% yield. The identity of this product was supported by the presence of an O–H stretch at 3534 cm^{-1} in the infrared spectrum and the absence of signals in the region of the ^{1}H NMR spectrum in which aromatic proton signals are expected.

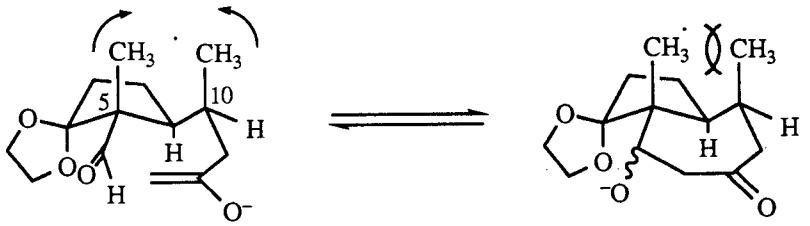
Swern oxidation[100] of hydroxy-ketone **197** gave the air-sensitive keto-aldehyde **198**. Subjection of keto-aldehyde **198** to conditions used previously for the corresponding reaction in the helenanolide series (excess 10% KOH, MeOH, 2 h) led, quite unexpectedly, to the total recovery of starting material. Puzzled by the failure of the aldol reaction, we studied the effect of varying the KOH concentration and stoichiometry.[109] In some cases, TLC suggested the formation of a product that was more polar than the starting keto-aldehyde **198**. Even so, product conversions were unacceptably low (<10%).

At this point we decided to re-examine the body of spectroscopic evidence we had obtained for keto-aldehyde **198**. The infrared spectra of **198** shows a weak absorption at 2731 cm^{-1} that can be assigned to the stretching of the aldehydic C–H bond. A broad absorption at 1718 cm^{-1} supports the presence of a carbonyl group in **198**; however, it was not possible to discern separate peaks for stretches due to the aldehyde or ketone carbonyl groups. Normally, aldehyde carbonyl stretching bands are found between 1720–1740 cm^{-1} while ketone carbonyl stretching bands are found between 1700–1725 cm^{-1}.

In the 400 MHz ^{1}H NMR spectrum the singlet at 9.48 ppm arises from resonance of the aldehydic proton. The singlet at 2.12 ppm can be assigned to the protons of the terminal acetyl unit while the two singlets at 1.07 and 0.69 ppm can be assigned to the methyl groups at C(5) and

C(10), respectively. The presence of a multiplet at 3.69–3.85 ppm confirms that the ethylene ketal moiety is still present in **198** and has not been inadvertently hydrolyzed during intervening chemical operations. With the aid of a COSY spectrum (*cf.* Table 5.13, p. 159) the remainder of the spectrum could be assigned to protons at C(1), C(2), C(3), C(9), and C(10). Of note in the 75 MHz ^{13}C NMR spectrum are the two signals at δ 208.2 and 207.5 ppm that support the presence of the ketone and aldehyde carbonyl groups, respectively, in keto-aldehyde **198**. The APT and mass spectral data also confirm unambiguously that we have indeed synthesized the correct product, the keto-aldehyde **198**.

We turned our attention back to our aldol cyclization problem and sought an explanation for this recalcitrant reaction. After examining a molecular model of **198**, we speculated that in order for intramolecular aldol reaction to occur, the enolate generated upon treatment of keto-aldehyde **198** with base adopts a conformation similar to that depicted by **198a** in Equation 2.5.



198a **199** (2.5)

However, in the process of attaining this conformation **198a**, the two methyl groups at C(5) and C(10) approach each other, resulting in an unfavorable steric interaction. Consequently, the equilibrium shown in Equation 2.5 favors **198a**, and not **199**.

It is pertinent to note that in the corresponding reaction in the helenanolide series (**179** → **180**; *cf.* Equation 2.3, p. 48) the configuration at C(10) of **179** is reversed. Consequently the C(5)–C(10) interaction encountered in the transformation of **179** → **180**, *en route* to enone **140**, involves only a methyl group and a proton, and is not as severe as the 1,3-*syn*-dimethyl interaction encountered here in the transformation of **198a** → **199** (Equation 2.5).

We were aware that if the aldol reaction were conducted at elevated temperatures then it would be possible to obtain the thermodynamically more stable α,β-unsaturated ketone.[109] We

thought if we could promote enone formation the overall reaction equilibrium would be driven further to product formation. Consequently we carried out the aldol reaction, using 2% aqueous KOH in refluxing methanol, for 24 h. This time, TLC analysis of the product mixture indicated that in addition to recovered starting material (~80%), there were two additional products. The first, isolated in ~10% yield was more polar than the starting keto-aldehyde **198** and had the same TLC R_f value of the polar product observed originally (*cf.* p. 56). This polar product was identified as the intermediate hydroxy-ketone **199** (*cf.* Scheme 2.19) on the basis of its infrared and ^{1}H NMR spectrum. The second product, also isolated in ~10% was slightly less polar than the starting material and was determined spectroscopically to be the desired ketal-enone **200**. Attempts to increase the amount of enone formed by prolonging the reaction, to as long as three days, were not successful. By changing the solvent from methanol (bp 65 °C) to ethanol (bp 78 °C) it was possible to obtain a marginally better, but still unacceptable product yield of ~20%.

At this time we began to explore the use of other reagent combinations[109] that had been documented in the literature. Initially we investigated the use of NaOH, KOH, and Bu_4NOH (Triton-B®) in ether solvents such as THF, DME, and diglyme.[109] In general the results of these experiments were similar to those reported above in that the problem of low reaction efficiency still persisted.

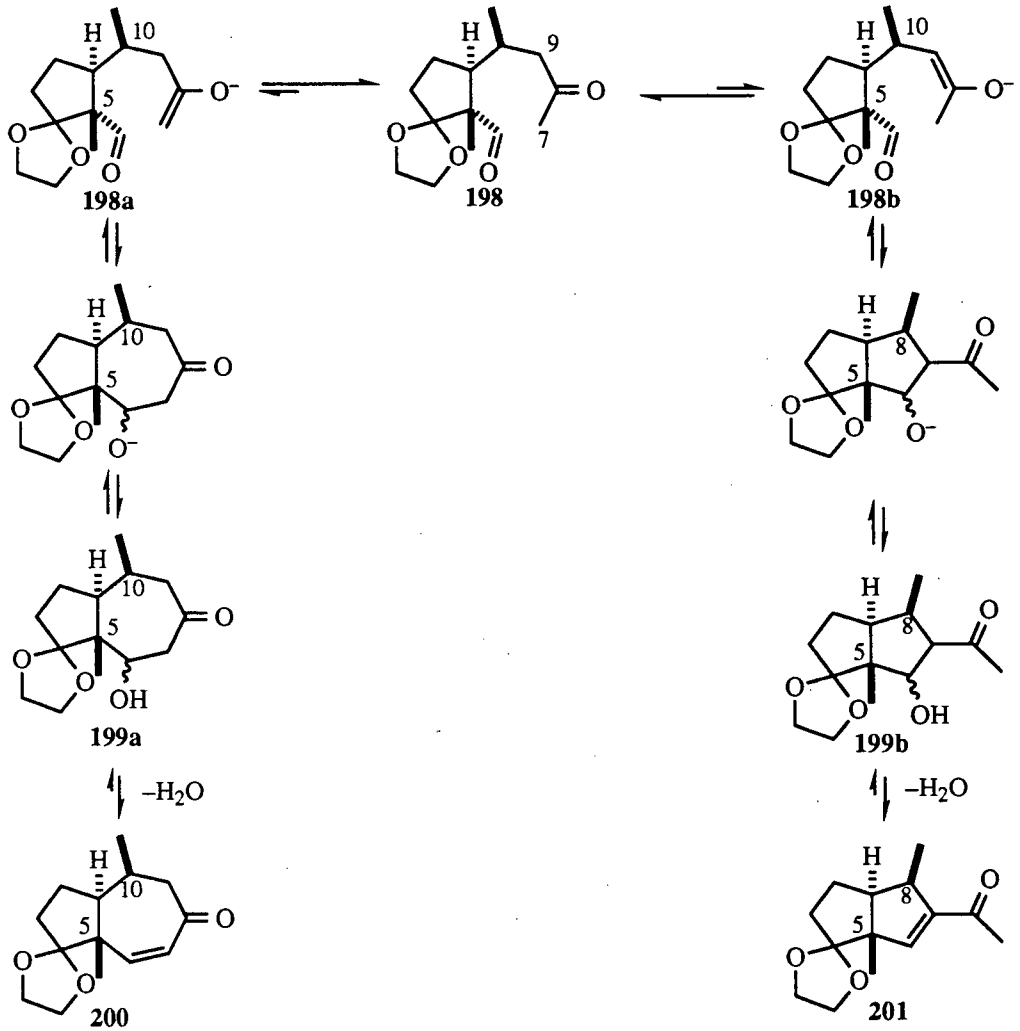
Interestingly, when Bu_4NOH (40% solution in water) was used in refluxing DME or diglyme, it was possible to isolate a 6:1:1.5 mixture (by weight) of the starting material (**198**), ketal-enone **200**, and a product whose TLC R_f values in a number of solvent systems were just slightly greater than that of the desired ketal-enone **200**. Examination of this new product by infrared spectroscopy revealed no absorptions above 3000 cm^{-1} and an absence of the aldehydic C–H stretch previously observed in the starting material at 2731 cm^{-1}. However, the presence of an absorption at 1688 cm^{-1} suggested the presence of an enone carbonyl in this yet unknown structure. The 400 MHz ^{1}H NMR spectrum exhibited a doublet at 6.48 ppm, which falls in the range expected normally for the β–proton of an α,β-unsaturated carbonyl system.[101] A multiplet between 3.85–4.02 ppm can be assigned to the protons of the ethylene ketal unit. The three-

proton singlet at 2.28 ppm is in the range expected for a methyl group adjacent to a carbonyl group. Signals at 1.13 ppm (d, J = 7.5 Hz, 3H) and 1.05 (s, 3H) suggest the presence of two other methyl groups in the molecule. With the aid of a COSY spectrum (*cf.* Table A.3, p. 230) it was determined that these data were consistent with those expected of the strained, substituted *trans*-fused bicyclo[3.3.0]octene **201** (*cf.* Scheme 2.19).

That a strained *trans*-fused bicyclo[3.3.0]octene system was formed unexpectedly is not a precedent, however. Other examples of synthesized *trans*-fused bicyclo[3.3.0]octane derivatives can be found in the literature.[110] A rationale (*cf.* Scheme 2.19) can be advanced to explain the formation of **202** in this case. When keto-aldehyde **198** ($pK_{a\ (\alpha\ protons)} \sim 20$) and hydroxide ($pK_{a\ (H_2O)} = 15.7$) are mixed, proton abstraction occurs initially at the more accessible position (that is, at C(7)) to provide the 'kinetic' enolate **198a**. Equilibration of enolate **198a** with unreacted keto-aldehyde **198** results in the formation of the more substituted, 'thermodynamic' enolate **198b**. The aldol reaction of the kinetic enolate **198a**, followed by protonation, results in the formation of a hydroxy-ketone **199a** in which there is a 1,3-*syn*-dimethyl interaction between the C(5) and C(10) methyl groups. On the other hand, aldol reaction of the thermodynamic enolate **198b**, followed by protonation, results in the formation of a hydroxy-ketone **199b** in which there is a similar steric interaction as well as additional ring strain[110a–c] that arises from the *trans*-fused bicyclo[3.3.0]octane ring system. Thus, it is presumed that at low temperatures (e.g. room temperature), only the equilibria leading to the formation of **199a** are favored, and those leading to **199b** are disfavored. By contrast, at elevated temperatures, the dehydration reactions of **199a** and **199b** to yield the thermodynamically more stable enones **200** and **201**, respectively, are both favored.

A number of other reaction conditions were also evaluated, including 1% KOH/Et_2O;[111] NaOMe/MeOH;[109] KOBu^t/HOBu^t;[112] LiI/Et_2O;[113] Et_2AlOEt/toluene;[114] NaH, toluene;[115a,116] *p*-TsOH/C_6H_6;[115a] PPTS/C_6H_6;[115b] $H_3B\ O_3$/toluene;[117] HOAc/piperidine/C_6H_6;[118] and HCl/HOAc.[119] All of these methods failed to promote the required intramolecular aldol reaction or condensation in acceptable efficiency or yield. As a related example, an unsuccessful attempt

by Klipa and Hart to prepare bicyclo[3.3.0]oct-4-en-3-one via aldol condensation (5% KOH, EtOH, reflux) has been documented.[116]



Scheme 2.19. Competing Aldol Condensation Pathways of Keto-aldehyde **198**.

Finally, after considerable experimentation it was found that treatment of a ~0.1 M solution of keto-aldehyde **198** with 10% aqueous KOH (~5 eq) followed by reaction for 12–16 days at room temperature resulted in the successful production of hydroxy-ketone **199** with minimal starting material (<5%) remaining, as detected by GLC. Crude hydroxy-ketone **199** was not purified but was converted directly to ketal-enone **200** via a mesylation (MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C)–dehydromesylation (DBU, CH_2Cl_2) sequence. Ultimately, ketal-enone **200** was obtained in 70% yield from keto-aldehyde **198**. The *syn* relationship between the C(5) and C(10)

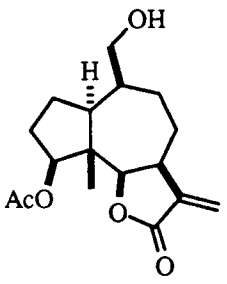
methyl groups in ketal-enone **200** was confirmed by the results of an NOE experiment [400 MHz] in which irradiation of the C(5) methyl signal (1.19 ppm) resulted in enhancement of the C(10) methyl signal (1.07 ppm), and *vice versa.*

The completion of the ambrosanolide synthesis followed a plan analogous to that described previously for the synthesis of helenanolides. Thus, ketal-enone **200** was deprotected with 1 M HCl in acetone[102] to yield enedione **202**. Stereo- and chemoselective reduction ($NaBH_4$, EtOH, –10 °C)[103] of the C(4) carbonyl group yielded hydroxy-enone **158** as a single diastereomer; no traces of the alternative C(4) diastereomer was detected or isolated. Finally, catalytic hydrogenation of **158** (H_2, 10% Pd-C, EtOH) provided the (–)-hydroxy-ketone **128**. All of these reactions proceeded uneventfully and in high yield. Attempts to determine the C(4) configuration of **158** or **128** through NOE experiments (*cf.* Table 5.14, p. 164) were met with difficulties similar to those described earlier (*cf.* pp. 50–51), although in the case of **128**, selective irradiation of both H(4) [3.60 ppm] and the C(5)-methyl [0.70 ppm] signals was possible. No NOE was observed between H(4) and the C(5)-methyl signals. Ultimately, the C(4)-hydroxy group was assigned a β-configuration on the basis of arguments similar to those made earlier for hydroxy-enone **182** (*cf.* pp. 50–51).

Hydroxy-ketone **128** has been converted previously to confertin (**102**) while the *t*-butyl ether of **128** has been converted to (±)-damsin (**103**) by Quallich and Schlessinger (*cf.* Scheme 2.3). Thus, our synthesis of hydroxy-enone **158** and hydroxy-ketone **128** represents a formal, enantiospecific synthesis of (+)-confertin (**102**) and (+)-damsin (**103**).

Spectroscopic data for all relay compounds (*viz.* **140**, **123**, **103**, and **102**) were in agreement with those reported previously in the literature.[83,85,86–88] Minor modifications of the two routes to the helenanolides and ambrosanolides presented in this chapter[120] could lead to the enantiospecific synthesis of other pseudoguaianolides and their analogues. It is envisaged, for example, that protection of the hydroxyl group of ketal-alcohol **185** (Scheme 2.16) will provide an intermediate that could be of value in a projected synthesis of enantiopure hysterin (**203**).[80b] In summary, the syntheses of hydroazulenoid ketones **140**, **123**, **103**, and **102** (Scheme 2.11)

from (–)-camphor (***ent*-9**) represent formal syntheses of (+)-carpesiolin (**96**), (–)-helenalin (**95**), (+)-bigelovin (**97**), (+)-mexicanin I (**98**), (+)-linifolin A (**99**), (–)-damsin (**158**), and (+)-confertin (**128**).[120]



hysterin (203)

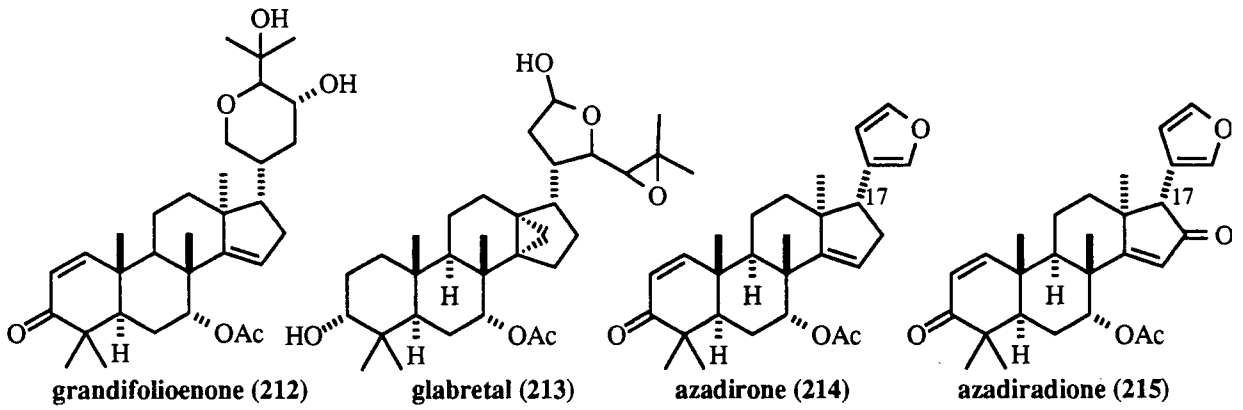
Chapter 3

An Enantiospecific Synthetic Approach to the Limonoids

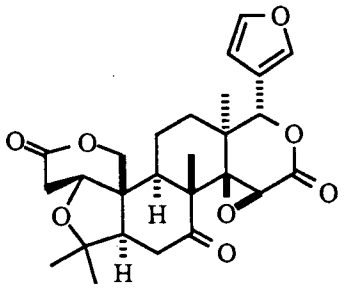
3. An Enantiospecific Synthetic Approach to the Limonoids[140]

(a) Introduction

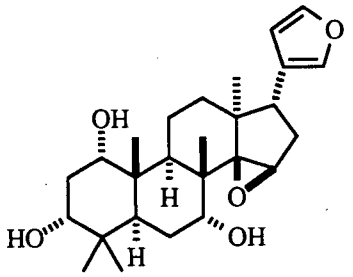
The limonoids[121] are a group of complex, structurally diverse tetranortriterpenoids found generally in plants belonging to the Meliaceae, Rutaceae, and Cneoraceae families. Some representative limonoid structures are given in Scheme 3.1. Many members of this family of compounds display anti-malarial, insect antifeedant or insecticidal properties.[121,122] Biosynthetically,[121a] the limonoids are believed to be derived from the triterpenoids euphol (**204**; *cf.* Scheme 3.2) and tirucallol (**205**) through the loss of a four-carbon unit. Euphol (**204**) and tirucallol (**205**), in turn, are derived from 2,3-oxidosqualene (**206**). A possible biogenesis of the limonoids is outlined in Scheme 3.2. Cyclization of 2,3-oxidosqualene (**206**) yields a tetracyclic alcohol **207** which is transformed into euphol (**204**) and tirucallol (**205**) after a series of proton and methyl shifts. Subsequently, euphol (**204**) and tirucallol (**205**) are converted to apo-euphol (**208**) and apo-tirucallol (**209**). Although the exact biosynthetic route to the limonoids is unknown, it has been speculated that apo-euphol (**208**) and apo-tirucallol (**209**) are converted first to a protolimonoid intermediate, in which the C(20)-side chain is highly oxidized. The compounds grandifolioenone (**212**) and glabretal (**213**) are representative examples of protolimonoids. Subsequently, the loss of a four-carbon unit from the protolimonoid side chain followed by the formation of a 3-furyl substituent at C(17) leads to the formation of a tetracyclic limonoid such as azadirone (**214**) or azadiradione (**215**).



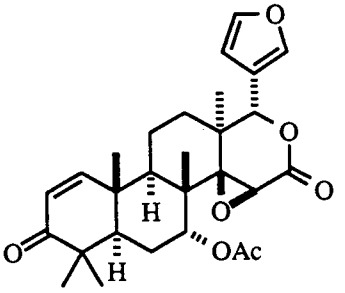
grandifolioenone (212) **glabretal (213)** **azadirone (214)** **azadiradione (215)**



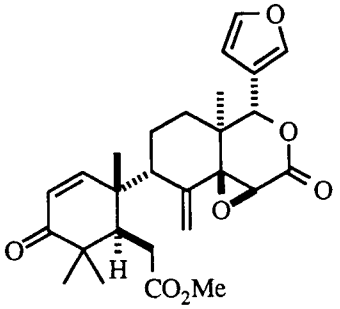
limonin (216)



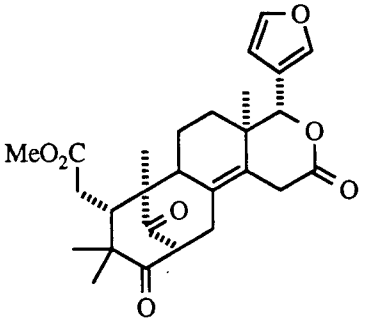
havenensin (217)



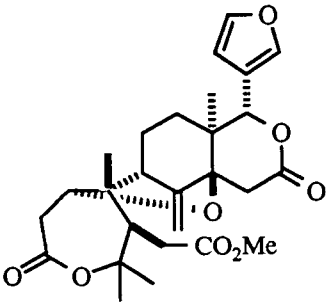
gedunin (218)



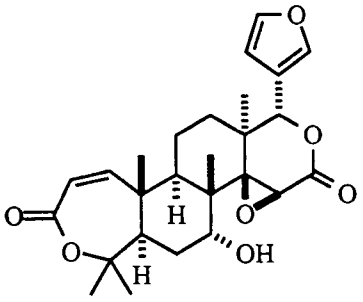
andirobin (219)



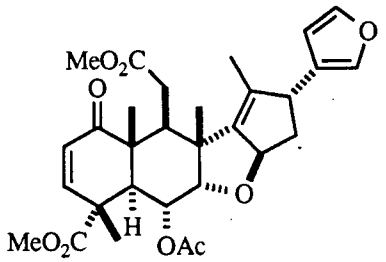
mexicanolide (220)



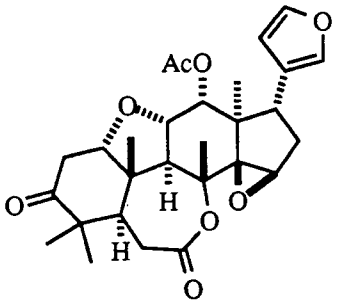
methyl ivorensate (221)



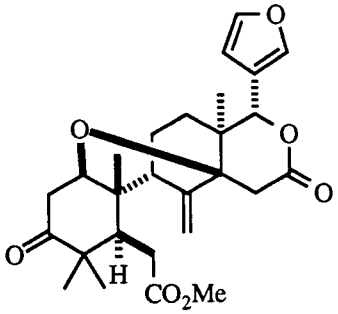
obacunol (222)



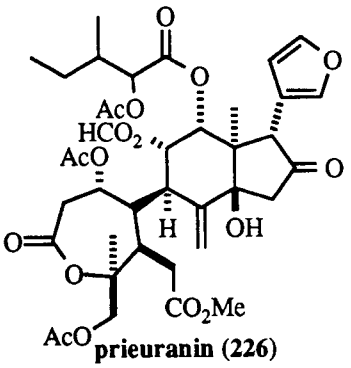
nimbin (223)



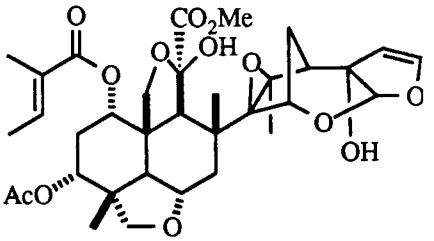
toonafolin (224)



methyl angolensate (225)

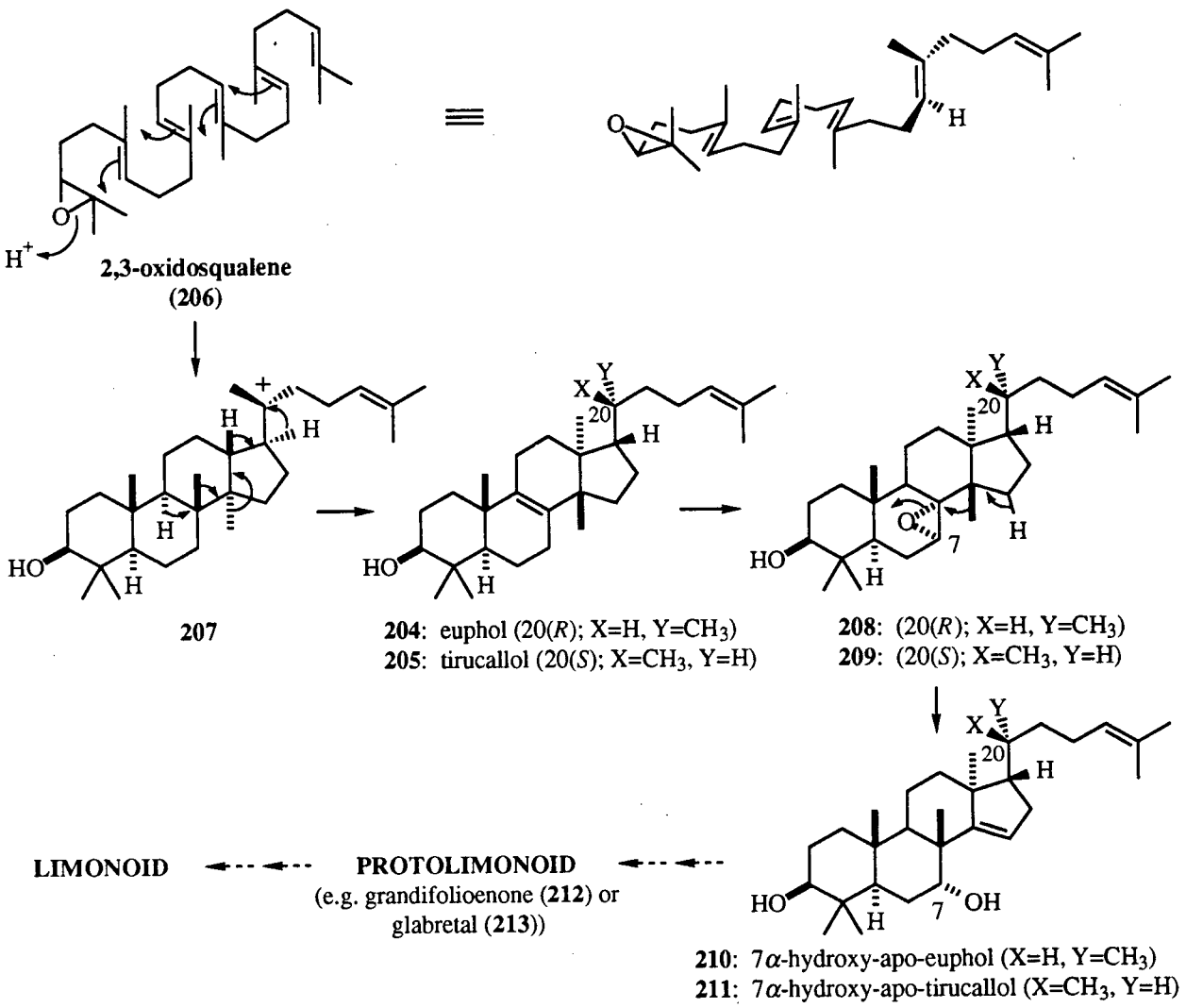


prieuranin (226)



azadiractin (227)

Scheme 3.1. Structures of Representative Limonoids.



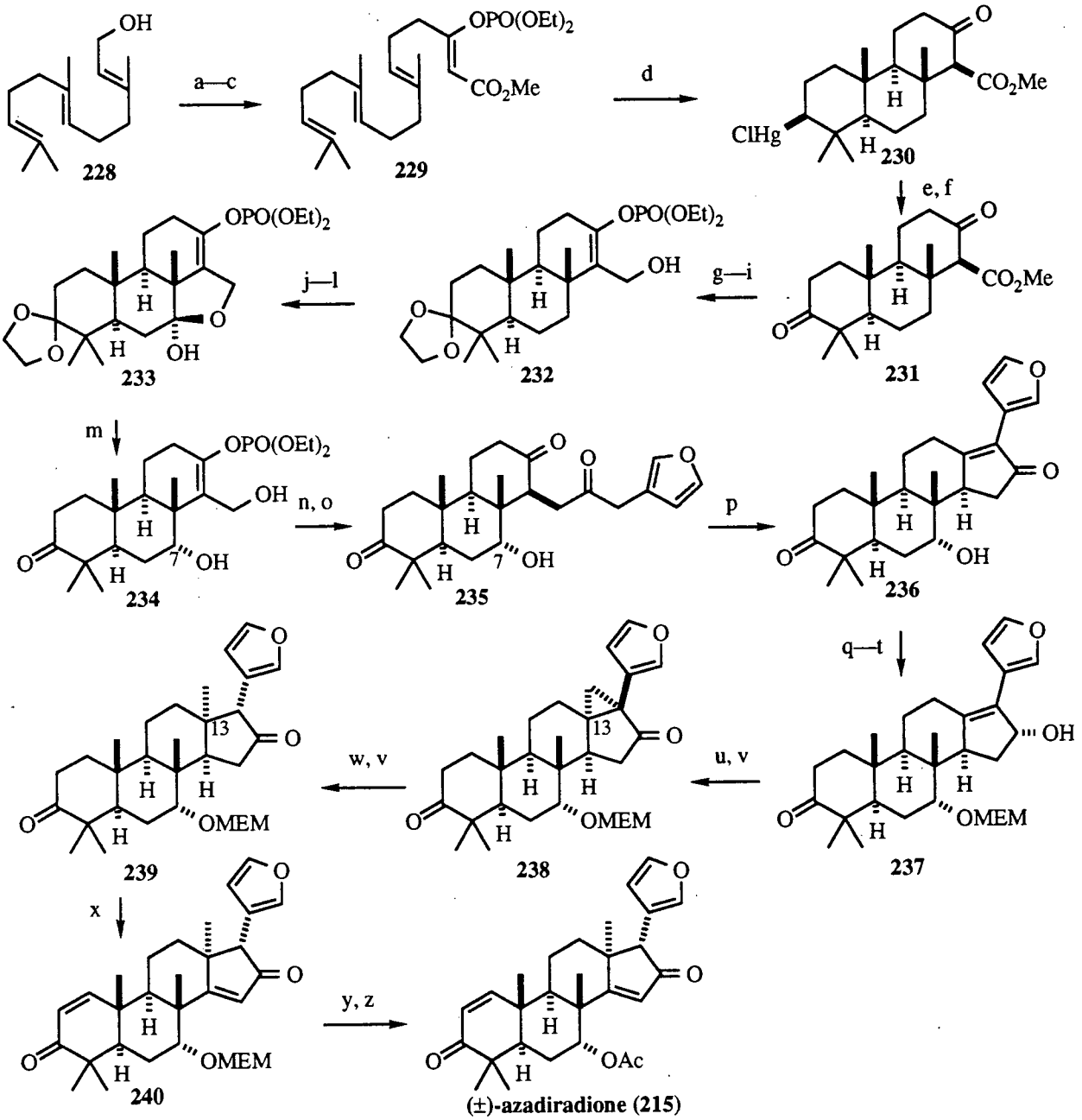
Scheme 3.2. Proposed Biogenesis of the Limonoids.[121a]

Further structural modifications can occur, as illustrated by the diverse structures presented in Scheme 3.1. In many cases, further oxygenation can occur at various positions in the basic limonoid skeleton. Epoxidation of the C(14)–C(15) double bond is common and the A and D rings can undergo Baeyer-Villiger-type oxidation to produce lactone rings [*cf.* limonin (**216**), gedunin (**218**), mexicanolide (**220**), and obacunol (**222**)]. On the other hand, the B and C rings can be cleaved to yield seco-limonoid derivatives [*cf.* andirobin (**219**), nimbin (**223**), prieuranin (**226**), and azadiractin (**227**)]. These modifications can take place either singly or in combination, and ultimately give rise to limonoids of considerable structural complexity.

(b) Previous Synthetic Routes to Limonoids and Analogues

Literature reports concerning synthetic approaches to limonoids and limonoid model systems remain generally scarce. It is perhaps due to the structural complexity of the limonoids that no total synthesis of members of this family has been documented until mid-1989 when Corey and co-workers published a total synthesis of (±)-azadiradione (**215**) starting from *trans*, *trans*-farnesol (**228**; Scheme 3.3).[123]

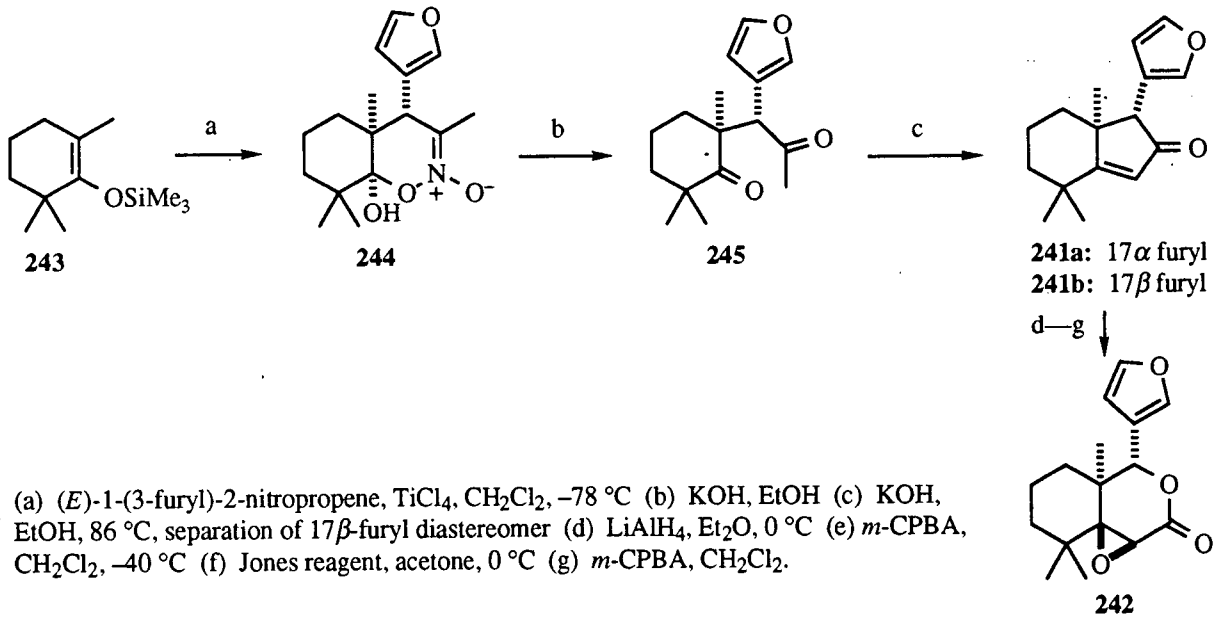
trans, *trans*-Farnesol (**228**) was converted in three steps to the tetraenol phosphate **229**. Treatment of **229** with mercury(II) trifluoroacetate in nitromethane promoted a polyolefin cyclization reaction to provide tricyclic keto-ester **230**. The chloromercurio group in **230** was replaced by a hydroxyl group upon treatment with oxygen gas in the presence of sodium borohydride in DMF, and subsequent Jones oxidation yielded the diketo-ester **231**. The preparation of the allylic alcohol **232** from **231** was achieved through standard reactions. Installation of a 7α-hydroxyl group was accomplished via application of Barton's method and proceeded through the intermediate hemiketal **233**. Hydrolysis of the hemiketal followed by selective reduction of the C(7)-keto group yielded keto-diol **234**. Conjugate addition of the sodium salt of 3-(2-nitroethyl)furan to the α,β-unsaturated ketone generated in situ from **234** and subsequent Nef reaction afforded the hydroxy-triketone **235**. Intramolecular aldol condensation of **235** yielded the tetracyclic enone **236**. Subsequent conversion to the allylic alcohol **237** was carried out via conventional means. Hydroxyl-directed cyclopropanation of the allylic alcohol **237** followed by Dess-Martin oxidation yielded the diketone **238**. Installation of the C(13)-methyl group was accomplished via dissolving metal mediated opening of the cyclopropyl ring. A further Dess-Martin reaction yielded diketone **239**. α-Phenylselenenylation of **239** followed by oxidation and selenoxide fragmentation led to the formation of bis-enone **240**. Finally, replacement of the methoxyethoxymethyl protective group with an acetyl group completed the total synthesis of (±)-azadiradione (**215**).[123] According to Corey and co-workers,[123] azadiradione (**215**) has been converted previously to several other tetracyclic limonoids and therefore, their synthesis of azadiradione constitutes a formal synthesis of other limonoids.



(a) MsCl, Et_3N, CH_2Cl_2, –20 °C (b) LiBr, THF, –20 °C (c) methyl acetoacetate sodio and lithio dianion, THF; $(EtO)_2POCl$, –78→ –20 °C (d) $Hg(O_2CCF_3)_2$, CH_3NO_2, 0 °C; aq. NaCl (e) O_2, $NaBH_4$, DMF; 1 N H_2SO_4, 10 °C (f) Jones reagent, 0 °C (g) NaH, THF, reflux; $(EtO)_2POCl$, 0 °C (h) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux (i) DIBAL, $PhCH_3$, –20 °C; aq. HCl, MeOH (j) HO_3SONO, C_5H_5N, 0 °C; MeOH (k) hν, CH_2Cl_2, 50 °C; separation of aldehyde (l) 1 N HCl, CH_3CHO (m) $Me_4N^+{}^-B(OAc)_3H$, Me_2CO, HOAc, –78 °C (n) $Na^+{}^-CH(NO_2)$-CH_2-(3-furyl), EtOH, reflux (o) 12 N HCl, EtOH, 10 °C (p) NaOEt, EtOH, 70 °C (q) MEM-Br, TBAI, Pr^i_2NEt, CH_3CN, 70 °C (r) $LiBu^s_3BH$, THF, –78 °C (s) DEAD, PPh_3, THF, $PhCO_2H$ (t) NaOH, EtOH (u) CH_2I_2, Zn–Ag, 0 °C (v) Dess-Martin periodinane, CH_2Cl_2 (w) Li, NH_3 (x) LDA, THF, –78 °C; PhSeBr; 30% H_2O_2, H_2O–C_5H_5N, warm (y) Me_3SiBr, CH_2Cl_2, –20 °C (z) Ac_2O, DMAP, THF.

Scheme 3.3. Corey and Hahl: Total Synthesis of (±)-Azadiradione.[123]

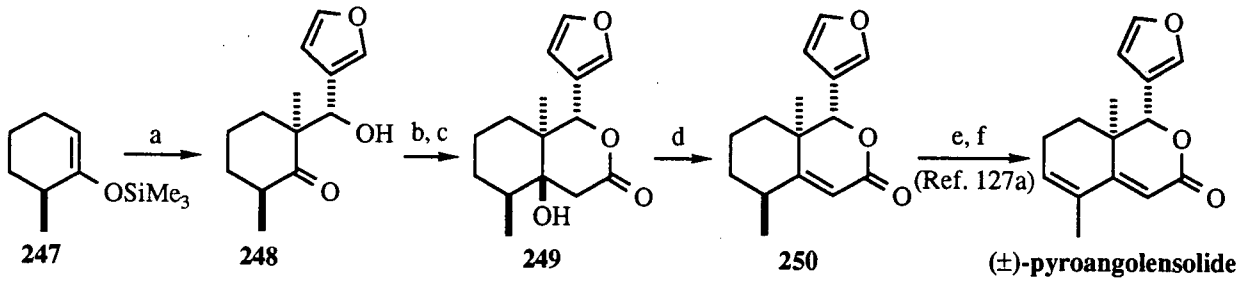
In the subsequent year, Fernández Mateos and de la Fuente Blanco reported the synthesis of bicyclic enone **241a** and bicyclic epoxy-lactone **242** (Scheme 3.4).[124] Due to the structural similarity of **241a** and **242** to the C,D-ring system of azadiradione (**215**) and gedunin (**218**; Scheme 3.1), respectively, the authors suggested that **241a** and **242** could be used to probe the structure-activity relationships in limonoids. Their approach is summarized in Scheme 3.4 and started with the stereoselective addition of (*E*)-1-(3-furyl)-2-nitro-1-propene to the trimethylsilyl enol ether **243** to provide as the major diastereomer the bicyclic silyl nitronate **244**. Hydrolysis of **244** followed by a Nef reaction and aldol condensation yielded a 4:1 mixture of epimeric enones **241a** and **241b**, respectively. The 17α-epimer (**241a**) was separated and converted further to the epoxy-lactone **242** after reduction, epoxidation, Jones oxidation, and Baeyer-



(a) (*E*)-1-(3-furyl)-2-nitropropene, $TiCl_4$, CH_2Cl_2, –78 °C (b) KOH, EtOH (c) KOH, EtOH, 86 °C, separation of 17β-furyl diastereomer (d) $LiAlH_4$, Et_2O, 0 °C (e) *m*-CPBA, CH_2Cl_2, –40 °C (f) Jones reagent, acetone, 0 °C (g) *m*-CPBA, CH_2Cl_2.

Scheme 3.4. Fernández Mateos and de la Fuente Blanco: Synthesis of Limonoid Analogues.[124]

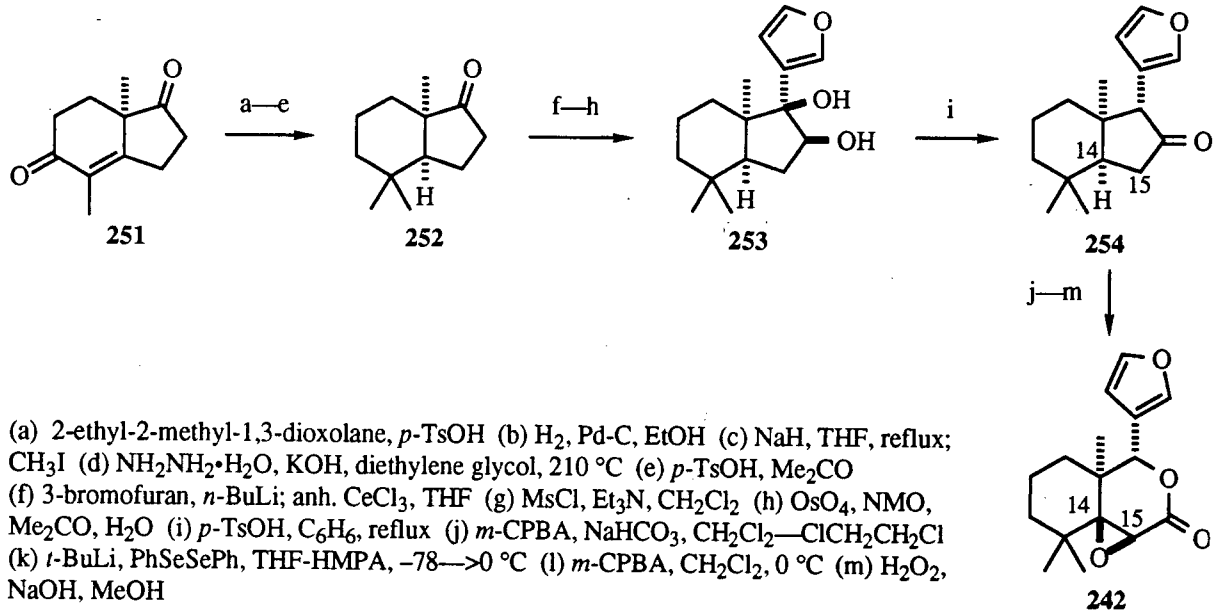
Villiger oxidation steps. Recent papers[125] from the same research group present alternative syntheses of enone **241a** in which the use of an intramolecular diazo-ketone cyclization is featured. In addition, a further report[126] from the Fernández Mateos group describes the formal synthesis of (±)-pyroangolensolide (**246**; *cf.* Scheme 3.5), a bicyclic, unsaturated lactone[127] that is derived from the pyrolysis[127c,d] of natural methyl angolensolate (**225**, Scheme 3.1).



(a) 3-furaldehyde, $TiCl_4$, , CH_2Cl_2, –78 °C (b) Ac_2O, C_5H_5N, 0 °C (c) LDA, Et_2O, –78 °C (d) $SOCl_2$, C_5H_5N (e) NBS, CCl_4 (f) K_2CO_3, MeOH

Scheme 3.5. Fernández Mateos and de la Fuente Blanco: Synthesis of (±)-Pyroangolensolide.[126]

Lhommet and co-workers have reported an alternative approach to the Fernández Mateos bicyclic epoxy-lactone **242**.[128] The synthesis, summarized in Scheme 3.6, involves the initial conversion of the Wieland-Miescher ketone analogue **251** to bicyclic ketone **252**. Addition of 3-(dichlorocerio)furan to ketone **252** followed by dehydration and osmium tetroxide mediated dihydroxylation provided diol **253**. Subsequent pinacol rearrangement[128] of **253** and acid-



(a) 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH (b) H_2, Pd-C, EtOH (c) NaH, THF, reflux; CH_3I (d) $NH_2NH_2{\cdot}H_2O$, KOH, diethylene glycol, 210 °C (e) *p*-TsOH, Me_2CO (f) 3-bromofuran, *n*-BuLi; anh. $CeCl_3$, THF (g) MsCl, Et_3N, CH_2Cl_2 (h) OsO_4, NMO, Me_2CO, H_2O (i) *p*-TsOH, C_6H_6, reflux (j) *m*-CPBA, $NaHCO_3$, CH_2Cl_2—$ClCH_2CH_2Cl$ (k) *t*-BuLi, PhSeSePh, THF-HMPA, –78—>0 °C (l) *m*-CPBA, CH_2Cl_2, 0 °C (m) H_2O_2, NaOH, MeOH

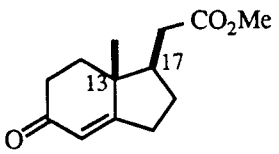
Scheme 3.6. Lhommet *et al.*: Synthesis of a Limonoid Intermediate.[128]

catalyzed epimerization[128] yielded the ketone **254**. Baeyer-Villiger oxidation followed by introduction of the C(14)–C(15) double bond (triterpenoid numbering) and enone epoxidation

completed the synthesis of racemic epoxy-lactone **242**. If desired, however, the enedione **251** that was used as a starting material in this synthesis could be obtained in enantiopure form[128] and the synthesis of **242** could therefore be considered enantiospecific.

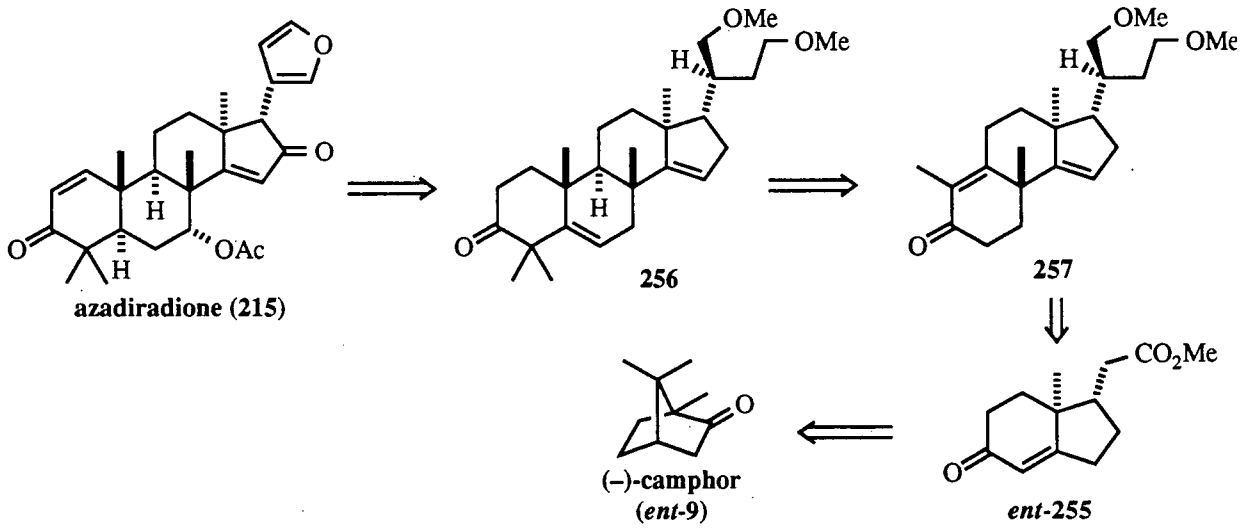
Finally, extensive investigations by Ley and co-workers[122] have been directed towards a total synthesis of azadirachtin (**227**) and structural analogues. Due to space constraints in this thesis, this large body of work will not be summarized.

In 1992 our research group published an enantiospecific synthesis of bicyclic enone-ester **255** from (+)-camphor (**9**).[45] Our interest in the area of limonoid synthesis resulted from our recognition that enone-ester **255** and its enantiomer (***ent*-255**) has considerable potential as C,D-ring intermediates in steroid and triterpenoid synthesis, respectively. In particular, we noted that the relative and absolute configurations of the two stereocenters of *ent*-enone ester (***ent*-255**), at C(13) and C(17) are identical to those found in the tetracyclic limonoids.



255

In devising a preliminary synthetic strategy we considered azadiradione (**215**) as our initial target molecule. Concern for the lability of the furan moiety in **215** under acidic and oxidative conditions[129] prompted us to defer the construction of the furan ring to a relatively late stage in our synthetic plan (*cf.* Scheme 3.7). With this consideration in mind, we envisioned that the target limonoid, azadiradione (**215**), could be derived from an advanced, tetracyclic intermediate such as bis(alkoxy)-dienone **256**. In turn, dienone **256** could be derived from the tricyclic enone **257** through appropriate annulation and alkylation procedures. Finally, enone **257** could arise from the known *ent*-enone-ester (***ent*-255**), which can be prepared conveniently from (–)-camphor (***ent*-9**) or (–)-borneol (**159**). Our progress in this area is documented in the remainder of this chapter.

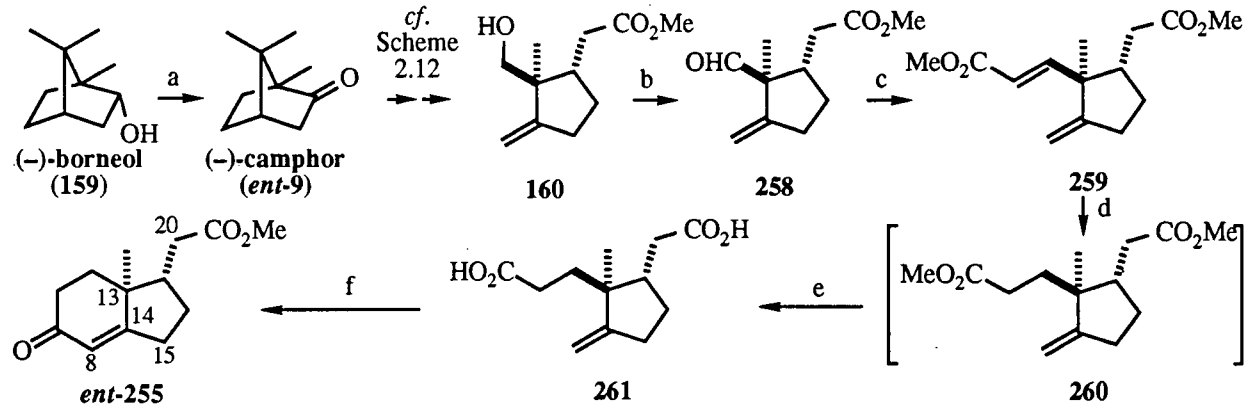


Scheme 3.7. Synthetic Plan for a Proposed Limonoid Synthesis.

(c) Results and Discussion

i. Preparation of Bicyclic Enone 267 from (–)-Camphor (ent-9)

In the first stage of our synthetic approach to the limonoids we needed to prepare *ent*-enone-ester (***ent*-255**)[45] in sufficient quantities. For this purpose we needed to employ (–)-camphor (***ent*-9**) as our starting material, and as mentioned previously (p. 40), this could also be



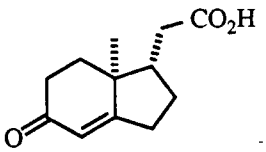
(a) CrO_3, aq. H_2SO_4, acetone, 0 °C [97%] (b) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; Et_3N, –78 °C → r.t. [92%] (c) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF [96%] (d) Mg, MeOH, 0 °C (e) KOH, H_2O, MeOH [86%, from **259**] (f) $(CF_3CO)_2O$, CH_2Cl_2; *p*-TsOH, MeOH [89%].

Scheme 3.8. Preparation of Bicyclic (–)-Keto-enone (***ent*-255**).[38,39,45]

prepared via Jones oxidation of (–)-borneol (**159**). (–)-Camphor (***ent*-9**) was then converted to (+)-hydroxy-ester (**160**) via the six-step route[38,39,45] described earlier in this thesis (Scheme 2.12).

Swern oxidation[100] of (+)-hydroxy-ester **160** (Scheme 3.8) provided the ester-aldehyde **258**. Treatment of aldehyde **258** with the sodium salt of trimethyl phosphonoacetate (Horner-Wadsworth-Emmons reaction)[130] yielded the α,β–unsaturated ester **259** as a single diastereomer. The large coupling constant (J = 16.0 Hz) between the two olefinic protons at C(11) and C(12) (triterpenoid numbering) suggested[101] that the double bond had been formed with an (*E*) or *trans* stereochemistry. Subsequent chemoselective reduction of the unsaturated ester **259** with magnesium in methanol[131] yielded, presumably, the intermediate diester **260** which was not isolated, but hydrolyzed directly with aqueous potassium hydroxide solution to yield diacid **261**.

Treatment of the crystalline diacid **261** with trifluoroacetic anhydride (2 eq.) in dichloromethane[132] effected a cyclization reaction to afford the bicyclic enone-acid **261a**, which



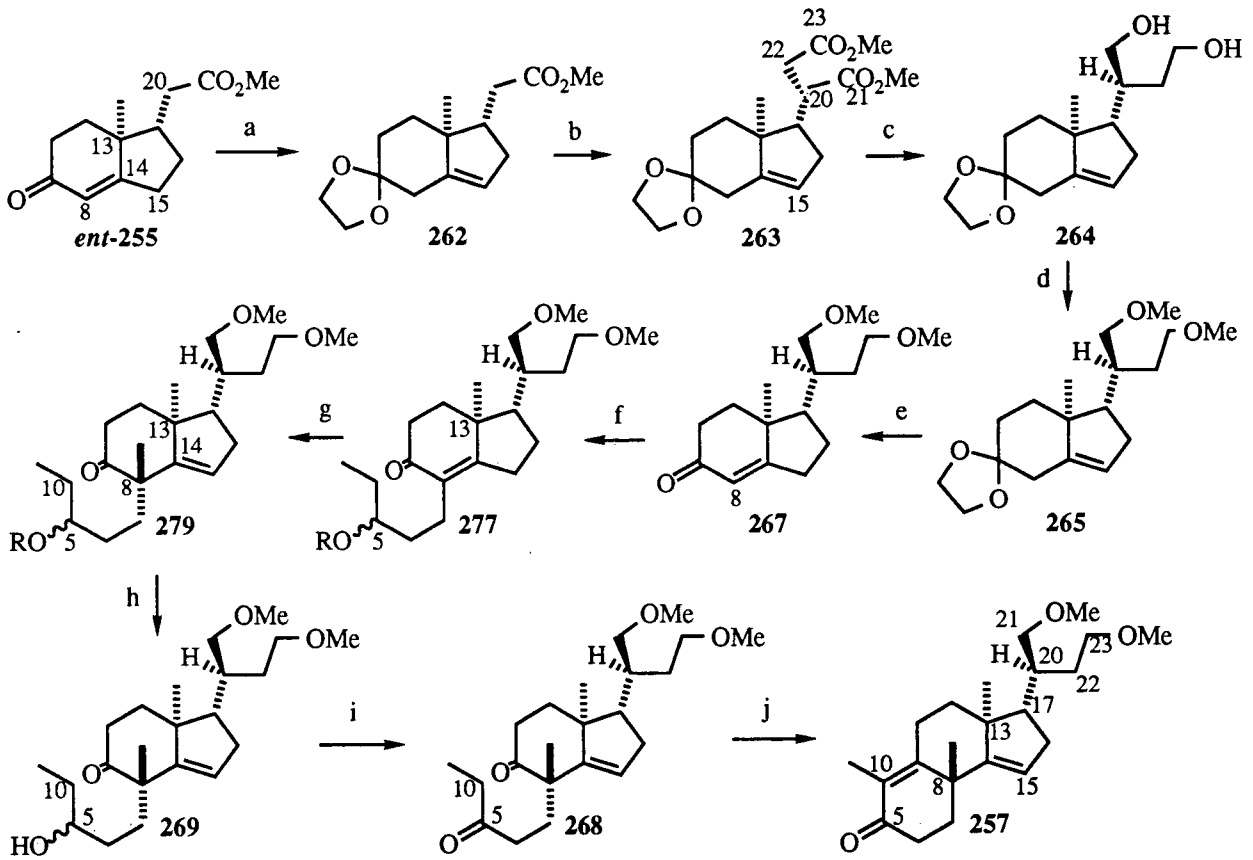
261a

can be isolated if desired. However, if the dichloromethane solvent is removed by evaporation and replaced with dry, distilled methanol, then subsequent addition of *p*-toluenesulfonic acid promotes a further esterification reaction and the product that is isolated under these circumstances is the bicyclic enone-ester ***ent*-255**.

Spectroscopic data obtained for the enone-ester ***ent*-255** prepared above were consistent with those reported previously in the literature. Thus, the presence of two carbonyl stretching absorptions at 1740 and 1662 cm^{-1} support the presence of an ester group and an α,β-unsaturated ketone group, respectively. Similarly, the two signals in the 50 MHz ^{13}C NMR spectrum at 198.7 and 177.5 ppm further confirm the presence of the enone and ester carbonyl groups, while the two signals at 173.0 and 122.0 ppm can be assigned to C(14) and C(8), respectively, which form part of the enone system. Of note in the 400 MHz ^{1}H NMR spectrum is the resonance for the C(8) enone vinyl proton at 5.80 ppm, which appears as a broad singlet. It is believed that the broadness of this signal is a result of additional long-range coupling of H(8)

with one or both of the H(15) protons. Furthermore, the singlet at 3.71 ppm can be assigned to the methyl ester (–CO_2Me) protons while the singlet at 1.05 ppm can be assigned to the protons of the angular C(13) methyl group. The remainder of the ^{1}H NMR spectrum, as well as the APT and mass spectra, are consistent with those expected for enone-ester ***ent*-255**.

As our synthetic plan (Scheme 3.7) suggested, the next stage of the project was to add a two-carbon unit to C(20) so as to permit the future construction of a furan ring at that position. In preparation for this alkylation reaction, bicyclic enone-ester ***ent*-255** was converted



(a) $(CH_2OH)_2$, PPTS, C_6H_6, reflux [82%] (b) LDA, THF, –78 °C; $BrCH_2CO_2Me$, TBAI, –78 °C—>r.t. 93%, based on recovered **262**] (c) DIBAL, THF, 0 °C [85%] (d) NaH, THF; CH_3I [90%] (e) 1 M HCl, Me_2CO [92%] (f) NaH, DMSO; 1-iodo-3-(*t*-butyldiphenylsilyloxy)pentane (**270b**) [65%] (g) NaH, DMSO; CH_3I [80%] (h) TBAF, THF [90%] (i) CrO_3, aq. H_2SO_4, Me_2CO, 0 °C [87%] (j) *p*-TsOH, C_6H_6, reflux [84%].

Scheme 3.9. Preparation of Tricyclic Enone (**257**) from (–)-Enone-ester ***ent*-255**. [N.B. R = TBDPS]

to the bicyclic ketal-ester **262** (Scheme 3.9) through treatment with ethylene glycol, pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene.[92b,c] The use of *p*-toluenesulfonic acid as an

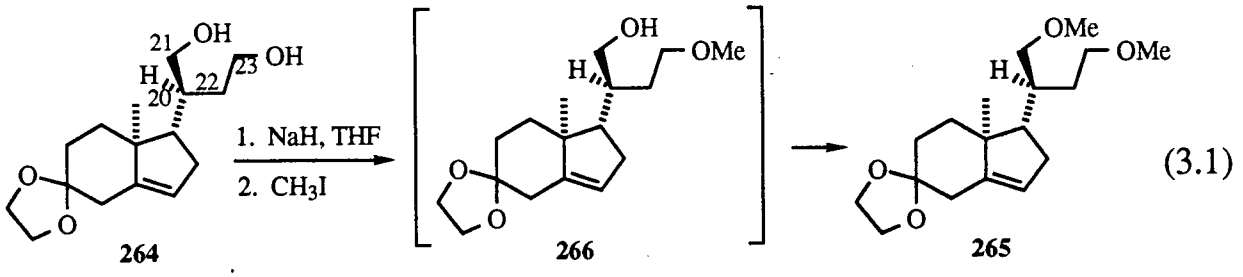
alternative acid catalyst[92a] in this reaction resulted in gradual decomposition of enone-ester ***ent*-255** to a dark-brown tar from which only low yields of ketal-ester **262** could be isolated. As expected, the infrared spectrum of ketal-ester **262** showed only a single ester carbonyl absorption, at 1742 cm^{-1}. Other spectroscopic data (^1H NMR, low and high resolution mass spectra) supported the identification of the reaction product as being the ketal-ester **262**.

Subsequently, α-alkylation of the methyl ester was attempted. Treatment of a solution of lithium diisopropylamide and ketal-ester **262** in THF with methyl bromoacetate resulted in only ~50% conversion of starting material to the desired product. Adjustment of reaction times and reactant concentrations did not improve the efficiency of the reaction. However, upon addition of dry tetrabutylammonium iodide or lithium iodide (0.3–0.5 eq.)[133] to the reaction mixture, complete conversion of starting material to product (>90% yield) was achieved.

The ketal-diester **263** was obtained as a single diastereomer, as ascertained by 400 MHz ^1H NMR spectroscopy, TLC, and GLC. The diastereoselectivity of the alkylation reaction with methyl bromoacetate can be explained using a rationale[94] analogous to that presented in the previous chapter of this thesis (*cf.* Scheme 2.15, p. 44). Actually, the exact configuration at C(20) is of no concern to us because we realize that at a later stage in the synthetic plan, this particular carbon will become sp^2 hybridized. In any case, we assumed that the C(20) configuration of our product was that predicted by our model, and shown in structure **263**.

The infrared spectrum of ketal-diester **263** exhibited a carbonyl stretching band at 1741 cm^{-1}. The 400 MHz ^1H NMR spectrum of **263** exhibited, most notably, the presence of two singlets at 3.64 and 3.68 ppm that represent the protons of the two methyl ester (methoxycarbonyl) groups. The integrity of the ketal protective group is apparent because of the four-proton multiplet at 3.84–4.00 ppm, while the vinyl proton H(15) is represented by a broad singlet at 5.27 ppm. The 75 MHz ^{13}C NMR spectrum is likewise consistent with that expected for ketal-diester **263**. The two signals at 172.4 and 175.4 ppm can be assigned to the two carbonyl carbons (C(21) and C(23)) of ketal-diester **263**.

Having established the identity of ketal-diester **263** it was decided that the ester functional groups should be protected to permit the eventual construction of the tetracyclic limonoid skeleton. Thus, reduction of the ketal-diester **263** using either lithium aluminum hydride or diisobutylaluminum hydride in THF yielded ketal-diol **264**. Although the yields of the products obtained using either reagent were comparable, the work-up of the reaction involving lithium aluminum hydride was cumbersome on account of the viscous and gelatinous nature of the aqueous phase. The infrared spectrum of ketal-diol **264** exhibited a broad absorption at 3340 cm^{-1} that corresponds to an O–H stretching vibration. Subsequent treatment of ketal-diol **264** with sodium hydride (2.2–2.5 eq) followed by methyl iodide (2.2–2.5 eq) yielded dimethoxy-ketal **265** after 8 h. The progress of the reaction could be followed conveniently by TLC. It was observed that if the reaction mixture was analyzed by TLC prior to the reaction reaching completion, an additional product, whose R_f in 50% acetone–pet. ether (0.49) was intermediate between that of the starting ketal-diol **264** (0.28) and dimethoxy-ketal **265** (0.67). The identity of this new intermediate was not determined, but is assumed to be the hydroxy-methoxy-ketal **266** (Equation 3.1). It is possible that because the C(21)-hydroxyl group in **264** is closer to the tertiary C(20) carbon than the C(23) hydroxyl group, the C(21)-hydroxyl group is more hindered than that at C(23), and hence, undergoes methylation less readily than the C(23) hydroxyl group.



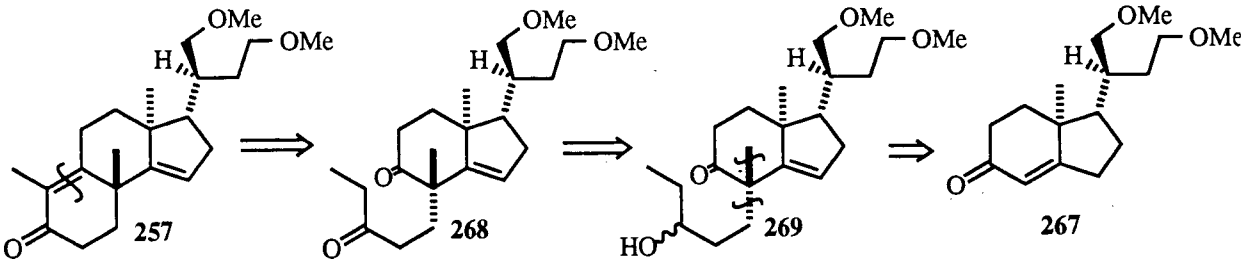
264 **266** **265** (3.1)

Finally, hydrolysis of the ketal[102] in dimethoxy-ketal **265** yielded dimethoxy-enone **267** in which provision has been made for the later construction of the furanoid side-chain unit that is a structural feature of most tetracyclic limonoids. The presence of an enone functional group was supported by an infrared band at 1660 cm^{-1} (C=O stretch). The 400 MHz ^1H NMR spec-

trum of **267** exhibited a broad singlet at 5.71 ppm, which is assigned to vinyl proton H(8). The chemical shift of the H(8) signal is consistent with that expected for α-vinyl protons of α,β-unsaturated ketone systems. Proton signals for the two methoxy groups occur at 3.27 and 3.31 ppm.

ii. Preparation of Tricyclic Enone 257 from Bicyclic Enone 267.

With the dimethoxy-enone **267** in hand we were ready to undertake construction of the B-ring and introduce the C(8) methyl group that is present in many of the the limonoids, including azadiradione (**215**). Retrosynthetic analysis (Scheme 3.10) suggested that the tricyclic enone **257** could be constructed through intramolecular aldol condensation of the diketone **268**. Diketone **268** could, in turn, be obtained from hydroxy-ketone **269**, and **269** can be derived from dimethoxy-enone **267** through successive alkylation of **267** with a suitably functionalized five-carbon alkyl halide and methyl iodide.

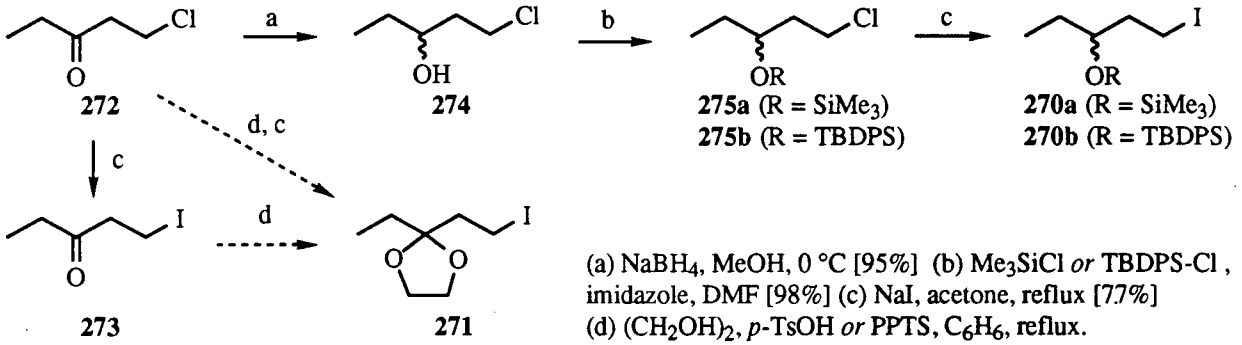


Scheme 3.10. Retrosynthetic Analysis of Tricyclic Dienone **257.**

Structural considerations suggested that a possible five-carbon alkylating agent could be 1-iodo-3-silyloxypentane (**270**; Scheme 3.11). In work related to the preparation of Wieland-Miescher ketone analogues, Mander and co-workers employed 1-iodo-3,3-ethylenedioxypentane (**271**)[134] and 1-iodo-3-(trimethylsilyloxy)pentane (**270a**)[134] as alkylating agents. In our hands, the preparation of ketal-iodide **271** from commercially available 1-chloro-3-pentanone (**272**) was only marginally successful. Although 1-chloro-3-pentanone (**272**) could be converted to the corresponding iodide **273**, reaction of iodide **273** with ethylene glycol or 2,2-

ethylenedioxybutane[135] and *p*-toluenesulfonic acid in refluxing benzene yielded a mixture of products from which only a small amount of the desired ketal-iodide **271** could be separated inconveniently through repeated distillation under reduced (~0.1 mm Hg) pressure. Reversing the order of the iodination and ketalization steps was equally unsatisfactory.

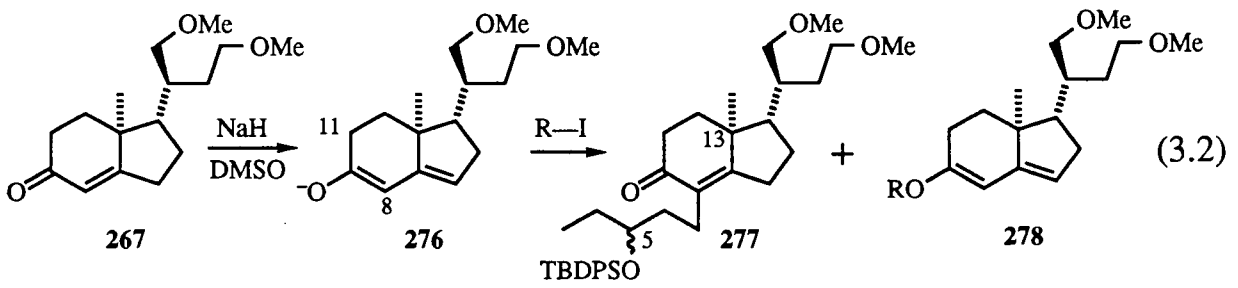
Accordingly, we turned our attention to the synthesis of the alternative 1-iodo-3-(*t*-butyldiphenylsilyloxy)pentane **270b** (Scheme 3.11). Our synthesis of 1-iodo-3-(*t*-butyldiphenylsilyloxy)pentane (**270b**) was based on Mander's procedure[134] for the preparation of the trimethylsilyloxy analogue **270a** (in order to improve the hydrolytic stability of our alkylating agent, however, we chose instead to replace the trimethylsilyl protective group in **270a** with the more robust *t*-butyldiphenylsilyl group). Thus, commercially available 1-chloro-3-pentanone (**272**) was reduced using sodium borohydride in methanol to yield racemic 1-chloro-3-pentanol (**274**). Protection of the hydroxyl group of **274** with *t*-butyldiphenylsilyl chloride and imidazole in DMF[93] yielded silyloxy-chloride **275b**. Finally, conversion of the chloride **275b** to iodide **270b** was accomplished through a Finkelstein reaction (NaI, acetone, reflux).[136]



Scheme 3.11. Preparation of 1-Iodo-3-(*t*-butyldiphenylsilyloxy)pentane (**270b**).

Many examples illustrating the α-alkylation of enones[135,137] have been documented in the literature. The use of sodium hydride in dry dimethyl sulfoxide[138] as a reliable method for the chemoselective formation of the thermodynamic dienolate of α,β-unsaturated ketones has been documented amply in the literature. Addition of sodium hydride to dimethyl sulfoxide that had been distilled from calcium hydride resulted in proton transfer to form the

methylsulfinylmethyl, or 'dimsyl'[138] anion. Subsequent addition of an enone, such as dimethoxy-enone **267**, resulted in formation of the thermodynamic dienolate **276** (Equation 3.2).



(3.2)

[R = 3-(*t*-butyldiphenylsilyloxy)pent-1-yl]

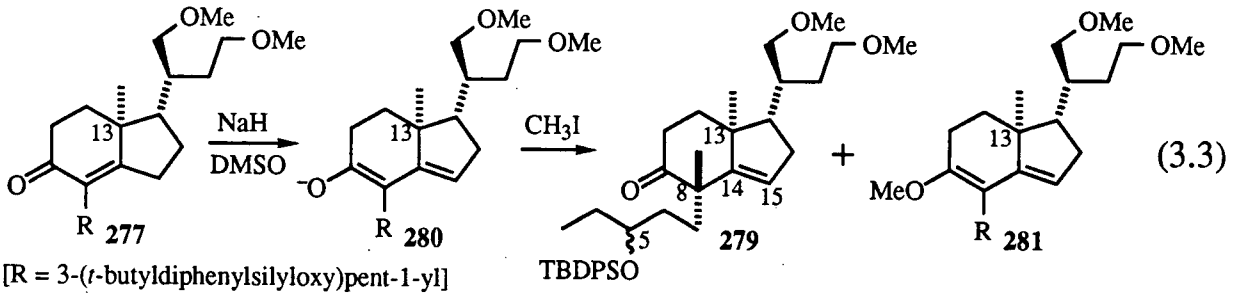
Addition of racemic silyloxy-iodide **270b** to the reaction gave a mixture of products. The desired α-alkylated enone **277** was obtained as a mixture of diastereomers [TLC R_f (60% EtOAc–pet. ether): 0.28 and 0.31] that were not separated. The combined yield of the two diastereomers **277** was 65%. In addition, a considerably less polar compound [TLC R_f (60% EtOAc–pet. ether): 0.86] was isolated in ~28% yield. Unfortunately, this latter by-product could not be purified sufficiently to allow detailed characterization. Instead, based on literature precedent,[137c] the by-product was assumed to be the dienol ether **278**, formed as a result of *O*-alkylation of the thermodynamic dienolate **276** with silyloxy-iodide **270b**. That subsequent reaction of the supposed dienol ether **278** with 1 M HCl resulted in near-quantitative recovery of dimethoxy-enone **267** supports the proposal that the by-product was likely the dienol ether **278**. The spectral characteristics of the recovered enone **267** were identical in all respects to that of the enone sample that was used for the alkylation reaction.

The infrared spectrum of alkylated enone **277** exhibited a carbonyl stretching absorption at 1653 cm^{-1}. Although the observed absorption occurs below the range normally expected for α,β-unsaturated carbonyl groups,[101] it is pertinent to note that in a structurally similar bicyclic α-alkylated α,β-unsaturated ketone[135] a carbonyl absorption occurred at 1655 cm^{-1}. The 400 MHz ^1H NMR spectrum provided further evidence in support of the identity of alkylated enone **277**. Although the spectrum of **277** indicated that enone **277** was present as a 50:50 mixture of

diastereomers, it was still possible to correlate parts of the spectrum to the structure of **277**. For example, the combined signals at 7.60–7.72 (m, 4H), 7.30–7.42 (m, 6H) and 1.04 (s, 9H) all supported the presence of a *t*-butyldiphenylsilyl protective group in the molecule. The three-proton triplet at 0.77 ppm could be assigned to the terminal methyl group of the newly added alkyl chain while the three-proton singlet at 0.99 ppm could be assigned to the protons of the C(13)-methyl group.

With regards to the regiochemistry of the alkylation reaction, the absence of signals between 4.5–6.0 ppm of the spectrum indicates there are no vinyl protons present in enone **277**, and supports the presumption that alkylation at C(8) of dienolate **276** has occurred. Had alkylation at C(11) occurred instead, a vinyl proton would still be present at C(8) and would have given rise to a signal between 4.5–6.0 ppm.[101]

At this point, a second, similar alkylation of enone **277** with methyl iodide yielded the β,γ-unsaturated enone **279** (*cf.* Equation 3.3). Thus, treatment of the epimeric enones **277** with methylsulfinylmethylsodium ('dimsylsodium'),[138] prepared *in situ* by reaction of sodium hydride with dry dimethyl sulfoxide, yielded dienolate **280**. It was expected that due to steric considerations, alkylation with methyl iodide would occur from the face of the enolate opposite the C(13) methyl group. The progress of the alkylation reaction was monitored by TLC, and after the starting material (**277**) had been consumed totally, the desired β,γ-unsaturated enone **279** was obtained as a 1:1 mixture of C(5) diastereomers. A minor by-product (*cf.* **281**, Equation 3.3) arising from the *O*-alkylation of dienolate **280** with methyl iodide was also isolated.



[R = 3-(*t*-butyldiphenylsilyloxy)pent-1-yl]

(3.3)

The 400 MHz ^{1}H NMR spectrum of the product (**279**) showed considerable doubling and overlap of signals due to the presence of diastereomeric compounds. Regardless, it is possible to discern two pairs of three-proton singlets at 0.90 and 0.92 ppm, and 0.99 and 1.06 ppm that could be assigned to the C(13)-methyl groups and the newly introduced C(8)-methyl groups of the two diastereomeric ketones **279**. In addition, the doublets of doublets at 5.26 and 5.31 ppm can be assigned to the C(15) vinyl protons for the diastereomeric ketones **279** and provide evidence that alkylation had occurred at C(8) and that the double bond that had previously occupied the C(8)–C(14) positions is now found between C(14) and C(15), as expected. Indeed, the carbonyl absorption of ketones **279** now falls at 1708 cm^{-1} which is in the range expected for non-conjugated carbonyl groups.

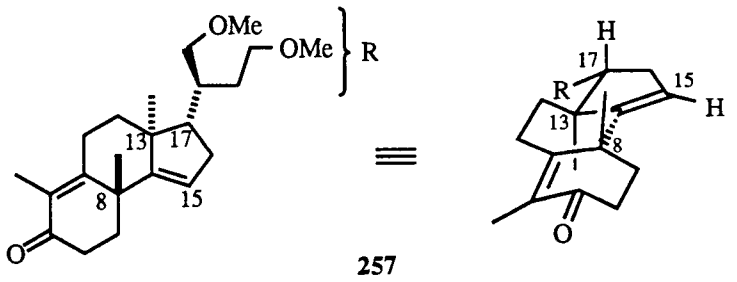
Unfortunately, due to the complexity of the ^{1}H NMR spectrum, which exhibited many overlapping signals arising from the two epimeric products, it was not possible at this point to perform an NOE experiment to determine the configuration at C(8). Accordingly it was decided to postpone stereochemical determination to a later stage of the project.

Cleavage of the silyl protective group[93] in **279** occurred without incident. Treatment of enone **279** with tetrabutylammonium fluoride (2 eq) in THF yielded the epimeric hydroxy-enones **269** (ν_{O-H} = 3456 cm^{-1}; $\nu_{C=O}$ = 1709 cm^{-1}), which were not purified further but submitted directly to Jones oxidation conditions [CrO_3, aqueous H_2SO_4, acetone][139] to afford diketone **268** in 87% yield. As expected, the infrared absorption at 3456 cm^{-1} is no longer present in the spectrum of diketone **268**. A peak at 1713 cm^{-1}, however, does support the presence of carbonyl groups in the molecule. With the loss of the stereocenter at C(5) the 400 MHz ^{1}H NMR spectrum is simplified greatly. For example, the ^{1}H NMR spectrum supports the presence of three methyl groups in **268**, as evidenced by signals at 0.99 (t, 3H; C(10)-methyl group), 1.01 (s, 3H; C(13)-methyl group), and 1.16 (s, 3H; C(8)-methyl group) ppm. The doublet of doublets at 5.46 ppm represents the C(15)-vinyl proton while the two singlets at 3.27 and 3.31 ppm can be assigned to the protons of the two methoxy groups.

Finally, diketone **268** was allowed to undergo acid-catalyzed intramolecular aldol condensation [*p*-TsOH, C_6H_6, reflux][109] to afford the tricyclic enone **257** in 84% yield. The infrared spectrum of tricyclic enone **257** exhibited a carbonyl stretching vibration at 1662 cm^{-1} and also, absorptions at 1625 and 1602 cm^{-1} representing the C=C absorptions. In the 400 MHz NMR spectrum, the three-proton doublet at 1.75 ppm can be assigned to the C(10)-methyl group, and is within the range expected for a methyl group that is adjacent to a vinyl group. The two singlets at 3.29 and 3.32 ppm can be assigned to the methoxy protons while the singlets at 0.82 and 1.31 ppm can be assigned to the C(13)-methyl and C(8)-methyl protons, respectively.

Irradiation of the signal at 0.82 ppm resulted in enhancement of the multiplet at 1.69–1.87 ppm, but not the doublet at 1.75 ppm (*cf.* Table 5.18, p. 187). Through the aid of a COSY spectrum (*cf.* Table 5.19, p. 188), this multiplet was assigned to H(22), H(20), and H(12). Furthermore, enhancements of the two singlets at 3.32 and 3.29 ppm [–OMe, –OMe] and the signal at 3.30–3.38 [H(21)] were observed. These results suggest that it would be reasonable to assign the signal at 0.82 ppm to the C(13)-methyl protons. By elimination, the singlet at 1.31 ppm is assigned to the C(8)-methyl protons.

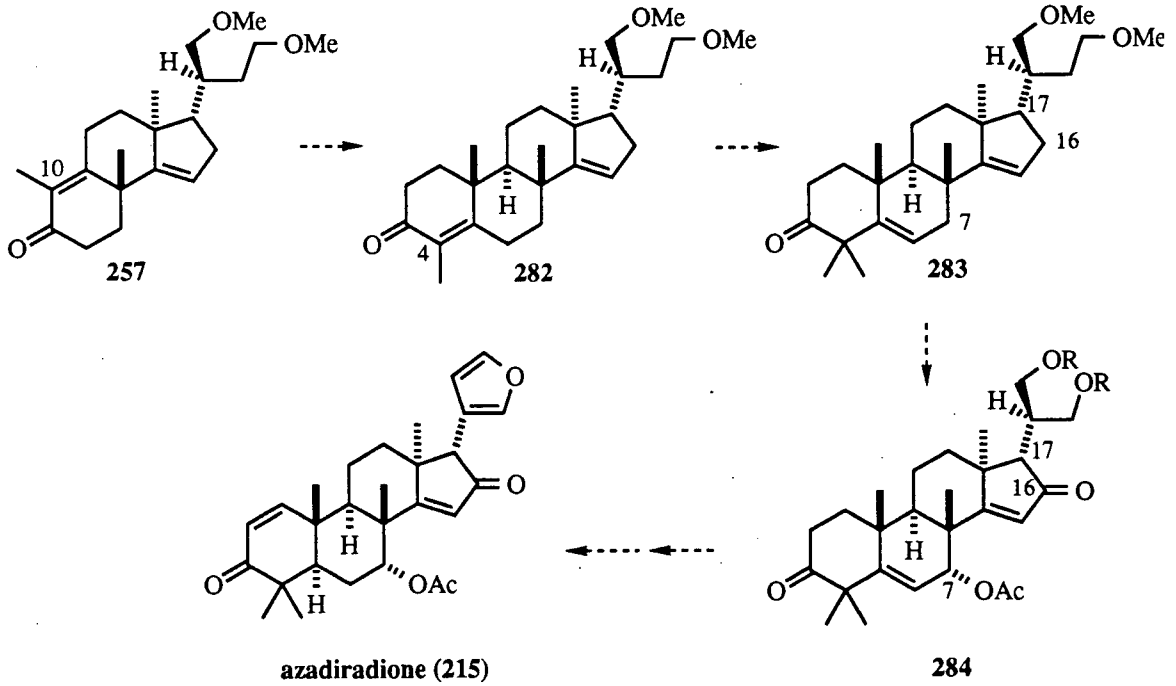
We now sought to establish the stereochemistry of the C(8)-methyl group using data gained from NOE experiments (*cf.* Table 5.18, p. 187). Irradiation of the C(13)-methyl signal did not result in enhancement of the intensity of the C(8)-methyl signal. Back-irradiation of the C(8)-methyl signal resulted in enhancement of not the C(13)-methyl signal, but instead, the H(15) vinyl proton signal, among others. Similarly, irradiation of the H(15) vinyl signal (5.41–5.48 ppm) resulted in enhancement of the C(8)-methyl signal, among others. Examination of molecular models of enone **257** and its C(8) epimer suggested that the presence of an NOE between the C(8)-methyl group and H(15) would be more likely if the C(8)-methyl group adopted a β-orientation, that is, *anti* to the C(13)-methyl group. Thus, we feel confident that the correct structure for our tricyclic enone product is that represented by structure **257**.



257

iii. Future Directions

Because of time and material constraints it was decided not to undertake further synthetic studies on tricyclic enone **257** at this time. Thus, in summary, the tricyclic enone **257**, a potential BCD-ring intermediate for the enantiospecific synthesis of limonoids, has been prepared[140] in



Scheme 3.12. Projected Completion of the Limonoid Synthesis.

ten steps from bicyclic enone-ester ***ent*-255** which was derived from (–)-camphor (***ent*-9**). It is proposed (Scheme 3.12) that further C(10)-alkylation of dienone **257** followed by cyclization (*cf.* Robinson annulation) would yield dienone **282.** Subsequent C(4)-methylation of tetracyclic dienone **282** should provide dienone **283**, an intermediate in which provision has been made for

the introduction of a furanoid unit at C(17) as well as oxygen functionality at C(7) and C(16), to yield acetoxy-diketone **284** and thence, azadiradione (**215**).

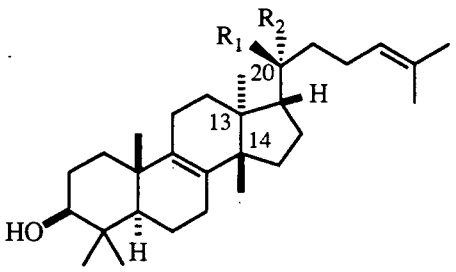
Chapter 4

Further Studies on the Chemistry of 4-Methylcamphor: A Multiple Rearrangement Process in the Bromination of *endo*-3-Bromo-4-methylcamphor

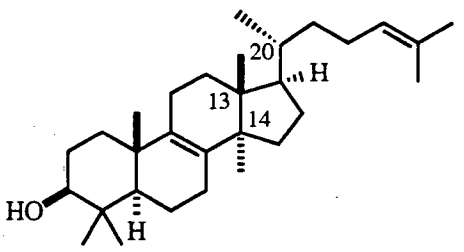
4. Further Studies on the Chemistry of 4-Methylcamphor: A Multiple Rearrangement Process in the Bromination of *endo*-3-Bromo-4-methylcamphor

(a) Introduction

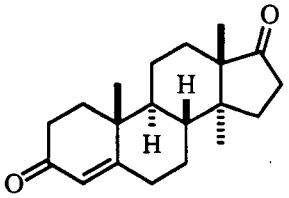
Our ongoing interest in triterpenoid and steroid synthesis led us to consider as potential targets the euphane (e.g. euphol (**204**; Scheme 4.1)) and tirucallane (e.g. tirucallol (**205**)) triterpenoids, both of which have the (13α,14β) absolute configuration as drawn, as well as the lanostane (e.g. lanosterol (**285**)) triterpenoids and 14α-methyl steroids (e.g. 14α-methylandrostenedione (**286**) and 14α-methylestrone (**287**)), both of which have the opposite, (13β,14α) absolute configuration as drawn. Despite the biosynthetic importance of many of these compounds, few total syntheses of representative members of these classes of compounds have been reported.



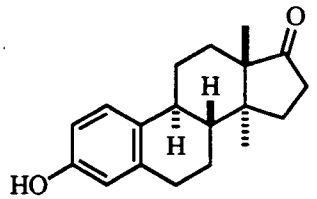
euphol (204; R_1 = H; R_2 = CH_3)
tirucallol (205; R_1 = CH_3; R_2 = H)



lanosterol (285)



14α-methylandrost-4-en-3,17-dione (286)



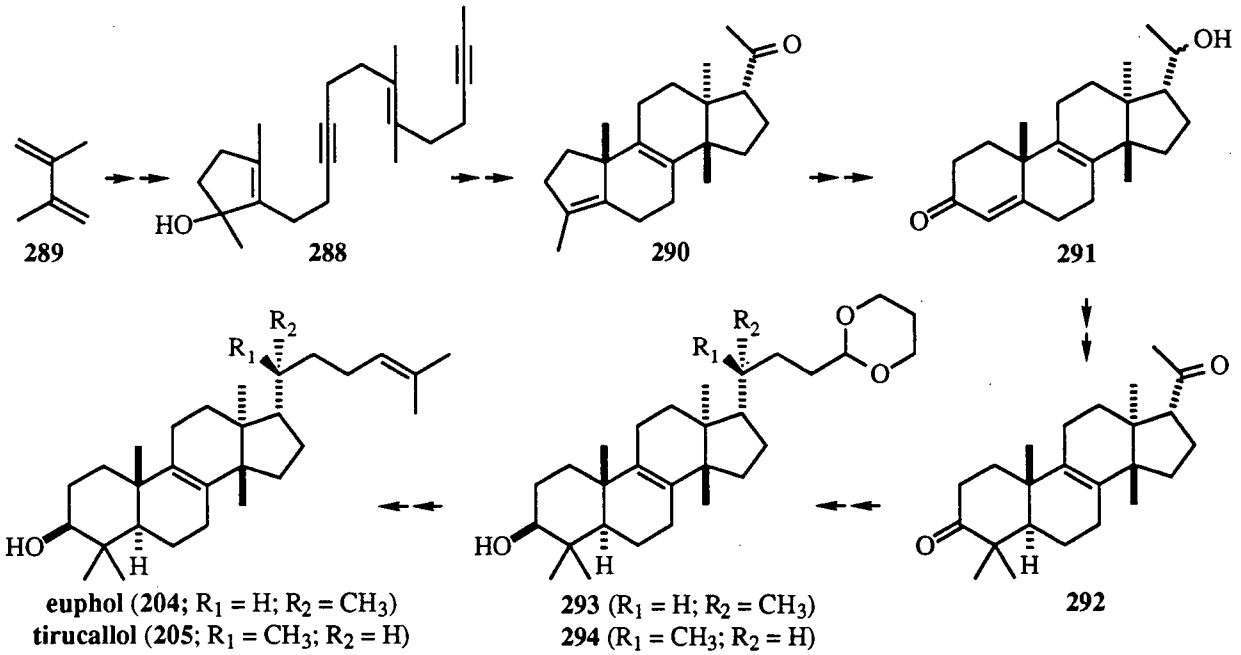
14α-methylestrone (287)

Scheme 4.1. Structures of Representative 14-Methyltriterpenoids and 14-Methyl Steroids.

(b) Previous Synthetic Routes to Euphanes, Tirucallanes, Lanostanes, and 14-Methyl Steroids

The first successful total synthesis of a euphane or tirucallane triterpenoid[141] was not published until 1990, when the late W.S. Johnson and his co-workers at Stanford reported a total

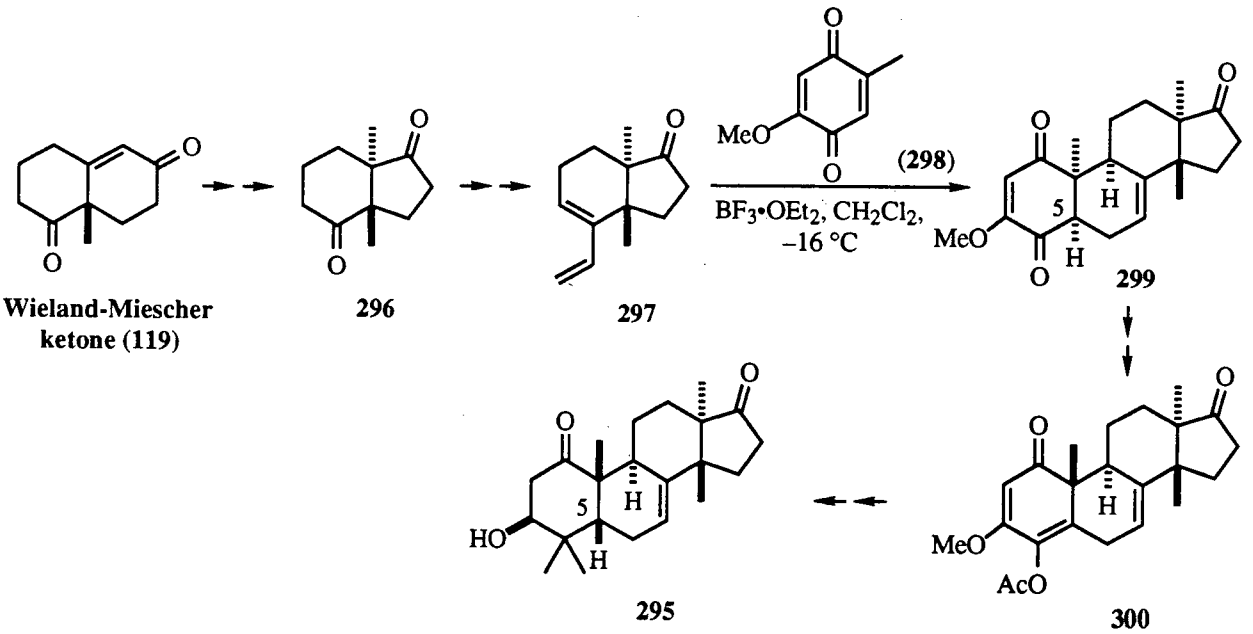
synthesis of euphol (**204**) and tirucallol (**205**) that was based on a biomimetic polyolefin cyclization strategy (Scheme 4.2). Dienediynol **288** was prepared from 2,3-dimethyl-1,3-butadiene (**289**) in eight steps. Treatment of **288** with 5:1 formic acid–pentane at 0 °C followed by methanolysis of the resulting enol formate yielded tetracyclic ketone **290** in 89% yield. Reduction of the C(20) keto group (triterpenoid numbering) followed by A-ring expansion via tandem ozonolysis–aldol condensation yielded hydroxy-enone **291**. Conventional reactions were used to convert **291** to enedione **292**. Enedione **292** was converted to a mixture of C(20)-epimeric hydroxy-acetals **293** and **294** that were separable by chromatography. Hydroxy-acetal **293** was converted to (±)-euphol (**204**) in three steps while hydroxy-acetal **294** was converted to (±)-tirucallol (**205**), also in three steps.



Scheme 4.2. Johnson *et al.*: Total Synthesis of (±)-Euphol (**204**) and (±)-Tirucallol (**205**).[141]

Five years before Johnson and co-workers reported their synthesis of euphol (**204**) and tirucallol (**205**), Kolaczkowski and Reusch documented their attempt to synthesize a euphane triterpenoid.[142] Although they were not successful in achieving their goal, they did succeed in completing a total synthesis of a compound (**295**) possessing the 5-*epi*-euphane ring system. A

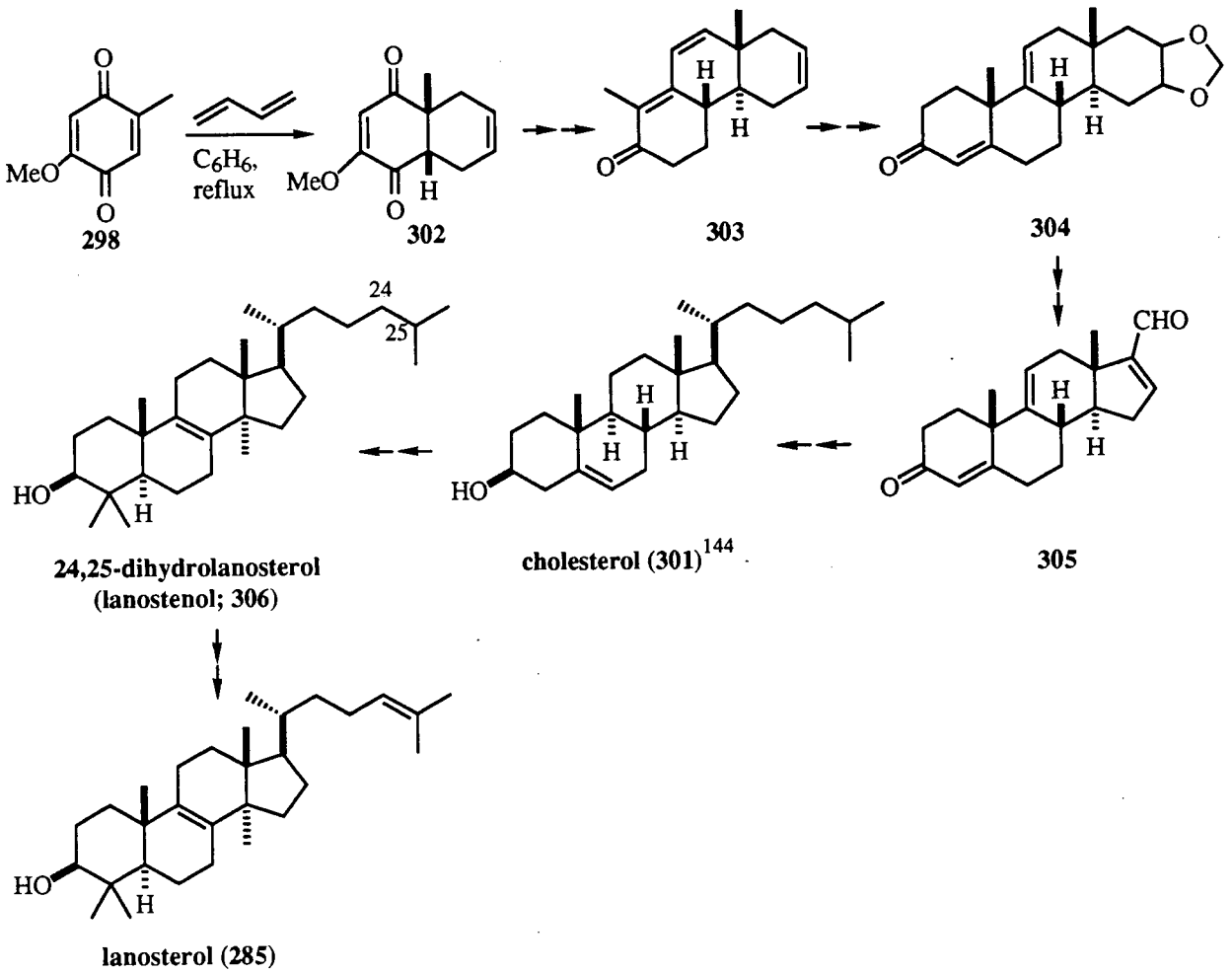
summary of the synthesis is presented in Scheme 4.3. Racemic Wieland-Miescher ketone (**119**) was converted in two steps to the hydrindandione **296** in which the relative configuration of the two angular methyl groups is *anti*, as required for the euphane skeleton. Transformation of **296** to the dienone **297** set the stage for a Lewis acid catalyzed Diels-Alder reaction with 2-methoxy-5-methyl-1,4-benzoquinone (**298**) to yielded the tetracyclic trione **299**. Unfortunately at this stage of the synthesis, all attempts by Kolaczkowski and Reusch to epimerize the C(5) stereocenter were unsuccessful. Carrying on, however, enol acetate formation followed by photoepimerization provided dione **300**. Conventional reactions were used to convert **300** to the hydroxy-diketone **295**, which bears the 5-*epi*-euphane carbon skeleton.[142]



Scheme 4.3. Kolaczkowski and Reusch: Synthesis of the (±)-5-*epi*-Euphane Ring System.[142]

As for the lanostane triterpenoids, the first synthesis of lanosterol (**285**), from cholesterol (**301**), was reported in 1957 by Woodward, Barton, and their respective co-workers (Scheme 4.4).[143] However, Woodward and co-workers had previously completed a 37-step total synthesis of cholesterol (**301**)[144] following a synthetic plan that was based on a CD* (**302**) → BCD* (**303**) → ABCD* (**304**) → ABCD (**305**) strategy; the notation D* → D represents the

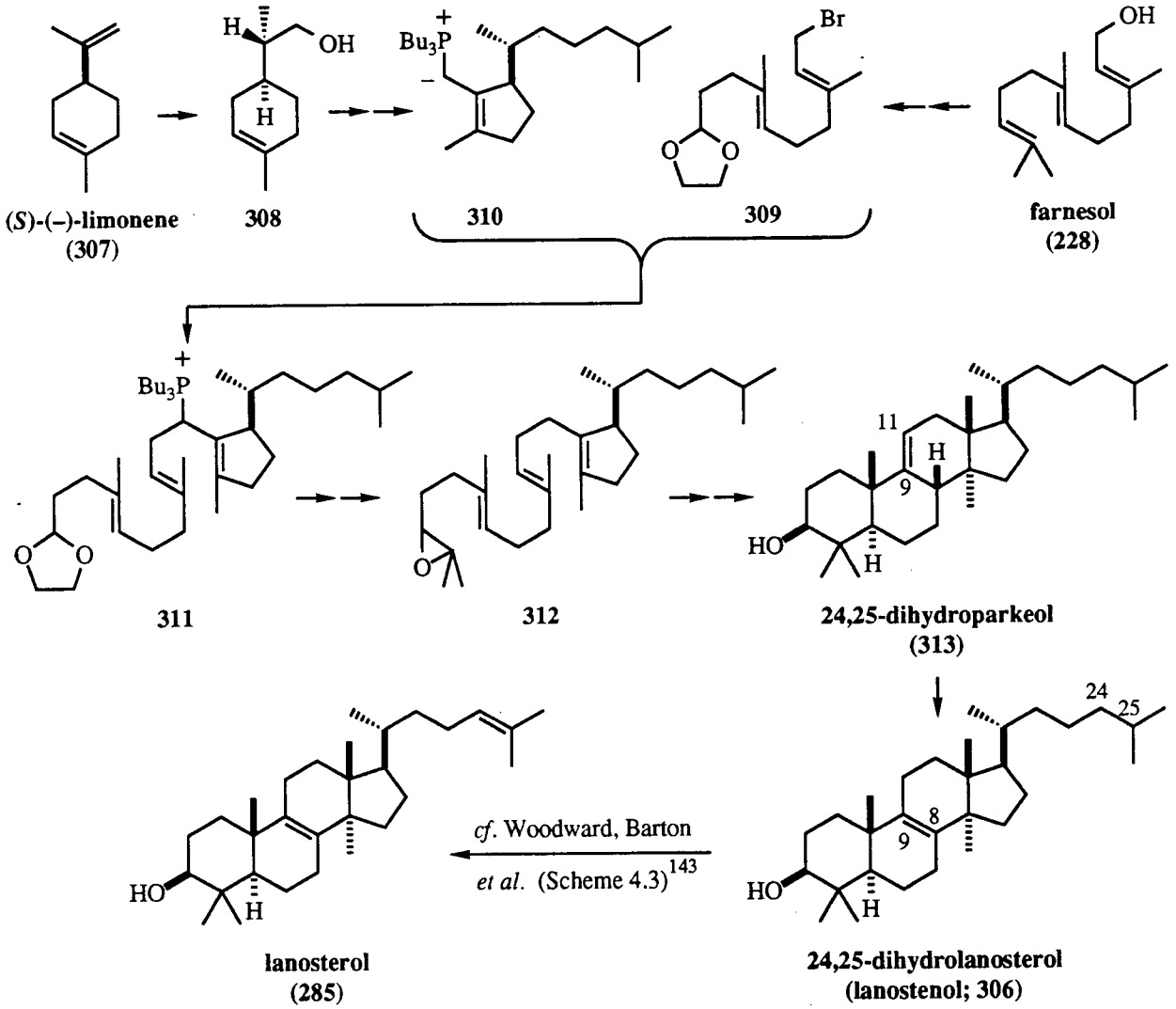
contraction of a six-membered ring (D*) to the required five-membered D-ring. Thus, the synthesis of lanosterol (**285**) from cholesterol (**301**) represents also the first total synthesis of this important natural product.[143]



Scheme 4.4. Woodward, Barton, *et al.*: Total Synthesis of (±)-Lanosterol (**285**).[143]

During the course of studies on polyolefin cyclizations by van Tamelen and Anderson, a synthesis of 24,25-dihydrolanosterol (lanostenol; **306**) from (*S*)-(–)-limonene (**307**) was developed (Scheme 4.5).[145] (*S*)-(–)-Limonene (**307**) was first converted to the cyclopentenol derivative **308**, which would eventually become the D-ring of the target molecule. Nucleophilic substitution of the bromo group in ketal-bromide **309**, prepared from farnesol (**228**), with the ylide **310** derived from **308** followed by functional group manipulations yielded epoxy-triene

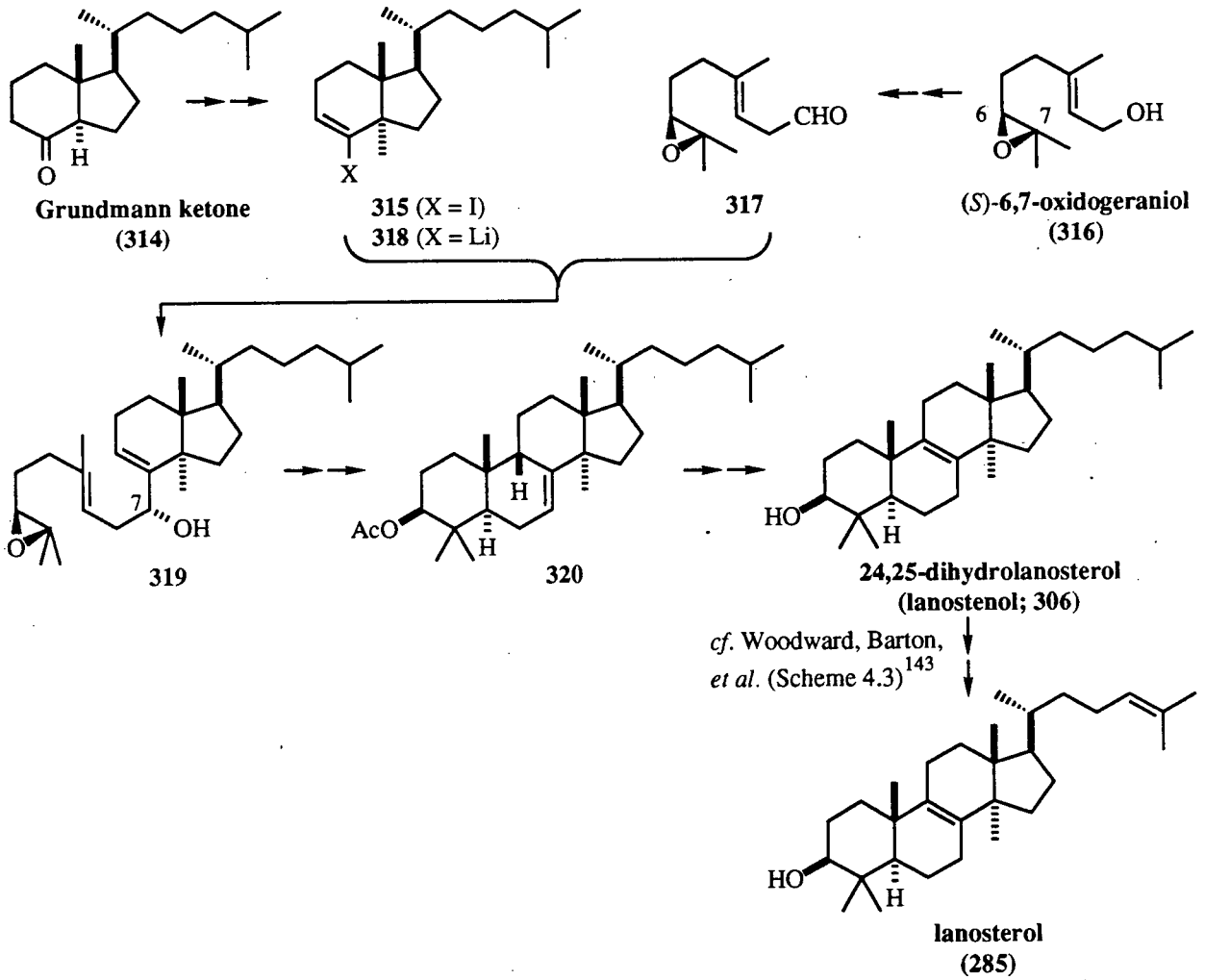
312. Treatment of epoxy-triene **312** with tin(IV) chloride yielded a mixture of four isomeric tetracyclic alcohols from which 24,25-dihydroparkeol (**313**) was isolated as a minor (3.5%) product. Acid-catalyzed isomerization of the $\Delta^{9,11}$ double bond in **313** to the $\Delta^{8,9}$ position furnished 24,25-dihydrolanosterol (lanostenol; **306**), which was also an intermediate in the total



Scheme 4.5. van Tamelen and Anderson: Formal, Enantiospecific Synthesis of Lanosterol.[145]

synthesis of lanosterol by Woodward, Barton, and their respective co-workers.[143] As well, in view of the fact that both enantiomers of the monoterpenoid limonene are readily available,[13] the preparation of 24,25-dihydrolanosterol (**306**) by van Tamelen and Anderson[145] therefore constitutes a formal, enantiospecific synthesis of lanosterol (**285**).

Recently, a considerably more concise, formal, convergent synthesis of (±)-lanosterol (**285**) was reported by Corey and co-workers (Scheme 4.6).[146] Initially the Grundmann ketone (**314**) was converted to the bicyclic vinyl iodide **315**. Concurrently, (*S*)-6,7-oxidogeraniol (**316**)

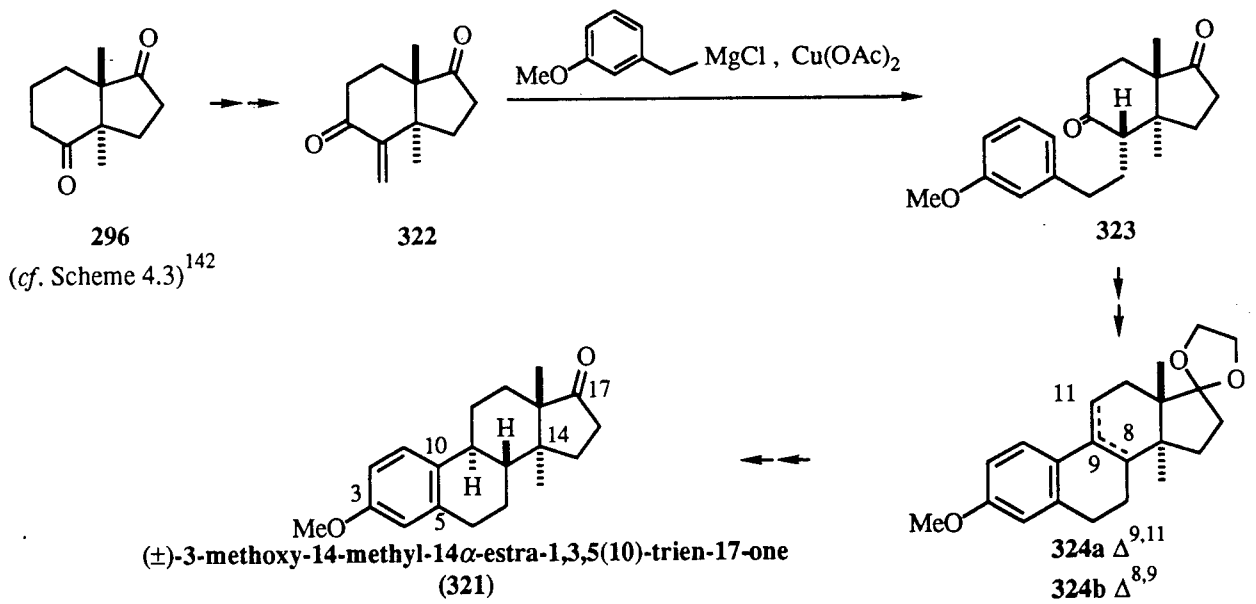


Scheme 4.6. Corey *et al.*: Formal, Enantiospecific Synthesis of Lanosterol.[146]

was converted to epoxy-aldehyde **317**. Addition of the vinyllithium compound **318,** derived from iodide **315**, to an ethereal solution of epoxy-aldehyde **317** in the presence of magnesium bromide furnished a 1:1 mixture of diastereomeric epoxy-alcohols from which the 7α epimer **319** (steroid/triterpenoid numbering system) could be separated by chromatography. Conversion of the 7α-hydroxyl group to a silyl group permitted the execution of a Lewis acid promoted polyolefin cyclization followed by acetylation to yield the tetracyclic acetate **320**, and in three

further steps, 24,25-dihydrolanosterol (lanostenol; **306**).[143] The successful preparation of **306** completes a formal, enantiospecific synthesis[146] of the triterpenoid (±)-lanosterol (**285**).

The synthesis of 14α-methyl steroids has been an ongoing theme in the research program of Bull and co-workers in South Africa. A representative 14α-methyl steroid is the 14α-methylestrone derivative **321**, whose total synthesis was reported by Bull and Bischofberger in 1983 (Scheme 4.7).[147] The synthesis starts with the Reusch diketone **296** (*cf.* Scheme 4.3).[142] Elaboration of **296** to the enedione **322** followed by conjugate addition of *m*-methoxybenzylmagnesium chloride in the presence of copper(II) acetate yielded diketone **323**. Acid-catalyzed ring closure followed by dehydration and ketalization yielded a 1:1 mixture of isomeric tetracyclic ketals **324a** and **324b**. Treatment of the $\Delta^{9,11}$ unsaturated compound **324a** with lithium in liquid ammonia followed by aqueous trifluoroacetic acid yielded the 14α-methylestrone derivative (**321**).[147] Interestingly, the bioactivity of 14α-methyl steroids have



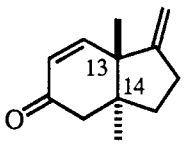
Scheme 4.7. Bull and Bischofberger: Total Synthesis of a 14α-Methyl Steroid, (±)-3-methoxy-14-methyl-14α-estra-1,3,5(10)-trien-17-one (**321**).[147]

not, to our knowledge, been examined. It is conceivable, however, that because of their structural similarity to natural steroids, 14α-methyl steroids, in general, could have potential clinical applications. Development of reliable synthetic routes to 14α-methyl steroids would

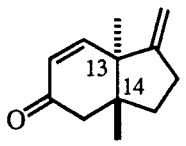
lead to the increased availability of these compounds and in turn, could stimulate further studies on their biochemical and pharmacological properties.

(c) The Use of 4-Methylcamphor in Triterpenoid and Steroid Synthesis

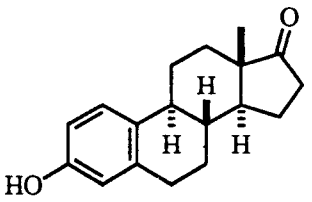
In devising our strategy for the synthesis of members of the euphane, tirucallane, lanostane, and 14α-methyl steroid families, we chose to draw on experience gained previously from our own research program. In 1987, Hutchinson and Money published an enantiospecific synthesis of estrone (**326**)[40] in which (+)-camphor (**9**) was converted to the bicyclic C,D enone **325** *en route* to (–)-estrone (*ent*-estrone; ***ent*-326**; Scheme 4.8). By analogy, we envisioned that each of euphol (**204**) and tirucallol (**205**) could be derived from an analogous bicyclic enone ***ent*-328** in which there is present an extra methyl group at C(14) (triterpenoid/steroid numbering) *anti* to the C(13)-methyl group. Recognizing that enone **325** was derived from camphor (**9**), we reasoned that because the C(14) position in the triterpenoid (or steroid) C,D ring system corresponds to C(4) in the original camphor (or bornane) system, it should be possible to synthe-



328



***ent*-328**



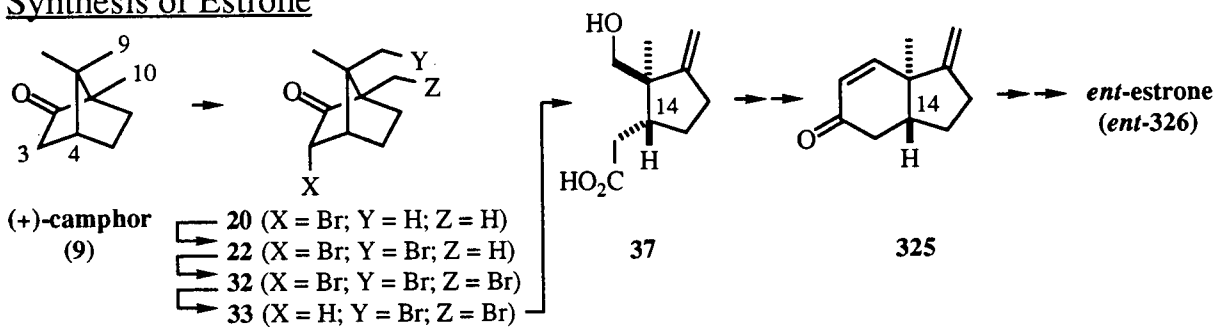
estrone (326)

size the 13,14-*anti*-dimethyl-enone **328** or its enantiomer if only we employed the appropriate enantiomer of 4-methylcamphor (**87**) as starting material instead. Indeed, an efficient route to 4-methylcamphor (**87**) from camphor (**9**) has been devised previously by our group (*cf.* Scheme 1.21).[72] Although our original route provided material that was only ~60% enantiopure, we have recently reported an alternative enantiospecific synthesis of ~100% enantiopure 4-methylcamphor (**87**).[73]

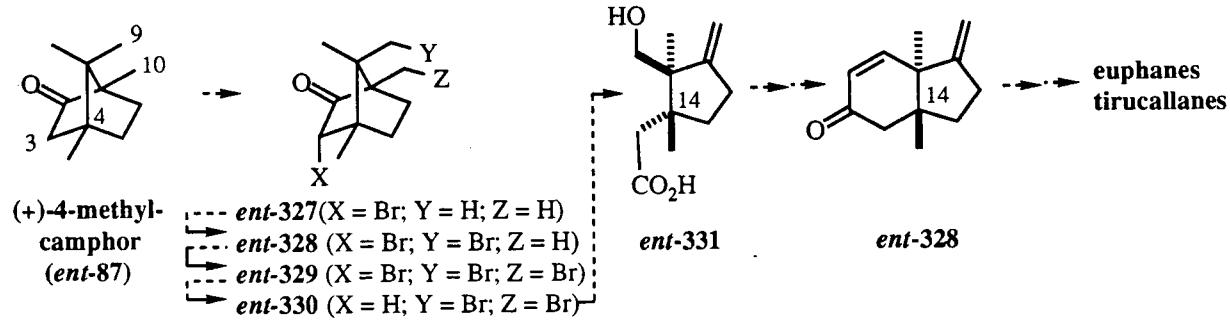
In the above-mentioned synthesis of estrone (**326**) by Hutchinson and Money (*cf.* Scheme 4.8),[40] camphor (**9**) was brominated successively to provide *endo*-3-bromocamphor (**20**), *endo*-3,9-dibromocamphor (**22**), and thence *endo*-3,9,10-tribromocamphor (**32**). Subsequent chemoselective debromination of **32** with zinc in 1:1 acetic acid–diethyl ether yielded 9,10-dibromocamphor (**33**), and base-promoted ring cleavage of 9,10-dibromocamphor (**33**) yielded a cyclopentanoid hydroxy-acid **37** that could be elaborated to the bicyclic C,D enone intermediate **325** in three further steps.

By analogy (*cf.* Scheme 4.8), we thought it would be reasonable to brominate 4-methylcamphor (**87**) successively to yield *endo*-3-bromo-4-methylcamphor (**327**), *endo*-3,9-dibromo-4-methylcamphor (**328**), *endo*-3,9,10-tribromo-4-methylcamphor (**329**), and thence 9,10-dibromo-4-methylcamphor (**330**). Subsequent base-promoted ring cleavage of 9,10-dibromo-4-methylcamphor (**330**) would be expected to provide hydroxy-acid **331** which would be used in turn to prepare the C,D enone **328**. The enantiomeric C,D enone ***ent*-328** would, of course, be derived from the enantiomeric 4-methylcamphor (***ent*-87**). However, upon execution of this synthetic plan, it was soon observed that the bromination of *endo*-3-bromo-4-methylcamphor (**327**) proceeded abnormally. The product of the bromination was determined to be a tribrominated camphor derivative, and not *endo*-3,9-dibromo-4-methylcamphor (**328**) as expected. On the basis of spectroscopic data available at the time, it was assumed that the identity of this product was *endo*-3,9,10-tribromo-4-methylcamphor (**329**). Proceeding further, chemoselective debromination of **329** to yield "9,10-dibromo-4-methylcamphor" (**330**) occurred uneventfully, but in the following step, all attempts to effect base-promoted ring cleavage of **330** failed. After considering the implications of these unexpected results it was subsequently proposed that the bromination had not yielded *endo*-3,9,10-tribromo-4-methylcamphor (**329**) as

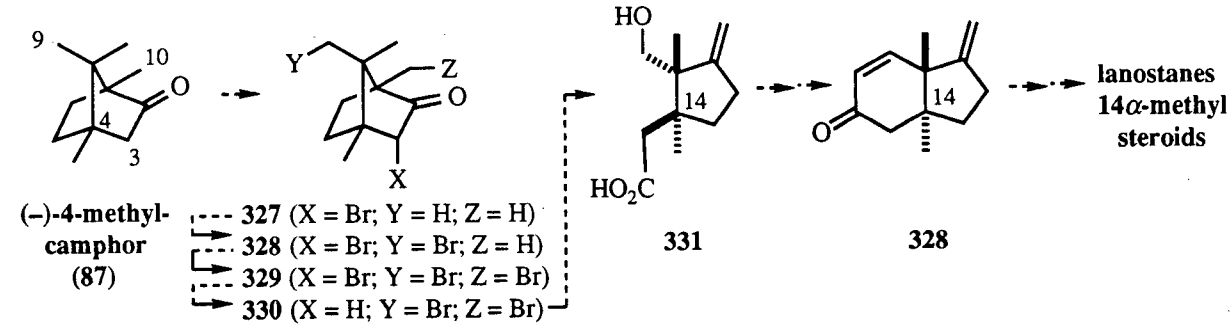
Synthesis of Estrone[40]



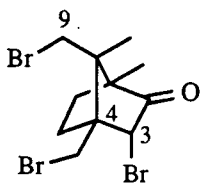
Proposed Approach to the Euphanes and Tirucallanes



Proposed Approach to the Lanostanes and 14α-Methyl Steroids



Scheme 4.8. Comparison of the Proposed Routes to the Euphanes, Tirucallanes, Lanostanes, and 14α-Methyl Steroids to the Hutchinson-Money Synthesis of Estrone.[40]



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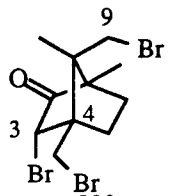


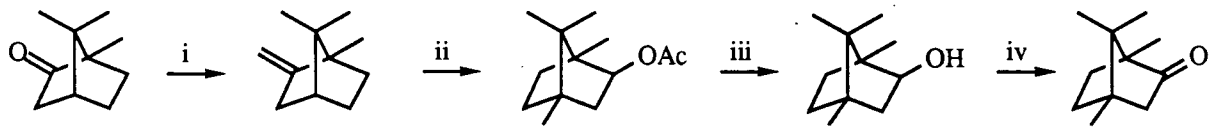
***ent*-332**

expected, but possibly, the isomeric *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**).[148] A detailed review of these observations, as well as the evaluation of a proposed mechanism for the "anomalous" bromination of *endo*-3-bromocamphor (**327**) to yield **332** will constitute the remainder of this chapter.

(d) Results and Discussion

i. Preparation of 4-Methylcamphor (87), endo*-3-Bromo-4-methylcamphor (327), and* endo*-3,9-Dibromo-4-(bromomethyl)camphor (332).*

The first stage of the project involved the preparation of 4-methylcamphor (**87**; *cf.* Schemes 1.22 and 4.9).[72] To this end, enantiopure (+)-camphor (**9**) was treated with the ylide generated *in situ* from reaction of methyltriphenylphosphonium bromide and *n*-butyllithium in THF to provide 2-methylenebornane (**88**). Treatment of 2-methylenebornane (**88**) with a cata-



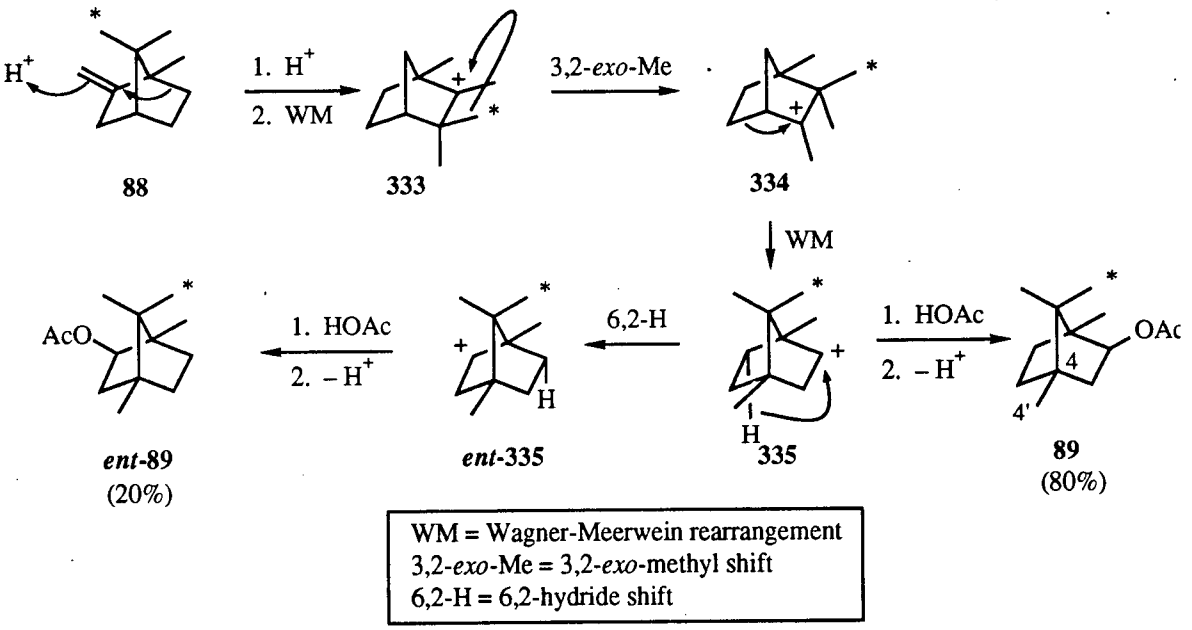
(+)-camphor (9) — **(–)-2-methylene bornane (88)** — **(+)-4-methylisobornyl acetate (89)** — **(+)-4-methyl-isoborneol (90)** — **(–)-4-methyl-camphor (87)**

(i) $CH_3PPh_3^+Br^-$, BuLi, THF, reflux [87%] (ii) H_2SO_4, HOAc [73%] (iii) $LiAlH_4$, THF, 0 °C; H_2O [99%] (iv) CrO_3, aq. H_2SO_4, acetone, 0 °C [99%].

Scheme 4.9. Money *et al.*: Preparation of (–)-4-Methylcamphor (**87**) from (+)-Camphor.[72]

lytic amount of concentrated sulfuric acid in acetic acid resulted in acid-catalyzed rearrangement of the bornane skeleton followed by capture of acetic acid and proton loss to yield 4-methylisobornyl acetate (**89**). Reduction of acetate **89** with lithium aluminum hydride afforded 4-methylisoborneol (**90**), and subsequent Jones oxidation provided 4-methylcamphor (**87**).

Despite that enantiopure (+)-camphor (**9**) was used as starting material, the product that was obtained, 4-methylcamphor (**87**), was found to be only 60% enantiopure. Although the specific rotation of the 4-methylcamphor (**87**) so obtained was in agreement with those quoted previously by others,[23a] a 400 MHz ^{1}H NMR spectrum of the same sample of **87** recorded in the presence of a chiral shift reagent, Eu(hfc)$_3$, showed clearly *two* sets of signals arising from the two enantiomers of 4-methylcamphor (**87**).[72] Comparison of appropriate ^{1}H NMR integral values revealed that the enantiomers were present in a ~4:1 ratio (~60% *e.e.*). That the 4-methylcamphor (**87**) obtained through our synthetic route (Scheme 4.9) exhibited a specific rotation that was in agreement with those reported elsewhere[23a] in the literature despite being an unequal mixture of enantiomers suggests that none of the literature routes to 4-methylcamphor (**87**) published before 1990 yields enantiopure products.

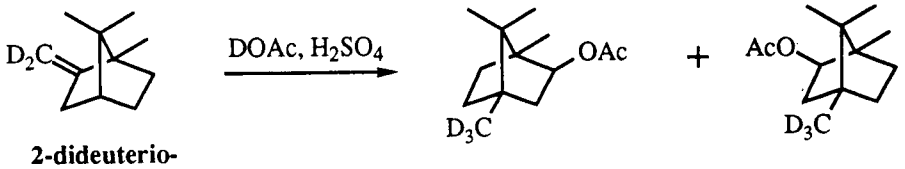


Scheme 4.10. Mechanism for the Transformation of (–)-2-Methylenebornane (**88**) to (+)-4-Methylisobornyl Acetate (**89**) (60% *e.e.*).[65,72]

The loss of enantiopurity in the product can be explained by the mechanism outlined in Scheme 4.10. Initial protonation of 2-methylenebornane (**88**) and Wagner-Meerwein rearrangement yields a tertiary carbocation **333** that then undergoes a 3,2-*exo*-methyl shift to

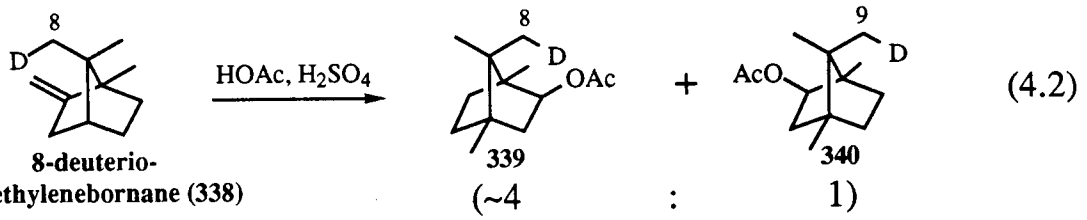
yield a new carbocation **334**. A further Wagner-Meerwein rearrangement of **334** gives rise to **335**, which can react with acetic acid to afford 4-methylisobornyl acetate (**89**) after proton loss. Alternatively, carbocation **335** can undergo a competing 6,2-hydride shift to yield the enantiomeric carbocation ***ent*-335**, which can also be intercepted by acetic acid to yield the enantiomeric 4-methylisobornyl acetate (***ent*-89**). If the rate at which the 6,2-hydride shift occurs in **335** is faster than that at which **335** is captured by acetic acid then it would be possible to obtain an unequal product mixture of enantiomeric 4-methylisobornyl acetates **89** and ***ent*-89**.

The validity of this mechanistic proposal has been evaluated through experiments[65,72] involving the use of deuterium-labelled substrates.[149] In one experiment (Equation 4.1), treatment of 2-dideuteriomethylenebornane (**336**) with deuterioacetic acid (CH_3CO_2D) and sulfuric acid (H_2SO_4) led to the formation of 4-trideuteriomethylisobornyl acetate (**337**), presumably as an unequal mixture of enantiomers as described previously. That 4-(trideuteriomethyl)isobornyl acetate (**337**) was obtained as product[65,72] is consistent with the proposed reaction pathway (*cf.* Scheme 4.10), which predicts that the exocyclic methylene group in 2-methylenebornane (**88**) becomes the C(4)-methyl group in 4-methylisobornyl acetate (**89**).



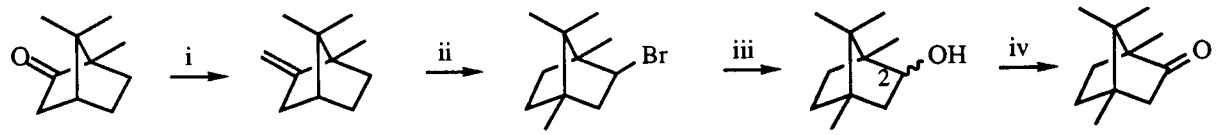
2-dideuterio-methylenebornane (336) **337** ***ent*-337** (4.1)

In another experiment (Equation 4.2),[65,72] 8-deuterio-2-methylenebornane (**338**) was subjected to acid-catalyzed rearrangement conditions (HOAc, H_2SO_4) to yield a 4:1 mixture of 8-deuterio-4-methylisobornyl acetate (**339**) and 9-deuterio-4-methylisobornyl acetate (**340**), respectively. It is interesting to note that the structures of **339** and **340** belong to opposite enantiomeric series. This result provides support for the proposal that the carbocation **335** (Scheme 4.10) can give rise to both of the enantiomeric acetates **89** and ***ent*-89**.



8-deuterio-2-methylenebornane (338) → **339** (~4 : **340** 1) (4.2)

Recently, an alternative, analogous procedure (Scheme 4.11) has been developed in which enantiopure (+)-camphor (**9**) was converted to 4-methylcamphor (**87**) *with no detectable loss of enantiopurity* (NMR, GLC).[73] Unfortunately, the yield of one of the synthetic steps, namely the conversion of 4-methylisobornyl bromide (**91**) to the diastereomeric alcohols **90** and **92** remains unoptimized and low-yielding (~40%). Because the remainder of the chemistry in



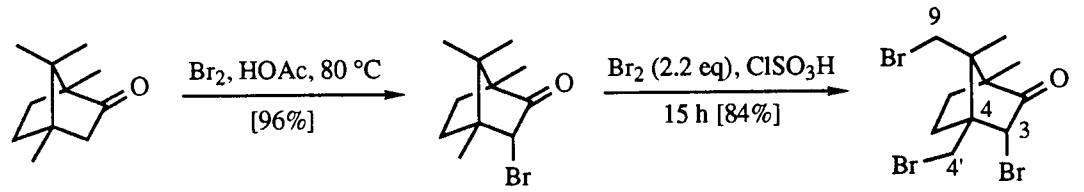
(+)-camphor (9) → **(–)-2-methylene bornane (88)** → **4-methylisobornyl bromide (91)** → **90** (*exo*-2-hydroxy) **92** (*endo*-2-hydroxy) → **(–)-4-methyl-camphor (87)**

(i) $CH_3PPh_3^+Br^-$, BuLi, THF, reflux [87%] (ii) 45% HBr, HOAc [87%] (iii) Mg, Et_2O; O_2; H_3O^+ [40%] (iv) CrO_3, aq. H_2SO_4, acetone, 0 °C [97%].

Scheme 4.11. Money and Palme: Preparation of Enantiopure (–)-4-Methylcamphor (**87**) from (+)-Camphor.[73]

this project does not involve the use of chiral reagents it was deemed sufficient to use the enantiomerically impure material obtained through our original route (Scheme 4.9).

In the next stage of the project, 4-methylcamphor (**87**) was converted (Scheme 4.12) to *endo*-3-bromo-4-methylcamphor (**327**)[72] by treatment with bromine in acetic acid at 80 °C. Subsequent reaction of **327** with bromine (2.2 eq) in chlorosulfonic acid yielded a tribromocamphor that was identified on the basis of spectroscopic data to be *endo*-3,9-bromo-4-(bromomethyl)camphor (**332**).[72]



(–)-4-methyl-camphor (87) → ***endo*-3-bromo-4-methylcamphor (327)** → ***endo*-3,9-dibromo-4-(bromomethyl)camphor (332)**

Scheme 4.12. Bromination of 4-Methylcamphor (**87**).[72]

The structure of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) was verified primarily through its 400 MHz ^{1}H NMR spectrum (Figure 4.1, p. 102). The signal at 4.92 ppm (d, J = 1.2 Hz, 1H) was assigned to the H(3_{exo}) proton on the basis of its chemical shift. The COSY spectrum (*cf.* Table 5.21, p. 198) of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) showed a correlation betwen the H(3_{exo}) signal and that at 1.82 ppm, suggesting that the latter signal could be assigned to the C(5_{exo}) proton. The group of four doublets between 3.4–4.1 ppm arise collectively from resonance of the C(9) and C(4') protons. The COSY spectrum suggests that the doublets at 4.06 and 3.52 ppm represent the diastereotopic protons of one of C(9) or C(4') while the doublets at 3.74 and 3.46 ppm represent the diastereotopic protons of the other, remaining carbon. Furthermore, a COSY correlation between the doublet at 3.74 ppm and the three-proton singlet at 1.24 ppm suggests that the two signals could be assigned to one of the diastereotopic C(9) protons and the C(8) protons, respectively. Presumably, this particular COSY correlation arises from the long-range (^4J or W-) coupling of H(9) to H(8). Having assigned one of the H(9) protons facilitated assignment of the doublet at 3.52 ppm to the other H(9) proton. The doublets at 4.06 and 3.52 ppm represent the two diastereotopic H(4') protons. The singlet at 1.03 ppm can be assigned to H(10).

By elimination, the remaining four signals between 1.45–2.25 ppm must represent the four protons associated with C(5) and C(6). The assignment of these signals to specific protons was performed recently with the aid of HETCOR (*cf.* Table 5.22, p. 198) and difference NOE experiments (*cf.* Table 5.20, p. 197). It has already been established that the signal at 1.82 ppm

arises from resonance of H(5_{exo}). The HETCOR spectrum shows that this proton signal and that at 2.19 ppm both correlate with the same ^{13}C signal. Thus, the signal at 2.19 ppm represents H(5_{endo}). During the course of a difference NOE experiment, irradiation of the H(5_{endo}) signal resulted in enhancement of the intensities of peaks at 4.06 and 3.52 (H(4')), 1.82 (H(5_{exo})), 1.52, and very weakly, at 1.70 ppm. Furthermore, irradiation of the C(10) methyl signal at 1.03 ppm resulted in intensity enhancements of signals at 1.70 ppm and 1.52 ppm, as well as the signals for H(8) and H(9) at 1.24 and 3.46 ppm, respectively. Irradiation of the H(9) proton signal at 3.74 ppm, on the other hand, caused enhancement of the geminal H(9) and H(5_{exo}) signals [3.46 and 1.82 ppm, respectively] as well as that at 1.70 ppm. From the results of these three NOE experiments, it could be deduced that the signal at 1.70 ppm corresponded to the H(6_{exo}) proton and that at 1.52 ppm corresponded to the H(6_{endo}) proton.

Further difference NOE experiments were performed and the results of these experiments are summarized in Table 5.20 (p. 197). In summary, the NMR spectral data provide support for our revised proposal that bromination of *endo*-3-bromo-4-methylcamphor (**327**) had occurred at C(9) and C(4') *rather than at C(10) as originally anticipated.* Finally, the structure of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) has been confirmed also by X-ray crystallographic analysis.[150]

ii. A Proposed Mechanism for the Bromination of endo*-3-Bromo-4-methylcamphor (327).*

A plausible mechanism for the remarkable transformation of *endo*-3-bromo-4-methylcamphor (**327**) to *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) is presented in Scheme 4.13. In the presence of two equivalents of bromine and chlorosulfonic acid, the carbonyl group of *endo*-3-bromo-4-methylcamphor (**327**) is protonated initially. Subsequent Wagner-Meerwein rearrangement leads to the tertiary carbocation **342** which undergoes a

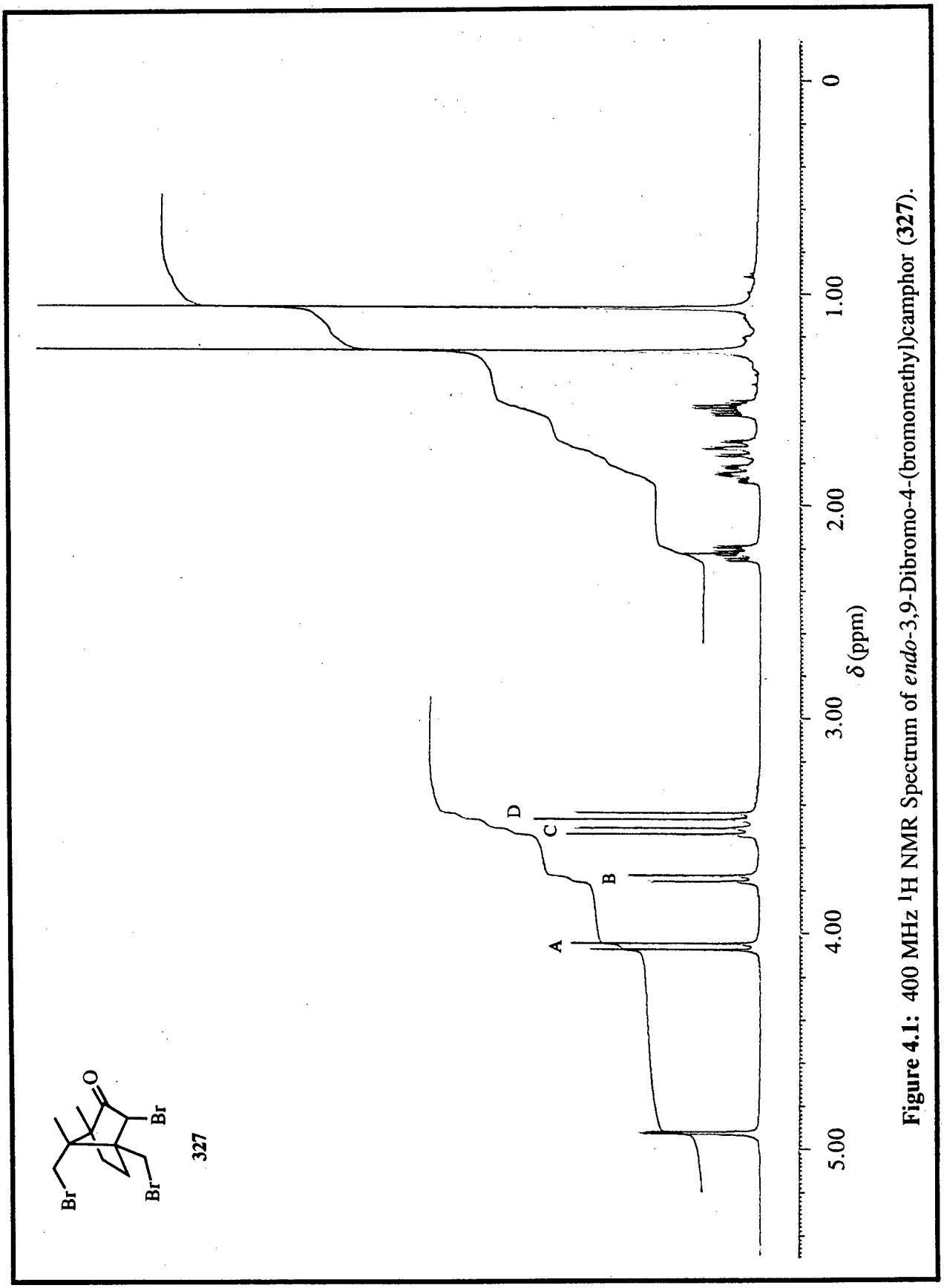
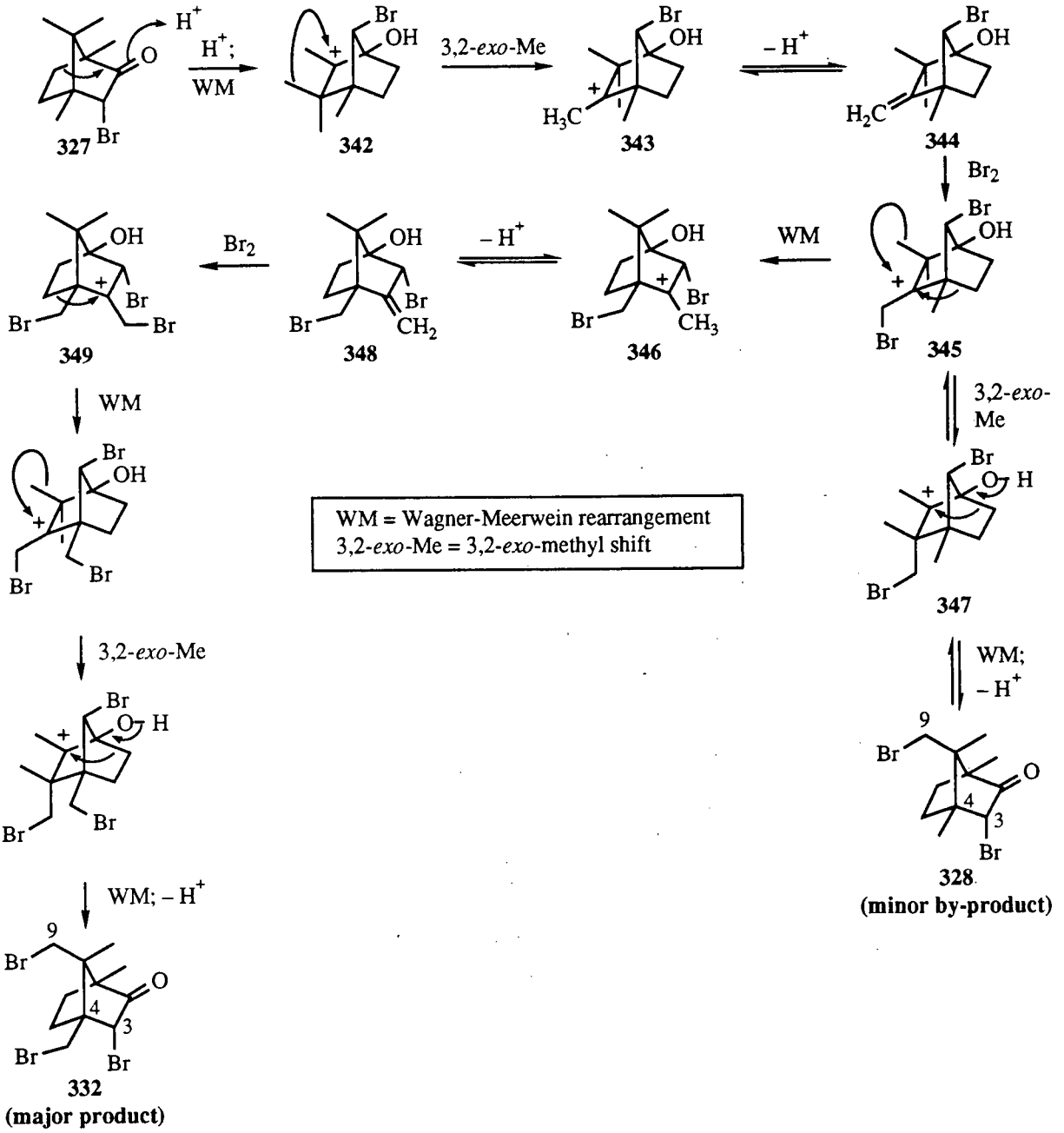


Figure 4.1: 400 MHz ^{1}H NMR Spectrum of *endo*-3,9-Dibromo-4-(bromomethyl)camphor (**327**).



Scheme 4.13. Proposed Reaction Pathway for the Bromination of *endo*-3-Bromo-4-Methyl-camphor (**327**).

further 3,2-*exo*-methyl shift to yield carbocation **343**. Carbocation **343** can lose a proton to generate the exocyclic alkene intermediate **344**. Electrophilic bromination of the alkene **344** yields the dibromo-carbocation **345**, which can either undergo a Wagner-Meerwein

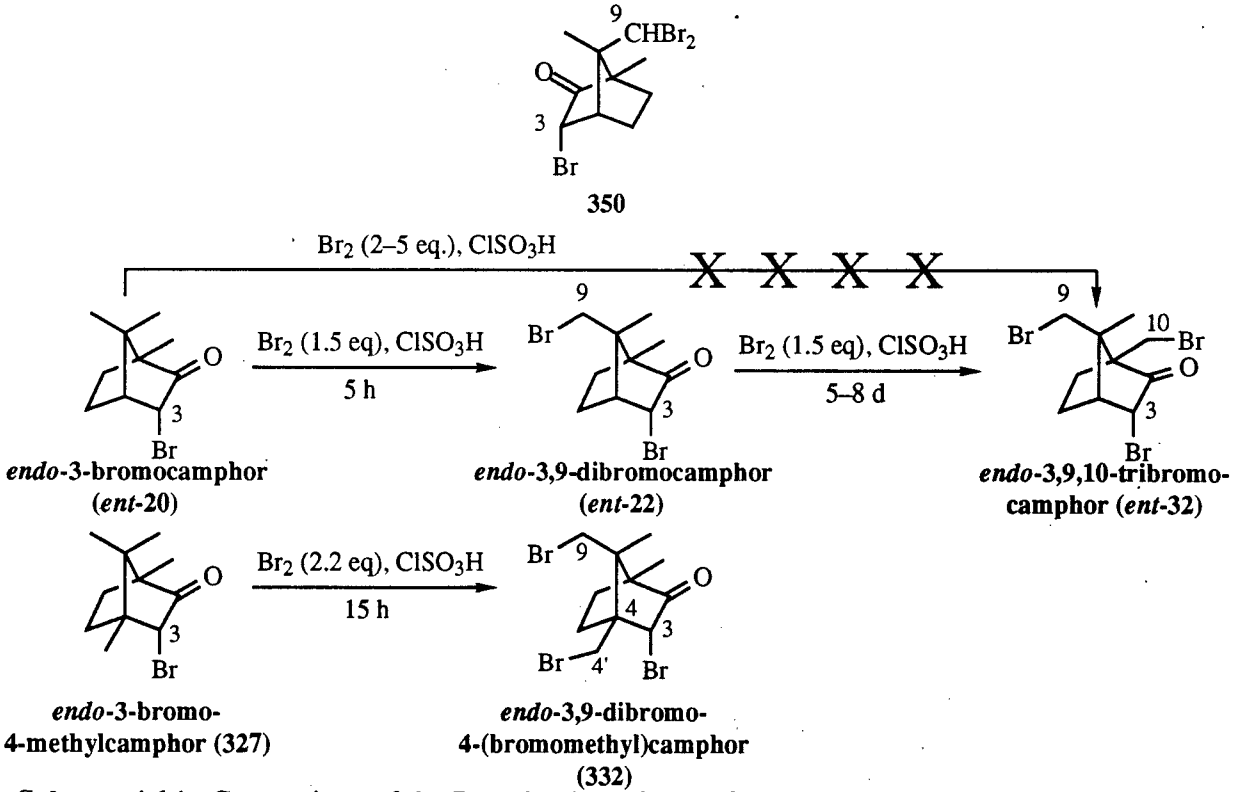
rearrangement to provide carbocation **346** or a competing 3,2-*exo*-methyl shift to provide carbocation **347**.

On the one hand, loss of a proton from **346** yields another exocyclic alkene **348** that can undergo a further electrophilic bromination step to yield tribromo-carbocation **349**. Subsequent Wagner-Meerwein rearrangement of **349** followed by 3,2-*exo*-methyl shift and a further Wagner-Meerwein rearrangement yields, after proton loss, *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) as the major product of the reaction.

In the alternative pathway, carbocation **347** can undergo Wagner-Meerwein rearrangement and proton loss to yield *endo*-3,9-dibromo-4-methylcamphor (**328**) as a minor side-product. However, attempts to find reaction conditions that promoted exclusive formation of *endo*-3,9-dibromo-4-methylcamphor (**328**) were unsuccessful. For example, when the reaction of *endo*-3-bromo-4-methylcamphor (**327**) with bromine (2.2 eq.) in chlorosulfonic acid was stopped after 5 min, GLC analysis showed that the major components present in the product mixture (~1:1) were starting material (**327**) and *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**); *endo*-3,9-dibromo-4-methylcamphor (**328**) was present to only a small (<5%) extent. However, another experiment was carried out in which *endo*-3-bromo-4-methylcamphor (**327**) was allowed to react with only one equivalent of bromine in chlorosulfonic acid. Under these reaction conditions, the starting material was totally consumed after 5 h, and it was possible to isolate a ~1:1 mixture of *endo*-3,9-dibromo-4-methylcamphor (**328**) and *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; ~61% combined yield). These two bromocamphor derivatives **328** and **332** could be separated easily. When purified 3,9-dibromo-4-methylcamphor (**328**) was treated with one further equivalent of bromine in chlorosulfonic acid, only one product was isolated. The isolated product was identified as *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) and its spectroscopic characteristics (^{1}H, ^{13}C NMR, and IR spectra) were identical to those obtained for a sample of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) obtained through the conventional route, that is, from *endo*-3-bromo-4-methylcamphor (**327**).

These observations seem to suggest that carbocation **345** (Scheme 4.13) has a greater tendency to undergo Wagner-Meerwein rearrangement to yield **346** than to undergo the competing 3,2-*exo*-methyl shift to yield **347**. Alternatively, it may be that the bromination pathway does initially proceed via **347** to yield *endo*-3,9-dibromo-4-methylcamphor (**328**), but in the presence of sufficient quantities of bromine, **328** readily undergoes further bromination to yield the observed major product, *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**).

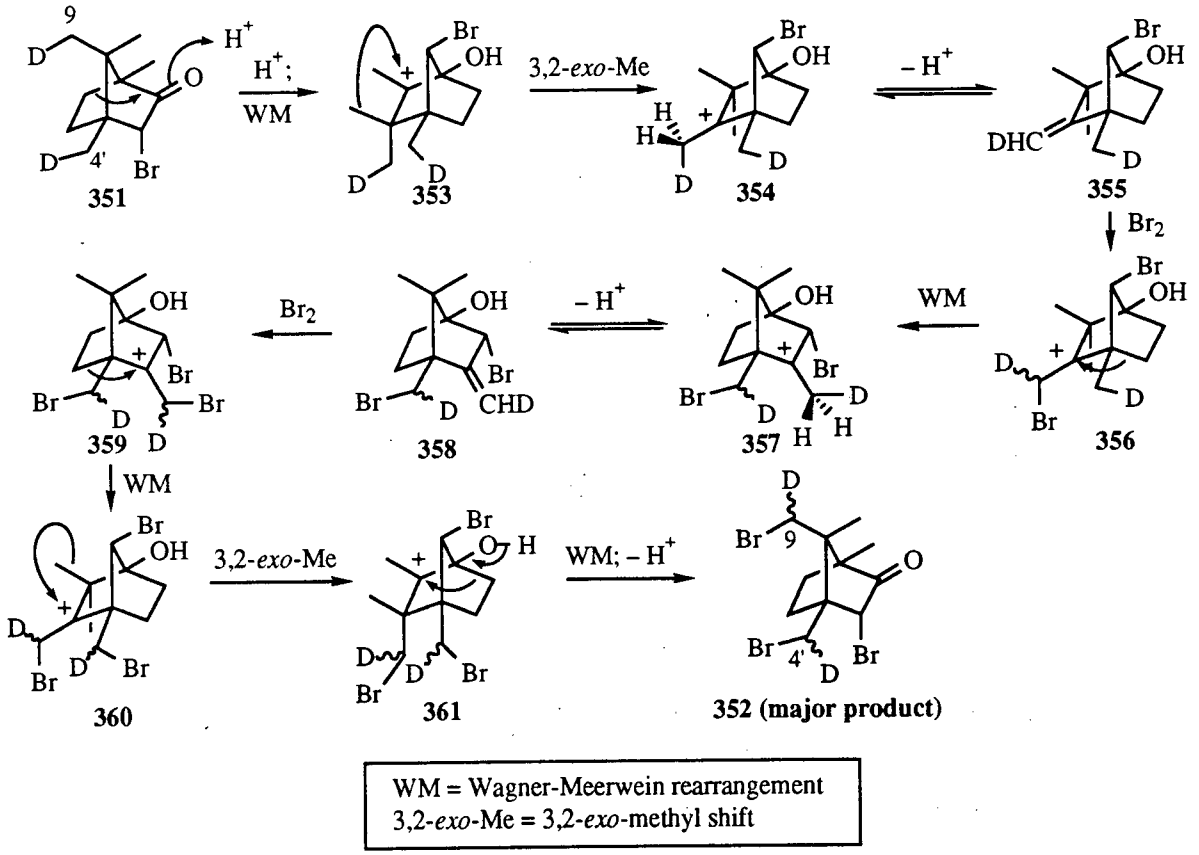
By contrast, it is interesting to note that *endo*-3-bromocamphor (***ent*-20**) undergoes bromination under similar conditions [Br_2 (1.5 eq), $ClSO_3H$] to yield *endo*-3,9-dibromocamphor (***ent*-22**) as the major (~70–80%) product (*cf.* Scheme 4.14).[31,37,45] Addition of further amounts of bromine and chlorosulfonic acid to the reaction mixture and prolonging the reaction time does not result in significant production of a tribrominated compound analogous to *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**).[63] Instead, there is a small increase in the amount of



Scheme 4.14. Comparison of the Bromination of *endo*-3-Bromocamphor (***ent*-20**) and *endo*-3-Bromo-4-methylcamphor (**327**) under $Br_2/ClSO_3H$ Conditions.

endo-3,9,9-tribromocamphor (**350**)[46d] that is formed when excess bromine is present in the reaction mixture. Curiously however, only after the 3,9-dibromocamphor (***ent*-22**) has been isolated and purified by recrystallization, can bromination (Br_2, $ClSO_3H$) take place to yield *endo*-3,9,10-tribromocamphor (***ent*-32**). A convincing explanation for this unusual, but reproducible observation cannot be readily formulated. Suffice it to say that the factors governing the particular rearrangement pathways undergone by the carbocationic intermediates (e.g. Scheme 4.13) are presently not well understood.

iii. Evaluation of the Proposed Bromination Pathway Using endo*-3-Bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) as a Labelled Substrate.*

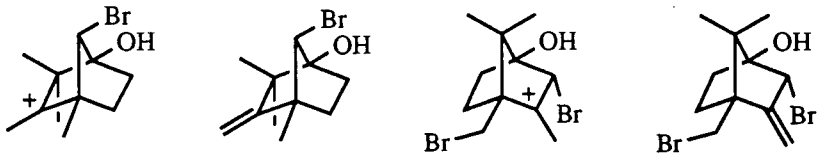


Scheme 4.15. Reaction Pathway for the Bromination of *endo*-3-Bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**). [N.B. In the transformations **354** → **355** and **357** → **358**, alternative loss of D^+ can occur in place of H^+ as indicated in this scheme (see text and Scheme 4.17).]

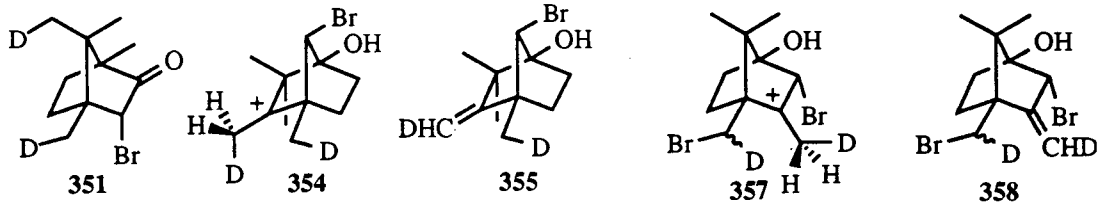
If the sequence of reactions formulated in Scheme 4.13 does in fact represent the pathway taken during the bromination reaction, then two predictions can be made. First, it is predicted that none of the carbon atoms in the starting *endo*-3-bromo-4-methylcamphor (**327**) should change their relative positions during the course of the multiple rearrangement–bromination sequence. In other words, if a label such as deuterium or ^{13}C were to be incorporated into the starting material **327**, then it should remain on the same carbon in the product **332**.

To test this hypothesis, it was proposed to study the bromination of the doubly labelled, *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**). According to the proposed reaction pathway it was predicted that the two deuterium labels of **351** should remain on C(9) and C(4') in the final product, *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**).

Secondly, the reaction pathway postulated above (Scheme 4.13) for the bromination of *endo*-3-bromo-4-methylcamphor (**327**) proposes also the existence of two exocyclic alkene intermediates **344** and **348**, which are derived from loss of a proton from the corresponding methyl groups in structures **343** and **346**, respectively. However, if *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) were used as a substrate in the same bromination reaction (*cf.* Scheme 4.15), the corresponding mechanistic intermediates **354** and **357** can undergo not only similar proton loss, but deuteron loss as well. Whereas the loss of a proton would lead to



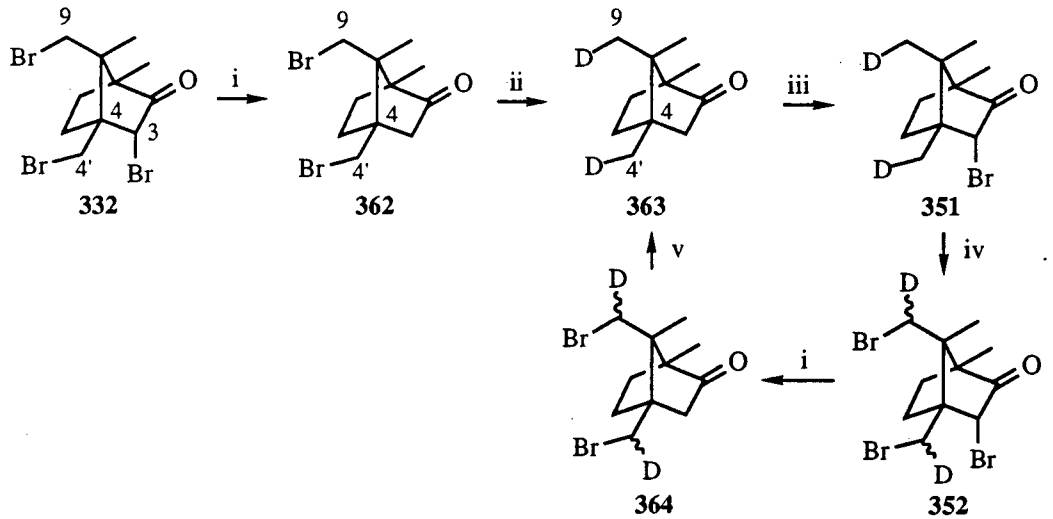
343 **344** **346** **348**



351 **354** **355** **357** **358**

the formation of a –CHDBr group after bromination, loss of a deuteron would yield a $–CH_2Br$ group. From previous experiments,[46a,72] it has been observed that $–C\underline{H}_2X$ and corresponding –CHDX protons (X = H or Br) have slightly different ^1H NMR chemical shifts. One could therefore use ^1H NMR spectroscopy as a means for detecting the presence of the two –CHDBr-containing diastereomers and the $–CH_2Br$-containing by-products. If the $–CH_2Br$-containing by-products are detected, indirect support for the existence of exocyclic methylene intermediates such as **355** and **358** in the proposed bromination mechanism would thus be gained.

At this juncture, we needed to prepare *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**), which we wished to use as a probe to study the multiple rearrangement–bromination mechanism outlined in Schemes 4.13 and 4.15. Thus, chemoselective debromination of the 3-bromo substituent in *endo*-3,9-bromo-4-(bromomethyl)camphor (**332**) using zinc powder in 1:1 HOAc–diethyl ether yielded 9-bromo-4-(bromomethyl)camphor (**362**).[72] Reaction of 9-bromo-4-(bromomethyl)camphor (**362**) with tributyltin deuteride and a catalytic amount of azobis(isobutyronitrile) in refluxing benzene yielded 9-deuterio-4-(deuteriomethyl)camphor (**363**).[72]



(i) Zn, HOAc–Et_2O, 0 °C (ii) Bu_3SnD, AIBN, C_6H_6, reflux (iii) Br_2, HOAc, 80 °C (iv) Br_2, $ClSO_3H$, 15 h (v) Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 4.16. Conversion of *endo*-3,9-Dibromo-4-(bromomethyl)camphor (**332**) to 9-deuterio-4-(deuterio)camphor (**363**). Conversion of 9-deuterio-4-(deuterio)camphor (**363**) to Derivatives for Use in Investigating the Mechanism of the Bromination of *endo*-3-Bromo-4-methylcamphor (**327**).

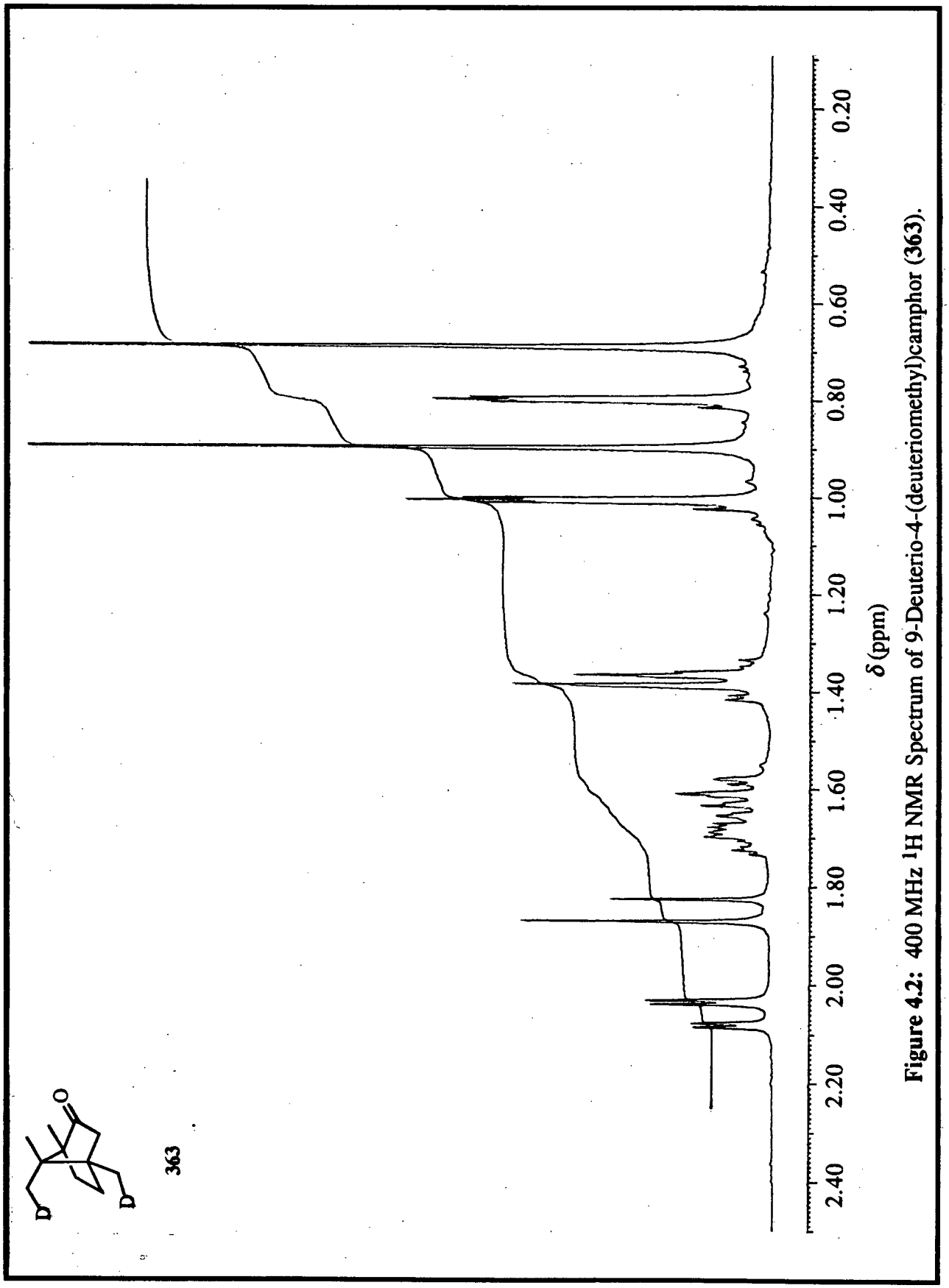


Figure 4.2: 400 MHz ^{1}H NMR Spectrum of 9-Deuterio-4-(deuteriomethyl)camphor (**363**).

The 400 MHz ^{1}H NMR spectrum (Figure 4.2, p. 109) of 9-deuterio-4-(deuteriomethyl)camphor (**363**) exhibits, most characteristically, four signals between 0.69–1.02 ppm. The two apparent triplets at 1.00 and 0.80 ppm can be assigned to the C(9) or C(4') protons on the basis of the observed multiplicities. Furthermore, the triplet signal at 0.80 showed a correlation with the singlet at 0.69 ppm in the 400 MHz COSY spectrum (*cf.* Table 5.23, p. 202). This correlation could arise as a result of long-range (^4J or W-) coupling between the C(9) and C(8) protons. By elimination, the triplet at 1.00 ppm and the singlet at 0.90 ppm are assigned to the C(4') and C(10) protons, respectively.

The chemical shifts of the C(4') and C(9) protons of **363** (1.00 and 0.80 ppm) are shifted upfield relative to the chemical shifts of the corresponding protons of 4-methylcamphor (**87**) at 1.02 and 0.81 ppm, respectively. In addition, two weak singlets do appear at the latter chemical shifts in the NMR spectrum of 9-deuterio-4-(deuteriomethyl)camphor (**363**); their significance will be discussed shortly. The signals at 2.08 and 2.03 ppm correspond to the C(3) *exo* and *endo* protons, respectively, while the multiplets between 1.30–1.75 ppm can be assigned to the four protons bonded to C(5) and C(6).

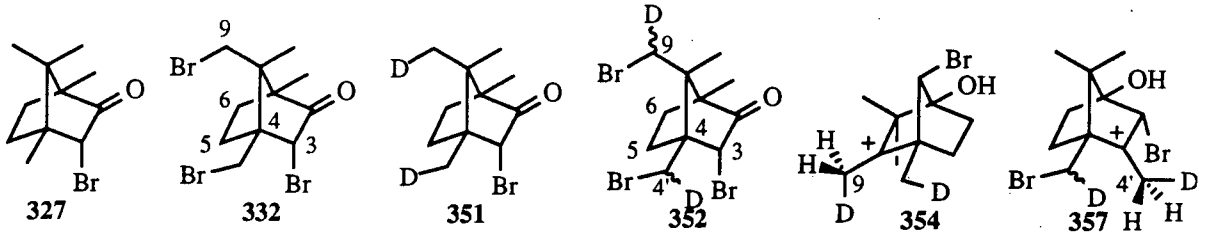
Noteworthy in the 75 MHz ^{13}C NMR spectrum of **363** is the presence of two triplets at 15.5 and 15.1 ppm which represent, collectively, the C(9) and C(4') carbons. The observed coupling constants for both signals are 19 Hz, and correspond to the one-bond (^1J) coupling of a ^{13}C (spin ½) nucleus with a deuterium (spin 1) nucleus. Finally, mass spectral data confirm that two deuterium atoms have indeed been incorporated into the product, and that the identity of the product is 9-deuterio-4-(deuteriomethyl)camphor (**363**).

Subsequent treatment of 9-deuterio-4-(deuteriomethyl)camphor (**363**) with bromine in acetic acid at 80°C yielded *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**), whose structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. With the dideuterated bromocamphor derivative **351** in hand, we were now ready to submit **351** to the conditions of the bromination reaction of interest (*cf.* Scheme 4.16, step (iv)), identify the products that would be formed in the reaction, and study the fate of the deuterium labels in **351**

after the reaction. Thus, treatment of *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) with bromine (2.2 eq) in chlorosulfonic acid yielded a product mixture in which the major product (~90–95%) was purified by chromatography and tentatively identified as *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) by analogy to the corresponding reaction involving the unlabelled compound **332**.

The 400 MHz ^{1}H NMR spectrum of *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**; *cf.* Figure 4.3, p. 112) was recorded and assigned by comparison with that for the corresponding unlabelled compound, *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; *cf.* Figure 4.1, p. 102). The spectra for **352** and **332** are similar. Both spectra show signals at 1.24 and 1.04 ppm that can be assigned to the C(8) and C(10) protons of **352** and **332**. Not unreasonably, the signals for the H(3_{exo}), H(5_{exo}), H(5_{endo}), H(6_{exo}), and H(6_{endo}) protons are also at the same chemical shifts in both spectra. The most pronounced difference between the two spectra, however, occurs in the region in which the C(9) and C(4') protons resonate, that is, between 3.4–4.1 ppm.

To explain that there are four signals associated with the C(9) and C(4') protons in **352** one must be mindful that each of C(9) and C(4') in *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) are stereocenters originating from the loss of either diastereotopic C(9) or C(4') proton from the intermediate carbocations **354** or **357**, respectively (see Schemes 4.15 and 4.17). Consequently, depending on the configurations of C(9) and C(4') in **352**, there could arise four different signals for the two C(9) and C(4') protons in **352**, as is observed.



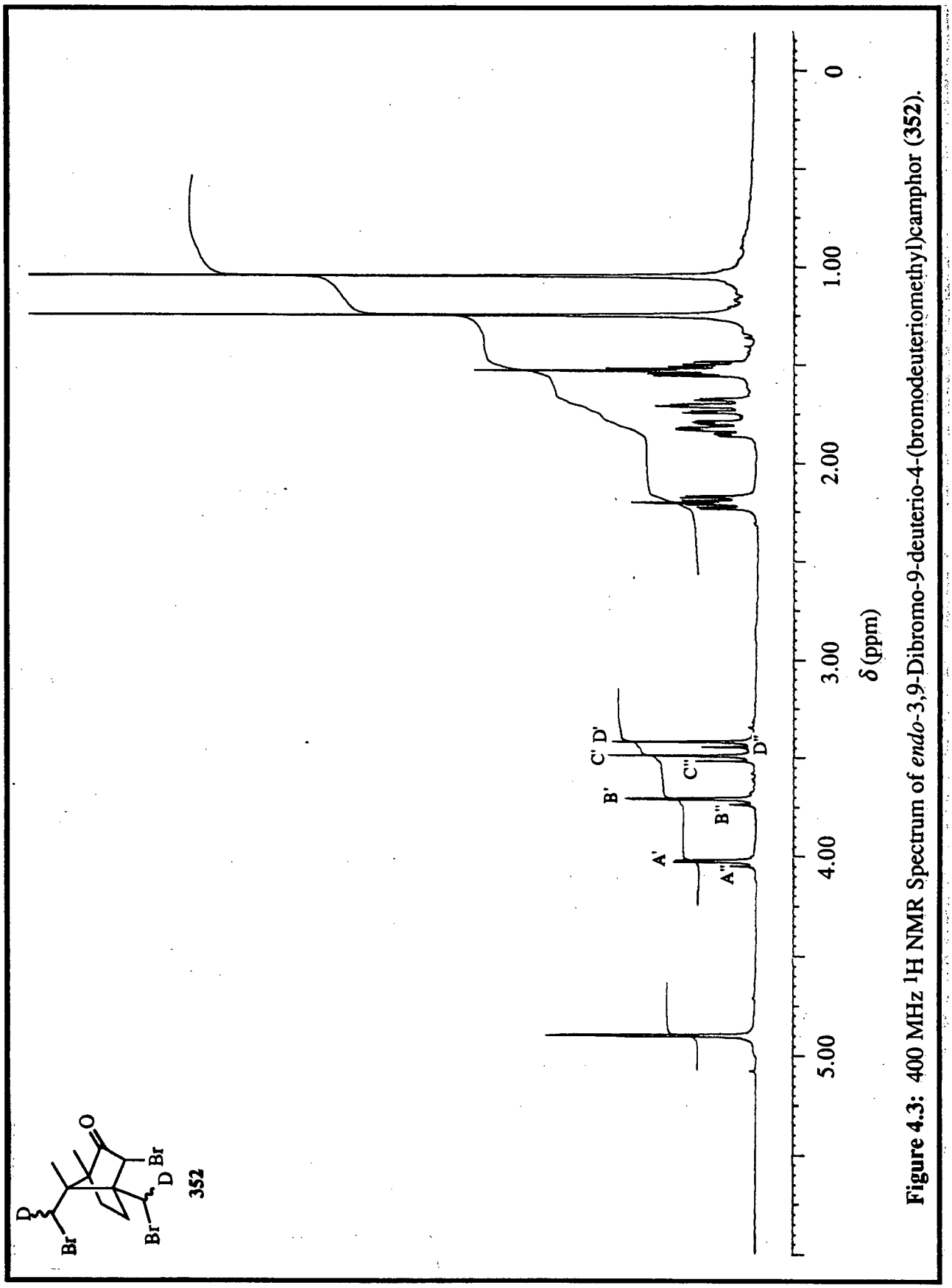
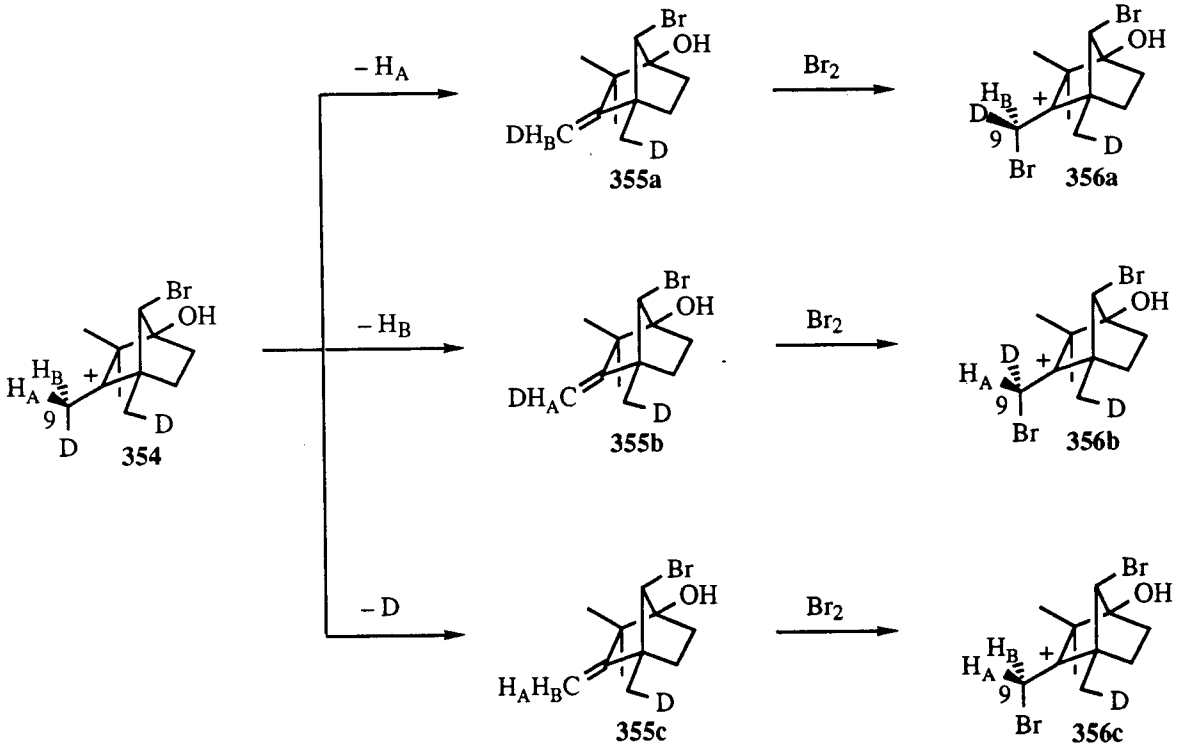


Figure 4.3: 400 MHz ^{1}H NMR Spectrum of *endo*-3,9-Dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**).

Whereas in the spectrum of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) the four signals between 3.4–4.1 ppm representing the diastereotopic protons of C(9) and C(4') are doublets, labelled A through D in Fig. 4.1 (p. 102), one notices that in the spectrum of the deuterated analogue **352**, the same four signals are now apparent singlets, labelled A' through D' in Figure 4.3 (p. 112). The change in multiplicity in these four particular signals, which were previously assigned to H(9) and H(4') in **332**, suggests that the deuterium labels reside on C(9) and C(4) of **352** and thus provides support for our prediction (p. 107) that the carbon atoms of **351** (or **327**) do not change their relative positions over the course of the bromination.

In addition, we proposed that not only can either proton from the original C(9) and C(4') be lost from each of intermediates **354** and **357** (Scheme 4.17), the deuterium labels can be lost



Scheme 4.17. Possible Fates of Carbocation **354** During the Bromination of *endo*-3-Bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**). [N.B. Carbocation **357** (Scheme 4.15) behaves similarly to provide analogous carbocations **358a,b,c** and **359a,b,c**.]

as well. If the deuterium labels are indeed lost, the resulting brominated intermediates **356c** and **359c** (Scheme 4.17) would have $-CH_2Br$ groups at one or both of C(9) or C(4'). As in the ^1H

NMR spectrum of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; *cf.* Figure 4.1, p. 102), each diastereotopic proton of the $-CH_2Br$ groups would appear as a doublet at a chemical shift that is distinct from that of the corresponding signal of the compound bearing a –CHDBr group. Indeed, the 400 MHz ^1H NMR spectrum provides evidence that compounds containing $-CH_2Br$ groups are present. The four small signals in the spectrum (Figure 4.3, p. 112), marked A" through D" and assigned to the $-CH_2Br$ protons, can be interpreted as being parts of doublets [*cf.* Figure 4.1, p. 102] in which the right half of each doublet has been obscured by the adjacent singlet (A' through D') arising from the corresponding proton in the deuterated compound **352**. In fact, the chemical shifts of the four weak signals (A" through D") in the spectrum of the product mixture correspond to those of signals A through D in the spectrum of authentic *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**) [*cf.* Figure 4.1, p. 102].

The purity of the starting material, 9-deuterio-(4-deuteriomethyl)camphor (**363**) must also be taken into account when assessing the significance of the appearance of $-CH_2Br$-containing compounds. 9-Deuterio-4-(deuteriomethyl)camphor (**363**) was prepared via the reaction of 9-bromo-4-(bromomethyl)camphor (**362**) with commercially available tributyltin deuteride,[149] whose deuterium isotopic purity was claimed by the suppliers (Fluka) to be ≥97%. The small amount (≤3%) of tributyltin hydride present in the reagent resulted in the substitution of one or both of the bromo groups in **362** with a hydrogen rather than a deuterium atom. In practice, the resulting minor by-products could not be separated from the desired 9-deuterio-4-(deuteriomethyl)camphor (**363**), and consequently had to be carried through the subsequent series of reactions.

At this point, we wished to determine the fraction of non-deuterated by-products present in our sample of 9-deuterio-4-(deuteriomethyl)camphor (**363**). Closer examination of the ^1H NMR spectrum of 9-deuterio-4-(deuteriomethyl)camphor (**363**), assigned previously (p. 110), reveals that it differs from the spectrum of 4-methylcamphor (**87**) in that the resonances for the C(9) and C(4') deuteriomethyl groups at 0.80 and 1.00 ppm are broad triplets due to coupling of the C(9) and C(4') protons with the respective geminal deuterium atoms. It is assumed that the

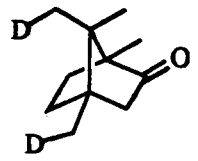
chemical shifts of each pair of diastereotopic protons on C(9) and C(4') are coincident. Slightly downfield of each of these triplets are two small singlets, at 0.81 and 1.02 ppm. It is noteworthy that the chemical shifts of these two singlets are coincident with those for the C(9) and C(4') methyl groups in 4-methylcamphor (**87**). It is believed that the two residual signals arise from the by-products formed as a result of the reaction of 9-bromo-4-(bromomethyl)camphor (**362**) with the tributyltin hydride impurity in the tributyltin deuteride reagent. For the sake of convenience in the subsequent discussion, these two signals will henceforth be termed the 'protio signals', arising from the 'protio impurity.' Likewise, the adjacent triplets will be termed the 'deuterio signal.' It was determined through comparison of the normalized integrals of the protio and deuterio signals that the protio impurities accounted for (4±2)% of the total product mixture. The uncertainty in the figure arises mainly from the uncertainties associated with measuring the integrals on the spectra.

Thus, in consideration of the protio impurity already present in the starting 9-deuterio-4-(deuteriomethyl)camphor (**363**), we could not immediately claim that the presence of de-deuterated by-products in the *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) product mixture provided support for the proposal that deuterium loss can occur during the bromination process; the de-deuterated by-products could, after all, just have been derived from the protio impurity in the original 9-deuterio-4-(deuteriomethyl)camphor (**363**) sample. However, we realized that the same amount of protio impurity present in the original 9-deuterio-4-(deuteriomethyl)camphor (**363**) sample must be carried through the synthetic sequence to *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) because no loss of deuterium was expected in the intermediate conversion of **363** to *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**). Thus, if a significant increase in the amount of protio impurity in the *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) product mixture was noted, we could then attribute the increase to have originated from the bromination reaction (**351** → **352**).

Having already estimated the amount of protio impurity in the original 9-deuterio-4-(deuteriomethyl)camphor (**363**) sample, we now sought to determine the relative amount of protio impurity present in the *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) mixture. For this purpose, the apparent singlet (B") at 3.73 ppm [H(9) signal; *cf.* Figure 4.3] is assumed to represent the left-hand branch of a doublet that would normally be present in a spectrum of authentic *endo*-3,9-bromo-4-(bromomethyl)camphor (**332**; *cf.* Figure 4.1); the missing right-hand branch of the doublet is obscured, presumably, by the adjacent, more intense deuterio signal (B'). For simplicity, *it is also assumed that the integrations of both branches of the doublet are equal.* The fraction of protio impurity in the total sample of **352**, which comprises both the protio and deuterio compounds, can be estimated by dividing twice the integral of B" by the sum of the integrals of B' and B". It was thus determined that the amount of protio by-products present in the product mixture is approximately (25±8)%. The error in this value takes into account the uncertainty in measurement of the integrals on the spectrum and also the assumption that the integration of the obscured right-hand branch of the doublet is the same as that of the observed left-hand branch (B").

At this point, we decided to convert *endo*-3,9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) into 9-bromo-9-deuterio-4-(bromodeuteriomethyl)-camphor (**364**) (Zn, HOAc–Et_2O) and thence back to 9-deuterio-4-(deuteriomethyl)camphor (**363**) (Bu_3SnH, AIBN, C_6H_6, reflux). Over the course of these two subsequent transformations the protio content determined above for the sample of *endo*-3,9-bromo-9-deuterio-4-(bromodeuteriomethyl)-camphor (**352**) was not expected to change. Thus, it was expected that similar comparisons of the integrals of appropriate signals in the ^1H NMR spectra of **363** and **364** could serve as a means for verifying the above determination of the protio content in **352**.

Examination of the ^1H spectrum for 9-bromo-9-deuterio-4-(bromodeuteriomethyl)-camphor (**364**) provided further estimates for the protio content in the sample. From the H(4')



363

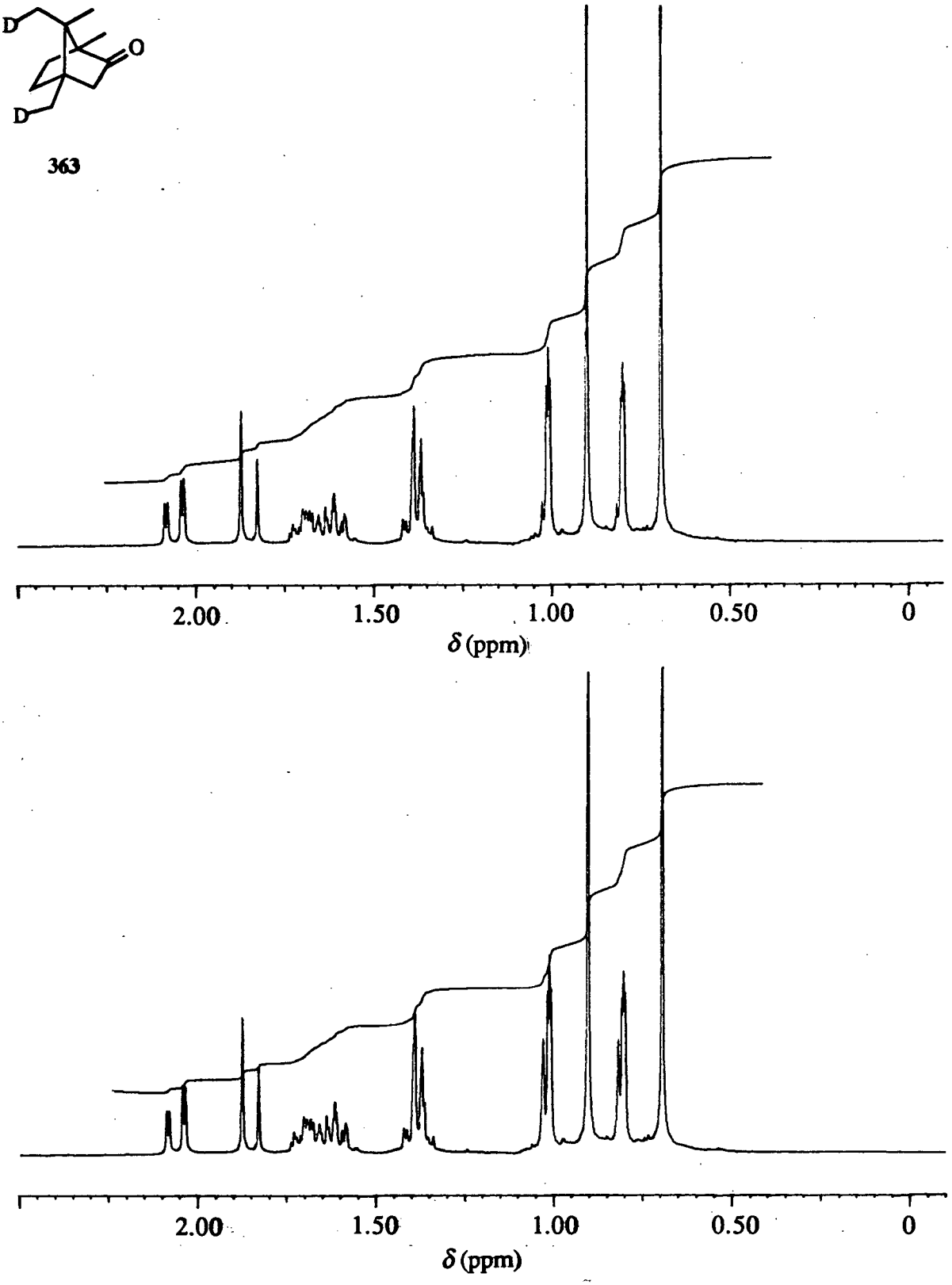


Figure 4.4: 400 MHz ^{1}H NMR Spectra of 9-Deuterio-4-(deuteriomethyl)camphor (**363**) recorded before (top) and after (bottom) the bromination cycle (*cf.* Scheme 4.16).

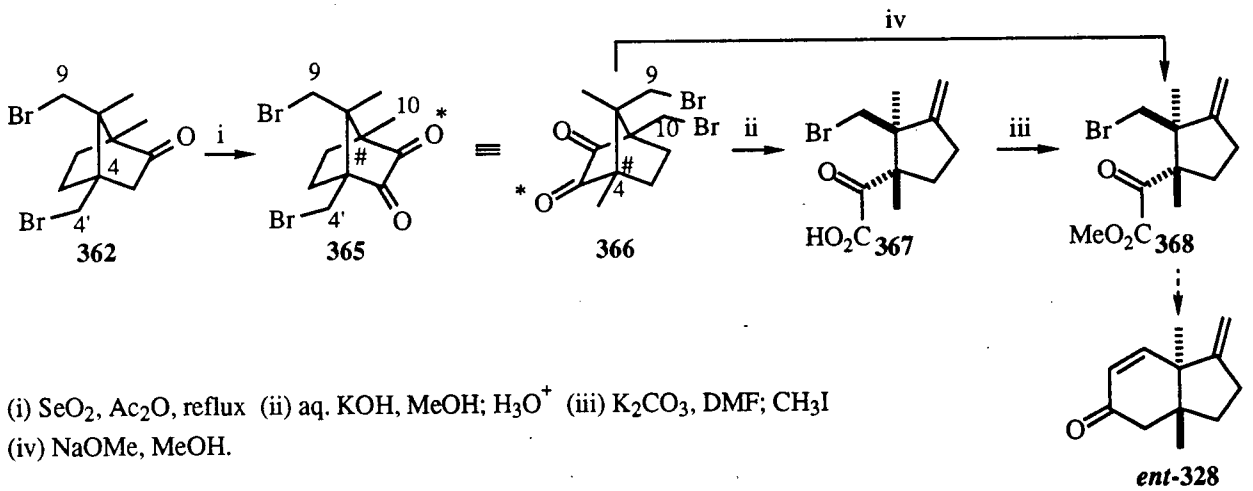
signals at 3.95 (protio) and 3.90 ppm (deuterio), the protio content was estimated to be (27±7)% while the H(9) signals at 3.30 (protio) and 3.26 (deuterio) ppm provided an estimate of (29±7)%. Similarly, in the spectrum of 9-deuterio-4-(deuteriomethyl)camphor (**363**), prepared from 9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**364**), the protio content was found to be (25±7)%, which is consistent with the values obtained above from the spectra of *endo*-3,9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) and 9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**364**). Moreover, the increase in protio content in **363** [(25±7)% from (4±2)%; *cf.* p. 115] before and after the bromination cycle **363** → **351** → **352** → **364** → **363** (Scheme 4.16) is evident when the ^{1}H NMR spectra (Figure 4.4, p. 117) of the two samples of 9-deuterio-4-(deuteriomethyl)camphor (**363**) are compared.

In summary, after the bromination of *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)-camphor (**351**) it was found that the content of the protio impurity in the product (**352**) is roughly (25±7)%, which is significantly more than the amount of protio impurity (4±2)% present in the original 9-deuterio-4-(deuteriomethyl)camphor (**363**) sample. The marked increase in protio impurity after the bromination reaction can be attributed to the loss of a deuteron from intermediates **354** and **357** (Scheme 4.15) in the proposed mechanism, and thus provides indirect support for our proposal that incorporation of bromine into *endo*-3-bromo-4-methylcamphor (**327**) involves exocyclic methylene intermediates such as **344** and **348** (Scheme 4.13). Moreover, as described earlier (pp. 111–113), that the product arising from the bromination of *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) was shown to be *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) suggests that the deuterium atoms that were present in the starting *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) have not changed their relative positions in the product (**352**). These two results are consistent with, and therefore support the proposed mechanism for the bromination of *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) and *endo*-3-bromo-4-methylcamphor (**327**) outlined in Scheme 4.15 and 4.13, respectively. As an extension to this work, similar tracer studies using other

deuterium-labelled 4-methylcamphor derivatives could be used to obtain further evidence to support the validity of the proposed bromination mechanism.

iv. Future Directions

Current efforts in our laboratory[151] are directed towards the development of a synthetic route from 9-bromo-4-(bromomethyl)camphor (**362**) to the bicyclic enone ***ent*-328**. Oxidation of 9-bromo-4-(bromomethyl)camphor (**362**) with selenium dioxide in refluxing acetic anhydride[66] yielded 9-bromo-4-(bromomethyl)camphorquinone (**365**), which also can be regarded in an alternative representation, after renumbering, as 9,10-dibromo-4-methylcamphorquinone (**366**). Like 9,10-dibromocamphor (**33**, Scheme 1.9, p. 13), 9,10-dibromo-4-methylcamphorquinone (**366**) also possesses an α,α-disubstituted-β-bromoketone sub-unit that makes possible the



(i) SeO_2, Ac_2O, reflux (ii) aq. KOH, MeOH; H_3O^+ (iii) K_2CO_3, DMF; CH_3I
(iv) NaOMe, MeOH.

Scheme 4.18. Proposed Use of 4-Methylcamphor and Derivatives as Intermediates in Triterpenoid and Steroid Synthesis.

application of a Grob fragmentation reaction (NaOMe, MeOH; or KOH, MeOH; K_2CO_3, DMF, then CH_3I)[39] to yield bromo-keto-ester (**368**). It is anticipated that bromo-keto-ester **368** can be transformed into bicyclic enone ***ent*-328**, a valuable intermediate in our projected synthetic route to the euphane and tirucallane triterpenoids. Furthermore, by starting with the enantiomeric 4-methylcamphor (***ent*-87**), it would be possible to obtain bicyclic enone **328** which could also be used to gain access to the lanostane triterpenoids and 14α-methyl steroids.

Chapter 5

Experimental Section

5. Experimental Section

(a) General Experimental

All reactions involving air- or moisture-sensitive reagents were conducted under argon atmosphere. Where no reaction temperature has been noted in a particular experimental procedure, that reaction was carried out at room temperature [(22 ± 2) °C]. Unless specified otherwise, THF and diethyl ether were distilled[152] over sodium/benzophenone while dichloromethane, benzene, toluene, acetonitrile, triethylamine, diisopropylamine, piperidine and dimethyl sulfoxide were distilled over calcium hydride. Methanol was distilled from magnesium turnings in the presence of several crystals of iodine. Methanesulfonyl chloride was distilled over phosphorus pentoxide. Ethylene glycol was distilled over calcium oxide and stored over 4 Å molecular sieves. Methyl iodide, allyl bromide, 2-methyl-1,3-dithiane, and DBU were passed through a short (~5 × 0.5 cm) column of oven-dried (160 °C) basic alumina (Brockmann Activity I) immediately prior to use. $CDCl_3$ was stored over anhydrous potassium carbonate. PPTS was prepared and purified according to the method outlined by Grieco and co-workers.[92b] LDA was prepared *in situ* according to the method described by White and Heathcock.[153] For ozonolysis reactions, ozone was generated (~4% O_3 in O_2) using a Welsbach Model T-23 laboratory ozonator. Extraction solvents and all other reagents were used as received.

The concentrations of commercially obtained butyllithium solutions were determined periodically by the method of Kofron and Baclawski.[154a] Solutions of lithium triethylborohydride were used as received. If desired, however, concentrations of organoboron reagents can be determined by the method outlined by Brown.[154b]

Gas-liquid chromatography (GLC) was performed on a Hewlett-Packard HP-5830A gas chromatograph employing an HP-1 (0.2 mm × 12 m × 0.33 μm) capillary column. Thin-layer chromatography (TLC) was performed on commercially available aluminum or plastic sheets pre-coated with silica gel 60 F_{254} (Merck 5554, 0.2 mm thickness). Visualization of thin-layer chromatograms was accomplished with ultraviolet light (254 nm), 2% phosphomolybdic acid

spray, or 1% *p*-anisaldehyde spray. Radial chromatography was performed on a Harrison Research Chromatotron®, Model 7924T, using circular glass plates (1 mm or 2 mm thickness × 11.25 cm radius) coated with Merck Silica Gel 60 F_{254} containing gypsum. Flash column chromatography was performed according to the method reported by Still and co-workers.[155] The evaporation of solvents under reduced pressure (~20–30 Torr) was accomplished using a Büchi rotary evaporator.

All 400 MHz ^1H and 100 MHz ^{13}C NMR spectra were recorded on a Bruker WH-400 spectrometer while 75 MHz ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer, and 200 MHz ^1H and 50 MHz ^{13}C NMR spectra on an Bruker AC-200 spectrometer. COSY and difference NOE experiments were performed on the Bruker WH-400 instrument while HETCOR experiments were performed on the Varian XL-300 instrument. NMR signal positions (δ) are reported in parts per million and are referenced to the residual proton signal of $CHCl_3$ (7.24 ppm) or the carbon signal of $^{13}\underline{C}DCl_3$ (77.0 ppm), as appropriate. Throughout this chapter, the abbreviations used to denote NMR signal multiplicities are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), etc. In referring to ^1H NMR signals for diastereotopic protons, the notations $H(x_A)$ and $H(x_B)$ have been used to denote signals resonating at higher and lower field, respectively.

Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier transform spectrophotometer. Abbreviations that have been used in the experimental section to describe IR signals are: br (broad), ν (stretching vibration), sym (symmetric vibration), and asym (asymmetric vibration). Low and high resolution electron impact mass spectra were acquired on a Kratos MS-50 mass spectrometer while desorption chemical ionization mass spectra were recorded on a Delsi Nermag R-10-10C instrument. Melting points were measured on a Reichert hot stage and are uncorrected. Specific rotations were recorded on a Jasco J-710 or Perkin-Elmer 141 spectropolarimeter in a 0.1 or 1.0 dm cell, respectively. Microanalyses were

performed by Mr. P. Borda of the UBC Microanalytical Laboratory on a Carlo-Erba CHN elemental analyzer, model 1106 or Fisons CHN-O elemental analyzer, model 1108.

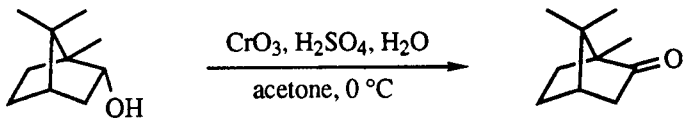
(b) Safety Considerations

All chemical manipulations described in this chapter were conducted in a well-ventilated fumehood in accordance with guidelines outlined in Material Safety Data Sheets (MSDSs) for individual reagents. Appropriate personal protective equipment was worn at all times. The toxicity and hazards of all newly synthesized compounds are unknown, and it is therefore advisable that such compounds be handled with caution. The disposal of chemicals was carried out in accordance with guidelines prescribed by the University of British Columbia Department of Health, Safety & Environment (formerly Occupational Health & Safety) and by accepted literature methods.[156]

(c) Experimental Procedures

The experimental procedures in the following section are arranged in order of occurrence in appropriate synthetic plans. Selected unsuccessful procedures and procedures for compounds that are not part of a finalized synthetic plan have been relegated to the Appendix. The Index of Experimental Procedures (p. xi) may be used to assist in locating specific procedures.

(–)-Camphor (*ent*-9)



159 ***ent*-9**

To a solution of (–)-borneol (**159**; 171.3 g, 1.110 mol) in acetone (400 mL) at 0 °C was added, dropwise over 1 h, Jones reagent [prepared from chromium(VI) oxide (104.0 g, 1.040 mol), water (350 mL), and concentrated sulfuric acid (100 mL) **[CAUTION: The addition of concentrated sulfuric acid to the solution of chromium(VI) oxide in water is exothermic.**

The use of an external ice-water cooling bath is strongly advised during the preparation of the Jones reagent]. The dark orange-green reaction mixture was stirred at 0 °C for 2 h after which saturated aq. $NaHSO_3$ (~200 mL) was added. The reaction mixture was poured into water (~500 mL). The organic phase was withdrawn while the aqueous phase was extracted with Et_2O (3 × 500 mL). The organic extracts were washed with water (4 × 500 mL), neutralized with saturated aq. $NaHCO_3$ (2 × 500 mL), washed with brine (3 × 500 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield (–)-camphor (***ent*-9**) as a volatile, white solid (165.1 g, 97%) that could be used directly in the next reaction without further purification; mp 177–179 °C (*lit.* 178–180 °C;[156]); $[\alpha]_D^{25}$ –43.7 (*c* 1.02, EtOH) (*lit* [157]. $[\alpha]_D^{20}$ –43 (*c* 10, EtOH)).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.32 (ddd, J = 17.0, 5.0, 2.5 Hz, 1H; H(3_{exo})), 2.10 (dd, J = 5.0, 5.0 Hz, 1H; H(4)), 1.92–2.01 (m, 1H; C(5_{exo})), 1.86 (d, J = 17.0, 5.0 Hz, 1H; H(3_{endo}), 1.69 (ddd, J = 14.0, 14.0, 4.5 Hz, 1H; H(6_{exo})), 1.29–1.45 (m, 2H), 0.96 (s, 3H; H(9)), 0.92 (s, 3H; H(10)), 0.84 (s, 3H; H(8)).

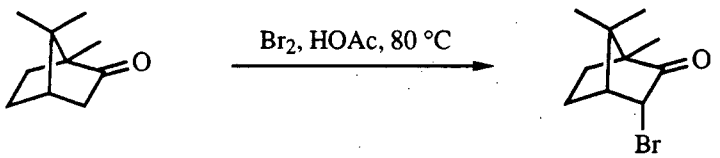
IR (neat film): 2970, 2915, 2890, 1735 ($\nu_{C=O}$) cm^{-1}.

EIMS *m/z* (rel intensity): 152 (M^+; 26.7), 110 (13.0), 109 (28.9), 108 (52.8), 95 (100).

Exact mass calcd for $C_{10}H_{16}O$ 152.1201 , found 152.1204.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.75; H, 10.56.

(–)-*endo*-3-Bromocamphor (*ent*-20)

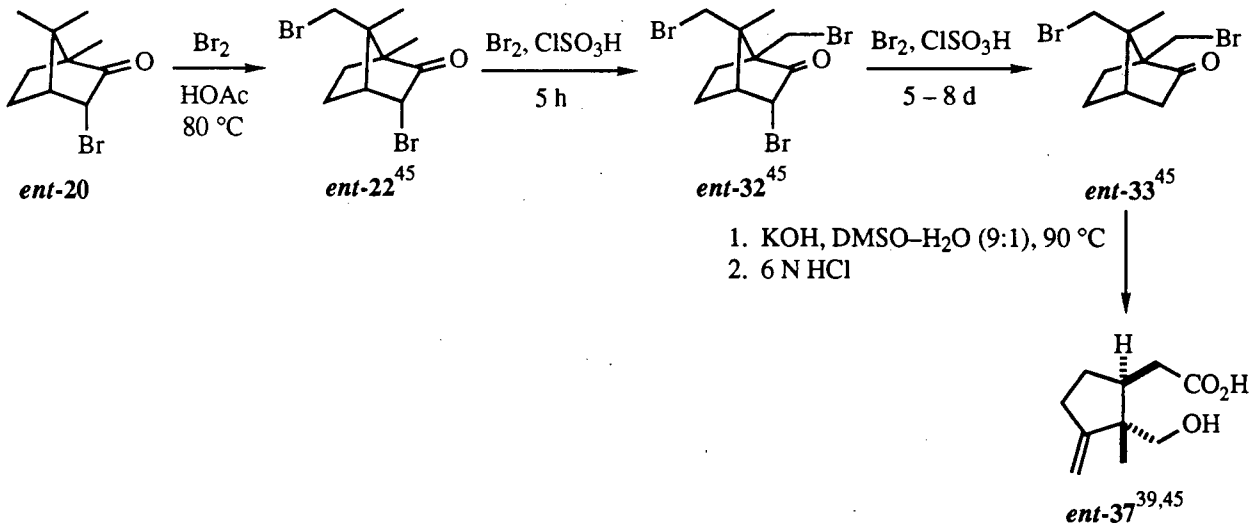


***ent*-9** ***ent*-20**

To a solution of (–)-camphor (***ent*-9**; 143.0 g, 0.939 mol) in glacial acetic acid (500 mL) at 80 °C was added, dropwise over 40 min, a solution of bromine (58 mL, 180 g, 1.1 mol) in

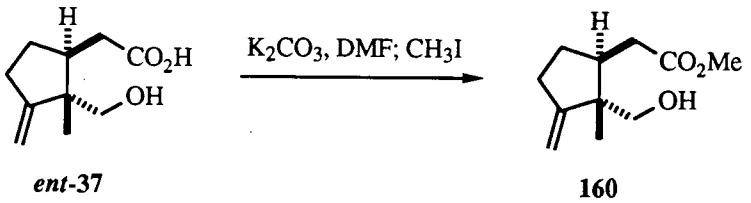
glacial acetic acid (60 mL). The red-orange solution was stirred at 80 °C for 18 h, allowed to cool to room temperature, and poured cautiously into a saturated aq. $NaHSO_3$ solution (~250 mL). The aqueous solution was decanted and extracted with Et_2O (3 × 500 mL) while the precipitated crude product was dissolved in Et_2O (250 mL). The combined organic solutions were washed with water (2 × 1 L), neutralized with saturated aq. $NaHCO_3$ (3 × 500 mL), washed with brine (3 × 500 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a light orange-brown solid. Recrystallization of the orange-brown solid from 95% ethanol yielded *endo*-3-bromocamphor (***ent*-20**) as white crystals (154.1 g, 71%). Spectroscopic data obtained for ***ent*-20** were in agreement with those reported in the literature.[30,65]

(–)-*endo*-3,9-Dibromocamphor (*ent*-22)[45]
(–)-*endo*-3,9,10-Tribromocamphor (*ent*-32)[45]
(–)-9,10-Dibromocamphor (*ent*-33)[45]
(+)-Hydroxy-acid (*ent*-37)[39]



The title compounds ***ent*-22**, ***ent*-32**, ***ent*-33**, and ***ent*-37** were prepared according to literature methods.[39,45] All spectroscopic data were in agreement with those reported in the literature.[37, 45]

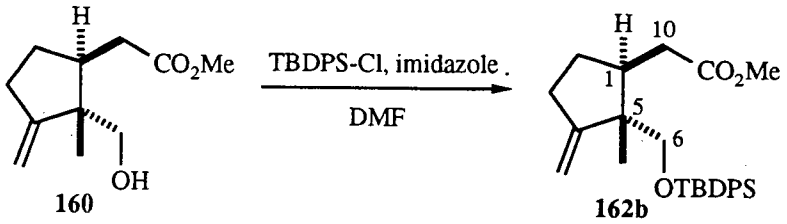
(+)-Hydroxy-ester (160)[45]



ent-**37** **160**

Hydroxy-ester **160**[39,45] was prepared according to a method reported earlier by our research group.[45] Purification of hydroxy-ester **160** was accomplished via flash column chromatography (5% EtOAc–CH_2Cl_2). Spectroscopic data obtained for **160** were in agreement with those reported in the literature.[45]

***t*-Butyldiphenylsilyloxy-ester (162b)**



160 **162b**

To a solution of hydroxy-ester (**160**)[39,45] (6.4421 g, 32.49 mmol) and imidazole (11.06 g, 162.4 mmol) in spectro grade DMF (40 mL) was added *t*-butyldiphenylsilyl chloride (9.9 mL, 11 g, 39 mmol).[93] The reaction mixture was stirred at room temperature for 5 h after which it was partitioned between water (200 mL) and Et_2O (100 mL). The aqueous phase was extracted further with Et_2O (2 × 50 mL). The combined extracts were then washed with water (50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a colorless oil. Further purification by flash column chromatography (5% EtOAc–pet. ether) yielded pure silyloxy-ester (**162b**) as a colorless oil (13.4679 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.72 (m, 4H; $-C_6\underline{H}_5$), 7.35–7.45 (m, 6H; $-C_6\underline{H}_5$), 4.89 (bs, 1H; $=C\underline{H}_AH_B$), 4.72 (bs, 1H; $=CH_A\underline{H}_B$), 3.68 (s, 3H; $-CO_2\underline{Me}$), 3.49 (d, J = 10.0

Hz, 1H; $H(6)_A$), 3.44 (d, J = 10.0 Hz, 1H; $H(6)_B$), 2.61 (dd, J = 15.0, 4.0 Hz, 1H; $H(10)_A$), 2.49–2.59 (m, 1H; H(1)); 2.23–2.44 (m, 2H; $H(3)_A$, $H(3)_B$), 2.12 (dd, J = 15.0, 10.0 Hz, 1H; $H(10)_B$), 1.85–1.94 (m, 1H; $H(2)_A$), 1.24–1.37 (m, 1H; $H(2)_B$), 1.06 (s, 9H; Bu^t), 0.92 (s, 3H; C(5)–$\underline{C}H_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.0 ($\underline{C}$=O), 157.9 (C(4)=$\underline{C}H_2$); 135.7, 133.5, 129.5, and 127.6 (aromatic carbons); 105.5 (C(4)), 70.8 (C(6)), 51.4 (–O$\underline{C}H_3$), 48.6, 42.2 (C(1)), 35.9, 32.2, 29.2, 26.8 ($C(\underline{C}H_3)_3$), 19.7 ($\underline{C}(CH_3)_3$), 19.3 (C(5)–$\underline{C}H_3$).

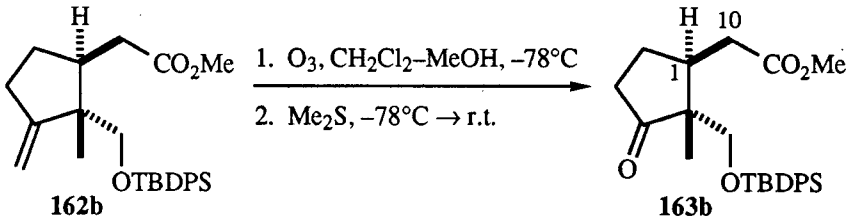
IR (neat film): 3071 ($\nu_{=C\text{-}H\ (aromatic)}$), 3060 ($\nu_{=C\text{-}H\ (aromatic)}$), 2956, 2894, 2858, 1741 ($\nu_{C=O}$), 1650 ($\nu_{C=C}$), 1590, 1472, 1429, 1194 (ν_{C-O}) cm^{-1}.

EIMS *m/z* (rel intensity): 436 (0.1; M^+), 405 (1.7; $(M - OMe)^+$), 379 (87.3; $(M - t\text{-}Bu)^+$), 347 (9.1), 318 (2.5), 213 (100).

Exact mass calcd for $C_{31}H_{42}O_5Si$ 436.2434 , found 436.2428.

Anal. Calcd for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8.31. Found: C, 74.31; H, 8.27.

Keto-ester (163b)



162b **163b**

A stream of ozonized oxygen (~4% O_3 in O_2) was bubbled into a solution of silyloxy-ester (**162b**) (12.4231 g, 28.45 mmol) in 1:1 CH_2Cl_2–MeOH (200 mL) at –78 °C until a faint blue color persisted (~1 h). Excess ozone was purged with oxygen gas (~10 min). Dimethyl sulfide (20 mL) was added and the reaction mixture was allowed to warm to room temperature over 12 h. The solution was concentrated to a clear, pale yellow oil that was then purified by flash column chromatography (20% Et_2O–pet. ether) to yield pure keto-ester (**163b**) as a viscous, clear, colorless oil (11.4776 g, 92%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61–7.67 (m, 4H; $-C_6\underline{H}_5$), 7.33–7.44 (m, 6H; $-C_6\underline{H}_5$), 3.78 (d, J = 9.2 Hz, 1H; H(6_A)), 3.68 (s, 3H; $-OC\underline{H}_3$), 3.32 (d, J = 9.2 Hz; H(6_B)), 3.02–3.12 (m, 1H; H(10_A)), 2.34–2.48 (m, 2H; H(10_B), H(3_A)), 2.12–2.30 (m, 3H; H(1), H(2_A), H(3_B)), 1.44–1.58 (m, 1H; H(2_B)), 0.99 (s, 9H; Bu^t), 0.71 (s, 3H; C(5)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 217.5 ($\underline{C}$=O), 172.3 ($\underline{C}O_2Me$), 135.7, 132.3, 129.7, 127.7, 66.2 (C(6)), 53.0, 51.6, 38.2, 37.2, 35.0, 26.8 ($-C(\underline{C}H_3)_3$) , 25.4, 19.2, 13.8 (C(5)–$\underline{C}H_3$).

IR (neat film): 3073, 3050, 2948, 2858, 1741 ($\nu_{C=O}$), 1467, 1428, 1101 (ν_{C-O}) cm^{-1}.

EIMS *m/z* (rel intensity): 407 (0.7; $(M - OMe)^+$), 381 (25; $(M - t\text{-Bu})^+$), 349 (2.1), 321 (1.8), 307 (4.5), 105 (100).

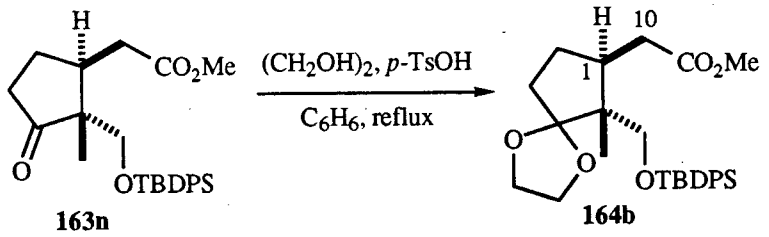
Exact mass calcd for $C_{22}H_{25}O_4Si$ $(M - t\text{-Bu})^+$ 381.1522, found 381.1523.

Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 70.99; H, 7.91.

Table 5.1. Spectral Data from COSY Spectrum of Keto-ester **163b**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assign-ment
7.61–7.67	$-C_6H_5$	7.33–7.44	$-C_6H_5$
7.33–7.44	$-C_6H_5$	7.61–7.67	$-C_6H_5$
3.78	H(6_A)	3.32	H(6_B)
3.32	H(6_B)	3.78	H(6_A)
3.02–3.12	H(10_A)	2.34–2.48, 2.12–2.30	H(10_B) H(1)
2.34–2.48	H(10_B), H(3_A)	3.02–3.12, 2.12–2.30, 1.44–1.58	H(10_A) H($2_{A,B}$) H(3_B)
2.12–2.30	H(1), H(2_A,3_B)	3.02–3.12, 2.34–2.48, 1.44–1.58	H($10_{A,B}$) H(3_A), H(2_B)
1.44–1.58	H(2_B)	2.34–2.48, 2.12–2.30	H(1, 2_A) H($3_{A,B}$)

Ketal-ester (164b)



163n **164b**

To a solution of keto-ester (**163b**) (11.3824 g, 25.95 mmol) in dry, distilled benzene (200 mL) was added dry ethylene glycol (29 mL, 32 g, 519.0 mmol) and *p*-toluenesulfonic acid (0.4936 g, 2.595 mmol). The heterogeneous mixture was stirred vigorously at reflux in a Dean-Stark apparatus for 18 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (200 mL) and poured into water (~250 mL). The organic phase was separated while the aqueous phase was extracted once more with Et_2O (200 mL). The combined organic solutions were washed with water (250 mL), saturated aq. $NaHCO_3$ (250 mL), and brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated to yield a clear, straw yellow oil. Subsequent purification by flash column chromatography (20% EtOAc–pet. ether) yielded pure ketal-enone (**164b**) as a viscous, clear, colorless syrup (11.4846 g; 92%); $[\alpha]_D^{25}$ –17.7 (*c* 0.793, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67–7.76 (m, 4H; –$C_6\underline{H}_5$), 7.32–7.46 (m, 6H; –$C_6\underline{H}_5$), 3.72–3.84 (m, 4H; –$OC\underline{H}_2C\underline{H}_2O$–), 3.60–3.70 (m, 2H; $H(6_A)$, $H(6_B)$), 3.62 (s, 3H; $CO_2\underline{Me}$), 2.72 (dd, J = 15, 4 Hz, 1H; $H(10_A)$), 2.51–2.62 (m, 1H; H(1)), 2.17 (dd, J = 15, 11 Hz, 1H; $H(10_B)$), 1.85–2.01 (m, 1H; $H(2_A)$), 1.78–1.84 (m, 1H; $H(3_A)$), 1.64–1.67 (m, 1H; $H(3_B)$), 1.27–1.40 (m, 1H; $H(2_B)$), 1.06 (s, 9H; Bu^t), 0.97 (s, 3H; C(5)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6 ($\underline{C}O_2Me$), 135.6, 133.6, 129.5, 127.5, 118.8 (C(4)), 68.1 (C(6)), 64.6 (ketal –$O\underline{C}H_2CH_2O$–), 64.2 (ketal –$OCH_2\underline{C}H_2O$–), 51.2 (–$O\underline{C}H_3$), 49.5 (C(5)), 40.0 (C(1)), 36.9 (C(10)), 33.4 (C(3)), 26.9 (–$C(\underline{C}H_3)_3$), 25.9 (C(2)), 19.3 (–$\underline{C}(CH_3)_3$), 13.6 (C(5)–CH_3).

IR (neat film): 3072 ($\nu_{=C-H}$), 3055 ($\nu_{=C-H}$), 2949, 2873, 1739 ($\nu_{C=O}$), 1589, 1470, 1429, 1152, 1099, 1005 cm^{-1}

EIMS *m/z* (rel intensity): 451 ($(M - OMe)^+$; 77), 425 ($(M - Bu^t)^+$; 98), 395 (8), 381 (55), 349 (9), 321 (12), 307 (11), 271 (6), 243 (17), 213 (100).

Exact mass calcd for $C_{24}H_{29}O_5Si$ $(M - Bu^t)^+$: 425.1784, found 425.1786;

Exact mass calcd for $C_{27}H_{35}O_4Si$ $(M - OMe)^+$: 451.2304, found 451.2308;

Anal. Calcd for $C_{28}H_{38}O_5Si$: C, 69.67; H, 7.93. Found: C, 69.58; H, 7.96.

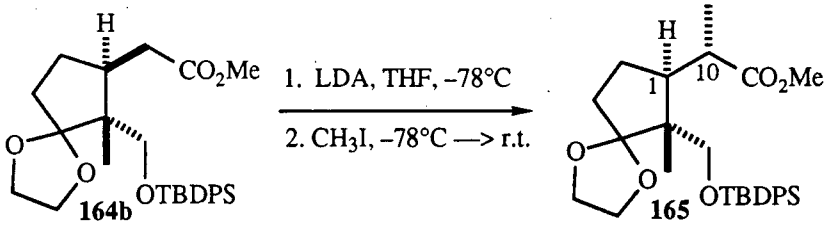
Table 5.2. Spectral Data from COSY Spectrum of Ketal-ester **164b**.

400 MHz ^1H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assign-ment
7.67–7.76	$-C_6H_5$	7.32–7.46	$-C_6H_5$
7.32–7.46	$-C_6H_5$	7.67–7.76	$-C_6H_5$
2.72	$H(10_A)$	2.51–2.62, 2.17	H(1), $H(10_B)$
2.51–2.62	H(1)	2.72, 2.17	$H(10_{A,B})$,
2.17	$H(10_B)$	2.72, 2.51–2.62	$H(10_A)$, H(1)
1.85–2.01	$H(2_A)$	1.78–1.84, 1.64–1.67, 1.27–1.40	$H(3_{A,B})$, $H(2_B)$
1.78–1.84	$H(3_A)$	1.85–2.01, 1.64–1.67, 1.27–1.40	$H(3_B)$, $H(2_{A,B})$
1.64–1.67	$H(3_B)$	1.85–2.01, 1.78–1.84, 1.27–1.40	$H(3_A)$, $H(2_{A,B})$
1.27–1.40	$H(2_B)$	1.85–2.01, 1.78–1.84, 1.64–1.67	$H(2_A)$ $H(3_{A,B})$

Table 5.3. Spectral Data from HETCOR Spectrum of Ketal-ester **164b**.

75 MHz ^{13}C NMR Spectrum Signal Positions [δ_C (ppm)]	Assign-ment	HETCOR Correlations Signal Positions [δ_H (ppm)]	Assign-ment
135.6, 133.6, 129.5, 127.5	$-C_6H_5$	7.67–7.76, 7.32–7.46	$-C_6H_5$
68.1	C(6)	3.60–3.70	$H(6_A,6_B)$
64.6	ketal	3.72–3.84	ketal
64.2	ketal	3.72–3.84	ketal
51.2	$-CO_2Me$	3.62	$-CO_2Me$
40.0	C(1)	2.51–2.62	H(1)
36.9	C(10)	2.72, 2.17	$H(10_A)$ $H(10_B)$
33.4	C(3)	1.78–1.84, 1.64–1.67	$H(3_A,3_B)$
26.9	$-CMe_3$	1.06	$-CMe_3$
25.9	C(2)	1.85–2.01, 1.27–1.40	$H(2_A,2_B)$
13.6	C(5)–Me	0.97	C(5)–Me

Ketal-ester (165): Stereoselective Alkylation of Ketal-ester (164b) with Methyl Iodide



To an ice-cold solution of diisopropylamine (0.73 mL, 0.53 g, 5.2 mmol) in THF (5 mL) was added n-butyllithium (3.35 mL, 1.6 M in hexane, 5.19 mmol) in one portion. The colorless solution was stirred at 0 °C for 40 min and then cooled to –78 °C. After ~5 min, a solution of ketal-ester (**164b**) (2.0879 g, 4.326 mmol) in THF (10 mL) was added by cannula. After a further 1.0 h, methyl iodide (0.32 mL, 0.74 g, 5.2 mmol) was added. The reaction mixture was stirred at –78 °C for 2 h and then allowed to warm to room temperature, at which it was stirred for 15 h. Water (20 mL) was added, cautiously at first, and the organic phase was separated.

The aqueous phase was extracted with ether (3 × 20 mL). The combined extracts were washed with brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to a pale yellow oil. Subsequent purification by flash column chromatography (10% EtOAc–pet. ether) yielded ketal-ester (**165**) as a clear, colorless oil (2.0409 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.70 (m, 4H; $-C_6\underline{H}_5$), 7.33–7.44 (m, 6H; $-C_6\underline{H}_5$), 3.79–3.90 (m, 4H; $-OC\underline{H}_2C\underline{H}_2O-$), 3.68 (d, J = 8 Hz, 1H; $H(6_A)$), 3.36 (d, J = 8 Hz, 1H; $H(6_B)$), 3.27 (s, 3H; $-CO_2\underline{Me}$), 2.47 (dq, J = 9.5, 6.9 Hz, 1H; H(10)), 2.28–2.38 (m, 1H; H(1)), 1.71–1.85 (m, 3H; $H(3_A)$, $H(3_B)$, $H(2_A)$), 1.28–1.35 (m, 1H; $H(2_B)$), 1.08 (d, J = 6.9 Hz, 3H; C(10)–$C\underline{H}_3$), 1.04 (s, 9H; Bu^t), 0.97 (s, 3H; C(5)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.1 ($-\underline{C}O_2Me$), 135.8, 135.8, 135.7, 134.0, 133.8, 129.4, 127.6, 127.5, 119.1 (C(4)), 68.0, 64.6, 64.5, 51.2, 50.0, 44.4, 41.0, 33.5, 27.0, 23.7, 19.5, 16.5, 13.7.

IR (neat film): 3072 ($\nu_{=C-H}$), 3022 ($\nu_{=C-H}$), 2951, 2883, 2850, 1737 ($\nu_{C=O}$), 1590($\nu_{C=C}$), 1470, 1462, 1429, 1391, 1161, 1112, 1068 cm^{-1}.

DCI-MS (NH_3) *m/z* (rel intensity): 497 ($(M + H)^+$; 100), 465 ($(M - OMe)^+$; 5.3), 441 (7.5), 439 ($(M - Bu^t)^+$; 56.2), 241 ($(M - TBDPSO)^+$; 28.1).

Exact mass calcd for $C_{25}H_{31}O_5Si$ $(M - Bu^t)^+$ 439.1941, found 439.1944.

Anal. Calcd for $C_{29}H_{40}O_5Si$: C, 70.12; H, 8.12. Found: C, 70.04; H, 8.05.

Table 5.4. Results of NOE Experiments for Ketal-ester **165**.

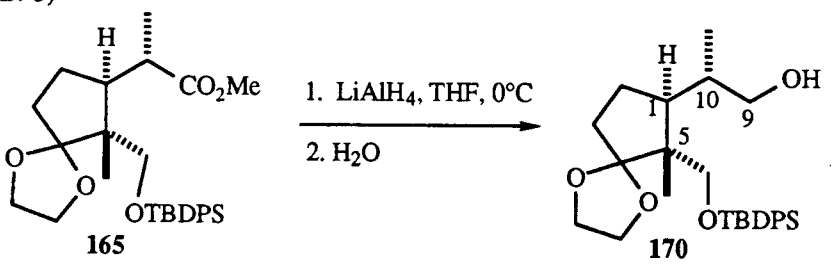
Proton(s) Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
3.27	$-CO_2Me$	7.65–7.70, 7.33–7.44 3.68, 3.36, 2.47, 2.28–2.38, 1.08, 1.04	$-C_6H_5$, H(6), H(10), H(1), C(10)-Me, Bu^t
2.47	H(10)	7.65–7.70, 7.33–7.44, 3.68, 3.27, 1.08, 1.04, 0.97	$-C_6H_5$, H(6), Bu^t, C(10)-Me, C(5)-Me
1.08, 1.04**	C(10)-Me, Bu^t	7.65–7.70, 7.33–7.44, 3.27, 2.28–2.38, 2.47, 1.71–1.85 (part of multiplet), 1.28–1.35	$-C_6H_5$, $-CO_2Me$, H(1), H(10), H(2)
0.97	C(5)-Me	3.68, 3.36, 3.27, 2.47, 1.71–1.85, 1.08	H(6), $-CO_2Me$, H(10), C(10)–Me

*Only those protons that can be assigned unambiguously have been recorded.
**All attempts to irradiate selectively the signals at 1.08 and 1.04 ppm were unsuccessful.

Table 5.5. Spectral Data from COSY Spectrum of Ketal-ester **165**.

400 MHz ^1H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
7.65–7.70	$-C_6H_5$	7.33–7.44	$-C_6H_5$
7.33–7.44	$-C_6H_5$	7.65–7.70	$-C_6H_5$
3.68	$H(6_A)$	3.36	$H(6_B)$
3.36	$H(6_B)$	3.68	$H(6_A)$
2.47	H(10)	2.28–2.38, 1.08	H(1), C(10)-Me
2.28–2.38	H(1)	2.47, 1.711.85 (part of multiplet), 1.28–1.35	H(10) $H(2_A,2_B)$
1.71–1.85	$H(2_A)$, $H(3_A,3_B)$	2.28–2.38, 1.28–1.35	H(1), $H(2_A)$
1.28–1.35	$H(2_B)$	2.28–2.38, 1.71–1.85	H(1), $H(2_B)$, $H(3_A,3_B)$
1.08	C(10)-Me	2.47	H(10)

Ketal-alcohol (170)



To an ice-cold suspension of lithium aluminum hydride (0.1471 g, 3.876 mmol) in THF (10 mL) was added by cannula an ice-cold solution of ketal-ester **165** (1.9254 g, 3.876 mmol) in THF (30 mL). The grey suspension was stirred at 0 °C for 1 h, then diluted with dry Et_2O (30 mL) and quenched cautiously by dropwise addition of water (10 mL). The mixture was stirred at room temperature for 1 h. The organic layer was then separated while the aqueous layer was extracted further with ether (4 × 10 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide a colorless syrup. Subsequent purification by flash column chromatography (15% acetone–pet. ether) yielded pure ketal-alcohol **170** as a clear, viscous syrup (1.5588 g, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63–7.73 (m, 4H; –$C_6\underline{H}_5$), 7.34–7.45 (m, 6H; –$C_6\underline{H}_5$), 3.66–3.77 (m, 4H; –$OC\underline{H}_2C\underline{H}_2O$–), 3.64 (d, J = 10.5 Hz, 1H; $H(6_A)$), 3.60 (d, J = 10.5 Hz, 1H; $H(6_B)$), 3.39–3.50 (m, 2H; H(9)), 2.02–2.10 (m, 1H), 1.62–1.82 (m, 5H), 1.39–1.50 (m, 1H), 1.09 (s, 9H; Bu^t), 0.94 (s, 3H; C(5)–$C\underline{H}_3$), 0.92 (d, J = 6 Hz, 3H; C(10)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9, 135.8, 133.6, 129.6, 127.6, 119.4, 68.2, 67.5, 64.5, 64.1, 50.0, 43.4, 36.6, 33.0, 27.1, 23.0, 19.4, 15.3, 14.3.

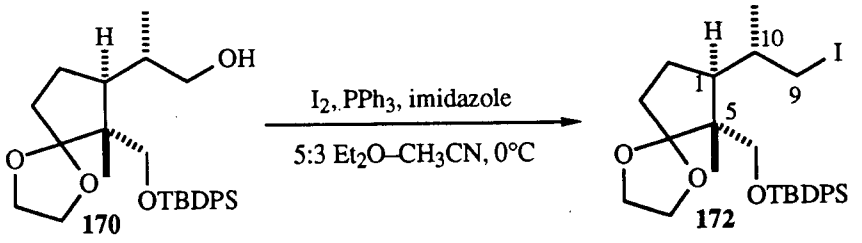
IR (neat film): 3451 (broad, ν_{O-H}), 3072 ($\nu_{=C-H}$), 3049 ($\nu_{=C-H}$), 2975, 2961, 2890, 2880, 1590 ($\nu_{C=C}$), 1473, 1428, 1391, 1113, 1080 cm^{-1}.

DCI-MS (NH_3) *m/z* (rel intensity): 469 ($(M + H)^+$; 32), 213 (44), 199 (100), 195 (48), 181 (16), 165 (11), 151 (28), 135 (24), 121 (16), 105 (14), 99 (76), 86 (19).

Exact mass calcd for $C_{28}H_{41}O_4Si$ [$(M + H)^+$]: 469.2774, found 469.2791.

Anal. Calcd for $C_{28}H_{41}O_4Si$: C, 71.75; H, 8.60. Found: C, 71.80; H, 8.73.

Ketal-iodide (172)



To an ice-cold, colorless solution of ketal-alcohol **170** (1.3929 g, 2.972 mmol), triphenylphosphine (1.1692 g, 4.458 mmol) and imidazole (0.3035 g, 4.458 mmol) in 5:3 diethyl ether-acetonitrile (30 mL) were added iodine crystals (0.9806 g, 3.863 mmol) in several portions over 5 min until a pale yellow endpoint was reached.[96] The ice bath was removed and the solution was stirred at room temperature for 5 h. The reaction mixture was partitioned between H_2O (50 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (50 mL). The combined extracts were washed successively with saturated aqueous $NaHSO_3$ (2 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), and brine (3 × 50 mL) dried over anhydrous $MgSO_4$. Removal of solvent by rotary evaporation yielded a white, pasty oil. Subsequent purification of the crude product by flash chromatography (10% Et_2O–pet. ether) yielded pure ketal-iodide **172** as a clear, colorless, viscous oil (1.3736 g, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.71 (m, 4H; –$C_6\underline{H}_5$), 7.34–7.44 (m, 6H; –$C_6\underline{H}_5$), 3.73–3.80 (m, 3H; ketal), 3.56–3.66 (m, 3H; ketal, H(6)), 3.44 (dd, J = 9.3, 3.7 Hz, 1H; $H(9_A)$), 3.11 (dd, J =9.3, 7.6 Hz, 1H; $H(9_B)$), 1.94 (unresolved ddd, J =17.5, 8.0, 1.0 Hz, 1H, $H(3_A)$), 1.61–1.77 (m, 4H; $H(3_B)$, $H(2_A)$, H(10), H(1)), 1.34–1.45 (m, 1H; $H(2_B)$), 1.12 (s, 9H; Bu^t), 1.00 (d, J = 6.6 Hz, 3H; C(10)–$C\underline{H}_3$), 0.93 (s, 3H; C(5)–$C\underline{H}_3$)

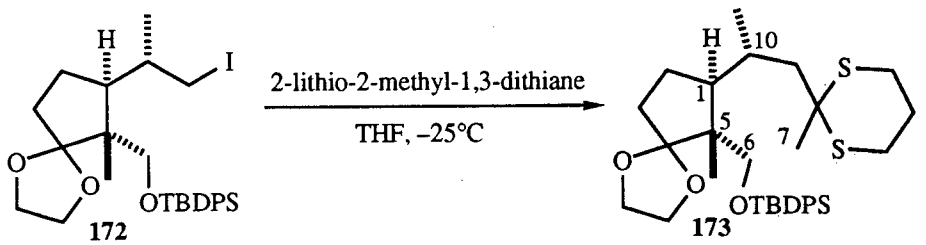
^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.88, 133.5, 129.5, 127.6, 119.4, 67.9, 64.7, 64.2, 50.1, 48.2, 36.1, 32.9, 27.1, 23.5, 19.4, 18.5, 13.6.

IR (neat film): 3070 ($\nu_{=C-H}$), 3052 ($\nu_{=C-H}$), 2952, 2885, 1590 ($\nu_{C=C}$), 1470, 1391, 1115, 1075 cm^{-1}.

DCI-MS (NH_3) *m/z* (rel intensity): 579 ($(M + H)^+$; 100), 521 (23), 477 (24), 457 (67), 323 (54), 195 (18), 183 (12).

Exact mass calcd for $C_{28}H_{40}IO_3Si$ $(M + H)^+$: 579.1751, found 579.1766.

Ketal-dithiane (173)



To a solution of 2-methyl-1,3-dithiane[97] (0.88 mL, 0.99 g, 7.4 mmol; **CAUTION: STENCH!**) in THF (15 mL) at –25 °C was added *n*-butyllithium (5.3 mL, 1.55 M in hexane, 8.2 mmol), dropwise over 15 min.[97] The colorless solution was stirred at –25 °C for 3 h. A solution of ketal-iodide **172** (2.3765 g, 4.1072 mmol) in THF (50 mL) was cooled to –25 °C and added dropwise to the reaction mixture by cannula over ~10 min. The pale yellow solution was stirred at (-25 ± 5) °C for 12 h after which it was allowed to warm to room temperature and partitioned between H_2O (50 mL) and Et_2O (50 mL). The aqueous layer was extracted further with Et_2O (3 × 50 mL). The combined ether extracts were washed successively with H_2O (50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a pale yellow oil. Purification of the crude product by flash chromatography (10% EtOAc–pet. ether) yielded pure ketal-dithiane **173** as a clear, colorless, viscous oil (2.0746 g, 86%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.73 (m, 4H; –$C_6\underline{H}_5$), 7.32–7.41 (m, 6H; –$C_6\underline{H}_5$), 3.74–3.84 (m, 4H; –$OC\underline{H}_2C\underline{H}_2O$–), 3.65 (d, J = 10.5 Hz, 1H; $H(6_A)$), 3.60 (d, J =10.5 Hz, 1H; $H(6_B)$), 2.67–2.84 (m, 4H; –$SC\underline{H}_2CH_2C\underline{H}_2S$–), 1.93–2.08 (m, 4H; H(10), $H(3_A)$, H(9)), 1.83–1.91 (m, 2H; –$SCH_2C\underline{H}_2CH_2S$–), 1.68–1.80 (m, 3H; $H(2_A)$, $H(3_B)$, H(1)), 1.57 (s,

3H; H(7)), 1.51–1.64 (m, 1H; $H(2_B)$), 1.08 (s, 9H; Bu^t), 1.02 (d, J = 7.3 Hz, 3H; C(10)–$C\underline{H}_3$), 0.98 (s, 3H; C(5)–$C\underline{H}_3$)

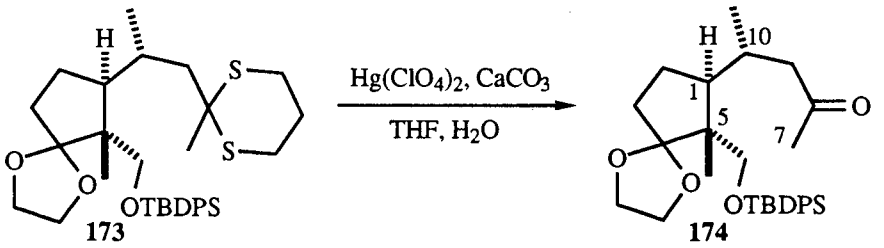
^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9, 135.8, 133.9, 133.8, 129.4, 127.5, 119.1, 68.8, 64.5, 50.8, 49.9, 49.7, 49.3, 34.1, 29.7, 28.1, 27.1, 26.7, 25.2, 20.3, 19.4, 19.3, 14.5.

IR (neat film): 3076 ($\nu_{=C-H}$), 3045 ($\nu_{=C-H}$), 2960, 2932, 2880, 2850, 1590 ($\nu_{C=C}$), 1472, 1428, 1390, 1280, 1112, 1082 cm^{-1}

EIMS *m/z* (rel intensity): 584 ($(M^+$; 0.3), 527 (11), 483 (2), 419 (1), 409 (2), 379 (2), 349 (2), 335 (4), 307 (2), 295 (1), 285 (6), 267 (14), 255 (3), 199 (71), 133 (100).

Exact mass calcd for $C_{33}H_{48}O_3S_2Si$: 584.2814, found 584.2818.

Silyloxy-ketone (174)



To a mixture of ketal-dithiane **173** (1.3063 g, 2.233 mmol) and calcium carbonate (0.5588 g, 5.583 mmol) in THF (15 mL) was added dropwise over 5 min a solution of mercuric perchlorate trihydrate (1.5193 g. 3.349 mmol) in water (4 mL).[99] The reaction mixture was stirred for another 5 min, then diluted with Et_2O (80 mL) and poured into water (100 mL). The organic layer was washed further with water (100 mL) and brine (2 × 100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield a viscous, clear, colorless syrup. Subsequent purification by flash column chromatography (30% Et_2O–pet. ether) provided pure silyloxy-ketone **174** as a clear, colorless syrup (1.0281 g, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.70 (m, 4H; –$C_6\underline{H}_5$), 7.32–7.42 (m, 6H; –$C_6\underline{H}_5$), 3.74–3.82 (m, 3H; ketal), 3.65–3.72 (m, 1H; ketal), 3.59 (d, J = 10.0 Hz, 1H; $H(6_A)$), 3.55 (d, J = 10.0 Hz, 1H; $H(6_B)$), 2.61–2.71 (m, 1H; $H(9_A)$), 2.05–2.17 (m, 1H; $H(9_B)$), 1.97 (s, 3H; H(7)), 1.59–1.86 (m, 5H), 1.33–1.44 (m, 1H), 1.08 (s, 9H; Bu^t), 0.97 (s, 3H; C(5)–$C\underline{H}_3$), 0.82 (d, J = 5.5 Hz, 3H; C(10)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.9 (C(8)), 135.8, 133.8, 133.6, 129.6, 127.6, 119.5, 68.2, 64.6, 64.3, 51.1, 50.1, 48.0, 32.9, 30.2, 27.0, 23.5, 19.4, 18.0, 13.8.

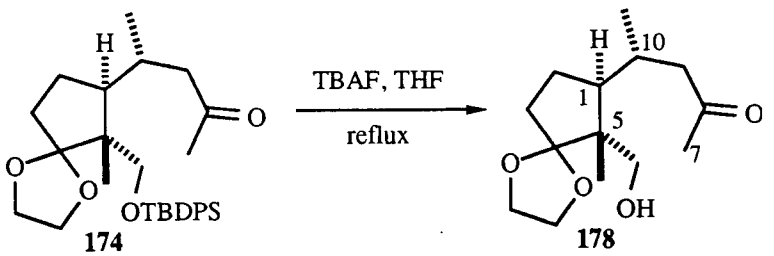
IR (neat film): 3072 ($\nu_{=C-H}$), 3045 ($\nu_{=C-H}$), 2960, 2928, 2881, 2850, 1717 ($\nu_{C=O}$), 1590 ($\nu_{C=C}$), 1472, 1428, 1361, 1309, 1151, 1113, 1076 cm^{-1}.

DCI-MS (NH_3) *m/z* (rel intensity): 512 ($(M + NH_4^+)^+$; 100), 495 ($(M + H)^+$; 65), 479 (19), 454 (3), 437 (11), 417 (5), 392 (1), 360 (0.9), 330 (0.6), 274 (0.5).

Exact mass calcd for $C_{30}H_{43}O_4Si$ [$(M + H)^+$; DCI]: 495.2931, found 495.2939.

Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 72.65; H, 8.51.

Hydroxy-ketone (178)



TBAF (9.7 mL, 1 M in THF, 9.735 mmol) was added to a solution of silyl ketone (**174**) (0.9633 g, 1.947 mmol) in THF (25 mL) and the resulting pale yellow solution was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (100 mL), washed with water (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide a clear, colorless oil. Purification of the oil

by flash column chromatography (60% EtOAc–pet. ether) yielded pure hydroxy-ketone (**178**) as a clear, viscous, colorless oil (0.4658 g, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84–3.99 (m, 4H; –OC$\underline{H}_2$C$\underline{H}_2$O–), 3.61 (dd, J = 12.4, 2.8 Hz, 1H; simplifies to (d, J = 12.4 Hz) upon addition of D_2O; H(6_A)), 3.27 (dd, J = 12.4, 10.4 Hz, 1H; simplifies to (d, J = 12.4 Hz) upon addition of D_2O; H(6_B)), 2.95 (dd, J = 10.5, 2.8 Hz, 1H; exchanges with D_2O; –O$\underline{H}$), 2.67 (dd, J = 17.0, 2.8 Hz, 1H; H(9_A)), 2.34 (dd, J = 17.0, 9.0 Hz, 1H; H(9_B)), 2.15 (s, 3H; H(7)), 2.02–2.18 (m, 2H; H(10), H(1)), 1.62–1.83 (m, 3H; H(3_A), H(3_B), H(2_A)), 1.38–1.48 (m, 1H; H(2_B)), 0.83 (d, J = 6.1 Hz, 3H; C(10)–C$\underline{H}_3$), 0.80 (s, 3H; C(5)–C$\underline{H}_3$).

IR (neat film) 3533 (broad, ν_{O-H}), 2970, 2881, 1713 ($\nu_{C=O}$), 1413, 1361, 1324, 1152, 1069, 1043 cm^{-1}.

EIMS *m/z* (rel intensity): 256 (M^+; 0.2), 241 ($(M - CH_3)^+$; 1.0), 238 ($(M - H_2O)^+$; 5.7), 225 (3.2), 213 (0.5), 197 (4.3), 99 (100).

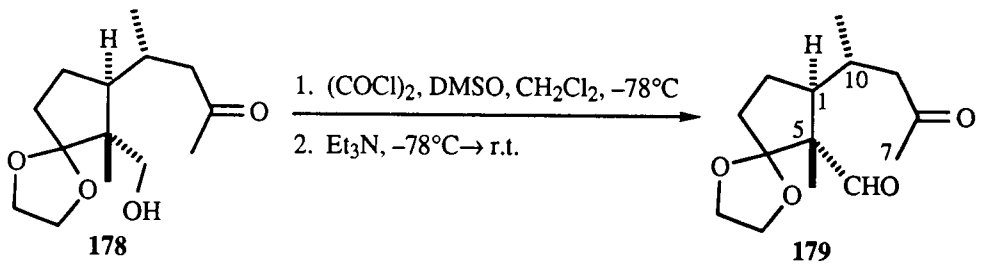
Exact mass calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1669.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.71; H, 9.49.

Table 5.6. Spectral Data from COSY Spectrum of Hydroxy-ketone **178**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
3.61	$H(6_A)$	3.27, 2.95	$H(6_B)$, –OH
3.27	$H(6_B)$	3.61, 2.95	$H(6_A)$, –OH
2.95	–OH	3.61, 3.27	$H(6_A,6_B)$
2.67	$H(9_A)$	2.34, 2.02–2.18 (part of multiplet), 0.83	$H(9_B)$, H(10), C(10)-Me
2.34	$H(9_B)$	2.67, 2.02–2.18 (part of multiplet)	$H(9_A)$, H(10), C(10)-Me
2.02–2.18	H(10), H(1)	2.67, 2.34, 0.83	$H(9_A,9_B)$ C(10)-Me
1.62–1.83	$H(3_A,3_B)$ $H(2_A)$	1.38–1.48	$H(2_B)$
1.38–1.48	$H(2_B)$	1.63–1.83	$H(3_A,3_B, 2_A)$
0.83	C(10)-Me	2.67, 2.34, 2.02–2.18 (part of multiplet)	$H(9_A,9_B)$ H(10)

Keto-aldehyde (179)



178 **179**

To a solution of oxalyl chloride (93 μL, 0.13 g, 1.1 mmol) in dry CH_2Cl_2 (5.0 mL) at –78 °C was added dropwise over 10 min a solution of dry DMSO (82 μL, 0.90 g, 1.1 mmol) in CH_2Cl_2 (5.0 mL).[100] The clear, colorless solution was stirred at –78 °C for 30 min after which a solution of the hydroxy-ketone **178** (0.2265 g, 0.8835 mmol) in CH_2Cl_2 (5.0 mL) was added

dropwise by cannula over 5 min. The reaction mixture was stirred at –78 °C for a further hour. Triethylamine (0.62 mL, 0.45 g, 4.4 mmol) was added and the solution was allowed to warm to room temperature over 1 h, and was stirred subsequently at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (~100 mL), washed with ice-cold 0.5 M HCl (2 × 25 mL), water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a pale yellow oil. Purification of the oil by flash chromatography (50% Et_2O–pet. ether) provided pure keto-aldehyde **179** as a clear, colorless oil (0.2038 g, 91%) [N.B. Due to the air sensitivity of **179**, this compound was stored at –10 °C under argon].

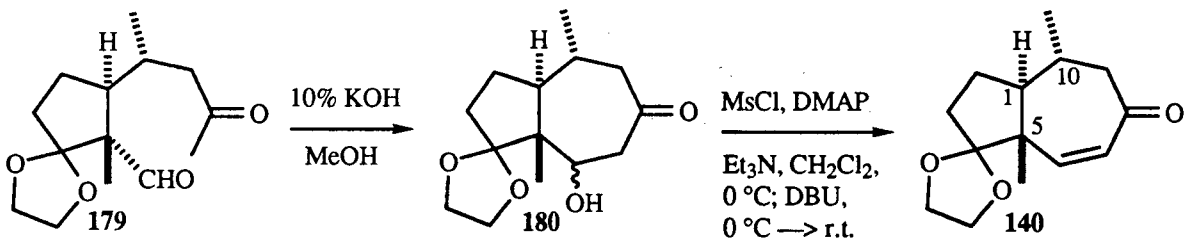
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (s, 1H; –C<u>H</u>O), 3.68–4.92 (m, 4H; –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 2.51 (ddd, J = 19.0, 10.5, 3.1 Hz, 1H; H(9_A)), 1.75–2.15 (m, 6H; H(10), H(9_B), H(1), H(3_A), (H(3_B), (H(2_A)), 2.06 (s, 3H; (H(7))), 1.36–1.50 (m, 1H; H(2_A)), 1.07 (s, 3H; C(5)–C<u>H</u>$_3$), 0.89 (d, J = 6.5 Hz, 3H; C(10)–C<u>H</u>$_3$).

IR (neat film): 2970, 2885, 2735 ($\nu_{C-H,\ aldehyde}$), 1715 ($\nu_{C=O}$), 1469, 1370, 1160, 1058 cm^{-1}.

EIMS *m/z* (rel intensity): 254 (M^+; 0.5), 239 ($(M - CH_3)^+$; 0.3), 225 (0.2), 222 ($(M - CHO)^+$; 0.5), 196 ($(M - H_2C{=}C(OH)CH_3)^+$; 0.9 (McLafferty)), 181 (0.8), 99 (100).

Exact mass calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1515.

Bicyclic ketal-enone (140)



To a solution of keto-aldehyde **179** (0.1931 g, 0.7592 mmol) in spectro grade methanol (6.5 mL) was added, in one portion, a 10% aqueous potassium hydroxide solution (1.3 mL, 130

mg, 2.3 mmol). The reaction mixture was stirred at room temperature under argon for 2 h after which it was neutralized by addition of 1 M HCl (~2.5 mL). The mixture was extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated to yield the crude aldol **180** as a viscous, colorless syrup (0.1831 g) that was used in the subsequent reaction without further purification; **IR (neat film):** 3519 (br; ν_{O-H}), 2962, 2896, 1697 ($\nu_{C=O}$), 1461, 1380, 1344, 1170, 1129, 1073, 1023, 950 cm^{-1}.

To an ice-cold solution of aldol **180** (0.1831 g, 0.7199 mmol), triethylamine (180 μL, 0.109 g, 1.08 mmol), and DMAP (0.0879 g, 0.7199 mmol) in dry CH_2Cl_2 (8 mL) was added methanesulfonyl chloride (84 μL, 0.12 g, 1.08 mmol). The cloudy, straw yellow solution was stirred at 0 °C for 1.5 h after which DBU (215 μL, 0.219 g, 1.44 mmol), pre-purified by passage down a column of basic alumina, was added and the solution was allowed to warm to room temperature. The clear, pale yellow solution was stirred for 2.5 h and then poured into a 1:1 diethyl ether-water mixture (50 mL). The aqueous layer was extracted further with diethyl ether (2 × 25 mL). Combined extracts were washed with water (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and brine (3 × 25 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale yellow oil. Subsequent purification of the oil by flash column chromatography (50% Et_2O–pet. ether) yielded pure ketal-enone **140** as a colorless oil (0.1472 g, 82% from the keto-aldehyde **179**); $[\alpha]_D^{25}$ –15.7 (*c* 0.896, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.40 (d, J = 12.0 Hz, 1H; H(6)), 5.91 (d, J = 12.0 Hz, 1H; H(7)), 3.86–4.04 (m, 4H; –OC$\underline{H}_2$C$\underline{H}_2$O–), 2.92 (dd, J = 13.0, 6.5 Hz, 1H; H(9β)), 2.29 (dd, J = 13.0, 4.6 Hz, 1H; H(9α)), 1.89–2.06 (m, 3H; H(10), H(1), and H(3_A)), 1.72–1.86 (m, 2H; H(2_A) and H(3_B)), 1.36–1.46 (m, 1H; H(2_B)), 1.12 (s, 3H; C(5)–C$\underline{H}_3$), 1.01 (d, J = 6.4 Hz, 3H; C(10)–C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.4 (C=O), 148.4 (C(6)), 130.5 (C(7)), 119.3 (C(4)), 65.5 (—O$\underline{C}H_2CH_2O$–), 64.0 (–$OCH_2\underline{C}H_2O$–), 51.8 (C(9)), 49.9 (C(1)), 31.6 (C(10)), 31.1 (C(3)), 25.2 (C(2)), 20.7 (C(10)–$\underline{C}H_3$), 15.9 (C(5)–$\underline{C}H_3$).

IR (neat film): 2959, 2878, 1672 ($\nu_{C=O}$), 1626 (shoulder; $\nu_{C=C}$), 1460, 1439, 1390, 1344, 1165 ($\nu_{C-O,\,asym}$), 1061 ($\nu_{C-O,\,sym}$), 950, 756 cm^{-1}.

EIMS *m/z* (rel intensity): 236 (M^+; 0.6), 193 (0.2), 176 (0.2), 165 (0.3), 153 (0.4), 147 (0.3), 135 (0.4), 126 (0.9), 107 (1), 99 (100)

Exact mass calcd for $C_{14}H_{20}O_3$: 236.1412, found 236.1410.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.05; H, 8.48.

Table 5.7. Results of NOE Experiments for Ketal-enone **140**.

Proton Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
2.92	H(9β)	2.29, 1.12, 1.89–2.06 (part of multiplet)	H(9α), C(5)–Me H(10)
2.29	H(9α)	2.92, 1.01	H(9β), C(10)–Me
1.12	C(5)-Me	2.92, 5.91 1.89–2.06 (part of multiplet), 1.72–1.86 (part of multiplet)	H(9β), H(7)
1.01	C(10)-Me	2.29, 1.89–2.06 (part of multiplet)	H(9α), H(10)

*Only those protons that can be assigned unambiguously have been recorded.

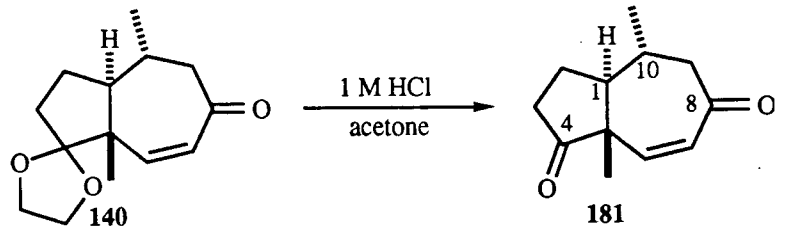
Table 5.8. Spectral Data from COSY Spectrum of Ketal-enone **140**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
6.40	H(6)	5.91	H(7)
5.91	H(7)	6.40	H(6)
2.92	H(9β)	2.29, 1.89–2.06 (part of multiplet)	H(9α), H(10)
2.29	H(9α)	2.92, 1.89–2.06 (part of multiplet)	H(9β), H(10)
1.89–2.06	H(10), H(1), H(3_A)	2.92, 2.29, 1.72–1.86, 1.36–1.46, 1.01	H(9α,9β), H(2_A,2_B,3_B) C(10)–Me
1.72–1.86	H(2_A,3_B)	1.89–2.06 (part of multiplet), 1.36–1.46	H(1), H(2_B), H(3_A)
1.36–1.46	H(2_B)	1.89–2.06 (part of multiplet), 1.72–1.86	H(1), H(2_A), H(3_A,3_B)
1.01	C(10)-Me	1.89–2.06 (part of multiplet)	H(10)

Table 5.9. Spectral Data from HETCOR Spectrum of Ketal-enone **140**.

75 MHz ^{13}C NMR Spectrum Signal Positions [δ_C (ppm)]	Assign-ment	HETCOR Correlations Signal Positions [δ_H (ppm)]	Assign-ment
148.4	C(6)	6.40	H(6)
130.5	C(7)	5.91	H(7)
65.5, 64.0	ketal	3.86–4.04	ketal
51.8	C(9)	2.92, 2.29	H(9)
49.9	C(1)	1.89–2.09 (part of multiplet)	H(1)
31.6	C(10)	1.89–2.09 (part of multiplet)	H(10)
31.1	C(3)	1.89–2.09 (part of multiplet), 1.72–1.86 (part of multiplet)	H(3)
25.2	C(2)	1.72–1.86 (part of multiplet), 1.36–1.46	H(2)
20.7	C(10)-Me	1.01	C(10)-Me
15.9	C(5)-Me	1.12	C(5)-Me

Bicyclic Keto-enone (181)



Ketal-enone **140** (53.6 mg, 0.227 mmol) was dissolved in acetone (3.0 mL) and 1 M HCl (3.0 mL) was added. The colorless solution was stirred at room temperature for 3 h after which it was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with water (1 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a colorless oil. Subsequent purification of the oil by flash chromatography (50% Et_2O–pet. ether) yielded pure keto-enone **181** as a white, crystalline solid (38.7 mg, 89%); mp = 71.5–72.5 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (d, J = 12.7 Hz, 1H; H(6)), 5.98 (dd, J = 12.7, 1.4 Hz, 1H; H(7)), 3.03 (dd, J = 12.8, 7.8 Hz, 1H; $H(9_A)$), 2.45–2.58 (m, 1H; $H(3_A)$), 2.33 (ddd, J = 13.0, 3.5, 1.4 Hz, 1H; $H(9_B)$), 2.02–2.24 (m, 3H; $H(3_B)$, $H(2_A)$, H(10)), 1.82–1.91 (m, 1H; H(1)), 1.55–1.66 (m, 1H; $H(2_B)$), 1.14 (s, 3H; C(5)–$C\underline{H}_3$), 1.12 (d, J = 6.8 Hz, 3H; C(10)–$C\underline{H}_3$).

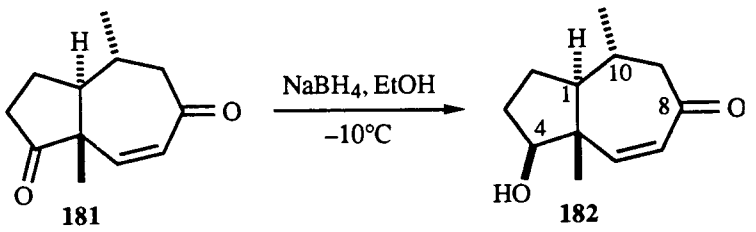
^{13}C NMR ($CDCl_3$, 75 MHz): δ 217.2 (C(3)), 202.3 (C(8)), 147.2 (C(6)), 131.6 (C(7)), 54.6 51.4, 50.7, 35.7, 31.0, 24.3, 20.3, 15.8.

IR (neat film): 2965, 2925, 2860, 2742, 2672, 1742 ($\nu_{C=O,\ \text{saturated ketone}}$), 1672 ($\nu_{C=O,\ \text{unsaturated ketone}}$), 1458 cm^{-1}.

EIMS *m/z* (rel intensity): 192 (M^+; 100), 177 ($(M - CH_3)^+$; 4.8), 164 (48.3), 159 (7.9).

Exact mass calcd for $C_{12}H_{16}O_2$: 192.1150, found 192.1148.

Bicyclic Hydroxy-enone (182)



181 182

To a solution of keto-enone **181** (22.1 mg, 115 μmol) in absolute ethanol (1.0 mL) at –10 °C was added solid sodium borohydride (1.2 mg, 31 μmol) in one portion.[103] The resulting clear, colorless solution was stirred at –10 °C for 10 min, and then neutralized by addition of 1 M HCl (3 drops). The reaction mixture was diluted with diethyl ether (50 mL) and poured into water (25 mL). The aqueous phase was extracted further with diethyl ether (2 × 15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to yield a white, sticky foam. Subsequent purification by flash column chromatography (90% diethyl ether–pet. ether) yielded the desired hydroxy-enone **182** (18.9 mg; 85%) as a clear, colorless film.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (d, J = 11.6 Hz, 1H; H(6)), 5.91 (dd, J = 11.6, 1.5 Hz, 1H; H(7)), 3.58–3.64 (m, 1H; H(4)), 3.06 (dd, J =12.4, 7.8 Hz, 1H; $H(9_A)$), 2.25 (ddd, J = 12.7, 3.5, 1.4 Hz, 1H; $H(9_B)$), 1.99–2.09 (m, 1H; $H(3_A)$), 1.82–1.98 (m, 2H; H(10), $H(2_A)$), 1.62 (bs, 1H; exchanges with D_2O; –OH), 1.34–1.58 (m, 3H; H(1), $H(3_B)$, $H(2_B)$), 1.03 (s, 3H; C(5)–CH_3), 1.00 (d, J = 6.7 Hz, 3H; C(10)–CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.9 (C(8)), 151.0 (C(6)), 130.1 (C(7)), 50.7, 49.8, 49.4, 32.3, 26.70, 25.7, 20.7, 10.5.

IR (neat film): 3363 (broad, ν_{O-H}), 2956, 2925, 2873, 1687 ($\nu_{C=O}$), 1458, 1376, 1262, 1142, 1107, 1072, 1025 cm^{-1}.

EIMS *m/z* (rel intensity): 194 (M^+; 35.0), 179 ($(M - CH_3)^+$; 6.5), 161 (7.0), 150 (100), 135 (35.0).

Exact mass calcd for $C_{12}H_{18}O_2$: 194.1307, found 194.1311.

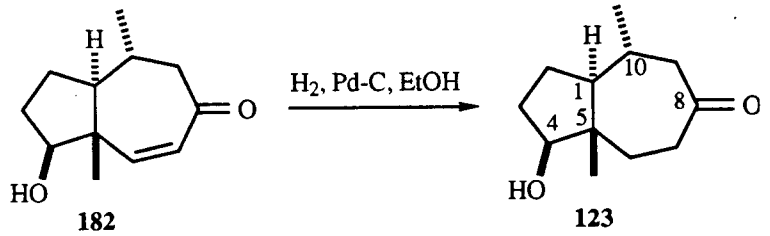
Results of NOE experiment:

Irradiation of the signal at δ 3.58–3.64 [H(4)] resulted in enhancement of signal intensities at 6.62 [H(6)], 1.99–2.09 [H(3_A)], 1.82–1.98, 1.62 [–OH], and 1.34–1.58 ppm.

Table 5.10. Spectral Data from COSY Spectrum of Hydroxy-enone **182**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
6.62	H(6)	5.91	H(7)
5.91	H(7)	6.62, 2.25	H(6), H(9_B)
3.58–3.64	H(4)	1.99–2.09, 1.62, 1.34–1.58 (part of multiplet)	H(3_A), –OH, H(3_B)
3.06	H(9_A)	2.25, 1.82–1.98 (part of multiplet)	H(9_B), H(10)
2.25	H(9_B)	5.91, 3.06, 1.82–1.98 (part of multiplet)	H(7), H(9_A), H(10)
1.99–2.09	H(3_A)	3.58–3.64 1.82–1.98 (part of multiplet) 1.34–1.58 (part of multiplet)	H(4), H(2_A, 2_B, 3_B)
1.82–1.98	H(10), H(2_A)	3.06, 2.25, 1.99–2.09 1.34–1.58	H(9_A, 9_B, 1) H(2_B, 3_A, 3_B)
1.62	–OH	3.58–3.64	H(4)
1.34–1.58	H(1), H(2_B), H(3_B)	3.58–3.64, 1.99–2.09 1.82–1.98	H(4), H(3_A) H(10), H(2_A)
1.00	C(10)-Me	1.82–1.98 (part of multiplet)	H(10)

Hydroxy-ketone (123)



To a solution of hydroxy-enone (**182**) (12.5 mg, 63.0 μmol) in absolute ethanol (1.5 mL) was added 10% palladium on charcoal (5 mg). The mixture was stirred under an atmosphere of hydrogen (ambient pressure) for 3 h, then diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The Celite® pad was washed further with Et_2O (50 mL). The filtrate was concentrated to yield a clear, colorless film. Purification by flash column chromatography (90% Et_2O–pet. ether) yielded pure hydroxy-ketone (**123**) as a clear, colorless film (11.6 mg; 95%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.60–3.66 (m, 1H; H(4)), 3.10 (dd, J = 12.5, 7.5 Hz, 1H), 2.25 (ddd, J = 12.5, 3.0, 1 Hz, 1H), 1.72–2.10 (m, 5H), 1.32–1.57 (m, 4H), 1.03 (s, 3H; C(5)–C$\underline{H}_3$), 0.96 (d, J = 7.0 Hz, 3H; C(10)–C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.0 (C(8)), 79.8 (C(4)), 50.7, 49.5, 45.4, 41.5, 40.9, 35.6, 30.1, 23.3, 13.2, 10.5.

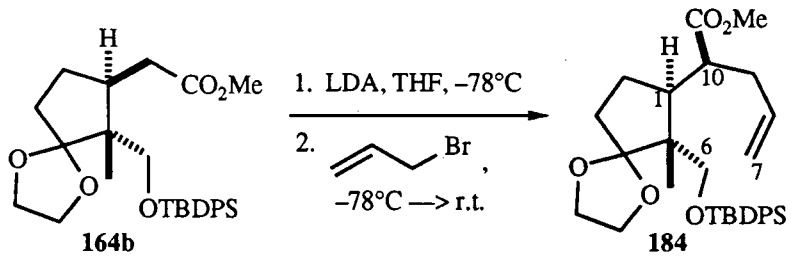
IR (neat film): 3400 (broad, ν_{O-H}), 2970, 2885, 1695 ($\nu_{C=O}$), 1477, 1392, 1112 cm^{-1}.

EIMS *m/z* (rel intensity): 196 (M^+; 20.3), 181 (10.5), 178 (2.5), 99 (100).

Exact mass calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1468.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.50; H, 10.31.

Ketal-ester (184): Stereoselective Alkylation of Ketal-ester (164b) with Allyl Bromide



n-Butyllithium (5.8 mL, 1.55 M in hexane, 8.9 mmol) was added dropwise over 5 min to a solution of diisopropylamine (1.3 mL, 0.90 g, 8.9 mmol) in THF (15 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and then cooled to –78 °C. Ketal-ester **164b** (3.3224 g, 6.883 mmol), dissolved in THF (25 mL), was added and the reaction mixture was stirred at -78 °C for 45 min. Allyl bromide (0.77 mL, 1.1 g, 8.9 mmol) was then added and the mixture was stirred at –78 °C for a further 2 h before being allowed to warm to room temperature over 15 h. The solution was partitioned between ether (50 mL) and water (50 mL). The aqueous layer was further extracted with ether (2 × 50 mL) and the combined extracts were washed with brine (3 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide a pale yellow oil. Purification of the crude product by flash chromatography (10% EtOAc–pet. ether) yielded the ketal-ester **184** (3.4002 g; 95%) as a viscous, colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.70 (m, 4H; –$C_6\underline{H}_5$), 7.30–7.42 (m, 6H; –$C_6\underline{H}_5$), 5.09–5.20 (m, 1H; H(8)), 4.90–5.00 (m, 2H; H(7)), 3.79–3.91 (m, 4H; –$OC\underline{H}_2C\underline{H}_2O$–), 3.69 (d, J = 8.0 Hz, 1H; $H(6_A)$), 3.34 (d, J = 8.0 Hz, 1H; $H(6_B)$), 3.20 (s, 3H; –$CO_2\underline{Me}$), 2.46 (ddd, J = 9.5, 9.5, 3.0 Hz, 1H; H(10)), 2.27–2.36 (m, 2H; H(1), $H(9_A)$), 2.09–2.19 (m, 1H; $H(9_B)$), 1.75–1.84 (m, 3H; $H(3_A)$, $H(3_B)$, $H(2_A)$), 1.31–1.41 (m, 1H; $H(2_A)$), 1.04 (s, 9H; Bu^t), 0.99 (s, 3H; C(5)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.4 (–$\underline{C}O_2$Me), 135.8, 135.7, 135.2, 134.0, 133.8, 122.4, 127.6, 119.0, 116.6, 67.9, 64.7 64.5, 50.8, 50.0, 47.3, 43.6, 35.4, 33.4, 27.0, 24.02, 19.4, 13.6.

IR (neat film): 3073 ($\nu_{=C-H}$), 3050 ($\nu_{=C-H}$), 2948, 2858, 1735 ($\nu_{C=O}$), 1642 ($\nu_{C=C}$), 1590 ($\nu_{C=C}$), 1472, 1429, 1391, 1371, 1318, 1112 cm^{-1}.

EIMS *m/z* (rel intensity): 522 (M^+, 1.0), 491 (4.8), 465 (100), 435 (8.9), 421 (29.0), 409 (8.4), 387 (8.5).

Exact mass calcd for $C_{31}H_{42}O_5Si$ 522.2801, found 522.2807.

Anal. Calcd for $C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 71.30; H, 8.03.

Table 5.11. Results of NOE Experiments for Ketal-ester **184**.

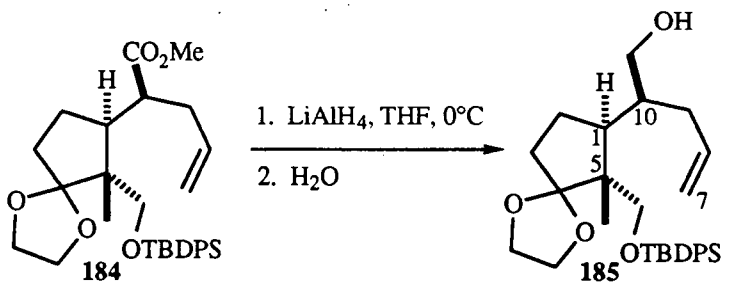
Proton(s) Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
0.99, 1.04**	C(5)-Me and Bu^t	3.69, 3.34, 3.20 2.46, 1.75–1.84 (part of multi-plet), 1.31–1.41	H(6_A, 6_B), –CO_2Me, H(10), H(2_B)
2.46	H(10)	5.09–5.20, 3.34, 3.20, 2.27–2.36, 2.09–2.19, 0.99	H(8, 6_B, 9_A, 9_B, 1), –CO_2Me, C(5)-Me
3.20	–CO_2Me	2.46, 2.27–2.36, 2.09–2.19, 0.99	H(10, 1, 9_A, 9_B), C(5)–Me
3.69	H(6_A)	7.64–7.70, 7.30–7.42, 3.34, 2.46, 0.99	–Ph, H(6_B), C(5)–Me
3.34	H(6_B)	7.64–7.70, 7.30–7.42, 3.69, 2.46, 0.99	–Ph, H(6_A), H(10), C(5)–Me

*Only those protons that can be assigned unambiguously have been recorded.
** All attempts to irradiate selectively the singlets at 0.99 and 1.04 were unsuccessful.

Table 5.12. Spectral Data from COSY Spectrum of Ketal-ester **184**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
7.64–7.70	–Ph	7.30–7.42	–Ph
7.30–7.42	–Ph	7.64–7.70	–Ph
5.09–5.20	H(8)	4.90–5.00, 2.27–2.36 (part of multiplet), 2.09–2.19	H(7), H(9_A), H(9_B)
4.90–5.00	H(7)	5.09–5.20	H(8)
3.69	H(6_A)	3.34	H(6_B)
3.34	H(6_B)	3.69	H(6_A)
2.46	H(10)	2.27–2.36, 2.09–2.19	H(1, 9_A, 9_B)
2.27–2.36	H(1, 9_A)	2.46, 2.09–2.19, 1.75–1.84 (part of multiplet), 1.31–1.41	H(10, 9_B), H(2_A, 2_B)
2.09–2.19	H(9_B)	2.46, 2.27–2.36 (part of multiplet)	H(10), H(9_A)
1.75–1.84	H(3_A,3_B) H(2_A)	2.27–2.36 (part of multiplet), 1.31–1.41	H(1), H(2_B)
1.31–1.41	H(2_B)	2.27–2.36 (part of multiplet), 1.75–1.84	H(1), H(2_A), H(3_A, 3_B)

Ketal-alcohol (185)



To a suspension of lithium aluminum hydride (0.3703 g, 9.757 mmol) in THF (10 mL) at 0 °C was added the ester **184** (3.4002 g, 6.504 mmol) in THF (50 mL). The reaction was allowed to proceed at 0 °C for 2 h before being quenched by cautious, dropwise addition of water (~10 mL). The two-phase mixture was stirred for a further 30 min, and the aqueous phase

was then extracted with ether (5 × 25 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a viscous, colorless oil. Purification of this crude product by flash chromatography (20% EtOAc–pet. ether) yielded the ketal-alcohol **185** (3.0497 g; 95%) as a colorless syrup.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.72 (m, 4H; –$C_6\underline{H}_5$), 7.32–7.42 (m, 6H; –$C_6\underline{H}_5$), 5.77–5.89 (m, 1H; H(8)), 4.98–5.09 (m, 2H; H(7)), 3.57–3.74 (m, 6H), 3.50–3.57 (m, 1H; simplifies to 3.52 (dd, J = 11.5, 4.0 Hz) upon addition of D_2O; C(10)–$C\underline{H}_2$OH), 3.42–3.50 (m, 1H), 2.18–2.32 (m, 2H), 1.97–2.07 (m, 1H), 1.88 (bs, 1H; exchanges with D_2O; –O$\underline{H}$), 1.61–1.83 (m, 4H), 1.38–1.48 (m, 1H), 1.09 (s, 9H; Bu^t), 0.95 (s, 3H; C(5)–$C\underline{H}_3$).

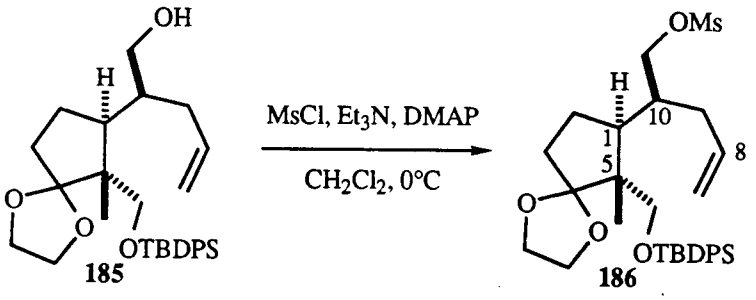
IR (neat film): 3479 (broad, ν_{O-H}), 3072 ($\nu_{=C-H}$), 3050 ($\nu_{=C-H}$), 2956, 2870, 1639 ($\nu_{C=C}$), 1590 ($\nu_{C=C}$), 1472, 1428, 1392, 1365, 1318, 1190, 1112, 1085 cm^{-1}.

EIMS *m/z* (rel intensity): 494 (M^+, 1.1), 479 (0.2), 465 (1.2), 437 (69.9), 409 (10.9), 393 (5.7), 375 (16.4).

Exact mass calcd for $C_{30}H_{42}O_4Si$ 494.2852, found 494.2844.

Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 72.87; H, 8.65.

Ketal-mesylate (186)



To a solution of alcohol **185** (2.2749 g, 4.598 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added DMAP (0.2808 g, 2.299 mmol), triethylamine (0.77 mL, 0.56 g, 5.5 mmol), and methanesulfonyl chloride (0.43 mL, 0.63 g, 5.5 mmol). The colorless solution was stirred at 0

°C for 2.5 h, then diluted with CH_2Cl_2 (50 mL), washed with water (1 × 100 mL), ice-cold 0.1 M HCl (2 × 100 mL), water (3 × 100 mL), and brine (3 × 100 mL), and dried over anhydrous $MgSO_4$. Concentration of the organic layer under reduced pressure yielded chromatographically pure ketal-mesylate **186** (2.5584 g; 97%) that could be used in the subsequent reaction without further purification. For characterization purposes, a small quantity of the crude ketal-mesylate **186** (~20 mg) was purified by radial chromatography (20% EtOAc–pet. ether).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61–7.68 (m, 4H; –$C_6\underline{H}_5$), 7.34–7.42 (m, 6H; –$C_6\underline{H}_5$), 5.70–5.82 (m, 1H; H(8)), 5.03–5.12 (m, 2H; H(7)), 4.21 (dd, J = 8.0, 4.0 Hz, 1H; –$C\underline{H}_AH_B$OMs), 4.07 (dd, J = 8.0, 4.0 Hz, 1H; –$CH_A\underline{H}_B$OMs), 3.63–3.81 (m, 4H; –$OC\underline{H}_2C\underline{H}_2O$–), 3.60 (d, J = 10.5 Hz, 1H; H(6_A)), 3.55 (d, J = 10.5 Hz, 1H; H(6_B)), 2.78 (s, 3H; –$SO_2\underline{Me}$), 2.37 (ddd, J = 13.4, 6.0, 0.9 Hz, 1H; H(9_A)), 2.22–2.30 (m, 1H; H(3_A)), 1.93–2.09 (m, 2H; H(10), H(9_B)), 1.62–1.79 (m, 3H; H(2_A), H(3_B), H(1)), 1.42–1.52 (m, 1H; H(2_B)), 1.05 (s, 9H; Bu^t), 0.99 (s, 3H; C(5)–$C\underline{H}_3$).

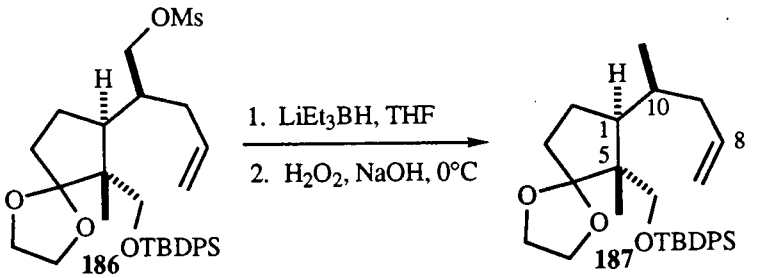
^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.8, 135.6, 113.5, 113.5, 129.6, 128.0, 127.7, 127.6, 127.4, 118.7, 117.2, 71.2, 68.7, 64.3, 64.1, 49.9, 42.5, 38.1, 36.5, 33.0, 32.1, 27.0, 22.6, 19.3, 14.0.

IR (neat film): 3072 ($\nu_{=C-H}$), 3050 ($\nu_{=C-H}$). 2957, 2884, 2858, 1640 ($\nu_{C=C}$), 1590 ($\nu_{C=C}$), 1472, 1428, 1360, 1177, 1112 cm^{-1}.

EIMS *m/z* (rel intensity): 572 (M^+, 0.1), 557 (0.1), 515 (8.5), 493 (5.4), 471 (1.4), 419 (16.4).

Exact mass calcd for $C_{31}H_{44}O_6SSi$ 572.2628, found 572.2619.

Ketal-alkene (187): Reduction of Ketal-mesylate 186



To a solution of mesylate **186** (2.5560 g, 4.462 mmol) in THF (50 mL) at 0 °C was added lithium triethylborohydride (SuperHydride®; 9.8 mL, 1.0 M in THF, 9.8 mmol).[104] The clear, colorless solution was stirred at 0 °C for 5 min and at room temperature for 18 h. The cloudy reaction mixture was cooled to 0 °C, at which 3 M NaOH (2.0 mL) and 30% hydrogen peroxide (2.0 mL) were added successively. The solution was stirred at room temperature for 1 h, during which a white precipitate formed, and then partitioned between Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted once more with Et_2O (50 mL). The combined extracts were washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide a colorless oil. Subsequent purification of the oil by flash chromatography (5% EtOAc–pet. ether) yield pure ketal-alkene **187** as a clear, colorless oil (1.9033 g, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.73 (m, 4H; –$C_6\underline{H}_5$), 7.34–7.46 (m, 6H; –$C_6\underline{H}_5$), 5.18–5.30 (m, 1H; H(8)), 4.93–5.00 (m, 2H; H(7)), 3.71–3.83 (m, 4H; –$OC_2C\underline{H}_2O$–), 3.65 (d, J = 9.0 Hz, 1H; $H(6_A)$), 3.58 (d, J = 9.0 Hz, 1H; $H(6_B)$), 2.19–2.26 (m, 1H), 1.50–1.85 (m, 6H), 1.32–1.42 (m, 1H), 1.05 (m, 9H; Bu^t), 0.98 (s, 3H; C(5)–$C\underline{H}_3$), 0.82 (d, J = 6.6 Hz, 3H; C(10)–$C\underline{H}_3$)

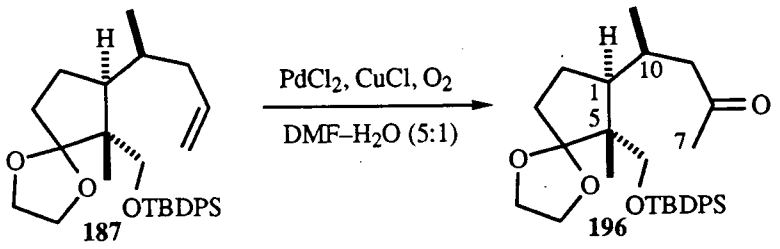
^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.8, 135.7, 134.0, 133.8, 129.4, 127.5, 123.1, 119.7, 67.9, 64.6, 64.3, 50.1, 48.0, 45.4, 38.3, 33.6, 33.4, 27.0, 25.5, 24.4, 23.6, 21.6, 19.4, 18.0, 14.0.

IR (neat film): 3072 ($\nu_{=C-H}$), 3050 ($\nu_{=C-H}$), 2959, 2880, 1640 ($\nu_{C=C}$), 1590 ($\nu_{C=C}$), 1472, 1428, 1113 cm^{-1}.

EIMS *m/z* (rel intensity): 478 (M^+; 0.4), 437 (0.3), 421 ($(M - Bu^t)^+$; 54.5), 391 (44.9), 377 (22.5), 343 (4.1), 161 (100).

Exact mass calcd for $C_{30}H_{42}O_3Si$ 478.2903, found 478.2901.

Silyloxy-ketone (196)



A suspension of palladium(II) chloride (0.1282 g, 0.7228 mmol), copper(I) chloride (0.3582 g, 0.361 mmol) in 7:1 DMF–H_2O (10 mL) was stirred under oxygen atmosphere for 2 h.[105] To this green-brown suspension was added a solution of the terminal alkene **187** (1.7303 g; 3.6142 mmol) in 9:1 DMF–H_2O (40 mL). The mixture was stirred under oxygen for 18 h and filtered through a pad of Celite.® The Celite® pad was washed with Et_2O (~50 mL). The filtrate was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL), and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a golden-yellow oil. Subsequent purification by flash chromatography (20% EtOAc–pet. ether) yielded pure silyloxy-ketone **196** as a clear, colorless oil (1.5412 g, 86%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.71 (m, 4H; $-C_6\underline{H}_5$), 7.32–7.42 (m, 6H; $-C_6\underline{H}_5$), 3.72–3.84 (m, 4H; $-OC\underline{H}_2C\underline{H}_2O-$), 3.60 (d, J = 10.0 Hz, 1H; $H(6_A)$), 3.55 (d, J = 10.0 Hz, 1H; $H(6_B)$), 2.52–2.62 (m, 1H; $H(9_A)$), 2.06–2.16 (m, 1H; $H(9_B)$), 2.09 (s, 3H; H(7)), 1.62–

1.92 (m, 5H), 1.20–1.34 (m, 1H), 1.07 (s, 9H; Bu^t), 0.97 (s, 3H; C(5)–C$\underline{H}_3$), 0.82 (d, J = 8.0 Hz, 3H; C(10)–C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.0 (C(8)), 135.8, 133.8, 133.6, 129.6, 127.6, 119.6, 68.2, 64.6, 64.3, 51.1, 50.1, 48.1, 32.9, 30.3, 27.0, 23.6, 19.4, 18.1, 13.8.

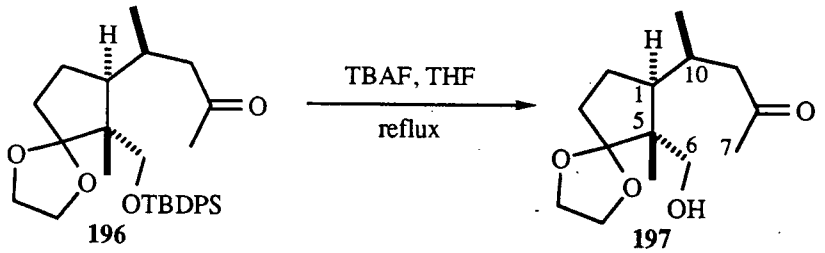
IR (neat film): 3070 ($\nu_{=C-H}$), 3050 ($\nu_{=C-H}$), 2958, 2882, 1716 ($\nu_{C=O}$), 1472, 1428, 1361, 1153, 1112 cm^{-1}.

DCI-MS (NH_3) *m/z* (rel intensity): 495 ((M + H)$^+$; 100), 494 (M$^+$; 11.8), 477 (58.3), 437 ((M – Bu^t)$^+$; 73.8), 433 (23.9), 417 (11.4), 375 (11.4).

Exact mass calcd for $C_{26}H_{33}O_4Si$ (M – *t*-Bu)$^+$ 437.2148, found 437.2145.

Anal. Calcd for $C_{30}H_{42}O_4Si$: C, 72.83; H, 8.56. Found: C, 72.62; H, 8.56.

Hydroxy-ketone (197)



TBAF (37.0 mL, 1 M in THF, 37.1 mmol) was added to a solution of silyl ketone (**196**) (1.8855 g, 3.710 mmol) in THF (35 mL) and the resulting pale yellow solution was refluxed for 5 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (150 mL), washed with water (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide a clear, colorless oil. Purification of the oil by flash column chromatography (60% EtOAc–pet. ether) yielded pure hydroxy-ketone (**197**) as a clear, viscous, colorless oil (0.9251 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84–4.01 (m, 4H; –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 3.60 (dd, J = 12.7, 3.0 Hz, 1H; simplifies to (d, J = 12.7 Hz) upon addition of D_2O; H(6_A)), 3.38 (dd, J = 12.7, 9.8 Hz, 1H; simplifies to (d, J = 12.7 Hz) upon addition of D_2O; H(6_B)), 2.90 (dd, J = 9.8, 3.0 Hz, 1H; exchanges with D_2O; –O<u>H</u>), 2.51 (dd, J = 16.0, 1.5 Hz, 1H; H(9_A)), 2.21 (dd, J = 16.0, 9.0 Hz, 1H; H(9_B)), 2.10 (s, 3H; H(7)), 2.00–2.15 (m, 2H), 1.58–1.85 (m, 3H), 1.26–1.37 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H; C(10)–C<u>H</u>$_3$), 0.84 (s, 3H; C(5)–C<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.6 (C(8)), 120.8 (C(4)), 66.1, 64.4, 63.2, 49.4, 48.8, 43.3, 31.6, 30.9, 30.4, 24.2, 18.8, 13.4.

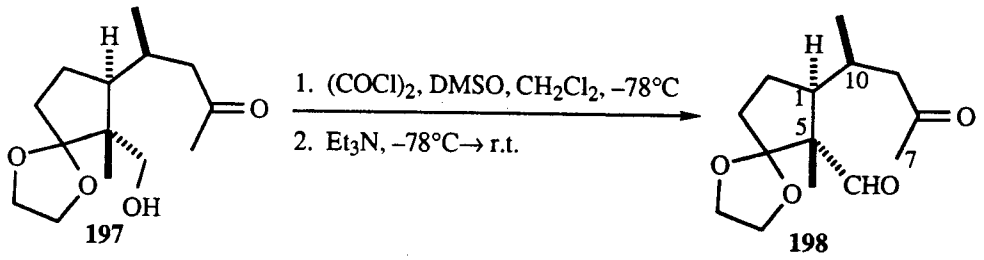
IR (neat film): 3534 (broad, ν_{O-H}), 2969, 2882, 1713 ($\nu_{C=O}$), 1467, 1412, 1151, 1068, 1043 cm^{-1}.

EIMS *m/z* (rel intensity): 256 (M^+; 0.1), 238 ($(M - H_2O)^+$; 3.4), 225 (1.3), 213 (0.8), 197 (3.4), 99 (100).

Exact mass calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1677.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.69; H, 9.52.

Keto-aldehyde (198)



197 198

To a solution of oxalyl chloride (0.27 mL, 0.39 g, 3.1 mmol) in dry CH_2Cl_2 (5.0 mL) at –78 °C was added dropwise over 10 min a solution of dry DMSO (0.24 mL, 0.26 g, 3.4 mmol) in CH_2Cl_2 (5.0 mL).[100] The clear, colorless solution was stirred at –78 °C for 30 min after which a solution of the hydroxy-ketone **197** (0.6646 g, 2.5926 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise by cannula over 5 min. The reaction mixture was stirred at –78 °C for a further

hour. Triethylamine (1.8 mL, 1.3 g, 13 mmol) was added and the solution was allowed to warm to room temperature over approximately 2 h and was stirred subsequently at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (~100 mL), washed with ice-cold 0.5 M HCl (2 × 25 mL), water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a pale yellow oil. Purification of the oil by flash chromatography (75% Et_2O–pet. ether) provided pure keto-aldehyde **198** as a clear, colorless oil (0.5844 g, 89%) [N.B. Due to the air sensitivity of (**198**), this compound was stored at –10 °C under argon].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.48 (s, 1H; –C<u>H</u>O), 3.69–3.85 (m, 4H; –OC<u>H$_2$</u>C<u>H$_2$</u>O–), 2.46–2.55 (m, 2H; H(9_A), H(1)), 2.29 (dd, J = 16.0, 10.0 Hz; H(9_B)), 2.12 (s, 3H; H(7)), 1.90–2.05 (m, 3H; H(10), H(2_A), H(3_A)), 1.75–1.85 (m, 1H; H(3_B)), 1.34–1.46 (m, 1H; H(2_B)), 1.07 (s, 3H; C(5)–C<u>H$_3$</u>), 0.69 (d, J = 6.5 Hz, 3H; C(10)–C<u>H$_3$</u>).

^{13}C NMR (CDCl3, 50 MHz): δ 208.2 (C(8)), 207.5 (–<u>C</u>HO), 121.6 (C(4)), 65.5 (–OC<u>H$_2$</u>–CH_2O), 64.2 (–OC<u>H$_2$</u>CH_2O–), 59.5, 48.9, 48.6, 34.49, 31.5, 30.7, 25.4, 19.5, 10.3.

IR (neat film): 2977, 2882, 2731 ($\nu_{C-H,\ aldehyde}$), 1718 ($\nu_{C=O}$), 1468, 1362, 1158, 1069 cm^{-1}.

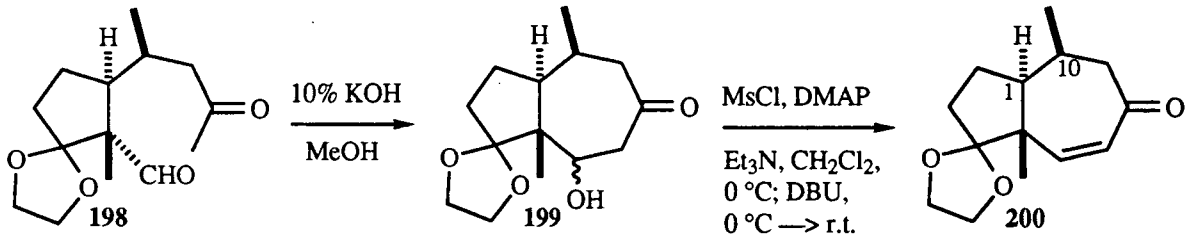
EIMS *m/z* (rel intensity): 254 (0.7), 236 (0.4), 225 (0.3), 196 (1.1), 181 (1.0), 99 (100).

Exact mass calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1511.

Table 5.13. Spectral Data from COSY Spectrum of Keto-aldehyde **198**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
2.46–2.55	H(1, 9_A)	2.29, 1.90–2.05, 1.34–1.46	H(9_B, 2_A, 2_B)
2.29	H(9_B)	2.46–2.55 (part of multiplet) 1.90–2.05 (part of multiplet)	H(9_A), H(10)
1.90–2.05	H(10), H(2_A,3_A)	2.46–2.55, 2.29, 1.75–1.85, 1.34–1.46	H(1,9_A,9_B,2_B) H(10, 3_B) C(10)–Me
1.75–1.85	H(3_B)	1.90–2.05 (part of multiplet) 1.34–1.46	H(2_A, 3_A), H(2_B)
1.34–1.46	H(2_B)	2.46–2.55 (part of multiplet) 1.90–2.05 (part of multiplet) 1.75–1.85	H(1), H(2_A, 3_A), H(3_B)
0.69	C(10)-Me	1.90–2.05 (part of multiplet)	H(10)

Bicyclic Ketal-enone (200)



To a solution of keto-aldehyde (**198**) (0.1184 g, 0.4655 mmol) in spectro grade methanol (5.0 mL) was added, in one portion, a 10% aqueous potassium hydroxide solution (1.3 mL, 130 mg, 2.3 mmol). The reaction mixture was stirred at room temperature under argon for 12 days after which it was neutralized by addition of 1 M HCl (~2.7 mL). The mixture was extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated to yield the intermediate aldol **199** as a viscous, colorless syrup that was used in the subsequent part without further purification.

Bicyclic Hydroxy-ketone (199)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.19 (bs, 1H; exchanges with D_2O; –O<u>H</u>), 3.97–4.02 (m, 1H; H(6)), 3.89–3.97 (m, 4H; –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 3.36 (dd, J = 11.0, 4.0 Hz, 1H; H(9_A)), 2.83–2.92 (m, 1H; H(1)), 2.58–2.65 (m, 2H; H(7)), 2.34 (dd, J = 11.0, 5.5 Hz, 1H; H(9_B)), 2.10–2.22 (m, 1H; H(10)), 1.73–1.90 (m, 3H), 1.61–1.72 (m, 1H), 0.96 (d, J = 8.5 Hz, 3H; C(10)–C<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.9 (C(8)), 121.2 (C(4)), 68.4 (C(6)), 64.9 (–OC<u>H</u>$_2$CH$_2$O–), 63.4 (–OCH$_2$C<u>H</u>$_2$O–), 52.4, 50.0, 46.5, 42.0, 32.8, 31.2, 22.3, 15.8, 14.9.

IR (neat film): 3513 (broad, ν_{O-H}), 2958, 2924, 2878, 1692 ($\nu_{C=O}$), 1476, 1457, 1436, 1351, 1328, 1315 cm^{-1}.

EIMS *m/z* (rel intensity): 254 (M^+; 52.8), 237 (12.0), 225 (4.4), 212 (11.1), 192 (10.8), 183 (22.4), 99 (100).

Exact mass calcd for $C_{14}H_{22}O_4$: 254.1518, found 254.1510.

To an ice-cold solution of aldol **199**, triethylamine (97 μL, 0.071 g, 0.70 mmol), and DMAP (0.0568 g, 0.4649 mmol) in dry CH_2Cl_2 (5 mL) was added methanesulfonyl chloride (54 μL, 0.080 g, 0.70 mmol). The cloudy, straw yellow solution was stirred at 0 °C for 2 h after which DBU (140 μL, 0.142 g, 0.931 mmol), pre-purified by passage down a column of basic alumina, was added and the solution was allowed to warm to room temperature. The clear, pale yellow solution was stirred for 2 h and then poured into a 1:1 diethyl ether-water mixture (50 mL). The aqueous layer was extracted further with diethyl ether (2 × 25 mL). Combined extracts were washed with water (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and brine (3 × 25 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale yellow oil. Subsequent purification of the oil by flash column chromatography (70% Et_2O–pet. ether) yielded pure ketal-enone (**200**) as a colorless oil (0.0768 g, 70% from the keto-aldehyde (**198**)).

Bicyclic Ketal-enone (200)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.36 (d, J = 12.0 Hz, 1H; H(6)), 5.95 (dd, J = 12.0, 1.3 Hz, 1H; H(7)), 3.86–3.99 (m, 4H; –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 2.62–2.72 (m, 2H; H(9)), 2.44–2.52 (m, 1H; H(1)), 2.23–2.30 (m, 1H; H(10)), 1.75–1.89 (m, 3H), 1.61–1.71 (m, 1H), 1.19 (s, 3H; C(5)–C<u>H</u>$_3$), 1.07 (d, J = 7.4 Hz, 3H; C(10)–CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.6 (C(8)), 149.4 (C(6)), 130.3 (C(7)), 119.1 (C(4)), 65.4 (-OC<u>H</u>$_2$CH$_2$O–), 64.0 (–OCH$_2$C<u>H</u>$_2$O–), 53.4, 51.9, 45.2, 31.6, 30.7, 22.0, 18.1, 16.4.

IR (neat film): 2959, 2878, 1672 ($\nu_{C=O}$), 1460, 1286, 1241, 1165, 1061 cm^{-1}.

EIMS *m/z* (rel intensity): 236 (M^+; 0.5), 221 (0.3), 208 (0.3), 193 (1.0), 99 (100).

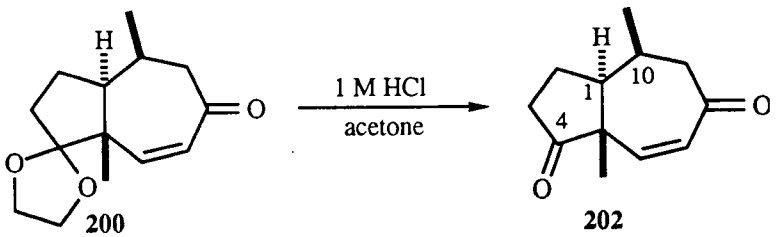
Exact mass calcd for $C_{14}H_{20}O_3$: 236.1412, found 236.1415.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.24; H, 8.57.

Results of NOE Experiments:

Irradiation of the signal at δ 1.19 ppm resulted in enhancements of signal intensities at 1.07, 1.75–1.89, and 6.36 ppm, while irradiation of the signal at δ 1.07 ppm resulted in enhancements of signal intensities at 1.19, 1.61–1.71, 1.75–1.89 (part of multiplet), 2.23–2.30, and 2.62–2.72 ppm.

Keto-enone (202)



Ketal-enone (**200**) (33.5 mg, 0.142 mmol) was dissolved in acetone (2.0 mL) and 1 M HCl (2.0 mL) was added. The colorless solution was stirred at room temperature for 3 h after which it was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined extracts were washed with water (1 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a colorless oil. Subsequent purification of the oil by flash chromatography (70% Et_2O–pet. ether) yielded pure keto-enone (**202**) as a colorless film (24.4 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.87 (d, J =11.6 Hz, 1H; H(6)), 6.00 (dd, J = 11.6, 1.6 Hz, 1H; H(7)), 2.72 (d, J = 11.7 Hz, 1H; $H(9_A)$), 2.66 (ddd, J = 11.7, 7.1, 1.5 Hz, 1H; $H(9_B)$), 2.12–2.58 (m, 4H), 1.90–1.98 (m, 2H), 1.22 (s, 3H; C(5)–$C\underline{H}_3$), 1.12 (d, J = 7.0 Hz, 3H; C(10)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 216.8 ($\underline{C}$=O), 201.9 ($\underline{C}$=O), 148.8 (C(6)), 131.3 (C(7)), 55.2, 51.2, 47.5, 36.4, 30.9, 22.5, 18.3, 17.2.

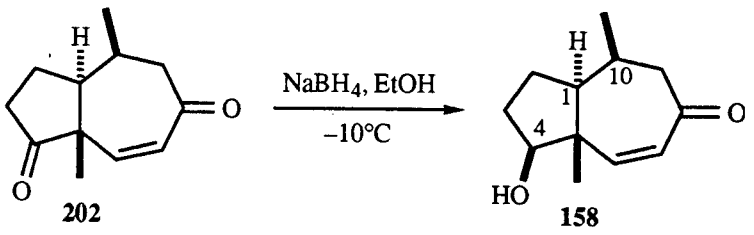
IR (neat film): 2965, 2930, 2876, 2860, 1740 ($\nu_{C=O,\ saturated\ ketone}$), 1677 ($\nu_{C=O,\ unsaturated\ ketone}$), 1625 ($\nu_{C=C}$), 1464, 1396, 1381 cm^{-1}

EIMS *m/z* (rel intensity): 192 (M^+; 100), 177 (7.1), 164 (52.0), 148 (41.3), 135 (48.3), 123 (84.0).

Exact mass calcd for $C_{12}H_{16}O_2$: 192.1150, found 192.1148.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.05; H, 8.42.

Hydroxy-enone (158)



202 158

To a solution of keto-enone (**202**) (15.7 mg, 81.6 μmol) in absolute ethanol (1.0 mL) at –10 °C was added solid sodium borohydride (0.9 mg, 22 μmol) in one portion.[103] The resulting clear, colorless solution was stirred at –10 °C for 10 min, and then neutralized by addition of 1 M HCl (3 drops). The reaction mixture was diluted with diethyl ether (50 mL) and poured into water (25 mL). The aqueous phase was extracted further with diethyl ether (2 × 15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and brine (1 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to yield a colorless film. Flash column

chromatography (90% diethyl ether–pet. ether) yielded the desired hydroxy-enone (**158**) (13.4 mg; 85%) as a clear, colorless film; $[\alpha]_D^{25}$ –20 (*c* 0.67, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.58 (d, J = 11.7 Hz, 1H; H(6)), 5.91 (dd, J = 11.7, 1.6 Hz, 1H; H(7)), 3.69 (dd, J = 8.0, 8.0 Hz, 1H; H(4)), 2.73 (dd, J = 11.0, 11.0 Hz, 1H; $H(9_A)$), 2.59 (partially resolved ddd, J = 11.0, 7.7, 1.6 Hz, 1H; $H(9_B)$), 2.20–2.30 (m, 1H), 1.95–2.11 (m, 2H), 1.84 (ddd, J = 19.0, 12.5, 5.3 Hz, 1H), 1.43–1.66 (m, 3H), 1.09 (s, 3H; C(5)–C$\underline{H}_3$), 1.04 (d, J = 7.0 Hz, 3H; C(10)–C$\underline{H}_3$).

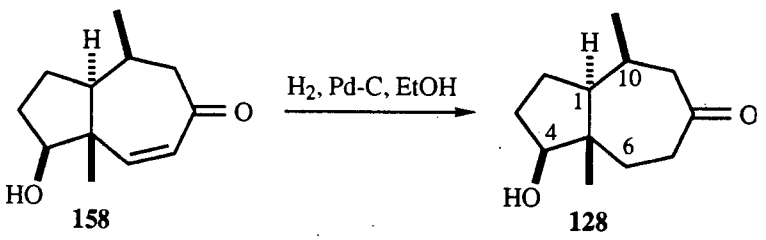
^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.8 (C(8)), 152.0 (C(6)), 129.5 (C(7)), 79.3 (C(4)), 51.4, 45.1, 31.2, 29.7, 28.8, 22.7, 18.0, 11.7.

IR (neat film): 3492 (broad, ν_{O-H}), 2970, 2875, 1672 ($\nu_{C=O}$), 1469, 1391, 1116, 1070 cm^{-1}

EIMS *m/z* (rel intensity): 194 (M^+; 40.4), 179 (5.8), 161 (7.5), 150 (100), 135 (37.2).

Exact mass calcd for $C_{12}H_{18}O_2$: 194.1307, found 194.1310.

Hydroxy-ketone (128)



To a solution of hydroxy-enone (**158**) (10.2 mg, 51.9 μmol) in absolute ethanol (1.5 mL) was added 10% palladium on charcoal (2.5 mg). The mixture was stirred under an atmosphere of hydrogen (ambient pressure) for 4 h, then diluted with Et_2O (50 mL) and filtered through a pad of Celite®. The Celite® pad was washed further with Et_2O (50 mL). The filtrate was concentrated to yield a clear, colorless film. Purification by flash column chromatography (90%

Et_2O–pet. ether) yielded pure hydroxy-ketone (**128**) as a clear, colorless film (9.4 mg; 93%); $[\alpha]_D^{25}$ –15 (*c* 0.47, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.60 (dd, J = 8.5, 8.5 Hz, 1H; H(4)), 2.78 (dd, J = 11.2, 4.1 Hz, 1H; H(9_A)), 2.40–2.52 (m, 3H; H(9_B), H(7_A), H(7_B)), 2.03–2.14 (m, 2H; H(10), H(3_A), 1.89 (ddd, J = 14.7, 4.5, 4.5 Hz, 1H; H(6_A)), 1.65–1.79 (m, 2H; H(2_A), H(1)), 1.36–1.61 (m, 4H; simplifies upon addition of D_2O; H(2_B), H(3_B), H(6_B), –O<u>H</u>), 0.93 (d, J = 7.5 Hz, 3H; C(10)–C<u>H</u>$_3$), 0.70 (s, 3H; C(5)–C<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.6 (C(8)), 80.8 (C(4)), 51.7 (C(1)), 49.8 (C(9)), 46.6, 41.2 (C(7)), 32.7, 31.4 (C(10)), 29.2 (C(3)), 23.4, 14.3 (C(10)–<u>C</u>H$_3$), 11.3 (C(5)–<u>C</u>H$_3$).

IR (neat film): 3420 (broad, ν_{O-H}), 2965, 2870, 1698 ($\nu_{C=O}$), 1475, 1391, 1112, 1075 cm^{-1};

EIMS *m/z* (rel intensity): 196 (18.3), 178 (64), 168 (73.6), 153 (42.1), 97 (100).

Exact mass calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1472.

Table 5.14. Results of NOE Experiments for Hydroxy-ketone **128**.

Proton Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
3.60	H(4)	2.03–2.14 (part of multiplet) 1.89, 1.65–1.79, 1.36–1.61	H(3_A), H(6_A)
0.93	C(10)-Me	2.78, 2.03–2.14, 1.36–1.61, 0.70	H(9_A), C(5)–Me
0.70	C(5)–Me	2.40–2.52, 1.89, 1.65–1.79, 1.36–1.61, 0.93	H(6_A), C(10)-Me

*Only those protons that can be assigned unambiguously have been recorded.

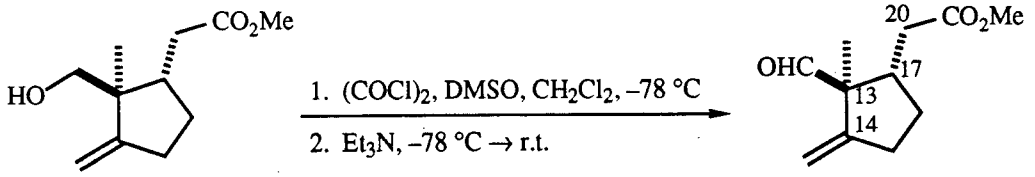
Table 5.15. Spectral Data from COSY Spectrum of Hydroxy-ketone **128**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
3.60	H(4)	2.03–2.14 (part of multiplet) 1.36–1.61 (part of multiplet)	H(3_A, 3_B), –OH
2.78	H(9_A)	2.40–2.52 (part of multiplet) 2.03–2.14 (part of multiplet), 0.93	H(9_B), H(10), C(10)–Me
2.40–2.52	H(7_A,7_B) H(9_B)	2.78, 2.03–2.14 (part of multiplet), 1.36–1.61 (part of multiplet)	H(9_A, 10) H(6_A, 6_B)
2.03–2.14	H(10,3_A)	3.60, 2.78, 2.40–2.52 (part of multiplet), 1.65–1.79, 1.36–1.61 (part of multiplet), 0.93	H(4, 9_A, 9_B) H(2_A, 2_B, 3_B)
1.89	H(6_A)	2.40–2.52 (part of multiplet) 1.36–1.61 (part of multiplet)	H(7_A, 7_B), H(6_B)
1.65–1.79	H(1, 2_A)	2.03–2.14, 1.36–1.61 (part of multiplet)	H(10, 2_B), H(3_A, 3_B)
1.36–1.61	H(2_B,3_B) H(6_B), –OH	3.60, 2.40–2.52 (part of multiplet), 2.03–2.14 (part of multiplet), 1.89, 1.65–1.79	H(4, 7_A, 7_B), H(1, 2_A, 3_A) H(6_A)
0.93	C(10)-Me	2.78, 2.03–2.14 (part of multiplet)	H(9_A, 10)

Table 5.16. Spectral Data from HETCOR Spectrum of Hydroxy-ketone **128**.

75 MHz ^{13}C NMR Spectrum Signal Positions [δ_C (ppm)]	Assign-ment	HETCOR Correlations Signal Positions [δ_H (ppm)]	Assign-ment
80.8	C(4)	3.60	H(4)
51.7	C(1)	1.65–1.79 (part of multiplet)	H(1)
49.8	C(9)	2.78, 2.40–2.52 (part of multiplet)	H(9)
41.2	C(7)	2.40–2.52 (part of multiplet)	H(7)
32.7	C(6)	1.89, 1.36–1.61 (part of multiplet)	H(6)
31.4	C(10)	2.03–2.14 (part of multiplet)	H(10)
29.2	C(3)	2.03–2.14 (part of multiplet), 1.36–1.61 (part of multiplet)	H(3)
23.4	C(2)	1.65–1.79 (part of multiplet), 1.36–1.61 (part of multiplet)	H(2)
14.3	C(10)–Me	0.93	C(10)-Me
11.3	C(5)–Me	0.70	C(5)-Me

Keto-aldehyde (258)



160 **258**

To a solution of oxalyl chloride (5.9 mL, 8.6 g, 68 mmol) in dry CH_2Cl_2 (50 mL) at –78 °C was added dropwise over 30 min a solution of dry DMSO (5.2 mL, 5.7 g, 73 mmol) in CH_2Cl_2 (50 mL).[100] The clear, colorless solution was stirred at –78 °C for 30 min after which a solution of the hydroxy-ester **160** (11.1537 g, 56.26 mmol) in CH_2Cl_2 (100 mL) was added dropwise by cannula over 30 min. The reaction mixture was stirred at –78 °C for a further hour. Triethylamine (23.5 mL, 17.1 g, 169 mmol) was added and the solution was allowed to warm to

room temperature over approximately 1.5 h and was stirred subsequently at room temperature for 10 h. The reaction mixture was diluted with water (~50 mL) and the organic layer withrawn. The aqueous layer was extracted further with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with 1 M HCl (2 × 50 mL), water (2 × 50 mL), saturated aq. $NaHCO_3$ (1 × 50 mL), brine (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated to provide the crude product as a pale yellow oil. Purification of the oil by flash chromatography (30% Et_2O–pet. ether) provided pure ester-aldehyde **258** as a clear, colorless oil (10.1841 g, 92%); $[\alpha]_D^{24}$ +47.2 (*c* 1.86, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.21 (s, 1H; –C<u>H</u>O), 5.02 (dd, *J* = 2.0, 2.0 Hz, 1H; =C<u>H</u>$_A$H$_B$), 4.69 (dd, *J* = 2.0, 2.0 Hz, 1H; =CH$_A$<u>H</u>$_B$), 3.67 (s, 3H; –O<u>Me</u>), 2.61–2.71 (m, 1H; H(15$_A$)), 2.42 (dddd, *J* = 17.0, 8.0, 4.5, 1.5 Hz, 1H), 2.28–2.38 (m, 1H; H(17)), 2.26 (dd, *J* = 7.4, 2.5 Hz, 2H; –C<u>H</u>$_2$CO$_2$Me), 1.89–1.99 (m, 1H; H(16$_A$), 1.36–1.49 (m, 1H; H(16$_B$); 0.97 (s, 3H; C(13)–C<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.4 (–<u>C</u>HO), 172.5 (–<u>C</u>O$_2$Me), 153.5 (H$_2$C=<u>C</u>), 110.1 (H$_2$<u>C</u>=C), 59.5 (C(13)), 51.5 (–CO$_2$<u>Me</u>), 41.0 (C(17)), 31.2, 31.7, 29.9, 15.8 (C(13)–<u>C</u>H$_3$).

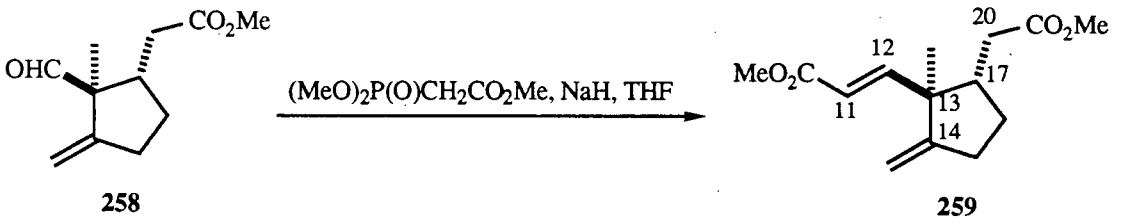
IR (neat film): 3090 ($\nu_{=C-H}$), 2960, 2895, 2850, 2820, 2725 ($\nu_{-\underline{C}HO}$), 1740 ($\nu_{C=O,\ ester}$), 1710 ($\nu_{C=O,\ aldehyde}$), 1650 ($\nu_{C=C}$), 1438, 1198, 898 cm^{-1}

EIMS *m/z* (rel intensity): 182 (M^+; 10.5), 167 ($(M - CH_3)^+$; 24.5), 151 ($(M - OMe)^+$; 11.5), 123 (19.9), 107 (100).

Exact mass calcd for $C_{11}H_{16}O_3$: 196.1099, found 196.1091.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.21; H, 8.36.

Unsaturated Diester (259)



258 **259**

To a suspension of sodium hydride (2.67 g, 60% dispersion in mineral oil; 1.5968 g, 66.54 mmol) in THF (100 mL) was added a solution of trimethyl phosphonoacetate (10.8 mL, 12.1 g, 66.5 mmol) in THF (100 mL) dropwise over 15 min. The resulting thick, white, pasty mixture was stirred at room temperature for 1.5 h. A solution of ester-aldehyde **258** (10.1063 g, 55.43 mmol) in THF (100 mL) was added dropwise over 30 min, after which the reaction mixture was stirred for a further 18 h. Water (100 mL) and Et_2O (100 mL) were added, and the organic layer was withdrawn. The aqueous phase was extracted further with Et_2O (2 × 100 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (3 × 100 mL), dried over anhydrous $MgSO_4$, and evaporated to yield a pale yellow oil. Subsequent purification by flash column chromatography [30% Et_2O–pet. ether] yielded pure unsaturated diester **259** (12.4625 g, 96%) as a clear, colorless oil; $[\alpha]_D^{26}$ +38.3 (*c* 1.00; $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.88 (d, J = 16.0 Hz, 1H; MeO_2C-CH=C<u>H</u>-), 5.85 (d, J = 16.0 Hz, MeO_2C-C<u>H</u>=CH-), 4.93 (dd, J = 2.5, 2.5 Hz, 1H; =C<u>H</u>$_A$H$_B$), 4.70 (dd, J = 2.5, 2.5 Hz; 1H; =CH$_A$<u>H</u>$_B$), 3.75 (s, 3H; –CO_2<u>Me</u>), 3.65 (s, 3H; –CO_2<u>Me</u>), 2.50–2.58 (m, 1H), 2.40–2.48 (m, 1H), 2.28–2.39 (m, 2H), 2.11–2.20 (dd, J = 15.1, 9.5 Hz, 1H; –CH$_A$<u>H</u>$_B$$CO_2$Me), 1.97–2.05 (m, 1H; H(16$_A$)), 1.43–1.53 (m, 1H; H(16$_B$)), 1.02 (s, 3H; C(13)–C<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7 (–<u>C</u>O_2Me), 166.8 (–<u>C</u>O_2Me), 157.3 (H_2C=<u>C</u>), 155.0 (C(12)), 119.0 (C(11)), 107.6 (H_2<u>C</u>=C), 51.2 (–CO_2<u>Me</u>), 50.5 (C(20), 45.6 (C(17)), 34.3, 30.4, 28.7, 18.5 (C(13)–<u>C</u>H_3).

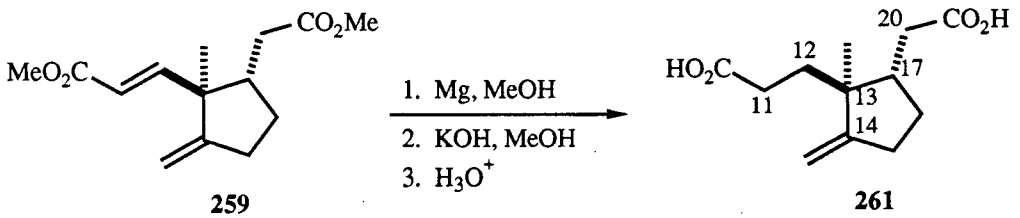
IR (neat film): 3090 ($\nu_{=C-H}$), 2960, 2925, 2855, 1735 ($\nu_{C=O,\ saturated\ ester}$), 1720 ($\nu_{C=O,\ unsaturated\ ester}$), 1650 ($\nu_{C=C}$), 1438, 1312, 1095, 1076, 890 cm^{-1}

EIMS *m/z* (rel intensity): 254 (M^+; 3.2), 223 ($(M - OMe)^+$; 51.3), 195 ($(M - CO_2Me)^+$; 14.5), 180 (65.2), 107 (100).

Exact mass calcd for $C_{14}H_{20}O_4$: 252.1361, found 252.1367.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.76; H, 8.01.

Diacid (261)



259 **261**

To a solution of the unsaturated diester **259** (12.4020, 49.154 mmol) in dry methanol (300 mL) at 0 °C was added magnesium turnings (3.584 g, 147.5 mmol) in small portions over 20 min.[131] The solution was stirred at 0 °C for 2 h, allowed to warm to room temperature, and stirred for a further 12 h at room temperature. A solution of potassium hydroxide (6.89 g, 123 mmol) in water (250 mL) was added and the resulting thick, translucent mixture was stirred vigorously for 2.5 h. The reaction mixture was poured into an ice-cold 1 M HCl (~300 mL) and neutralized by further addition of 6 M HCl (~15 mL). The aqueous mixture was extracted with ethyl acetate (3 × 250 mL). The combined extracts were washed with water (2 × 250 mL) and brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated to a viscous, colorless oil. Trituration of the oil in ice-cold pet. ether (~20 mL) followed by filtration of the resulting solid yielded pure diacid **261** as a white, crystalline solid (9.5937 g, 86%); $[\alpha]_D^{26}$ +59.1 (*c* 0.89, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.20–12.50 (bs, 2H; $-CO_2\underline{H}$), 4.93 (dd, J = 2.5, 2.0 Hz, 1H; $=C\underline{H}_AH_B$), 4.72 (dd, J = 2.5, 2.0 Hz, 1H; $=CH_A\underline{H}_B$), 2.43–2.55 (m, 2H), 2.24–2.38 (m, 3H), 2.13–2.20 (m, 1H), 2.00–2.10 (m, 2H), 1.85–1.95 (m, 2H), 1.30–1.42 (m, 1H), 0.89 (s, 3H; C(13)–$C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 181.0 ($-\underline{C}O_2H$), 180.2 ($-\underline{C}O_2H$), 157.6 ($H_2C=\underline{C}$), 105.2 ($H_2\underline{C}=C$), 47.0, 41.3, 34.7, 32.0, 31.3, 29.4, 28.6, 23.8.

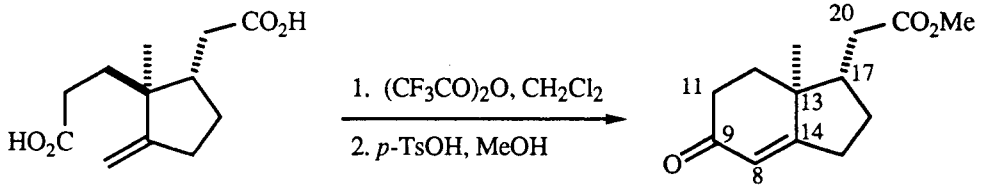
IR (neat film): 3450–2300 (broad, ν_{O-H}), 2960, 2945, 1710 ($\nu_{C=O}$), 1655 ($\nu_{C=C}$), 1410, 1302, 885 cm^{-1}

EIMS *m/z* (rel intensity): 208 ($(M - H_2O)^+$; 23.0), 190 (6.7), 180 (5.7), 16 (50.7), 153 (100).

Exact mass calcd for $C_{12}H_{16}O_3$ ($(M - H_2O)^+$): 208.1099, found 208.1112.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.66; H, 7.89.

Bicyclic Enone-ester (*ent*-255)



261 ***ent*-255**

To a solution of diacid **261** (9.3180 g, 41.18 mmol) was dissolved in dry CH_2Cl_2 (600 mL) and trifluoroacetic anhydride (14.5 mL, 21.6 g, 103 mmol) was added in one portion.[132] The originally colorless reaction mixture, which darkened over time to a pale straw-yellow color, was stirred at room temperature for 2.5 h. The solvent was removed under reduced pressure to leave a dark-brown, viscous syrup. The syrup was dissolved in dry methanol (250 mL) and *p*-toluenesulfonic acid (0.7833 g, 4.118 mmol) was added. The colorless reaction mixture was stirred for 15 h, and the solvent was then removed under reduced pressure. The resulting orange-brown oil was partitioned between ethyl acetate (300 mL) and water (100 mL).

The organic phase was withdrawn, while the aqueous phase was extracted once more with ethyl acetate (100 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (2 × 250 mL), brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a yellow-brown oil. Further purification of this oil by flash column chromatography [75% Et_2O–pet. ether or 60% EtOAc–pet. ether] yielded pure ester-enone ***ent*-255** (8.0121 g, 89%) as a clear, colorless oil; $[\alpha]_D^{26}$ –84.5 (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (s, 1H; H(8)), 3.71 (s, 3H; –O<u>Me</u>), 2.68 (ddt, 18.0, 11.2, 2.1 Hz, 1H; –C<u>H</u>$_2$C(O)-), 2.44–2.57 (m, 3H; –C<u>H</u>$_2$C(O)-, –C<u>H</u>$_2$CO$_2$Me, H(12$_A$)), 2.39 (ddd, *J* = 18.0, 5.4, 2.1 Hz, 1H; H(12$_B$)), 2.30 (dd, *J* = 15.0, 9.2 Hz, 1H; –C<u>H</u>$_2$CO$_2$Me), 2.05–2.14 (m, 2H; H(16$_A$), H(17)), 1.97 (ddd, *J* = 15.0, 6.2, 2.1 Hz, 1H; H(15$_A$)), 1.80 (ddd, *J* = 15.0, 14.5, 2.0 Hz, 1H; H(15$_B$), 1.54–1.66 (m, 1H, H(16$_B$)), 1.05 (s, 3H; C(13)–C<u>H</u>$_3$).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.7 (C(9)), 177.5 (–<u>C</u>O$_2$Me), 173.0 (C(14)), 122.0 (C(8)), 51.6 (–CO$_2$<u>Me</u>), 46.7 (C(17)), 44.1, 34.6, 34.0, 33.1, 27.4, 27.4, 16.4 (C(13)–<u>C</u>H$_3$).

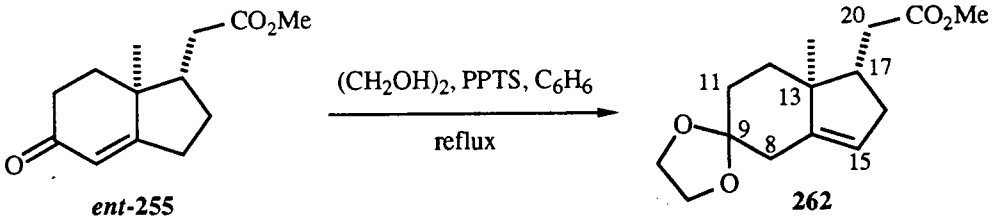
IR (neat film): 2950, 2928, 2882, 1740 ($\nu_{C=O,\ ester}$), 1662 ($\nu_{C=O,\ enone}$), 1622 ($\nu_{C=C}$), 1438, 1198, 1170, 999 cm^{-1}

EIMS *m/z* (rel intensity): 222 ($(M^+$; 33.6), 207 ($(M - CH_3)^+$; 15.4), 194 (22.4), 191 (21.8), 180 (43.2), 121 (100).

Exact mass calcd for $C_{13}H_{18}O_3$: 222.1256, found 222.1260.

Anal. Calcd for $C_{13}H_{18}O_3$ C, 70.24; H, 8.16. Found: C, 69.98; H, 8.00.

Ketal-ester (262)



ent-255 262

To a solution of (+)-enone-ester ***ent*-255** (7.8219 g, 35.18 mmol) in benzene (200 mL) was added pyridinium *p*-toluenesulfonate (1.7682 g, 7.04 mmol) and the mixture was refluxed for 18 h. The reaction mixture was partitioned between brine (100 mL) and ether (100 mL). The organic phase was separated, while the aqueous phase was extracted with ether (2 × 100 mL). The combined extracts were washed with water (2 × 250 mL), saturated aqueous $NaHCO_3$ (2 × 250 mL), and brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale yellow oil. Subsequent purification by flash column chromatography (20% EtOAc–pet. ether) yielded ketal-ester **262** (7.6827 g, 82%) as a clear, colorless oil; $[\alpha]_D^{26}$ –16.3 (*c* 0.99, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.33 (m, 1H), 3.93–4.00 (m, 4H; –OC<u>H</u>$_2$C<u>H</u>$_2$O–), 3.67 (s, 3H; –O<u>Me</u>), 2.32–2.52 (m, 6H), 1.99–2.07 (m, 1H), 1.79–1.88 (m, 1H), 1.65–1.74 (m, 2H), 1.51–1.59 (m, 1H), 0.92 (s, 3H; C(13)–C<u>H</u>$_3$).

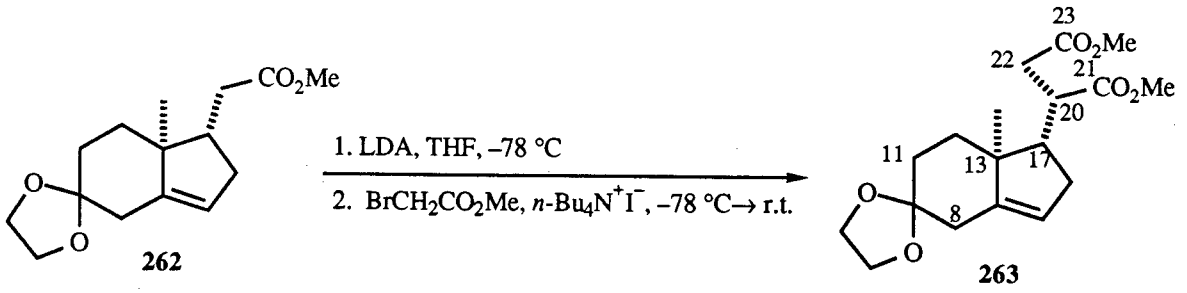
IR (neat film): 2960, 2900, 2860, 1742 ($\nu_{C=O,\ ester}$), 1438, 1360, 1096, 1022 cm^{-1}

EIMS *m/z* (rel intensity): 266 (M^+; 2.1), 235 ($(M - OMe)^+$; 1.2), 99 (100).

Exact mass calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1522.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.30.

Ketal-diester (263)



To a solution of diisopropylamine (2.68 mL, 1.93 g, 19.1 mmol) in THF (25 mL) at 0 °C was added *n*-butyllithium (12.3 mL, 1.55 M in hexane, 19.1 mmol) dropwise over 5 min. The solution was stirred at 0 °C for 30 min, then cooled to –78 °C. A solution of ketal-ester **262** (3.9163 g, 14.704 mmol) in THF (40 mL) at –78 °C was added by cannula and the reaction mixture was stirred for 30 min. Methyl bromoacetate (2.78 mL, 4.50 g, 29.4 mmol) and solid tetrabutylammonium iodide (2.7157 g, 7.352 mmol)[133] were added successively to the reaction mixture. The solution was allowed to warm to room temperature over ~2 h and was stirred for a further 16 h. Water (~100 mL) was added and the organic phase was separated. The aqueous phase was extracted further with ether (3 × 50 mL). The combined extracts were washed successively with saturated aqueous $Na_2S_2O_3$ solution (2 × 50 mL), water (1 × 50 mL), and brine (3 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a pale yellow oil. Subjection of the crude product to flash column chromatography (20% EtOAc–pet. ether) yielded recovered starting material (0.3129 g) and upon further elution, the desired ketal-diester **263** (4.2495 g, 93% based on recovered starting material) as a clear, colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27 (bs, 1H; H(15)), 3.84–4.00 (m, 4H; –OC<u>H$_2$</u>C<u>H$_2$</u>O–), 3.68 (s, 3H, –CO$_2$<u>Me</u>), 3.64 (s, 3H, –CO$_2$<u>Me</u>), 2.93 (ddd, J = 11.0, 11.0, 4.1 Hz, 1H; H(20)), 2.66 (dd, J = 16.4, 11.0 Hz, 1H; H(22)); 2.48 (dd, J = 16.4, 4.2 Hz, 1H; H(22)); 2.27–2.41 (m, 3H; H(16), H(8_A), H(8_B)), 2.09–2.18 (m, 1H; H(17)), 1.94–2.05 (m, 1H;

H(16)), 1.76 (ddd, J = 14.9, 14.9, 4.4 Hz, 1H; H(11_A)), 1.39–1.65 (m, 3H); H(12_A), H(12_B), H(11_B)), 1.03 (s, 3H; H(18)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.4 (–$\underline{C}O_2$Me), 172.4 (–$\underline{C}O_2$Me), 148.1 (C(14)), 120.5 (C(15)), 109.0 (C(9)), 64.5 (–O$\underline{C}H_2CH_2O$–), 64.4 (–$OCH_2\underline{C}H_2O$–), 53.9 (C(20)), 51.8 (–O$\underline{Me}$), 51.7 (–O$\underline{Me}$), 45.6, 42.2 (C(17)), 36.6, 36.2, 35.8, 35.0, 31.0, 15.5.

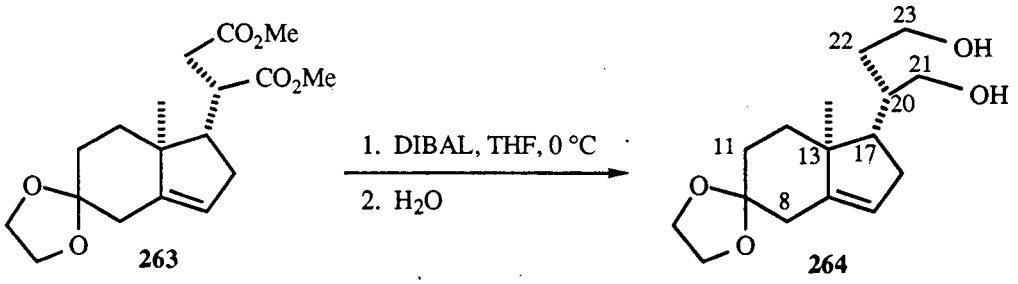
IR (neat film): 2951, 2890, 1741 ($\nu_{C=O}$), 1665 ($\nu_{C=C}$), 1437, 1360, 1265, 1207, 1165, 1096 cm^{-1}

EIMS *m/z* (rel intensity): 338 (M^+; 1.9), 323 (0.1), 307 (2.5), 276 (0.6), 265 (0.2), 249 (0.5), 99 (100).

Exact mass calcd for $C_{18}H_{26}O_6$: 338.1729, found 338.1729.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.98; H, 7.77.

Ketal-diol (264)



To a solution of ketal-diester **263** (2.4967 g, 7.378 mmol) in dry THF (35 mL) at 0 °C was added DIBAL (32 mL, 1 M in THF, 32 mmol) dropwise over 11 min. The colorless solution was stirred at 0 °C for 90 °C. Water (20 mL) was added dropwise and the mixture was stirred at room temperature for 2 h. A further portion of water (100 mL) was added and the organic layer was separated. The aqueous layer was extracted further with ether (5 × 50 mL). The combined organic extracts were washed with brine (3 × 100 mL), dried over anhydrous $MgSO_4$ and concentrated to provide a colorless, viscous syrup. Subsequent purification by flash

column chromatography (45% acetone–pet. ether) yielded pure ketal-diol **264** as a clear, viscous syrup (1.7764 g, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.21 (bs, 1H; H(15)), 3.87–3.98 (m, 4H; –OC$\underline{H}_2$C$\underline{H}_2$O–), 3.74–3.83 (m, 2H; H(22_A), H(21_A)), 3.64–3.71 (m, 1H; H(22_B)), 3.55 (dd, J = 11.2, 6.1 Hz, 1H; H(21_B)), 2.68 (bs, 2H; –O$\underline{H}$, –O$\underline{H}$), 2.25–2.42 (m, 3H), 1.78–2.06 (m, 6H), 1.53–1.70 (m, 3H), 0.98 (s, 3H; C(13)–C$\underline{H}_3$).

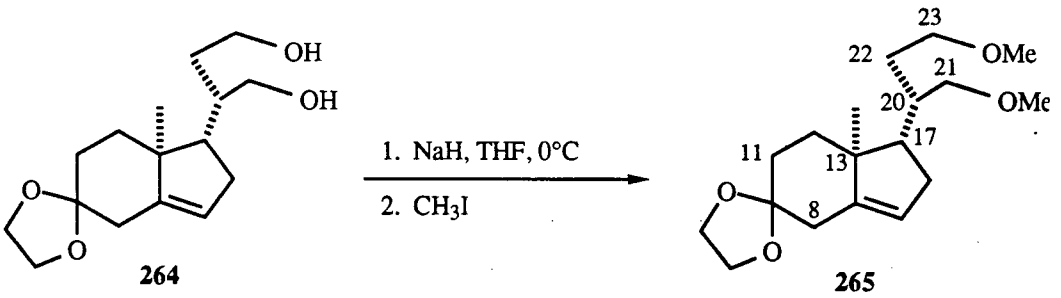
^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.6 (C(14)), 121.7 (C(15)), 109.1 (C(9)), 64.6, 64.5, 64.4, 60.6 (C(21), C(23), –O$\underline{C}$H$_2$$\underline{C}H_2$O–), 51.5 (C(20) or C(17)), 45.9, 40.0 (C(17) or C(20)), 37.9, 36.4, 35.7, 34.4, 31.2, 15.9.

IR (neat film): 3340 (ν_{O-H}), 2930, 1620 ($\nu_{C=C}$), 1438, 1378, 1110, 1072 cm^{-1}

DCI-MS (NH_3) *m/z* (rel intensity): 283 ((M+H)$^+$; 96.0), 282 (M$^+$; 5.2), 265 ((M–OH)$^+$; 13.2), 221 (23.5), 99 (100).

Exact mass calcd for $C_{16}H_{26}O_4$: 282.1831, found 282.1840.

Dimethoxy-ketal (265)



264 **265**

To a suspension of sodium hydride (94.6 mg, 60% dispersion in mineral oil, 3.94 mmol) in THF (10 mL) was added a solution of ketal-diol **264** (445.2 mg, 1.577 mmol) in THF (10 mL) and the resulting mixture was stirred for 1 h at room temperature. Methyl iodide (0.25 mL, 0.56 g, 3.9 mmol) was added and the reaction was allowed to proceed for a further 8 h at room temperature. Water (~50 mL) was added dropwise, cautiously at first, and the organic layer was

separated. The aqueous layer was extracted further with ether (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL) dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow-orange oil. Subsequent purification by flash column chromatography (30% EtOAc–pet. ether) yielded pure dimethoxy-ketal **265** (439.4 mg, 90%) as a clear, colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.30 (bs, 1H; H(15)), 3.87–3.98 (m, 4H; –OC$\underline{H}_2$C$\underline{H}_2$O–), 3.38–3.44 (m, 3H; $H(21_A)$, $H(23_A)$, $H(23_B)$), 3.24–3.32 (m, 1H; $H(21_B)$), 3.31 (s, 3H; –O$\underline{Me}$), 3.27 (s, 3H; –O$\underline{Me}$), 2.27–2.42 (m, 3H; $H(16_A)$, $H(8_A)$, $H(8_B)$), 1.89–2.05 (m, 2H; $H(16_B)$, $H(11_A)$), 1.70–1.89 (m, 4H; $H(22_A)$, H(20), $H(11_B)$, $H(12_A)$), 1.49–1.67 (m, 3H; $H(22_B)$, H(17), $H(12_B)$, 0.96 (s, 3H; C(13)–C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.7 (–$\underline{C}O_2$Me), 146.9 (C(14)), 121.5 (C(15)), 109.2 (C(9)), {64.4, 64.3 (–O$\underline{C}H_2\underline{C}H_2$O–)}, 51.3, 47.6, 45.6, 36.7, 36.3, 36.2, 34.8, 31.0, 16.3 (C(13)–$\underline{C}H_3$).

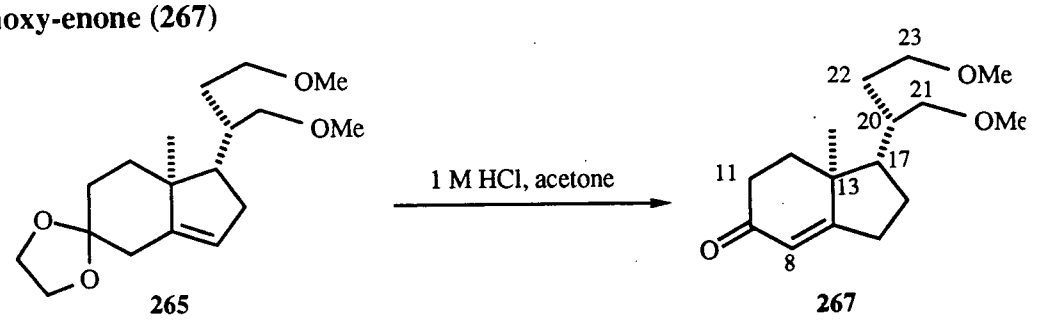
IR (neat film): 2947, 2883, 2805, 1455, 1355, 1106, 955, 798 cm^{-1}

EIMS *m/z* (rel intensity): 310 (M^+; 9.1), 278 ($(M - MeOH)^+$; 1.1), 265 (12.0), 195 (5.0), 147 (10.9), 99(100).

Exact mass calcd for $C_{18}H_{30}O_4$: 310.2144, found 310.2143;

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.71; H, 9.75.

Dimethoxy-enone (267)



265 **267**

A solution of dimethoxy-ketal (**265**; 0.4394 g, 1.415 mmol) and 1 M HCl (8 mL) in acetone (8 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into brine (100 mL) and the aqueous solution was extracted with ether (3 × 50 mL). Subsequently, the combined organic phases were neutralized with saturated $NaHCO_3$ (3 × 50 mL) washed with water (1 × 100 mL) and brine (3 × 100 mL) dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield a cloudy, colorless oil. Subsequent purification by flash column chromatography (60% EtOAc–pet. ether) yielded pure dimethoxy-enone **267** (0.2970 g, 92%) as a clear, pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.71 (bs, 1H; H(9)), 3.42 (bd, J = 5.7 Hz, 1H; $H(23_A)$), 3.40 (bd, J = 5.7 Hz, 1H; $H(23_B)$), 3.30–3.36 (m, 2H; $H(21_A)$, $H(21_B)$), 3.31 (s, 3H; –OMe), 3.27 (s, 3H; –OMe), 2.62 (ddt, J = 19.8, 10.8, 2.2 Hz, 1H; $H(15_A)$), 2.35–2.55 (m, 2H; $H(11_A)$, $H(15_B)$), 2.30 (dddd, J = 17.8, 5.0, 1.3, 0.7 Hz, 1H; $H(11_B)$), 2.08 (ddd, J = 13.2, 5.3, 2.2 Hz, 1H; $H(12_A)$), 1.95 (dddd, J = 12.5, 12.5, 6.6, 2.2 Hz, 1H; $H(16_A)$), 1.86 (ddd, J = 13.5, 13.5, 5.0 Hz, 1H; ($H(12_B)$), 1.71–1.81 (m, 3H; H(17), H(20), $H(22_A)$), 1.50–1.66 (m, 2H; $H(16_B)$, $H(22_B)$), 1.08 (s, 3H; C(13)–CH_3).

IR (neat film): 2980, 2948, 2902, 2835, 1660 ($\nu_{C=O}$), 1456, 1202, 1106 cm^{-1}

EIMS *m/z* (rel intensity): 266 (M^+; 16.6), 251 ($(M - CH_3)^+$; 46.5), 234 ($(M - MeOH)^+$; 202 ($(M - 2MeOH)^+$; 15.1), 121 (94.0).

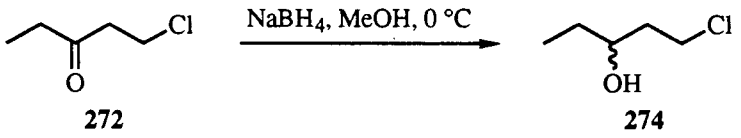
Exact mass calcd for $C_{16}H_{26}O_3$: 266.1882, found 266.1880.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84 Found: C, 72.20; H, 9.86.

Table 5.17. Spectral Data from COSY Spectrum of Dimethoxy-enone **267**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
5.71	H(9)	2.61	H(15)
3.42	H(23_A)	3.40, 1.71–1.81 (part of multiplet) 1.50–1.66 (part of multiplet)	H(22_A, 22_B) H(23_B)
3.40	H(23_B)	3.42, 1.71–1.81 (part of multiplet)	H(23_A, 22_A)
3.30–3.36	H(21_A) H(21_B)	3.30–3.36*, 1.71–1.81 (part of multiplet)	H(21_A, 21_B), H(20, 22_A)
2.62	H(15_A)	5.71, 2.35–2.55 (part of multiplet) 1.95, 1.50-1.66 (part of multiplet)	H(15_B, 9) H(16_A, 16_B)
2.35–2.55	H(11_A), H(15_B)	2.62, 2.30, 2.35–2.55 (part of multiplet), 2.08, 1.95, 1.86, 1.50-1.66 (part of multiplet)	H(11_A, 11_B), H(12_A, 12_B) H(16_A, 16_B) H(15_A)
2.30	H(11_B)	2.35–2.55 (part of multiplet), 2.08, 1.86	H(11), H(12_A, 12_B)
2.08	H(12_A)	2.35–2.55 (part of multiplet), 2.30, 1.86	H(11_A, 11_B) H(12_B)
1.95	H(16_A)	2.62, 2.35–2.55 (part of multiplet), 1.71–1.81 (part of multiplet), 1.50–1.66 (part of multiplet)	H(15_A, 15_B), H(16_B), H(17)
1.86	H(12_B)	2.35–2.55 (part of multiplet), 2.30, 2.08	H(11_A, 11_B), H(12_A)
1.71–1.81	H(17), H(20), H(22_A)	3.42, 3.40, 3.30–3.36, 1.95, 1.50–1.66	H(21_A, 21_B), H(23_A, 23_B), H(16_A, 16_B), H(22_B),
1.50–1.66	H(16_B) H(22_B)	3.42, 2.62, 2.35–2.55 (part of multiplet), 1.95, 1.71–1.81 (part of multiplet)	H(23_A, 22_A), H(15_A, 15_B), H(16_A)

(±)-1-Chloro-3-pentanol (274)



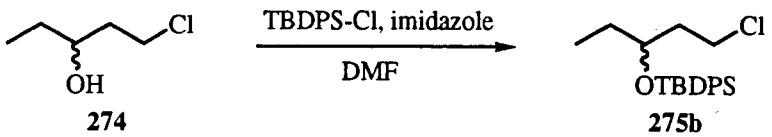
272 **274**

To a solution of distilled 1-chloro-3-pentanone (**272**; 5.9420 g, 49.28 mmol) in methanol (50 mL) at 0 °C was added solid sodium borohydride (1.3982 g, 36.96 mmol) in several portions over 10 min. The clear, colorless solution was stirred at 0 °C for 30 min. 1 M HCl (~10 mL) and brine (50 mL) were added and the solution was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with water (1 × 50 mL), saturated aq. $NaHCO_3$ (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield (±)-1-chloro-3-pentanol (**274**) as a colorless liquid (5.5241 g, 95%) that could be used in the subsequent reaction without further purification.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.65–3.80 (m, 3H; H(1), H(3)), 2.06 (bs, 1H; exchanges with D_2O; –OH), 1.82–1.96 (m, 2H; H(2)), 1.53 (dt, J = 9.5, 8.0 Hz, 2H; H(4)), 0.95 (t, J = 8.0 Hz, 3H; H(5)).

IR (neat film): 3332 (broad, ν_{O-H}), 2966, 2931, 2879, 1459 cm^{-1}.

(±)-1-Chloro-3-(*t*-butyldiphenylsilyloxy)pentane (275b)



274 **275b**

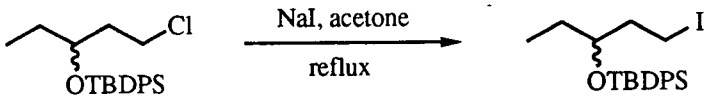
To a solution of (±)-1-chloro-3-pentanol (**274**; 5.3277 g, 43.46 mmol) and imidazole (14.8275 g, 217.80 mmol) in spectro DMF (40 mL) was added *t*-butyldiphenylsilyl chloride (13.3 mL, 14.3 g, 52.2 mmol).[93] The colorless solution was stirred for 3 h after it was partitioned between water (50 mL) and Et_2O (50 mL). The organic phase was removed while

the aqueous phase was extracted further with Et_2O (3 × 50 mL). The combined extracts were then washed with water (100 mL) and brine (3 × 100 mL), and dried over anhydrous $MgSO_4$. Subsequent concentration of the extracts under reduced pressure afforded (±)-1-chloro-3-(*t*-butyldiphenylsilyloxy)pentane (**275b**) as a viscous, colorless oil (15.3065 g, 98%) that could be used in the subsequent reaction without further purification.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60–7.72 (m, 4H; $-C_6\underline{H}_5$), 7.25–7.40 (m, 6H; $-C_6\underline{H}_5$), 3.82 (quint, J = 9.0 Hz, 1H; H(3)), 3.53 (t, J = 11.5 Hz, 2H; H(1)), 1.87–1.95 (m, 2H; H(2)), 1.45 (dt, J = 9.0, 8.0 Hz, 2H; H(4)), 1.04 (s, 9H; Bu^t), 0.73 (t, J = 8.0 Hz, 3H; H(5)).

IR (neat film): 3070 ($\nu_{=C-H}$), 2955, 2940, 2857, 1592 ($\nu_{C=C}$), 1427, 1109 cm^{-1}.

(±)-1-Iodo-3-(*t*-butyldiphenylsilyloxy)pentane (270b)



275b **270b**

A solution of 1-chloro-3-(*t*-butyldiphenylsilyloxy)pentane (**275b**; 11.2798 g, 31.25 mmol) and anhydrous sodium iodide (9.3672 g, 62.49 mmol) in spectro grade acetone (200 mL)[134,136] was refluxed for 24 h and then allowed to cool to room temperature. The reaction mixture was diluted with Et_2O (100 mL), and poured into brine (100 mL). The organic layer was withdrawn while the aqueous layer was extracted with a further portion of Et_2O (100 mL). The combined organic solutions were washed with saturated aq. $NaHSO_3$ (1 × 100 mL) and brine (2 × 100 mL).

The solution was concentrated under reduced pressure to yield crude (±)-1-iodo-3-(*t*-butyldiphenylsilyloxy)pentane (**270b**) as a colorless oil. Further purification of the product **270b** by flash column chromatography (5% Et_2O–pet. ether) yielded pure (±)-1-iodo-3-(*t*-butyldiphenylsilyloxy)pentane (**270b**) as a colorless syrup (10.8213 g, 77%).

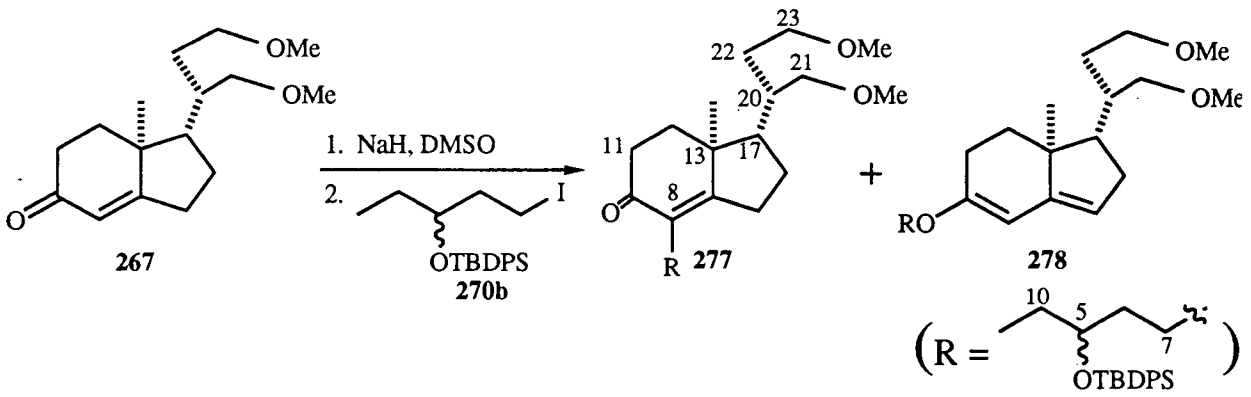
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60–7.70 (m, 4H; $-C_6\underline{H}_5$), 7.25–7.40 (m, 6H; $-C_6\underline{H}_5$), 3.63 (quint, J = 7.0 Hz, 1H; H(3)), 3.09 (t, J = 8.5 Hz, 2H; H(1)), 1.80–2.00 (m, 2H; H(2)), 1.38 (dt, J = 9.0, 8.0 Hz, 2H; H(4)), 0.99 (s, 9H; Bu^t), 0.69 (t, J = 8.0 Hz, 3H; H(5)).

IR (neat film): 3070 ($\nu_{=C-H}$), 2956, 2940, 2857, 1592 ($\nu_{C=C}$), 1466, 1100 cm^{-1}.

DCI-MS (NH_3) *m/z* (rel intensity): 453 ((M + H)$^+$; 58.0), 412 (37.2), 395 ((M – Bu^t)$^+$; 54.6), 196 (100).

Exact mass calcd for $C_{21}H_{30}IOSi$ [(M + H)$^+$] 453.1070 , found 453.1111.

Dimethoxy-enone (277)



A suspension of sodium hydride (28.3 mg, 60% dispersion in mineral oil, 0.589 mmol) in dry, distilled DMSO (8 mL)[138] was stirred at room temperature for 10 min and at 80 °C for 2 h. The mixture was cooled to room temperature, after which a solution of the bicyclic dimethoxy-enone **267** (130.8 mg, 0.491 mmol) in dry, distilled DMSO (2.5 mL) was added dropwise by syringe over 5 min. After a further 2 h, a solution of 1-iodo-3-(*t*-butyldiphenylsilyloxy)pentane (**270b**; 288.8 mg, 0.638 mmol) in dry DMSO (2.0 mL) was added dropwise by syringe over 5 min. The reaction mixture was stirred for 18 h after which it was poured into a separatory funnel containing brine (25 mL) and ether (50 mL). The organic layer was withdrawn wile the aqueous layer was extracted further with ether (2 × 50 mL). The combined extracts were washed with water (50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to an

orange-yellow oil. Purification by flash column chromatography (30% EtOAc–pet. ether) yielded, in order of elution, the dienol ether **278** (80.6 mg) as a pale yellow oil, and then the desired bicyclic enone **277** (188.9 mg, 65%) as a pale yellow oil.

Bicyclic Dimethoxy-enone (277)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.72 (m, 4H; –$C_6\underline{H}_5$), 7.30–7.42 (m, 6H; –$C_6\underline{H}_5$), 3.69 (bquint, J = 5.5 Hz, 1H; H(5)), 3.38–3.45 (m, 2H; –$C\underline{H}_2$OMe), 3.30–3.35 (m, 2H; –$C\underline{H}_2$OMe), 3.33 (s, 3H; –O$\underline{Me}$), {3.28, 3.27 (s, 3H; –O$\underline{Me}$)}, 2.41–2.53 (m, 1H), 2.16–2.38 (m, 3H), 1.96–2.10 (m, 3H), 1.84–1.94 (m, 1H), 1.64–1.82 (m, 5H), 1.38–1.60 (m, 4H), 1.23–1.36 (m, 1H), 1.04 (s, 9H; t-$\underline{Bu}$), 0.99 (s, 3H; C(18)), 0.77 (t, J = 7.4 Hz, 3H; C(10)–CH_3).

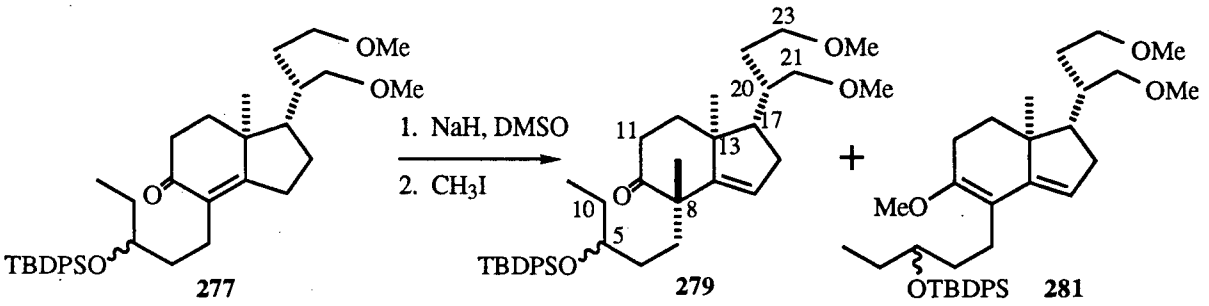
IR (neat film): 3070 ($\nu_{=C-H}$), 3055 ($\nu_{=C-H}$), 2965, 2925, 2860, 1654 ($\nu_{C=O}$), 1605 ($\nu_{C=C}$), 1460, 1428, 1372, 1191, 1095 cm^{-1}

DCI-MS (NH_3) *m/z* (rel intensity): 590 (M^+, 0.2), 561 ($(M - Et)^+$; 1.3), 547 (10.1), 533 ($(M - Bu^t)^+$; 79.3).

Exact mass calcd for $C_{37}H_{54}O_4Si$ 590.3791, found 590.3805.

Anal. Calcd for $C_{37}H_{54}O_4Si$: C, 75.19; H, 9.23 Found: C, 75.30; H, 9.10

β,γ-Unsaturated Enone (279)



A suspension of sodium hydride (28.0 mg, 60% dispersion in mineral oil, 0.583 mmol) in dry, distilled DMSO (8 mL)[138] was stirred at room temperature for 10 min and at 80 °C for 2 h. The mixture was cooled to room temperature, after which a solution of the bicyclic enone **277** (265.0 mg, 0.4484 mmol) in dry, distilled DMSO (2 mL) was added dropwise by syringe over 5 min. After a further 2 h, a solution of methyl iodide (33.5 μL, 76.4 mg, 0.538 mmol) in dry DMSO (0.5 mL) was added dropwise by syringe over 1 min. The reaction mixture was stirred for 6 h after which it was poured into a separatory funnel containing brine (25 mL) and ether (50 mL). The organic layer was withdrawn wile the aqueous layer was extracted further with ether (2 × 50 mL). The combined extracts were washed with water (50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to an orange-yellow oil. Purification by flash column chromatography (30% EtOAc–pet. ether) yielded, in order of elution, the dienol ether **281** (80.6 mg) as a pale yellow oil, and then the desired bicyclic enone **279** (217.6 mg, 80%) as a pale yellow oil.

β,γ-Unsaturated Enone (279)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.69 (m, 4H; –$C_6\underline{H}_5$), 7.30–7.42 (m, 6H; –$C_6\underline{H}_5$), {5.31 (dd, J = 3.5, 1.4 Hz); 5.26 (dd, J = 3.5, 1.2 Hz), 1H; H(15)}, 3.55–3.65 (m, 1H), 3.39–3.46 (m, 2H), {3.34, 3.35 (s, 3H; –O<u>Me</u>)}, 3.29–3.38 (m, 2H), 3.28 (s, 3H; –O<u>Me</u>), 2.44–2.58 (m, 1H), 2.20–2.33 (m, 2H), 1.69–2.08 (m, 6H), 1.21–1.66 (m, 7H), 1.01 (s, 9H; *t*-

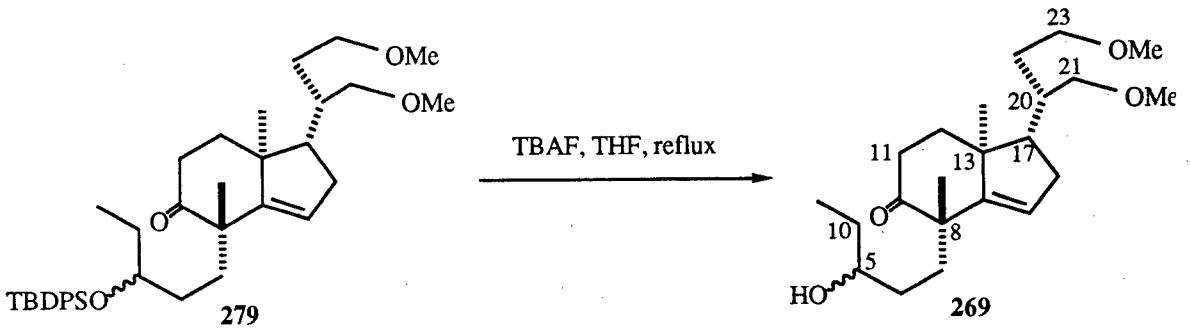
Bu), {0.99, 1.06 (s, 3H)}, {0.90, 0.92 (s, 3H)}, {0.73 (t, J = 7.4 Hz); 0.77 (t, J = 7.5 Hz), 3H; C(10)–CH_3}.

IR (neat film): 3071 ($\nu_{=C-H}$), 3052 ($\nu_{=C-H}$), 2960, 2916, 2832, 1708 ($\nu_{C=O}$), 1460, 1427, 1378, 1108 cm^{-1}

EIMS *m/z* (rel intensity): 604 (M^+; 0.6), 575 ($(M - Et)^+$; 0.6), 561 (23.2), 547 ($(M - Bu^t)^+$; 44.7), 515 (4.3), 485 (5.2).

Exact mass calcd for $C_{38}H_{56}O_4Si$: 604.3948, found 604.3908.

Keto-alcohol (269)



A solution of the silyloxy-ketone **279** (206.7 mg, 0.3417 mmol) and tetrabutylammonium fluoride (680 μL, 1 M in THF, 0.680 mmol) in THF (4.0 mL) was refluxed for 2 h before being diluted with Et_2O (25 mL) and then poured into brine (20 mL). After the organic phase was removed the aqueous mixture was extracted with ether (5 × 20 mL). The combined extracts were washed with water (1 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale brown-yellow oil. Further purification by flash column chromatography (60% EtOAc–pet. ether) yielded pure keto-alcohol **269** as a clear, colorless, viscous film (113.0 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ {5.49 (partially resolved dd, J = 3.2, 1.1 Hz); 5.44 (dd, J =3.6, 1.3 Hz), 1H; H(15)}, 2.58 (ddd, J = 17.6, 12.0, 5.8 Hz, 1H; H(11)), 3.48 (bs, 1H; –OH),

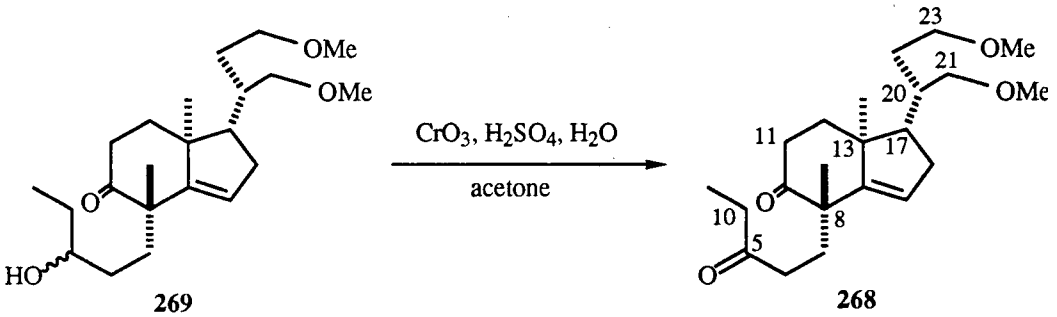
3.29–3.45 (m, 5H; –C<u>H</u>$_2$OMe, –C<u>H</u>$_2$OMe, H(5)), {3.30, 3.32 (s, 3H, –O<u>Me</u>)}, {3.26, 3.27 (s, 3H, –O<u>Me</u>)}, 1.20–2.42 (m, 15H), {0.89 (t, J = 7.4 Hz); 1.02 (t, J = 7.2 Hz), 3H; H(19)}, {1.07, 1.16 (s, 3H, H(8'))}, {0.93, 1.04 (s, 3H; H(18))}.

IR (neat film): 3456 (broad; ν_{O-H}), 2955, 2945, 2870, 1709 ($\nu_{C=O}$), 1457, 1375, 1244, 1109 cm^{-1}

EIMS *m/z* (rel intensity): 366 (M^+; 11.5), 351 ($(M - CH_3)^+$; 7.2), 346 ($(M - H_2O)^+$; 6.5), 335 (5.5), 316 (1.5).

Exact mass calcd for $C_{22}H_{38}O_4$: 366.2770, found 366.2772.

Diketone (268)



To a solution of keto-alcohol **269** (60.7 mg, 0.166 mmol) in acetone (5.0 mL) at 0 °C was added, dropwise over 1 min, a solution of chromium(VI) oxide (16.6 mg, 0.166 mol) and concentrated sulfuric acid (~0.3 mL) in water (1.0 mL). Saturated aqueous sodium bisulfite solution (~1 mL) was added and the reaction mixture was partitioned between brine (50 mL) and ether (50 mL). The organic layer was separated while the aqueous layer was extracted once more with ether (25 mL). The combined extracts were washed with water (2 × 50 mL), saturated aqueous sodium bicarbonate (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated to a pale yellow oil. Subsequent purification by flash column chromatography (20% EtOAc–pet. ether) yielded pure diketone **268** (52.7 mg, 87%) as a clear, colorless film.

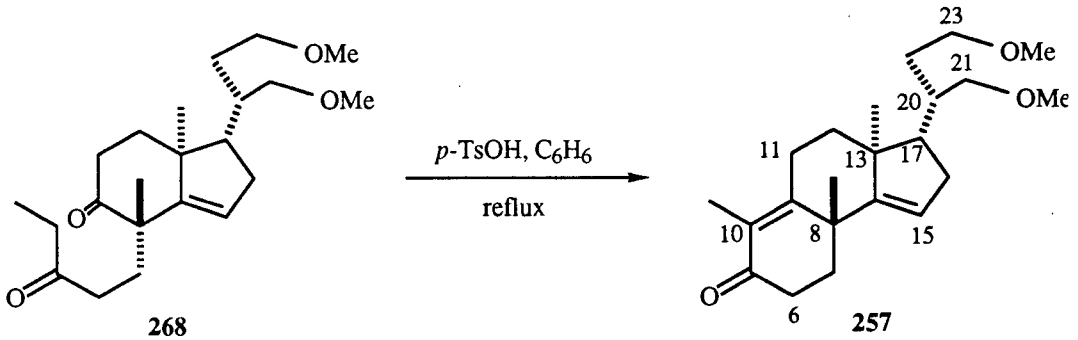
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (dd, J = 3.4, 1.4 Hz, 1H, H(15)), 3.40–3.48 (m, 2H; $H(21_A)$, $H(23_A)$), 3.31–3.38 (m, 2H; $H(21_B)$, $H(23_B)$), 3.31 (s, 3H; –OMe), 3.27 (s, 3H; –OMe), 2.58 (ddd, J = 16.8, 11.2, 5.5 Hz, 1H; $H(11_A)$), 2.16–2.42 (m, 5H; $H(11_B)$, $H(10_{A,B})$, $H(16_{A,B})$), 1.90–2.05 (m, 4H), 1.69–1.89 (m, 5H), 1.51–1.62 (m, 1H; H(23)), 1.16 (m, 3H; H(8')), 1.01 (s, 3H, H(18)), 0.99 (t, J = 7.4 Hz, 3H; H(19)).

IR (neat film): 2971, 2927, 2875, 1713 ($\nu_{C=O}$), 1460, 1376, 1114 cm^{-1}

EIMS *m/z* (rel intensity): 364 (M^+; 4.7), 349 ($(M - CH_3)^+$; 31.2), 332 (29.8), 314 (21.1), 301 (9.3).

Exact mass calcd for $C_{22}H_{36}O_4$: 364.2643, found 364.2622.

Tricyclic Dienone (257)



268 257

To a solution of diketone **268** (23.2 mg, 0.0636 mmol) in dry, distilled benzene (15 mL) was added *p*-toluenesulfonic acid (2.4 mg, 0.0127 mmol). The mixture was refluxed in a Dean-Stark apparatus for 2 h, allowed to cool to room temperature, diluted with ether (~25 mL), and washed successively with saturated aqueous sodium bicarbonate (2 × 25 mL), water (1 × 25 mL), and brine (3 × 25 mL). The organic phase was dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure to afford a orange-yellow film. Purification by flash column chromatography (20% EtOAc–pet. ether) yielded pure tricyclic enone **257** (18.6 mg, 84%) as a clear, colorless film; $[\alpha]_D^{26}$ –12.5 (*c* 0.93, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41–5.48 (m, 1H; H(15)), 3.44 (d, J = 6.2 Hz, 1H; $H(23_A)$), 3.42 (d, J = 6.2 Hz, 1H; $H(23_B)$), 3.38 (dd, J = 9.4, 3.4 Hz, 1H; $H(21_A)$), 3.30–3.35 (m, 1H; $H(21_B)$), 3.32 (s, 3H; –OMe), 3.29 (s, 3H; –OMe), 2.50–2.65 (m, 2H; H(17), $H(6_A)$), 2.39 (ddd, J = 17.6, 4.7, 2.5 Hz, 1H; $H(6_B)$), 2.24–2.35 (m, 2H; $H(11_A)$, $H(16_A)$), 1.92–2.07 (m, 4H; $H(16_A)$, $H(7_A)$, $H(7_B)$, $H(11_B)$), 1.69–1.87 (m, 4H; $H(22_A)$, H(20), $H(12_A)$, $H(12_B)$), 1.75 (d, J = 0.9 Hz, 3H; C(10)-Me), 1.53–1.64 (m, 1H; $H(22_B)$), 1.31 (s, 3H; C(8)–Me), 0.82 (s, 3H; C(13)–Me).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.0 (C(5)), 163.6 , 158.8, 129.2, 120.3, 73.0, 70.8, 58.6, 58.6, 52.3, 47.1, 38.8, 37.5, 36.2, 35.8, 35.1, 34.3, 30.2, 27.4, 26.6, 19.0, 10.8.

IR (neat film): 2929, 2870, 2829, 1662 ($\nu_{C=O}$), 1625 ($\nu_{C=C}$), 1602 ($\nu_{C=C}$), 1449, 1372, 1098 cm^{-1}

EIMS *m/z* (rel intensity): 346 (M^+; 9.6), 331 ($(M - CH_3)^+$; 11.6), 314 (19.2), 299 (29.0), 213 (100).

Exact mass calcd for $C_{22}H_{34}O_3$: 346.2508, found 346.2510.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.31; H, 9.91.

Table 5.18. Results of NOE Experiments for Tricyclic Enone **257**.

Proton Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments**
5.41–5.48	H(15)	2.24–2.35 (U), 1.92–2.07 (part of multiplet), 1.31	H(16), C(8)-Me
1.31	C(8)-Me	5.41–5.48, 2.50–2.65 (U), 2.39, 1.92–2.07 (part of multiplet)	H(15), H(6)
0.82	C(13)-Me	3.30–3.38, 3.32, 3.29, 1.92–2.07 (part of multiplet), 1.69–1.87 (excluding singlet at 1.75)	H(21), –OMe, –OMe,

* The notations (D) and (U) refer to the downfield and upfield parts of multiplets, respectively, whose chemical shifts are given.

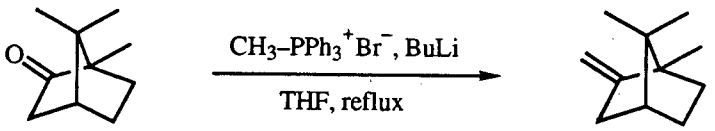
** Only those protons that can be assigned unambiguously have been recorded.

Table 5.19. Spectral Data from COSY Spectrum of Tricyclic Enone **257**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations* Signal Positions [δ (ppm)]	Assign-ment
5.41–5.48	H(15)	2.24–2.35 (U), 1.92–2.07	H(16_A, 16_B),
3.44	H(23_A)	1.53–1.64, 1.69–1.87	H(22_A, 22_B)
3.42	H(23_B)	1.53–1.64, 1.69–1.87	H(22_A, 22_B)
3.38	H(21_A)	1.69–1.87	H(20)
3.30–3.35	H(21_B)	1.69–1.87	H(20)
2.50–2.65 (D)	H(17)	1.69–1.87, 2.24–2.35 (U)	H(20), H(16_A)
2.50–2.65 (U)	H(6_A)	1.92–2.07, 2.39	H(6_B, 7_A, 7_B)
2.39	H(6_B)	2.50–2.65 (U), 1.92–2.07	H(6_A, 7_A, 7_B)
2.24–2.35 (D)	H(11_A)	1.92–2.07, 1.69–1.87	H(11_B, $12_{A,B}$)
2.24–2.35 (U)	H(16_A)	5.41–5.48, 2.50–2.65 (D), 1.69–1.87	H(15), H(17), H(16_B)
1.92–2.07	H(16_B), H(11_B), H(7_A,7_B)	5.41–5.48, 2.50–2.65 (U), 2.39, 2.24–2.35 (D), 1.69–1.87, 1.31	H(15), H(6_A), H(6_B), H(11_A) H(12_A, 12_B), C(10)-Me
1.69–1.87; 1.75	H(22_A), H(20), H($12_{A,B}$) C(10)-Me	3.44, 3.42, 3.38, 3.30–3.35 2.50–2.65 (D), 2.24–2.35 (U), 1.92–2.07, 1.53–1.64	H(23_A, 23_B), H(17,21_A,21_B) H(11_A, 11_B), H(22_B)
1.53–1.64	H(22_B)	3.44, 3.42, 1.69–1.87 (U)	H(23_A, 23_B) H(20)
1.31	C(10)-Me	1.92–2.07 (U)	H(11_B)

*The notations (D) and (U) refer to the downfield and upfield parts of the multiplet whose chemical shift range is given.

(–)-2-Methylenebornane (88)[72]



9 **88**

To a suspension of methyltriphenylphosphonium bromide (154.7 g, 0.4330 mol) in THF (400 mL) was added *n*-butyllithium (307 mL, 1.55 M in hexane, 0.476 mol) dropwise over 0.5 h. The resulting red-orange solution was stirred at 50 °C for 2 h, and then allowed to cool to room temperature. A solution of (+)-camphor (**9**; 41.2 g, 0.271 mol) in THF (160 mL) was added dropwise over 0.5 h. The reaction mixture was refluxed for 12 h and allowed to cool to room temperature. The volume of the reaction mixture was reduced to ~300 mL by rotary evaporation and then poured into water (300 mL). The organic layer was removed while the aqueous layer was extracted with pet. ether (3 × 200 mL). The combined organic layers were washed successively with water (1 × 500 mL) and brine (3 × 500 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a white slush. Further purification by flash column chromatography [100% pet. ether] provided 2-methylenebornane (**88**) as a volatile, white, waxy solid (55.4507 g, 85%); mp 69.5–71.0 °C (*lit.*[72] mp 68–70 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.69 (bs, 1H; $=C\underline{H}_AH_B$), 4.61 (dd, J = 3.0, 2.0 Hz, 1H; $=CH_A\underline{H}_B$), 2.38 (bd, J = 16.0 Hz, 1H; H(3_{exo})), 1.91 (dt, J =16.0, 1.5 Hz, 1H; H(3_{endo})), 1.68–1.80 (m, 2H; H(5_{exo}), H(4)), 1.64 (ddd, J = 11.9, 11.9, 3.6 Hz, 1H; H(6_{exo})), 1.16–1.30 (m, 2H; H(5_{endo}), H(6_{endo})), 0.92 (s, 3H; H(9)), 0.89 (s, 3H; H(10)), 0.76 (s, 3H; H(8)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2 (C(2)), 101.2 ($=\underline{C}H_2$), 51.4, 47.2, 44.8, 37.0, 35.2, 28.0, 19.6, 19.0, 12.5.

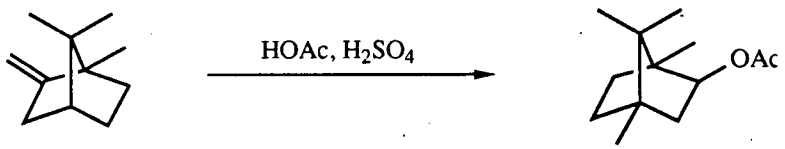
IR ($CHCl_3$): 2900, 2875, 1652 ($\nu_{C=C}$), 1472, 1448, 1382, 1365, 878 cm^{-1}

EIMS *m/z* (rel intensity): 150 (M^+; 10.2), 135 ($(M - CH_3)^+$; 8.6), 69 (80.6), 55 (26.9).

Exact mass calcd for $C_{11}H_{18}$: 150.1409, found 150.1413.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.71; H, 12.10.

(+)-4-Methylisobornyl acetate (89)[72]



88 **89**

To a solution of 2-methylenebornane (**88**; 28.6912 g, 0.1909 mol) in glacial acetic acid (125 mL) was added concentrated sulfuric acid (3.0 mL) dropwise over ~1–2 min. The colorless solution was stirred for 30 min and then diluted with Et_2O (~150 mL) and poured into water (150 mL). The organic phase was withdrawn while the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined extracts were washed with water (3 × 150 mL), neutralized with saturated aq. $NaHCO_3$ (3 × 150 mL), and washed with brine (3 × 150 mL). After the organic layer was dried over anhydrous $MgSO_4$, the solvent was removed by rotary evaporation to yield 4-methylisobornyl acetate (**89**) as a volatile, clear, colorless liquid (33.4923 g, 83%) that could be used directly in the subsequent step. However, further purification of the product acetate **89** could be accomplished by flash column chromatography [5% Et_2O–pet. ether].

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.65 (dd, J = 11.5, 7.8 Hz, 1H; H(2)), 2.01 (s, 3H; –C(O)C$\underline{H}_3$), 1.82 (dd, 18.0, 7.8 Hz, 1H; H(3_{exo})), 1.36–1.54 (m, 3H; H(3_{endo}), H(5_{exo}), H(6_{exo})), 1.10–1.19 (m, 2H; H(5_{endo}), H(6_{endo})), 0.90 (s, 3H; H(4')), 0.86 (s, 3H; H(10)), 0.83 (s, 3H; H(8)), 0.70 (s, 3H; H(9)).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.5 ($\underline{C}$=O), 80.0 (C(2)), 50.4, 47.7, 46.8, 45.4, 34.3, 33.1, 21.2, 17.6, 17.5, 15.6, 12.0.

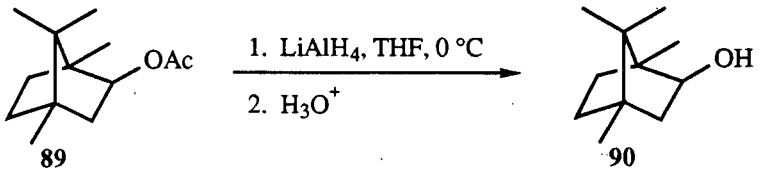
IR (neat film): 2955, 2855, 1740 ($\nu_{C=O}$), 1458, 1362, 1242, 1040 cm^{-1}

EIMS *m/z* (rel intensity): 210 (M^+; 2.0), 150 (50.9), 135 (48.3), 109 (82.3), 43 ($CH_3C{\equiv}O^+$; 100).

Exact mass calcd for $C_{13}H_{22}O_2$: 210.1620, found 210.1622.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.82; H, 10.70.

(+)-4-Methylisoborneol (90)[72]



89 90

To a suspension of lithium aluminum hydride (12.0869 g, 0.3185 mol) in THF (250 mL) at 0 °C was added, dropwise over 20 min, a solution of 4-methylisobornyl acetate (**89**; 33.4923 g, 0.1592 mol) in THF (100 mL). The reaction mixture was stirred at 0 °C for 5 h. The reaction was then quenched by cautious, dropwise addition of water (~100 mL). The quenched mixture was stirred for a further hour, then diluted with a further aliquot of water (~100 mL). The pasty white solid in the reaction mixture was dissolved by cautious, dropwise addition of 6 M HCl (~10 mL). The aqueous solution was then extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed successively with water (2 × 300 mL), neutralized with saturated aq. $NaHCO_3$ (2 × 500 mL), washed with brine (3 × 300 mL), dried over anhydrous $MgSO_4$, and concentrated to yield 4-methylisoborneol (**90**) as a white solid (26.0655 g, 97%) that could be used directly in the next reaction. Further purification could be accomplished by flash column chromatography [60% Et_2O–pet. ether]; mp 193.5–195.0 °C (*lit.*[72] 195–196.5 °C;.193–194 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.59 (dd, J = 11.7, 4.9 Hz, 1H; H(2)), 1.74 (dd, J = 18.6, 11.7 Hz, 1H; H(3_{exo})), 1.58 (bs, 1H; exchanges with D_2O; –OH), 1.34–1.55 (m, 3H), 0.98–

1.15 (m, 2H), 0.96 (s, 3H; H(4')), 0.92 (s, 3H; H(10)), 0.89 (s, 3H; H(8)), 0.68 (s, 3H; H(9)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 78.7 (C(2)), 50.8, 47.1, 46.6, 34.5, 33.3, 18.0, 17.8, 15.8, 12.0.

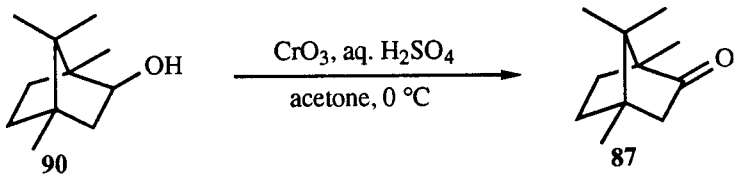
IR ($CHCl_3$): 3420 (ν_{O-H}), 2960, 2890, 1460, 1040 cm^{-1}

EIMS *m/z* (rel intensity): 168 (M^+; 2.1), 150 ($(M - H_2O)^+$; 14.4), 109 (100), 41 (70.6).

Exact mass calcd for $C_{11}H_{20}O$: 168.1514, found 168.1514.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.57; H, 11.99.

(–)-4-Methylcamphor (87)[72]



90 **87**

To a solution of 4-methylisoborneol (**90**; 30.4403 g, 0.1809 mol) in acetone (75 mL) at 0 °C was added, dropwise over 20 min, Jones reagent [prepared from chromium(VI) oxide (18.09 g, 0.1809 mol), water (40 mL), and concentrated sulfuric acid (10 mL)]. The dark orange-green reaction mixture was stirred at 0 °C for 2 h after which saturated aq. $NaHSO_3$ (~20 mL) was added. The reaction mixture was poured into water (~200 mL) and extracted with Et_2O (3 × 100 mL). The organic extracts were washed with water (4 × 250 mL), neutralized with saturated aq. $NaHCO_3$ (2 × 250 mL), washed with brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield 4-methylcamphor (**87**) as a volatile, white solid (29.6423 g, 99%) that could be used directly in the next reaction. Further purification could be accomplished by flash column chromatography [5% Et_2O–pet. ether]; mp 160–162 °C (*lit.*[72] 167–168 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (dd, J = 18.1, 3.0 Hz, 1H; H(3_{exo}), 1.85 (d, J = 18.1 Hz, 1H; H(3_{endo})), 1.57–1.73 (m, 2H), 1.33–1.42 (m, 2H), 1.02 (s, 3H; H(4')), 0.90 (s, 3H; H(10)), 0.81 (s, 3H; H(9)), 0.69 (s, 3H; H(8)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.3 (C(2)), 59.7, 49.0, 48.1, 45.5, 34.3, 29.6, 17.5, 15.8, 15.5, 10.1.

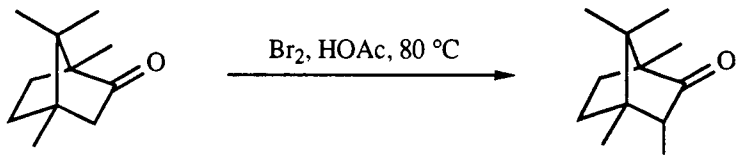
IR ($CHCl_3$): 2970, 2895, 1735 ($\nu_{C=O}$), 1418, 1381 cm^{-1}

EIMS *m/z* (rel intensity): 166 (M^+; 39.8), 138 (13.9), 109 (94.8), 83 (19.6), 82 (100).

Exact mass calcd for $C_{11}H_{18}O$: 166.1358, found 166.1360.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.67; H, 11.03

***endo*-3-Bromo-4-methylcamphor (327)**[72]



87 327

To a solution of 4-methylcamphor (**327**; 27.6423 g, 0.1663 mmol) in glacial acetic acid (250 mL) at 80 °C was added, dropwise over 30 min, a solution of bromine (9.4 mL, 29 g, 0.18 mmol) in glacial acetic acid (10 mL). The red-orange solution was stirred at 80 °C for 18 h, allowed to cool to room temperature, and poured cautiously into a saturated aq. $NaHSO_3$ solution (~100 mL). The aqueous solution was decanted and extracted with Et_2O (2 × 250 mL) while the precipitated crude product was dissolved in Et_2O (250 mL). The combined organic solutions were washed with water (2 × 1 L), neutralized with saturated aq. $NaHCO_3$ (3 × 500 mL), washed with brine (3 × 500 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to a light orange-brown solid. Recrystallization of the orange-brown solid from methanol yielded *endo*-3-bromo-4-methylcamphor as white crystals (24.8824 g, 61%). Subsequent purification of the mother liquor by flash column chromatography [10% Et_2O–pet.

ether] yielded a minor by-product 3,3-dibromo-4-methylcamphor (**369**; 1.2241 g) and upon further elution, *endo*-3-bromo-4-methylcamphor (**327**; 14.2946 g, 35%; total yield 96%) as a volatile, white solid; mp 119.5–121.5 °C (*lit.*[72] 119.5–120.5 °C).

endo-*3-Bromo-4-methylcamphor (327)*

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.28 (d, J = 1.4 Hz, 1H; H(3_{exo})), 2.00–2.10 (m, 1H; H(5_{exo})), 1.48–1.67 (m, 2H), 1.33–1.42 (m, 1H), 1.03 (s, 3H; H(4')), 0.97 (s, 3H; H(10)), 0.95 (s, 3H; H(9)), 0.78 (s, 3H; H(8)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.3 (C(2)), 60.4 (C(3)), 59.0, 50.8, 47.0, 30.1, 29.1, 17.4, 17.1, 13.8, 10.2.

IR ($CHCl_3$): 2960, 2925, 2880, 1747 ($\nu_{C=O}$), 1451, 1396 cm^{-1}

EIMS *m/z* (rel intensity): 246/244 (M^+; 5.0/4.9), 165 ($(M - Br)^+$; 48.1), 137 (52.1), 123 (45.0), 109 (75.7).

Exact mass calcd for $C_{11}H_{17}{}^{79}BrO$: 244.0462, found 244.0467.

Exact mass calcd for $C_{11}H_{17}{}^{81}BrO$: 246.0442, found 246.0439.

Anal. Calcd for $C_{11}H_{17}BrO$: C, 53.89; H, 6.99. Found: C, 53.59; H, 7.02.

3,3-Dibromo-4-methylcamphor (369)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.29–2.44 (m, 1H), 1.80–2.04 (m, 1H), 1.50–1.64 (m, 2H), 1.30 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H).

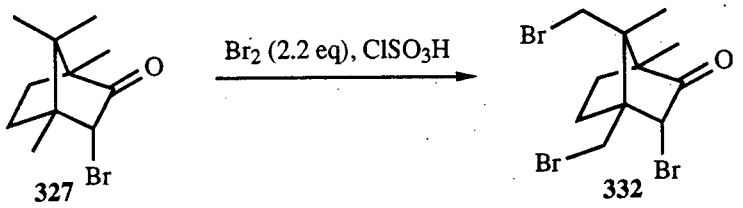
EIMS *m/z* (rel intensity): 326/324/322 (M^+; 2.6/5.9/2.9), 245/243 ($(M - Br)^+$; 30.9/31.1).

Exact mass calcd for $C_{11}H_{16}{}^{79}Br{}^{79}BrO$: 321.9567, found 321.9570.

Exact mass calcd for $C_{11}H_{16}{}^{79}Br{}^{81}BrO$: 323.9547, found 323.9552.

Exact mass calcd for $C_{11}H_{16}{}^{81}Br{}^{81}BrO$: 325.9527, found 325.9525.

***endo*-3,9-Dibromo-4-(bromomethyl)camphor (332)**[72]



To a 250-mL, single-neck, round-bottom flask containing *endo*-3-bromo-4-methylcamphor (**327**; 24.8824 g, 0.1015 mmol) and immersed in an ice-water bath was added in rapid succession chlorosulfonic acid (20 mL) and bromine (12.0 mL, 37.3 g, 0.233 mmol). The solution was stirred at 0 °C for 10 min and then at room temperature for 18 h. The reaction mixture was poured cautiously onto ice (~200 mL) and saturated aq. $NaHSO_3$ (100 mL) was added slowly. The aqueous mixture was extracted with dichloromethane or chloroform (5 × 100 mL). The organic extracts were washed with water (5 × 500 mL), neutralized with saturated aq. $NaHCO_3$ (3 × 250 mL), washed with brine (3 × 250 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a yellow-brown solid. Subsequent purification of the solid by recrystallization [4:5 MeOH–$CHCl_3$; 90 mL] yielded pure *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; 22.4142 g, 55%). The mother liquor was purified further, in two batches, by flash column chromatography (15% Et_2O–pet. ether) to yield the by-products, *endo*-3,9-dibromo-4-methylcamphor (**328**; 0.5897 g), *endo*-3,9,9-tribromo-4-(bromomethyl)camphor (**370**; 0.5779 g), and upon further elution, the desired *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; 12.0203 g, 29%; total yield 84%) as a white solid; mp 142.0–143.0 °C (*lit.*[72] 142.5–143.5 °C).

endo-*3,9-dibromo-4-(bromomethyl)camphor (332)*

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.92 (d, J = 2.3 Hz, 1H; H(3_{exo})), 4.06 (d, J = 11.6 Hz, 1H; H($4'_A$)), 3.74 (d, J = 11.0 Hz, 1H; H(9_A)), 3.52 (d, J = 11.6 Hz, 1H; H($4'_B$)), 3.46 (d, J = 11.0 Hz, 1H; H(9_B)), 2.19 (ddd, J = 13.5, 9.7, 4.0 Hz, 1H; H(5_{endo})), 1.82 (dddd, J =

13.5, 13.5, 5.0, 2.3 Hz, 1H; H(5_{exo}), 1.70 (ddd, J = 13.5, 13.5, 3.9 Hz, 1H; H(6_{exo})), 1.52 (ddd, J = 13.5, 9.7, 5.0 Hz, 1H; H(6_{endo})), 1.24 (s, 3H; H(8)), 1.03 (s, 3H; H(10)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.6 (C(2)), 61.1, 55.4, 54.2, 50.6, 35.8, 31.3, 29.6, 28.2, 16.7, 10.4.

IR ($CHCl_3$): 2924, 2935, 2850, 1745 ($\nu_{C=O}$), 1456, 1425, 1396, 1380, 1256 cm^{-1}

EIMS *m/z* (rel intensity): 406/404/402/400 (M^+; 0.4/1.8/2.0/0.7), 325/323/321 ($(M - Br)^+$; 17.1/41.7/18.8), 245/243 ($(M - 2Br)^+$; 14.0/18.8), 201/199 (28.7/22.2).

Exact mass calcd for $C_{11}H_{15}{}^{79}Br^{79}Br^{79}BrO$: 399.8672, found 399.8675.

Exact mass calcd for $C_{11}H_{15}{}^{79}Br^{79}Br^{81}BrO$: 401.8652, found 401.8667.

Exact mass calcd for $C_{11}H_{15}{}^{79}Br^{81}Br^{81}BrO$: 403.8632, found 403.8637.

Exact mass calcd for $C_{11}H_{15}{}^{81}Br^{81}Br^{81}BrO$: 405.8612, found 405.8605.

Anal. Calcd for $C_{11}H_{15}Br_3O$: C, 32.79; H, 3.75. Found: C, 33.05; H, 3.78.

endo-*3,9-dibromo-4-methylcamphor (**328**)*

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.28 (bs, 1H; H(3_{exo})), 3.54 (d, J = 9.9 Hz, 1H; H(9_A)), 3.46 (d, J = 9.9 Hz, 1H; H(9_B)), 2.01–2.17 (m, 1H), 1.57–1.68 (m, 2H), 1.33–1.42 (m, 1H), 1.12 (s, 3H; H(4')), 1.02 (s, 3H; H(10)), 0.98 (s, 3H; H(8)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.3 (C(2)), 60.1 (C(1)), 59.8 (C(3)), 52.2, 49.5, 36.6 (C(9)), 29.8, 29.0, 15.3, 15.1, 11.3.

Exact mass calcd for $C_{11}H_{16}{}^{79}Br^{79}BrO$: 321.9567, found 321.9564.

Exact mass calcd for $C_{11}H_{16}{}^{79}Br^{81}BrO$: 323.9547, found 323.9552.

Exact mass calcd for $C_{11}H_{16}{}^{81}Br^{81}BrO$: 325.9527, found 325.9529.

endo-*3,9,9-Tribromo-4-(bromomethyl)camphor (**370**)*

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.28 (s, 1H; H(9)), 5.05 (d, J = 0.7 Hz, 1H; H(3)), 4.19 (d, J = 10.5 Hz, 1H; H($4'_A$)), 3.47 (d, J = 10.5 Hz, 1H; H($4'_B$)), 2.10–2.21 (m, 2H), 1.71–1.85 (m, 2H), 1.49 (s, 3H; H(8)), 1.24 (s, 3H; H(10)).

EIMS *m/z* (rel intensity): 486/484/482/480/478 (M^+; 0.4/2.1/3.2/2.2/0.5),.

Exact mass calcd for $C_{11}H_{14}{}^{79}Br^{79}Br^{79}Br^{79}BrO$: 477.7777, found 477.7780.

Exact mass calcd for $C_{11}H_{14}{}^{79}Br^{79}Br^{79}Br^{81}BrO$: 479.7757, found 479.7761.

Exact mass calcd for $C_{11}H_{14}{}^{79}Br^{79}Br^{81}Br^{81}BrO$: 481.7737, found 481.7745.

Exact mass calcd for $C_{11}H_{14}{}^{79}Br^{81}Br^{81}Br^{81}BrO$: 483.7717, found 483.7722.

Exact mass calcd for $C_{11}H_{14}{}^{81}Br^{81}Br^{81}Br^{81}BrO$: 485.7697, found 384.7704.

Table 5.20. Results of NOE Experiments for *endo*-3,9-Dibromo-4-(bromomethyl)camphor (**332**).

Proton Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
4.92	H(3_{exo})	4.06, 3.52, 1.24	H($4'_A$, $4'_B$, 8)
4.06	H($4'_A$)	4.92, 3.52, 2.19, 1.82	H(3, $4'_A$, 5_{endo}, 5_{exo})
3.74	H(9_A)	3.46, 1.82, 1.70	H(9_B, 5_{exo}, 6_{exo})
2.19	H(5_{endo})	4.06, 3.52, 1.82, 1.70, 1.52	H($4'_A$, $4'_B$, 5_{exo}), H(6_{exo}, 6_{endo})
1.52	H(6_{endo})	2.19, 1.70, 1.03	H(5_{endo}, 6_{exo}, 10)
1.24	H(8)	4.92, 3.46, 1.03	H(3_{exo}, 9_B, 10)
1.03	H(10)	3.46, 1.70, 1.52, 1.24	H(9_B, 6_{exo}, 6_{endo}, 8)

*Only those protons that can be assigned unambiguously have been recorded.

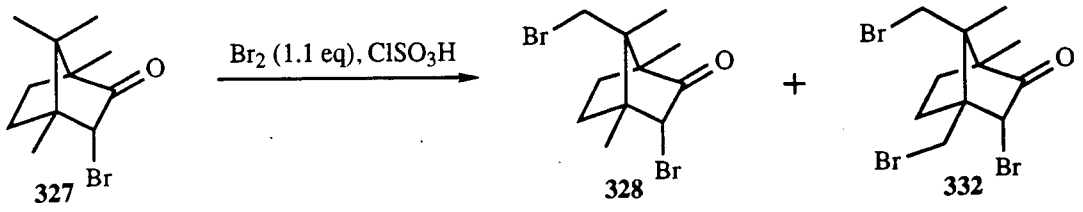
Table 5.21. Spectral Data from COSY Spectrum of *endo*-3,9-Dibromo-4-(bromomethyl)-camphor (**332**).

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
4.92	H(3_{exo})	1.82	H(5_{exo})
4.06	H($4'_A$)	3.52	H($4'_B$)
3.74	H(9_A)	3.46, 1.24	H(9_B), H(8)
3.52	H($4'_B$)	4.06	H($4'_A$)
3.46	H(9_B)	3.74	H(9_A)
2.19	H(5_{endo})	1.82, 1.70, 1.52	H(5_{exo}), H($6_{endo\ and\ exo}$)
1.82	H(5_{exo})	2.19, 1.70, 1.52	H(5_{endo}), H($6_{endo\ and\ exo}$)
1.70	H(6_{exo})	2.19, 1.82, 1.52	H($5_{endo\ and\ exo}$), H(6_{endo})
1.52	H(6_{endo})	2.19, 1.82, 1.70	H($5_{endo\ and\ exo}$), H(6_{exo})
1.24	H(8)	3.74	H(9_A)

Table 5.22. Spectral Data from HETCOR Spectrum of *endo*-3,9-Dibromo-4-(bromomethyl)-camphor (**332**).

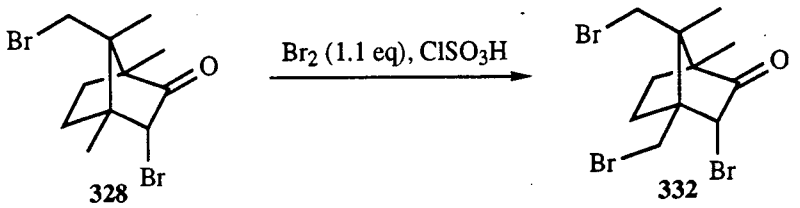
75 MHz ^{13}C NMR Spectrum Signal Positions [δ_C (ppm)]	Assign-ment	HETCOR Correlations Signal Positions [δ_H (ppm)]	Assign-ment
61.1	C(3)	4.92	H(3_{exo})
35.8	C(4')	4.06, 3.52	H(4')
31.3	C(9)	3.74, 3.46	H(9)
29.6	C(6)	1.70, 1.52	H(6)
28.2	C(5)	2.19, 1.82	H(5)
16.7	C(8)	1.24	H(8)
10.4	C(10)	1.03	H(10)

Attempted Preparation of *endo*-3,9-Dibromo-4-methylcamphor (328)



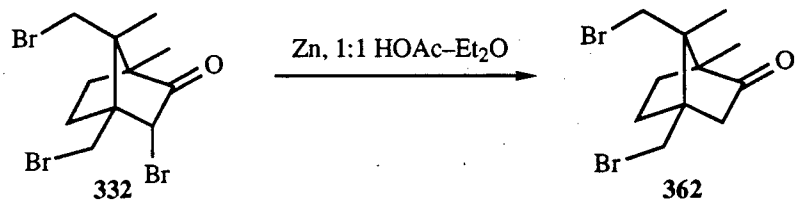
endo-3-Bromo-4-methylcamphor (**327**; 1.0473 g, 4.2719 mmol) was dissolved at 0 °C in chlorosulfonic acid (2.0 mL) and bromine (0.3 mL, 0.8 g, 5 mmol) was added immediately. The solution was stirred at room temperature for 5 h. The reaction mixture was worked up according to the procedure outlined on p. 195. Subsequent purification of the solid by flash column chromatography [15% Et_2O–pet. ether] yielded as the major products *endo*-3,9-dibromo-4-methylcamphor (**328**; 0.5511 g) and *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; 0.5707 g), the spectral characteristics of both were in accordance with those obtained previously (see pp. 195–6).

Conversion of *endo*-3,9-Dibromo-4-methylcamphor (328) to *endo*-3,9-Dibromo-4-(bromomethyl)camphor (332)



endo-3,9-Dibromo-4-methylcamphor (**328**; 0.5274 g, 1.628 mmol) was dissolved in a solution of bromine (0.1 mL, 0.3 g, 2 mmol) in chlorosulfonic acid (1.0 mL) and was stirred at room temperature for 1 h. Work-up and purification of the product according to methods outlined on p. 195 yielded *endo*-3,9,9-tribromo-4-(bromomethyl)camphor (**370**; 0.0959 g) and *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; 0.4162 g, 63%), whose 400 MHz ^1H NMR spectral characteristics were identical to those presented previously (see pp. 195–6).

9-Bromo-4-(bromomethyl)camphor (362)[72]



332 **362**

To a cloudy, ice-cold solution of *endo*-3,9-dibromo-4-(bromomethyl)camphor (**332**; 22.4142 g, 55.62 mmol) in 1:1 glacial acetic acid–Et_2O (500 mL) at 0 °C was added zinc dust (7.2735 g, 111.2 mmol) in ~5 portions over 15–20 min, such that the temperature of the reaction mixture did not exceed 10 °C. The reaction mixture was stirred at 0 °C for 1 h after which it was filtered through a Celite® pad. The Celite® pad was washed further with Et_2O (200 mL). The filtrate was then washed with water (4 × 250 mL), neutralized with saturated aq. $NaHCO_3$ (3 × 500 mL), washed with brine (3 × 500 mL), dried over anhydrous $MgSO_4$, and concentrated to a light brown solid. The crude solid was triturated in ice-cold methanol (~15–20 mL) to yield pure 9-bromo-4-(bromomethyl)camphor (**362**, 8.0775 g, 45%) as white crystals. Subsequent purification of the mother liquor by flash column chromatography [20% Et_2O–pet. ether] yielded a further quantity of pure 9-bromo-4-(bromomethyl)camphor (**362**; 6.4791 g, 36%; total yield 81%) as a white solid; mp 54.0–55.0 °C (*lit.*[72] 53–55 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.95 (d, J = 10.3 Hz, 1H; H(4'$_A$)), 3.61 (dd, J = 11.0, 0.6 Hz, 1H; H(9$_A$)), 3.57 (d, J = 10.3 Hz, 1H; H(4'$_B$)), 3.30 (d, J = 11.0 Hz, 1H; H(9$_B$)), 2.29 (dd, J = 8.5, 2.6 Hz, 1H; H(3$_{exo}$)), 2.26 (d, J = 8.5 Hz, 1H; H(3$_{endo}$)), 1.82–1.96 (m, 2H), 1.65–1.75 (m, 1H), 1.43–1.53 (m, 1H), 0.99 (s, 3H; H(8)), 0.95 (s, 3H; H(10)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.4 (C(2)), 61.9, 52.0, 51.3, 47.7, 36.1, 35.8, 31.8, 28.4, 15.3, 10.6.

IR ($CHCl_3$): 2960, 2925, 2838, 2829, 1743 ($\nu_{C=O}$), 1458, 1425, 1378, 1319, 1248 cm^{-1}

EIMS *m/z* (rel intensity): 326/324/322 (M^+; 11.4/23.9/12.7), 245/243 ($(M - Br)^+$; 56.2/56.2), 217/215 (35.5/35.2), 201/199 (83.9/76.6), 163(50.3).

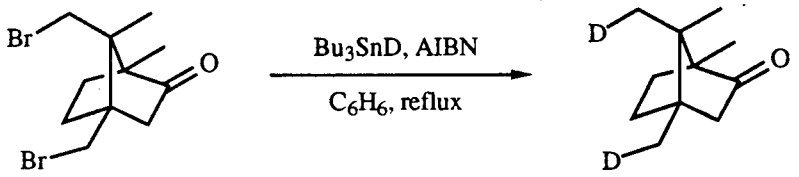
Exact mass calcd for $C_{11}H_{16}{}^{79}Br^{79}BrO$: 321.9567, found 321.9585.

Exact mass calcd for $C_{11}H_{16}{}^{79}Br^{81}BrO$: 323.9547, found 323.9543.

Exact mass calcd for $C_{11}H_{16}{}^{81}Br^{81}BrO$: 325.9527, found 325.9532.

Anal. Calcd for $C_{11}H_{16}Br_2O$: C, 40.77; H, 4.98. Found: C, 40.96; H, 5.01.

9-Deuterio-4-(deuteriomethyl)camphor (363)[72]



362 **363**

To a solution of 9-bromo-4-(bromomethyl)camphor (**362**; 3.0525 g, 9.4196 mmol) in dry benzene (70 mL) was added AIBN (0.3313 g, 2.018 mmol) and then tributyltin deuteride (6.2 mL, 6.7 g, 23 mmol) in three portions. The reaction mixture was refluxed for 17 h after which it was cooled to room temperature. Methanol (50 mL) was added and the combined solvents were removed under reduced pressure to produce the crude product as a pale yellow slush. Purification by flash column chromatography (1.5% Et_2O–pet. ether) provided 9-deuterio-4-(deuteriomethyl)camphor (**363**) as slushy, volatile, white crystals (1.2143 g, 58%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.07 (dd, J = 18.2, 3.0 Hz, 1H; H(3_{exo}), 1.85 (d, J = 18.2 Hz, 1H; H(3_{endo})), 1.57–1.73 (m, 2H), 1.32–1.42 (m, 2H), 1.00 (t, J = 1.9 Hz, 2H; H(4')), 0.90 (s, 3H; H(10)), 0.80 (t, J = 1.9 Hz, 2H; H(9)), 0.69 (s, 3H; H(8)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 218.9, 59.4, 48.7, 47.8, 45.2, 34.0, 29.4, 17.2, 15.3 (t, $^1J_{^{13}C-^2H}$ = 19.0 Hz), 14.9 (t, $^1J_{^{13}C-^2H}$ = 18.9 Hz), 9.9.

IR ($CHCl_3$): 2970, 2895, 1735 ($\nu_{C=O}$), 1418, 1381 cm^{-1}

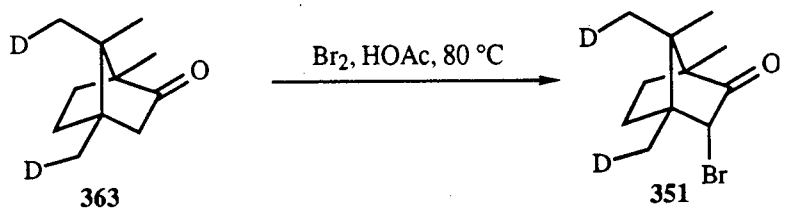
EIMS *m/z* (rel intensity): 168 (M^+; 56.0), 140 (19.3), 124 (75.2), 111 (67.4), 96 (21.5), 84 (100).

Exact mass calcd for $C_{11}H_{16}D_2O$: 168.1481, found 168.1483.

Table 5.23. Spectral Data from COSY Spectrum of 9-Deuterio-4-(deuteriomethyl)camphor (**363**).

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assign-ment
2.07	H(3_{exo})	1.85, 1.57–1.73 (part of multiplet)	H(3_{endo}, 5_{exo})
1.85	H(3_{endo})	2.07	H(3_{exo})
1.57–1.73	H(5_{exo}) H(6_A)	2.07, 1.32–1.42	H(3_{exo}, 6_B)
1.32–1.42	H(5_{endo}), H(6_B)	1.57–1.73	H(5_{exo}), H(6_A)
0.80	H(9)	0.69	H(8)
0.69	H(8)	0.80	H(9)

***endo*-3-Bromo-9-deuterio-4-(deuteriomethyl)camphor (351)**



To a solution of 9-deuterio-4-(deuteriomethyl)camphor (**363**) (1.1587 g, 6.8857 mmol) in glacial acetic acid (4.5 mL) was added a solution of bromine (1.5 mL, 4.8 g, 15 mmol) in glacial acetic acid (1.5 mL). The reaction mixture was heated at 80 °C for 18 h and was then poured into ice-cold, saturated aqueous sodium bisulfite solution (20 mL). The aqueous mixture was extracted with Et_2O (3 × 25 mL) and the combined extracts washed successively with saturated aq. $NaHSO_3$ (1 × 50 mL), $NaHCO_3$ (3 × 50 mL), water (4 × 50 mL), and brine (2 × 50 mL). The organic solution was then dried over anhydrous $MgSO_4$ and concentrated under reduced

pressure to provide a viscous brown syrup. Subsequent purification by flash column chromatography (5% Et_2O–pet. ether) yielded *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**) as white crystals (0.8125 g, 48%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.28 (d, J = 1.4 Hz, 1H; H(3_{exo})), 2.00–2.10 (m, 1H; H(5_{exo})), 1.48–1.67 (m, 2H), 1.33–1.42 (m, 1H), 0.99 (t, J = 1.9 Hz, 3H; H(4')), 0.97 (s, 3H; H(10)), 0.95 (t, J = 1.9 Hz, 3H; H(9)), 0.78 (s, 3H; H(8)).

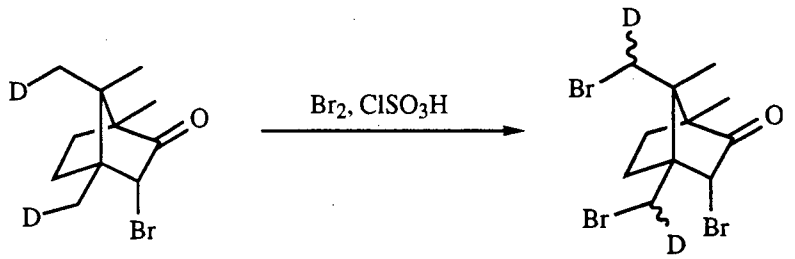
^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.3 (C(2)), 60.4, 59.0, 50.8, 47.0, 30.1, 29.1, 17.4, 16.9 (t, $^1J_{^{13}C-^2H}$ = 19.0 Hz), 13.5 (t, $^1J_{^{13}C-^2H}$ = 19.3 Hz).

EIMS *m/z* (rel intensity): 248/246 (M^+; 11.0/11.6), 167 ($(M - Br)^+$; 100), 139 (90.9).

Exact mass calcd for $C_{11}H_{15}{}^{79}BrD_2O$: 246.0586, found 246.0596.

Exact mass calcd for $C_{11}H_{15}{}^{81}BrD_2O$: 248.0566 found 248.0573.

***endo*-3,9-Dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (352)**



351 **352**

To an ice-cold solution of *endo*-3-bromo-9-deuterio-4-(deuteriomethyl)camphor (**351**; 1.6246 g, 6.5727 mmol) in chlorosulfonic acid (5.0 mL) was added bromine (0.76 mL, 2.4 g, 15 mmol) in one portion. The reaction mixture was stirred at 0 °C for 1 min and at room temperature for 15 h and then poured cautiously onto ice (~25 mL) containing saturated aq $NaHSO_3$ solution (~25 mL). The precipitated solid was collected by suction filtration, re-dissolved in diethyl ether (100 mL), and then washed successively with saturated aq. $NaHSO_3$ (1 × 50 mL), neutralized with saturated aq. $NaHCO_3$ (3 × 100 mL), and washed with brine (3 × 100

mL). Solvent removal under reduced pressure yielded crude product as an off-white powder. Subsequent purification by flash column chromatography (15% Et_2O–pet. ether) provided *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**) as colorless needles (0.9845 g, 63%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.92 (d, J = 2.3 Hz, 1H; H(3_{exo})), 4.01/3.48 (bs, 1H; H(4')), 3.70/3.41 (bs, 1H; H(9)), 2.19 (ddd, J = 13.5, 9.7, 4.0 Hz, 1H; H(5_{endo})), 1.82 (dddd, J = 13.5, 13.5, 5.0, 2.3 Hz, 1H; H(5_{exo}), 1.70 (ddd, J = 13.5, 13.5, 3.9 Hz, 1H; H(6_{exo})), 1.52 (ddd, J = 13.5, 9.7, 5.0 Hz, 1H; H(6_{endo})), 1.24 (s, 3H; H(8)), 1.03 (s, 3H; H(10)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.0, 61.1, 55.4, 54.1, 50.4, 35.7 (t, $^1J_{^{13}C-^2H}$ = 23.5 Hz), 31.1 (t, $^1J_{^{13}C-^2H}$ = 23.4 Hz), 29.6, 28.2, 16.7, 10.4.

EIMS *m/z* (rel intensity): 408/406/404/402 (M^+; 1.4/4.5/5.8/2.2), 327/325/323 ($(M - Br)^+$; 47.8/100/52.8), 299/297/295 (4.6/10.7/5.4).

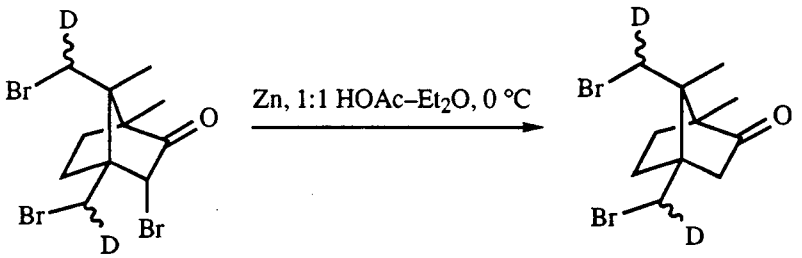
Exact mass calcd for $C_{11}H_{13}{}^{79}Br^{79}Br^{79}BrD_2O$: 401.8795, found 401.8778.

Exact mass calcd for $C_{11}H_{13}{}^{79}Br^{79}Br^{81}BrD_2O$: 403.8775, found 403.8782.

Exact mass calcd for $C_{11}H_{13}{}^{79}Br^{81}Br^{81}BrD_2O$: 405.8755, found 405.8763.

Exact mass calcd for $C_{11}H_{13}{}^{81}Br^{81}Br^{81}BrD_2O$: 407.8735, found 407.8748.

9-Bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (364)



352 **364**

To a solution of *endo*-3,9-dibromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**352**; 0.9375 g, 2.315 mmol) in 2:1 HOAc–Et_2O (6.0 mL) at 0 °C was added zinc dust (0.3813 g,

5.832 mmol) in one portion. The reaction was allowed to proceed at 0 °C for 3.0 h. Solid materials in the reaction mixture were removed by filtration. The filtrate was diluted with Et_2O (~100 mL), washed successively with water (3 × 50 mL), saturated aqueous $NaHCO_3$ (1 × 50 mL), and brine (2 × 50 mL), and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure yielded a golden-yellow product that was purified further by radial chromatography (2 mm plate; 5% Et_2O–pet. ether or 2.5% EtOAc–pet. ether) to yield 9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**364**) as a white solid (0.6115 g, 82%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.90/3.53 (bs, 1H; H(4')), 3.56/3.26 (bs, 1H; H(9)), 2.29 (dd, J = 8.5, 2.6 Hz, 1H; H(3_{exo})), 2.26 (d, J = 8.5 Hz, 1H; H(3_{endo})), 1.82–1.96 (m, 2H), 1.65–1.75 (m, 1H), 1.43–1.53 (m, 1H), 0.99 (s, 3H; H(8)), 0.95 (s, 3H; H(10)).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.9 (C(2)), 61.6, 51.7, 50.9, 47.4, 35.8 (t, $^1J_{^{13}C-^2H}$ = 19.1 Hz), 35.6 (t, $^1J_{^{13}C-^2H}$ = 21.4 Hz), 31.6, 28.1, 15.1, 10.4.

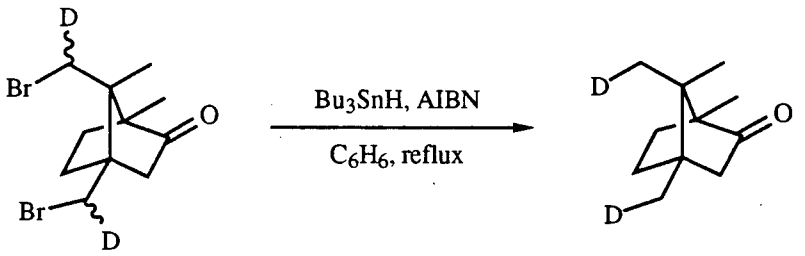
EIMS *m/z* (rel intensity): 328/326/324 (M^+; 18.5/38.4/21.0), 284/282/280 (10.6/22.2/12.1), 247/245 ($(M - Br)^+$; 87.7/93.2).

Exact mass calcd for $C_{11}H_{14}{}^{79}Br^{79}BrD_2O$: 323.9691, found 323.9684.

Exact mass calcd for $C_{11}H_{14}{}^{79}Br^{81}BrD_2O$: 325.9671, found 325.9677.

Exact mass calcd for $C_{11}H_{14}{}^{81}Br^{81}BrD_2O$: 327.9651, found 327.9640.

Debromination of 9-Bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (364) to Yield 9-Deuterio-4-(deuteriomethyl)camphor (363).



363 **363**

To a solution of 9-bromo-9-deuterio-4-(bromodeuteriomethyl)camphor (**364**; 101 mg, 0.310 mmol) in dry benzene (5.0 mL) was added AIBN (0.110 g, 66.7 μmol) and then tributyltin hydride (205 μL, 221 mg, 0.759 mmol). The reaction mixture was refluxed for 2 h after which it was cooled to room temperature. The solvent was removed under reduced pressure to yield an oily residue that was purified directly by flash column chromatography (1.5% Et_2O–pet. ether) to afford 9-deuterio-4-(deuteriomethyl)camphor (**363**) as white crystals (33.5 mg, 64%).

References and Notes

References and Notes

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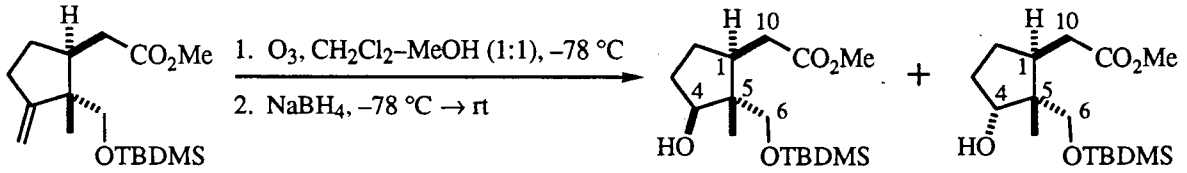
Appendix

Supplementary Experimental Procedures

Appendix: Supplementary Experimental Procedures

Preparation of Hydroxy-esters 161a and 161b

Method 1: From Silyloxy-ester 162a



162a **161a** **161b**

A stream of ozonized oxygen (~4% O_3 in O_2) was bubbled into a solution of silyloxy-ester **162a** (178.4 mg, 0.4086 mmol) in 1:1 CH_2Cl_2–MeOH (10 mL) at –78 °C for 15 min. Excess ozone was purged with oxygen gas (~5 min). Solid sodium borohydride (54.1 mg, 1.43 mmol)[91b–c] was added in small portions over ~15 min while the reaction mixture was allowed to warm to room temperature (~20–25 min). The reaction mixture was then stirred for a further 1 h at room temperature after which it was poured into brine (20 mL). The organic layer was removed while the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic phases were washed with brine (3 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a pale yellow oil. Purification of the oil by flash column chromatography (30% EtOAc–pet. ether) yielded the minor hydroxy-ester diastereomer **161b** (24.6 mg; 14%) and subsequently, the major hydroxy-ester diastereomer **161a** (143.4 mg; 80%), both as colorless oils.

*Hydroxy-ester **161a***

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.06–4.15 (m, 1H; simplifies to (dd, J = 8.5, 8.5 Hz) upon addition of D_2O; H(4)), 3.55 (s, 3H; –CO_2Me), 3.51 (d, J = 9.1 Hz, 1H; H(6_A)), 3.46 (d, J = 9.1 Hz, 1H; H(6_B)), 2.19–2.30 (m, 2H; simplifies to (dd, J = 18.5, 8.2 Hz) upon addition of D_2O; H(10_A), –OH), 2.03–2.12 (m, 2H; H(10_B), H(1)), 1.92–2.02 (m, 1H; H(3_A)), 1.80–1.90 (m, 1H; H(2_A)), 1.46–1.58 (m, 1H; H(2_B)), 1.31–1.42 (m, 1H; H(3_B)),

1.06 (s, 9H; Bu^t), 0.83 (s, 3H; C(5)–CH_3), 0.09 (s, 3H; –Si<u>Me</u>$_2Bu^t$), 0.02 (s, 3H; –Si<u>Me</u>$_2Bu^t$).

IR (neat film): 3402 (ν_{O-H}), 2960, 2859, 1739 ($\nu_{C=O}$), 1113 cm^{-1}

EIMS *m/z* (rel intensity): 285 ($(M - OMe)^+$; 0.2), 259 ($(M - Bu^t)^+$; 4.7), 201 (1.5), 184 (0.8), 99 (100).

Exact mass calcd for $C_{12}H_{23}O_4Si$ [$(M - Bu^t)^+$]: 259.1366, found 259.1372.

Results of NOE experiment:

Irradiation of the signal at 4.06–4.15 [H(4)] resulted in the enhancement of signal intensities at 2.19–2.30 [part of multiplet], 2.03–2.12 [part of multiplet], 1.80–1.90 [$H(2_A)$], 1.06 [Bu^t], 0.09 [–Si<u>Me</u>$_2Bu^t$], 0.02 [–Si<u>Me</u>$_2Bu^t$].

Table A.1. Spectral Data from COSY Spectrum of Hydroxy-ester **161a**.

400 MHz ^1H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assign-ment
4.06–4.15	H(4)	2.19–2.30 (part of multiplet), 1.92–2.02, 1.31–1.42	–OH, $H(3_A, 3_B)$
2.19–2.30	$H(10_A)$, –OH	4.06–4.15, 2.03–2.12	H(4), $H(10_B)$, H(1)
2.03–2.12	$H(10_B)$, H(1)	2.19–2.30 (part of multiplet), 1.80–1.90, 1.46–1.58	$H(10_A)$, $H(2_A, 2_B)$
1.92–2.02	$H(3_A)$	4.06–4.15, 1.80–1.90, 1.46–1.58, 1.31–1.42	H(4), $H(3_B)$, $H(2_A, 2_B)$
1.80–1.90	$H(2_A)$	2.03–2.12 (part of multiplet), 1.92–2.02, 1.46–1.58, 1.31–1.42	H(1), $H(2_B)$, $H(3_A, 3_B)$
1.46–1.58	$H(2_B)$	2.03–2.12 (part of multiplet), 1.92–2.02, 1.80–1.90, 1.31–1.42	H(1), $H(2_A)$, $H(3_A, 3_B)$
1.31–1.42	$H(3_B)$	4.06–4.15, 1.92–2.02, 1.80–1.90, 1.46–1.58	H(4), $H(3_A)$, $H(2_A, 2_B)$

*Hydroxy-ester **161b***

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.94–4.00 (m, 1H; simplifies to (dd, J = 7.5, 2.0 Hz) upon addition of D_2O; H(4)), 3.62 (bs, 2H; H(6)), 3.58 (s, 3H; $-CO_2Me$), 3.18 (d, J = 3.5 Hz, 1H; exchanges with D_2O; –OH), 2.42–2.55 (m, 1H; H(1)), 1.95–2.14 (m, 4H; H(10), $H(3_A)$, $H(2_A)$), 1.51–1.62 (m, 1H; $H(3_B)$), 1.21–1.34 (m, 1H; $H(2_B)$), 1.05 (s, 9H; Bu^t), 0.69 (s, 3H; C(5)–CH_3), 0.05 (s, 3H; –Si$\underline{Me_2}Bu^t$), –0.02 (s, 3H; –Si$\underline{Me_2}Bu^t$).

IR (neat film): 3402 (ν_{O-H}), 2957, 2865, 1735 ($\nu_{C=O}$), 1102 cm^{-1}

EIMS *m/z* (rel intensity): 285 ($(M - OMe)^+$; 1.9), 259 ($(M - Bu^t))^+$; 14.5), 201 (4.1), 184 (2.0), 99 (100).

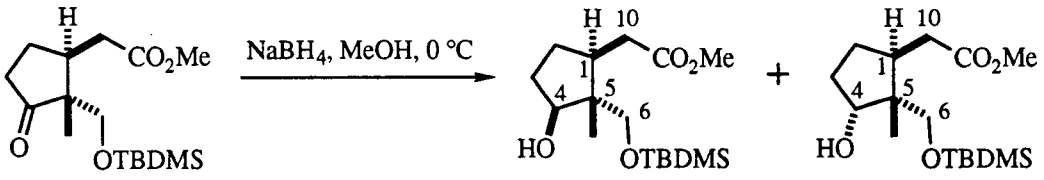
Exact mass calcd for $C_{12}H_{23}O_4Si$ [$(M - Bu^t)^+$]: 259.1366, found 259.1369.

Table A.2. Results of NOE Experiments for Hydroxy-ester **161b**.

Proton Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
3.94–4.00	H(4)	3.62, 3.18, 1.95–2.14 (part of multiplet), 1.51–1.62, 0.69	H(6), –OH, $H(3_B)$, C(5)–CH_3
0.69	C(5)–CH_3	3.94–4.00, 3.62, 1.95–2.14 (part of multiplet), 1.51–1.62, 1.21–1.34	H(4), H(6), $H(3_B)$, $H(2_B)$

*Only those protons that can be assigned unambiguously have been recorded.

Method 2: ***From Keto-ester 163a***

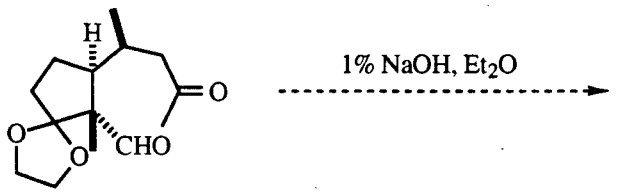


163a **161a** **161b**

To a solution of keto-ester **163a** (0.1003 g, 0.3189 mmol) in spectro grade methanol (10 mL) at 0 °C was added solid sodium borohydride (0.0145 g, 0.383 mmol). The clear, colorless

solution was stirred at 0 °C for 30 min, and then neutralized with 1 M HCl. The reaction mixture was diluted with Et_2O (50 mL) and poured into brine. The organic phase was removed and the aqueous phase was extracted further with Et_2O (2 × 50 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (2 × 100 mL) and brine (3 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated to yield crude hydroxy-esters **161a** and **161b** as a viscous oil (0.9981 g). ^1H NMR analysis of the crude product revealed that the two hydroxy-esters **161a** and **161b** were present as a ~3:1 mixture of diastereomers. Spectroscopic data for **161a** and **162b** were identical to those reported above.

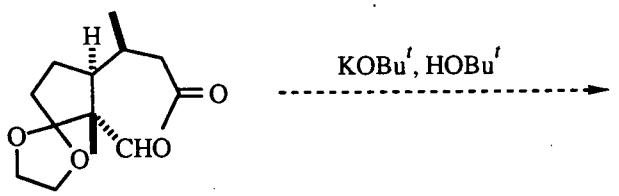
Attempted Intramolecular Aldol Condensation of Keto-aldehyde 198 Using 1% NaOH/Diethyl Ether.[111]



198

Keto-aldehyde **198** (9.9 mg, 0.039 mmol) was dissolved in reagent grade diethyl ether (~1.5 mL) and 1% aqueous sodium hydroxide (~1.0 mL) was added. The resulting two-phase mixture was stirred vigorously. No reaction was evident after 2 d, and the experiment was abandoned.

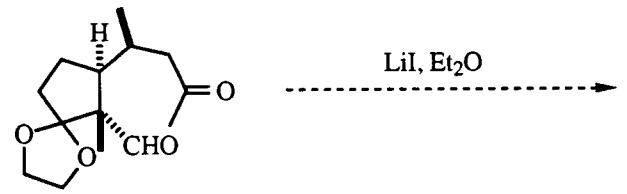
Attempted Potassium *t*-Butoxide Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.[112]



198

Potassium *t*-butoxide (62.2 mg, 0.554 mmol) was added to a solution of keto-aldehyde **198** (18.8 mg, 0.0736 mmol) in *t*-butanol (~0.7 mL).[112] The reaction mixture was stirred for 5 d, after which TLC revealed that the consumption of keto-aldehyde **198** was negligible; only a very faint spot with an R_f corresponding to that for hydroxy-ketone **199** could be detected. The experiment was abandoned.

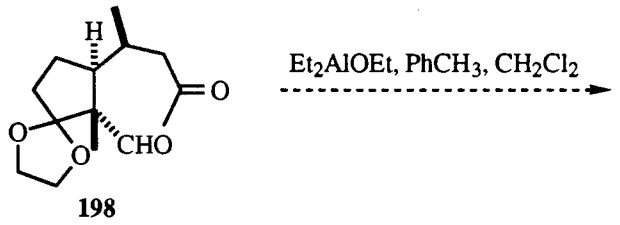
Attempted Lithium Iodide Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.[113]



198

To a solution of keto-aldehyde **198** (11.5 mg, 0.0452 mmol) in anhydrous diethyl ether (1.0 mL) was added anhydrous lithium iodide (15.1 mg, 0.113 mmol).[113] The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After 48 h, no conversion of starting material to products was observed. The reaction was worked up as usual and the starting material was recovered (10.8 mg; 94% recovery) by flash column chromatography (75% Et_2O–pet. ether). Similar results were obtained when only 0.5 mL of anhydrous Et_2O was used as solvent.

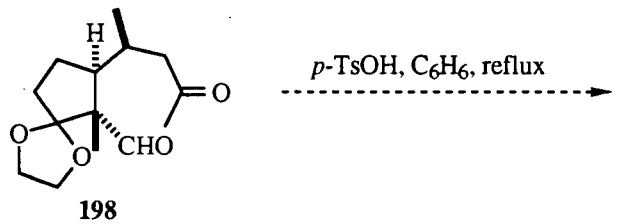
Attempted Diethylaluminum Ethoxide Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.[114]



198

Keto-aldehyde **198** (23.8 mg, 0.0936 mmol) was dissolved in dry dichloromethane (0.5 mL) and diethylaluminum ethoxide (0.58 mL, 1.6 M in toluene, 0.94 mmol) was added.[114] The colorless solution was stirred at (80 ± 5) °C for 3 d. Although all starting material (**198**) had been consumed, TLC analysis showed that the reaction mixture consisted of an inseparable mixture of products that were more polar than the starting material.

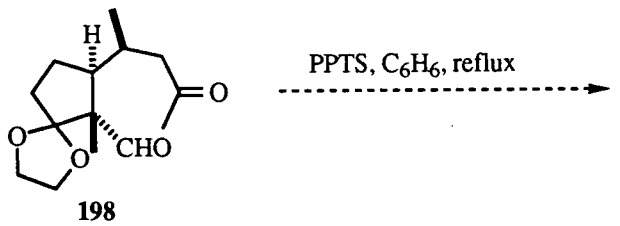
Attempted *p*-Toluenesulfonic Acid Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.[115a]



198

p-Toluenesulfonic acid (~2.0 mg, 0.011 mmol) was added to a solution of keto-aldehyde **198** (14.1 mg, 0.0554 mmol) in dry benzene (10 mL) and the mixture was refluxed in a Dean-Stark apparatus.[115a] After 3.5 d, TLC analysis revealed that significant decomposition of starting material into a complex mixture of products had occurred, although a spot with an R_f corresponding to that of ketal-enone **200** could also be observed. The reaction mixture was worked up through standard procedures. Flash column chromatography (75% Et_2O–pet. ether) of the crude product yielded a negligible amount of ketal-enone (3.1 mg, 21%).

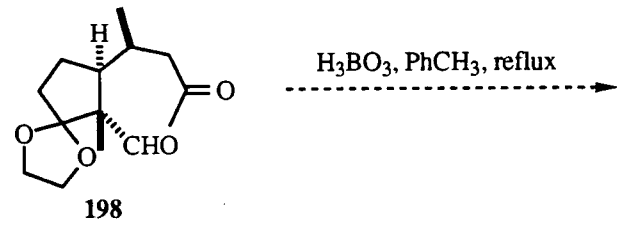
Attempted Pyridinium *p*-Toluenesulfonate Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.



198

The PPTS-mediated aldol condensation of keto-aldehyde **198** was attempted via a procedure similar to that followed for the corresponding reaction involving *p*-toluenesulfonic acid (*vide supra*). No reaction was observed for 5 d, and the experiment was therefore abandoned.

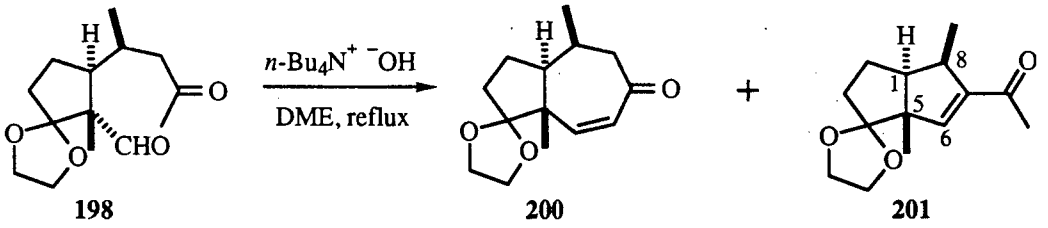
Attempted Boric Acid Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.[117]



198

To a solution of keto-aldehyde **198** (15.2 mg, 0.0597 mmol) in dry benzene or toluene (5.0 mL) was added boric acid crystals (3.0 mg, 0.049 mmol).[117] The mixture was refluxed in a Dean-Stark apparatus for 5 d. The thin-layer chromatogram of the final product mixture showed an intense spot corresponding to starting material (**198**) and a very faint spot whose R_f coincided with that of authentic ketal-enone **200**. The experiment was abandoned. Similar results were obtained when the amount of solvent was reduced (1.0 mL, 2.0 mL, or 3.0 mL) and no Dean-Stark apparatus was used.

Attempted Tetrabutylammonium Hydroxide Mediated Intramolecular Aldol Condensation of Keto-aldehyde 198.



198 **200** **201**

A solution of keto-aldehyde (25.4 mg, 0.0998 mmol) and tetrabutylammonium hydroxide (0.35 mL, 40% solution in water, 0.50 mmol) in reagent grade dimethoxyethane (2.0 mL) was refluxed for 7 d. The reaction mixture was diluted with Et_2O (50 mL), washed with water (2 × 50 mL) and brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield a pale yellow oil. Purification of the oil by radial chromatography (1 mm plate; 20% Et_2O–pet. ether) yielded, in order of elution, ketal-enone **201** (16.1 mg; 82% based on recovered starting material), ketal-enone **200** (2.7 mg, 14% based on recovered starting material), and recovered keto-aldehyde **198** (4.2 mg). Spectroscopic data for ketal-enone **200** were identical to those reported on p. 161.

*Bicyclic Ketal-enone **201***

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.48 (d, J = 2.1 Hz, 1H; H(6)), 3.85–4.02 (m, 4H; –OC$\underline{H_2}$C$\underline{H_2}$O–), 3.22 (qdd, J = 7.5, 7.5, 2.1 Hz, 1H; H(8)), 2.28–2.36 (m, 1H; H(1)), 2.28 (s, 3H; –C(O)C$\underline{H_3}$), 1.53–1.73 (m, 4H; H(2), H(3)), 1.13 (d, J = 7.5 Hz, 3H; C(8)-C$\underline{H_3}$), 1.05 (s, 3H; C(5)–C$\underline{H_3}$).

IR (neat film): 2944, 2912, 2896, 2864, 1688 ($\nu_{C=O}$), 1472, 1408 cm^{-1}

Exact mass calcd for $C_{14}H_{20}O_3$: 236.1412, found 236.1420.

Table A.3. Spectral Data from COSY Spectrum of Ketal-enone **201**.

400 MHz ^{1}H NMR Spectrum Signal Positions [δ (ppm)]	Assign-ment	COSY Correlations Signal Positions [δ (ppm)]	Assignment
6.48	H(6)	3.22	H(8)
3.22	H(8)	6.48, 2.28–2.36, 1.13	H(6), H(1), C(8)–C$\underline{H}_3$
2.28–2.36	H(1)	3.22, 1.53–1.73 (part of multiplet)	H(8), H(2)
1.53–1.73	H(2, 3)	2.28–2.36	H(1)
1.13	C(8)-CH_3	3.22	H(8)

Table A.4. Results of NOE Experiments for Ketal-enone **201**.

Proton Irradiated (ppm)	Assignment	NOE Correlations (ppm)	Assignments*
6.48	H(6)	3.85–4.02, 2.28, 1.05	-ketal, –C(O)C$\underline{H}_3$, C(5)–C$\underline{H}_3$
3.22	H(8)	2.28–2.36, 2.28, 1.13	C(1), –C(O)C$\underline{H}_3$, C(8)–C$\underline{H}_3$
1.13	C(8)–CH_3	6.48, 3.22, 1.53–1.73, 1.05	H(6), H(8), C(5)–C$\underline{H}_3$

*Only those protons that can be assigned unambiguously have been recorded.